CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # :	201688
Drug Name:	TOBI® Podhaler™ (tobramycin inhalation powder)
Indication Sought:	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Applicant:	Novartis Pharmaceuticals, Inc.
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1. EXECUTIVE SUMMARY

1.1 Introduction

The Applicant, Novartis Pharmaceuticals, Inc., has submitted NDA 201688 to support the approval of TOBI® Podhaler™ (tobramycin inhalation powder (TIP)) as a 4 x 28mg, b.i.d. treatment for the management of cystic fibrosis patients with *Pseudomonas aeruginosa.* NDA 201688 includes two placebo-controlled studies (TBM100C2301 and TBM100C2303) and one active controlled study (Study TBM100C2302), hereafter referred to as Studies C2301, C2303 and C2302, respectively. Studies C2301 & C2303 had both evaluated a primary endpoint defined as the relative change from baseline in FEV1 percent predicted following 28 days of TIP/placebo therapy. Study C2302 was primarily a safety study comparing TIP vs. TOBI (300 mg b.i.d) over three 8 week cycles where each cycle consisted of 4 weeks of on-therapy followed by 4 weeks of off-therapy. As a secondary objective, Study C2302 also compared TIP vs. TOBI over the three cycles based on efficacy related endpoints such as relative changes from baseline in FEV1 percent predicted.

The Applicant first conducted Study C2301 in support of the proposed indication but had subsequently used a new manufacturing process for the to-be-marketed TIP product (i.e. TIP_{new}). In an Applicant meeting of April 2008, the Agency expressed concerns regarding potential effects associated with a change in the TIP manufacturing process and recommended that the Applicant conduct an additional adequate and well controlled study in a TOBI naïve study population to evaluate TIP_{new} against placebo. In response to this recommendation, the Applicant conducted a pivotal double-blind placebo controlled study, Study C2303, using an 8 week period (4 weeks of on-therapy followed by 4 weeks of off therapy) in TOBI naïve patients with cystic fibrosis due to *PA*. However, the Applicant had difficulties completing the planned enrollment into Study C2303 and had considered terminating enrollment early with fewer subjects than planned. As discussed with the Applicant during a January 28, 2011 meeting, the Agency recommended against terminating Study C2303 enrollment early given the potential risk of showing no treatment benefit of TIP over placebo as this may impact the ability to evaluate the effects of TIP_{new} on efficacy and safety, especially since TIP_{new} was evaluated in only Study C2303.

However, the Applicant did not follow this recommendation and chose to terminate enrollment in Study C2303 despite it being substantially smaller than planned with only 62 subjects (32 in TIP arm, 30 in Placebo arm) vs. the planned number of 100 subjects. Study C2303 was further limited by missing data resulting from the study conduct of this trial. Three patients (2 Placebo, 1 TIP) had faulty or inadequate spirometry measurements at baseline. An additional 7 patients (1 Placebo, 6 TIP) had missing values in the primary outcome due to missing or inadequate spirometry measurements at Day 29. Two patients randomized to TIP had also mistakenly received placebo. Since one TIP patient who mistakenly received placebo also had a missing/inadequate spirometry measurement at Day 29, 24 (75%) of TIP patients could be appropriately assessed in the primary analysis

which is less than half of the initially planned number of randomized TIP subjects (i.e. 50 subjects).

It should also be noted that due to the controversial nature of this submission, an Anti-infective Drugs Advisory Committee (AIDAC) meeting was held on September 5, 2012 to discuss the efficacy and safety findings. Committee members voted 13 to 1 in favor of TIP being safe and effective therapy in the treatment of cystic fibrosis due to *PA*. Several committee members cited similar FEV1 % predicted measurements between TIP and TOBI across the three cycles in Study C2302 (open-label) as a reason for voting in favor of TIP.

1.2 Conclusions and Recommendations

This submission provided some persuasive evidence of a treatment benefit for patients with cystic fibrosis due to *PA* using TIP. Study C2301 provided adequate evidence of a TIP treatment benefit, while Study C2303 provided only weak evidence since the primary endpoint was not met. Additionally, Study C2302, an open-label comparative safety study, provided some weak supportive evidence towards the overall risk/benefit assessment. Such evidence was limited by several factors including the open-label study design, lack of a prospectively planned primary analysis, uncertainty in treatment effects compared to placebo, potential biases due to significantly higher discontinuation rates in TIP patients and unfavorable comparisons in relative changes following on-therapy periods of other cycles (i.e. Cycles 1 & 2), as discussed in 'Study C2302' below.

Overall, we considered this submission to be potentially approvable depending on the considerations and recommendations from the other review disciplines, the final product labeling and the Applicant's agreement to all necessary post-marketing commitments. However, there are still several concerns with this submission related to the usability of the product, increases in tobramycin minimum inhibitory concentrations (MICs) for *Pseudomonas aeruginosa* isolates, patient exclusions, reliability of spirometry used in FEV1 % predicted measurements, regional effects, sustainability of effects and supportive analyses (e.g. rates of new anti-pseudomonal antibiotic use, rates of respiratory hospitalization). Note that these conclusions and recommendations are primarily based on our evaluation of efficacy from the studies summarized below:

Study C2301

In Study C2301, the Reviewer's primary analysis considered findings in the sensitivity interim analysis (SIA) population (N=61) and also included a sensitivity analysis in the All Randomized Safety population (N=95) to account for potential biases from the exclusion of 34 treated patients from the SIA population (Tables 5 & 6, respectively). These analyses based on a non-parametric analysis of covariance (ANCOVA) model showed significance with observed p-values of p=0.0061 and p=0.023 in the sensitivity interim analysis (SIA) and All Randomized Safety populations. Parametric ANCOVA tests also showed a TIP benefit over placebo of 12.44% (12.54% vs. 0.09%), p=0.0017 in the SIA population and 8.14% (6.87% vs. -1.26%), p=0.009 in the All Randomized Safety population. However, overall evidence of efficacy in Study C2301 was not considered to

be robust for several reasons which included regional effects, unclear sustainability of effects and limited evidence from supportive analyses, as discussed below:

Regional effects appeared to be strong with patients from Europe driving primary analysis findings (Table 19). In Europe, TIP vs. placebo comparisons showed a mean (median) relative change of 17.16% (19.25%) vs. -0.35% (1.19%), a mean treatment difference of 17.51% (95% CI: 8.14%, 26.89%), p=0.001. In North America, however, TIP vs. placebo comparisons were less favorable with a mean (median) change of 1.25% (-1.90%) vs. -2.65% (-2.56%), a mean treatment difference of 3.90% (95% CI: -6.43%, 14.23%), p=0.438. Note that Study C2302 also showed disparities for relative changes in FEV1 % predicted for TIP patients across regions where the mean relative change at Week 5 was 4.41% in Europe vs. 0.46% in the US (Table 21).

Unclear sustainability of treatment effects within and across cycles was due to lack of a placebo controlled arm outside the first cycle and substantial increases in missing data after Week 5 (Table 15). In addition to these limitations, observed findings did not appear to be favorable (Table 16 and Figures 10 & 11). For example, the mean relative change from baseline decreased within the first cycle from 12.26% (Week 5) to 6.83% (Week 9) and across the 3 cycles following the on-therapy periods (i.e. Week 9 vs. Week 13 & Week 21) from 12.26% vs. 8.81% & 9.08%. Similar steep drops in relative changes across cycles were also observed for median relative changes (i.e. 9.52% vs. 5.74% & 6.25%). In further comparisons of sustainability among patients in the placebo arm who switched over to TIP at Week 9, the mean (median) relative change of 9.85% (4.24%) at Week 13 dropped to 6.97% (1.87%) at Week 25.

In addition, supportive analyses provided only limited evidence due to low event rates and the lack of significant findings (Table 7). In Cycle 1, rates of anti-pseudomonal antibiotics use, as determined by the FDA Clinical Reviewer, were 6/46 (13.1%) in TIP patients vs. 9/49 (18.4%) in placebo patients, a -5.3% difference favoring TIP, p=0.477. Rates in respiratory related hospitalization also favored TIP at 2/46 (4.4%) vs. 6/49 (12.2%), a -7.8% difference, p=0.166.

Study C2303

In Study C2303, the Reviewer's primary analysis considered findings in the ITT population (N=62). This analysis, a non-parametric analysis of covariance (ANCOVA), failed to show a significant treatment benefit (p-value = 0.233, Table 9). Parametric ANCOVA tests also failed to show significance with an adjusted mean treatment difference of 5.91% (8.19% for TIP vs. 2.27% for Placebo), p=0.167. In addition, relative changes did not appear to be sustained within the cycle, dropping from 5.82% at Week 5 to 3.77% at Week 9 (Table 18). Subgroup analyses showed relative changes to be especially unfavorable in patients with greater disease severity (i.e. FEV1 % predicted < 50% at screening) as well as patients under the age of 13 years (Table 20). Furthermore, supportive analyses, such as comparisons in rates of new anti-pseudomonal antibiotics use (i.e. 3/32 (9.4%) for TIP vs. 3/30 (10.0%) for placebo) and respiratory related hospitalization (0/32 (0.0%) for TIP vs. 1/30 (3.3%) were not informative due to low event rates (Table 10).

Study C2302

Study C2302 compared TIP vs. TOBI over 3 cycles (24 weeks) in TOBI experienced patients using an open label design with a primary (secondary) objective of evaluating safety (efficacy) outcomes. Although this study appears to offer some supportive evidence, the interpretation of efficacy findings was limited by several factors. For example, the Applicant's finding of non-inferiority (NI) of TIP vs. TOBI for relative changes from baseline in FEV1 % predicted at Week 21 using a 6% NI margin could not be clearly interpreted. First, for confirmatory evidence of efficacy, we rely upon adequate and well-controlled trial(s) that are prospectively planned for the primary analysis and its inference. Study C2302 was an open-label study that did not control for potential biases and did not have a prospectively planned primary analysis. Second, for comparisons of non-inferiority, we rely upon adequate justification of the NI margin based on historical studies. The Applicant assumed a 6% NI margin based on the original TOBI studies of 1997 which may not be appropriate for Study C2302 given its patient population (i.e. mostly adult, TOBI experienced) and unclear constancy of treatment effect assumptions. Due to the emergence of resistance, effects of TOBI over placebo in the current study may be substantially smaller than effects observed in the original TOBI studies which enrolled mostly younger, TOBI naïve patients. Note that other limitations with NI findings included potential biases from significantly higher rates of missing data in TIP patients at Week 21, p=0.031 (Table 12) and inconsistencies across cycles following on-therapy periods where findings for Cycle 1 (Week 5) and Cycle 2 (Week 13) were less favorable than at Cycle 3 (Week 21) (Table 13 & Figure 7).

There were also several negative findings in this Study C2302. Of the 517 randomized (treated) patients, discontinuation rates were 83/308 (27.0%) for TIP vs. 38/209 (18.2%) for TOBI (p=0.022) and discontinuations rates due to adverse events were 13.0% for TIP vs. 8.1% for TOBI (p= 0.084), (Figure 6). Reviewer analyses of relative changes based on imputed data also tended to favor TOBI over TIP (Table 13 and Figure 7). At the end of the on-therapy period of Cycle 2 (Week 13), the treatment difference favoring TOBI over TIP approached statistical significance using the Wilcoxon Rank Sum test (p=0.055). In both treatment arms, relative improvements tended to be modest following on-therapy periods and further reduced following off-therapy periods. However, only TIP patients showed negligible mean relative changes (i.e. 1% or less) following all on-therapy periods (i.e. Week 5, 13, 21) for several subgroups including patients from the US, patients of ages ≥ 20 years, patients with FEV1 % predicted at baseline ≥ 50%, and female patients (Tables 21-24). Evidence of efficacy also did not appear to be favorable based on differences in the rates of new anti-pseudomonal antibiotic use during the study which were 64.9% (TIP) vs. 54.5% (TOBI), a 10.4% difference significantly favoring TOBI, p=0.018 (Table 14).

1.3 Brief Overview of Clinical Studies

Table 1: Overview of Studies C2301 & C2303

	Study C2301	Study C2303
Type of Study:	Phase 3 randomized, double-blind study designed to assess the safety and efficacy of a 28 day course of TIP versus placebo in cystic fibrosis (CF) patients with cystic fibrosis due to *PA*.	
Objective:	Demonstrate the efficacy of a 28 day bid dosing regimen of TIP versus placebo.	
Treatment Arms:	Two arms: TIP and Placebo with 1:1 Randomization	
Sample Size:	61 Sensitivity Interim Analysis (SIA ITT) patients (29 in TIP arm, 32 in Placebo arm)	62 ITT patients (32 in TIP arm, 30 in Placebo arm)
Primary Endpoints:	Relative change in FEV1 percent predicted from baseline to the end of cycle 1 dosing (Day 28).	Relative change in FEV1 percent predicted from baseline to the end of cycle 1 dosing (Day 29).
Study Design:	CF patients aged 6 to 21 years with no prior exposure to inhaled anti-pseudomonals for at least 4 months start study therapy on Day 1 and receive a 28 day course of TIP/Placebo. Patients followed to the end of cycle 1 dosing at Day 28 (Study C2301) or Day 29 (Study C2303) for the primary efficacy assessment.	

Source: Reviewer Table

Table 2: Overview of Study C2302

Type of Study:	Randomized, open-label, multicenter, phase 3 trial to assess the safety of TIP compared to TOBI® in cystic fibrosis subjects
Primary Objective:	Primary objective: AEs, SAEs, hematology, chemistry, urinalysis, audiology, airway reactivity (FEV1), VS, PE, serum tobramycin concentration
Secondary objective:	Lung function (change in FEV1 % predicted), treatment satisfaction questionnaire for medication (TSQM), administration time, *P.aeruginosa* suppression, hospitalization
Treatment Arms:	Two arms: TIP and TOBI® with 3:2 Randomization
Sample Size:	517 randomized (treated) patients (308 in TIP arm, 209 in Placebo arm)
Primary Endpoints:	No primary endpoints were defined.
Study Design:	CF patients aged ≥ 6 years with no prior exposure to inhaled anti-pseudomonals for 1 month start study therapy on Day 1 and receive 3 cycles of 28 days on treatment and 28 days off treatment.

Source: Reviewer Table

2. INTRODUCTION

2.1 Overview

The Applicant has submitted NDA 201688 in support of the use of TOBI Podhaler for (b) (4) of cystic fibrosis patients with *Pseudomonas aeruginosa*. TOBI Podhaler is a drug-device combination of tobramycin dry inhalation powder (TIP) that is inhaled through the use of the T-326 inhaler. Four 28 mg capsules of TIP are punctured and inhaled twice a day for 28 day cycles of on/off therapy.

2.1.1 Class and Indication

Tobramycin inhalation powder hard capsule (TIP™) is a new formulation of tobramycin for inhalation to be delivered with the T-326 Inhaler, a dry powder inhaler (DPI). TIP is formed of low density particles (PulmoSpheres®, the Applicant's proprietary spray drying technology) with favorable aerodynamic characteristics (i.e. suitable for delivery to the lung) and high porosity. TOBI Podhaler was developed as an alternative to TOBI inhalation solution. TOBI solution is a nebulized therapy developed by the Applicant and approved in 1997 for a similar indication. This therapy is associated with significant treatment burden because of the maintenance/disinfection required for both nebulizer and compressor as well as the time needed for nebulization.

2.1.2 Applicant's Rationale for Current Submission

According to the Applicant:

The TIP/T-326 Inhaler drug-device combination presents a substantial improvement in design compared to the TOBI formulation and delivery system resulting in a reduced administration time, a decrease in the complexity of equipment, increased portability, no need for an external power supply, no need for refrigeration of drug product and reduced maintenance. The use of TIP as an alternative to nebulized liquid tobramycin solution will be simpler and quicker. TIP is intended to offer comparable efficacy and safety as TOBI but with decreased dosing time and simpler administration. As such, simplication of delivery of an efficacious dose of a new formulation for a medication that has an extensively described safety profile is important for patients infected with *P. aeruginosa*.

2.2 Data Sources

This application has included the appropriate data sets (both raw and derived) and documentation, as indicated in our filing review. Based on this information, the Review could reproduce the Applicant's primary and secondary analysis findings.

Data reviewed were from the following:

\\CDSESUB1\evsprod\Nda201688\0000 (NDA submission)

The datasets and locations used to for analyzing the primary and secondary endpoints in the placebo controlled studies are provided below

Dataset	Description of Dataset	Location
AEFF	Study C2301- Efficacy	\\Cdsesub1\evsprod\NDA201688\0000\m5\datasets\tbm100c2301\analysis\aeff.xpt'
AEFF	Study C2303- Efficacy	\\Cdsesub1\evsprod\NDA201688\0000\m5\datasets\tbm100c2303\analysis\aeff.xpt'

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality were considered acceptable following the Applicant's responses to our information request. Data sets and documentation were easily located by the Reviewer and were well documented. The Reviewer could reproduce the Applicant's primary analysis results as well as understand how the primary endpoint was derived. The level of effort to process the data in this submission was minimal and did not require any collaboration with the Computational Science Center.

3.2 Evaluation of Efficacy (Study C2301- Controlled)

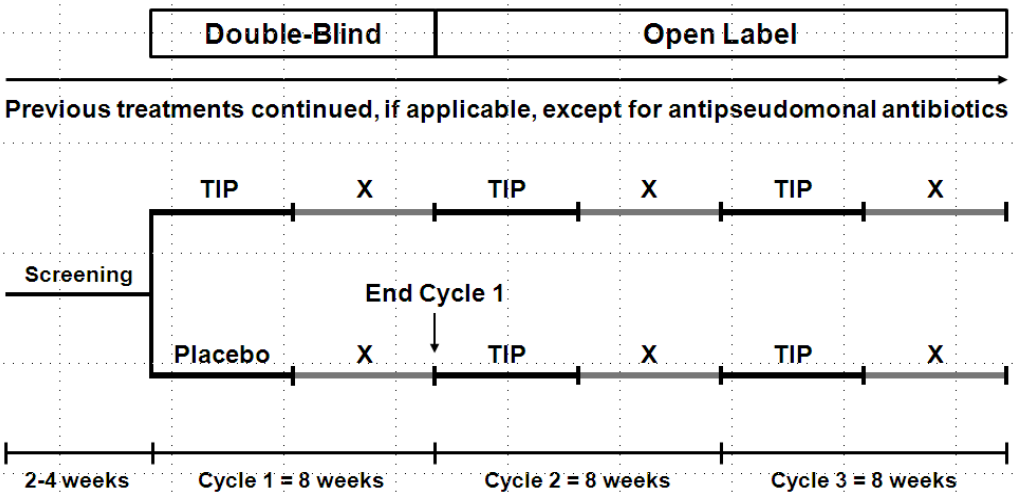
3.2.1 Study Design and Endpoints

Study Objective: The study objective was to demonstrate the efficacy of a 28 day bid dosing regimen of TIP versus placebo, as measured by the relative change from baseline in FEV1 percent predicted (Day 1) to the end of cycle 1 dosing (Day 28).

Study Population: This study randomized 102 patients (48 TIP, 54 Placebo) in a 1:1 ratio to receive TIP (112 mg, 4x28mg capsules) b.i.d. or matching placebo using a T-326 dry powder inhaler. Patients were enrolled between September 2005 and February 2007 at 33 investigative sites in North America (24 patients), Latin America (39 patients), and Europe (39 patients). The study population included patients between the ages of 6 and 21 years diagnosed with cystic fibrosis due to *Pseudomonas aeruginosa* who had no exposure to inhaled anti-pseudomonal antibiotics within 4 months prior to screening and had a screening FEV_1 % predicted between 25% and 80%.

***Study Design*:** Study C2301 was a double-blind, placebo-controlled trial over an 8 week period (1 cycle) consisting of 4 weeks of on-therapy (TIP vs. Placebo) followed by 4 weeks of off-therapy (Figure 1). This study also included an open label extension period of two cycles (16 weeks) in which all patients received TIP therapy. Patients were followed for a total of 24 weeks, an 8 week placebo-controlled period followed by a 16 week open label extension period.

Figure 1: Study Design (C2301)



TIP = tobramycin inhalation powder, X = Standard of care in off-treatment period
Randomization was at Baseline (i.e. Start of Cycle 1), Study visits were at Screening , Baseline, and at Weeks 2, 5, 9, 13, 17, 21, 25. There were also interim contacts at Weeks 3 & 7.
Source: Partially Adapted from Applicant Figure 7-1 in the briefing document

Primary Analysis Population: The Applicant's primary analysis population based on the amended study protocol was the SIA population which included 61 patients (29 TIP, 32 Placebo). Since the SIA excluded 34 of 95 patients in the Randomized Safety population who may be informative in evaluating the primary outcome, FDA Reviewer sensitivity analyses considered the All Randomized Safety Population to account for these patients and address possible biases in SIA analyses resulting from their exclusion. (See 'Sensitivity Analysis using All Randomized Safety Population (FDA Reviewer)' in Section 3.2.4 for further details).

Endpoints:

Primary Endpoint: The primary endpoint was the relative change in FEV_1 % predicted from baseline (Day 1 of drug treatment) to the end of study drug treatment (Day 28).

Other (exploratory) endpoints: The Applicant had amended the study protocol such that there would be no formal testing of secondary endpoints in the event of early stopping in the original interim analysis due to limited power. The following pre-specified endpoints were considered to be exploratory:

- Incidence of anti-pseudomonal antibiotics usage and number of days used anti-pseudomonal antibiotics in Cycle 1 (on and off treatment).
- Incidence of respiratory related hospitalization and number of days hospitalized in Cycle 1 (on and off treatment).

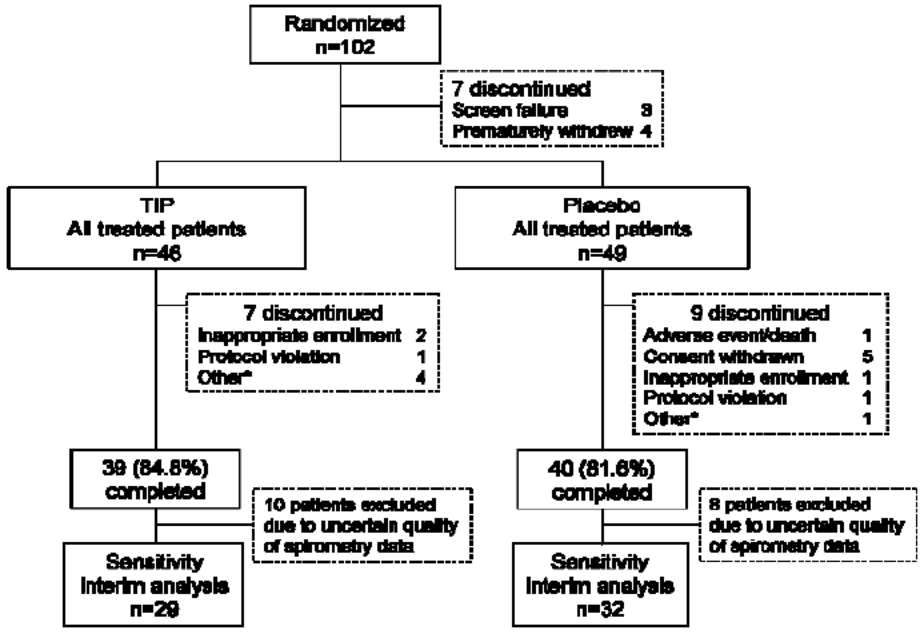
- Incidence of anti-pseudomonal antibiotics usage and respiratory related hospitalization (i.e., % subjects who were both users and hospitalized) in Cycle 1 (on and off treatment).
- Relative change from baseline in FVC % predicted in all cycles
- Relative change from baseline in FEF25-75 % predicted in all cycles

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition:

Patient disposition in Study C2301 for all randomized patients is shown in Figure 2. Of all randomized patients (N=102), there were 7 patients who were screen failures or had prematurely discontinued without receiving any treatment therapy. This resulted in an All Randomized Safety population of 95 treated patients (46 TIP, 49 Placebo) in which 16 patients discontinued (7 TIP and 9 Placebo patients) and another 18 patients (10 TIP and 8 Placebo) had unacceptable spirometry or FEV1 data quality, as determined by an external expert panel. These 34 patients in the All Randomized Safety population were excluded from the SIA population which consisted of only 61 patients (29 TIP, 32 Placebo). Further details regarding the rationale used for the sample size as well as patient disposition are provided in Tables 26 & 27 of the Appendix.

Figure 2: Patient Disposition (C2301)



*Includes moved, intolerant of inhaler, non-compliance and self discontinuation

Source: Applicant SCE Figure 2-1

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Demographic and Baseline Characteristics: Table 3 shows the demographic and baseline characteristics of patients included in the All Randomized Safety and SIA analysis populations. Baseline characteristics were generally balanced across the TIP and placebo arms in both populations. However, the distributions for many of these characteristics changed substantially when considering the SIA vs. the All Randomized Safety population. For example, the proportion of TIP patients from Europe was larger in the SIA vs. the All Randomized Safety population at 58.6% vs. 39.1%. Such a change in the distribution can lead to potential biases because findings for TIP patients were much stronger in Europe. For example, in Study C2301, the mean (median) relative change from baseline at Day 28 in FEV1 % predicted for TIP patients was 17.16% (19.25%) in Europe vs. 1.25% (-1.90%) in North America (Table 19). Substantially larger mean relative changes among TIP patients in Europe vs. the US were also noted in Study C2302 (Table 21). As stated previously, the FDA Reviewer sensitivity analysis would include randomized patients who received study drug to evaluate the sensitivity of the treatment effect to patient exclusions.

Table 3: Demographic and Baseline Characteristics (C2301 SIA)

Variable	Randomized Safety Population (N=95)		SIA Population (N=61)	
	TIP N=46	Placebo N=49	TIP N=29	Placebo N=32
Gender; n(%)				
Male	19 (41.3)	23 (46.9)	13 (44.8)	18 (56.3)
Female	27 (58.7)	26 (53.1)	16 (55.2)	14 (43.8)
Disease severity; n(%)				
FEV1 % pred. < 50%	17 (37.0)	18 (36.7)	10 (34.5)	10 (31.3)
FEV1 % pred. ≥ 50%	29 (63.0)	31 (64.3)	19 (65.5)	22 (68.8)
Age group; n(%)				
≥ 6 yrs to < 13 yrs	21 (45.7)	24 (49.0)	11 (37.9)	13 (40.6)
≥ 13 yrs to < 22 yrs	25 (54.3)	25 (51.0)	18 (62.1)	19 (59.4)
Race; n(%)				
Caucasian	37 (80.4)	43 (87.8)	25 (86.2)	29 (90.6)
Other	9 (19.6)	6 (12.2)	4 (13.8)	3 (9.4)
Age (years)				
Mean (± SD)	13.4 ± 4.42	13.2 ± 3.91	13.8 ± 3.82	14.1 ± 4.16
Region; n(%)				
North America	11 (23.9)	12 (24.5)	9 (31.0)	11 (34.4)
Latin America	17 (37.0)	17 (34.7)	3 (10.3)	5 (15.6)
Europe	18 (39.1)	20 (40.8)	17 (58.6)	16 (50.0)

Source: Reviewer Table

3.2.3 Statistical Methodologies

A brief summary of the basic statistical methodologies used in the Applicant's interim/ primary analyses and the FDA primary analysis are described below.

Applicant's Interim Analyses:

Study C2301 had originally planned to enroll 140 subjects with the potential for early stopping at the interim analysis when the 80th randomized subject completed Cycle 1 dosing on Day 28. An information-based group sequential procedure was used for the analysis of the primary efficacy endpoint involving one interim analysis with early superiority testing for efficacy and a potential sample size re-estimation based on the observed standard deviation but not the observed treatment difference (Mehta CR, Tsiatis AA, Drug Information Journal (2001)). The sequential boundaries and stopping rule at the interim and final analyses were based on the Lan-DeMets procedure with an alpha-spending function that resembles the O'Brien-Fleming boundaries (i.e. a Gamma spending function (Hwang, Shih and DeCani, 1990)). This analysis procedure ensures control of the overall Type I error at the 0.05 level. In the original interim analysis (OIA) the stopping boundary of 0.0080 (two-sided) was calculated using EAST software (version 3.0) assuming a treatment difference of 11% in the mean relative change in FEV1 % predicted from baseline to pre-dose Day 28 of Cycle 1, a standard deviation of 20%, 90% power, overall 1-sided α level of 0.025, 2 planned looks, a total sensitivity interim sample size n_1, and information fraction I ($I = n_1 /140$, where 140 is the originally planned sample size for the study). Based on the OIA, the stopping boundary was crossed early with an observed p-value of $0.0001 < 0.0080$ (two-sided OIA stopping boundary). No sample size re-estimation was performed.

However, due to subsequent concerns related to the reliability of spirometry used at Latin American sites, the OIA may not be reliable. Consequently, efficacy findings would depend on a sensitivity interim analysis (SIA) which would exclude all Latin American patients with unreliable FEV1 percent predicted measurements due to unreliable spirometry. The SIA was conducted using the same approach as in the OIA, essentially as if the OIA was never conducted. In contrast to the OIA which was planned for a total size of n=80 subjects (actual n=79), the SIA was planned for different scenarios of possible sample sizes between 53 and 79 subjects depending upon how many of the 26 Latin America subjects would be excluded from the OIA data, based on the review by the external expert panel. Since the expert review panel excluded 18 of the 26 Latin American subjects, the SIA stopping boundary was based on an $n=79-18=61$ subjects and was calculated to be 0.0044 (Table 4). Note that the smaller sample size for the SIA versus the OIA translates into larger critical values and thus smaller significance levels, making it harder to reject the null hypothesis. Based on the SIA, the stopping boundary was crossed early with an observed p-value of $0.0016 < 0.0044$. Table 4 provides the efficacy boundaries (two-sided) used for all of the possible scenarios of the SIA. Note that no sample size re-estimation was performed in the SIA.

Table 4: Efficacy Stopping Boundaries and Significance Levels (α two sided) under Total Sample Size (n_1) Scenarios for the SIA (C2301 SIA)

Sensitivity Interim Analysis				Final Analysis			
n_1	I_1	z_1	α_1	n_f [a]	I_f	z_f	α_f
80[b]	0.571	2.644	0.0082	140	1	1.986	0.0500
79[b]	0.564	2.653	0.0080	140	1	1.986	0.0500
78	0.557	2.664	0.0078	140	1	1.985	0.0500
77	0.550	2.674	0.0074	140	1	1.985	0.0500
76	0.543	2.685	0.0072	140	1	1.984	0.0500
75	0.536	2.696	0.0070	140	1	1.984	0.0500
74	0.529	2.706	0.0068	140	1	1.983	0.0500
73	0.521	2.718	0.0066	140	1	1.983	0.0500
72	0.514	2.729	0.0064	140	1	1.982	0.0500
71	0.507	2.739	0.0062	140	1	1.982	0.0500
70	0.500	2.750	0.0060	140	1	1.981	0.0500
69	0.493	2.761	0.0058	140	1	1.981	0.0500
68	0.486	2.771	0.0056	140	1	1.980	0.0500
67	0.479	2.782	0.0054	140	1	1.980	0.0500
66	0.471	2.794	0.0052	140	1	1.979	0.0500
65	0.464	2.805	0.0050	140	1	1.979	0.0500
64	0.457	2.815	0.0048	140	1	1.978	0.0500
63	0.450	2.826	0.0048	140	1	1.978	0.0500
62	0.443	2.837	0.0046	140	1	1.978	0.0500
61	**0.436**	**2.848**	**0.0044**	**140**	**1**	**1.977**	**0.0500**
60	0.429	2.859	0.0042	140	1	1.977	0.0500
59	0.421	2.871	0.0040	140	1	1.976	0.0500
58	0.414	2.882	0.0040	140	1	1.976	0.0500
57	0.407	2.893	0.0038	140	1	1.976	0.0500
56	0.400	2.904	0.0036	140	1	1.975	0.0500
55	0.393	2.915	0.0036	140	1	1.975	0.0500
54	0.386	2.926	0.0034	140	1	1.975	0.0500
53	0.379	2.937	0.0034	140	1	1.974	0.0500

Subscripts "f" & "1" denote "final" & "interim", "nf" is sample size for the final analysis. [a] Initially planned total sample size for study, n=140. [b] n=80 planned sample size for original interim analysis, (n=79 actual). Stopping boundary for SIA shown in **bold**.

Source: Partially Adapted from Applicant CSR Table 4-1

Applicant's Primary Analysis:

The Applicant's pre-specified primary analysis included 58 of 61 SIA patients with observed changes from baseline for FEV1 % predicted at Day 28. Three patients (2 TIP, 1 Placebo) with missing values for the relative change in FEV1 % predicted at Day 28 were excluded from this analysis. An analysis of covariance (ANCOVA) with factors for treatment, age, region and baseline FEV1 % predicted in the model was performed based on the observed data.

FDA Reviewer's Primary Analysis:

The Reviewer's primary analysis included all 61 SIA patients. For the 3 patients excluded from the Applicant's primary analysis, a value of -0.57% was imputed. Under the Reviewer's imputation scheme, a value of -0.57% corresponds to the minimum of 0 and the least favorable treatment mean among the 59 patients with observed values at Day 28 (i.e. mean of -0.57% in the placebo arm). This imputation scheme assumes that patients with missing FEV1 % predicted measurements at a given visit would have had a relative change that was not greater than '0' (i.e. no improvement from baseline) and was not favorable to the other group mean (i.e. no treatment benefit). The Reviewer's primary

analysis considered a non-parametric test (i.e. test based on the rank of the relative changes in FEV1 % predicted rather than the actual values) using an ANCOVA model with factors for treatment, age, region and baseline FEV1 % predicted. (See Section 4.1 for details on why non-parametric analyses were used). In addition, the Reviewer's primary analysis included a sensitivity analysis of all randomized (treated) patients to account for biases which may result from the exclusion of 34 treated patients (17 in each arm) who may be informative.

3.2.4 Results and Conclusions

Primary Analysis Results (Applicant and FDA Reviewer):
In the Applicant's initial primary analysis, results from the original interim analysis were favorable with an observed p-value that crossed the pre-defined two-sided group sequential stopping boundary of 0.0080 (i.e. p=0.0001 < 0.0080). However, due to FEV1 data quality concerns in 18 patients, a sensitivity interim analysis (SIA) was performed. In the SIA, the observed p-value crossed the pre-defined, two-sided stopping boundary for the scenario of 61 included subjects (p=0.0016 < 0.0044).

Table 5 shows results from the Applicant primary analysis (i.e. parametric ANCOVA) and FDA Reviewer primary analysis (i.e. non-parametric ANCOVA based on ranks). Additional results from unadjusted analyses (i.e. Applicant t-test, Reviewer t-test and Wilcoxon Rank Sum test) as well as the FDA Reviewer parametric ANCOVA are also shown. Both the Applicant and FDA Reviewer primary analyses showed significantly larger relative changes from baseline in FEV1 % predicted favoring TIP over Placebo at Day 28, regardless of the testing approach used. Note that in Reviewer analyses, the non-parametric tests were found to be more conservative than the corresponding parametric tests (e.g. p=.0061 vs. p=.0017 in the ANCOVA).

Table 5: Applicant and FDA Reviewer Analysis of Primary Endpoint: Relative Change (%) from Baseline in FEV1 % Predicted at Day 28 (C2301 SIA)

	TIP (N=29) n=27[1]	Placebo (N=32) n=31[1]	Mean Difference (SE)	95% CI for Difference	P-value
Applicant Analysis					
Adjusted Mean (%)	13.97	0.68	13.29 (3.98)	(5.31, 21.28)	**p=.0016[2]**
Unadjusted Mean (%)	13.21	-0.57	13.79 (3.95)	(5.87, 21.70)	p=.0010[3]
FDA Reviewer Analysis					
Adjusted Mean (%)	12.54	0.09	12.44 (3.77)	(4.89, 20.00)	p=.0017[4] **p=.0061[2]**
Unadjusted Mean (Median) (%)	12.26 (9.52)	-0.57 (-0.29)	12.83 (3.80)	(5.23, 20.44)	p=.0013[3] p=.0052[5]

[1] 3 patients (2 TIP 1 Placebo) with missing Day 28 FEV1 % predicted measurements were excluded from the Applicant analysis and had values of -0.57% imputed in the Reviewer analysis [2] Applicant (Reviewer) primary analysis- parametric (non-parametric) ANCOVA test adjusted for

age, region and baseline FEV1 % predicted. [3] Parametric t-test [4] Parametric ANCOVA [5] Non-parametric Wilcoxon Rank Sum test
Source: Reviewer Table

Sensitivity Analysis using All Randomized Safety Population (FDA Reviewer):
In Table 6, the primary analysis also included an FDA Reviewer sensitivity analysis which considered the All Randomized Safety population (N=95) in Study C2301 to assess potential biases from the 34 treated patients excluded from the SIA population. Although non-parametric analyses were primarily considered, parametric analyses were also performed. However, since imputation of substantial missing data in parametric analyses can severely deflate variance estimates, the Reviewer estimated the variance using only those patients with observed data (i.e. non-imputed data).

Based on Reviewer sensitivity analyses, findings were significant at the α=.05 level but only marginally so using the Wilcoxon rank sum test (p=0.035). Estimates for the mean treatment difference were 8.1% in the all randomized (treated) analysis, substantially below what was observed in the Reviewer analysis of SIA patients (e.g. 12.4% to 12.8% in Table 5). While this sensitivity analysis in all randomized (treated) patients does not suggest that patient exclusions were likely to have affected the significance of findings, it does suggest a high degree of uncertainty in assessing the strength of significant findings. Note that 7 randomized (untreated) subjects (2 TIP, 5 Placebo) were excluded from this analysis, but these patients were not found to impact findings.

Table 6: FDA Reviewer Sensitivity Analysis of the Primary Endpoint: Relative Change (%) from Baseline in FEV1 % Predicted at Day 28 Using Imputed Data (C2301 All Randomized Safety)

Relative Changes Using Imputed Data[1]	TIP N=46	Placebo N=49	Mean Treatment Difference (SE)	95% CI for Difference	P-value
Adjusted Mean (%)	6.87	-1.26	8.14 (3.07)	(2.00, 14.28)	p=.009[2,3] p=.023[2]
Unadjusted Mean (%)	7.52	-0.57	8.09 (3.08)	(1.92, 14.26)	p=.010[3,4] p=.035[5]

[1] Missing data for 37 subjects (19 TIP, 18 Placebo) were imputed using the observed placebo group mean value of -0.57%. [2] Parametric (non-parametric) ANCOVA based on values (ranks) adjusted for covariates of age and region. [3] Variance estimate based on observed cases only. [4] Parametric t-test, [5] Non-parametric Wilcoxon Rank Sum test
Note: 7 randomized (untreated) subjects (2 TIP, 5 Placebo) were excluded from the analysis.
Source: Reviewer Table

Supportive Analyses (FDA Reviewer):
Supportive analyses in Study C2301 were also limited as a result of using a sample size that was substantially smaller than the planned sample size of 140 subjects. The decision to use a smaller sample size was based on the original interim analysis in which early efficacy was observed for the primary endpoint. The study protocol was also amended such that there would be no formal testing of any secondary outcome measure (i.e. all secondary outcomes were considered to be exploratory). Table 7 shows findings from exploratory/other analyses using the All Randomized Safety Population (n=95). This table shows that in Cycle 1, rates of anti-pseudomonal antibiotics use, as determined by the FDA Clinical Reviewer, were 6/46 (13.1%) in TIP patients vs. 9/49 (18.4%) in placebo patients, a -5.3% difference favoring TIP which was not significant, p=0.477. Rates in respiratory related hospitalization also favored TIP at 2/46 (4.4%) vs. 6/49 (12.2%) but inferences were limited by low event rates and the lack of significant findings, p=0.166.

Table 7: Supportive Analyses- Anti-Pseudomonal Antibiotic Use and Respiratory Related Hospitalization in Cycle 1 (C2301 All Randomized Safety)

	TIP (N=46)	**Placebo (N=49)**	**Treatment Diff. (95% CI)** [1]
Rates of Antibiotic Use & Hospitalization in Cycle 1			
Any New Anti-Pseudomonal Antibiotic Use	6/46 (13.1)	9/49 (18.4)	-5.3 (-20.5, 10.0), p=0.477
Respiratory Related Hospitalization	2/46 (4.4)	6/49 (12.2)	-7.8 (-4.0, 20.7), p=0.166

[1]Confidence Interval Based on the Normal Approximation to the Binomial Distribution
Source: Reviewer Table

Conclusions:
Both the Applicant and FDA Reviewer analyses showed significantly larger relative changes from baseline in FEV1 % predicted favoring TIP over Placebo at Day 28, regardless of the testing approach used. Findings based on all randomized (treated subjects), though significant, were only slightly below the α=0.05 significance level based on the Wilcoxon rank sum test (p=0.035). These analyses, by imputing values -0.57% (i.e. the placebo group mean) for the 37/95 (39%) of randomized (treated) patients with missing relative changes, could limit the influence of potential biases in analyses based on the SIA population.

Supportive analyses based on other endpoints of Reviewer interest were limited due to the smaller than planned sample size. For example, analyses based on rates of anti-pseudomonal antibiotic use and rates of respiratory hospitalization favored the TIP arm but were not significant. Other factors limiting the robustness of primary analysis findings included uncertainty due to substantial patient exclusions, unclear reliability of spirometry, variability in relative changes by region (e.g. Europe vs. North America), unclear sustainability of relative changes within and across cycles and the unkown effects of using an older TIP manufacturing process (TIP_{old}) in comparison to the manufacturing process used in the to-be-marketed TIP product (TIP_{new}).

3.3 Evaluation of Efficacy (Study C2303- Controlled)

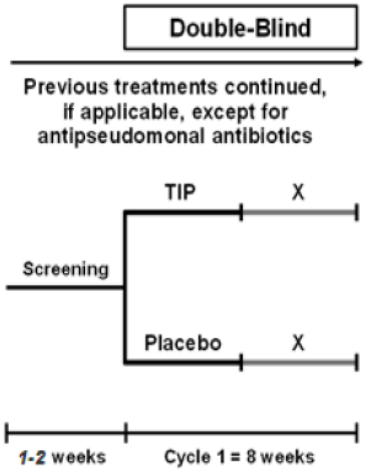
3.3.1 Study Design and Endpoints

Study Objective:
The study objective was to demonstrate the efficacy of a 28 day bid dosing regimen of TIP versus placebo, as measured by the relative change in FEV1 percent predicted from baseline (Week 1/cycle 1, Day 1) to the end of cycle 1 dosing (Week 5/cycle 1, Day 29)

Study Population:
The study population included patients between the ages of 6 and 21 years diagnosed with cystic fibrosis due to *PA* who had no exposure to inhaled anti-pseudomonal antibiotics within 4 months of screening and had a screening FEV_1 % pred. between 25% and 80%.

***Study Design*:**
Study C2303 was a double-blind, placebo-controlled trial over an 8 week period (1 cycle) consisting of 4 weeks of on-therapy (TIP vs. Placebo) followed by 4 weeks of off-therapy. This trial randomized 62 patients (32 TIP, 30 Placebo) 1:1 to receive TIP (112 mg, 4x28mg capsules) or matching placebo using a T-326 dry powder inhaler. Patients were enrolled between June 2009 and May 2011 at 18 investigative sites in the following 8 countries: Bulgaria (n=12), Egypt (n=8), Estonia (n=7), India (n=1), Latvia (n=5), Lithuania (n=3), Romania (n=3) and Russia (n=23). Unlike Study C2301, Study C2303 did not include an open label extension period which followed each treatment arm.

Figure 3: Study Design (C2303)



Randomization was at Baseline (i.e. Start of Cycle 1), Study visits were at Screening , Baseline, and at Weeks 5, 9. There was also an interim contact at Weeks 3.
Source: Partially adapted from Applicant Figure 7-10 in the AC meeting briefing document

Primary Endpoint:
The primary endpoint for this trial was the relative change in FEV1 % predicted from baseline to the end of study drug treatment (Day 29).

Primary Analysis Population:
The primary analysis population included 62 patients in the ITT population who received study drug treatment, 32 in the TIP arm and 30 in the placebo arm. Three ITT patients (1 TIP, 2 Placebo) did not have any baseline FEV1 % predicted measurements, 7 ITT patients (6 TIP, 1 Placebo) had missing or inadequate spirometry and Day 29 and 2 ITT patients (both TIP) had mistakenly received placebo instead of TIP therapy. One of the two TIP patients mistakenly being given Placebo was also counted above as having missing or inadequate spirometry at Day 29. Note that Study C2303 had originally planned to enroll 100 subjects but due to challenges with enrolling TOBI naïve patients, enrollment was terminated early.

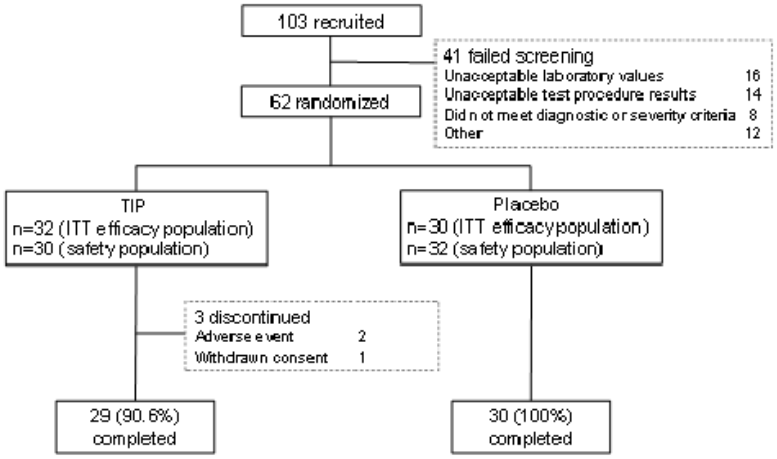
Other (exploratory) endpoints:
The Applicant did not formally test any secondary endpoints. The following pre-specified endpoints were considered to be exploratory:

- Incidence of anti-pseudomonal antibiotics usage and number of days used anti-pseudomonal antibiotics.
- Incidence of respiratory-related hospitalization and number of days hospitalized
- Incidence of anti-pseudomonal antibiotics usage and respiratory-related hospitalization (i.e., % subjects who were both users and hospitalized)
- Relative change from baseline in FVC % predicted
- Relative change from baseline in FEF25-75 % predicted

3.3.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition:
Patient disposition in Study C2303 for all randomized patients is shown in Figure 4. Of the 62 patients randomized to the ITT efficacy population, there were 32 TIP and 30 placebo patients. Since two patients in the TIP arm mistakenly received placebo and were included in the Placebo arm for the safety population, the safety population included 30 TIP and 32 placebo patients. In the ITT population, there were 3/32 (9.4%) of TIP patients who discontinued versus 0/30 (0%) of Placebo patients who discontinued. Further details regarding the rationale used for sample size and patient disposition are provided in Tables 26 & 27 in the Appendix.

Figure 4: Patient Disposition (C2303)



Source: Applicant's Figure 2-2 in Summary of Clinical Efficacy

Demographic and Baseline Characteristics:
Table 8 shows the demographic and baseline characteristics of patients included in the ITT. Characteristics were generally balanced across the treatment arms, however, a larger proportion of females were enrolled in TIP vs. the placebo arm (71.9% vs. 56.7%).

Table 8: Demographic and Baseline Characteristics (C2303 ITT)

Variable		ITT Population (N=62)	
		TIP (N=32)	**Placebo (N=30)**
Gender n (%)	Male	9 (28.1)	13 (43.3)
	Female	23 (71.9)	17 (56.7)
Severity n (%)[1]			
FEV1 % pred < 50%		10 (31.3)	9 (30.0)
FEV1 % pred ≥ 50%		22 (68.8)	21 (70.0)
Age group; n (%)			
≥ 6 yrs to < 13 yrs		16 (50.0)	14 (46.7)
≥ 13 yrs to ≤ 21 yrs		16 (50.0)	16 (53.3)
Race	Caucasian	31 (96.9)	30 (100)
	Other	1(3.1)	0 (0)
Age (years)			
Mean ± SD (Median)		13.1 ± 4.25 (12.5)	12.7 ± 4.70 (14.0)

[1] Screening FEV1 % predicted value. If missing, baseline FEV1 % predicted value used.
Source: Reviewer Table

3.3.3 Statistical Methodologies

A brief summary of the basic statistical methodologies used in the Applicant and FDA Reviewer primary analysis is described below.

Applicant*:* The Applicant's pre-specified primary analysis considered relative changes from baseline to Day 29. This analysis excluded 3 patients (1 TIP, 2 Placebo) with missing FEV1 % predicted values at baseline and imputed values of '0' for 7 patients (6 TIP, 1 placebo) with missing FEV1 % predicted values at Day 29. The Applicant's primary analysis used an analysis of variance (ANOVA) model with factors of treatment, screening FEV1 % predicted (<50% and ≥50%) and age (<13 years and ≥13 years). The choice of covariates in the ANOVA was based on the randomization stratification factors.

FDA Reviewer: The FDA Reviewer's primary analysis also excluded 3 patients with missing FEV1 % predicted values at baseline, imputed values of '0' for 7 patients with missing FEV1 % predicted values at Day 29, and used an ANOVA model with factors screening FEV1 % predicted (<50% and ≥50%) and age (<13 years and ≥13 years). However, unlike the Applicant, the Reviewer primary analysis considered a non-parametric ANOVA based on the rank of the relative changes rather than the actual values. (See Section 4.1 for details on why non-parametric analyses were used).

The Reviewer also conducted parametric analyses for comparison with non-parametric analyses. However, unlike Applicant parametric analyses, Reviewer parametric analyses estimated the variance of the treatment difference in a more conservative manner, using only those patients with observed data (i.e. non-imputed data). Note that single imputation methods (e.g. imputing '0' for each missing value), though adequate for point estimation, may fail to estimate the variance in an unbiased manner, especially if missing data is substantial. This is because substantial missing data requiring the imputation of a large number of '0' values can severely underestimate the variance. Note also that under the parametric model testing assumptions, subjects are assumed to have constant variance such that the addition of new patients in the analysis would not be expected to change the variance estimate.

3.3.4 Results and Conclusions

Results:
Primary Analysis: Table 9 shows results from the Applicant primary analysis (i.e. parametric ANOVA) and the Reviewer primary analysis (i.e. non-parametric ANOVA). Additional results from unadjusted analyses (i.e. Applicant t-test, FDA Reviewer t-test and Wilcoxon Rank Sum test) as well as the FDA Reviewer parametric ANOVA are also shown. Regardless of the testing approach used, Study C2303 failed to show a significant relative change from baseline in FEV1 % predicted favoring TIP over Placebo at Day 29. In the Reviewer's primary analysis based on a non-parametric ANOVA, treatment differences failed to show significance (p=0.233). In Reviewer analyses, non-parametric tests were more conservative than the parametric tests (p=0.233 vs. p=0.167 using an ANOVA). From Table 9, we also note that the median treatment difference for relative changes favoring TIP over Placebo (i.e. 3.17%−2.71%=0.46%) was substantially smaller than the corresponding mean difference (i.e. 5.82%). This indicates that differences in relative changes are highly, positively skewed and suggests the need for non-parametric

testing. It should also be noted that the imputation scheme in which a value of '0' is imputed in patients with missing relative change can exaggerate the skewness of the distribution.

Table 9: Applicant and Reviewer Analysis of the Primary Endpoint: Relative Change from Baseline in FEV1 % Predicted at Day 29 Using Imputed Data (C2303 ITT)

	TIP (N=32) n=31[1]	Placebo (N=30) n=28[1]	Mean Treatment Difference (SE)	95% CI	P-value
Applicant Analysis					
Adjusted Mean	8.2	2.3	5.9 (4.03)	(-2.2, 14.0)	**p=.148[2]**
Unadjusted Mean	8.3	2.4	5.8 (4.00)	(-2.2, 13.8)	p=.151[3]
Reviewer Analysis					
Adjusted Mean	8.19	2.27	5.91 (4.22)	(-2.54, 14.37)	p=.167[4,5] **p=.233[2]**
Unadjusted Mean (Median)	8.27 (3.17)	2.45 (2.71)	5.82 (4.19)	(-2.56, 14.20)	p=.170[3,4] p=.244[6]

[1] 3 Patients (1 TIP, 2 Placebo) with missing baseline FEV1 % predicted measurements were excluded from both the Applicant and Reviewer analyses. [2] Applicant (Reviewer) primary analysis- parametric (non-parametric) ANOVA adjusted for screening FEV1 % predicted (< 50% and ≥ 50%) and age (< 13 years and ≥ 13 years). [3] Parametric t-test [4] Variance estimates in Reviewer parametric analyses included only patients with observed values (i.e. non-imputed values). [5] Parametric ANOVA [6] Non-parametric Wilcoxon Rank Sum test.
Source: Reviewer Table

Supportive Analyses:
Supportive analyses in Study C2303 were limited due to the small numbers of patients requiring new anti-pseudomonal antibiotics or a respiratory related hospitalization over the 8 week study period. In Study C2303, the proportion of patients requiring anti-pseudomonal antibiotics was only 6/62 (9.7%) and this was similar between the TIP and placebo arms at 3/32 (9.4%) vs. 3/30 (10.0%), as shown in Table 10. However it should be noted that one patient with new antibiotic use in the TIP arm had mistakenly received placebo. Respiratory related hospitalizations were also rare in this study with only one patient (a placebo patient) having a respiratory related hospitalization.

Table 10: Supportive Analyses: Anti-pseudomonal Antibiotic Use, Respiratory Related Hospitalization (C2303 ITT)

	TIP (N=32)	Placebo (N=30)
Rates of Antibiotic Use & Hospitalization in 8 Week Study Period		
Any New Anti-pseudomonal Antibiotic Use	3/32 (9.4%)	3/30 (10.0%)
Respiratory Related Hospitalization	0/32 (0%)	1/30 (3.3%)

Source: Reviewer Table

Conclusions:
The Reviewer's primary analysis based on non-parametric testing failed to demonstrate a significant relative improvement from baseline in FEV1 % predicted at Day 29 (p=0.233). Additional sensitivity analyses also failed to show significance. The level of evidence presented from the primary analysis is not acceptable for drawing valid statistical inferences since the possibility of chance findings cannot safely be ruled out. Supportive analyses were also lacking due to the smaller than planned sample size. For example, comparisons of anti-pseudomonal antibiotics usage in the ITT population (n=62) were not informative since only 6 patients (3 per arm) had used new anti-pseudomonal antibiotics. Similarly, comparisons in hospitalization due to a respiratory event were also not informative due to the occurrence of only one such hospitalization across both treatment arms. In addition, there were concerns regarding the sustainability of treatment effects (Day 29 vs. Day 57) and the consistency of treatment effects across several subgroups, as discussed in Sections 4.2 & 5.1, respectively.

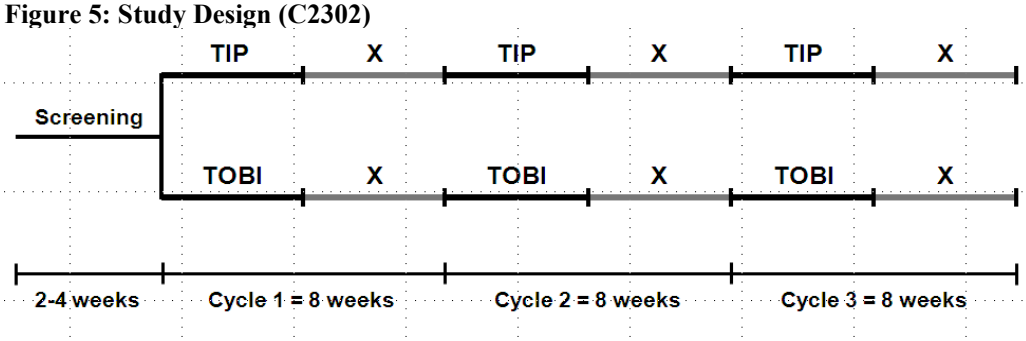
3.4 Evaluation of Efficacy (Study C2302- Open-label)

3.4.1 Study Design and Endpoints

Study Objective:
The primary objective was to evaluate the safety of twice-daily (b.i.d.) dosing of TIP delivered with the T-326 Inhaler, compared with TOBI delivered with the PARI LC PLUS jet nebulizer and DeVilbiss PulmoAide compressor or suitable alternative, across 3 cycles of therapy where each cycle consists of 28 days on-therapy followed by 28 days off-therapy.

Study Design:
Study C2302 was an open-label, comparative study over a 24 week period (3 cycles) consisting of 4 weeks of on-therapy (TIP vs. TOBI) followed by 4 weeks of off-therapy (Figure 5). The open-label design was necessitated by the very different modes of delivery (dry powder inhaler vs. nebulizer). This study randomized a total of 553 patients from 127 sites to receive TIP (112 mg, 4x28mg capsules) via the T-326 dry powder inhaler or TOBI (5 mL of a 60 mg/mL solution via the PARI LC Plus nebulizer and DeVilbiss PulmoAide compressor or suitable alternative) in a 3:2 ratio. Patients were enrolled between February 2006 and March 2009. The 517 ITT patients were from the following regions: North America (326 patients), Europe and rest of the world (175 patients) and Latin America (16 patients).

Figure 5: Study Design (C2302)



X= Standard Care during off-TIP/TOBI therapy period.
Randomization was at Baseline (i.e. Start of Cycle 1).
Study visits were at Screening , Baseline, and at Weeks 2, 5, 9, 13, 17, 21, 25.
Source: Partially adapted from Applicant Figure 7-5 in the AC briefing document

Study Population:
The study population included patients diagnosed with cystic fibrosis due to *Pseudomonas aeruginosa* who were 6 years and older, who had no exposure to inhaled anti-pseudomonal antibiotics within 1 month prior to screening and who had a screening FEV_1 % predicted between 25% and 75%.

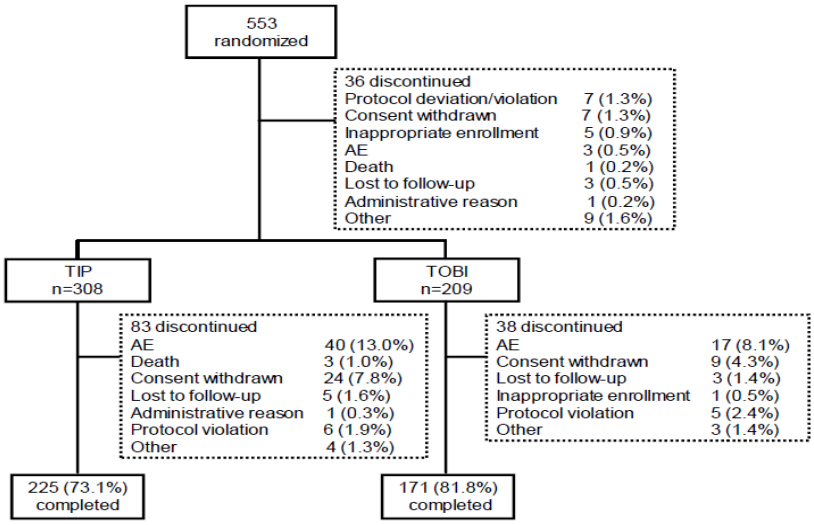
Endpoints:
There was no primary efficacy variable for this study. Secondary efficacy variables included spirometry measurements such as relative changes in FEV1 % predicted from baseline at all scheduled post-treatment visits (Weeks 2, 5, 9, 13, 17, 21 and 25), changes in *PA* density, changes in *PA* tobramycin minimum inhibitory concentration (MIC) susceptibility and time to first hospitalization due to a respiratory SAE. An additional secondary endpoint was the report of treatment satisfaction.

Analysis Population:
The ITT (identical to the All Randomized Safety Population) was the main analysis population for efficacy and safety. The ITT included 517 patients (308 TIP and 209 TOBI) who were randomized and treated with study therapy.

3.4.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition:
Of the 553 (329 TIP, 224 TOBI) randomized patients, there were 36 patients (21 TIP, 15 TOBI) who were discontinued prior to receiving study therapy and excluded from the ITT. Of the remaining 517 ITT patients, a larger percentage of discontinuations (27.0% TIP vs. 18.2% TOBI) and discontinuations due to adverse events (13.0% TIP vs. 8.1% TOBI) were observed for TIP patients (Figure 6).

Figure 6: Patient Disposition (C2302)



Note: Among the 517 treated patients (308 TIP, 209 TOBI), discontinuation rates and discontinuation rates due to AEs were higher in the TIP arm at 27.0% (TIP) vs. 18.2% (TOBI), p=.022 and at 13.0% (TIP) vs. 8.1% (TOBI), p=.084, respectively.
Source: Adapted from Applicant Figure 2-3 in Summary of Clinical Efficacy

Demographic and Baseline Characteristics: In Table 11, patients were generally balanced between the treatment groups with respect to demographic and baseline characteristics. Study C2302 included a relatively small percentage of patients under 13 years of age (less than 9% of ITT) and a relatively large percentage of patients at or above 20 years of age (over 69% of ITT). Approximately, 63% and 34% of patients were from North America and Europe, respectively.

Table 11: Demographic and Baseline Characteristics (C2302 ITT)

Variable	ITT Population (N=517)	
	TIP (N=308)	**TOBI (N=209)**
Age group; n (%)		
≥ 6 yrs to < 13 yrs	28 (9.1)	18 (8.6)
≥ 13 yrs to < 20 yrs	66 (21.4)	48 (23.0)
≥ 20 yrs	214 (69.5)	143 (68.4)
Gender n (%)		
Male	171 (55.5)	115 (55.0)
Female	137 (44.5)	94 (45.0)
Race		
Caucasian	279 (90.6)	189 (90.4)
Other	29 (9.4)	20 (9.6)
Region		
North America	195 (63.3)	131 (62.7)
Europe and rest of world	104 (33.8)	71 (34.0)

Latin America	9 (2.9)	7 (3.3)
Disease severity; n (%)[1]		
FEV1 % pred < 50%	128 (41.6)	89 (42.6)
FEV1 % pred ≥ 50%	180 (58.4)	120 (57.4)
Age (years)		
Mean ± SD (Median)	25.9± 11.36 (24.0)	25.2± 10.20 (24.0)

[1] Screening FEV1 % predicted value. If missing, baseline FEV1 % predicted value used.
Source: Reviewer Table

3.4.3 Statistical Methodologies

Applicant's Analysis:
There was no primary efficacy endpoint defined in this study. Efficacy analysis was based on the ITT population. All analyses were based on observed data; no imputation was performed for missing data. Secondary efficacy variables included relative changes in FEV1 % predicted from baseline to each post-baseline visit. A planned analysis of non-inferiority of TIP vs. TOBI based on a one-sided 85% confidence interval calculated from an analysis of covariance (ANCOVA) of relative change in FEV1 % predicted from baseline to pre-dose Day 28 of Cycle 3 was also performed. The non-inferiority (NI) margin of $\Delta = 6\%$ was pre-defined. However, based on the Division's current thinking, interpretation of these findings is uncertain since an appropriate NI margin cannot be clearly justified for the endpoint based on relative changes from baseline in FEV1 % predicted.

FDA Reviewer Analysis:
The Reviewer's analysis of relative changes in FEV1 % predicted across time points included all 517 ITT patients. Under the Reviewer's imputation scheme, a value corresponding to the minimum of 0 and the least favorable treatment mean among the patients with observed values at each time point was imputed. The Reviewer's analyses of relative changes were based on unadjusted estimates.

3.4.4 Results and Conclusions

Results:

Sustainability of Relative Changes in FEV1 % Predicted:
As noted earlier, patients in Study C2302 received three 8 week cycles (24 weeks) of on/off therapy where each cycle consisted of 4 weeks of on-therapy (TIP vs. TOBI) followed by 4 weeks of off-therapy. This design allows for treatment comparisons of longer term efficacy (TIP vs. TOBI) based on relative changes from baseline in FEV1 % predicted at several time points throughout the 24 week study period (i.e. Visits at Weeks 2, 5, 9, 14, 17, 21 & 25). This design also allows for comparisons of relative changes across time points within each of the treatment arms. However, there were factors which limited the strength of treatment comparisons and within treatment comparisons over time.

One factor was high rates of missing data (esp. between Week 9 and Week 21) which also varied across visits. For example, in the TIP arm missing data rates were 5.5% at Week 2 vs. 26.3% at Week 21 (Table 12). To address this factor, Reviewer analyses imputed missing values at each visit using the minimum of 0 and the least favorable group mean among observed patients. While this may limit potential biases from missing data, there is still considerable uncertainty in relative changes due to high overall rates of missing data as well as differences in the rates of missing data within and between treatment arms across visits. Note that since missing data are likely to be informative (non-random) with a negative impact on relative improvements in FEV1 % predicted, analyses based on observed cases may involve strong biases favoring the time point (or treatment) with higher rates of missing data.

Table 12: Number (%) of Patients with Missing FEV1 % Predicted Measurements by Visit (C2302 ITT)

Visit:	TIP (N=308)	TOBI (N=209)
Week 2	17 (5.5%)	14 (6.7%)
Week 5	40 (13.0%)	15 (7.2%)
Week 9	41 (13.3%)	25 (12.0%)
Week 13	56 (18.2%)	31 (14.8%)
Week 17	69 (22.4%)	34 (16.3%)
Week 21	81 (26.3%)	38 (18.2%)
Week 25	86 (27.9%)	40 (19.1%)

Comparisons in rates of missing data were significantly higher in TIP patients at Week 5 (p=.036), Week 21 (p=.031) and Week 25 (p=.022)
Source: Reviewer Table

Table 13 shows the sustainability of treatment effects at each visit based on mean and median relative changes in the Reviewer's analysis. Figure 7 graphically shows treatment comparisons of mean relative changes from baseline in FEV1 % predicted across visits with vertical bars representing the 95% confidence interval for the estimate. TIP patients had a mean relative change from baseline in FEV1 % predicted of 6.77% at Week 2 which dropped to 2.46% & -0.52% at Weeks 5 & 9 of Cycle 1 and varied between 0.99% and 2.28% in Cycles 2 and 3. TOBI patients had a mean relative change of 6.80% at Week 2 which dropped to 3.33% & 0.52% at Weeks 5 & 9 of Cycle 1 and varied between -0.41% and 3.67% in Cycles 2 and 3. Overall, TIP patients fared slightly worse than TOBI patients over the first two cycles, with slightly smaller mean improvements following the on-therapy periods at Weeks 5 & 13 of 2.46% & 1.87% for TIP patients vs. 3.33% & 3.67% for TOBI patients. However, TIP patients fared slightly better than TOBI patients following the on-therapy period in Cycle 3 (2.28% vs. 1.90%).

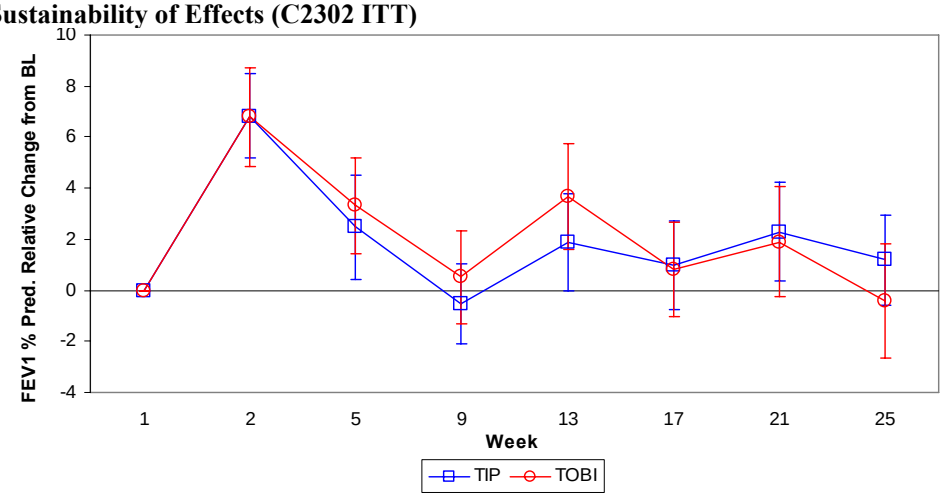
Table 13: Reviewer's Analysis of Sustainability of Relative Changes from Baseline in FEV1 % Predicted at All Visits Using Imputed Data (C2302 ITT)

Visit:	TIP N=308 Mean (Median)	TOBI N=209 Mean (Median)	Mean Difference: TIP-TOBI (SE)	95% CI	P-value
Week 2	6.77 (4.47)	6.80 (3.77)	-0.02 (1.30)	(-2.57, 2.52)	p=.987[1] p=.898[2]
Week 5	2.46 (0.00)	3.33 (1.98)	-0.87 (1.49)	(-3.80, 2.07)	p=.561[1] p=.164[3]
Week 9	-0.52 (-0.52)	0.52 (-0.52)	-1.04 (1.22)	(-3.44, 1.36)	p=.395[1] p=.324[3]
Week 13	1.87 (0.00)	3.67 (0.00)	-1.80 (1.47)	(-4.69, 1.08)	p= .219[1] p=.055[3]
Week 17	0.99 (0.00)	0.82 (0.00)	0.17 (1.32)	(-2.44, 2.77)	p=.901[1] p=.863[3]
Week 21	2.28 (0.00)	1.90 (0.00)	0.38 (1.49)	(-2.55, 3.32)	p=.798[1] p=.736[3]
Week 25	1.21 (-0.41)	-0.41 (-0.41)	1.62 (1.28)	(-0.90, 4.14)	p= .207[1] p=.176[2]

[1] Parametric t-test, [2] Wilcoxon Rank Sum test: p-value denotes significance of TIP benefit over TOBI [3] Wilcoxon Rank Sum test: p-value denotes significance of TOBI benefit over TIP

Source: Reviewer Table

Figure 7: Mean FEV1 % Predicted Relative Changes Across Visits: Evaluation of the Sustainability of Effects (C2302 ITT)



Source: Reviewer Figure

Exploratory/Other Analyses: In Table 14, exploratory/other analyses of Reviewer interest in Study C2302 included the rates of new anti-pseudomonal antibiotic use and respiratory related hospitalization over the 24 week study period. The proportion of patients requiring new anti-pseudomonal antibiotics in this study was significantly higher in the TIP vs. the TOBI arm at 200/308 (64.9%) vs. 114/209 (54.5%), p=0.018. However, rates of

respiratory related hospitalizations were similar between the treatment arms (i.e. only slightly higher in TIP arm).

Table 14: Other Analyses- Anti-pseudomonal Antibiotic Use and Respiratory Related Hospitalization Over 3 cycles (C2302 ITT)

	TIP (N=308)	TOBI (N=209)	Treatment Difference (95% CI[1]), p-value
Rates of Antibiotic Use & Hospitalization Over 3 Cycles			
New Anti-pseudomonal Antibiotic Use	200 (64.9%)	114 (54.5%)	10.4% (1.8%, 18.9%), p=0.018
Respiratory Related Hospitalization	75 (24.4%)	46 (22.0%)	2.3% (-5.2%, 9.6%), p=0.537

[1]Confidence Interval Based on the Normal Approximation to the Binomial Distribution
Source: Reviewer Table

Conclusions:
Study C2302 was primarily a safety study which did allow for some assessments of efficacy. However, several concerns were raised regarding the overall evidence of efficacy presented:

Open-label design: This study uses an open label design with the primary objective of evaluating safety outcomes and a secondary objective of evaluating efficacy outcomes. However, because it is open-label, it has the potential to bias both safety and efficacy evaluations.

Limited Interpretation of Efficacy Findings: Although this study appears to offer some supportive evidence, the interpretation of these findings was limited by several factors. For example, the Applicant's finding of non-inferiority (NI) of TIP vs. TOBI for relative changes from baseline in FEV1 % predicted at Week 21 using a 6% NI margin could not be clearly interpreted. First, for confirmatory evidence of efficacy, we rely upon adequate and well-controlled trial(s) that are prospectively planned for the primary analysis and its inference. Study C2302 was an open-label study that did not control for potential biases and did not have a prospectively planned primary analysis. Second, for comparisons of non-inferiority, we rely upon adequate justification of the NI margin based on historical studies. The Applicant assumed a 6% NI margin based on the original TOBI studies of 1997 which may not be appropriate for Study C2302 given its patient population (i.e. mostly adult, TOBI experienced) and unclear constancy of treatment effect assumptions. Due to the emergence of resistance, effects of TOBI over placebo in the current study may be substantially smaller than effects observed in the original TOBI studies which enrolled mostly younger, TOBI naïve patients. Note that there were other limitations such as potential biases from significantly higher rates of missing data in the TIP arm at Week 21, p=0.031 (Table 12) and inconsistencies of findings across cycles where comparisons following on-therapy periods in Cycle 1 (Week 5) and Cycle 2 (Week 13) were less favorable than at Cycle 3 (Week 21) (Table 13 & Figure 7).

Unfavorable Efficacy Findings: There were also unfavorable efficacy findings in this study. Of the 517 randomized (treated) patients, discontinuation rates were 83/308 (27.0%) for TIP vs. 38/209 (18.2%) for TOBI (p=0.022) and discontinuations rates due to adverse events were 13.0% for TIP vs. 8.1% for TOBI (p= 0.084), (Figure 6). Reviewer analyses of relative changes based on imputed data also tended to favor TOBI over TIP (Table 13 and Figure 7). At the end of the on-therapy period of Cycle 2 (Week 13), the treatment difference favoring TOBI over TIP approached statistical significance using the Wilcoxon Rank Sum test (p=0.055). In both treatment arms, relative improvements tended to be modest following on-therapy periods and further reduced following off-therapy periods. However, only TIP patients showed negligible mean relative changes (i.e. 1% or less) following all on-therapy periods (i.e. Week 5, 13, 21) for several subgroups including patients from the US, patients of ages ≥ 20 years, patients with FEV1 % predicted at baseline ≥ 50%, and female patients (Tables 21-24). Evidence of efficacy also did not appear to be favorable based on differences in the rates of new anti-pseudomonal antibiotic use during the study which were 64.9% (TIP) vs. 54.5% (TOBI), a 10.4% difference significantly favoring TOBI, p=0.018 (Table 14).

Sustainability of Improvements in FEV1 % Predicted: For both TIP and TOBI, improvements from baseline in FEV1 % predicted were modest during the on-therapy period and were substantially reduced during the off-therapy period. In TIP patients, both mean and median FEV1 % predicted measurements dropped below their baseline levels following the first cycle of on/off therapy. It should be noted that evaluation of the sustainability of improvements was limited by high rates of missing data which varied across visits and tended to be greater in TIP patients.

Missing Data: As stated above, significant differences in rates of missing data made treatment comparisons in Study C2302 challenging. Reviewer analyses imputed missing data using the minimum of 0 and the least favorable group mean, however, it is not clear as to whether such an imputation would be conservative enough to account for the imbalance in treatment groups with respect to discontinuation rates, especially for discontinuations due to adverse events.

Subgroup Analyses: As stated above, there were several subgroups in which mean relative changes in TIP patients were small or negligible (i.e. 1% or less) following on therapy periods (i.e. Week 5, 13, 21). These subgroups include patients from the US, patients aged 20 years and above, patients with FEV1 % predicted at baseline ≥ 50%, and female patients (Tables 21-24). Mean relative changes for TOBI patients tended to be slightly higher than in TIP patients for these subgroups following on-therapy periods.

3.5 Evaluation of Safety

Refer to the safety review of the medical officer, Dr. Shrimant Mishra.

3.6 Summary and Conclusions

Based on our review of the three clinical studies submitted, there is some persuasive evidence of a treatment benefit for patients with cystic fibrosis due to *PA* using TIP. Study C2301 provided adequate evidence of a TIP treatment benefit, while Study C2303 provided only weak evidence since the primary endpoint was not met. Additionally, Study C2302, an open-label comparative safety study, provided some weak supportive evidence towards the overall risk/benefit assessment. However, such evidence was limited by several factors including the open-label study design, lack of a prospectively planned primary analysis, uncertainty in treatment effects compared to placebo, potential biases due to significantly higher discontinuation rates in TIP patients and unfavorable comparisons in relative changes following on-therapy periods of other cycles.

Overall, we considered this submission to be potentially approvable depending on the considerations and recommendations from the other review disciplines, the final product labeling and the Applicant's agreement to all necessary post-marketing commitments. However, there are still several concerns with this submission related to the usability of the product, increases in tobramycin minimum inhibitory concentrations (MICs) for *Pseudomonas aeruginosa* isolates, patient exclusions, reliability of spirometry used in FEV1 % predicted measurements, regional effects, sustainability of effects and supportive analyses (e.g. rates of new anti-pseudomonal antibiotic use, rates of respiratory hospitalization).

4. EXPLORATORY/SENSITIVITY ANALYSES

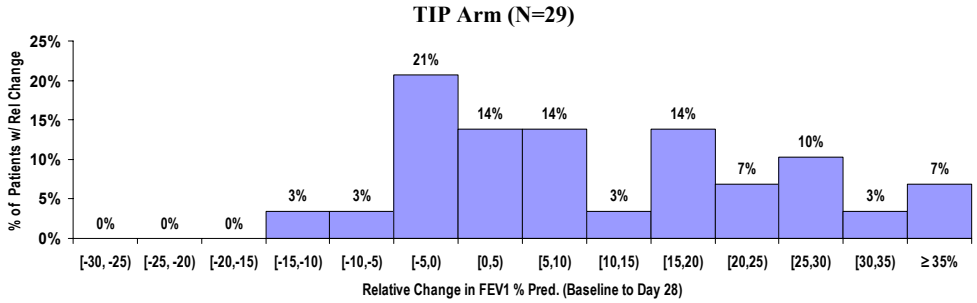
4.1 Distribution of Relative Changes in FEV1 % Predicted

Study C2301:
Distribution of Relative Changes in FEV1 % Predicted:
Figure 8 shows the Study C2301 distributions of TIP and Placebo relative changes in FEV1 % predicted from baseline to Day 28. Relative changes for TIP patients were highly skewed in the positive direction with a mean of 12.26% vs. a median of 9.52%. This positive skewness was primarily observed in patients under the age of 13 years and in patients with FEV1 $\geq$ 50% predicted at baseline where the mean relative changes greatly exceeded median relative changes (Table 19). In Figure 8, relative changes for Placebo patients were not directionally skewed with a mean (median) of -0.57% (-0.29%), but did exhibit relative "heaviness" near the outer regions of the distribution (e.g. for relative changes of approximately $\pm$ 20% or 1.5 standard deviations from the mean of -0.57%).

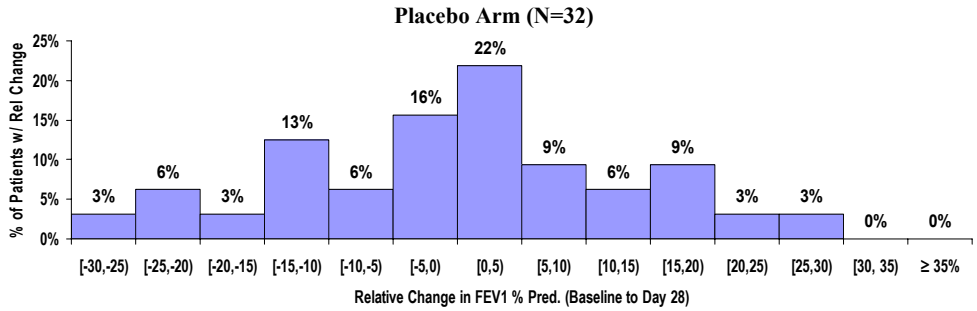
In Figure 8, comparisons of TIP vs. Placebo distributions of relative changes strongly favored TIP patients in the extreme tail regions of the distributions, especially the right (positive) tail. In the right tail, the most favorable (next most favorable) relative change among TIP patients of 56.4% (48.2%) exceeded the most favorable (next most favorable) relative change in the Placebo arm of 25.3% (23.9%) with a treatment difference of 31.1% (24.3%). In the left tail, treatment differences of 18.1% (17.5%) for the least favorable (next least favorable) relative change were not as pronounced as in the right tail but were still relatively large compared to treatment differences in the middle of the distribution which fell below 10% (e.g. TIP median = 9.5%, Placebo median = -0.3%). Based on the

distributions of the two treatments, TIP therapy appears to provide an exaggerated benefit over placebo in a small number of patients with more extreme relative changes. This can lead to potential biases and violate the normality assumptions needed for parametric testing. As stated above, Reviewer analyses considered non-parametric testing for the primary analysis to negate any impact due to influential observations.

Figure 8: Distribution of FEV1 % Predicted Relative Changes (C2301 SIA)



Mean=12.26%, Median=9.52%, Std. dev=16.28%, Most (least) favorable: 56.4%, 48.2% (-10.2%, -6.1%)



Mean=-0.57%, Median=-0.29%, Std. dev=13.39%, Most (least) favorable: 25.3%, 23.9% (-28.3%, -23.6%, -21.8%, -19.8%)

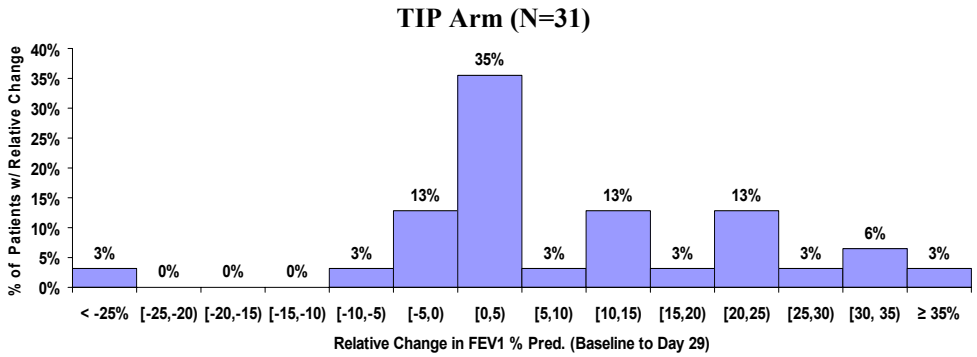
Source: Reviewer Figure

`***Study C2303*:**

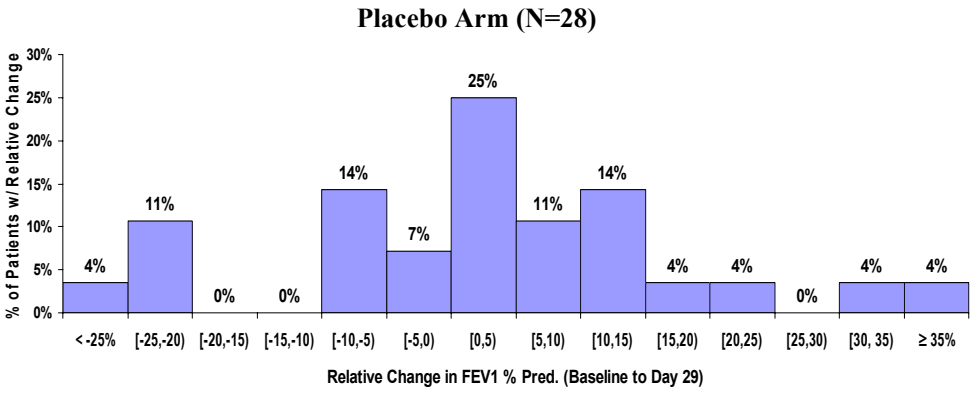
Distribution of Relative Changes in FEV1 % Predicted:
Figure 9 shows the distributions of relative changes in FEV1 % predicted from baseline to Day 29 by treatment arm in the Reviewer primary analysis. TIP relative changes were highly skewed in the positive direction with a mean of 8.27% vs. a median of 3.17%. In contrast, relative changes in the Placebo arm were not directionally skewed and had a similar mean and median of 2.45% and 2.71%, respectively. As was observed for Study C2301, the distribution for Placebo patients in Study C2303 showed relative "heaviness" in the outer tail regions, especially in the left tail region. For example, among the 28 patients in the Placebo arm who were included in the Reviewer's primary analysis, 4 patients (14%) had large (unfavorable) relative changes at Day 29 that were 25% (1.6 standard deviations) or more below the mean of 2.45%.

When comparing the distributions of relative changes between the treatment arms, the most pronounced differences favoring TIP over placebo were in patients with relative changes in the negative tail of the distributions. For example, aside from the outlying TIP observation of -36.7%, the next less favorable relative change in the TIP arm was only -6.9%. In the placebo arm, 7 (25%) of the patients had relative changes of -7% or worse and 4 patients (14%) had relative changes of -22.8% or worse.

Figure 9: Distribution of FEV1 % Predicted Relative Changes (C2303 ITT)



Mean=8.27, Median=3.17%, Std. dev=14.93%, Most (least) favorable: 35.7%, 34.6%, 31.0%, 29.3% (-36.7%, -6.9%)



Mean=2.45%, Median=2.71%, Std. dev=15.77%, Most (least) favorable: 38.5%, 31.7% (-28.3%, -23.9%, -23.5%, -22.8%)

Source: Reviewer Figure

Comparison of Relative Changes in FEV1 % Predicted in Studies C2301 and C2303
Overall improvements with TIP therapy in Study C2303 were not as clear as in Study C2301 due to several factors. These factors included limitations in study enrollment where a small than planned sample size was used (61 patients vs. 100 patients) in addition to an unexpectedly high dilution of TIP effects in the primary analysis. This dilution resulted from the imputation of missing Day 29 FEV1 % predicted measurements with a value of '0' (6 cases) and the mis-dispensation of placebo instead of TIP study drug (2 cases). Since one of the TIP patients who mistakenly received Placebo also had a missing Day 29 measurement, 7 of 31 (22.6%) TIP patients included in the Reviewer's primary analysis failed to have their treatment effects properly measured. Furthermore, these improper measurements occurred at a much higher rate in the TIP arm vs. the Placebo arm (22.6% vs. 3.6%).

In addition, influential cases may have also contributed to the differences in Study C2301 and Study C2303. In Study C2303, there were 3 potentially influential cases (i.e. cases which are substantially higher/lower than all other cases in that treatment arm across both studies), none of which favored TIP therapy. This includes observed relative changes of -36.7% in the TIP arm and 38.5% & 31.7% in the placebo arm. In Study C2301, there were 2 influential observations, both favoring TIP (i.e. relative changes of 56.4% & 48.2%).

4.2 Sustainability of Relative Changes in FEV1 % Predicted

Study C2301: Sustainability of Relative Changes in FEV1 % Predicted: As noted earlier, Study C2301 patients were followed for 3 cycles, receiving either on/off TIP vs. Placebo therapy in the first 8 weeks (first cycle) and on/off TIP therapy in the following 16 weeks (second and third cycle). Since all patients would receive two or three cycles of TIP therapy, this design allows for an evaluation of the sustainability of the relative improvements from baseline in FEV1 % predicted. However such an evaluation was limited by several factors which can confound comparisons.

One factor was that comparisons of TIP improvements in FEV1 % predicted across cycles were not placebo-controlled in Cycles 2 & 3. Therefore, comparisons of improvements at different visits were all relative to baseline measurements within a treatment arm. These types of comparisons are limited because they can be more easily influenced by potential confounding variables specific to the cycle or time point considered. The Reviewer considered placebo-controlled comparisons as providing the most reliable evidence of sustainability of relative changes in FEV1 % predicted.

Another factor was substantial missing data that varied between treatments or across visits and cycles. For example, comparisons of relative changes between treatments from Week 2 to Week 9 can be confounded by missing data rates which remained constant in TIP patients at 10.3% but increased rapidly in Placebo patients from 0% to 15.6% (Table 15). Similarly, comparisons of relative changes in TIP patients across visits (following on-therapy periods) can be confounded by rapidly increasing rates of missing data across the 3 cycles (i.e. 6.9% at Week 5 vs. 17.2% at Week 13 vs. 20.7% at Week 21).

Table 15: Number (%) of Patients with Missing FEV1 % Predicted Measurements by Visit (C2301 SIA)

Visit:	TIP (N=29)	Placebo (N=32)
Week 2	3 (10.3%)	0
Week 5[1]	**2 (6.9%)**	**1 (3.1%)**
Week 9	3 (10.3%)	5 (15.6%)
Week 13	5 (17.2%)	5 (15.6%)
Week 17	6 (20.7%)	7 (21.9%)
Week 21	6 (20.7%)	7 (21.9%)
Week 25	6 (20.7%)	8 (25.0%)

[1]Primary endpoint evaluated at Week 5
Source: Reviewer Table

To address these limitations, Reviewer analyses imputed missing values at each time point using the minimum of 0 and the least favorable group mean. Note, however, that there is no clear solution for handling these trends in missing data. Since missing data is likely to be informative (non-random) with a negative impact on relative improvements in FEV1 % predicted, analyses based on observed cases may involve strong biases favoring the time point (or treatment) with higher rates of missing data. Analyses based on imputed data (e.g. Reviewer analyses) can serve to reduce the influence of such biases but may still involve substantial uncertainty when rates of informative missing data are relatively high.

Although there were limiting factors, Reviewer analyses evaluated the sustainability of relative changes in FEV1 % predicted in Table 16 with graphical representations for mean and median relative changes in Figures 10 & 11. In Table 16 & Figure 10, mean relative changes from baseline in FEV1 % predicted at Week 5 dropped substantially both within and across cycles. The drop within cycles (i.e. within cycle 1) can be observed at Week 5 (following the on-therapy period) vs. Week 9 (following the off-therapy period) where the mean relative change decreased from 12.26% to 6.83%. The drop across cycles can be observed at Week 9 vs. Week 13 & Week 21 (following the on-therapy periods for cycles 1 vs. 2 & 3), where mean relative change was 12.26% vs. 8.81% & 9.08%. In Table 16 & Figure 11, steep drops in relative changes across cycles were also observed for median relative changes. In TIP patients, the median change at Week 5 of 9.52% dropped to 5.74% & 6.25% at Weeks 13 & 21.

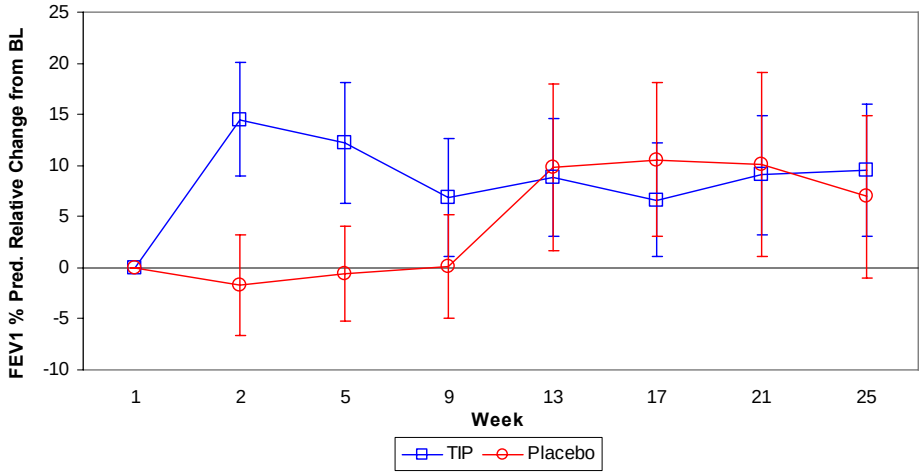
Sustainability was also assessed among patients in the placebo arm who received TIP in the extension period. These patients experienced a mean (median) relative change of 9.85% (4.24%) following their first course of TIP therapy at Week 13. This improvement was sustained over the following 8 weeks, but had dropped substantially by the end of Cycle 3 (Week 25) with a mean (median) relative change of 6.97% (1.87%).

Table 16: Reviewer Analysis of the Sustainability of Relative Changes from Baseline in FEV1 % Predicted in Subjects Using Imputed Data (C2301 SIA)

Visit	TIP N=29 Mean (Median)	Placebo N=32 Mean (Median)	Mean Difference (SE)	95% CI	P-value
Cycle 1- TIP vs. Placebo					
Week 2	14.50 (11.02)	-1.70 (-1.81)	16.19 (3.78)	(8.63, 23.75)	p=.0001[1] p=.0004[2]
Week 5	**12.26 (9.52)**	**-0.57 (-0.29)**	**12.83 (3.80)**	**(5.23, 20.44)**	p=.0013[1] p=.0070[2]
Week 9	6.83 (9.56)	0.09 (0.00)	6.73 (3.91)	(-1.10, 14.57)	p=.091[1] p=.059[2]
Cycles 2,3- TIP vs. TIP (All Patients Received TIP after Week 9)					
Week 13	**8.81 (5.74)**	**9.85 (4.24)**	**-1.03 (5.17)**	-	-
Week 17	6.65 (4.89)	10.58 (4.02)	-3.93 (4.84)	-	-
Week 21	**9.08 (6.25)**	**10.09 (4.15)**	**-1.01 (5.60)**	-	-
Week 25	9.51 (8.40)	6.97 (1.87)	3.54 (5.28)	-	-

[1] Parametric t-test, [2] Wilcoxon rank sum test
Source: Reviewer Table

Figure 10: Mean FEV1 % Predicted Relative Changes Across Visits: Evaluation of the Sustainability of Effects (C2301 SIA)



Note: Patients in the placebo arm received TIP therapy from Week 9 to Week 25. Error bars represent 95% confidence intervals for mean relative changes.
Source: Reviewer Figure

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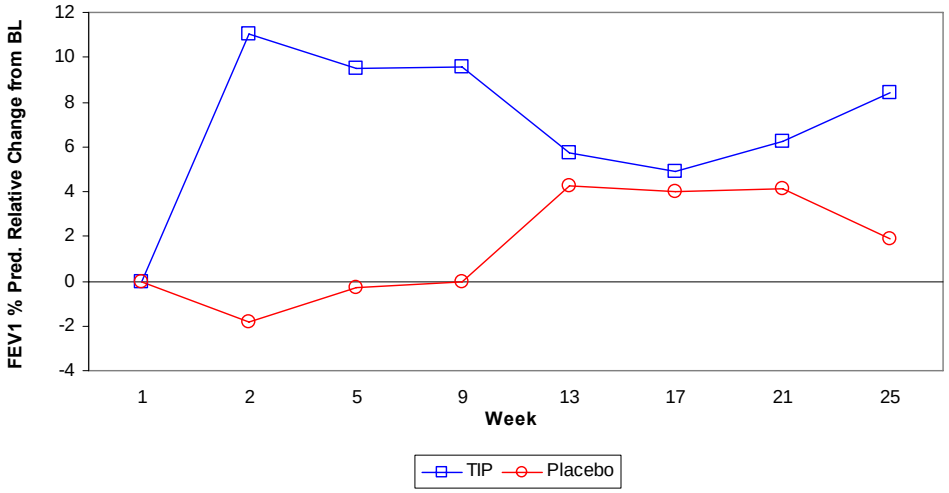
Figure 11: Median FEV1 % Predicted Relative Changes Across Visits: Evaluation of the Sustainability of Effects (C2301 SIA)



Note: Patients in the placebo arm received TIP therapy from Week 9 to Week 25.
Source: Reviewer Figure

Study C2303:

Sustainability of Relative Changes in FEV1 % Predicted:
As stated above, patients in Study C2303 received 4 weeks of on-therapy (TIP vs. Placebo) followed by 4 weeks of off-therapy. However, unlike Study C2301, Study C2303 did not include an open label extension phase for each of the treatment arms. In Study C2303, evaluation of the sustainability of relative changes in FEV1 % predicted across the first cycle was limited by substantial missing data which were highly variable across visits, being substantially higher in the TIP arm at Week 5 (i.e. 19.4% vs. 3.6%) and substantially lower in the TIP arm at Week 9 (i.e. 9.7% vs. 17.9%) (Table 17). Large changes in treatment differences of missing data from Week 5 to Week 9 can confound changes in treatment differences of relative changes over the same period. To address the limitation, Reviewer analyses imputed missing values at each visit using the minimum of 0 and the least favorable group mean among those patients with observed relative changes at that visit. This may serve to limit potential biases from missing data. However, there is still considerable uncertainty from a strong and varying influence of the imputation scheme.

Table 17: Number (%) of Patients with Missing FEV1 % Predicted Measurements by Visit (C2303 ITT)

Visit at:	**TIP (N=31[1])** **n (%)**	**Placebo (N=28[1])** **n (%)**
Week 5	6/31 (19.4%)	1/28 (3.6%)
Week 9 (End of Study)	3/31 (9.7%)	5/28 (17.9%)

[1] 3 ITT patients (1 TIP, 2 Placebo) were excluded due to a missing FEV1 % pred. value at baseline

Source: Reviewer Table

In Table 18, treatment differences in mean relative changes of FEV1 % predicted dropped from 5.82% (Week 5) to 3.77% (Week 9) despite treatment differences in missing data favoring TIP patients over the same period. Treatment differences in median relative changes also dropped from (3.17% − 2.71%) = 0.46% at Week 5 to (1.06% − 2.01%) = -0.95% at Week 9. These findings indicate a lack of sustainability of the TIP benefit over placebo across the 4 week off-therapy period following the course of TIP therapy.

Table 18: Reviewer Analysis of Sustainability of Relative Changes from Baseline in FEV1 % Predicted at Week 5 vs. Week 9 Using Imputed Data (C2303 ITT)

	TIP N=29	Placebo N=32	Mean Treatment Difference (SE)	95% CI for Difference	P-value
Week 5					
Mean (Median)	8.27 (3.17)	2.45 (2.71)	5.82 (4.19)	(-2.56, 14.20)	p=.170[1] p=.244[2]
Week 9					
Mean (Median)	8.54 (1.06)	4.78 (2.01)	3.77 (5.16)	(-5.77, 13.30)	p=.468[1] p=.607[2]

[1] Parametric t-test where variance estimates of the mean treatment difference included only patients with observed values (i.e. non-imputed values). [2] Wilcoxon Rank Sum test where the observed p-value denotes the significance of the observed TIP benefit over placebo based on ranks.
Source: Reviewer Table

Study C2302:
Refer to Section 3.4.4 for a discussion of the sustainability of relative changes.

5. SPECIAL/SUBGROUP ANALYSES

5.1 Subgroup Analyses by Age, Gender, Race, Region, and Disease Severity

Study C2301:
In Study C2301, subgroup analyses for the primary endpoint imputed missing values with a value of -0.57%, as performed in the primary analysis. These subgroup analyses were limited by the small number of subjects included in the SIA primary analysis population (i.e. 61 subjects, 29 TIP & 32 Placebo). Relative changes from baseline in FEV1 % predicted at Day 28 were generally robust across all subgroups except for region. Subgroup analyses by region show that treatment differences in Study C2301 were mostly driven by patients from Europe. Patients from North America did not appear to benefit from TIP therapy. Mean (median) relative improvements from baseline to Day 28 were 17.16% (19.25%) in Europe vs. 1.25% (-1.90%) in North America. These regional differences raise concerns regarding the robustness of study findings as well as possible biases in SIA based analyses related to the over representation of patients from Europe. As shown in Table 3, the SIA was more heavily represented by patients from Europe at 17/29 (58.6%) vs. 18/46 (39.1%) in the All Randomized Safety Population.

Table 19: Subgroup Analyses of Primary Endpoint (C2301 SIA)

Relative Change from Baseline in FEV1 % Predicted at Day 28 (Imputed Data)				
Subgroup	**Subgroup Division**	**TIP (N=29)**	**Placebo (N=32)**	**Treatment Difference (95% CI), p-value[1,2]**
		Mean (Median)	Mean (Median)	
Disease Severity	FEV1< 50% pred. N=20	11.59 (12.73) n=10	-1.47 (0.67) n=10	13.06 (-1.60, 27.72), =0.078
	FEV1 ≥ 50% pred. N=41	12.62 (7.39) n=19	-0.16 (-0.93) n=22	12.78 (3.39, 22.17), p=0.009
Region	North America N=20	1.25 (-1.90) n=9	-2.65 (-2.56) n=11	3.90 (-6.43, 14.23), p=0.438
	Latin America N=8	17.54 (-0.57) n=3	3.30 (1.90) n=5	14.24 (-30.21, 58.69), p=0.463
	Europe N=33	17.16 (19.25) n=17	-0.35 (1.19) n=16	17.51 (8.14, 26.89), p=0.001
Age Group	< 13 N=24	11.77 (7.39) n=11	-2.04 (0.77) n=13	13.81 (0.96, 26.67), p=0.036
	≥ 13 N=37	12.57 (14.50) n=18	0.44 (-0.57) n=19	12.13 (2.10, 22.15), p=0.019
Gender	Male N=31	8.23 (9.52) n=13	-2.35 (-2.21) n=18	10.57 (-0.08, 21.22), p=0.052
	Female N=30	15.54 (8.55) n=16	1.71 (1.19) n=14	13.83 (2.39, 25.28), p=0.020

[1]Parametric t-test [2]P-values should not be used for statistical inference due to lack of multiplicity adjustments and potential inflation of type-I error rates.
Source: Reviewer Table

Study C2303:
In Study C2303, subgroup analyses for the primary endpoint were limited due to the small number of subjects included in the ITT primary analysis population (i.e. 62 subjects, 32 TIP & 30 placebo) from which only 59 subjects (31 TIP & 28 Placebo) had available baseline FEV1 % predicted measurements and could be included in the analyses. In Table 20, TIP relative changes from baseline in FEV1 % predicted at Day 29 were most favorable in patients 13 years of age or older as well as in patients with FEV1 ≥ 50% predicted at baseline. Relative changes from TIP vs. Placebo therapy were also slightly more favorable among females. However, it should be noted that these analyses may be unduly influenced by an extreme observation, a 7 year old male TIP patient with a FEV1 < 50% predicted at baseline, who had a -36.7% relative change from baseline at Day 29.

Table 20: Subgroup Analyses of Primary Endpoint (C2303 ITT)

Relative Change from Baseline in FEV1 % Predicted at Day 28 (Imputed Data)				
Subgroup	**Subgroup Division**	**TIP (N=32) n=31**	**Placebo (N=30) n=28**	**Mean Treatment Difference (95% CI), p-value[1,2]**
		Mean (Median)	**Mean (Median)**	
Disease Severity	FEV1 < 50% Pred. N=16	3.57 (0) n=9	8.82 (3.82) n=7	-5.25 (-27.1, 16.58), p=0.614
	FEV1 ≥ 50% Pred. N=43	10.19 (5.64) n=22	0.33 (2.56) n=21	9.87 (1.80, 17.94), p=0.018
Age Group	< 13 N=28	3.72 (1.55) n=15	2.53 (2.56) n=13	1.19 (-11.85, 14.23), p=0.850
	≥ 13 N=31	12.53 (8.18) n=16	2.37 (3.06) n=15	10.16 (-0.22, 20.54), p=0.055
Gender	Male N=21	6.39 (0) n=9	2.18 (4.55) n=12	4.21 (-14.35, 22.76), p=0.640
	Female N=38	9.04 (3.56) n=22	2.65 (1.53) n=16	6.39 (-1.98, 14.75), p=0.130

[1] Unadjusted parametric t-test, [2] P-values should not be used for statistical inference due to lack of multiplicity adjustments and potential inflation of type-I error rates.
Source: Reviewer Table

Study C2302:
In Study C2302, relative changes from baseline in FEV1 % predicted were highly dependent upon the region considered with substantially larger improvements occurring in European vs. US sites, especially for patients in the TOBI arm (Table 21). Relative changes also depended on the age group of patients considered with larger relative changes occurring in younger patients (Table 22). There was also a dependence of relative changes on baseline FEV1 % predicted (≥ 50% vs. < 50%), with larger relative changes occurring in patients with baseline FEV1 % predicted < 50% (Table 23). A further dependence was observed based on gender with larger relative improvements observed in male patients (Table 24).

In these subgroup analyses where sample sizes were relatively large, each subgroup division was analyzed independently with missing data imputed based on the minimum of 0 and the least favorable group mean at each visit using only patients within that subgroup division. For example, a patient from European missing data in the subgroup analysis by region would have values imputed using only subjects from 'Europe.'

In Table 21, changes in FEV1 % predicted were substantially higher in Europe vs. the US. For the US, relative changes were generally similar between TIP and TOBI patients, except for Week 25 where TOBI patients experienced a substantial drop and fared worse than TIP patients (p=0.092). For Europe, changes in FEV1 % predicted favored TOBI over TIP during the first two cycles. Using a non-parametric Wilcoxon rank sum test, treatment differences approached significance at Week 9 (p=.090), Week 13 (p=.081) and

Week 17 (p=.096). Relative changes following end of on-therapy periods at Weeks 5, 13 & 21 were large for patients in Europe (esp. in TOBI arm) but were small or negligible in US patients, ranging from 0.34% to 0.91% (TIP arm) and -0.38% to 1.97% (TOBI arm).

Table 21: Relative Changes by Region Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Region	**Europe (N=175)**			**US (N=326)**		
Visit	**TIP (N=104)**	**TOBI (N=71)**	**Mean Diff ± SE**	**TIP (N=195)**	**TOBI (N=131)**	**Mean Diff ± SE**
Week 2	8.01 (5.53)	8.98 (5.33)	-0.98 ± 2.43	5.72 (3.57)	5.99 (3.06)	-0.27 ± 1.54
Week 5	**4.41 (0)**	**6.81 (2.73)**	**-2.40 ± 2.77**	**0.46 (0)**	**1.40 (0)**	**-0.94 ± 1.64**
Week 9	-0.74 (-0.74)	1.95 (0)	-2.69 ± 2.16[1]	-1.06 (-1.06)	-0.88 (-1.06)	-0.18 ± 1.43
Week 13	**2.76 (0)**	**6.77 (1.90)**	**-4.01 ± 2.77[1]**	**0.91 (0)**	**1.97 (0)**	**-1.07 ± 1.70**
Week 17	0.76 (0)	3.06 (1.64)	-2.30 ± 2.50[1]	0.52 (-0.73)	-0.73 (-0.73)	1.24 ± 1.52
Week 21	**4.02 (0)**	**5.37 (0.95)**	**-1.35 ± 2.61**	**0.34 (-0.38)**	**-0.38 (-0.38)**	**0.72 ± 1.69**
Week 25	2.18 (0)	2.85 (0)	-0.67 ± 2.44	-0.41 (-2.89)	-2.89 (-2.89)	2.48 ±1.47[2]

[1] P-values for the treatment difference favoring TOBI at Week 9, Week 13, Week 17 were p= .090, p=.081, p=.096 using a rank sum test. [2] P-value of 0.092 using a t-test. Sixteen patients from Latin America sites are not shown. FEV1 % predicted measurements at end of on-therapy periods are shown in **bold.**
Source: Reviewer Table

In Table 22, changes in FEV1 % predicted were highest in younger patients with the 6 to 12 year age group experiencing the largest relative change, the 13 to 19 year age group experiencing the next largest relative changes and the 20 year and above age group experiencing the smallest relative changes. In the 6 to 12 age group, mean (median) estimates were highly variable due to small sample sizes and could not be observed to consistently favor either treatment arm. For the 13 to 19 age group, relative changes were substantially smaller than in the 6 to 12 year age group, especially at later study visits, but tended to slightly favor TIP over TOBI for most visits. For the 20 year and above age group, relative changes were much lower than in the two younger age groups and tended to slightly favor the TOBI arm. Relative changes following the end of on-therapy periods at Weeks 5, 13 & 21 were large in patients under 20 years of age but were small or negligible in patients 20 years or older, ranging from 0.19% to 0.49% (TIP arm) and 0.70% to 2.24% (TOBI arm).

Table 22: Relative Changes by Age Group Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Age Group	**6 to 12 Years (N=47)**		**13 to 19 Years (N=113)**		**≥ 20 Years (N=357)**	
Visit	**TIP (N=28)**	**TOBI (N=19)**	**TIP (N=66)**	**TOBI (N=47)**	**TIP (N=214)**	**TOBI (N=143)**
Week 2	9.73 (10.72)	12.51 (11.54)	11.21 (9.85)	9.21 (6.09)	5.02 (2.77)	5.24 (3.06)
Week 5	**6.30 (1.27)**	**11.59 (7.14)**	**7.33 (4.42)**	**4.30 (2.65)**	**0.45 (0)**	**1.91 (0.85)**
Week 9	0.90 (1.37)	10.86 (8.62)	1.17(0)	0.36 (0)	-1.35 (-1.35)	-0.88 (-1.35)
Week 13	**3.72 (-0.59)**	**11.27 (7.69)**	**5.56 (0)**	**4.96 (2.56)**	**0.49 (0)**	**2.24 (0)**
Week 17	7.86 (7.66)	5.99 (0.50)	2.71 (0.21)	2.04 (0)	-0.61 (-0.61)	-0.36 (-0.61)
Week 21	**10.36 (6.34)**	**8.73 (5.75)**	**5.64 (3.18)**	**2.79 (0.55)**	**0.19 (0)**	**0.70 (0)**
Week 25	9.48 (8.20)	7.95 (0.57)	3.15 (0)	2.22 (0)	-1.24 (-2.83)	-2.83 (-2.83)

FEV1 % predicted measurements at end of on-therapy periods are shown in **bold.**
Source: Reviewer Table

In Table 23, changes from baseline in FEV1 % predicted were highest in patients with baseline FEV1 % predicted < 50%, esp. TIP patients. Treatment means for the '≥ 50%' and '< 50%' subgroups were similar, however, relative changes in TIP patients appeared to be more sensitive to a change in baseline FEV1 % predicted category (i.e. ≥ 50% vs. < 50%). Among TIP patients, mean relative changes in FEV1 % predicted following on-therapy periods at Weeks 5, 13 & 21 were approximately 3.2% to 3.5% greater for patients with a baseline FEV1 % predicted of < 50% vs. a baseline FEV1 % predicted of ≥ 50%.

Table 23: Relative Changes by Baseline FEV1 % Pred. Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Baseline FEV1 % Predicted:	**≥ 50% (N=300)**			**< 50% (N=217)**		
Visit	**TIP (N=180)**	**TOBI (N=120)**	**Mean Diff ± SE**	**TIP (N=128)**	**TOBI (N=89)**	**Mean Diff ± SE**
Week 2	5.66 (3.68)	5.01 (3.63)	0.66 ± 1.47	8.33 (6.63)	9.21 (5.26)	-0.88 ± 2.31
Week 5	**1.00 (0)**	**3.24 (2.28)**	**-2.24 ± 1.68**	**4.50 (0)**	**3.44 (1.82)**	**1.06 ± 2.69**
Week 9	-1.11 (-1.11)	-0.84 (-1.11)	-0.26 ± 1.44	0.31 **(0)**	2.34 **(0)**	-2.03 ± 2.12
Week 13	**0.53 (0)**	**2.58 (0)**	**-2.04 ± 1.65**	**3.75 (0)**	**5.16 (0)**	**-1.41 ± 2.64**
Week 17	0.49 (-0.03)	-0.03 (-0.03)	0.52 ± 1.45	1.68 **(0)**	1.96 **(0)**	-0.29 ± 2.44
Week 21	**0.96 (0)**	**1.02 (0)**	**-0.06 ± 1.71**	**4.15 (0)**	**3.09 (0)**	**1.06 ± 2.65**
Week 25	0.43 (-1.62)	-1.62 (-1.62)	2.05 ± 1.55	2.12 (0)	1.06 (0)	1.06 ± 2.18

FEV1 % predicted measurements at end of on-therapy periods are shown in **bold.**
Source: Reviewer Table

In Table 24, relative changes in FEV1 % predicted were largest in males, esp. for TOBI. Mean relative changes in FEV1 % predicted following on-therapy periods at Weeks 5, 13, 21 were 1.7% to 3.3% greater in males vs. females among TIP patients and 2.7% to 4.7% greater in males vs. females among TOBI patients. Treatment means within each of the male and female subgroups were similar. In males, differences favored TOBI patients at Weeks 9 & 13, but were not statistically significant (i.e. p=.107, p=.060, respectively).

Table 24: Relative Changes by Gender Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Gender	**Male (N=286)**			**Female (N=231)**		
Visit	**TIP (N=171)**	**TOBI (N=115)**	**Mean Diff ± SE**	**TIP (N=137)**	**TOBI (N=94)**	**Mean Diff ± SE**
Week 2	7.83 (6.19)	7.41 (5.26)	0.42 ± 1.73	5.45 (3.76)	6.04 (3.05)	-0.59 ± 1.96
Week 5	**3.88 (0)**	**4.94 (2.66)**	**-1.06 ± 2.18**	**0.68 (0)**	**1.35 (0)**	**-0.67 ± 1.95**
Week 9	0.01 (0)	2.38 (0.33)	-2.37± 1.68[1]	-1.34 (-1.94)	-1.94 (-1.94)	0.61 ± 1.77
Week 13	**2.61 (0)**	**5.80 (1.72)**	**-3.19 ± 2.09[2]**	**0.94 (0)**	**1.08 (0)**	**-0.13 ± 2.01**
Week 17	1.90 (0)	1.93 (0)	-0.03 ± 1.96	-0.29 (-0.69)	-0.69 (-0.69)	0.39 ± 1.70
Week 21	**3.76 (0)**	**3.11 (0)**	**0.65 ± 2.16**	**0.45 (0)**	**0.43 (0)**	**0.02 ± 1.99**
Week 25	1.98 (-0.06)	-0.06 (-0.06)	2.04 ± 1.85	0.24 (-0.89)	-0.89 (-0.89)	1.13 ± 1.73

Source: Reviewer Table

[1]P-value for treatment difference was 0.107 using rank sum test. [2]P-value for treatment difference was 0.060 using rank sum test. FEV1 % predicted measurements at end of on-therapy periods are shown in **bold.**

5.2 Subgroup Analyses by Tobramycin Minimum Inhibitory Concentrations (MICs)

In Study C2302, subgroup analyses were performed to investigate a possible MIC shift from the patient's baseline to termination visit. An increase in tobramycin resistance was observed in the TIP arm as compared to the TOBI arm. Table 25 shows a significantly larger proportion of patients in the TIP arm who had an MIC shift of greater than or equal to a 4 (or 8) fold increase. These findings raise concerns since increased MICs and resistance may have consequences for the treatment clinical outcome. Refer to the microbiological review by Dr. Coderre for further details regarding this issue.

Table 25: Categorical Change in Tobramycin MIC from Baseline (C2302 ITT)

MIC Shift (Baseline to Termination Visit)	TIP (N=308) n=298[1]	TOBI (N=209) n=202[1]	Difference
% of Patients with MIC[2] Shift			
≥ 2 fold increase	132 (44.3)	74 (36.6)	7.6% (-1.1, 16.2), p=.088
≥ 4 fold increase	89 (29.9)	38 (18.8)	11.1% (3.4, 18.4), p=0.005
≥ 8 fold increase	63 (21.1)	24 (11.9)	9.3 (2.6, 15.6), p=0.007

[1] 298 TIP patients and 202 TOBI patients with MIC values at both baseline and termination visits were included in these analyses
[2] Maximum MIC values from all bio-types are used.
Source: Reviewer Table

6. SUMMARY AND CONCLUSIONS

6.1 Statistical Issues and Collective Evidence

Major Issues Relating to Collective Evidence

The following are major statistical issues and findings relating to the collective evidence of efficacy in controlled studies C2301 and C2303. Issues and findings were considered major if they were likely to have a substantial impact on overall evidence:

Lack of significance in primary analysis (Study C2303 only)
In Study C2303, the Reviewer's primary analysis based on a non-parametric ANCOVA failed to demonstrate a significant relative improvement from baseline in FEV1 % predicted at Day 29 (p=0.233). Additional sensitivity analyses using parametric testing with or without adjustment for covariates also failed to show significance. Primary analysis findings from Study C2303 also appeared to be inconsistent with those of Study C2301, the adjusted mean difference in relative changes for Study C2303 of 5.91% (95% CI: -2.54%, 14.37%) was substantially below that of Study C2301 which was 12.44% (95% CI: 4.89%, 20.00%).

Substantial Patient Exclusions and Missing Data
In Study C2301, the Applicant's primary analysis based on the SIA population included only 61/95 (64%) of the All Randomized Safety population. Due to large number of treated patients who were excluded, the interpretation of findings was seriously limited as the patients who dropped out could be informative. The Reviewer's primary analysis included a sensitivity analysis which included all randomized (treated) patients to account for potential biases due to the exclusion of 34 treated patients from the SIA. In addition to these 34 excluded patients, the Applicant's primary analysis of SIA subjects (based on

only observed cases) had excluded 3 SIA patients (2 TIP, 1 Placebo) with missing relative change measurements at Day 28. Both the Reviewer's primary analysis and the sensitivity analysis accounted for these 3 patients by imputing values based on the minimum of '0' and the least favorable group mean.

In Study C2303, there were no large patient exclusions since the primary analysis was based on the ITT population (n=62). However, 10 ITT patients (16.1%) had missing data, 3 patients (1 TIP, 2 Placebo) did not have any baseline FEV1 % predicted measurements and 7 patients (6 TIP, 1 Placebo) had missing or inadequate spirometry at Day 29. There were also 2 patients (both TIP) with faulty data who had mistakenly received placebo instead of TIP therapy, one of these two patients was counted above as having missing or inadequate spirometry at Day 29. However, unlike Study C2301, Study C2303 did attempt to account for missing data since the pre-specified testing approach in the Applicant's primary analysis imputed values of '0' for patients with missing relative changes at Day 29.

High degree of skewness in primary outcome in TIP patients
In both studies, the distributions of relative changes in TIP patients were skewed in the positive direction with a mean substantially greater than the median. The mean vs. median relative change was 12.26% vs. 9.52% in Study C2301 and 8.27% vs. 3.17% in Study C2303. However, mean and median relative changes were similar in the placebo arm in both studies. Due to the skewness in the TIP distributions, Reviewer primary analyses were based on non-parametric testing (i.e. non-parametric ANCOVA in Study C2301 and non-parametric ANOVA in Study C2303).

Unclear sustainability of relative changes within or across cycles
Study C2301 followed patients for 3 cycles (24 weeks) where Cycle 1 was placebo-controlled and Cycles 2 & 3 were open-label in which all patients received TIP on/off therapy. In this study, the mean relative change from baseline decreased within the first cycle from 12.26% (Week 5) to 6.83% (Week 9) and across the 3 cycles following the on-therapy periods (i.e. Week 9 vs. Week 13 & Week 21) from 12.26% vs. 8.81% & 9.08%. Similar steep drops in relative changes across cycles were also observed for median relative changes (i.e. 9.52% vs. 5.74% & 6.25%). Patients in the placebo arm who started their first course of TIP therapy at Week 9 experienced a drop in the mean (median) relative change of 9.85% (4.24%) at Week 13 to 6.97% (1.87%) at Week 25 (Table 16 and Figures 10 & 11).

Unlike Study C2301, Study C2303 could not make comparisons across cycles since patients were only followed for 1 cycle (8 weeks). In Study C2303, mean relative changes did not appear to be sustained within the cycle, dropping from 5.82% (at Week 5) to 3.77% (at Week 9) (Table 17).

Lack of robustness across subgroups
In Study C2301, favorable mean (median) changes in FEV1 % predicted were observed for patients in Europe (n=33), however, patients in North America (n=20) did not appear to benefit from TIP therapy. Mean (median) relative improvements from baseline to Day

28 were 17.16% (19.25%) in Europe vs. 1.25% (-1.90%) in North America. In Study C2303, regional comparisons could not be made since patients from North America were not enrolled. However, patients with FEV1 % predicted at baseline < 50% and patients < 13 years did not appear to benefit from TIP therapy (Table 20).

Limited supportive analyses

In Study C2301, supportive analyses were limited by a substantially smaller sample size of 102 randomized subjects vs. the planned sample size of 140 subjects. The decision to use a smaller sample size was based on the original interim analysis in which early efficacy was observed for the primary endpoint. The study protocol was also amended such that there would be no formal testing of any secondary outcome measure (i.e. all secondary outcomes were considered to be exploratory). These design measures limited the study's potential to provide strong supportive evidence. However, regardless of these design modifications, actual findings failed to suggest any clear TIP benefit over placebo based on supportive endpoints of Reviewer interest such as rates of new anti-pseudomonal antibiotics use and respiratory hospitalizations (Table 7).

In Study C2303, supportive findings were also limited by a smaller than planned sample size. Actual findings failed to suggest any clear TIP benefit over placebo based on supportive endpoints of Reviewer interest such as rates of new anti-pseudomonal antibiotics use and respiratory hospitalizations (Table 10).

Uncertainties in findings due to a TIP formulation change (Study C2301 only)

Study C2301 evaluates TIP_{old} or an older formulation of TIP using a different manufacturing process from the proposed (to-be marketed) TIP formulation (i.e. TIP_{new}). Therefore, this study cannot control for the unknown effects that modifications in the manufacturing process could have on treatment effect estimates in the primary analysis as well as estimates in other study analyses.

Additional Statistical Issues

Limited Interpretation of Efficacy Findings (Study C2302): Since Study C2302 was an open-label study that did not have a prospectively planned primary analysis, interpretations of both efficacy and safety findings were limited. Inferences regarding efficacy of non-inferiority in relative changes at Week 21, as made by the Applicant, were especially problematic due to a lack of adequate evidence from historical studies to reliably estimate an appropriate NI margin for this study given several uncertainties which included the patient population of Study C2302 (TOBI experienced patients who were mostly adults) and the constancy of treatment effect assumption. There were also significantly higher rates of missing data in the TIP arm at Week 21, p=0.031 (Table 12) and inconsistencies of findings across cycles where comparisons following on-therapy periods in Cycle 1 (Week 5) and Cycle 2 (Week 13) were less favorable than at Cycle 3 (Week 21) (Table 13 & Figure 7).

Unfavorable Findings (Study C2302): There were several unfavorable findings in this study. Of the 517 randomized (treated) patients, discontinuation rates were 83/308 (27.0%) for TIP vs. 38/209 (18.2%) for TOBI (p=0.022) and discontinuations rates due to adverse events were 13.0% for TIP vs. 8.1% for TOBI (p= 0.084), (Figure 6). Reviewer analyses of relative changes based on imputed data also tended to favor TOBI over TIP (Table 13 and Figure 7). At the end of the on-therapy period of Cycle 2 (Week 13), the treatment difference favoring TOBI over TIP approached statistical significance using the Wilcoxon Rank Sum test (p=0.055). Evidence of efficacy also did not appear to be favorable based on differences in the rates of new anti-pseudomonal antibiotic use during the study which were 64.9% (TIP) vs. 54.5% (TOBI), a 10.4% difference significantly favoring TOBI, p=0.018 (Table 14).

Protocol violations at Site 284 (Study C2303 only):
The FDA Division of Scientific Investigations (DSI) conducted an inspection of Site 284 in which numerous enrollment and randomization errors were noted. These patients included:

- Subject 001 who had an issue with a missing screening spirometry report.
- Subjects 002 & 003 had a screening % predicted out of range at 80.2% and 100.7%, resp. (However, they had baseline FEV1 % pred. within range)
- Subjects 004 & 005 were randomized to the wrong FEV1 % predicted strata,
- Subject 008 had a missing screening value. (This patient was excluded from Reviewer analyses).

Given the DSI findings, the Reviewer examined if there were other cases where screening FEV1% predicted values were out of range. There was one other case, patient number 00001 from site 231, where the FEV1 % predicted value was below range at 21.5% at screening. However, the baseline FEV % predicted for this patient was within range at 26.6%.

Since patients with screening FEV1 % predicted values out of range all had baseline % predicted values within range, inclusion of their relative change measurements in the analyses was not too concerning in Reviewer analyses. Similarly, the 2 patients randomized to the wrong strata would have little effect on primary analysis findings. Therefore, additional sensitivity analyses excluding these patients were not performed.

6.2 Conclusions and Recommendations

Based on the totality of the evidence presented, this submission provided some persuasive evidence of a treatment benefit for patients with cystic fibrosis due to *PA* using TIP. Study C2301 provided adequate evidence of a TIP treatment benefit, while Study C2303 provided only weak evidence since the primary endpoint was not met. Additionally, Study C2302, an open-label comparative safety study, provided some weak supportive evidence towards the overall risk/benefit assessment. However, such evidence was limited by several factors including the open-label study design, lack of a prospectively planned primary analysis, uncertainty in treatment effects compared to placebo, potential biases due to significantly higher discontinuation rates in TIP patients and unfavorable comparisons in relative changes following on-therapy periods of other cycles (i.e. Cycles 1 & 2), as discussed in 'Study C2302' below.

Overall, we considered this submission to be potentially approvable depending on the considerations and recommendations from the other review disciplines, the final product labeling and the Applicant's agreement to all necessary post-marketing commitments. However, there are still several concerns with this submission related to the usability of the product, increases in tobramycin minimum inhibitory concentrations (MICs) for *Pseudomonas aeruginosa* isolates, patient exclusions, reliability of spirometry used in FEV1 % predicted measurements, regional effects, sustainability of effects and supportive analyses (e.g. rates of new anti-pseudomonal antibiotic use, rates of respiratory hospitalization). Note that these conclusions and recommendations are primarily based on our evaluation of efficacy from the studies summarized below:

Study C2301

In Study C2301, the Reviewer's primary analysis considered findings in the sensitivity interim analysis (SIA) population (N=61) and also included a sensitivity analysis in the All Randomized Safety population (N=95) as to account for potential biases from the exclusion of 34 treated patients from the SIA population (Tables 5 & 6, respectively). These analyses based on a non-parametric analysis of covariance (ANCOVA) showed significance with observed p-values of p=0.0061 and p=0.023 in the sensitivity interim analysis (SIA) and All Randomized Safety populations. Parametric ANCOVA tests also showed a TIP benefit over placebo of 12.44% (12.54% vs. 0.09%), p=0.0017 in the SIA population and 8.14% (6.87% vs. -1.26%), p=0.009 in the All Randomized Safety population. However, overall evidence of efficacy in Study C2301 was not considered to be robust for several reasons which included regional effects, unclear sustainability of effects and limited evidence from supportive analyses, as discussed below:

Regional effects appeared to be strong with patients from Europe driving primary analysis findings (Table 19). In Europe, TIP vs. placebo comparisons showed a mean (median) relative change of 17.16% (19.25%) vs. -0.35% (1.19%), a mean treatment difference of 17.51% (95% CI: 8.14%, 26.89%), p=0.001. In North America, however, TIP vs. placebo comparisons were less favorable and failed to show a meaningful benefit with a mean (median) change of 1.25% (-1.90%) vs. -2.65% (-2.56%), a mean treatment difference of 3.90% (95% CI: -6.43%, 14.23%), p=0.438. Note that Study C2302 also showed disparities for relative changes in FEV1 % predicted for TIP patients across regions where the mean relative change at Week 5 was 4.41% in Europe vs. 0.46% in the US (Table 21).

There was also unclear sustainability of treatment effects within and across cycles. First, comparisons of sustainability relative to placebo were limited due to lack of placebo controlled arm outside the first cycle and substantial increases in missing data after Week 5 (Table 15). Second, comparisons did not appear to be favorable (Table 16 and Figures 10 & 11). The mean relative change from baseline decreased within the first cycle from 12.26% (Week 5) to 6.83% (Week 9) and across the 3 cycles following the on-therapy periods (i.e. Week 9 vs. Week 13 & Week 21) from 12.26% vs. 8.81% & 9.08%. Similar steep drops in relative changes across cycles were also observed for median relative changes (i.e. 9.52% vs. 5.74% & 6.25%). In further comparisons of sustainability among patients in the placebo arm who switched over to TIP at Week 9, the mean (median) relative change of 9.85% (4.24%) at Week 13 dropped to 6.97% (1.87%) at Week 25.

In addition, supportive analyses provided only limited evidence due to low event rates and the lack of significant findings (Table 7). In Cycle 1, rates of anti-pseudomonal antibiotics use, as determined by the FDA Clinical Reviewer, were 6/46 (13.1%) in TIP patients vs. 9/49 (18.4%) in placebo patients, a -5.3% difference favoring TIP, p=0.477. Rates in respiratory related hospitalization also favored TIP at 2/46 (4.4%) vs. 6/49 (12.2%), a -7.8% difference, p=0.166.

Study C2303

In Study C2303, the Reviewer's primary analysis considered findings in the ITT population (N=62). This analysis, a non-parametric analysis of covariance (ANCOVA), failed to show a significant treatment benefit (p-value = 0.233, Table 9). Parametric ANCOVA tests also failed to show significance with an adjusted mean treatment difference of 5.91% (8.19% for TIP vs. 2.27% for Placebo), p=0.167. In addition, relative changes did not appear to be sustained within the cycle, dropping from 5.82% at Week 5 to 3.77% at Week 9 (Table 18). Subgroup analyses showed relative changes to be especially unfavorable in patients with greater disease severity (i.e. FEV1 % predicted < 50% at screening) as well as patients under the age of 13 years (Table 20). Furthermore, supportive analyses, such as comparisons in rates of new anti-pseudomonal antibiotics use (i.e. 3/32 (9.4%) for TIP vs. 3/30 (10.0%) for placebo) and respiratory related hospitalization (0/32 (0.0%) for TIP vs. 1/30 (3.3%) were not informative due to low event rates (Table 10).

Study C2302

Study C2302 compared TIP vs. TOBI over 3 cycles (24 weeks) in TOBI experienced patients using an open label design with a primary (secondary) objective of evaluating

safety (efficacy) outcomes. Although this study appears to offer some supportive evidence, the interpretation of these findings was limited by several factors. For example, the Applicant's finding of non-inferiority (NI) of TIP vs. TOBI for relative changes from baseline in FEV1 % predicted at Week 21 using a 6% NI margin could not be clearly interpreted. First, for confirmatory evidence of efficacy, we rely upon adequate and well-controlled trial(s) that are prospectively planned for the primary analysis and its inference. Study C2302 was an open-label study that did not control for potential biases and did not have a prospectively planned primary analysis. Second, for comparisons of non-inferiority, we rely upon adequate justification of the NI margin based on historical studies. The Applicant assumed a 6% NI margin based on the original TOBI studies of 1997 which may not be appropriate for Study C2302 given its patient population (i.e. mostly adult, TOBI experienced) and unclear constancy of treatment effect assumptions. Due to the emergence of resistance, effects of TOBI over placebo in the current study may be substantially smaller than effects observed in the original TOBI studies which enrolled mostly younger, TOBI naïve patients. Note that other limitations with NI findings included potential biases from significantly higher rates of missing data in TIP patients at Week 21, p=0.031 (Table 12) and inconsistencies across cycles following on-therapy periods where findings for Cycle 1 (Week 5) and Cycle 2 (Week 13) were less favorable than at Cycle 3 (Week 21) (Table 13 & Figure 7).

There were also several negative findings in this Study C2302. Of the 517 randomized (treated) patients, discontinuation rates were 83/308 (27.0%) for TIP vs. 38/209 (18.2%) for TOBI (p=0.022) and discontinuations rates due to adverse events were 13.0% for TIP vs. 8.1% for TOBI (p= 0.084), (Figure 6). Reviewer analyses of relative changes based on imputed data also tended to favor TOBI over TIP (Table 13 and Figure 7). At the end of the on-therapy period of Cycle 2 (Week 13), the treatment difference favoring TOBI over TIP approached statistical significance using the Wilcoxon Rank Sum test (p=0.055). In both treatment arms, relative improvements tended to be modest following on-therapy periods and further reduced following off-therapy periods. However, only TIP patients showed negligible mean relative changes (i.e. 1% or less) following all on-therapy periods (i.e. Week 5, 13, 21) for several subgroups including patients from the US, patients of ages ≥ 20 years, patients with FEV1 % predicted at baseline ≥ 50%, and female patients (Tables 21-24). Evidence of efficacy also did not appear to be favorable based on differences in the rates of new anti-pseudomonal antibiotic use during the study which were 64.9% (TIP) vs. 54.5% (TOBI), a 10.4% difference significantly favoring TOBI, p=0.018 (Table 14).

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APPENDIX

Table 26: Rationale for Sample Size (Studies C2301 & C2303)

	Study C2301	**Study C2303**
Initial Planned Sample Size:	140 enrolled subjects	100 enrolled subjects
Original Interim Analysis (OIA):	Potential for early stopping for efficacy after ~ 80 (79 actual) subjects complete Cycle 1 dosing *(Trial stopped early for efficacy based on OIA).*	No interim analyses planned.
Sensitivity Interim Analysis (SIA):	OIA later found problematic due to unreliable spirometry data in L. American sites. (SIA used instead). SIA 'repeated' the OIA removing 18 patients with faulty spirometry data. SIA was performed on 79-18=61 subjects. *(Trial stopped early for efficacy based on SIA).*	
Primary analysis population:	61 (29 TIP, 32 Placebo)	62 (32 TIP, 30 Placebo)
Rationale for sample size:	Early stopping for efficacy while trying to ensure robust spirometry data.	Maximum feasible recruitment

Source: Reviewer Table

Table 27: Patient Disposition (Studies C2301 & C2303)

	Study C2301	**Study C2303**
Randomized:	102 (48 TIP, 54 Placebo)	62 (32 TIP, 30 Placebo)
Randomized (Treated):	95 (46 TIP, 49 Placebo)	62 (32 TIP, 30 Placebo)
Patients excluded from primary analysis population: Discontinued Had unreliable spirometry	34 (17 TIP, 17 Placebo) 16 (7 TIP, 9 Placebo) 18 (10 TIP, 8 Placebo)	0
Primary analysis population:	61 (29 TIP, 32 Placebo)	62 (32 TIP, 30 Placebo)
Patients excluded from primary analysis (due to missing data):	3 (2 TIP, 1 Placebo) *No Day 28 measurement*	3 (1 TIP, 2 Placebo) *No BL measurement*

Source: Reviewer Table

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/s/

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