

Ease of use of tobramycin inhalation powder compared with nebulized tobramycin and colistimethate sodium: a crossover study in cystic fibrosis patients with pulmonary *Pseudomonas aeruginosa* infection

James Greenwood, Carsten Schwarz, Urte Sommerwerck, Edward F Nash, Michael Tamm, Weihua Cao, Paul Mastoridis, Laurie Debonnett and Kamal Hamed

Abstract

Background: This study assessed the ease of use of tobramycin inhalation powder (TIP) administered *via* T-326 inhaler *versus* tobramycin inhalation solution (TIS) and colistimethate sodium (COLI), both administered *via* nebulizers, for the treatment of chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF).

Methods: A real-world, open-label, crossover, interventional phase IV study was conducted in CF patients aged ≥ 6 years with forced expiratory volume in 1 second (FEV₁) $\geq 25\%$ to $\leq 90\%$ predicted. Patients were assigned to one of the three treatment arms in Cycle 1; all patients received TIP in Cycle 2. Each cycle consisted of 28 days on and 28 days off the treatment.

Results: A total of 60 patients [mean (standard deviation) age, 27.6 (8.4) years] were allocated to three treatment arms [TIS/TIP ($n = 14$); COLI/TIP ($n = 28$); TIP/TIP ($n = 18$)] in Cycle 1. The mean total administration time, which included device setup and cleaning, in Cycle 1 *versus* Cycle 2 for TIS/TIP, COLI/TIP, and TIP/TIP arms were 37.0 *versus* 5.0 min, 16.4 *versus* 3.8 min, and 4.2 *versus* 3.4 min, respectively. The difference in mean total administration time was significantly shorter in Cycle 2 than in Cycle 1 for TIS/TIP ($p = 0.0112$) and COLI/TIP ($p = 0.0016$) arms. Overall, 12 patients were found to have contaminated devices across the two treatment cycles. In the TIP/TIP arm, no contamination of the T-326 inhaler was observed in either cycle. Treatment satisfaction, assessed by the Treatment Satisfaction Questionnaire for Medication and ACCEPT[®] questionnaire, was better overall for TIP compared with TIS and COLI. There were no unexpected adverse events and most were mild or moderate in intensity.

Conclusion: The T-326 inhaler used to deliver TIP was easy to use, required shorter total administration time, and was much less frequently contaminated than the nebulizers. The safety findings observed for TIP were generally consistent with its established safety profile.

Keywords: device contamination, ease of use, nebulizer, *Pseudomonas aeruginosa*, T-326 inhaler, tobramycin

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Introduction

Cystic fibrosis (CF) patients are generally susceptible to respiratory infection caused by *Pseudomonas aeruginosa* (*Pa*), which is associated with progressive lung function decline and

increased morbidity and mortality.^{1,2} Tobramycin inhalation solution (TIS) has been established as an effective inhaled antibiotic for the treatment of chronic *Pa* pulmonary infection in patients with CF aged ≥ 6 years.^{3,4} Colistimethate sodium

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Correspondence to:

Kamal Hamed
Novartis Pharmaceuticals
Corporation, East Hanover,
NJ 07936-1080, USA
kamal.hamed@novartis.com

James Greenwood
Liverpool Heart and Chest
Hospital NHS Foundation
Trust, Thomas Drive,
Liverpool, UK

Carsten Schwarz
Department of Pediatric
Pneumology and
Immunology, Cystic
Fibrosis Centre Berlin,
Charité–University
Medicine Berlin, Berlin,
Germany

Urte Sommerwerck
Department of
Pneumology,
Ruhrlandklinik, West
German Lung Center,
University Hospital
of Essen, University
Duisburg-Essen, Essen,
Germany

Edward F Nash
West Midlands Adult Cystic
Fibrosis Centre, Heart of
England NHS Foundation
Trust, Birmingham, UK

Michael Tamm
Clinic of Pneumology and
Respiratory Cell Research,
University Hospital, Basel,
Switzerland

Weihua Cao
Novartis Pharmaceuticals
Corporation, East Hanover,
NJ, USA

Paul Mastoridis
Novartis Pharmaceuticals
Corporation, East Hanover,
NJ, USA

Laurie Debonnett
Novartis Pharmaceuticals
Corporation, East Hanover,
NJ, USA

(COLI) is also indicated for treating chronic pulmonary infection due to *Pa* in adult and pediatric CF patients.⁵ The administration of nebulized TIS and COLI for the treatment of *Pa* infection is complex, time consuming, and places a high burden on CF patients and their caregivers, posing a significant challenge to treatment adherence.^{4,6,7} In addition, nebulizers require regular maintenance, consisting of cleaning, disinfection, and drying for each use to minimize microbial contamination.^{8,9} Moreover, pathogens are commonly isolated from nebulizers and there is a concern that the nebulizer equipment may contribute to bacterial infection in the lower airways of CF patients.^{2,9} Tobramycin inhalation powder (TIP) has been developed for the suppressive management of pulmonary infection due to *Pa* in CF patients aged ≥ 6 years.¹⁰ TIP, delivered *via* the T-326 inhaler, was reported to have a safety and efficacy profile similar to that of TIS but with a substantially simplified method of administration, which has translated into increased patient convenience and adherence.^{6,11–13} This study was designed to compare the ease of use of TIP administered *via* the T-326 inhaler (Novartis Pharma AG, Basel, Switzerland) with TIS and COLI, both administered *via* nebulizers. Furthermore, the prevalence of microbial contamination of the devices used was also compared in this study.

Methods

This open-label, crossover, interventional, phase IV, 20-week trial was conducted at 22 centers in the United Kingdom (8), Spain (5), Germany (4), Switzerland (3), and Ireland (2). The study protocol was reviewed by an independent ethics committee/institutional review board for each center and was conducted according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each patient or their representative (parent or legal guardian). CF patients aged ≥ 6 years with forced expiratory volume in 1 second (FEV_1) $\geq 25\%$ to $\leq 90\%$ predicted were recruited if they had documented use of either COLI, TIS, or TIP for at least one cycle, and two positive cultures for *Pa* (either sputum, deep cough throat swab, or bronchoalveolar lavage), within the last 6 months. Patients with a current or past history of *Burkholderia cepacia* complex infection within 2 years prior to screening, hemoptysis >60 ml within 30 days of Visit 2, serum creatinine level ≥ 2 mg/dl, or a history of hearing loss or chronic

tinnitus deemed clinically significant by the investigator, were excluded from the study.

Study design

The study consisted of 6 visits (Figure 1(a)) over 20 weeks. Patients were assigned to one of the three treatment arms: COLI/TIP, TIS/TIP, or TIP/TIP.

In Cycle 1, patients in the COLI/TIP arm received nebulized COLI, 1 or 2 million units two or three times per day depending on local treatment guidelines for 56 days (no off-treatment period), administered using the patient's usual nebulizer, and patients in the TIS/TIP arm received nebulized TIS, 300 mg twice daily for 28 days administered using the patient's usual nebulizer, followed by 28 days off treatment. In Cycle 2 of these two arms, and in both Cycles 1 and 2 of the TIP/TIP arm, patients were treated with TIP, 112 mg (4×28 mg capsules) twice daily for 28 days followed by 28 days off treatment.

The three inhaled antibiotics were compared with each other with respect to ease of use in Cycle 1 in a real-world setting. Cycle 2 allowed the direct assessment of the 'switch experience' from nebulized antibiotics to TIP. The study was open-label as blinding the delivery device for TIP was not feasible, because a double-dummy design would have imposed a great burden on the patients for the feasibility of the study and conflict with measurement of the primary endpoint (ease of use).

Efficacy and patient-reported outcomes

Ease of use was measured by the mean cumulative time required to administer study treatments, including device setup/preparation, drug administration, and device cleaning (including disinfection, where applicable). The readiness of use of the study treatment was assessed as the sum of the time of start to the time of completion of delivery device preparation and the time of start to the time of completion of study treatment preparation. In addition, patient's satisfaction and acceptance of the treatment were assessed¹⁴ by using the Treatment Satisfaction Questionnaire for Medication (TSQM) and Chronic Treatment ACCEPTance (ACCEPT[®]) questionnaire.^{15,16} Patients aged ≥ 13 years completed the questionnaires by themselves in their local language in a quiet setting, and patients

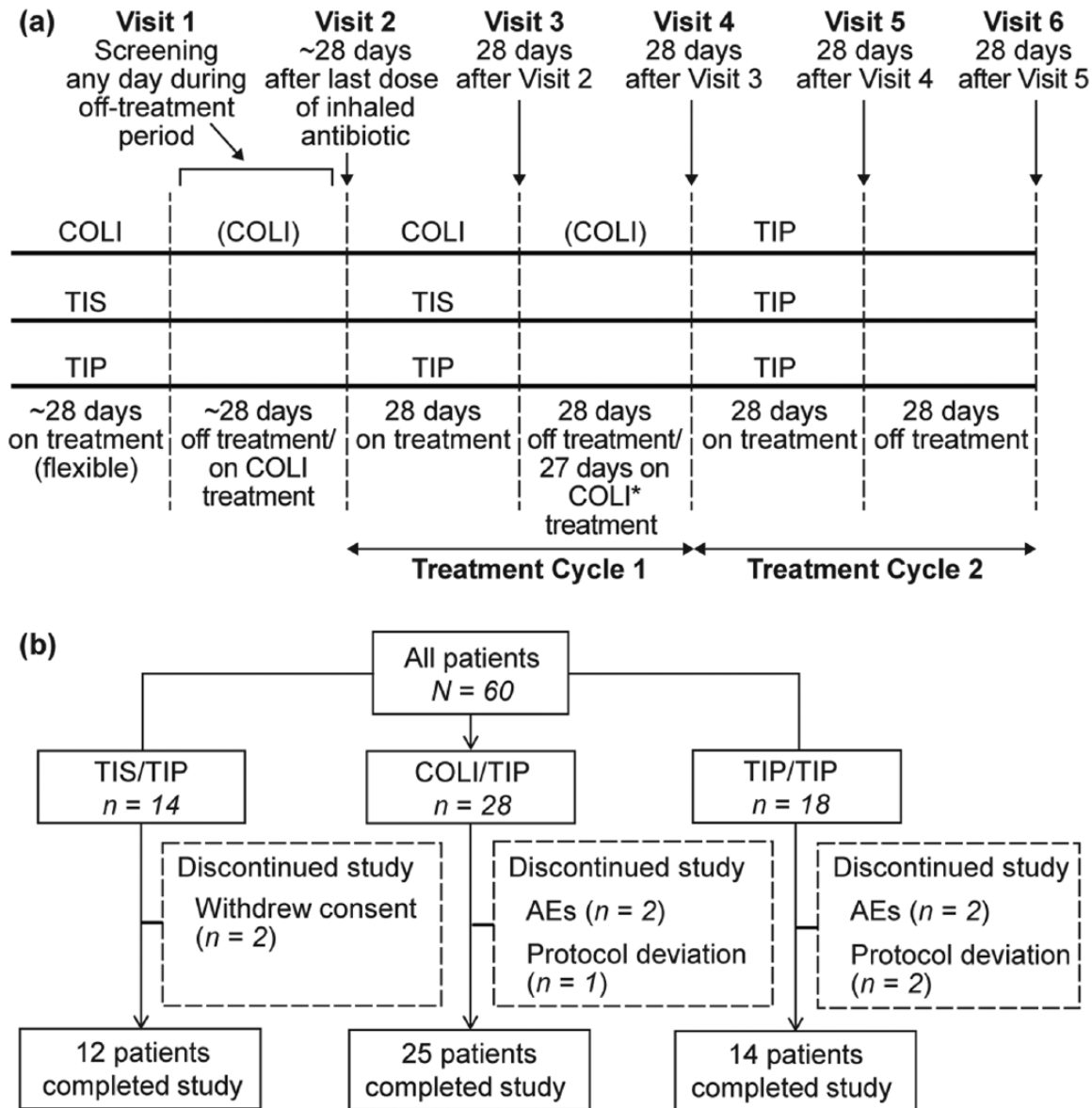


Figure 1. (a) Study design, (b) Patient disposition.

*Patients on continuous COLI were to observe a 24-h COLI-free period before the start of TIP at Visit 4.

Note: Patients with COLI could follow a cyclic or noncyclic regimen dependent on local treatment practice.

AEs, adverse events; COLI, colistimethate sodium; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

aged <13 years completed the questionnaires with the assistance of their parents or guardians. A patient preference survey was also conducted to evaluate the patients' experience in switching from COLI or TIS to TIP.

Microbial contamination of the delivery device with *Pa* and other pathogens was analyzed in terms of light, moderate or heavy growth. The minimum inhibitory concentration (MIC) of tobramycin and other selected antibiotics for *Pa*

isolated from patients' specimens was assessed. The other efficacy measures evaluated were change in sputum *Pa* density (\log_{10} colony-forming units (CFU)/g sputum), changes in clinical laboratory results and lung function [FEV₁, forced vital capacity (FVC), and forced expiratory flow between 25–75% of FVC (FEF_{25–75%})].

The delivery devices used by CF patients were assessed for microbial contamination and swabs were collected from four locations on the nebulizer

(mouthpiece, reservoir cup, filter, and tubing) and from the mouthpiece of the T-326 inhaler. Microbial contamination of the nebulizers was assessed at Visits 2 and 3 (the start and end of the first treatment period), Visits 4 and 5 (start and end of the second treatment period) and Visit 6 (end of study or discontinuation visit). Patients on TIP brought to their study visits the T-326 device used in the last week of TIP treatment. No assessment was required for the device at Visits 2 and 4, when the patients started the TIP treatment periods. If patients used nebulizers for inhaling any other medications they brought these nebulizers to their study Visits 2 and 6 for testing. Sputum specimens were collected from patients at clinic visits [1 (screening), 2, 3, 4, 5, and 6] for quantitative (CFUs) or semiquantitative culture of *Pa* (light, moderate, or heavy growth) and semiquantitative culture for non-*Pa* pathogens. These assessments were performed by a central laboratory. Cultures were performed on a variety of media designed to maximize growth of the pathogens most commonly isolated from the sputum of patients with CF. Cultures were evaluated after 24, 48, and 72 h.

Safety assessments

Safety evaluations consisted of the incidence and intensity of all adverse events (AEs), including cough, and serious AEs (SAEs) during both on- and off-treatment periods; physical condition; hematology and blood chemistry; urinalysis; audiology; and body weight.

Sample size and statistical analysis

A sample size of 15 patients per arm had 91% power to detect a difference in mean total administration time of 14 min as observed between TIS and TIP in the EAGER study,⁶ assuming a standard deviation (SD) of difference of 15 min or less and using a paired Student's *t*-test with a 0.05 two-sided significance level. These calculations were performed *a priori*.

All data summaries and analyses were performed primarily within the study arms as the characteristics of the patients may vary among these arms. Summary statistics were provided for the mean total administration time per cycle by treatment arm and for within-patient differences in mean total administration time between treatments (Cycle 2–Cycle 1) by treatment arm. Safety

analyses were based on descriptive statistics for AEs, cough rates, inhalation-associated cough, SAEs, airway reactivity, laboratory test results, audiology (where assessed), and vital signs that were summarized for each treatment and treatment cycle by arm.

Results

Study population

Of the 60 patients enrolled, the majority (51 patients; 85%) completed the study and nine patients (15%) discontinued the study. The reasons for discontinuation are listed in Figure 1(b). Patient baseline demographic and characteristics were comparable across the treatment arms. The mean age (SD) of the patient population was 27.6 years (± 8.40 ; Table 1). A total of four pediatric patients were enrolled, two patients each in the age groups of 6–12 and 13–17 years.

Efficacy results

Ease of use. Ease of use was considered a composite indicator of the speed, simplicity, and convenience of the study treatments. The mean total administration time including the time required to set up the delivery device, administer the drug, and clean the delivery device was significantly shorter in Cycle 2 (TIP treatment) than in Cycle 1 for the TIS/TIP and COLI/TIP arms (Table 2). However, the cumulative administration time between the treatment cycles remained similar for the TIP/TIP arm (Table 2). The mean administration time (excluding the setup, cleaning, and disinfection times) was significantly shorter in Cycle 2 than in Cycle 1 for all three treatment arms [difference in mean administration time, Cycle 2–Cycle 1: TIS/TIP, -9.8 ($p = 0.0005$); COLI/TIP, -5.3 ($p = 0.0001$); TIP/TIP, -0.3 ($p = 0.0464$)].

Microbial contamination of devices. A total of 12 patients were found to have contaminated devices across the treatment cycles; 11 patients had contaminated nebulizers and one patient had a contaminated T-326 inhaler (Table 3): COLI/TIP arm, 9 (32.1%); TIS/TIP arm, 2 (14.3%); and TIP/TIP arm, 1 (5.6%). In the COLI/TIP arm, the majority of pathogens were isolated (only once) from the devices that delivered COLI at Visits 2 and 3. Except for one patient with *Staphylococcus aureus* infection in the COLI/TIP arm, no

Table 1. Baseline demographic and disease characteristics.

Baseline characteristics*	TIS/TIP N = 14	COLI/TIP N = 28	TIP/TIP N = 18
Age (years), mean (SD)	27.4 (6.82)	28.4 (9.86)	26.6 (7.25)
Age group (≥ 18 years), n (%)	13 (92.9)	27 (96.4)	16 (88.9)
Sex (male), n (%)	10 (71.4)	18 (64.3)	11 (61.1)
Race, White, n (%)	14 (100.0)	28 (100.0)	18 (100.0)
Body mass index (kg/m ²), mean (SD)	21.7 (3.19)	21.4 (3.12)	21.2 (3.83)
FEV ₁ % predicted, mean (SD) [†]	55.0 (17.02)	59.1 (19.42)	62.6 (17.78)
FVC% predicted, mean (SD) [†]	67.7 (18.34)	80.1 (19.44)	78.6 (15.45)
FEF _{25-75%} predicted, mean (SD) [†]	30.6 (21.19)	32.5 (22.27)	37.3 (26.79)
Sputum density of <i>Pa</i> (log ₁₀ CFU/ml) – sum of all biotypes, mean (SD) [‡]	7.8 (1.88)	6.9 (2.22)	6.8 (2.46)
<i>Pa</i> tobramycin MIC, n (%)			
>8 µg/ml	6 (42.9)	6 (21.4)	6 (33.3)
≤8 µg/ml	8 (57.1)	21 (75.0)	12 (66.7)
Missing	0 (0.0)	1 (3.6)	0 (0.0)
Current use of long-acting bronchodilator, n (%)	1 (7.1)	5 (17.9)	10 (55.6)
Current use of short-acting bronchodilator, n (%)	3 (21.4)	7 (25.0)	11 (61.1)

*Baseline is defined as the last value before the first dose of study drug.
[†]Recalculated to avoid calculation errors and use of different formulas to calculate % predicted values by local labs, FEV₁% predicted/FVC% predicted/FEF_{25-75%} predicted are derived according to Quanjer *et al.*²⁷
[‡]Overall density defined as the sum of biotypes (mucoïd, dry and small colony variants).
CFU, colony-forming unit; COLI, colistimethate sodium; FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MIC, minimum inhibitory concentration; *Pa*, *Pseudomonas aeruginosa*; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

patient had the same pathogen isolated from the delivery device and sputum at Visits 2 and 3. In the TIP/TIP arm, no contamination was observed in the T-326 inhaler during either Cycle 1 or 2.

Pseudomonas aeruginosa sputum density and MIC. The absolute change in the number of *Pa* CFUs in the sputum was assessed after a period of up to 28 days of treatment. At Visit 3 (Cycle 1), the mean log reduction in *Pa* for the sum of all biotypes was 1.4 log₁₀ CFU in the TIS/TIP arm, 0.6 log₁₀ CFU in the COLI/TIP arm, and 1.7 log₁₀ CFU in the TIP/TIP arm. At Visit 5 (Cycle 2), the mean log reduction was slightly lower for the TIS/TIP arm and was similar for the other two arms. In general, the result of each biotype was comparable with the result observed for the sum of all biotypes.

Tobramycin MIC₅₀ and MIC₉₀ values showed that there was a 1-fold dilution increase in the

tobramycin MICs at Visit 5 compared with Visit 3 for the TIS/TIP arm (MIC₅₀: 4 µg/ml *versus* 2 µg/ml; MIC₉₀: 512 µg/ml *versus* 256 µg/ml) and the COLI/TIP arm (MIC₅₀: 4 µg/ml *versus* 2 µg/ml; MIC₉₀: 32 µg/ml *versus* 16 µg/ml). In the TIP/TIP arm, the MIC₅₀ and MIC₉₀ tobramycin values were stable up to Visit 5 (2 µg/ml and 64 µg/ml, respectively) and were further decreased to 1 µg/ml and 32 µg/ml, respectively, at the end of Visit 6.

Lung function. The assessment of lung function was an exploratory efficacy endpoint. At Visit 3, the mean FEV₁% predicted showed a relative increase from baseline in the TIS/TIP (2.2%) and COLI/TIP (3.9%) arms and a slight decrease from baseline in the TIP/TIP arm (-2.8%). However, at Visit 5, the FEV₁% predicted remained stable across the treatment arms, as compared with Visit 4. No notable difference was observed ($p > 0.05$) in absolute change from pre-dose

Table 2. Analysis of mean total administration* time in minutes.

	TIS/TIP N = 14	COLI/TIP N = 28	TIP/TIP N = 18
Cycle 1			
N	8	17	14
Mean (SD)	37.0 (22.06)	16.4 (9.54)	4.2 (2.02)
Cycle 2			
N	10	16	11
Mean (SD)	5.0 (2.04)	3.8 (1.70)	3.4 (2.06)
Time difference between Cycles 1 and 2 [†]			
N	7	11	11
Mean (SD)	-32.7 (23.90)	-13.3 (10.35)	-0.2 (0.92)
Cycle comparison			
95% CI	(-54.8, -10.6)	(-20.3, -6.4)	(-0.8, 0.4)
p-value [‡]	0.0112	0.0016	0.4380

Note: If the disinfection time was reported at least once in a day, all total administration times of that day were considered for calculating patient's mean total administration time. This applies for patients on TIS or COLI treatment in Cycle 1.
 Data of only patients with available mean total administration time of initial and second cycle were considered.
 *Total administration time, device setup time + administration time + device cleaning time + disinfection time (if available).
 †Time difference in the mean total administration time was calculated using within-patient differences, Cycle 2–Cycle 1.
 ‡p-values calculated using the paired Student's *t*-test and 95% CIs for the mean difference were displayed.
 CI, confidence interval; COLI, colistimethate sodium; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

value to the end of on-/off-treatment periods of any visits across all treatment arms. Similarly, the pre-dose FVC% and FEF_{25–75%} predicted relative change from start to end of on- and off-treatment periods at each visit showed no significant difference in any treatment arm.

TSQM, ACCEPT[®] and patient preference questionnaire results. The median scores for the TSQM questionnaire were high in Cycle 1 and were either sustained or further improved in Cycle 2 for the majority of domains, indicating treatment satisfaction in patients receiving TIP (Table 4). Improvements were reported in Cycle 2 in the COLI/TIP arm for the effectiveness, convenience, and global satisfaction domains; improvements were also reported for convenience in the TIS/TIP arm, although the scores for effectiveness and global satisfaction decreased in Cycle 2 from Cycle 1. Similar scores were reported between cycles for the TIP/TIP arm with the exception of a slight decrease in global satisfaction in Cycle 2 for the TIP/TIP arm.

Regarding the ACCEPT[®] questionnaire, in Cycle 2 the median scores for most of the domains were mostly improved or sustained from Cycle 1. At Visit 2 in the TIS/TIP arm, the median scores were improved from Cycle 1 for the domains of medication inconvenience (10 units improvement), long-term treatment (8.3 units improvement) and regime constraints (10 units improvement). The exception was that median scores decreased in Cycle 2 for the domains of effectiveness and general. In the COLI/TIP arm, the median scores were improved from Cycle 1 for the domains of medication inconvenience (20 units improvement), long-term treatment (12.5 units improvement) and regime constraints (10 units improvement). In the TIP/TIP arm, the median scores for most of the domains were high and comparable between the treatment cycles. Improvements were observed in Cycle 2 for the domains of medication inconvenience (5 units improvement), regime constraints (2.5 unit improvement), effectiveness (16.7 units improvement) and general (8.3 units improvement) (Table 4). Using a separate patient

Table 3. Delivery device cultures (density categories for pathogens including *Pa*).

Cycle/visit	Device	Pathogen	N*	Light	Moderate	Heavy
TIS/TIP (N = 14)						
Cycle 1						
Visit 2 (BSL)	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
Visit 3	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 2						
Visit 4	Nebulizer	<i>Pseudomonas aeruginosa</i> biotype 2, dry	1	1 (100.0)	0 (0.0)	0 (0.0)
Visit 5	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
	T-326 inhaler [†]	<i>Staphylococcus aureus</i>	1	1 (100.0)	0 (0.0)	0 (0.0)
COLI/TIP (N = 28)						
Cycle 1						
Visit 2 (BSL)	Nebulizer	<i>Acinetobacter baumannii</i>	7	0 (0.0)	0 (0.0)	1 (14.3)
		<i>Acinetobacter junii</i>	7	0 (0.0)	1 (14.3)	0 (0.0)
		<i>Acinetobacter lwoffii</i>	7	2 (28.6)	0 (0.0)	0 (0.0)
		<i>Haemophilus parainfluenza</i>	7	1 (14.3)	0 (0.0)	0 (0.0)
		<i>Ochrobactrum anthropi</i>	7	0 (0.0)	0 (0.0)	1 (14.3)
		<i>Pseudomonas fluorescens</i>	7	1 (14.3)	0 (0.0)	0 (0.0)
		<i>Pseudomonas putida</i>	7	1 (14.3)	0 (0.0)	0 (0.0)
		<i>Pseudomonas stutzeri</i>	7	0 (0.0)	1 (14.3)	0 (0.0)
		<i>Serratia liquefaciens</i>	7	1 (14.3)	0 (0.0)	0 (0.0)
		<i>Sphingobacterium multivorum</i>	7	1 (14.3)	0 (0.0)	0 (0.0)
		<i>Stenotrophomonas maltophilia</i>	7	1 (14.3)	0 (0.0)	0 (0.0)
Visit 3	Nebulizer	<i>Acinetobacter</i> species unspecified	6	1 (16.7)	0 (0.0)	0 (0.0)
		<i>Chryseobacterium indologenes</i>	6	0 (0.0)	1 (16.7)	0 (0.0)
		<i>Delftia acidovorans</i>	6	1 (16.7)	0 (0.0)	0 (0.0)
		<i>Pseudomonas fluorescens</i>	6	2 (33.3)	0 (0.0)	0 (0.0)
		<i>Sphingomonas paucimobilis</i>	6	0 (0.0)	0 (0.0)	1 (16.7)
		<i>Staphylococcus aureus</i>	6	1 (16.7)	0 (0.0)	0 (0.0)
Cycle 2						
Visit 4	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
Visit 5	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
	T-326 inhaler		0	0 (0.0)	0 (0.0)	0 (0.0)
TIP/TIP (N = 18)						
Cycle 1						
Visit 2 (BSL)	Nebulizer [‡]	<i>Pseudomonas aeruginosa</i> biotype 2, dry	1	0 (0.0)	1 (100.0)	0 (0.0)
Visit 3	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
	T-326 inhaler		0	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 2						
Visit 4	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
Visit 5	Nebulizer		0	0 (0.0)	0 (0.0)	0 (0.0)
	T-326 inhaler		0	0 (0.0)	0 (0.0)	0 (0.0)

Note: Commercial packs of TIP were used at Visit 4 (start of Cycle 2) by each patient.
All nebulizers used by the patients were analyzed, including those on other inhaled medications (e.g. mucolytics).
*Number of patients with any contaminated delivery device.
[†]*S. aureus* isolated (light growth) from one T-326 inhaler was not present in the patient's sputum.
[‡]*Pa* (moderate growth) was isolated from the nebulizer (medication not specified) at Visit 2.
BSL, baseline; COLI, colistimethate sodium; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

Table 4. Summary of the TSQM and ACCEPT® questionnaire results.

	TIS/TIP N = 14				COLI/TIP N = 28				TIP/TIP N = 18			
	Cycle 1 Visit 3		Cycle 2 Visit 5		Cycle 1 Visit 3		Cycle 2 Visit 5		Cycle 1 Visit 3		Cycle 2 Visit 5	
	n	Median	n	Median	n	Median	n	Median	n	Median	n	Median
TSQM												
Effectiveness	13	66.7	12	55.6	26	63.9	25	72.2	17	72.2	15	72.2
Side effects*	12	100.0	11	100.0	25	100.0	24	100.0	17	100.0	15	100.0
Convenience	12	63.9	11	77.8	25	61.1	24	83.3	17	77.8	15	77.8
Global satisfaction	12	71.4	11	64.3	25	64.3	24	75.0	17	78.6	15	71.4
ACCEPT®†												
Medication inconvenience	12	80.0	11	90.0	25	70.0	24	90.0	16	80.0	14	85.0
Long-term treatment	12	66.7	10	75.0	25	66.7	24	79.2	16	66.7	14	66.7
Regime constraints	11	80.0	10	90.0	25	70.0	23	80.0	16	70.0	14	72.5
Numerous medications, m/M [%]‡												
Yes, not easy to accept	2/11	18.2	3/9	33.3	0/25	0.0	2/23	8.7	4/16	25.0	3/14	21.4
Yes, easy to accept	4/11	36.4	5/9	55.6	20/25	80.0	16/23	69.6	10/16	62.5	9/14	64.3
No	5/11	45.5	1/9	11.1	5/25	20.0	5/23	21.7	2/16	12.5	2/14	14.3
Side effects	11	100.0	10	100.0	25	100.0	21	90.0	16	90.0	14	90.0
Effectiveness	11	83.3	10	58.3	24	66.7	23	66.7	16	75.0	14	91.7
General	11	66.7	10	50.0	25	66.7	23	66.7	16	75.0	14	83.3

Each domain score ranges between 0–100, with a higher score indicating a higher treatment satisfaction.

*All values expressed as median values, mean scores in the side effect domain ranged from 84.2–96.8 across treatment arms.

†Data are n, median unless otherwise specified.

‡Percentages are based on M.

COLI, colistimethate sodium; m, number of patients with the score; M, number of patients with data of the domain at the visit; n, number of patients with data of the domain at the visit; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution; TSQM, Treatment Satisfaction Questionnaire for Medication.

preference questionnaire, the majority of the patients showed either ‘strong’ or ‘somewhat’ preference to use TIP in the TIS/TIP (9 of 12 patients, 75.0%) and COLI/TIP (18 of 23 patients, 78.3%) arms. ‘Strong’ or ‘somewhat’ preference for TIS and COLI in the TIS/TIP and COLI/TIP arms were 16.7% (2 of 12 patients) and 8.7% (2 of 23 patients), respectively (Table 5).

Safety results

Treatment-emergent AEs (on and off treatment) were reported by 36 patients in Cycle 1 [(n/N,

); TIS/TIP: 6/14, 42.9%; COLI/TIP: 19/28, 67.9%; TIP/TIP: 11/18, 61.1%] and by 30 patients (57.7%) overall in Cycle 2 (Table 6).

The mean post-inhalation cough rates were comparable between the cycles for the COLI/TIP arm (0.56 at Visit 2 and 0.47 at Visit 3 *versus* 0.65 at Visit 4 and 0.51 at Visit 5). However, for the TIP/TIP arm, the post-inhalation cough rate was reduced over time, with a low cough rate in Cycle 2 than in Cycle 1 (0.40 at Visit 4 and 0.33 at Visit 5 *versus* 0.53 at Visit 2 and 0.56 at Visit 3, respectively).

Table 5. Adverse events, reported by at least two patients, regardless of study drug relationship, by preferred term and cycle.

	TIS/TIP N = 14	COLI/TIP N = 28	TIP/TIP N = 18
	n (%)	n (%)	n (%)
Cycle 1			
Number of patients treated in cycle in the analysis set	14 (100.0)	28 (100.0)	18 (100.0)
Patients* with AE(s)	6 (42.9)	19 (67.9)	11 (61.1)
Infective pulmonary exacerbation of cystic fibrosis	5 (35.7)	10 (35.7)	2 (11.1)
Cough	2 (14.3)	2 (7.1)	2 (11.1)
Nasopharyngitis	0 (0.0)	3 (10.7)	2 (11.1)
Headache	1 (7.1)	0 (0.0)	3 (16.7)
Sputum increased	1 (7.1)	0 (0.0)	3 (16.7)
Hemoptysis	0 (0.0)	0 (0.0)	2 (11.1)
Pyrexia	0 (0.0)	0 (0.0)	2 (11.1)
Cycle 2			
Number of patients treated in cycle in the analysis set	12 (100.0)	25 (100.0)	15 (100.0)
Patients* with AE(s)	8 (66.7)	12 (48.0)	10 (66.7)
Infective pulmonary exacerbation of cystic fibrosis	3 (25.0)	7 (28.0)	1 (6.7)
Cough	1 (8.3)	0 (0.0)	2 (13.3)
Hemoptysis	1 (8.3)	2 (8.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	3 (20.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	3 (20.0)
Sputum increased	0 (0.0)	0 (0.0)	2 (13.3)
*Patients with multiple incidences of the same AE are counted only once for the preferred term. AE, adverse events; CI, confidence interval; COLI, colistimethate sodium; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.			

Treatment-related AEs were reported in four patients (one each in the TIS/TIP and COLI/TIP arms and two in the TIP/TIP arm) in Cycle 1; none was considered severe. In Cycle 2, eight patients (15.4%) reported AEs that were suspected to be treatment related; three were severe (each with decreased FEV₁ and an upper respiratory tract infection, abnormal acoustic stimulation tests and tinnitus, and cough). Overall, four patients discontinued the study treatment due to SAEs; however, none of these events were suspected to be treatment related.

The frequency of airway reactivity (i.e. decrease of $\geq 20\%$ in post-dose FEV₁% predicted compared with the pre-dose value) from pre-dose to

15–45 min post-dose was low: one patient each at Visits 2 and 3 in the COLI/TIP arm and one patient at Visit 4 in the TIP/TIP arm.

Discussion

Despite recent advances in therapy and improvements in median survival age, the treatment burden of CF patients has increased, which is primarily associated with the number of nebulized medications.^{17–19} The complexity of nebulized therapy leads to reduced adherence.^{20,21} Moreover, lack of adherence with therapy has been considered an important cause for the increased hospitalization and pulmonary exacerbations in CF patients.^{17,22} The ease of use of

inhalers is an important factor in encouraging patient adherence with therapy, minimizing the handling errors and improving satisfaction.^{17,23} The present study showed that patients took significantly lower cumulative time to administer TIP than COLI or TIS. This resulted in approximately 13–33 min of time saving per administration with the T-326 inhaler used for TIP compared with nebulizers used for TIS and COLI. Ease of T-326 inhaler use for administration of TIP and reduction in administration time have been associated with improved adherence and clinical outcomes.⁶ In general, treatment satisfaction, as assessed by TSQM and ACCEPT[®] questionnaires showed better results for TIP, with higher scores for ‘convenience’ and greater acceptance for TIP, although there were decreases in scores reported in Cycle 2 compared with Cycle 1 in some of the domains for both the TSQM and ACCEPT[®] questionnaires. These patient-reported outcome measures were supported by the shorter cumulative administration time for TIP and a comparable efficacy profile as reported in other studies.¹¹ Furthermore, when assessing the patient’s preference of inhaled therapy, the majority of patients showed either ‘strong’ or ‘somewhat’ treatment preference for TIP in the TIS/TIP and COLI/TIP arms over the nebulizers, which emphasizes the ease of use of TIP over other nebulized drugs.

Several published studies have described frequent contamination of home nebulizers with microorganisms and reported that *Pa* constitutes the major contaminant.^{2,8} In the present study, the majority of pathogens were isolated from the nebulizer used to administer COLI in Cycle 1. The microbial contamination assessment suggested that the T-326 inhaler used for TIP was much less frequently contaminated, thus potentially reducing the sources of infection in CF patients compared with the nebulizers used for TIS or COLI. These results advocate the use of T-326 inhaler over nebulizers.

Consistent with previous studies,^{11,12} sputum *Pa* densities decreased in all the treatment arms. Although the mean FEV₁% predicted at the end of the on-treatment period in Cycle 1 showed a decrease in the TIP arm, and increases in the COLI and TIS arms, the mean FEV₁% predicted by the end of the on-treatment period in Cycle 2 remained stable across the three arms. Overall, TIP showed comparable efficacy with TIS and

COLI, which is in accordance with previous publications.^{6,17,24,25}

In addition, this study demonstrated that AEs were comparable in all three treatment arms and no unexpected safety events were reported. Although cough is a common AE with inhaled therapies,^{25,26} a clear trend was observed in the decreased frequency of post-inhalation cough over time from Cycle 1 to Cycle 2 in the TIP/TIP arm. Moreover, most cough events were of mild or moderate intensity in all the arms. Overall, TIP was well tolerated and the safety findings observed for TIP in this study were generally consistent with its established safety profile.^{6,12,26}

These results provide clinicians with further guidance on the relative differences between the speed and ease of use of inhalers and nebulizers as well as evidence on the prevalence of microbial contamination of the inhalation devices in the real-world setting. However, this was an open-label, non-randomized study, which carries the risk of reporting bias, particularly for the patient-reported outcomes. In addition, data on the nebulizer type were not collected, and therefore, results are applicable to nebulizers in general but not necessarily to any specific nebulizer.

Conclusions

In summary, the T-326 inhaler used to deliver TIP showed significantly shorter administration and cleaning times compared with nebulizers used for COLI and TIS, suggesting that TIP is easy to use in CF patients treated for pulmonary *Pa* infection. Ease of use was also supported by the outcomes of the TSQM and ACCEPT[®] questionnaires. Furthermore, the T-326 inhaler was much less frequently contaminated than the nebulizers, thus potentially reducing the sources of pathogenic bacteria in CF patients. In addition, this study provides further evidence on the efficacy of TIP as shown by the sustained suppression of *Pa* and stability in FEV₁% predicted.

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Conflict of interest statement

JG received honorarium for participation in a Novartis-sponsored advisory board and received educational grants to attend conferences from Novartis. CS received financial support from Novartis for an investigator-initiated trial. US, EFN, and MT have nothing to disclose. WC, PM, LD, and KH are full-time employees of Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA).

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