Published in final edited form as:

Curr Med Res Opin. 2013 August ; 29(8): 947–956. doi:10.1185/03007995.2013.805122.

Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial

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Abstract

Background—Tobramycin inhalation powder (TIP) was reported to be effective in two Phase III studies in patients with cystic fibrosis (CF) chronically infected with *Pseudomonas aeruginosa* (*Pa*). The EDIT study evaluated the efficacy and safety of TIP manufactured by an improved process in CF subjects aged 6–21 years.

Methods—CF patients with a forced expiratory volume in 1 second (FEV₁) 25% to 80% predicted, positive *Pa* cultures and inhaled antipseudomonal therapy naïve (or at least for past 4 months) were enrolled into this double-blind, multicenter trial. Patients were randomized to receive TIP or placebo (1:1) twice daily for one treatment cycle (28.5 days on drug, 28 days off drug). The primary endpoint was relative change in forced expiratory volume in 1 second (FEV₁) % predicted from baseline to Day 29. A pre-specified sensitivity analysis evaluated absolute change in FEV₁ % predicted. Other endpoints included *Pa* sputum density and safety.

Results—A total of 62 patients out of a target of 100 (mean age 12.9 years, baseline FEV₁ 59.2% predicted, *Pa* sputum density 7.4 log₁₀ colony forming units [CFU]) per gram were randomized. Mean treatment differences (TIP–placebo) were 5.9% (*p*=0.148) and 4.4% (*p*<0.05) for relative and absolute change in FEV₁ % predicted respectively. TIP significantly reduced *Pa* sputum density by –1.2 log₁₀ CFU (*p*=0.002). Treatment with TIP was well tolerated.

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Declaration of financial/other interests:

AGC and IG received reimbursement from Novartis to cover their costs as clinical investigators for this study. MWK has consulting relationships with Aradigm, CSL-Behring, Genentech, GlaxoSmithKline, KaloBios, Gilead Sciences, Inmed, Novartis Pharmaceuticals and Vertex Pharmaceuticals.

GA, FB and MH are employees of Novartis. SP and KT were employees of Novartis at the time this study was conducted. CMRO Peer Reviewers on this manuscript have received honoraria for their review work, but have no other relevant financial relationships to disclose.

Previously presented at: The 35th European Cystic Fibrosis Conference, Dublin, Ireland, 6–9 June 2012. Abstract publication: Galeva I, Konstan MW, Higgins M, Piggott S, Angyalosi G, Brockhaus F, Thomas K, Chuchalin AG. A challenging double-blind, placebo-controlled study of tobramycin inhalation powder in cystic fibrosis: results of the EDIT trial. *J Cyst Fibros* 2012;11(suppl 1):S12

Conclusions—Relative change in FEV₁ % predicted with TIP treatment was in the expected range based on the literature, but did not reach statistical significance versus placebo. Placebo control and use of treatment naïve patients led to significant recruitment challenges and an underpowered study with consequent impact on the generated data. However, significant improvements in other outcomes including absolute change in FEV₁ % predicted and reduction in *Pa* sputum density indicate that TIP is efficacious and well tolerated in CF patients.

Keywords

cystic fibrosis; tobramycin; inhalation therapy; dry powder inhaler; pseudomonas lung infection

Introduction

Cystic fibrosis (CF) affects an estimated 80,000 children and young adults worldwide¹. Chronic endobronchial infections, particularly with *Pseudomonas aeruginosa* (*Pa*), contribute to accelerated progressive obstructive disease which leads to major morbidity, reduced quality of life and, ultimately, mortality^{2,3}.

Tobramycin solution for inhalation (TIS [TOBI®]) 300 mg twice daily delivered via nebulizer has been reported to significantly improve lung function⁴, suppress *Pa*^{5,6}, reduce hospitalization rates⁷ and improve quality of life⁸ in CF patients chronically infected with *Pa*. However, administration of TIS is time consuming, and its use may be subject to limited patient adherence^{9,10}.

Tobramycin inhalation powder (TIP™)[†] consists of light porous particles that, as part of a novel drug/device combination, has been designed to improve ease of use compared with TIS. Easier and faster administration may improve adherence which could in turn improve outcomes in clinical practice^{11,12}. TIP has been reported to have a safety and efficacy profile similar to TIS but with significantly higher patient-reported scores for effectiveness, convenience and global satisfaction¹³.

To produce TIP consistently on a commercial scale it was necessary to make minor improvements to the manufacturing process. The droplet size of the feedstock was reduced and the design of the powder collection hardware was changed in order to improve the stability, consistency and yield from the manufactured batches. The qualitative and quantitative composition of TIP was not altered, nor was the device. The aerosol performance of TIP was not impacted by these improvements. The EDIT (Establish tobramycin Dry powder efficacy in cystic fibrosis) trial was conducted to evaluate the efficacy of TIP produced with the improved manufacturing process.

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Methods

Patients

Included patients were males and females aged 6–21 years with a diagnosis of CF, confirmed by at least one clinical feature of CF plus sweat chloride test > 60 mEq/L, known mutations in each cystic fibrosis transmembrane conductance regulator (CFTR) gene or abnormal nasal transepithelial potential difference (characteristic of CF). Patients were required to have a forced expiratory volume in 1 second (FEV₁) at screening $\geq 25\%$ and $\geq 80\%$ of normal predicted values for age, sex and height (Knudson criteria¹⁴). Eligible patients were also required to have a positive sputum or throat culture for *Pa* within 6 months of screening, and a positive sputum culture for *Pa* at the screening visit.

Patients were excluded if they had received any previous exposure to TIP; any inhaled antipseudomonal antibiotics within 4 months prior to screening, any systemic antipseudomonal antibiotics within 28 days prior to study drug administration, or loop diuretics within 7 days of first study drug administration; positive cultures for *Burkholderia cepacia* within 2 years prior to screening or at screening; hemoptysis > 60 mL at any time within 30 days of study drug administration; aminoglycoside hypersensitivity or adverse reaction to inhaled antibiotics; serum creatinine ≥ 2 mg/dL, blood urea nitrogen ≥ 40 mg/dL, or abnormal urinalysis ($\geq 2+$ proteinuria). The Supplementary Appendix provides full details of inclusion and exclusion criteria.

All patients enrolled were permitted to continue the standard care regimen they were receiving prior to enrolling in the study (e.g. bronchodilators, chronic macrolide antibiotics, inhaled hypertonic saline, dornase alfa, inhaled steroids and physiotherapy) provided these were started at least 28 days prior to study drug administration and remained stable throughout the study. Use of oxygen, nutritional supplements, and enzymes was unrestricted at all times. If patients required treatment with antipseudomonal antibiotics other than study drug for signs and/or symptoms of a pulmonary exacerbation, they were required to withdraw from the study.

The study was approved by an Institutional Review Board or Independent Ethics Committee for each center and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient or their legal representative (with the child's assent as appropriate) before randomization.

Study design

This was a double-blind, placebo-controlled, 1:1 randomized, Phase III study conducted in 17 centers in eight countries between June 2009 and May 2011. Following a 7-day screening period, patients received one cycle of treatment (28.5 days on [up to morning dose of Day 29] followed by 28 days off). Patients were randomized to receive TIP (112 mg tobramycin) or placebo twice daily, as capsules administered via the T-326 dry powder inhaler (Novartis Pharmaceuticals, San Carlos, CA, USA). This drug-device combination is currently authorized for use and marketed in the US, Canada, Europe, and several Latin American countries. Eligible patients were assisted and supervised by an independent study

coordinator during their first inhalation (additional information on device training can be found in the Supplementary Appendix).

Patients were randomized using a validated automated system (see Supplementary Appendix) and stratified by age and screening FEV₁ (% predicted). Blinding was maintained through matched packaging, labeling, schedule of administration and outer appearance of drug and device.

All patients completing the study could continue in two successive, open-label, single-arm extension studies, each comprising three cycles of TIP, thus allowing all patients access to active therapy. Further, in appropriate countries, subjects could have on-going access to inhaled tobramycin, e.g. through a patient access program upon completion of the trial.

Objectives, endpoints and assessments

The primary objective was to evaluate relative change in FEV₁ % predicted from baseline to Day 29 (TIP–placebo), where relative change was defined as $100 \times (\text{Day 29} - \text{baseline}) / \text{baseline}$. A pre-planned sensitivity analysis evaluated absolute FEV₁ % predicted change from baseline to Day 29. During each visit, lung function was measured using at least three acceptable forced expiratory maneuvers¹⁵. Spirometry data was transferred to a central site where an over-read review was conducted (see Supplementary Appendix) to ensure inclusion only of acceptable data where quality standards were met.

Secondary efficacy endpoints included: relative change in forced vital capacity (FVC) % predicted and forced expiratory flow (FEF)_{25–75} % predicted from baseline to Day 29; change from baseline in sputum density of *Pa* (log₁₀ colony forming units [CFUs] per gram sputum); rates of antipseudomonal antibiotic use and hospitalizations due to respiratory events. Sputum and serum samples were obtained on Days 1 and 29 for pharmacokinetic (PK) analyses.

Safety assessments included the incidence and severity of all adverse events (AEs) and serious AEs (SAEs) and regular monitoring of hematology, blood chemistry and urine protein, vital signs, physical condition and body weight. The Supplementary Appendix provides additional details of PK and safety assessments.

Statistical analysis

A sample size of 100 patients (50 per group) was estimated to provide 90% power to detect a treatment difference of 11% in mean relative change of FEV₁ % predicted from baseline (last measurement prior to first dose of study medication) to Day 29 (following completion of on-treatment period) at a 2-sided 5% significance level, assuming a standard deviation of 16% and drop-out rate <10%. These percentage change values were chosen based on a previously completed phase III trial (EVOLVE) with a very similar study protocol.¹⁶ An analysis of variance (ANOVA) model was used¹⁷, including screening FEV₁ (< 50 and 50% predicted) and age (< 13 and ≥ 13 years) as factors.

Pre-specified analyses—All efficacy analyses were performed on the intention-to-treat (ITT) population (all randomized patients who received at least one dose of study drug).

Missing Day 29 values were imputed with discontinuation visit measurement or the baseline value (hence change from baseline was 0) if no valid post-baseline measurement existed. Supportive analysis was also performed on the observed cases population, which excluded all patients with missing data at Day 29. A Bayesian analysis¹⁸ was performed using historical placebo information from three previous studies on TIP and TIS^{4,8,16} in which recruited patient populations were similar to the current study population. A further pre-planned analysis of absolute change from baseline to Day 29 in FEV₁ % predicted was evaluated for ITT and observed cases populations.

Relative changes in FVC and FEF_{25–75} % predicted and absolute change in sputum density of *Pa* from baseline to Day 29 were analyzed for the ITT population using the same ANOVA model as the primary endpoint¹⁷ with supportive analyses on the observed population also performed. Other endpoints were summarized with descriptive statistics.

All safety analyses were performed using the safety population (all randomized patients who received at least one dose of study drug) according to treatment received.

Post-hoc analyses—To provide further insight into the data, several post-hoc analyses were performed. A modified ITT population was defined, including discontinued patients (imputed with 0 change from baseline) but excluding patients with technically unacceptable FEV₁ measurements at Day 29 (assessed by the centralized over-read).

PK analysis post-database lock revealed that study drug had been mis-dispensed to two patients who received placebo instead of TIP. Efficacy assessments were analyzed on the basis of randomization but sensitivity analyses were performed for the primary endpoint and antipseudomonal antibiotic use based on actual treatment received. All safety and PK concentration data were also re-analyzed. Additional sensitivity analyses excluding a patient identified as an outlier based on PK values and FEV₁ were also performed.

Results

Recruitment

Despite extensive recruitment efforts over 20 months, considerably longer than planned, a limited number of eligible patients could be identified (Table S1). Reasons included the widespread use of inhaled tobramycin, ethical approval to participate in some countries because of the placebo-controlled design and a lack of infrastructure to carry out clinical trials to ensure Good Clinical Practice in others. Recruitment was closed once all options had been exhausted and the maximum feasible recruitment had been achieved (62 patients enrolled vs a target of 100).

Patients

Of 103 screened patients, 62 were randomized (Figure 1) from eight countries (Bulgaria, Estonia, Latvia, Lithuania, Romania, Russia, Egypt, and India). The most common reasons for failing screening at the baseline visit were *Pa* not isolated or FEV₁ % predicted values outside the prespecified inclusion/exclusion criteria.

All randomized patients received at least one dose of study medication and were included in the safety population. Based on the centralized quality over-read, three patients had no acceptable screening or baseline spirometry values (one receiving TIP, two receiving placebo) and were excluded from all change from baseline analyses of spirometry. In addition, seven patients had missing or unacceptable spirometry data at Day 29 but were unbalanced between groups (six TIP vs one placebo patient [ITT population], five TIP vs two placebo patients [safety population]). All seven patients were imputed with 0 in the primary analysis as none had post-baseline values to carry forward and were excluded from the observed-cases population.

Three TIP patients had major protocol violations. Two were mis-dispensed placebo instead of active treatment (and were therefore allocated to the placebo group for analysis of safety). One of these patients discontinued early due to an exacerbation of chronic bronchitis. The final patient did not fulfil the study inclusion criteria.

Overall, baseline demographic and clinical characteristics were similar in the two treatment groups (Table 1). The TIP group had a higher proportion of female patients (70.0% vs 59.4%) and $FEV_1 < 50\%$ predicted (23.3% vs 12.5%). All 62 patients in this study received concomitant therapies on or after start of study drug. The most frequently used medications included mucolytics, pancreatic enzyme preparations (by more than 70% patients), and selective β_2 -adrenoreceptor agonists. Rates of macrolide use were similar but the use of other classes of medication tended to be lower in the TIP group than in the placebo group.

Completion rates were 90.6% for TIP (including one who received placebo in error) and 100% for placebo. Compliance was high and similar for both groups (97.8% and 100.0% for the TIP and placebo randomized populations, respectively).

Efficacy

Spirometry—The treatment difference (least squares mean) in mean relative change in FEV_1 % predicted was 5.9% (95% confidence interval [CI]: -2.2, 14.0; $p=0.148$) in the ITT population and 7.9% -1.2, 16.9; $p=0.086$) in the pre-specified observed cases population (Table 2). A Bayesian analysis demonstrated statistically significant differences in the pre-specified observed cases population ($p=0.017$, equivalent to 2-sided p value of 0.034; [Table S2]). The treatment difference for absolute change in FEV_1 % predicted was 4.4% (95% CI: 0.0, 8.8; $p<0.05$, Table 2).

In the post-hoc mITT population (excluding patients with technically unacceptable FEV_1 measurements at Day 29) treatment differences of 7.1% ($p=0.107$) and 5.1% ($p=0.035$) for relative and absolute change in FEV_1 % predicted respectively were obtained.

A 7-year-old male (body mass index 9 kg/m², baseline FEV_1 0.355 L [33% predicted]) receiving TIP had an outlying response of -37% relative change from baseline in FEV_1 % predicted, and low tobramycin exposures in sputum and serum samples (see Figure S1 and Supplementary Appendix). Excluding this outlier (post-hoc), treatment differences in relative change in FEV_1 % predicted ranged from 7.3% ($p=0.058$) to 9.8% ($p=0.023$) depending on the analysis population (Table 2).

A further post-hoc analysis based on actual treatment received demonstrated treatment differences between TIP and placebo of 6.7% ($p=0.098$) for the ITT and 8.8% ($p=0.056$) for the observed-cases populations. Similarly, treatment effects of 8.3% ($p=0.03$) and 10.9% ($p=0.011$) were obtained for ITT and observed cases populations respectively for analyses based on actual treatment received excluding the outlier. Numerical improvements in FVC % predicted and FEF_{25–75} % predicted were observed for TIP compared with placebo (Table 3).

Microbiology—Sputum density of *Pa* (sum of all biotypes) showed a mean absolute decrease of 1.2 log₁₀ CFU with TIP versus no change with placebo (treatment differences of -1.2 [$-1.9, -0.5$], $p=0.002$ [ITT, Table 3]; -2.4 [$-3.2, -1.5$], $p<0.001$ [observed cases]).

Proportions of patients achieving particular thresholds for reductions in *Pa* sputum density were consistently higher for TIP than placebo (Figure 2). Clearance rates for *Pa* were significantly higher with TIP than placebo (41.4% vs 0% at Day 29).

Antipseudomonal antibiotic use and hospitalizations—Three patients in each group (based on ITT population) reported new antipseudomonal antibiotic use although the average number of days of use was numerically lower for TIP patients than placebo (mean [standard deviation]: 8.3 [7.5] vs 13.0 [2.7] days). Based on actual treatment received, two (6.7%) TIP versus four (12.5%) placebo patients used new antipseudomonal antibiotics, or one (3.3%) TIP versus four (12.5%) placebo patients, excluding the data from one patient who had preplanned prophylactic IV antibiotics. Hospitalization due to respiratory events occurred in only one patient (placebo arm).

Pharmacokinetics

Mean trough and peak serum concentrations of tobramycin after TIP administration at the end of the 4-week treatment cycle were 0.41 µg/mL and 1.48 µg/mL respectively (based on treatment received). The highest individual observed tobramycin concentration was 3.39 µg/mL, measured 0–1 hours post-dose, at the end of the cycle. Mean maximum sputum concentrations of tobramycin were 1,140 and 1,739 µg/g at Days 1 and 29 respectively.

Safety

AEs occurred in eight (26.7%) TIP-treated and 11 (34.4%) placebo patients; all were mild to moderate in severity. The most common single AEs for TIP were cough and hypoacusis, each reported in 3 [10%] patients. By comparison, cough was not observed in patients receiving placebo, while incidence of hypoacusis was similar (seen in 2 [6.3%] patients) (Table S3). Taken together, there were fewer infections in TIP-treated patients (3 [10.0%] vs 8 [25.0%]), but more respiratory, thoracic and mediastinal disorders (4 [13.3%] vs 1 [3.1%]). Drug-related AEs occurred in five (16.7%) TIP-treated patients and two (6.3%) placebo patients. The difference was mainly accounted for by cough, suspected to be study-drug related for all three patients receiving TIP.

SAEs were reported by two patients receiving placebo (one with a fracture of the lower limb, the other with pneumonia). Neither was suspected to be study drug related or led to

discontinuation from the study. Two patients experienced AEs resulting in permanent study drug discontinuation, one due to bronchitis (placebo) and the other to pulmonary hemorrhage (TIP). Both were suspected to be study-drug related by the investigator. No major differences in any hematology, renal or biochemistry variables or acuity were observed.

Discussion

In the current study a treatment difference of 5.9% relative change from baseline in FEV₁ % predicted was observed for TIP vs placebo. While this did not achieve statistical significance ($p=0.148$) there were consistent numerical improvements in pre-specified sensitivity analyses, some of which were statistically significant. For absolute change in FEV₁ % predicted there was a 4.4% treatment difference between TIP and placebo ($p<0.05$).

This study was underpowered, despite every effort to recruit patients. The study design included placebo to enable a blinded comparison, and enrollment of patients who were antipseudomonal antibiotic-naïve and with FEV₁ < 80% predicted provided the best opportunity of demonstrating a positive treatment effect.⁷ To address possible ethical concerns of withholding treatment known to be effective (in patients randomized to placebo), the single-cycle design was established to demonstrate efficacy in the smallest possible number of patients for a short duration of time. No patient had active therapy withdrawn (since they had not received inhaled antipseudomonal therapy for 4 months) and all had enduring access to current treatment. Ultimately, however, patients could be enrolled into this study only where there was no, or very limited, access to inhaled antipseudomonal antibiotics due to the local healthcare situation, thus severely restricting the pool of eligible patients.

Interpretation of the primary endpoint should take several factors into account including the unavoidably smaller than planned sample size; a single outlier; the impact of the imputation scheme given the imbalance in missing data; and the mis-dispensation of study drug.

Firstly, an outlier patient showed an abnormally low treatment response compared with mean population values, despite no indicators such as recorded AEs or additional antibiotic use to suggest that a severe exacerbation occurred for this patient during the study. The use of relative versus absolute change from baseline may have exaggerated more extreme changes in the data, especially for patients with more advanced lung disease, and exacerbated the impact of this outlier.

Secondly, there was an unexpected imbalance between treatment groups in patients with missing data and so imputed with 0. Hence, the observed cases analysis, which excluded these missing values, may provide a more appropriate comparison. Indeed, observed data were used in an earlier placebo-controlled Phase III study¹⁷ in which statistical significance for change in FEV₁ (TIP–placebo) was reported. Thirdly, while the ITT principle was maintained for the efficacy analyses, two patients wrongly received placebo instead of TIP due to investigator error. This was confirmed by the PK findings post-database lock.

In addition, the placebo effect observed in this study was higher than previous inhaled tobramycin studies. The reason for this is not clear, but the close and frequent follow-up may be of overall benefit to patients. Compliance with patients' standard regimen (pancreatic enzymes, bronchodilators, etc) may also improve by being part of the study. However, the imbalance in concomitant medications such as pancreatic enzymes, macrolides, hypertonic saline and bronchodilators between treatment groups may also have influenced the results.

Despite these factors, the numerical improvements in FEV₁ % predicted reported in the current study were within the expected range (increased by 6.8–10%)^{4,19} for inhaled tobramycin observed in previous placebo-controlled trials^{4,8,19} and in patient populations with similar baseline characteristics¹⁶ and similar to those judged clinically acceptable for other CF treatments such as DNase and azithromycin^{20,21}.

PK data were consistent with previous successful TIP and TIS studies^{13,16} with sputum concentrations in excess (18–27-fold) of the observed maximum *Pa* isolates minimum inhibitory concentration. The T-326 Inhaler has a measured resistance of 0.079 cm H₂O^{0.5} LPM⁻¹ and was developed to ensure patients could generate adequate inspiratory flow for optimal medication dispersal.¹² Studies in addition to this one have shown the T-326 Inhaler to be successfully used by children as young as 6 years of age with varying disease severities.^{13,16} Pulmonary deposition data for TIP administration via the T-326 Inhaler have been published elsewhere.¹² The TIP particle size is 1–5 µm, reducing the likelihood of oropharyngeal deposition. Lung deposition is 34.2±17% of the starting dose, as compared to nebulized tobramycin (9.2±24%).¹²

TIP also significantly reduced the density of sputum *Pa* by 1.2 log₁₀ CFU at Day 29 compared with placebo (*p*=0.002) in the ITT population, but by 2.4 log₁₀ CFU (*p*<0.001) in the observed cases population which excluded patients with missing data at Day 29. These data are in agreement with significant reductions observed in previous clinical studies of TIP (a decrease of 1.91 and 2.61 log₁₀ CFU/g for non-mucoid and mucoid *Pa* compared to a decrease of 0.15 and 0.43 log₁₀ CFU/g respectively with placebo¹⁶) and TIS (a decrease of 0.8 log₁₀ CFU/g compared to an increase of 0.3 log₁₀ CFU/g with placebo⁴), which were also based on observed cases analyses^{4,8,16}. This result can be considered as clinically important for an antibiotic indicated for the treatment of chronic *Pa* infection in CF. The reasons for achieving statistical significant results with TIP for reduction in *Pa* sputum density while significance for change in FEV₁ was not consistently demonstrated are not fully understood, but may reflect not only the small sample size but also inherent differences in variability of these assessments. Further, relative changes in FEV₁ may not wholly reflect the impact of a therapy on the patient.

Overall, treatment with TIP was well tolerated in our study population. The greater prevalence of respiratory, thoracic and mediastinal disorders among TIP-treated patients is likely to be associated with local tolerability AEs of cough, dysphonia and dysgeusia. The reported cough rate for TIP of 10% was relatively low and the observed safety profile was consistent with previous Phase III trials^{13,16}.

Our study was limited by the number of patients feasible to recruit. The significant operational challenges we encountered have important consequences for similar future clinical trials investigating new formulations of established treatments and suggest the need to investigate different methodologies that avoid a placebo arm.²³ New ideas, knowledge and skills should be shared among the CF community to allow the successful completion of such trials in the future. In addition, observational studies without the strict inclusion criteria required for randomized controlled trials may provide greater insight into the effectiveness of therapies for CF across the full range of patients encountered in clinical practice.

Conclusions

In this unavoidably under-recruited study, relative change in FEV₁ % predicted with TIP did not achieve statistical significance compared with placebo. However, significant improvements in absolute change in FEV₁ % predicted and reductions in *Pa* sputum density were observed, which were comparable in magnitude to those reported in previous TIP studies. In addition, this study demonstrates that TIP has an acceptable safety profile when used to treat *Pa* infections in patients with CF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Transparency

Declaration of funding:

The study was sponsored by Novartis Pharma AG.

Role of the funding source:

This manufacturer of tobramycin, Novartis, was responsible for the design of the study and analysis of the data and, in collaboration with the other authors, was involved in interpretation and presentation of the data for this report.

The authors were assisted in the preparation of the manuscript by Mary Sayers, professional medical writer contracted to CircleScience (Macclesfield, UK), and Mark Fedele (Novartis). Writing support was funded by the study sponsor.

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Figure 1.

Patient disposition.

ITT = intention-to-treat, TIP = tobramycin inhalation powder.

* More than one reason could be given for discontinuing from screened period.

Unacceptable laboratory values = laboratory values falling outside inclusion/exclusion criteria, including *Pseudomonas aeruginosa* not isolated or *Burkholderia cepacia* detected; unacceptable test results = spirometry values falling outside inclusion/exclusion criteria, including percent predicted FEV₁ >80% or deviation by 10% from FEV₁ measured at screening

† Two patients in TIP group were misallocated study treatment and received placebo, therefore ITT and safety populations are different.

‡ Includes one patient randomized to TIP who received placebo and discontinued due to an adverse event of bronchitis.

Figure 2.
Proportion of patients achieving reductions in *Pa* sputum density at Day 29.
CFU = colony forming units, TIP = tobramycin inhalation powder.

Table 1

Baseline demographic and clinical characteristics (all randomized safety population).

	TIP (n=30)	Placebo (n=32)
Age, years: mean (SD)	12.9 (4.3)	12.9 (4.7)
Age group, n (%)		
< 13 years	15 (50.0)	15 (46.9)
13 years	15 (50.0)	17 (53.1)
Female sex, n (%)	21 (70.0)	19 (59.4)
Race, n (%)		
Caucasian	29 (96.7)	32 (100.0)
Asian	1 (3.3)	0 (0.0)
Weight, kg		
Mean (SD)	34.6 (13.6)	36.2 (15.2)
25 th , 50 th , 75 th percentiles	24.0, 32.3, 47.0	21.9, 32.8, 48.5
Height, cm		
Mean (SD)	143.5 (17.5)	145.5 (22.1)
25 th , 50 th , 75 th percentiles	130.0, 141.5, 159.0	123.0, 151.0, 160.5
Body mass index, kg/m ²		
Mean (SD)	16.1 (3.3)	16.4 (3.4)
25 th , 50 th , 75 th percentiles	13.8, 15.5, 18.8	13.8, 16.3, 17.7
Screening FEV ₁ % predicted: mean (SD) *	61.8 (17.5)	63.1 (18.7)
Screening FEV ₁ % predicted, n (%)		
25% – < 50%	7 (23.3)	4 (12.5)
50% – 80%	17 (56.7)	19 (59.4)
< 25% or > 80%	1 (3.3)	2 (6.3)
Missing [†]	5 (16.7)	7 (21.9)
Baseline FEV ₁ % predicted: mean (SD) [‡]	59.1 (18.2)	59.3 (16.6)
Baseline <i>Pa</i> sputum density, log ₁₀ (CFU): mean (SD) [§]	7.4 (1.5)	7.4 (1.6)
Baseline <i>Pa</i> tobramycin MIC, n (%)		
>8 µg/mL	1 (3.3)	3 (9.4)
Concomitant medications or therapies at study start, n (%) [¶]		
Mucolytics	24 (80.0)	26 (81.3)
Enzyme preparations	21 (70.0)	29 (90.6)
Selective β ₂ -adrenoreceptor agonists	5 (16.7)	13 (40.6)
Macrolides	5 (16.7)	10 (31.3)
Sodium chloride	4 (13.3)	8 (25.0)

TIP = tobramycin inhalation powder, SD = standard deviation, FEV₁ = forced expiratory volume in one second, *Pa* = *Pseudomonas aeruginosa*, CFU = colony forming unit, MIC = minimum inhibitory concentration.

* Mean screening FEV₁ % predicted (SD) in the intention-to-treat (as randomized) population was 60.2 (18.88) for TIP and 64.8 (16.88) for placebo.

[†]Any values that are listed as missing can include data that was captured but identified as unacceptable.

[‡]Baseline FEV₁ was defined as the last measurement prior to the first dose of study drug.

[§]Overall density, defined as the sum of biotypes (mucoid, dry and small colony variant).

[¶]One patient in the placebo group had sodium chloride (hypertonic saline) added during the study and was a protocol violator

Table 2

Relative and absolute change from baseline in % predicted FEV₁ to Day 29 in ITT, mITT and observed cases populations (TIP–placebo).

Analysis populations							
Pre-specified				Post-hoc			
	ITT		Observed cases		mITT		
	Mean change from baseline (SE)	Treatment difference, LSM (95% CI)	Mean change from baseline (SE)	Treatment difference, LSM (95% CI)	Mean change from baseline (SE)	Treatment difference, LSM (95% CI)	
Relative change from baseline to Day 29							
Analysed as randomized	TIP	8.2 (2.9)	5.9	10.3 (3.4)	7.9	9.7 (3.3)	7.1
	Placebo	2.3 (3.1)	(-2.2, 14.0)	2.4 (3.4)	(-1.2, 16.9)	2.5 (3.3)	(-1.6, 15.9)
			0.148		0.086		0.107
Post-hoc							
Excluding outlier	TIP	10.4 (2.8)	7.3	13.1 (3.3)	9.8	12.4 (3.1)	8.9
	Placebo	3.1 (2.9)	(-0.3, 14.8)	3.4 (3.1)	(1.4, 18.1)	3.5 (3.1)	(0.8, 17.0)
As treated†	TIP	8.8 (3.0)	6.7	11.1 (3.5)	8.8	10.6 (3.4)	8.2
	Placebo	2.1 (3.0)	(-1.3, 14.7)	2.3 (3.2)	(-0.2, 17.8)	2.4 (3.2)	(-0.5, 16.9)
			0.058		0.023		0.032
			0.098		0.056		0.064
			(-1.3, 14.7)		(-0.2, 17.8)		(-0.5, 16.9)
Absolute change from baseline to Day 29							
Analysed as randomized	TIP	4.9 (1.6)	4.4	6.1 (1.8)	5.6	5.7 (1.8)	5.1
	Placebo	0.5 (1.7)	(0.0, 8.8)	0.5 (1.8)	(0.7, 10.5)	0.6 (1.8)	(0.4, 9.8)
			0.050*		0.025		0.035
Post-hoc							
Excluding outlier	TIP	5.6 (1.6)	4.9	7.1 (1.9)	6.3	6.7 (1.8)	5.8
	Placebo	0.8 (1.7)	(0.6, 9.2)	0.9 (1.8)	(1.5, 11.1)	0.9 (1.7)	(1.1, 10.4)
As treated†	TIP	5.2 (1.6)	4.8	6.6 (1.9)	6.0	6.3 (1.8)	5.6
	Placebo	0.5 (1.6)	(0.4, 9.1)	0.5 (1.7)	(1.2, 10.9)	0.6 (1.7)	(1.0, 10.3)
			0.028		0.011		0.016
			0.032		0.016		0.019
			(0.4, 9.1)		(1.2, 10.9)		(1.0, 10.3)

FEV₁ = forced expiratory volume in 1 second, ITT = intention-to-treat, mITT = modified ITT, TIP = tobramycin inhalation powder, SE = standard error, LSM = least squares mean, CI = confidence intervals.

* Actual *p* value = 0.0496.

[†] All other data are as randomized i.e. include the two patients randomized to TIP but who received placebo in error.

Table 3

Change of secondary efficacy variables from baseline to Day 29.

Treatment	Treatment difference (TIP-placebo)			
	n	Mean change from baseline ^a (SE)	Mean* (SE)	95% CI p value
FVC % predicted				
TIP	31	5.8 (2.3)		
Placebo	28	1.6 (2.5)	4.2 (3.2)	(-2.2, 10.6) 0.196
FEF ₂₅₋₇₅ % predicted				
TIP	31	16.5 (5.9)		
Placebo	28	6.7 (6.3)	9.8 (8.1)	(-6.4, 26.0) 0.231
Pa sputum density (log ₁₀ CFU) ^b				
TIP	29	-1.2 (0.3)		
Placebo	26	0.0 (0.3)	-1.2 (0.4)	(-1.9, -0.5) 0.002

TIP = tobramycin inhalation powder; SE = standard error of the mean; Mean = least squares mean; CI = confidence intervals; FVC = forced vital capacity; FEF = forced expiratory flow; Pa = *Pseudomonas aeruginosa*; CFU = colony forming unit.

NB. These data include the 2 patients randomized to TIP but who received placebo in error.

* Mean = least squares mean

^a Model: response = treatment + screening FEF₁ % predicted (<50 and 50) + age (<13 and 13) + error. Response is percentage change for FVC and FEF, and absolute change for sputum density.

^b Pa sputum density refers to overall density (sum of all biotypes: mucoid, dry and small colony variant).