SAFETY, EFFICACY AND CONVENIENCE OF TOBRAMYCIN INHALATION POWDER IN CYSTIC FIBROSIS PATIENTS: THE EAGER TRIAL

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Abstract

Background—A light-porous-particle, dry-powder formulation of tobramycin was developed, using PulmoSphere® technology, to improve airway delivery efficiency, substantially reduce delivery time, and improve patient convenience and satisfaction. We evaluated the safety, efficacy and convenience of tobramycin inhalation powder (TIP™) versus tobramycin inhalation solution (TIS, TOBI®) for treating *Pseudomonas aeruginosa* infection in cystic fibrosis (CF) patients aged 6 years.

Methods—In this open-label study, 553 patients were randomized 3:2 to TIP (total 112 mg tobramycin) via the Novartis T-326 Inhaler or TIS 300 mg/5 mL via PARI LC® PLUS nebulizer

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twice daily for three treatment cycles (28 days on-drug, 28 days off-drug). Safety, efficacy, and treatment satisfaction outcomes were evaluated.

Results—TIP was generally well-tolerated; adverse events were similar in both groups. The rate of cough suspected to be study-drug related was higher in TIP-treated patients (TIP: 25.3%; TIS: 4.3%), as was the overall discontinuation rate (TIP: 26.9%; TIS: 18.2%). Increases in FEV_1 % predicted from baseline to Day 28 of Cycle 3 were similar between groups; mean reduction in sputum *Pseudomonas aeruginosa* density ($\log_{10}$ CFU/g) on Day 28 of Cycle 3 was also comparable between groups. Administration time was significantly less for TIP (mean: 5.6 versus 19.7 minutes, *p*<0.0001). Treatment satisfaction was significantly higher for TIP for effectiveness, convenience, and global satisfaction.

Conclusions—TIP has a safety and efficacy profile comparable with TIS, and offers a far more convenient treatment option for pseudomonas lung infection in CF.

Keywords

Introduction

Individuals with cystic fibrosis (CF) are highly susceptible to endobronchial infection with *Pseudomonas aeruginosa (Pa)*. For most patients, *Pa* infections begin in childhood and become chronic by early adulthood (1). Chronic *Pa* infection is associated with an accelerated decline in lung function, and increased morbidity and mortality (2-5). Consequently, effective treatment of *Pa* infection is crucial to the management of CF.

Tobramycin inhalation solution (TIS (6)) significantly improves lung function and quality of life, and reduces hospitalization rates, in CF patients chronically infected with *Pa* (7-10). Current treatment guidelines recommend TIS for the treatment of chronic *Pa* pulmonary infections in CF patients   6 years (TOBI® prescribing information; 11-13). Administration time is approximately 15-20 minutes per dose (excluding cleaning and sterilization) (13).

Treatment of *Pa* infection by inhaled antibiotics is time consuming and places a high burden on CF patients; adherence to treatment is a significant challenge (14-16). An innovative drug-device combination using a new dry-powder formulation of tobramycin has been developed to increase the convenience of administration for patients, which may increase treatment adherence and thereby clinical outcomes (17,18). Tobramycin inhalation powder (TIP™) is formed of light-porous-particles that are manufactured using an emulsion-based spray drying process (19). TIP is delivered via the T-326 Inhaler (Novartis Pharmaceuticals Corporation, USA), a dry powder inhaler (DPI). The device is portable, has no internal or external power source, and is designed to enhance drug delivery to the lung and shorten administration time (13). CF patients as young as 6 years old are capable of inhaling through a device with the internal resistance of the T-326 Inhaler (20). Previous studies showed that single-dose administration of TIP results in more efficient and rapid delivery of tobramycin than TIS in CF patients, while maintaining similar pharmacokinetic characteristics (13,21).

The *E*stablish *A* new *G*old standard *E*fficacy and safety with tobramycin in cystic fib*R*osis [EAGER] trial was designed to evaluate the safety, efficacy and convenience of the new inhaled formulation of tobramycin (TIP) versus TIS for treating *Pa* infection in CF patients.

Methods

This international study was conducted in 127 centers in 15 countries and was approved by an Institutional Review Board or Independent Ethics Committee for each center and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Patients

CF patients aged   6 years with forced expiratory volume in one second (FEV_1)   25 to   75% predicted based on Knudson equations (22) and sputum or throat cultures positive for *Pa* within 6 months of screening (and confirmed at enrollment) were eligible.

Study design

This two-arm, randomized, open-label study comprised three cycles; each cycle consisted of 28 days on-treatment followed by 28 days off-treatment. Total duration of treatment was 24 weeks (Figure 1A). Eligible patients were randomized 3:2 to TIP (four capsules/112 mg tobramycin) twice daily administered via the T-326 Inhaler, or TIS 300 mg/5 mL (TOBI®) twice daily administered via the PARI LC® PLUS jet nebulizer and DeVilbiss PulmoAide compressor or an equivalent alternative.

Study assessments

Safety assessments included the incidence and intensity of all adverse events (AEs) and serious AEs (SAEs), presence of airway reactivity to the drug (post-inhalation drop in FEV_1), and changes in hematology, blood chemistry, urine protein, audiology, physical condition and body weight.

The main efficacy measure was relative change in FEV_1 % predicted from baseline (pre-dose Day 1) at all scheduled post-treatment visits (Weeks 2, 5, 9, 13, 17, 21 and 25). Other efficacy measures included change in sputum *Pa* density (log_{10} CFU/g sputum), tobramycin susceptibility to *Pa* (assessed using minimum inhibitory concentrations [MIC]), antipseudomonal antibiotic use, and respiratory-related hospitalizations. Serum and sputum pharmacokinetics were assessed in a subset of the population.

Patient's self-reported treatment satisfaction was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM, a validated instrument) (23), which was modified by adding four study-specific questions: (I) How convenient or inconvenient is it to store the medication?; (II) How easy or difficult is it to put together the parts of the delivery device?; (III) How convenient or inconvenient would it be to use the delivery device away from home?; (IV) How convenient or inconvenient is it for you to take care of the delivery device? (Note: the standard fourteen questions of the TSQM were not altered). The TSQM domain scores were calculated as recommended by the instrument authors; described in

detail elsewhere (23). The TSQM domain scores range from 0 to 100 with higher scores representing higher satisfaction for that domain. The term 'medication' includes the combination of the medication and delivery device (aerosol machine/nebulizer or inhaler).

Statistical analyses

Sample size was based on the primary variable, safety; inclusion of 300 TIP patients was estimated to provide a 99.8% chance of observing at least one AE with a true incidence of 2% in the TIP group. Inclusion of 500 patients in total (TIP: 300; TIS: 200) would provide 96% power to demonstrate non-inferiority of TIP to TIS with regard to relative change from baseline in FEV_1 % predicted after three cycles, based on a non-inferiority margin of 6% and a one-sided significance level of 0.15 (assuming 1% true TIS-TIP treatment difference, and 20% standard deviation).

The primary objective was to evaluate the safety of TIP versus TIS (data are summarized descriptively). A pre-planned non-inferiority analysis compared the efficacy of TIP versus TIS, with regard to relative change in FEV_1 % predicted from baseline to the end of Cycle 3 dosing (pre-dose Day 28). Post-hoc sensitivity analyses assessed the impact of patient discontinuation. All randomized patients who received 1 dose of study drug were included in the safety and efficacy populations.

Results

A total of 553 patients were randomized; 517 received at least one dose of study medication and were included in the efficacy and safety populations. Baseline demographic and clinical characteristics were similar in the two treatment groups (Table 1). Use of TIS prior to screening was similar in both groups (TIP: 82.1%; TIS: 82.3%). Concomitant therapy was used by 99.7% of TIP-treated and 99.0% of TIS-treated patients.

The main cause for discontinuation was AEs (Figure 1B); more patients discontinued in Cycle 1 than in Cycles 2 and 3 for both groups. Adherence to therapy (based on the number of doses actually received versus the possible maximum) was generally high (>90% of doses) over all 3 cycles in both groups. All patients who completed the study without major protocol deviations were included in the per protocol (PP) population (TIP: 60.8%; TIS: 66.5%); failure to take at least 80% of the study drug was the most frequent reason for exclusion.

Safety

A higher percentage of TIP-than TIS-treated patients reported AEs (90.3% versus 84.2%, p<0.05) (Table 2). Most AEs were mild or moderate in intensity (TIP: 73.4%; TIS: 68.5%). The percentage of patients with AEs was highest in Cycle 1, in both groups (77.9% versus 66.5%), and decreased with each successive cycle (Cycle 2: 67.0% versus 66.3%; Cycle 3: 65.8% versus 58.5%).

Cough (not including productive cough) was the most frequently reported AE throughout the entire study period (TIP: 48.4%; TIS: 31.1%). As a baseline symptom, cough was present in a high proportion of patients (42%) in both groups. Most cough events were mild

or moderate in intensity. The frequency of severe cough events was low and balanced between groups (2.6% versus 1.9%). Less than 4% (12/308) of TIP-treated patients discontinued due to cough versus 1% (2/209) of TIS-treated patients. Cough events were suspected by the investigator as being related to study drug in 25.3% and 4.3% of patients in the TIP and TIS group, respectively. Other treatment-related AEs more commonly reported in the TIP group were dysphonia (13.6% versus 3.8%) and dysgeusia (3.9% versus 0.5%).

Clinically significant bronchospasm (defined as an acute relative change of 20% decrease in FEV_1 % predicted from pre-dose to 30-minutes post-dose) in any cycle was experienced by 5.2% and 5.3% of TIP- and TIS-treated patients, respectively.

The incidence of SAEs was similar in both groups (TIP: 27.4%; TIS: 29.2%). Lung disorders were the most commonly reported SAE in both groups (TIP: 19.5%; TIS: 18.7%). SAEs were reported by fewer patients in both groups, with each successive treatment cycle (Cycle 1: 15.5%; Cycle 2: 9.3%; Cycle 3: 7.4%). Three deaths were reported during the study. All were in the TIP group, although none was related to the study drug.

There were no clinically relevant changes from baseline to pre-specified time points for vital signs, and biochemical or hematological measures. There were few reports (4%) of renal function changes as measured by increases in serum creatinine, blood urea nitrogen, or proteinuria in both groups. The incidence of AEs related to renal and urinary disorders, including proteinuria, dysuria, polyuria and nephrolithiasis, was 1% in both groups.

Audiology was performed in a subpopulation of patients (TIP: 78 [25.3%]; TIS: 45 [21.5%]). Twenty (25.6%) TIP-treated and 7 (15.6%) TIS-treated patients experienced a decrease from baseline in any audiology test frequency at any visit; the decrease was of a similar degree in both groups. Using the criteria for either ear of 10 dB loss at three consecutive frequencies, 15 dB loss at two consecutive frequencies and 20 dB loss at any frequency, 3 (0.97%) TIP-treated and 2 (0.96%) TIS-treated patients were considered to have clinically significant hearing loss. Hearing complaints tended to be intermittent and transient.

Efficacy

Spirometry—Increases in FEV_1 % predicted from baseline to Day 28 of Cycle 3 were similar between groups (least squares [LS] mean difference 1.1% relative change [SE 1.75], Figure 2A). The lower limit (−0.67%) of the one-sided 85% [CI] (equivalent to 70% two-sided) was within the predefined 6% margin for predefined non-inferiority indicating that TIP was non-inferior to TIS. LS mean values from the PP population supported this analysis (LS mean difference in FEV_1 of 1.2%, lower limit of the one-sided 85% CI was −1.02%).

Microbiology—Mucoid and non-mucoid *Pa* sputum density showed a decrease from baseline in both groups at all time points (Figure 2B presents combined mean of all phenotypes). The mean change from baseline was greater in the TIP versus TIS group on Day 28 of Cycle 3 (mean change: −1.6 versus −0.92 $\log_{10}$ CFU/g for mucoid phenotype and − 1.77 versus −0.73 $\log_{10}$ CFU/g for non-mucoid phenotype, respectively). On Day 28 of Cycle 3, 11.6% of TIP and 9.9% of TIS patients had negative *Pa* cultures.

The MIC of tobramycin against *Pa* increased from baseline to Day 28 of Cycle 3 in both groups (4-fold increase: 67/199 [33.7%] versus 42/154 [27.3%]; 2-fold increase: 97/199 [48.7%] versus 61/154 [39.6%]).For patients with *Pa* isolates (all phenotypes) with an MIC <8 g/ml at baseline (TIP, 22.1%; TIS, 23.0%), 19.1% versus 14.9% of TIP- and TIS-treated patients had an MIC >8 g/ml at the end of Cycle 3.

Antipseudomonal antibiotic use and hospitalizations—The proportion of patients requiring any new antipseudomonal antibiotic was significantly higher with TIP than TIS (64.9% versus 54.5%, *p*=0.0148). However, the average number of days of antibiotic usage tended to be less in the TIP group (mean [SD]: 30.9 [23.34] versus 33.4 [24.42] days, *p*=0.2039). Most newly used antibiotics were administered orally; oral antibiotics were used in 55.5% and 39.7% of patients in the TIP and TIS groups, respectively. Ciprofloxacin was the most frequently used new anti-pseudomonal antibiotic during the study (47.7% versus 34.0%).

The number of patients hospitalized for respiratory-related events was similar in the TIP versus TIS group (24.4% versus 22.0%). The proportion of hospitalized patients receiving antibiotics (excluding inhaled antibiotics) was well matched between groups (22.1% versus 21.5%).

Administration time—Mean duration of administration was significantly less for TIP (5.6 minutes) than TIS (19.7 minutes, excluding cleaning and sterilization) at each study visit and overall (*p*<0.0001).

Patient-reported treatment satisfaction—Overall, patient satisfaction was higher with TIP (Table 3). LS mean scores were significantly higher (*p*<0.0001) with TIP than TIS at all visits for effectiveness (a higher score indicates higher satisfaction for that domain); this takes into account patients' assessment of the ability of their medication to treat or prevent their condition and relieve symptoms, as well as the time it takes to start working. Patients also reported treatment with TIP to be significantly more convenient than TIS for the entire study (*p*<0.0001); this takes into account patients' assessment of the overall convenience of treatment (e.g. ease of use and time). Furthermore, global satisfaction was reported to be statistically greater for TIP than TIS at all visits (*p*=0.0018). No difference in side effect ratings (patients' assessment of how bothersome the side effects are and their perception of the impact of the side effects on their physical and mental abilities) was reported between groups during the study (*p*=0.6833). The four supplementary questions relating to the use and maintenance of the inhalation devices (i.e. storage, device assembly, use of device away from home and device caretaking) all showed a significant difference in favor of TIP for the entire study period (*p*<0.0001).

Pharmacokinetics—Pharmacokinetic assessments were performed in 30 TIP-treated and 14 TIS-treated patients. Serum tobramycin concentrations were comparable for TIP and TIS. Sputum levels were generally higher for TIP 30-minutes post-dose (mean±SD on Day 28, Cycle 3: TIP, 1979±2770 μg/g; TIS, 1074±1182 μg/g). At baseline, more than 91.2% of TIP patients had *Pa* isolates with an MIC at least 20 times lower (64 g/mL or less) than the mean sputum concentration observed within 30 minutes of the first dosing in Cycle 1. At the end

of Cycle 3, 86.4% of TIP patients had *Pa* isolates (all phenotypes) with an MIC at least 30 times lower (64 g/mL or less) than the mean sputum concentration observed 30-minutes post-dose.

Discussion

This study demonstrates that the safety profile of a new drug-device combination of TIP delivered via the T-326 Inhaler, is similar to TIS, especially with regard to systemic safety. The results of safety analyses are supportive of previously published reports showing an acceptable safety profile for TIP, which is generally well-tolerated in most patients with CF (13, 18).

The dose of TIP (112 mg tobramycin) used in this study was chosen based on a previous study that showed it is pharmacokinetically equivalent to the licensed formulation of TIS (TOBI®) (16). In the present study, pharmacokinetic analysis confirmed that serum tobramycin concentrations were comparable for TIP and TIS post-inhalation. Importantly, systemic levels were low relative to those associated with producing toxicity with intravenous tobramycin (10-12 g/mL) (24).

AEs were similar in both groups; except for the incidence of cough, dysphonia and dysgeusia, which was higher in patients receiving TIP. Cough is a frequent event with all inhaled therapies (13). It is possible that the comparatively high powder 'payload' may underlie the higher reported cough rate in TIP-versus TIS-treated patients (as well as the local effect of dysphonia and dysgeusia). It is unclear if the high level of prior TIS use in these patients and the open-label design had an influence on the propensity to report cough as an AE for each treatment. Most cough events were mild or moderate in intensity in both groups. The frequency of cough was similar in patients using TIP, regardless of lung disease severity at baseline. While the majority of patients in the study were adults, it appeared that children and adolescents tended to cough more with TIP than adults, whereas the opposite was true for TIS. However, none of the children discontinued TIP treatment due to cough events. Cough in the absence of other AEs (i.e. cough not associated with other features suggestive of an exacerbation) led to discontinuation of five of the 308 patients randomized to TIP. Post-hoc analyses showed that cough did not appear to be related to bronchospasm; additionally, the number of patients experiencing a 20% decline in FEV_1 % predicted within 30-minutes of inhalation was similar in both groups. The incidence of SAEs was similar in TIP- and TIS-treated patients. TSQM side effect ratings showed no difference between groups, indicating that unwanted effects of TIP and TIS had a similar impact on patients' lives.

The overall discontinuation rate was higher with TIP (26.9%) than TIS (18.2%); however, there is no clear reason for the difference in discontinuation rates between groups. The main reason for discontinuation in both groups was an AE; most frequently cough and lung disorders (reported as pulmonary or CF exacerbations), although relatively few patients in either group discontinued due to cough or lung disorders.

The present study was also powered to assess the non-inferiority of TIP to TIS with regards to efficacy. The pre-planned efficacy analyses show that TIP was not inferior to TIS, in terms of maintenance of lung function. Importantly, the difference in discontinuation rates did not influence the non-inferiority conclusion, based on various sensitivity analyses. The results support those of a recent placebo-controlled trial that show TIP significantly improves lung function in CF patients (21).

In accordance with previous studies (6, 17), TIP and TIS both decreased sputum *Pa* densities (mucoid and non-mucoid phenotypes). Conversely, MICs increased from Day 1 to 28 in all 3 cycles. Exposure of bacterial populations to antibiotics may select for microbes with reduced susceptibility to these drugs over time (25). However, tobramycin susceptibility thresholds with parenteral administration might not be relevant to inhaled therapy, as drug concentrations achieved at the site of infection with inhaled antibiotics, including tobramycin, can be significantly higher than systemic concentrations (13). At the end of Cycle 3, most TIP patients (86.4%) had an MIC at least 30 times lower than the mean sputum concentration observed 30-minutes post-dose. The results of the pharmacokinetic analyses also showed that sputum concentrations were generally greater for TIP; however, the level of inter-subject variability was high, similar to previous studies. Based on these data we can conclude that TIP administration appears to result in lung exposure that is comparable to TIS.

The use of new anti-pseudomonal antibiotics was significantly greater in TIP-versus TIS-treated patients during the study. The difference does not appear to have been driven by events of a higher clinical intensity. In both groups, the majority of newly used anti-pseudomonal antibiotics were oral, with ciprofloxacin the most frequently used. These data suggest the difference is largely driven by oral ciprofloxacin use for milder events (i.e. those not needing intravenous antibiotics and/or hospitalization). It is possible that the higher incidence of cough in the TIP group may have driven the greater use of other antibiotics. Again, the influence of the open-label design cannot be excluded. Post-hoc sensitivity analyses suggest that the use of new anti-pseudomonal antibiotics did not alter the conclusion regarding the non-inferior efficacy of TIP versus TIS.

Delivery of antibiotics via inhalation is an attractive option for treating chronic lung infection in CF patients. However, aerosolized antibiotics such as TIS requires a compressor and nebulizer, and are associated with prolonged drug administration times (13). TIS is approved for use with the PARI-LC® PLUS nebulizer only, which requires 15-20 minutes to nebulize a dose. Faster nebulizers than the PARI-LC® PLUS have been developed since the approval of TIS and are available in some countries; however, they have not been adequately studied to demonstrate efficacy and safety with TIS. In the present study, administration times for TIP were approximately 14 minutes faster than TIS (excluding time required to set up, clean and disinfect the TIS nebulizer), consistent with previously reported administration times (13). This resulted in a 28 minute saving per day, equivalent to 13 hours per 4-week cycle, in addition to the reduced time required to set up and clean the T-326 Inhaler versus the PARI LC® PLUS nebulizer and compressor. Reducing administration time may have beneficial effects on adherence and clinical outcomes. The ease of use and convenience of TIP were highlighted in the treatment satisfaction responses

obtained via the TSQM. Mean patient assessments for effectiveness, convenience and global satisfaction domains were significantly greater for TIP than TIS; importantly, this difference was sustained over the course of the study. The four additional questions relating to the use and maintenance of the inhalation devices also showed a significant difference in favor of TIP.

In summary, the safety profile of TIP was comparable with the currently approved formulation of tobramycin, TIS, with the exception of cough, dysphonia and dysgeusia. Patient-reported satisfaction was significantly higher with TIP than TIS, which was related to the ease of use and convenience of TIP. Importantly, non-inferiority was demonstrated for TIP with regard to efficacy. Thus, the new drug-device combination for TIP could offer CF patients a much more convenient option for treating *Pa* infections, without compromising safety or efficacy.

Acknowledgments

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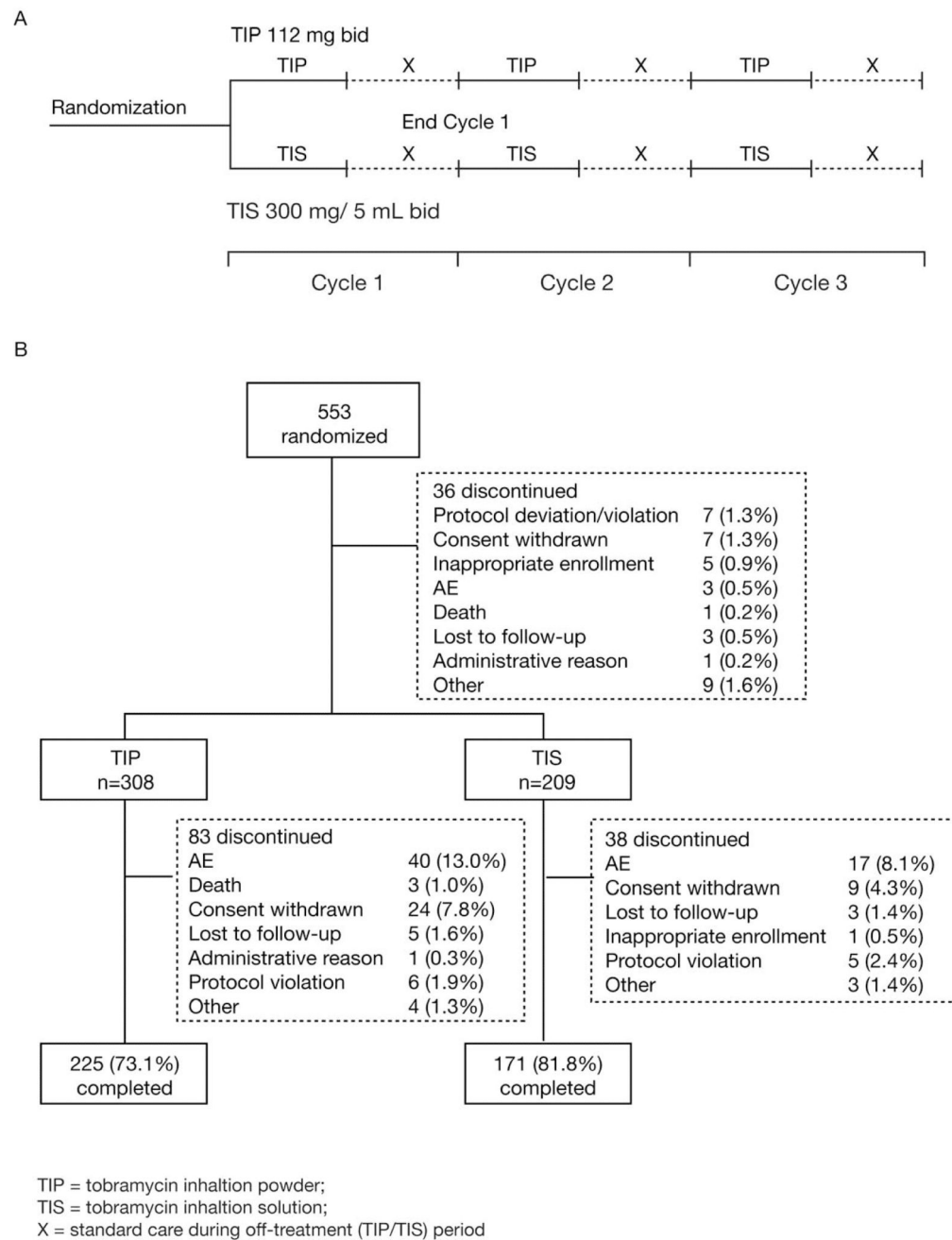
Figure 1.
Study design (A) and disposition (B).
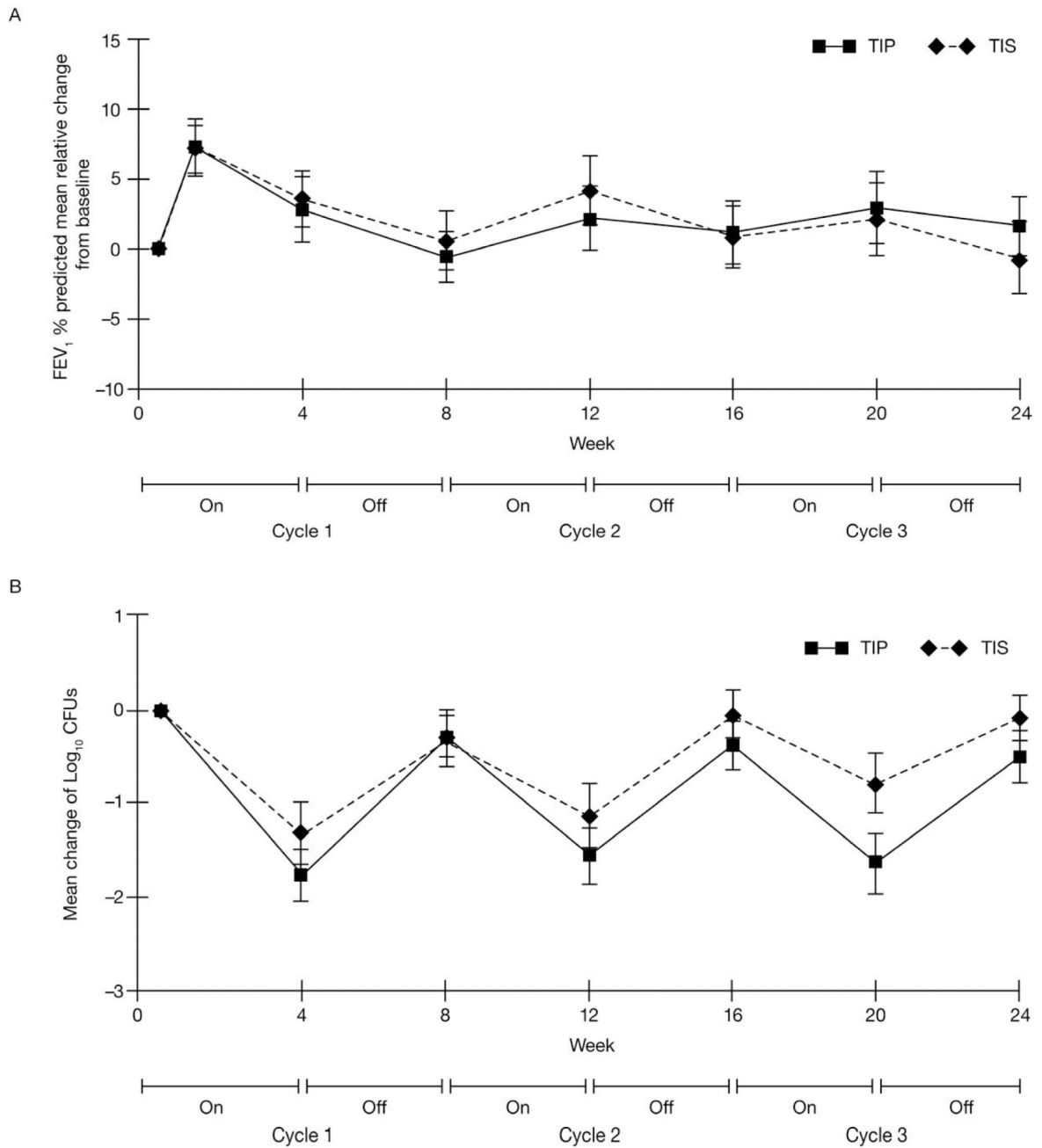
Figure 2.
Overall efficacy: A) relative change in FEV_1 % predicted from baseline over three cycles (Efficacy population); B) change from baseline in *Pseudomonas aeruginosa* sputum density (Efficacy population).

Table 1

Baseline demographic and clinical characteristics (Safety population).

	TIP (*n*=308)	TIS (*n*=209)
Age (years), mean (SD)	26 (11.4)	25 (10.2)
Age group, n (%)		
6 to <13 years	28 (9.1)	18 (8.6)
13 to <20 years	66 (21.4)	48 (23.0)
20 years	214 (69.5)	143 (68.4)
Sex, n (%)		
Males	171 (55.5)	115 (55.0)
Females	137 (44.5)	94 (45.0)
Race, n (%)		
Asian	2 (0.6)	2 (1.0)
Black	3 (1.0)	1 (0.5)
Caucasian	279 (90.6)	189 (90.4)
Hispanic	20 (6.5)	17 (8.1)
Other	4 (1.3)	0 (0.0)
Region, n (%)		
North America	195 (63.3)	131 (62.7)
Europe and rest of world[1]	104 (33.8)	71 (34.0)
Latin America	9 (2.9)	7 (3.4)
Body mass index (kg/m^2), mean (SD)	20.7 (4.0)	20.4 (3.5)
Screening FEV_1 % predicted, n (%)[2]		
25 to <50%	128 (41.6)	89 (42.6)
50 to <75%	180 (58.4)	120 (57.4)
Baseline FEV_1 % predicted, mean (SD)[2]	53 (14.2)	53 (15.9)
Chronic macrolide use, n (%)	187 (60.7)	125 (59.8)
Last use of antipseudomonal antibiotics prior to first dose (month), n (%)		
=1	78 (25.3)	46 (22.0)
>1–3	171 (55.5)	112 (53.6)
>3–6	33 (10.7)	24 (11.5)
>6	11 (3.6)	9 (4.3)
Never used	15 (4.9)	18 (8.6)
P.aeruginosa tobramycin MIC, n (%)[3]		
>8 µg/mL	68 (22.1)	48 (23.0)

[1] Rest of world including Australia and Israel

[2] Randomization is based on screen FEV_1% predicted. Baseline FEV_1 was defined as the last measurement prior to the first dose of study drug

[3] Maximum MIC of all *P. aeruginosa* phenotypes; TIP = tobramycin inhalation powder; TIS = tobramycin inhalation solution; SD = standard deviation; FEV_1 = forced expiratory volume in one second; MIC = minimum inhibitory concentration.

Table 2

Most common (5% in any group) adverse events occurring in Cycles 1–3 (Safety population).

n (%)	TIP (n=308)	TIS (n=209)
Any adverse event	278 (90.3)	176 (84.2)
Cough	149 (48.4)	65 (31.1)
Lung disorder[†]	104 (33.8)	63 (30.1)
Productive cough	56 (18.2)	41 (19.6)
Dyspnea	48 (15.6)	26 (12.4)
Pyrexia	48 (15.6)	26 (12.4)
Oropharyngeal pain	43 (14.0)	21 (10.5)
Dysphonia	42 (13.6)	8 (3.8)
Hemoptysis	40 (13.0)	26 (12.4)
Headache	35 (11.4)	25 (12.0)
Nasal congestion	25 (8.1)	15 (7.2)
Nausea	23 (7.5)	20 (9.6)
Rales	22 (7.1)	13 (6.2)
Rhinorrhea	22 (7.1)	15 (7.2)
Pulmonary function test decreased	21 (6.8)	17 (8.1)
Upper respiratory tract infection	21 (6.8)	18 (8.6)
Wheezing	21 (6.8)	13 (6.2)
Chest discomfort	20 (6.5)	6 (2.9)
Fatigue	20 (6.5)	10 (4.8)
Vomiting	19 (6.2)	12 (5.7)
Sinusitis	18 (5.8)	15 (7.2)
Pulmonary congestion	17 (5.5)	9 (4.3)

TIP = tobramycin inhalation powder; TIS = tobramycin inhalation solution.

[†]Lung disorders were generally reported by the investigator as a pulmonary or cystic fibrosis exacerbation

Table 3

Patient-reported treatment satisfaction from modified Treatment Satisfaction Questionnaire for Medication (Safety population).

	Average of LS means over visits		LS mean difference (SE)	p value
	TIP (*n*=308)	**TIS (*n*=209)**		
Effectiveness	74.8	65.4	9.36 (1.460)	<0.0001
Side effects	92.1	92.6	−0.50 (1.218)	0.6833
Convenience	82.7	58.4	24.35 (1.547)	<0.0001
Global satisfaction	76.2	71.0	5.20 (1.655)	0.0018

LS mean = least squares mean; TIP = tobramycin inhalation powder; TIS = tobramycin inhalation solution; SE = standard error. LS mean, LS mean difference (TIP–TIS), and p values are calculated from repeated measures model with treatment, baseline FEV_1 % predicted, age, chronic macrolide use, region, visit, visit-by-treatment interaction in the model. A higher score indicates higher satisfaction for that domain.