

Tobramycin inhalation powder for the treatment of pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: a review based on clinical evidence

Kamal Hamed and Laurie Debonnett

Abstract: Chronic airway infection with *Pseudomonas aeruginosa* is a major cause of increased morbidity and mortality in patients with cystic fibrosis (CF). The development and widespread use of nebulized antibacterial therapies, including tobramycin inhalation solution (TIS), has led to improvements in lung function and quality of life. However, the use of nebulizers is associated with various challenges, including extended administration times and the need for frequent device cleaning and disinfection. Multiple therapies are required for patients with CF, which poses a considerable burden to patients, and adherence to the recommended treatments remains a challenge. Tobramycin inhalation powder (TIP), delivered via the T-326 Inhaler, has been shown to have similar clinical efficacy and safety as compared to TIS, with improved patient convenience, satisfaction, and treatment adherence. Long-term safety studies have shown that TIP was well tolerated with no unexpected adverse events in patients with CF. This review of the TIP pivotal and postmarketing studies reinforces the well-established efficacy and safety profile of TIP and its ease of use.

Keywords: cystic fibrosis, equipment contamination, nebulizers and vaporizers, patient compliance, patient preference, *Pseudomonas aeruginosa*, tobramycin

Received: 16 November 2016; revised manuscript accepted: 6 January 2017.

Background

Cystic fibrosis (CF), an autosomal recessive genetic disorder, is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene located on chromosome 7 that encodes for a complex chloride channel found in exocrine tissues.^{1,2} Mutations in the *CFTR* gene lead to decreased chloride and bicarbonate secretion, and enhanced sodium absorption across the epithelial surfaces, resulting in dysfunction in salt-water balance and consequently thick and viscous secretions.³ Deranged ion transport in the lungs and other organs (pancreas, liver, intestine, and reproductive tract) that express *CFTR* causes various clinical complications.⁴

An estimated 70,000 patients worldwide have CF,⁵ including 28,983 patients in the US.⁶ The

majority of these patients develop respiratory failure due to progressive lung disease caused by chronic bacterial infection and concomitant airway inflammation.⁷ *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Stenotrophomonas maltophilia* are the most frequently isolated bacteria in patients with CF.⁶ *P. aeruginosa* has been considered as the predominant pathogen contributing to chronic lung disease,⁸ and airway infection caused by *P. aeruginosa* is a major predictor of morbidity and mortality in patients with CF.^{7,9} The inherent resistance of *P. aeruginosa* to antibacterial therapies¹⁰ and its persistence through production of a mucoid alginate matrix makes it difficult to eradicate from chronically infected airways.^{11,12} However, during the early colonization phase, *P. aeruginosa* strains

Ther Adv Respir Dis

2017, Vol. 11(5) 193–209

DOI: 10.1177/
1753465817691239

© The Author(s), 2017.

Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Correspondence to:

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

Laurie Debonnett
Novartis Pharmaceuticals
Corporation, One Health
Plaza, East Hanover, NJ
07936-1080, USA

are generally nonmucoid and are present at lower bacterial density, which makes them more susceptible to antibiotics.^{13,14} In clinical practice, treatment of chronic *P. aeruginosa* infection and *P. aeruginosa* eradication have been associated with increased survival of patients with CF.^{11,15}

Several antibiotics administered *via* different routes (parenteral, inhaled, and oral) are available for the treatment of CF patients and have been found to be efficacious;¹⁶ however, the optimal regimen and duration of therapy remain unclear. Moreover, inhalation of antibiotics has been recognized as a suitable option for delivering relatively high doses directly to the site of infection while minimizing systemic exposure, and achieving adequate local antibiotic concentrations to kill microbes.^{15,17} In recent years, new drug formulations and inhalation devices have been developed for effective management of *P. aeruginosa* infection in patients with CF.^{18–20} Inhaled antibiotics such as tobramycin, colistimethate sodium (COLI, approved only in the European Union), aztreonam, and levofloxacin are approved for the treatment of chronic *P. aeruginosa* lung infection in CF patients (Table 1).²¹ The dry powder inhalation formulation of tobramycin [tobramycin inhalation powder (TIP)] has also been approved in Europe and the US under the brand name TOBI® Podhaler™ (Novartis Pharma AG, Basel, Switzerland) for the management of CF patients with *P. aeruginosa* infection (Table 1).²²

The efficacy and safety of tobramycin inhalation solution (TIS) are well established in patients with CF aged ≥ 6 years.^{29,30} Therefore, the US treatment guidelines strongly recommend chronic use of inhaled tobramycin in patients with CF who have moderate-to-severe lung disease with persistent *P. aeruginosa*-positive airway cultures.^{31,32} As per the European consensus guideline recommendations, the therapeutic options for chronic *P. aeruginosa* infection in CF patients include either an intermittent (1-month on and 1-month off) regimen of inhaled aminoglycoside or continuous administration of inhaled colistin.³³ The European Cystic Fibrosis Society Standards of Care best practice guidelines reinforced the US treatment guideline recommendations for the use of TIS on alternate months in CF patients aged ≥ 6 years and further acknowledged that TIP has been shown to have similar efficacy to TIS.³⁴

Nebulized antibiotics and associated challenges in patients with cystic fibrosis

Nebulized antibiotics have been established as effective treatment options for chronic *P. aeruginosa* infection and are recommended for chronic use to improve lung function and quality of life in patients with CF.³² Despite guideline recommendations, there are several challenges associated with the real-world use of nebulized antibiotics.³⁵ Treatment burden is a major challenge for patients with CF, as they require daily administration of multiple inhaled therapies including bronchodilators, mucolytics, hypertonic saline, and antibiotics. Adult subjects have reported spending an average of 2 hours [108 minutes (SD \pm 58 min)] on daily CF treatments.^{36,37} Time hindrance results in poor treatment adherence, which is an important cause of increased pulmonary exacerbations and hospitalization in patients with CF.³⁸ In general, aerosolized antibiotics require a compressor and a nebulizer, and take approximately 20 minutes per dose (excluding cleaning and sterilization). Furthermore, nebulizers require regular cleaning after each use to prevent device contamination and to further ensure that the device performance is not compromised. As most patients do not clean their nebulizer as directed, this can lead to device contamination and potentially, transport of pathogens to the lower airways.^{39,40}

Tobramycin inhalation powder

TIP, an innovative drug–device combination, was developed with an aim to overcome the challenges associated with nebulized antibiotics, to minimize treatment burden, and to improve treatment adherence in patients with CF. TIP was developed using PulmoSphere™ (Novartis Pharma AG, Basel, Switzerland) technology (Figure 1).^{35,41}

TIP is manufactured *via* an emulsion-based spray-drying process that yields uniform-sized, spherical hollow porous particles (pulmospheres). It is delivered *via* the breath-actuated T-326 Inhaler, a portable, mechanical, capsule-based dry powder inhaler (DPI).³⁵ The drug delivery is largely independent of the patient's peak inspiratory flow rate (PIFR), thus reducing dosing variability.³⁵

Studies have shown that TIP improves intrapulmonary deposition efficiency and shorter administration time, when compared with nebulized

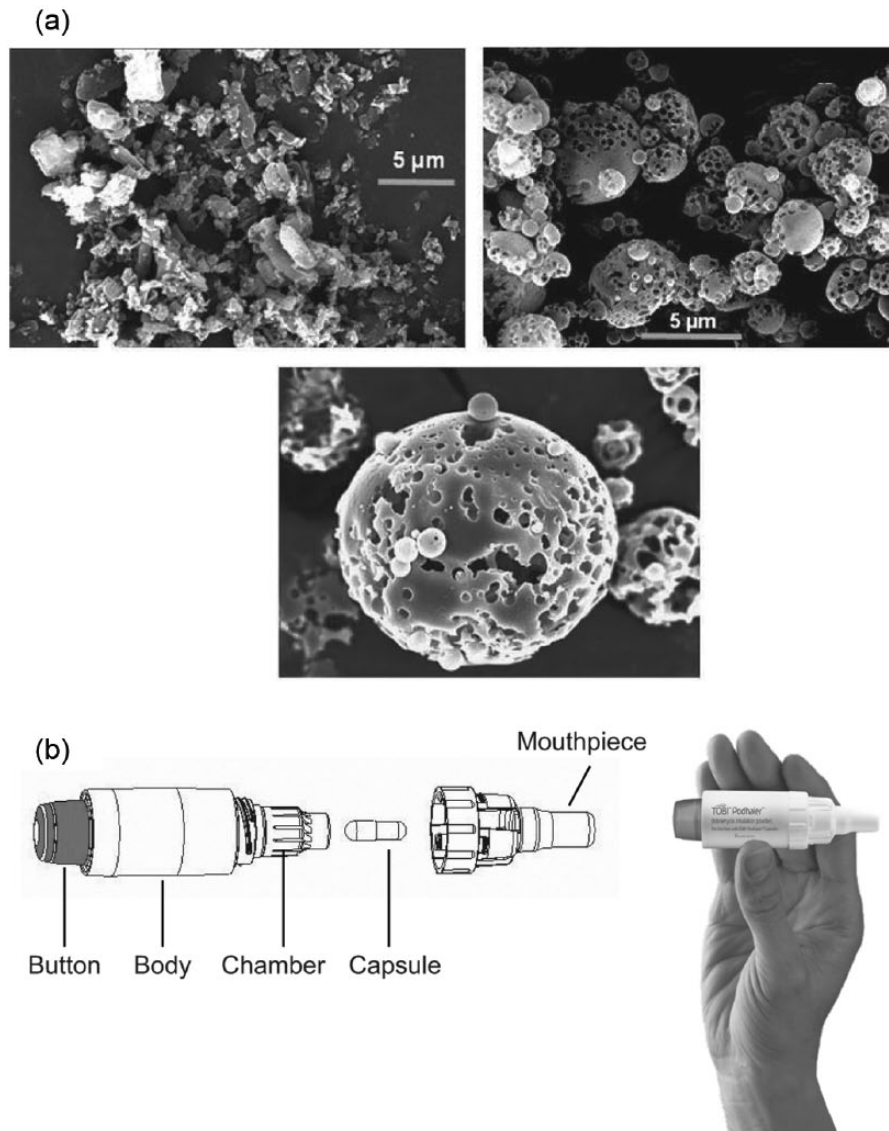


Figure 1. (a) Scanning electron microscopic image of typical micronized drug particles, TIP particles, and TIP particle [close up] and (b) T-326 Inhaler for use with TIP (TOBI® Podhaler™) (images included with permission from Geller *et al.*).³⁵

TIP, tobramycin inhalation powder.

tobramycin (TIS).^{42,43} In addition, inhalation *via* DPIs can be more convenient compared with nebulizers, as the DPIs are portable and do not require special storage conditions or any electrical sources.³⁵

A phase I pharmacokinetic study of TIP in patients with CF reported a mean administration time of 4.9 minutes with the T-326 Inhaler as compared to 15.8 minutes with nebulizers, excluding the nebulizer cleaning and disinfection time.⁴¹ Similarly, in a multicenter, randomized,

open-label, phase III trial (EAGER), the mean administration time was significantly lower for TIP as compared with TIS (5.6 *versus* 19.7 min; $p < 0.0001$), resulting in a time saving of 28 minutes per day, or 13 hours per cycle, excluding the nebulizer maintenance time.⁴³ A recent real-world study in patients with CF suggested that treatment adherence may be associated with improved clinical outcomes.³⁷ Collectively, these benefits can significantly decrease the treatment burden in patients with CF.

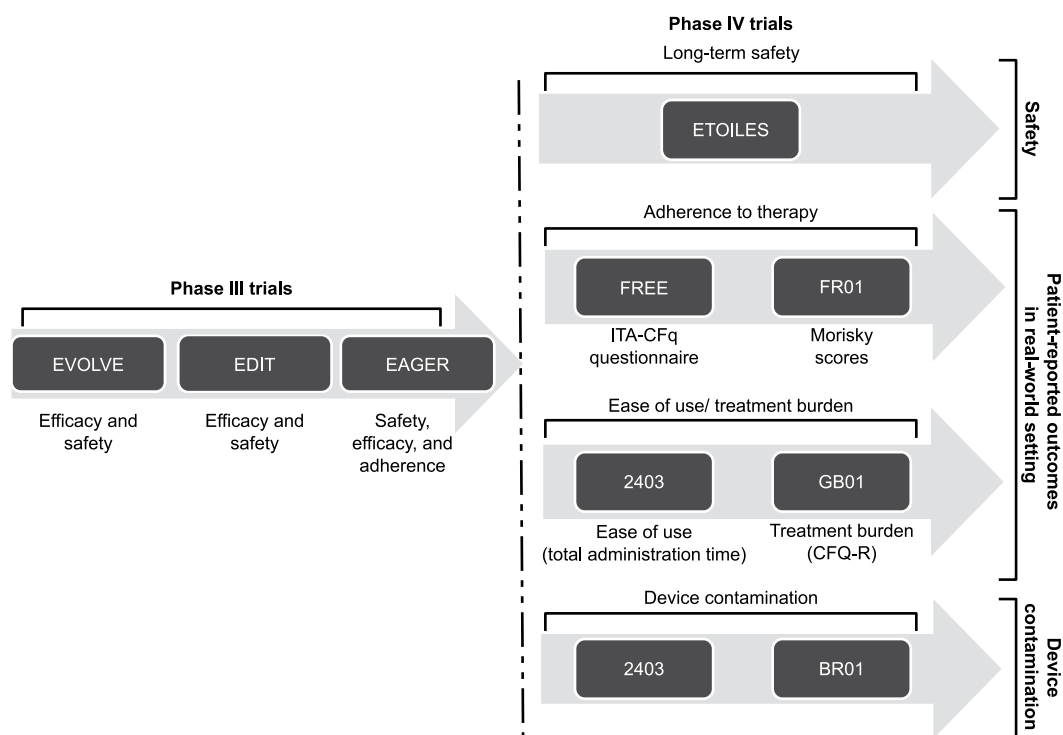


Figure 2. Overview of phase III and IV studies and evaluated endpoint.

ITA-CFq, Italian Treatment Adherence Cystic Fibrosis Questionnaire; CFQ-R, cystic fibrosis questionnaire: revised scale; TIP, tobramycin inhalation powder.

This comprehensive review, based on data from both pivotal clinical trials and real-world studies describes the efficacy, safety, and additional benefits (convenience, adherence, quality of life, and minimal device contamination) associated with the use of TIP in CF patients with chronic *P. aeruginosa* infection. The clinical studies identified include globally conducted phase III trials (EVOLVE, EDIT, and EAGER), phase IV studies across various countries (2403, FREE, FR01, GB01, and BR01), and a long-term safety study (ETOILES) to discuss the characteristics of TIP use in patients with CF (Figure 2).

Pharmacokinetics

The pharmacokinetic profile of TIP was evaluated in different clinical studies. In a multicenter, open-label, active-controlled, single-dose escalation, phase I study in CF patients aged ≥ 6 years with $FEV_1 \geq 40\%$ predicted, administration of TIP 112 mg (4×28 mg) capsules resulted in similar systemic exposure to that of TIS at the standard dose of 300 mg/5 ml.⁴¹ Furthermore, serum tobramycin concentrations were assessed in the EVOLVE study⁴⁴ and both serum and

sputum tobramycin concentrations were assessed in the EDIT and EAGER studies.^{43,45} Blood and sputum samples were collected between 0–6 and 0–2 hours postdose, respectively; such samples were also collected predose. Tobramycin was analyzed at a central laboratory. In the EVOLVE study, there was no evidence of serum tobramycin accumulation with successive cycles of TIP 112 mg (tobramycin peak levels: cycle 1, 1.99 ± 0.59 $\mu\text{g/ml}$ and cycle 2, 1.64 ± 0.96 $\mu\text{g/ml}$; tobramycin trough levels: cycle 1, 0.29 ± 0.27 $\mu\text{g/ml}$ and cycle 2, 0.38 ± 0.44 $\mu\text{g/ml}$).⁴⁴ In the EDIT study, the mean peak and trough serum concentrations of tobramycin after 28 days of treatment were 1.48 and 0.41 $\mu\text{g/ml}$, respectively, and the mean maximum sputum concentrations of tobramycin were 1140 and 1739 $\mu\text{g/g}$ at days 1 and 29, respectively.⁴⁵ Importantly, systemic levels were low, relative to those associated with toxicity with intravenous tobramycin (10–12 $\mu\text{g/ml}$).^{35,46} Moreover, the EAGER study showed that serum tobramycin concentrations were similar for TIP and TIS, and that sputum tobramycin concentrations were generally greater for TIP 30 minutes postdose on day 28 of the third cycle of treatment (mean \pm SD: TIP, 1979 ± 2770 $\mu\text{g/g}$;

Table 1. Inhaled antibiotics approved in Europe and the US.

Antibiotic	Agency	Approved indications	References
1 Aztreonam inhalation solution (Cayston®)	EMA/FDA	To suppress chronic pulmonary infections due to <i>Pseudomonas aeruginosa</i> in patients with CF, ≥6 years of age and FEV ₁ 25–75% predicted (EU) To improve respiratory symptoms in CF patients with <i>P. aeruginosa</i> , ≥7 years and with FEV ₁ 25–75% predicted (US) Treatment schedule is 28-days-on drug alternating with 28-days-off drug	CAYSTON® summary of product characteristics ²³ CAYSTON® prescribing information ²⁴
2 Colistimethate sodium inhalation solution (Colistin)	EMA	Colistin: For management of chronic infections due to <i>P. aeruginosa</i> in patients with CF, adults and children	Promixin® summary of product characteristics ²⁵
Colistimethate sodium inhalation powder (Colobreathe®)		Colobreathe®: For management of chronic infections due to <i>P. aeruginosa</i> in patients with CF aged ≥6 years Treatment schedule is a continuous regimen	Colobreathe® summary of product characteristics ²⁶
3 Levofloxacin nebulizer solution (QUINSAIR®)	EMA/FDA	For management of chronic pulmonary infections due to <i>P. aeruginosa</i> in adult patients with CF Treatment schedule is 28-days-on drug alternating with 28-days-off drug	Quinsair® summary of product characteristics ²⁷
4 Tobramycin inhalation solution (TOBI®) Tobramycin inhalation powder (TOBI® Podhaler™)	EMA/FDA	TOBI®: For management of CF patients with <i>P. aeruginosa</i> , ≥6 years and with FEV ₁ 25–75% predicted TOBI® Podhaler™: For management of CF patients with <i>P. aeruginosa</i> , ≥6 years and with FEV ₁ 25–80% predicted (US) or 25–75% predicted (EU) Treatment schedule is 28-days-on drug alternating with 28-days-off drug	TOBI® prescribing information ²⁸ TOBI® Podhaler™ prescribing information ²²

CF, cystic fibrosis; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; FEV₁, forced expiratory volume in 1 second; US, United States.

TIS, 1074 ± 1182 µg/g). Of note, serum-to-sputum tobramycin concentrations were comparable in both the EDIT and EAGER studies (data on file). In the EAGER study, the majority (>91%) of TIP patients had *P. aeruginosa* isolates with a minimum inhibitory concentration ≤64 µg/ml at baseline, that is, at least 20 times lower than the mean sputum concentration observed within 30 minutes of the first dose of TIP.⁴³

Clinical and microbiologic efficacy in phase III studies

The phase III clinical trials reviewed in this article primarily focused on the efficacy and safety of a drug–device combination of TIP (tobramycin 112 mg delivered *via* the T-326 Inhaler). TIP was evaluated in two placebo-controlled trials [EVOLVE and EDIT (latter included two extensions)] in relatively treatment-naïve patients (Table 2).^{44,45,47} Both EVOLVE and EDIT were similar in study design. Cycle 1 comprised a double-blind,

placebo-controlled period with 28-days-on and 28-days-off drug, whereas cycles 2 and 3 were open-label, crossover periods for EVOLVE and open-label extensions for EDIT. TIP was also evaluated in a comparative noninferiority study (EAGER) that compared TIP and TIS over a 24-week treatment period (three cycles each consisting of 28-days-on and 28-days-off drug).⁴³

In the EVOLVE study, TIP showed an improvement in forced expiratory volume in 1-second percent predicted (FEV₁ % predicted) *versus* placebo at day 28 of cycle 1 (least squares mean difference, 13.3; *p* = 0.0016). Similar changes in FEV₁% predicted were observed in patients switching from placebo to TIP in cycle 2, and these improvements were maintained through the end of the study. In addition, TIP also reduced *P. aeruginosa* sputum density, respiratory-related hospitalizations, and use of additional antipseudomonal antibiotics compared with placebo.⁴⁴ The results of the EDIT study showed that TIP

Table 2. Summary of key phase III studies.

Parameters	EVOLVE	EDIT, including extensions	EAGER
Study design	Randomized, double-blind, placebo-controlled trial*	Core study: Randomized, double-blind, placebo-controlled trial	Randomized, open-label, active-controlled, noninferiority trial
Treatment arms (28-days-on/28-days-off drug)	TIP: 112 mg bid (<i>n</i> = 46); placebo (<i>n</i> = 49)	TIP: 112 mg bid (<i>n</i> = 30); placebo (<i>n</i> = 32)	TIP: 112 mg bid (<i>n</i> = 308); TIS: 300 mg/5 ml bid (<i>n</i> = 209)
Primary objective	To demonstrate the efficacy of a 28-day bid dosing regimen of TIP <i>versus</i> placebo, as measured by the relative change in FEV ₁ % predicted from baseline to the end of cycle 1 dosing	To evaluate the efficacy of TIP manufactured by an improved process <i>versus</i> placebo, assessed by relative change in FEV ₁ % predicted from baseline to day 29	To evaluate the safety of bid dosing of TIP delivered with the T-326 inhaler, <i>versus</i> TOBI delivered with the PARI-LC® PLUS Jet nebulizer and DeVilbiss PulmoAide® compressor
Duration	24 weeks (1 cycle TIP or placebo followed by 2 cycles open-label TIP)	Core study: 8 weeks (1 cycle TIP or placebo) Extensions: Each consisted of 3 additional cycles of TIP	24 weeks (3 cycles TIP or TIS)
Patients	95 patients aged 6–21 years	62 patients aged 6–21 years	517 patients aged ≥6 years
Key efficacy endpoint			
Primary			
Change in FEV ₁ % predicted (mean treatment difference)	Baseline to day 28–TIP <i>versus</i> placebo: 13.3% (95% CI: 5.3 to 21.3; <i>p</i> = 0.0016)	Baseline to day 29–TIP <i>versus</i> placebo: 5.9% (95% CI: –2.2 to 14.0; <i>p</i> = 0.148)	Baseline to day 28 of cycle 3–TIP <i>versus</i> TIS [†] : 1.1% relative change (least squares mean difference)
Secondary			
Antibiotic (antipseudomonal) use	Antibiotic use–TIP <i>versus</i> placebo: 13.0% <i>versus</i> 18.4%	Antibiotic use–TIP <i>versus</i> placebo: 6.7% <i>versus</i> 12.5%	Antibiotic use–TIP <i>versus</i> TIS: 64.9% <i>versus</i> 54.5%
<i>Pseudomonas aeruginosa</i> sputum density log ₁₀ CFU/g	Nonmucoid–TIP <i>versus</i> placebo: –1.91 (SD: 2.54) <i>versus</i> –0.15 (0.68); mucoid–TIP <i>versus</i> placebo: –2.61 (2.53) <i>versus</i> –0.43 (1.05)	Sum of all biotypes–TIP <i>versus</i> placebo: –1.2 <i>versus</i> 0 (<i>p</i> = 0.002)	Nonmucoid–TIP <i>versus</i> TIS: –1.77 <i>versus</i> –0.73; mucoid–TIP <i>versus</i> TIS: –1.6 <i>versus</i> –0.92
Safety			
Overall AEs	TIP <i>versus</i> placebo: 23 (50.0%) <i>versus</i> 37 (75.5%)	TIP <i>versus</i> placebo: 8 (26.7%) <i>versus</i> 11 (34.4%)	TIP <i>versus</i> TIS [†] : 278 (90.3%) <i>versus</i> 176 (84.2%)
Cough	TIP <i>versus</i> placebo: 6 (13.0%) <i>versus</i> 13 (26.5%)	TIP <i>versus</i> placebo: 3 (10.0%) <i>versus</i> 0	TIP <i>versus</i> TIS: 149 (48.4%) <i>versus</i> 65 (31.1%)
Pulmonary exacerbation	TIP <i>versus</i> placebo: Cycle 1: 5 (10.9%) <i>versus</i> 6 (12.2%)	TIP <i>versus</i> placebo: 1 (3.3%) <i>versus</i> 0	TIP <i>versus</i> TIS: 104 (33.8%) <i>versus</i> 63 (30.1%)
Discontinuation	TIP <i>versus</i> placebo: 7 (15.2%) <i>versus</i> 9 (18.4%)	TIP <i>versus</i> placebo: 1 (3.3%) <i>versus</i> 1 (3.1%)	TIP <i>versus</i> TIS: 83 (26.9%) <i>versus</i> 38 (18.2%)
References	Konstan <i>et al.</i> ⁴⁴	Galeva <i>et al.</i> ⁴⁵ ; data on file	Konstan <i>et al.</i> ⁴³
*Cycle 1: double-blind, placebo-controlled; cycles 2 and 3: open-label. †The primary endpoint for the EAGER trial related to safety (efficacy was a secondary endpoint). AE, adverse event; bid, twice daily; CFU/g, colony forming units per gram; FEV ₁ , forced expiratory volume in 1 second; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution; SD, standard deviation.			

improved FEV₁% predicted compared with placebo after 28 days of treatment in cycle 1 (least squares mean difference, 5.9; $p = 0.148$). Patients who switched from placebo in the core trial to TIP in the study extensions had a mean relative increase in FEV₁% predicted of 13% after 28 days of treatment, and this was maintained for up to 7 cycles of treatment.^{45,47} In addition, TIP reduced *P. aeruginosa* sputum density and the need for other antipseudomonal antibiotics, as well as the incidence of respiratory-related hospitalizations compared with placebo. Furthermore, in addition to sustained improvement in lung function, the 1-year extension of the EDIT study showed sustained suppression of *P. aeruginosa* sputum density.⁴⁷

The EAGER study enrolled patients with prior exposure to inhaled antipseudomonal antibiotics. The increases in FEV₁% predicted from baseline to day 28 of cycle 3 were similar between the two arms. The results demonstrated similar efficacy and safety profiles for TIP and TIS over a 6-month study period with a significantly reduced administration time for TIP *versus* TIS (mean: 5.6 *versus* 19.7 minutes).⁴³ A significant improvement was reported in patient convenience and adherence with TIP when compared with TIS.^{37,43} Furthermore, subgroup analyses of the EAGER study based on gender and age group were also performed. The analysis by gender showed a trend toward greater improvements in FEV₁% predicted with TIP in male patients than in female patients, and in patients with FEV₁% predicted <50% compared with those with FEV₁% predicted >50% (10.1% *versus* -0.5%).⁴⁸ In the analysis by age, patients were categorized into three groups [≥ 6 to <13 years (children), ≥ 13 to <20 years (adolescents), and ≥ 20 years (adults)]. Comparable efficacy was observed in all age groups for both TIP and TIS. Improvements in FEV₁% predicted from baseline to end of cycle 3 were largest in children [4.7%; confidence interval (CI): -1.2 to 10.6], and patient-reported convenience was higher in patients receiving TIP *versus* TIS across all age groups.⁴⁹

Microbiologic endpoints were included to evaluate the efficacy of TIP and TIS in all three trials, with sampling of oropharyngeal swabs and sputum following consistent methodology and cultures done at the same central laboratory. In the EVOLVE and EDIT studies, *P. aeruginosa* sputum density was significantly reduced in the TIP arm compared

with placebo.^{44,45} In the EAGER study, a greater decline in mucoid and nonmucoid sputum *P. aeruginosa* densities from baseline to day 28 in the third cycle was observed in the TIP arm.⁴³ The details of phase III studies are presented in Table 2.

Phase IV studies

Several studies (ETOILES, 2403, FREE, FR01, BR01, and GB01) have been conducted to collect real-world data to investigate whether the features of TIP translate into real benefits when used in routine clinical practice as demonstrated in previous studies.^{37,50} The results of these real-world studies (ETOILES, 2403, FREE, FR01, and GB01) showed that TIP treatment was associated with lung function benefits and suppression of *P. aeruginosa* sputum density, which is consistent with the published reports from the phase III trials (Table 3).⁴³⁻⁴⁵ The 2403 study also compared the ease of use, device contamination, and safety parameters associated with TIP treatment *versus* TIS and COLI treatment. Similar to the phase III study results, study 2403 showed that the T-326 Inhaler used to deliver TIP was easy to use and required shorter total administration time as compared with nebulizers used to deliver TIS or COLI (Table 3).^{43,51} The ETOILES study evaluated the safety profile of TIP and the BR01 study evaluated device contamination with nebulizers. In addition, three phase IV studies (2403, FREE, and GB01) evaluated patient-reported outcomes assessing patient satisfaction and adherence with TIP treatment.

Patient-reported outcomes

Patient satisfaction, convenience and adherence were evaluated in phase III (EAGER) and phase IV (2403, FREE, FR01, and GB01) studies using different questionnaires such as the modified-treatment satisfaction questionnaire for medication (TSQM),^{54,55} ACCEPTance,⁵⁶ the revised cystic fibrosis questionnaire (CFQ-R),⁵⁷ the Italian CFQ (ITA-CFq), and the Morisky scale.⁵⁸ EAGER, 2403, FREE, and GB01 studies utilized the TSQM questionnaire for evaluating patients reported outcomes (effectiveness, satisfaction, convenience, and side effects). ACCEPTance and patient preference questionnaires were used in the 2403 study. Furthermore, CFQ-R and ITA-CFq were used in the GB01 and FREE studies, respectively (Table 4). The TSQM scores for the treatment satisfaction domain were significantly higher

Table 3. Summary of key phase IV studies.

Parameters	ETOILES	2403	FREE	FR01	GB01	BR01
Study design	Single-arm, open-label, multicenter, phase IV study*	Open-label, crossover, interventional study	Observational, longitudinal, multicenter cohort study	Postmarketing noninterventional, prospective, multicenter study in France	Combined prospective and retrospective, observational study in the United Kingdom	A descriptive study with a cross-sectional approach to assess the contamination profile of home nebulizers in Brazil
Objective	To assess the safety of TIP over 6 cycles of treatment in terms of the incidence of treatment-emergent AEs	To compare the ease-of-use of the T-326 Inhaler device used to deliver TIP with nebulizers used to deliver TIS, COLI, or other inhaled medications	To describe the adherence to treatment with TIP in patients with CF using ITA-CFq questionnaire	To evaluate the adherence to treatment with TIP, as measured using the Morisky score	To describe the change in treatment burden domain score of the revised CFQ-R at 1 month and 5 months after initiation of TIP	To evaluate the microbiologic contamination profile of the nebulizer device
Treatment arms (28-days-on/28-days-off drug)	TIP: 112 mg bid	TIP: 112 mg bid; TIS: 300 mg bid; COLI: 1 million or 2 million units bid/tid (cyclical or noncyclical regimen during cycle 1)	TIP: 112 mg bid	TIP: 112 mg bid; inhaled TIS, COLI and aztreonam	TIP: 112 mg bid	Not applicable
Duration	48 weeks (6 cycles)	20 weeks	6 months	12 months	6 months	12 months
Patients	157 patients aged ≥ 6 years	60 patients aged ≥ 6 years TIS/TIP (n = 14); COLI/TIP (n = 28); TIP/TIP (n = 18)	72 patients aged ≥ 12 and ≤ 35 years	126 patients aged ≥ 6 years	87 patients aged ≥ 14 years	77 patients aged ≥ 6 years (using same nebulizer for at least 3 consecutive months)
Primary clinical outcome†	No deaths and no new emerging safety signals were reported over the 1-year study period	Mean total administration time‡ of TIP compared to nebulized antibiotics; TIS/TIP: 37.0 versus 5.0 min; mean difference: -32.7 (23.9) [95% CI: -54.8 to -10.6; p = 0.0112]; COLI/TIP: 16.4 versus 3.8 min; mean difference: -13.3 (10.4) [95% CI: 20.3-6.4; p = 0.0016]; TIP/TIP: 4.2 versus 3.4 min	Adherence to TIP at the end of cycle 3 as measured by ITA-CFq scores was high (Table 4)	At 12-month follow-up: Adherence was better in children and teenagers compared to adults: 80%, 75% and 48.3%, respectively (Table 4)	All four domains of TSQM questionnaire were scored high indicating greater patient satisfaction (Table 4)	Cleaning nebulizers under tap water was a risk factor, increasing the chance of contamination by 4.29 (95% CI: 1.13-16.28; p = 0.03)
Secondary/exploratory outcome	FEV ₁ % predicted decreased from baseline to cycle 6: -1.9% (14.6); p = 0.199	FEV ₁ % predicted change: Cycle 1: TIS/TIP and COLI/TIP: Increase from baseline (2.2% and 3.9%, respectively); TIP/TIP: Decrease from baseline (-2.8%) Cycle 2: Stable across the treatment arms	FEV ₁ % predicted: 73.8 ± 23.9% at enrollment, 78.1 ± 20.7% at first follow-up visit, and 77.2 ± 17.9% at the second follow-up visit	FEV ₁ % predicted improved in 47.4% of patients, stabilized in 21.6%, and worsened in 30.9%	FEV ₁ % predicted change: Not statistically significant	Not evaluated

Table 3. (Continued)

Parameters	ETOILES	2403	FREE	FR01	GB01	BR01
<i>Pseudomonas aeruginosa</i> sputum density	After 6 cycles of TIP treatment, significant reductions in CFUs: Mucoid: 1.4- \log_{10} reduction, $p < 0.001$ Sum of all biotypes: 1.2- \log_{10} reduction, $p < 0.001$	Sum of all biotypes (cycle 1): TIS/TIP: mean log reduction of 1.4 \log_{10} CFU; COLI/TIP: mean log reduction of 0.6 \log_{10} CFU; TIP/TIP: mean log reduction of 1.7 \log_{10} CFU Cycle 2: slightly lower for the TIS/TIP arm and was similar for the other two arms	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Tobramycin MIC values	MIC ₉₀ : Stable at 2 $\mu\text{g/ml}$ (no change from baseline); MIC ₉₀ : Increased 4-fold (from 128 $\mu\text{g/ml}$ at baseline to 512 $\mu\text{g/ml}$ at the end of the study driven by a small subset of patients)	TIS/TIP and COLI/TIP: MIC ₅₀ and MIC ₉₀ : 1-fold dilution increase; TIP/TIP: MIC ₅₀ and MIC ₉₀ tobramycin values were stable up to cycle 2	Increased from enrollment to the second follow-up visit	Not evaluated	Not evaluated	Not evaluated
Safety						
AEs, n (%)	134 (85.4)*	Cycle 1: 36 (60.0%); Cycle 2: 30 (57.7%)	26 (31.7)	42 (35.3)	51 AEs reported in 43 patients	No AEs were reported during study
Cough	37 (23.6)	Cycle 1: 6 (10 %); Cycle 2: 3 (5.8%)	3 (3.7)	18 (15.1)	3 episodes	
Pulmonary exacerbation	87 (55.4)	Cycle 1: 17 (28.3); Cycle 2: 11 (21.1)	7 (8.5)	3 (2.5)	1 episode	
References	Sommerwerck <i>et al.</i> ⁵²	Greenwood <i>et al.</i> ⁵¹ ; Greenwood <i>et al.</i> ⁵³	Data on file	Data on file	Data on file	Data on file
*Safety was the primary objective of this study. †Patient reported outcomes are described in Table 4. ‡Time including the time required to set up the device, administer the drug, and clean the delivery device. AE, adverse event; bid, twice daily; CFQ-R, cystic fibrosis questionnaire: revised; CI, confidence interval; CFU, colony forming unit; COLI, colistimethate sodium; FEV ₁ , forced expiratory volume in 1 second; ITA-CFg, Italian Treatment Adherence Cystic Fibrosis Questionnaire; MIC, minimum inhibitory concentration; tid, thrice daily; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.						

Table 4. Summary of patient-reported outcomes assessed in key phase III* and IV† studies.

	Patient-reported outcome	Key finding
TSQM (median scores for domains): TIP versus TIS		
EAGER (phase III)	Effectiveness: 74.8 <i>versus</i> 65.4 (difference 9.36, SE = 1.46; $p = 0.0001$) Global satisfaction: 76.2 <i>versus</i> 71.0 (difference 5.20, SE = 1.66; $p = 0.002$) Convenience: 82.7 <i>versus</i> 58.4 (difference 24.35, SE = 1.55; $p < 0.0001$) Side effects: 92.1 <i>versus</i> 92.6 (difference 0.50, SE = 1.22; $p = 0.6833$)	Overall, patients showed greater treatment satisfaction with TIP
2403 (phase IV)	TIS/TIP arm: Cycle 2 (after crossover to TIP): Median scores were improved from cycle 1 only for convenience (13.9 units) COLI/TIP arm: Cycle 2 (after crossover to TIP): Median scores were improved from cycle 1 [effectiveness (8.3 units), convenience (22.2 units), and global satisfaction (10.7 units)] TIP/TIP arm: Effectiveness and convenience scores: cycle 2 scores were unchanged from those of cycle 1 Global satisfaction: median score decreased slightly (7.2 units) in cycle 2 from cycle 1 Side-effects: maximum score (100 units on a scale of 0–100) for all the treatment arms in both cycles, meaning patients did not report experiencing side effects from their medication	
FREE (phase IV)	Convenience domain: domain with highest improvement (enrollment: 74.2 ± 17.1 ; end of study: 77.8 ± 15.9 at the end of study); mean increase: 2.8 ± 17.9 (95% CI: -2.4 to 8.0) Efficacy domain: slight increase following the introduction of TIP (enrollment: 63.6 ± 19.8 ; end of study: 67.5 ± 15.1 at the end of study); mean increase: 1.8 ± 22.4 (95% CI: -4.6 to 8.2) Global satisfaction and side effects domains revealed no significant changes during the study when compared with baseline	
GB01 (phase IV)	All four domains were scored high, indicating greater patient satisfaction Mean increase of scores in four domains: Effectiveness: 5.0 points (SD: ± 24.1) at 1 month and 10.2 points (SD: ± 19.9) at 5 months Side effects: 5.2 points (SD: ± 18.7) at 1 month and 5.6 points (SD: ± 15.9) at 5 months Convenience: 25.6 points (SD: ± 23.5) at 1 month and 29.7 (SD: ± 24.6) points at 5 months global satisfaction: 12.9 points (SD: ± 23.6) at 1 month and 19.9 points (SD: ± 22.9) at 5 months	
ACCEPTance (median scores for domains)		
2403 (phase IV)	TIS/TIP arm: Cycle 2: Median scores were improved from cycle 1 (visit 3) for the domains of medication inconvenience (10 units), long-term treatment (8.3 units), and regime constraints (10 units) Median score for the domain of side effects reached the maximum satisfaction level (on a scale of 100 units) in both cycle 1 and cycle 2 Median scores decreased in cycle 2 for the domains of effectiveness and general COLI/TIP arm: Cycle 2: Median scores were improved for the domains of medication inconvenience (20 units), long-term treatment (12.5 units), and regime constraints (10 units) Median scores decreased in cycle 2 for the domain of side effects TIP/TIP arm: Cycle 2: Median scores were improved from cycle 1 for the domains of medication inconvenience (5 units), regime constraints (2.5 units), effectiveness (16.7 units), and general (8.3 units) The median score for the domain of side effects was the same in both cycles (90 units on a 0–100 scale) Median score for the domain of long-term treatment remained the same in both cycles (66.7 units on a 0–100 scale)	After crossover to TIP (cycle 2), TIS/TIP and COLI/TIP arms showed greater acceptance for TIP

Table 4. (Continued)

	Patient-reported outcome	Key finding
Patient preference		
2403 (phase IV)	The majority of patients demonstrated either 'strong' or 'somewhat' treatment preference for TIP in the TIS/TIP (9 out of 12 patients, 75.0%) and COLI/TIP (18 out of 23 patients, 78.3%) arms The majority ($\geq 78.3\%$) of patients demonstrated preference for TIP for the efficiency of saving time, portability, simplicity, and other advantages	Patient preference was high for TIP
FR01	12-month follow up (TIP <i>versus</i> previous treatments): 61 (88.4%) <i>versus</i> 4 (5.8%) Patient preference for TIP was higher in adult than in younger patients: 48 (87.3%) <i>versus</i> 12 (66.7%)	
ITA-CFq		
FREE (phase IV)	Adherence to TIP at the end of cycle 3 as measured by ITA-CFq scores was high: Enrollment: mean compliance score to nebulized antibiotics: 7.8 ± 3.2 (95% CI: 6.9–8.7) Follow-up visits 1 and 2: mean compliance scores to TIP: 9.4 ± 1.2 (95% CI: 9.0–9.7) and 9.5 ± 1.2 (95% CI: 9.1–9.8), respectively After initiation of TIP, treatment adherence increased by 20.5% at the first follow up at 3 months (9.4 ± 1.2), then remained stable up to the end of study (9.5 ± 1.2)	Patients were more compliant with TIP
CFQ-R		
FREE (phase IV)	No substantial impact of TIP was observed in terms of QoL, as assessed by the CFQ-R All domains remained roughly unchanged from baseline to study end	
GB01 (phase IV)	Mean increase from baseline in CFQ-R treatment burden domain scores [‡] at 1 and 5 months after initiation of TIP: 7.9 points (SD: ± 19.2) at 1 month ($p < 0.01$) and 6.5 points (SD: ± 20.3) at 5 months	
Morisky score		
FR01 (phase IV)	Adherence to TIP as measured by the Morisky score: Baseline visit: 50.0% of patients were compliant with previous inhaled treatment; mean Morisky score was $2.5 (\pm 1.2)$ 12-month follow up: 59.6% of patients were compliant with TIP treatment (95% CI: 45.3–72.4%); mean Morisky score was 2.7 (SD: ± 1.0) At 12-month follow up, adherence was better in children and teenagers compared with adults: 80%, 75%, and 48.3% of adherent patients with mean Morisky scores of 3.1 (SD: ± 0.7), 3.0 (SD: ± 0.8), and 2.5 (SD: ± 1.1), respectively	
Patient's diary		
FREE (phase IV)	Average number of missed antibiotic doses per patient during the past week was 0.5 ± 0.7 at first cycle, 0.4 ± 0.5 at second cycle, and 0.4 ± 0.8 at third cycle (the average number of antibiotic capsules used for each dose was always 4)	

*Konstan *et al.* 2011a. † Data on file. ‡Domains are scored out of 100 with a higher score indicating greater patient satisfaction. AEs, adverse events; CFQ-R, cystic fibrosis questionnaire: revised; CI, confidence interval; COLI, colistimethate sodium; ITA-CFq, Italian Treatment Adherence Cystic Fibrosis Questionnaire; QoL, quality of life; SE, standard error; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution; TSQM, treatment satisfaction questionnaire for medication.

for TIP with regard to effectiveness, convenience, and global satisfaction in EAGER (Table 4). Similarly, the 2403 study showed high scores for TSQM in cycle 1, which were either sustained or further improved in cycle 2 for the majority of domains, indicating greater treatment satisfaction in patients receiving TIP over TIS and COLI.⁵¹ In

the GB01 study, increases were seen in the scores for all four domains of TSQM (data on file).

A real-world study by Harrison and colleagues showed that the proportion of participants reporting 'excellent adherence' was increased by two-fold after switching from TIS to TIP (43–83%).³⁷

Another real-world study showed that the majority of patients expressed satisfaction with TIP administration time (100%), time to clean (97.1%), portability (97.1%), and ease of use (94.3%). Overall, the patient preference for TIP was based on shorter administration time, convenience, and ease of use.⁵⁹ In summary, results from various real-world studies are in line with the phase III clinical trial data that suggest improved patient adherence with TIP as compared with TIS.⁴³ The detailed patient reported outcomes from various studies are presented in Table 4.

Inhalation-device contamination

Various studies have investigated the role of home nebulizers as a source of contamination in patients with CF.^{39,40,60,61} An open-label, crossover, interventional phase IV study (2403) analyzed the contamination profile of both nebulizers and the T-326 inhaler, while a descriptive study, BR01, analyzed the contamination profile of nebulizers with regard to methods of cleaning to minimize contamination. In the 2403 study, microbial contamination of the nebulizers was assessed at the start and end of the first treatment period, second treatment period, and at the discontinuation visit if applicable. For patients on TIP, the T-326 Inhaler used in the last week of TIP treatment was cultured. Device samples were obtained from four locations on the nebulizer (mouthpiece, reservoir cup, filter, and tubing) and from one location on the T-326 Inhaler (mouthpiece). A central laboratory performed all device cultures, as well as sputum cultures from patients. The results of this study showed that the T-326 Inhaler used to deliver TIP was much less frequently contaminated than the nebulizers, thus potentially reducing the sources of pathogenic bacteria in patients with CF.⁵³ In the BR01 study, microbial contamination of the nebulizers was assessed using samples taken from the mouthpiece and the reservoir cup, and cultures were performed at a central laboratory. The latter study concluded that cleaning nebulizers with tap water increased the chance of contamination by 4.29 fold (Table 5). Assessment of contamination of various parts of the nebulizer showed that the frequency of contamination was 60.8% in the mouthpiece and 62.2% in the cup, which was consistent with the reported pattern of contamination profile of nebulizers.^{39,60}

Safety and tolerability

Inhaled tobramycin preparations have the advantage of minimal systemic exposure, and hence have a different adverse event (AE) profile compared with parenteral formulations.⁶² The phase III (EVOLVE, EDIT, and EAGER) and phase IV (ETOILES, 2403, FREE, FR01, and GB01) studies suggested that there were no unexpected safety signals with TIP treatment. In the EVOLVE study, the incidence of AEs reported among TIP-treated patients was lower (50.0%) when compared with placebo-treated patients (75.5%) in cycle 1.⁴⁴ The incidence of lung disorders (preferred term mainly for pulmonary exacerbations) was comparable in cycle 1; however, the frequency appeared to be higher for any given cycle in the TIP arm compared with the placebo arm (Table 2). The incidence rates of overall AEs were generally higher in the placebo arm *versus* the TIP arm in the first cycle of treatment.⁴⁴ A similar trend was observed for AEs and serious AEs (SAEs) in the EDIT study.⁴⁵ In the EAGER study, AEs were observed more frequently in the TIP arm than in the TIS arm throughout the three treatment cycles; however, the incidence decreased successively with each cycle.⁴³

In the ETOILES study ($n = 157$), safety was evaluated over a period of 48 weeks, along with supportive efficacy endpoints during 6 cycles of therapy in patients with CF. No new emerging safety signals were reported.⁵² The study findings were consistent with results from the 1-year extension of the EDIT study conducted to evaluate the safety and tolerability profile of TIP; no increased incidence of the different types of AEs with longer exposure to TIP was reported.⁴⁷

The data from phase IV studies showed that TIP was well tolerated, and safety findings from real-world studies are consistent with results of the phase III studies.

In general, the most common AEs in patients receiving TIP were cough and pulmonary exacerbations.^{43,45} Cough was the most common AE in the TIP groups in all three studies, EVOLVE, EDIT, and EAGER. However, there were no treatment discontinuations due to this AE (Table 2).^{44,45}

Postinhalation cough is reported as a common side effect associated with both wet- and dry-powder inhalation in patients with CF in various clinical

Table 5. Summary of key phase IV studies device contamination results.

Study number	2403	BR01
Treatment arms	TIS/TIP ($n = 14$); COLI/TIP ($n = 28$); TIP/TIP ($n = 18$)	Nebulizers ($n = 77$)
Results	<p>Contamination frequency: $n = 12$ (20%): COLI/TIP: 9 (32.1%); TIS/TIP: 2 (14.3%); TIP/TIP: 1 (5.6%)</p> <p>TIS/TIP: Cycle 1: No pathogen isolated from the devices Cycle 2: <i>Pseudomonas aeruginosa</i> was isolated from both the nebulizer (medication not specified) and the sputum <i>Staphylococcus aureus</i> was the only pathogen isolated (light growth) from one T-326 Inhaler and it was not present in the patient's sputum COLI/TIP: Cycle 1: The majority of pathogens were isolated (only once) from the devices that delivered COLI. Except for one patient with <i>S. aureus</i> in the COLI/TIP arm, no patient had the same pathogen isolated from the delivery device and sputum at visits 2 and 3 Cycle 2: No contamination was observed in the T-326 inhaler during cycle 2 TIP/TIP: Cycle 2: No contamination was observed in the T-326 Inhaler during cycles 1 or 2 <i>P. aeruginosa</i> was isolated from nebulizers (used for other nonspecified medication)</p>	<p>Contamination frequency: $n = 53$ (71.6%)</p> <p>Frequently isolated pathogen <i>Pseudomonas putida</i>: 6 (8.1%), <i>Stenotrophomonas maltophilia</i>: 5 (6.8%); <i>Chryseobacterium indologenes</i>: 5 (6.8%); nonalbicans <i>Candida</i> species: 16 (21.6%) Environmental fungal contaminants: 9 (12.2%)</p> <p>97.4% of patients reported cleaning their nebulizers</p> <p>Cleaning methods: Lathering and rinsing with tap water (66.2%) Tap water only (60.8%) Immersion in boiling water (52.7%)</p> <p>Cleaning nebulizers under tap water was a risk factor for device contamination (OR = 4.29; 95% CI: 1.13–16.28, $p = 0.03$)</p>
<p>CI, confidence interval; COLI, colistimethate sodium; OR, odds ratio; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.</p>		

studies.^{43,44,52} The reason for the relatively high incidences of cough, dysphonia, and dysgeusia could be the delivery of a relatively high powder load or deposition of tobramycin to the posterior pharynx causing irritation, which decreases with time.⁴³ Therefore, ETOILES used a specific case-report form to record and characterize postinhalation events (including cough), capturing time of onset and duration. In this study, 78 patients reported postinhalation cough, which was highest in cycle 1 (31.4%) and subsequently decreased during cycles 4–6 (21–22%). In most cases, the postinhalation cough was generally of short duration (<4 min) and decreased over time, with no action required, possibly due to patients becoming more experienced with the administration of TIP.⁵² Furthermore, there is growing evidence that proper inhalation techniques may result

in minimization of postinhalation cough for 'high-dose' dry powder products like TIP. Reduction in postinhalation cough was observed for inhaled drugs when a higher resistance DPI with a lower PIFR was used. The flow rate independence in total lung dose,^{in vitro} observed for TIP should allow patients to inhale comfortably without cough, while maintaining consistent drug delivery to the lungs.^{63–65} The ETOILES study reconfirmed that TIP continues to be well tolerated in patients with CF, with no increase in the frequency of AEs in the second year of treatment, and no new emerging safety signals.⁶⁶ Moreover, the postinhalation cough events were not associated with bronchospasm events.^{43,52}

Common measures to minimize postinhalation cough utilized during clinical trials were drinking

water, less forceful inhalation, and correction of inhalation technique.⁵² Additional cough-mitigation strategies include: (1) avoid pressing button more than once; (2) tilt head back slightly during inhalation; and (3) inhalation with a single, slow, and deep breath to minimize cough.

Conclusion

Nebulized antibiotics have significantly contributed to increasing the life expectancy in CF patients with chronic airway infection; however, the high treatment burden and nebulizer contamination are major concerns. TIP administered *via* the T-326 Inhaler is efficacious for the management of chronic pulmonary *P. aeruginosa* infection in patients with CF and may help alleviate this treatment burden. Controlled clinical and real-world studies have demonstrated comparable efficacy and safety of TIP with TIS treatment. TIP is considered easy to use by some patients as the total administration time in patients with CF was considerably less compared with that with TIS. Additionally, unlike nebulizers, the T-326 Inhaler does not require disinfection. Moreover, greater patient satisfaction demonstrated in various clinical trials suggests that the convenience and lower treatment burden associated with TIP use may result in improved adherence to therapy. Long-term safety and real-world studies suggest that TIP was well tolerated and its safety profile was generally consistent with the established safety profile from the phase III studies. Although postinhalation cough was the most commonly reported AE with TIP in clinical trials, it seemed to decrease over time and with proper administration measures that are important components of patient education. In addition to comparable efficacy and safety, TIP administered *via* the T-326 Inhaler may offer a therapeutic advantage over traditional nebulized formulations by demonstrating improved convenience and treatment adherence.

Acknowledgements

The authors acknowledge Anupama Tamta (Novartis Healthcare Pvt. Ltd., Hyderabad, India) for providing medical writing assistance for this manuscript.

Funding

The study was sponsored by Novartis Pharma AG.

Conflict of interest statement

KH and LD are full-time employees of Novartis Pharmaceuticals Corporation.

References


- Vallières E and Elborn JS. Cystic fibrosis gene mutations: evaluation and assessment of disease severity. *Adv Genomics Genet* 2014; 4: 161–172.
- Proesmans M. Best practices in the treatment of early cystic fibrosis lung disease. *Ther Adv Respir Dis* 2016; pii: 1753465816680573.
- Goss CH and Ratjen F. Update in cystic fibrosis 2012. *Am J Respir Crit Care Med* 2013; 187: 915–919.
- Ashlock MA, Beall RJ, Hamblett NM, *et al.* A pipeline of therapies for cystic fibrosis. *Semin Respir Crit Care Med* 2009; 30: 611–626.
- Cystic Fibrosis Foundation (CFF). *Patient registry 2012 annual data report*. Bethesda: Cystic Fibrosis Foundation, 2013.
- Cystic Fibrosis Foundation (CFF). *Patient registry 2015 annual data report*. Bethesda: Cystic Fibrosis Foundation, 2016.
- Lyczak JB, Cannon CL and Pier GB. Lung infections associated with cystic fibrosis. *Clin Microbiol Rev* 2002; 15: 194–222.
- Cystic Fibrosis Foundation (CFF). *Patient registry 2008 annual data report*. Bethesda: Cystic Fibrosis Foundation, 2009.
- Emerson J, Rosenfeld M, McNamara S, *et al.* *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* 2002; 34: 91–100.
- Tumbarello M, Repetto E, Trecarichi EM, *et al.* Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality. *Epidemiol Infect* 2011; 139: 1740–1749.
- Doring G and Hoiby N. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. *J Cyst Fibros* 2004; 3: 67–91.
- Doring G, Conway SP, Heijerman HG, *et al.* Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. *Eur Respir J* 2000; 16: 749–767.
- Gibson RL, Burns JL and Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003; 168: 918–951.

14. Rosenfeld M, Ramsey BW and Gibson RL. *Pseudomonas* acquisition in young patients with cystic fibrosis: pathophysiology, diagnosis, and management. *Curr Opin Pulm Med* 2003; 9: 492–497.
15. UK Cystic Fibrosis Trust Antibiotic Working Group. *Antibiotic treatment for cystic fibrosis*. 3rd ed. London: UK Cystic Fibrosis Trust, 2009.
16. Das RR, Kabra SK and Singh M. Treatment of *pseudomonas* and *Staphylococcus* bronchopulmonary infection in patients with cystic fibrosis. *ScientificWorldJournal* 2013: 645–653.
17. Geller DE. Aerosol antibiotics in cystic fibrosis. *Respir Care* 2009; 54: 658–670.
18. Anderson P. Emerging therapies in cystic fibrosis. *Ther Adv Respir Dis* 2010; 4: 177–185.
19. Ballmann M, Smyth A and Geller DE. Therapeutic approaches to chronic cystic fibrosis respiratory infections with available, emerging aerosolized antibiotics. *Respir Med* 2011; 105(Suppl. 2): S2–S8.
20. Heijerman H, Westerman E, Conway S, *et al.* Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2009; 8: 295–315.
21. Elborn JS, Vataire AL, Fukushima A, *et al.* Comparison of inhaled antibiotics for the treatment of chronic *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis: systematic literature review and network meta-analysis. *Clin Ther* 2016; 38: 2204–2226.
22. TOBI® Podhaler: prescribing information (tobramycin inhalation powder). East Hanover: Novartis Pharmaceuticals Corp, 2015.
23. CAYSTON®: summary of product characteristics (aztreonam for inhalation solution). Ireland: Gilead Sciences, 2016.
24. CAYSTON®: prescribing information (aztreonam for inhalation solution). Foster City: Gilead Sciences, Inc, 2014.
25. Promixin®: summary of product characteristics. Chichester: Profile Pharma Limited, 2015.
26. Colobreathe®: summary of product characteristics (colistimethate sodium inhalation powder). Dartford: Forest Laboratories UK Ltd, 2016.
27. Quinsair®: information summary of product characteristics. European Medicines Agency. Novato: Raptor Pharmaceuticals Inc, 2015.
28. TOBI®: prescribing information (tobramycin inhalation solution). East Hanover: Novartis Pharmaceuticals Corp, 2015.
29. Ramsey BW, Pepe MS, Quan JM, *et al.* Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999; 340: 23–30.
30. Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest* 2001; 120(Suppl. 3): 107S–113S.
31. Flume PA, O’Sullivan BP, Robinson KA, *et al.* Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007; 176: 957–969.
32. Mogayzel PJ Jr, Naureckas ET, Robinson KA, *et al.* Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2013; 187: 680–689.
33. Doring G, Flume P, Heijerman H, *et al.* Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros* 2012; 11: 461–479.
34. Smyth AR, Bell SC, Bojcin S, *et al.* European cystic fibrosis society standards of care: best practice guidelines. *J Cyst Fibros* 2014; 13(Suppl. 1): S23–S42.
35. Geller DE, Weers J and Heuerding S. Development of an inhaled dry-powder formulation of tobramycin using PulmoSphere technology. *J Aerosol Med Pulm Drug Deliv* 2011; 24: 175–182.
36. Sawicki GS, Sellers DE and Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros* 2009; 8: 91–96.
37. Harrison MJ, McCarthy M, Fleming C, *et al.* Inhaled *versus* nebulised tobramycin: a real world comparison in adult cystic fibrosis (CF). *J Cyst Fibros* 2014; 13: 692–698.
38. Eakin MN, Bilderback A, Boyle MP, *et al.* Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *J Cyst Fibros* 2011; 10: 258–264.
39. Blau H, Mussaffi H, Mei Zahav M, *et al.* Microbial contamination of nebulizers in the home treatment of cystic fibrosis. *Child Care Health Dev* 2007; 33: 491–495.
40. Lester MK, Flume PA, Gray SL, *et al.* Nebulizer use and maintenance by cystic fibrosis patients: a survey study. *Respir Care* 2004; 49: 1504–1508.
41. Geller DE, Konstan MW, Smith J, *et al.* Novel tobramycin inhalation powder in cystic fibrosis

- subjects: pharmacokinetics and safety. *Pediatr Pulmonol* 2007; 42: 307–313.
42. Newhouse MT, Hirst PH, Duddu SP, *et al.* Inhalation of a dry powder tobramycin PulmoSphere formulation in healthy volunteers. *Chest* 2003; 124: 360–366.
 43. Konstan MW, Flume PA, Kappler M, *et al.* Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: the EAGER trial. *J Cyst Fibros* 2011; 10: 54–61.
 44. Konstan MW, Geller DE, Minic P, *et al.* Tobramycin inhalation powder for *P. aeruginosa* infection in cystic fibrosis: the EVOLVE trial. *Pediatr Pulmonol* 2011; 46: 230–238.
 45. Galeva I, Konstan MW, Higgins M, *et al.* Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial. *Curr Med Res Opin* 2013; 29: 947–956.
 46. Sweetman SC. *Martindale: the complete drug reference*. London: Pharmaceutical Press, 2016, <http://www.medicinescomplete.com>.
 47. Konstan MW, Flume PA, Galeva I, *et al.* One-year safety and efficacy of tobramycin powder for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2016; 51: 372–378.
 48. Konstan M, Parkins M, Angyalosi G, *et al.* Tobramycin inhalation powder is as effective as Tobramycin inhalation solution in patients with cystic fibrosis: a subgroup analysis of the EAGER trial. *Poster (39401) presented at American Thoracic Society*, Philadelphia, PA, 2013.
 49. Geller DE, Nasr SZ, Piggott S, *et al.* Tobramycin inhalation powder in cystic fibrosis patients: response by age group. *Respir Care* 2014; 59: 388–398.
 50. Bilton D, Nash EF, Peckham D, *et al.* 74 An evaluation of treatment burden following initiation of TOBI Podhaler; in patients with CF. *J Cyst Fibros* 2014; 13: S65.
 51. Greenwood JSC, Sommerwerck U, Nash EF, *et al.* Ease of use of tobramycin inhalation powder compared with nebulized tobramycin and colistimethate sodium: a phase IV crossover study in cystic fibrosis patients with *Pseudomonas aeruginosa* infection. *Pediatr Pulmonol* 2016; 51: S361.
 52. Sommerwerck U, Virella-Lowell I, Angyalosi G, *et al.* Long-term safety of tobramycin inhalation powder in patients with cystic fibrosis: phase IV (ETOILES) study. *Curr Med Res Opin* 2016; 32: 1789–1795
 53. Greenwood JSC, Sommerwerck U, Nash EF, *et al.* Microbial contamination profile of TOBI Podhaler versus nebulizers used in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection: a real-world study. *Pediatr Pulmonol* 2016; 51: S315.
 54. Atkinson MJ, Sinha A, Hass SL, *et al.* Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004; 2: 12.
 55. Regnault A, Balp MM, Kulich K, *et al.* Validation of the Treatment Satisfaction Questionnaire for Medication in patients with cystic fibrosis. *J Cyst Fibros* 2012; 11: 494–501.
 56. Arnould B, Gauchoux R, Meunier J, *et al.* Validation of ACCEPT, a new generic measure to assess how patients with chronic diseases balance between the advantages and disadvantages of following the recommended treatment regimen in real-life. *ISPOR 16th Annual European Congress, Dublin, Ireland, 2013*.
 57. Quittner AL, Buu A, Messer MA, *et al.* Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005; 128: 2347–2354.
 58. Morisky DE, Green LW and Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; 24: 67–74.
 59. Greenberg J, Palmer JB, Chan WW, *et al.* Treatment satisfaction in cystic fibrosis: early patient experience with tobramycin inhalation powder. *Patient Prefer Adherence* 2016; 10: 2163–2169.
 60. Della Zuana A, Oliveira Garcia D, Juliani RC, *et al.* Effect that an educational program for cystic fibrosis patients and caregivers has on the contamination of home nebulizers. *J Bras Pneumol* 2014; 40: 119–127.
 61. Vassal S, Taamma R, Marty N, *et al.* Microbiologic contamination study of nebulizers after aerosol therapy in patients with cystic fibrosis. *Am J Infect Control* 2000; 28: 347–351.
 62. Hagerman JK, Hancock KE and Klepser ME. Aerosolised antibiotics: a critical appraisal of their use. *Expert Opin Drug Deliv* 2006; 3: 71–86.
 63. Tiddens HA, Geller DE, Challoner P, *et al.* Effect of dry powder inhaler resistance on the inspiratory flow rates and volumes of cystic

- fibrosis patients of six years and older. *J Aerosol Med* 2006; 19: 456–465.
64. Jaques A, Daviskas E, Turton J, *et al.* Inhaled mannitol improves lung function in cystic fibrosis. *Chest* 2008; 133: 1388–1396.
65. Haynes A, Geller D, Weers J, *et al.* Inhalation of tobramycin using simulated cystic fibrosis patient profiles. *Pediatr Pulmonol* 2016; 51: 1159–1167.
66. Virella-Lowell I, Sommerwerck U, Debonnett L, *et al.* Long-term safety and efficacy of tobramycin inhalation powder hard capsules (TIP™) in patients with cystic fibrosis: an extension to the ETOILES study. *Pediatric Pulmonol* 2015; 50: S364–S365.

Visit SAGE journals online
[journals.sagepub.com/
home/tar](http://journals.sagepub.com/home/tar)

 SAGE journals