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Tobramycin Inhalation Powder in Cystic Fibrosis Patients: Response by Age Group

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Abstract

Background: Tobramycin powder for inhalation (TIP™) is a drug–device combination designed to reduce treatment times and improve ease of use compared with tobramycin inhalation solution (TIS) in cystic fibrosis (CF) patients. However, the ability of patients to use dry powder inhalers, as well as efficacy of CF treatments, may vary by age.

Methods: EAGER was a randomized, 24-week, multi-center, open-label, parallel-group study designed to evaluate the safety of TIP versus TIS in 553 patients with CF and *Pa* infection aged ≥6 years. The main efficacy endpoint was forced expiratory volume in 1 second (FEV_1) % predicted at Week 20 (end of third cycle of treatment). A post-hoc analysis was undertaken in 517 patients who took ≥1 dose of study medication, to evaluate the relative efficacy and safety of TIP and TIS by age group (≥6 to <13 years: children [*n* = 46], ≥13 to <20 years: adolescents [*n* = 114], and ≥20 years: adults [*n* = 357]).

Results: Improvements in FEV_1 % predicted from baseline to end of Cycle 3 were greatest in children for both TIP and TIS. Treatment differences (TIP–TIS, 85% confidence intervals) were 4.7% (–1.2, 10.6), 3.7% (–0.1, 7.5), and –0.8% (–3.1, 1.5) in children, adolescents, and adults respectively. Sputum *Pa* density decreased from baseline with both treatments, with comparable treatment differences across age group after 3 cycles (children –0.93 [–2.4, 0.5]), adolescents –0.17 [–1.2, 0.8], and adults –0.89 [–1.3, –0.4]). Overall, patient satisfaction scores were greater in all patients with TIP, irrespective of age group. With the exception of cough and dysphonia, the safety profile of TIP was comparable to TIS irrespective of age.

Conclusions: TIP is comparable to TIS in efficacy outcomes and safety profile but leads to greater patient satisfaction across all age groups of patients.

Keywords: cystic fibrosis, topical anti-infective agents, tobramycin inhalation powder, *Pseudomonas aeruginosa*, age groups, drug delivery systems

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Introduction

Current treatment guidelines for cystic fibrosis (CF) recommend that patients with *Pseudomonas aeruginosa* (*Pa)* infection receive inhaled anti-pseudomonal antibiotic therapy, either as an important part of early eradication strategies,[1] or for long-term treatment of chronic *Pa* infection, to preserve lung function and decrease the need for additional intravenous antibiotics.[2] Until recently, the only approved inhaled antibiotics for patients with CF were nebulized solutions of tobramycin or aztreonam, which can be time-consuming to administer, a factor that may be associated with poor adherence to therapy.[3–5] In turn, poor adherence may have a detrimental impact on outcomes in CF.[6,7]

Nebulized tobramycin solution for inhalation (TIS) has been shown to significantly improve lung function and reduce morbidity and mortality in patients with CF and *Pa* infection.[8–11] However, administration time is approximately 20 minutes per dose (twice per day), excluding the time required to clean and disinfect the nebulizer,[12] which may adversely impact adherence.[5]

Tobramycin inhalation powder (TIP™) is a novel drug–device combination designed to reduce the overall time of administration and treatment burden for CF patients which results in better adherence to the medication compared with TIS.[13] TIP delivers light, porous, engineered particles via the portable T-326 dry powder inhaler.[14] The inhaler has low airflow resistance, which allows patients to generate high inspiratory rates and achieve reliable dose delivery. In studies in both healthy volunteers and patients with CF, TIP had a similar pharmacokinetic profile to TIS, but resulted in a more efficient and rapid delivery of tobramycin to the lungs.[14–16] However, effective use of dry powder inhalers among patients with chronic

respiratory diseases can be affected by factors such as age and disease severity.[17,18] Therefore, it is important to confirm that the observed pharmacokinetic profile of TIP translates into favorable clinical outcomes, particularly in patients with lower inspiratory effort, such as young children and patients with more severe disease. Furthermore, there is evidence to suggest that the efficacy of CF treatments may vary according to the age of patients, notwithstanding delivery route.[10,19,20]

The **E**stablish **A** new **G**old standard **E**fficacy and safety with tobramycin in cystic fib**r**osis (EAGER) trial[12] which evaluated the safety, efficacy, and convenience of TIP versus TIS for the treatment of *Pa* infection in CF patients (≥6 years) showed that TIP was comparable to TIS. The large EAGER trial cohort provided an opportunity to investigate the efficacy and safety profile of TIP in different age groups. Therefore, we undertook a post-hoc subgroup analysis of data from EAGER, with the objective of assessing the effect of TIP and TIS on the main efficacy endpoint of lung function and other secondary efficacy endpoints including microbiology and treatment satisfaction, and to compare their safety profiles in children, adolescents, and adults.

Methods

EAGER was a 24-week international, multi-center, open-label, active-controlled, randomized, parallel-group study (NCT00388505) designed to evaluate the safety of TIP compared to TIS, conducted between February 2006 and March 2009. It was approved by the Ethics Committee or Institutional Review Board at each study center and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

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Patients

Patients with CF aged ≥6 years with forced expiratory volume in 1 second (FEV_1) between 25 to 75% predicted[21] and sputum or throat-swab cultures positive for *Pa* within 6 months of screening (and confirmed at enrollment) were eligible.

Study Design

The detailed methodology of the EAGER trial has been described elsewhere.[12] The study was comprised of three treatment cycles, where each cycle had 28 days on treatment, followed by 28 days off treatment. The total duration of the study was 24 weeks. Eligible patients were randomized 3:2 to receive either TIP (four capsules/112 mg tobramycin) twice daily via the T-326 Inhaler or TIS 300 mg/5 ml (TOBI®) twice daily via the PARI LC® Plus jet nebulizer and DeVilbiss PulmoAide® compressor, or suitable alternative.

Study Assessments

The main efficacy measurement was relative change in FEV_1% predicted from baseline (pre-dose, Day 1) to end of dosing in Cycle 3. Other efficacy measures included change in sputum *Pa* density (log_{10} colony forming units (CFU)/g sputum), any other anti-pseudomonal antibiotic use (including any new antibiotics started during the study period), and hospitalizations for respiratory events. Patient-reported satisfaction with treatment was assessed using the validated Treatment Satisfaction Questionnaire for Medication (TSQM),[22] modified with the addition of four further questions relating to ease of use and convenience. Safety assessments included documented reporting of all adverse events (AEs).

Evaluation and Statistical Analyses

For this subgroup analysis, patients were segmented into the following pre-specified age groups: ≥6 to <13 years (children), ≥13 to <20 years (adolescents), and ≥20 years (adults).

The original sample size was based on the primary endpoint, safety. For efficacy, the inclusion of 500 patients (300 TIP; 200 TIS) provided 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). This efficacy endpoint (treatment difference in FEV_1% predicted) was estimated using an analysis of covariance including treatment, baseline FEV_1% predicted, chronic macrolide use, subgroup, and subgroup-by-treatment interaction in the model. Non-inferiority between treatment groups was demonstrated if the lower bound of the 85% confidence intervals (CIs) were higher than the lower defined margin (i.e. ≥6%). To retain consistency with the original study, summary statistics and 85% CIs for treatment differences in FEV_1 % predicted, sputum *Pa* density and TSQM were calculated for analyses by subgroup. The effect of age group on the primary endpoint was estimated using a generalized linear model with relative change in FEV_1 % predicted as the dependent variable.

All other endpoints in this post-hoc analysis are presented as descriptive statistics only.

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Results

In the original EAGER study, 517 out of 553 randomized patients received at least one dose of study medication (TIP, *n* = 308; TIS, *n* = 209) and were included in the efficacy and safety populations. Numbers of patients varied by age, with lower numbers in the two younger groups (children, *n* = 46; adolescents, *n* = 114; adults, *n* = 357) (Figure 1).

Baseline demographic and clinical characteristics (Table 1) were similar in both treatment groups as a whole, although there was a higher proportion of females in children treated with TIP, than in the same age group treated with TIS (60.7% versus 44.4%). Prior TIS use (defined as 'ever used') and baseline disease severity were also lower in children treated with TIP. Baseline mean FEV_1% predicted was relatively comparable between treatment groups in adolescents and adults, although children receiving TIP had a higher baseline value than those receiving TIS (mean FEV_1% predicted of 60.0% versus 50.4%).

Compliance with study medication was generally good (≥90% of doses taken overall) and comparable between treatments within each age group. The highest rates were observed in the youngest age group (average of 96.5–98.7% doses taken overall) compared with values in Adult groups of 89.6–93.7% doses taken. Overall discontinuation rates for TIP were 3.6% in children, 18.2% in adolescents, and 32.7% in adults, while the discontinuation rates with TIS were 16.7% in children and adolescents, and 18.9% in adults.

Efficacy

Spirometry

Improvements in unadjusted FEV_1% predicted relative change from baseline to the end of dosing in Cycle 3 were observed for both TIP and TIS across all age groups (Table 2). Least squares mean differences between treatment groups (TIP–TIS, controlling for baseline severity) decreased with advancing age: 4.7% (85% CI –1.2, 10.6) for children, 3.7% (–0.1, 7.5) for adolescents and –0.8% (–3.1, 1.5) for adults (Figure 2). Interaction testing found age group to be a significant factor for predicting relative change from baseline in FEV_1 % predicted in both TIP and TIS groups (p=0.0008). However there was insufficient power to distinguish between different treatment effects of TIP and TIS within each age group.

In all treatment cycles, and across all age groups, improvements in patients with more severe disease (<50% FEV_1% predicted) were greater than the improvements in those with less severe disease, for both treatment groups (TIP and TIS; Table 2).

Microbiology

Pa sputum density decreased from baseline in both treatment groups at all measured time points irrespective of patient age with no differences between TIP and TIS overall except among adults at end of Cycle 1 and Cycle 3, and adolescents at Week 16 (p≤0.02 in favor of TIP) (Table 3).

The magnitude of mean change from baseline was greater in the TIP treatment group, with the greatest reduction being seen in the youngest age group (Figure 3A). Furthermore, in the youngest age group, the magnitude of the reduction in *Pa* sputum density at the end of each dosing period increased with successive

treatment cycles and was greatest on Day 28 of Cycle 3, particularly in the TIP treatment group (Figure 3B, Table 3). In the remaining two age groups, the magnitude of the reduction in *Pa* sputum density at the end of each dosing period decreased with successive cycles and was greatest after Cycle 1 of medication (Figure 3B).

Anti-pseudomonal Antibiotic Use (any route) and Hospitalizations

Fewer children in the TIP group versus the TIS group were treated with concomitant anti-pseudomonal antibiotics (50.0% versus 83.3%, compared with 64.9% versus 54.5% across all age groups). Mean antibiotic treatment duration over the three cycles was longer for children treated with TIP compared with TIS (52.6 versus 38.2 days) when considering only those who received antipseudomonal antibiotics. Over the entire 6 to <13 year age group (including children who did not receive antibiotics), mean antibiotic treatment duration was shorter for all TIP-treated versus TIS-treated children (26.3 versus 31.8 days per patient). In the older age group (≥20 years), both of these trends were reversed (Figure 4). The most commonly prescribed anti-pseudomonal agents were oral antibiotics (quinolones). Percentages of patients receiving new intravenous antipseudomonal antibiotics were closely matched across all ages and treatment arms (32% versus 39% [children], 32% versus 31% [adolescents] and 36% versus 33% [adults] for TIP and TIS respectively).

The rate of hospitalizations due to respiratory events tended to be higher in the TIS-treated children and similar between the other treatment age groups (Figure 4). Mean duration of hospitalization in those who were hospitalized was similar between TIP and TIS-treated patients in the youngest and oldest age groups:

children, 17.8 versus 16.4 days; adults, 17.2 versus 14 days. In hospitalized adolescents, the mean duration of hospitalization was shorter in the TIP group (10.4 days) than in the TIS group (17.2 days). When all subjects were analyzed, including those not requiring hospitalization, overall mean duration of hospitalizations was lower for TIP-treated than TIS-treated patients across all age groups (Figure 5).

Patient-Reported Treatment Satisfaction

Scores for convenience were higher in patients receiving TIP, compared with TIS, across all age groups ($p \leq 0.0045$). Adolescent and adult patients were more satisfied with the effectiveness of treatment with TIP compared with TIS ($p \leq 0.0006$). Global satisfaction scores were also higher in the oldest patients receiving TIP, compared with those receiving TIS (least squares mean satisfaction score 75.1 versus 69.6 respectively; $p=0.0009$). There were no differences between treatments in patients' perceptions of side effects in any of the age groups (Table 4).

Safety

The frequency and pattern of AEs reported were broadly similar between both treatments and across all age groups, and are shown in Table 5.

However, cough and dysphonia were reported more frequently in the TIP-treated compared with TIS-treated patients across all age groups. Conversely, upper respiratory tract infections were three times more frequent in patients receiving TIS than in those receiving TIP in the two youngest age groups: 22.2% versus 7.1%, and 12.5% versus 4.5% in children and adolescents, respectively.

Fewer children on TIP discontinued study medication as a result of AEs compared with those on TIS (3.6% versus 11.1% patients, respectively), but the

opposite was true for Adult patients (18.2% patients on TIP discontinued versus 9.1% on TIS).

Discussion

This post-hoc analysis of the EAGER study shows that the efficacy of TIP, as measured by improvement in FEV_1% predicted and reduction in *Pa* sputum density, is maintained across different age groups. Also, the efficacy of TIP is similar to that of TIS across the different ages. While some treatment differences were seen for reduction in Pa sputum densities in the two older patient groups, the clinical relevance of this is unknown. Overall the results are consistent with the whole population data from the original study, showing non-inferiority of TIP to TIS.[12]

Interestingly, the largest numerical improvement in FEV_1% predicted was achieved with TIP in children aged 6–12 years with the lowest baseline lung function (FEV_1 <50% predicted). This may be counter-intuitive since the youngest, sickest children should have the most difficulty generating the required flow and volume necessary to ensure the aerosol reaches the lower airways. Tiddens et al.[23] investigated this concept in a study in which inspiratory profiles of CF patients of varying ages and disease severities were recorded using several resistors to simulate the representative resistance of DPIs. By reproducing the inspiratory profiles representative of the T-326 inhaler *in vitro* with a breath simulator, researchers demonstrated that even a low inspired flow of 30 L/min and volume of 0.6 L could empty a TIP capsule in two efforts, likely due to the improved flow characteristics of the light, porous particles[13] and to the low-to-medium resistance of the T-326 inhaler. This suggests that even the young and sick children with CF who have difficulty in

achieving the required inspiratory profile for adequate dosing of inhaled antibiotics via conventional nebulized systems can deliver the required dose of tobramycin to the lower airways using the TIP system. The treatment differences in relative change in FEV_1% predicted (TIP–TIS) of 4.7, 3.7, and –0.8% for children, adolescents, and adults respectively, indicate that younger children, including those with more severe disease, are able to use the T-326 Inhaler device as effectively as TIS.

Some interesting trends were detected in the different age groups in terms of antibiotic use and hospitalizations, although event rates were too low to allow statistical comparison of treatment effect within the subgroups for these endpoints. . For example, additional anti-pseudomonal antibiotic use was greater in patients receiving TIP than in those receiving TIS, although only in adolescents and adults. We suspect that the use of oral antibiotics may have been driven by the higher incidence of cough in the TIP group, which could have been interpreted by clinicians as symptoms of an exacerbation, or led to an increase in self-medication among patients. Despite this higher incidence, duration of use of antibiotics was shorter in patients receiving TIP compared with TIS (36.5 versus 55 days and 32.2 versus 36.4 days for adolescents and adults respectively). In addition, there were fewer hospitalizations in children treated with TIP than with TIS and the mean duration of hospitalization was also shorter. Including all subjects, the mean duration of hospital stay per patient was shorter for TIP than TIS in all age subgroups. It will be interesting to determine whether these trends are borne out in larger clinical studies and/or clinical practice.

Global satisfaction, measured by the TSQM, was higher in the two older patient groups treated with TIP compared with TIS. All groups were more satisfied

with the effectiveness of TIP than TIS ($p \leq 0.0006$ for the two older groups). The convenience domain was also rated higher in all age groups treated with TIP compared with TIS, which may reflect the average administration time for TIP of 6 minutes compared with 20 minutes for TIS (excluding the time required for cleaning and sterilization of the equipment).[12] This is likely to be appreciated by older patients who are both more independent and likely to be receiving more medications than the younger age group. It is also interesting to note that adults reported a greater level of satisfaction despite demonstrating lower lung function responses to TIP than the younger age group. This could suggest that patient satisfaction scores reflect a more holistic response to treatment that objective measures do not capture.

In terms of safety, the frequency of AEs was comparable between treatments and across all age groups with the exception of some respiratory symptoms, which were more prevalent in the TIP-treatment group, most notably cough and dysphonia. Cough is a common symptom of inhalation therapies[16] and of cystic fibrosis disease. The higher rates of cough and dysphonia may be attributable to the high 'payload' of powder in the TIP formulation.[16] Nevertheless, the severity of most AEs, including cough, was mild to moderate in both treatment arms,[12] and the impact of unwanted side effects on patients' lives was comparable between the treatment groups, as reflected by patients' perceptions of side effects in the TSQM. Furthermore, the overall pattern of discontinuation does not appear to be driven by the rate or nature of AEs, so differences between age groups are unlikely to be related to factors inherent to TIP. Persistence with TIP treatment appeared to be greatest in the youngest patients, who were likely to have less prior exposure to TIS.

Our results are consistent with previous intervention studies in CF in which the most robust results have been demonstrated in younger patients. In the original TIS Phase III trial,[10] the best FEV_1 response to tobramycin was seen in the 13–17 year old age group (compared with younger and older patients), while the *Pa* suppressive effect decreased with advancing age. A larger lung function response was also noted in patients aged 6–17 years than in adults in a study which compared two formulations of tobramycin solution for nebulization (Bramitob and TOBI).[24]

Similarly, in a study investigating FEV_1 decline with dornase alfa, a statistically significant improvement occurred in children aged 8–17 years old, but not adults,[25] while a 4-year trial of high dose ibuprofen[19] found that children under 13 years benefitted more than older subjects. In addition, in the AIR CF-1 study, patients <18 years had greater improvements in the Cystic Fibrosis Questionnaire-Revised respiratory symptom score following 4-weeks treatment with aztreonam lysine for inhalation versus placebo than adults (>20 points versus 6 points respectively).[20] Further, a review of pediatric data from studies conducted as part of the aztreonam for inhalation clinical development program found improvements in lung function among children and adolescents with aztreonam lysine for inhalation to be of a magnitude similar to or greater than that observed in adult patients, with the greatest improvements in adolescents.[26] In contrast, a recently reported study[27] found that adults had bigger gains in lung function with mannitol therapy. However, this result may have been driven by a positive response to the control treatment (i.e. low-dose mannitol) in the younger age groups.

It is not clear why treatment response should be greater in younger patients. Possible explanations may include better rates of adherence in the youngest age

group compared with older patients, and lower prior exposure to antibiotics among younger patients. While 'any prior' exposure to tobramycin did not appear to differ by age in our analysis, the lifetime length of exposure may have been less in children simply because they are younger and did not have chronic *Pa* infection as long. Thus, older patients with a more prolonged exposure to tobramycin may have a diminishing response over longer periods of time. Younger patients may also have more capacity to respond to treatment. Continuing lung growth in children, which has been correlated with improvements in maximal expiratory flows and 'upstream' airway conductance,[28] could facilitate response to treatment in some subjects. In addition, children demonstrate greater 'elasticity' of lung function, which declines over time.[29]

As patients with CF age and the disease progresses, repeated infections and chronic *Pa* infection lead to lung damage and permanent loss of lung function, which may also reduce their capacity to respond to treatment. Interestingly in our study, those with more severe disease seemed to achieve greater improvements in lung function (as measured by the change in FEV_1% predicted from baseline) after treatment with tobramycin than those with less severe disease (Table 2). However, it should be noted that, in our study, impairment of lung function at baseline was used as a measure of lung damage, since we did not assess the extent of bronchiectactic tissue or other measures of anatomical disease severity. TIP and TIS reduce the burden of *Pa* infection, which in younger patients with potentially less lung damage, can lead to a marked improvement in lung function. The less marked impact of TIP or TIS in patients with less severe impairment of FEV_1 may reflect the difficulty in achieving meaningful changes in this endpoint among patients with better lung function at baseline.[30] Clearly, further research is needed to understand what factors

could be driving this observation. Previous medication use may have an influence but information on this is limited in the current study.

Limitations

Our analysis was a post hoc subgroup analysis of a larger randomized trial, and therefore carries the potential for bias inherent in such an analysis. In addition, while the original study was not powered to detect statistical differences between subgroups, we have carried out statistical analyses of the treatment differences by subgroup for FEV_1% predicted, *Pa* sputum density and treatment satisfaction data. Although patients were randomized to treatment, randomization was not stratified by age, such that there were some differences between treatment groups within the age-related subgroups analyzed. Statistical comparisons by age subgroups, which in some cases included relatively small numbers of patients, should be interpreted with caution, because differences between groups may have occurred by chance. These types of analyses are at risk of type 1 error because of multiple comparisons. The fact that younger patients treated with TIP had better efficacy outcomes than with TIS may have been at least partially attributable to the less severe disease in children receiving TIP, although differences were not statistically significant. However, it has been noted that for the whole population in this study, those with more severe disease (i.e. <50% predicted) had better improvements in lung function. The impact of this finding is therefore unclear. The treatments were also open-label and this may have had some impact on the results, particularly on the patient-reported outcomes (TSQM). However, we observed consistent trends within each age group indicating that, overall, TIP was at least as effective as TIS, and these trends are consistent with the overall findings of the EAGER study.[12]

Conclusions

In summary, TIP was comparable to TIS for all age groups as measured by mean changes in lung function and *Pa* sputum density from baseline. Children treated with TIP tended to have greater (although not statistically significant) improvements in efficacy outcomes than with TIS, confirming that this age group is able to use the device effectively. With the exception of cough and dysphonia, the safety and tolerability profile of TIP was similar to that of TIS across all age groups. AEs suggestive of local tolerability such as cough are not unexpected, given the dry powder formulation.[30] Patient satisfaction, as measured by convenience of use, was higher with TIP than with TIS at all ages.

Relative to nebulized tobramycin treatment, the drug–device combination of TIP provides a faster,[15,16] more portable and convenient treatment option with similar efficacy, and can be used in patients with CF as young as 6 years.

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((Figure legends))

Figure 1: Patient disposition diagram by age group, based on CONSORT diagram for full population published in study by Konstan et al (12).

Figure 2. Relative change in FEV_1% predicted from baseline to end of dosing in Cycle 3.

Data are least square mean differences between treatment groups (TIP–TIS) in relative change in FEV_1% predicted from baseline to end of dosing in Cycle 3 with 85% one-sided confidence intervals. Dotted line represents the boundary for non-inferiority.

FEV_1, forced expiratory volume in 1 second; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

Figure 3a. Change in sputum *Pa* density from baseline to the end of treatment.

Data are mean change in *P. aeruginosa* sputum density (log_{10} CFUs) from baseline to end of dosing in Cycle 3 ± standard deviation (combined data for all biotypes: dry, mucoid, and small colony variant).

CFU, colony forming unit; *Pa*, *Pseudomonas aeruginosa;* TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

Figure 3b. Change in sputum *Pa* density from baseline over three cycles of treatment.

Data are mean change in *P. aeruginosa* sputum density (log_{10} CFUs) from baseline ± standard deviation (combined data for all biotypes: dry, mucoid, and small colony variant).

CFU, colony forming unit; *Pa*, *Pseudomonas aeruginosa*; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

Figure 4. Concomitant anti-pseudomonal antibiotic use.

Data are the percentage of patients receiving TIP and TIS for whom any anti-pseudomonal antibiotic use was recorded

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

Figure 5. Hospitalizations due to respiratory events.

Data are the percentage of patients hospitalized for respiratory events in patients receiving TIP and TIS.

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

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((Table captions))

Table 1. Baseline demographic and clinical characteristics.

Table 2. Mean ± SD relative change in FEV_1% predicted from baseline and treatment differences by age group, cycle, and baseline FEV_1% predicted.

Table 3. Change in *Pa* sputum density from baseline and treatment differences at the end of each dosing cycle by age group and treatment cycle.

Table 4. Patient-reported satisfaction with treatment as rated by the treatment satisfaction questionnaire for medication.

Table 5. Most frequent (≥10% in any group) AEs occurring across all cycles.

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Table 1. Baseline demographic and clinical characteristics.

Age group	≥6 to <13 years (*n* = 46)		≥13 to <20 years (*n* = 114)		≥20 years (*n* = 357)	
	TIP (*n* = 28)	TIS (*n* = 18)	TIP (*n* = 66)	TIS (*n* = 48)	TIP (*n* = 214)	TIS (*n* = 143)
Gender						
Male, *n* (%)	11 (39.3)	10 (55.6)	34 (51.5)	26 (54.2)	126 (58.9)	79 (55.2)
Female, *n* (%)	17 (60.7)	8 (44.4)	32 (48.5)	22 (45.8)	88 (41.1)	64 (44.8)
FEV_1% predicted, mean (SD)	60 (16.4)	50.4 (14.4)	57.3 (12.6)	55.9 (17.12)	50.7 (13.8)	52.0 (15.7)
Disease severity, FEV_1% predicted						
<50%, *n* (%)	7 (25.0)	9 (50.0)	18 (27.3)	16 (33.3)	97 (45.3)	70 (49.0)
≥50%, *n* (%)	21 (75.0)	9 (50.0)	48 (72.7)	32 (66.6)	117 (54.7)	73 (51.0)
Pa sputum density log_{10} CFUs, mean (SD)	7.67 (0.89)	7.31 (1.75)	7.30 (1.64)	7.16 (1.73)	7.16 (1.50)	7.42 (1.46)
Prior use of tobramycin						
Yes, *n* (%)	21 (75.0)	16 (88.9)	56 (84.9)	43 (89.6)	176 (82.2)	113 (79.0)
Prior ever use of antipseudomonal antibiotics						

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Yes, *n* (%)	28 (100.0)	18 (100.0)	65 (98.5)	45 (93.8)	200 (93.5)	128 (89.5)

CFU, colony forming unit; FEV_1, forced expiratory volume in 1 second; *Pa*, *Pseudomonas aeruginosa*; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

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Table 2. Mean (SD) relative change in FEV_1% predicted from baseline by age group, cycle, and baseline FEV_1% predicted.

Age group	≥6 to <13 years (*n* = 46)				≥13 to <20 years (*n* = 114)				≥20 years (*n* = 357)			
			Difference TIP–TIS				Difference TIP–TIS				Difference TIP–TIS	
	TIP (*n* = 28)	TIS (*n* = 18)	Mean (85% CI)	p value	TIP (*n* = 66)	TIS (*n* = 48)	Mean (85% CI)	p value	TIP (*n* = 214)	TIS (*n* = 143)	Mean (85% CI)	p value
FEV_1 <50%/≥50% populations, *n*	7/21	9/9			18/48	16/32			97/117	70/73		
Cycle 1 (Week 4)												
All patients	6.3 (29.9)	12.7 (22.9)	–6.4 (–19, 6.0)	0.46	8.3 (17.76)	4.8 (9.6)	3.5 (–0.8, 7.9)	0.24	0.5 (17.9)	2.0 (13.9)	–1.5 (–4.2, 1.2)	0.42
<50% FEV_1% predicted	41.8 (34.0)	21.8 (24.9)	20.0 (–2.4, 42.4)	0.20	17.6 (27.5)	10.1 (11.8)	7.5 (–5.2, 20.3)	0.39	4.2 (21.3)	3.7 (14.9)	0.5 (–4.0, 5.0)	0.87
≥50% FEV_1% predicted	–5.5 (16.5)	2.3 (15.9)	–7.8 (–17.9, 2.2)	0.26	5.4 (12.4)	2.8 (7.9)	2.6 (–1.1, 6.3)	0.31	–2.4 (14.1)	0.3 (12.7)	–2.7 (–5.8, 0.4)	0.21

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Cycle 3 (Week 20)												
All patients	10.4 (25.9)	9.4 (18.9)	1.0 (–10.2, 12.1)	0.089	6.8 (18.5)	3.9 (19.4)	2.9 (–2.8, 8.6)	0.47	0.3 (18.7)	0.9 (16.6)	–0.6 (–3.8, 2.6)	0.79
<50% FEV_1% predicted	38.0 (32.5)	15.6 (15.6)	22.4 (1.5, 43.4)	0.13	18.5 (23.3)	10.3 (28.1)	8.2 (–6.9, 23.2)	0.43	4.7 (22.5)	3.9 (17.8)	0.8 (–4.8, 6.3)	0.84
≥50% FEV_1% predicted	1.1 (15.3)	4.0 (20.9)	–2.9 (–13.2, 7.6)	0.69	3.2 (15.3)	0.8 (13.0)	2.4 (–2.9, 7.5)	0.52	–2.6 (15.1)	–2.0 (15.0)	–0.6 (–4.3, 3.0)	0.81

Data is mean relative change in % predicted FEV_1 with SD and mean treatment difference (85% CI).

FEV_1, forced expiratory volume in 1 second; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution; CI confidence interval.

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Table 3. Change in *Pa* sputum density from baseline at the end of each dosing cycle by age group and treatment cycle.

Age group	≥6 to <13 years (*n* = 46)				≥13 to <20 years (*n* = 114)				≥20 years (*n* = 357)			
			Difference TIP–TIS				Difference TIP–TIS				Difference TIP–TIS	
	TIP (*n* = 28)	TIS (*n* = 18)	Mean (85% CI)	p value	TIP (*n* = 66)	TIS (*n* = 48)	Mean (85% CI)	p value	TIP (*n* = 214)	TIS (*n* = 143)	Mean (85% CI)	p value
Cycle 1												
Baseline, raw value	7.67 (0.89)	7.31 (1.75)	0.36 (n/a)	n/a	7.30 (1.64)	7.16 (1.73)	0.14 (n/a)	n/a	7.16 (1.50)	7.42 (1.46)	–0.26 (n/a)	n/a
Week 4	–1.43 (1.46)	–0.95 (1.67)	–0.48 (–1.4, 0.5)	0.46	–1.76 (1.81)	–1.96 (2.22)	0.2 (–0.5, 0.9)	0.68	–1.79 (2.04)	–1.18 (2.00)	–0.61 (–0.1, –0.2)	0.02
Cycle 3												
Week 16	–1.26 (2.48)	–0.41 (1.02)	–0.85 (–2.1, 0.4)	0.32	–0.62 (1.71)	0.32 (1.20)	–0.94 (–1.5, –0.4)	0.02	–0.20 (1.72)	–0.10 (1.57)	–0.1 (–0.4, 0.2)	0.66
Week 20	–2.54	–1.23	–1.31 (–2.3,	0.07	–1.21	–0.69	–0.52 (–1.3,	0.36	–1.63	–0.73	–0.9 (–1.3, –	0.001

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(2.01)	(1.08)	–0.3)	(2.03)	(1.96)	0.3)	(2.02)	(1.81)	0.5)

Data are mean change from baseline in *Pa* density in sputum (log_{10} CFUs) unless otherwise stated, for sum of all biotypes with SD and mean treatment difference with 85% CI.

CFU, colony forming unit; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution; CI confidence interval.

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Table 4. Patient-reported satisfaction with treatment as rated by the treatment satisfaction questionnaire for medication.

Age group	≥6 to <13 years (*n* = 46)				≥13 to <20 years (*n* = 114)				≥20 years (*n* = 357)			
			Difference TIP–TIS				Difference TIP–TIS				Difference TIP–TIS	
	TIP (*n* = 28)	TIS (*n* = 18)	LSM (85% CI)	p value	TIP (*n* = 66)	TIS (*n* = 48)	LSM (85% CI)	p value	TIP (*n* = 214)	TIS (*n* = 143)	LSM (85% CI)	p value
Effectiveness	76.9	75.6	1.30 (–6.42, 9.02)	0.81	79.6	70.5	9.10 (5.36, 12.83)	0.0006	72.1	62.4	9.74 (7.06, 12.42)	<0.0001
Side-effects	92.8	98.7	–5.90 (–10.7, –1.09)	0.07	93.9	95.6	–1.68 (–4.21, 0.85)	0.34	91.5	91.5	–0.03 (–2.35, 2.28)	0.98
Convenience	82.8	65.7	17.10 (8.81, 25.38)	0.0045	81.6	63.7	17.91 (13.28, 22.55)	<0.0001	85.0	58.3	26.65 (23.92, 29.37)	<0.0001
Global satisfaction	77.7	78.0	–0.34 (–7.48, 6.80)	0.94	82.6	78.6	4.02 (–0.19, 8.23)	0.17	75.1	69.6	5.58 (2.52, 8.64)	0.009

Data (patient numbers and satisfaction scores) are LSMs for averages of the three treatment cycles, with measurements performed at the end of each on-treatment period. A higher score indicates higher satisfaction for that domain.

LSM, least square mean; SE, standard error; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution; CI confidence interval.

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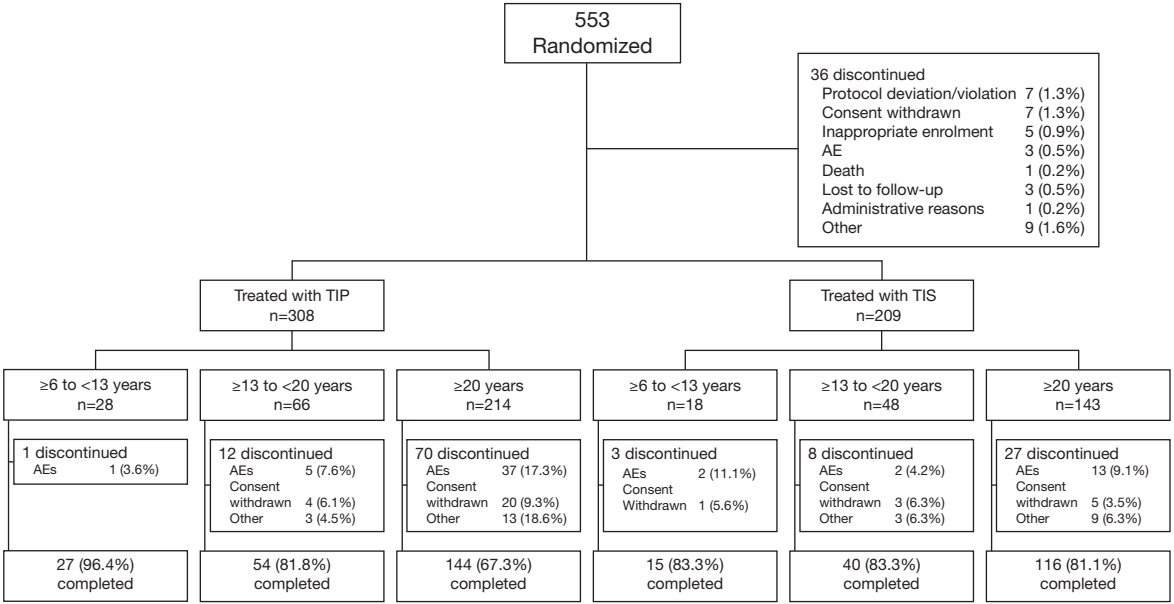
Table 5. Most frequent (≥10% in any group) AEs occurring across all cycles.

Age group	≥6 to <13 years (*n* = 46)		≥13 to <20 years (*n* = 114)		≥20 years (*n* = 357)	
	TIP (*n* = 28)	TIS (*n* =18)	TIP (*n* = 66)	TIS (*n* = 48)	TIP (*n* = 214)	TIS (*n* = 143)
Any AE, n (%)	25 (89.3)	15 (83.3)	59 (89.4)	39 (81.3)	194 (90.7)	122 (85.3)
Cough	18 (64.3)	4 (22.2)	35 (53.0)	13 (27.1)	96 (44.9)	48 (33.6)
Lung disorder[a]	5 (17.9)	9 (50.0)	20 (30.3)	11 (22.9)	78 (36.4)	43 (30.1)
Productive cough	5 (17.9)	3 (16.7)	13 (19.7)	4 (8.3)	38 (17.8)	34 (23.8)
Dysphonia	6 (21.4)	1 (5.6)	7 (10.6)	2 (4.2)	29 (13.6)	5 (3.5)
Hemoptysis	0 (0.0)	2 (11.1)	9 (13.6)	5 (10.4)	31 (14.5)	19 (13.3)
Oropharyngeal pain	5 (17.9)	1 (5.6)	13 (19.7)	2 (4.2)	25 (11.7)	19 (13.3)
Sinusitis	1 (3.6)	1 (5.6)	0 (0.0)	5 (10.4)	17 (7.9)	9 (6.3)
Upper respiratory tract	2 (7.1)	4 (22.2)	3 (4.5)	6 (12.5)	16 (7.5)	8 (5.6)

infection						
Rhinorrhea	6 (21.4)	1 (5.6)	6 (9.1)	2 (4.2)	10 (4.7)	12 (8.4)
Decreased appetite	4 (14.3)	(0.0)	3 (4.5)	2 (4.2)	6 (2.8)	5 (3.5)
Dysgeusia	3 (10.7)	0 (0.0)	4 (6.1)	0 (0.0)	5 (2.3)	1 (0.7)
Pneumonia	3 (10.7)	0 (0.0)	0 (0.0)	1 (2.1)	1 (0.5)	2 (1.4)

Events are ordered by decreasing frequency according to the TIP ≥20 year (adult) group. [a]Lung disorders were generally reported by the investigator as a pulmonary or cystic fibrosis exacerbation. A subject with multiple occurrences of the same AE is counted only once in that AE category.

AE, adverse event; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.


553
Randomized
36 discontinued
Protocol deviation/violation 7 (1.3%)
Consent withdrawn 7 (1.3%)
Inappropriate enrolment 5 (0.9%)
AE 3 (0.5%)
Death 1 (0.2%)
Lost to follow-up 3 (0.5%)
Administrative reasons 1 (0.2%)
Other 9 (1.6%)
Treated with TIP
n=308
Treated with TIS
n=209
≥6 to <13 years
n=28
≥13 to <20 years
n=66
≥20 years
n=214
≥6 to <13 years
n=18
≥13 to <20 years
n=48
≥20 years
n=143
1 discontinued
AEs 1 (3.6%)
12 discontinued
AEs 5 (7.6%)
Consent withdrawn 4 (6.1%)
Other 3 (4.5%)
70 discontinued
AEs 37 (17.3%)
Consent withdrawn 20 (9.3%)
Other 13 (18.6%)
3 discontinued
AEs 2 (11.1%)
Consent Withdrawn 1 (5.6%)
8 discontinued
AEs 2 (4.2%)
Consent withdrawn 3 (6.3%)
Other 3 (6.3%)
27 discontinued
AEs 13 (9.1%)
Consent withdrawn 5 (3.5%)
Other 9 (6.3%)
27 (96.4%) completed
54 (81.8%) completed
144 (67.3%) completed
15 (83.3%) completed
40 (83.3%) completed
116 (81.1%) completed

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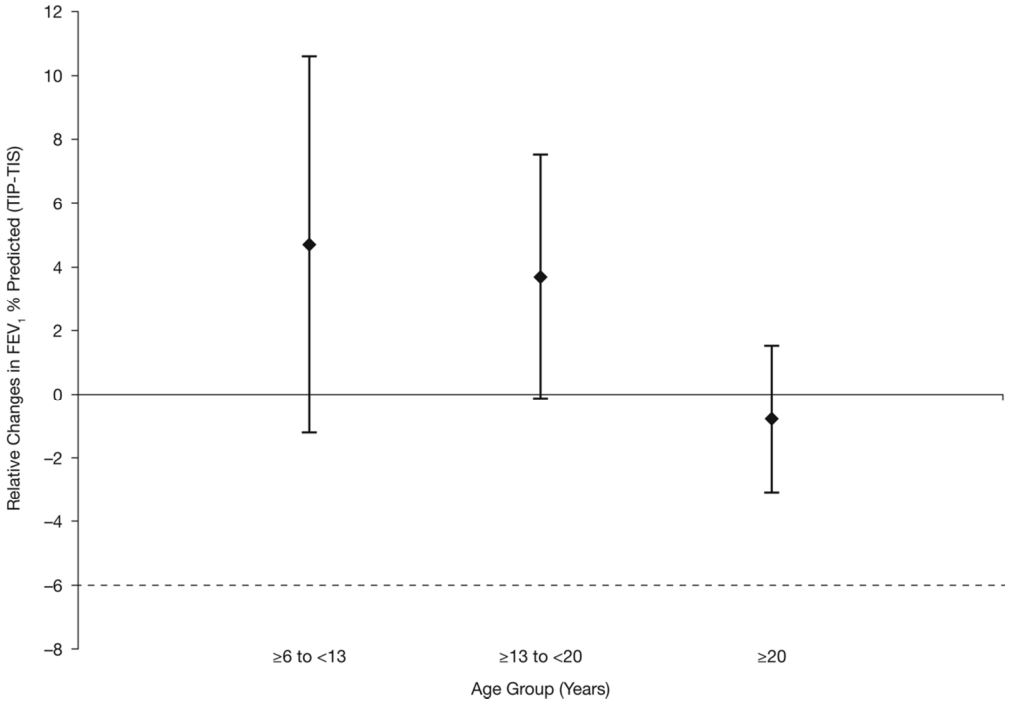
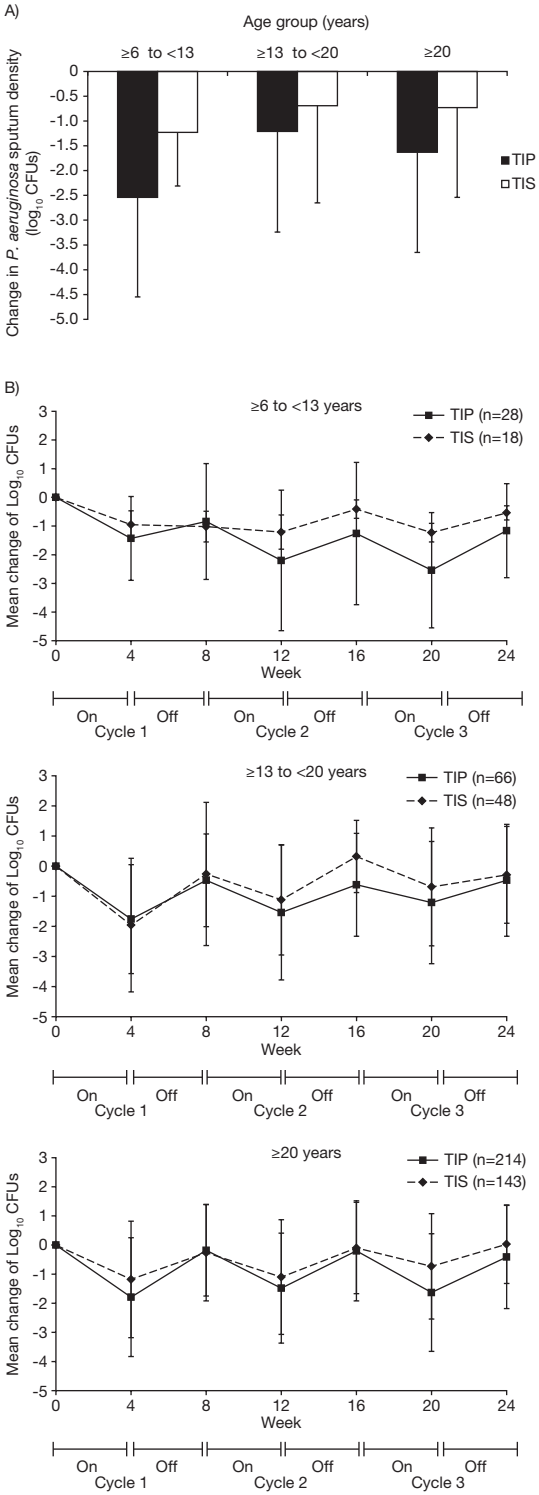
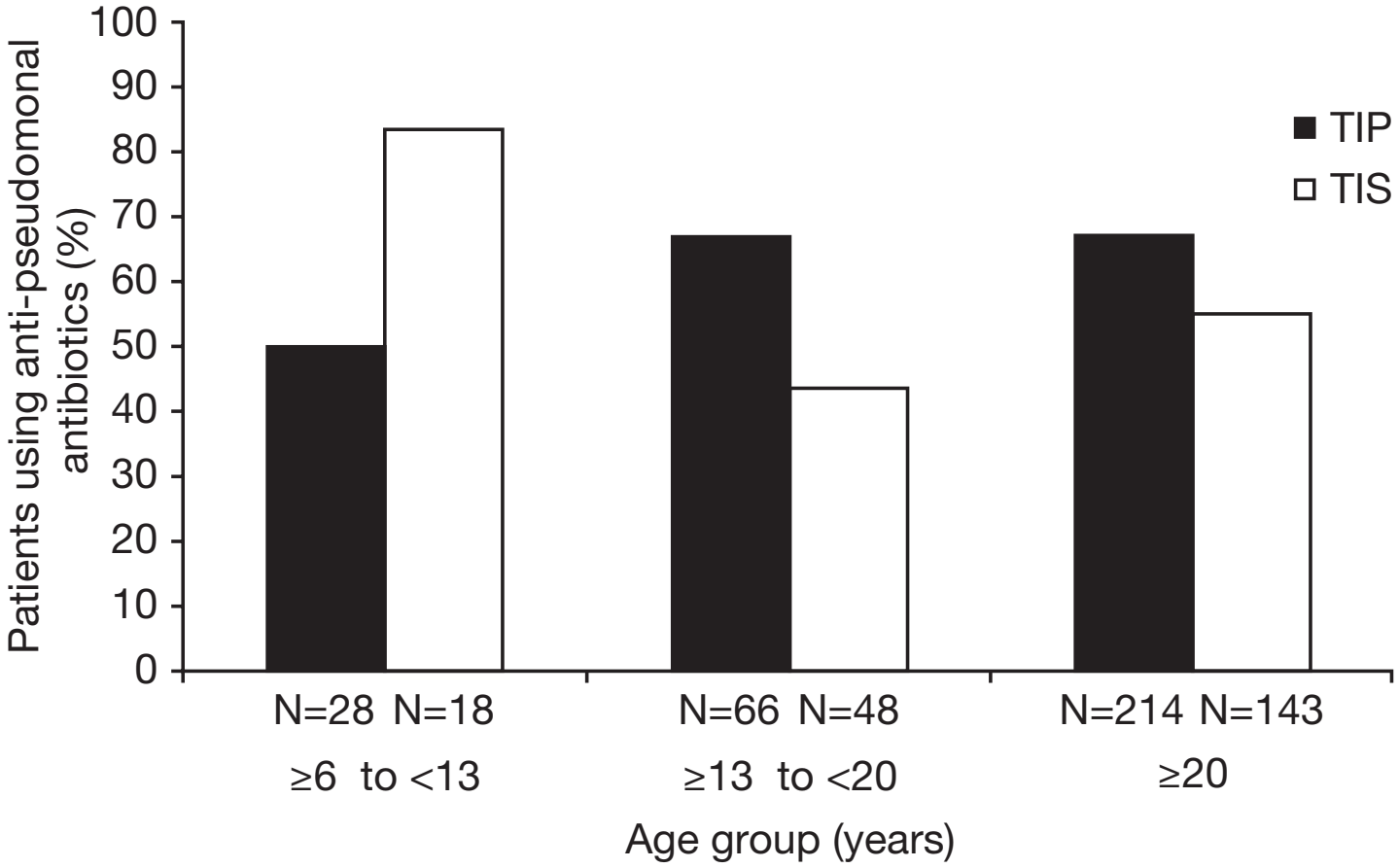
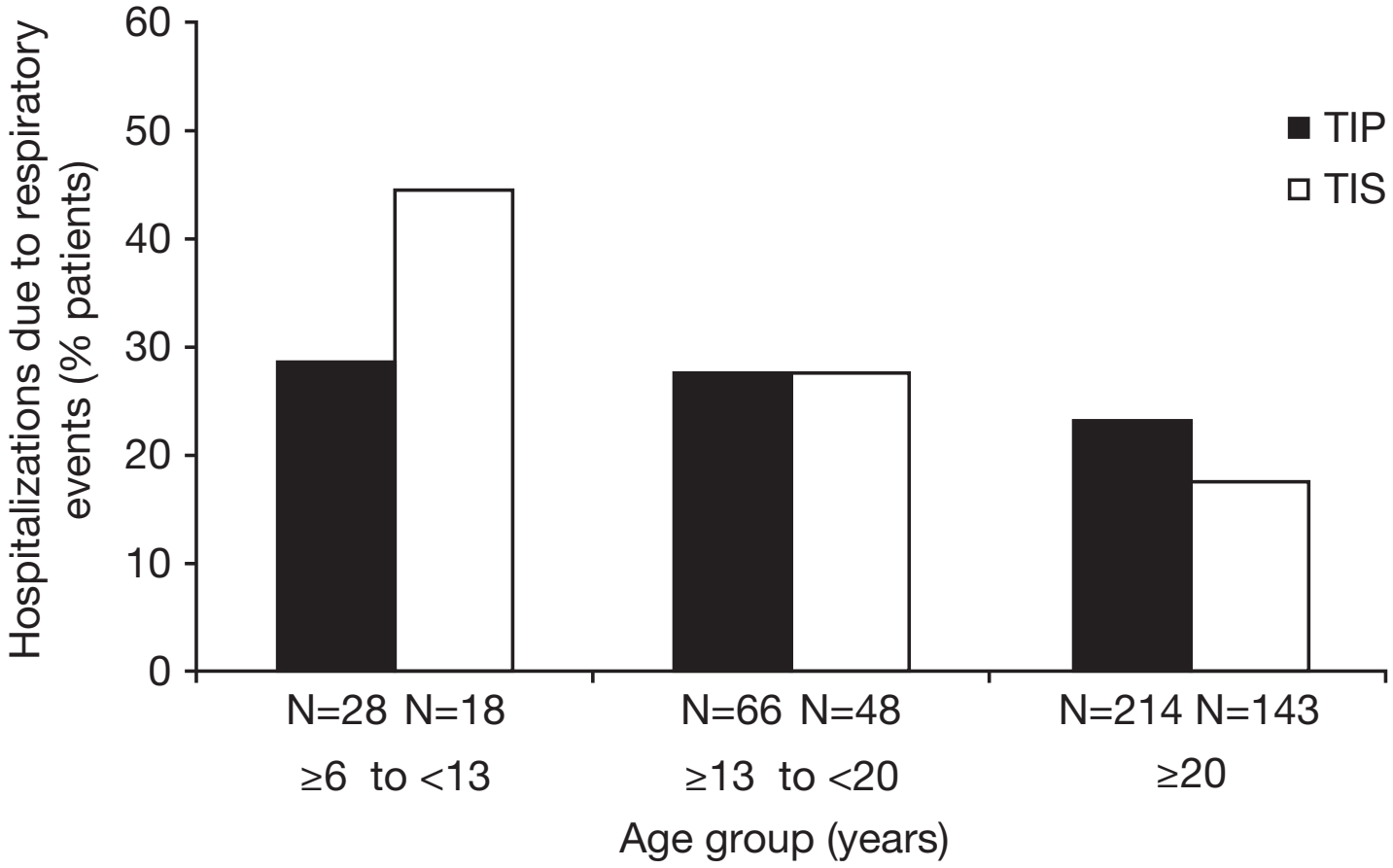


Relative change in FEV_1% predicted from baseline to end of dosing in Cycle 3.
Data are least square mean differences between treatment groups (TIP–TIS) in relative change in FEV_1% predicted from baseline to end of dosing in Cycle 3 with 85% one-sided confidence intervals. Dotted line represents the boundary for non-inferiority.
FEV_1, forced expiratory volume in 1 second; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

113x79mm (300 x 300 DPI)


A)
Age group (years)
≥6 to <13
≥13 to <20
≥20
Change in P. aeruginosa sputum density (log10 CFUs)
0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
TIP
TIS
B)
≥6 to <13 years
TIP (n=28)
TIS (n=18)
Mean change of Log10 CFUs
Week
On
Off
Cycle 1
Cycle 2
Cycle 3
≥13 to <20 years
TIP (n=66)
TIS (n=48)
≥20 years
TIP (n=214)
TIS (n=143)


Patients using anti-pseudomonal antibiotics (%)
100
90
80
70
60
50
40
30
20
10
0
TIP
TIS
N=28 N=18
≥6 to <13
N=66 N=48
≥13 to <20
N=214 N=143
≥20
Age group (years)


Hospitalizations due to respiratory events (% patients)
60
50
40
30
20
10
0
TIP
TIS
N=28 N=18
≥6 to <13
N=66 N=48
≥13 to <20
N=214 N=143
≥20
Age group (years)