

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201688s000

MEDICAL REVIEW(S)

NDA: 201688
Clinical Review: Shrimant Mishra, M.D.,
M.P.H.
SD# 34: Response to CR
Submitted: 11/27/2012

Background and Introduction

Tobramycin Inhalation Powder (TIP) is a proposed inhaled tobramycin product indicated for use in cyclical fashion in cystic fibrosis patients with respiratory colonization/infection by *Pseudomonas aeruginosa*. TIP was filed under NDA 201688 in Nov. 2011 and received a Complete Response (CR) on Oct. 19th, 2012. Though the drug was felt to have met sufficient regulatory clinical standards of safety and efficacy, deficiencies were noted during inspections of a sponsor (third party) facility (b) (4) that were unable to be remedied prior to the action date on the application. The following citation was issued in the CR letter (in italics):

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

The inspection of the (b) (4) and found deficiencies specifically related to environmental controls. The sponsor responded to the citations on (b) (4) but the responses were considered inadequate (please see CDRH memo below):

Fig. 1: CDRH Memo of Inspection Deficiencies For (b) (4) Facility

▪ **21 CFR 820.70(c)**

Failure to establish and maintain adequate procedures to control environmental conditions that could reasonably be expected to have an adverse effect on product quality, and failure to periodically inspect environmental control systems to verify that the system is adequate and functioning properly, as required by 21 CFR 820.70(c). For example:



This cite is supported by Observation 1 and 2 of the FDA 483, pages 13 – 15 of the EIR, and Exhibit Nos. 25 and 28.

The response dated (b) (4) is not adequate. The firm did not provide documentation, or a plan, which includes requirements to (b) (4). The firm notes that it will develop specifications for (b) (4); however, the firm failed to provide documentation of its respective protocol and evidence of its implementation. The firm states that it will revise its (b) (4) procedure to clearly list the two media to use, and train its employees on the revised procedure. The firm failed to provide documentation of the procedure and evidence of its implementation, specifically documentation of fung (b) (4).

After receiving the CR, the sponsor resubmitted its application for review in Nov. 2012. Agency review of the sponsor's responses to the inspection deficiencies are ongoing, however the sponsor was also required to submit updated safety information as part of its resubmission. The following updates were requested in the CR letter (in italics):

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

*1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:*

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.*
- Present tabulations of the new safety data combined with the original NDA data.*
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.*
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.*

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

The safety update provided in this submission adheres only partially to the above request. The update presents in-depth safety findings from the newly completed study C2303E2 and abbreviated safety information from the ongoing study C2401. Exposure information has also been updated, and case report forms and narratives for the

completed study C2303E2 have been provided. Also updated safety information from worldwide usage is provided in the form of a PSUR. However, this safety update does not provide retabulated and comparative safety data incorporating the safety data from the pivotal trials. This is likely acceptable because C2401 is an ongoing study and C2303E2 involved a very small sample size with baseline demographics that differed from those of the main safety study C2302. For example, C2302 was largely composed of adult subjects while C2303E2 was largely composed of adolescent/younger subjects. For these reasons, evaluating the new safety data in isolation is acceptable.

Given the rather quick turnaround (and subsequent recent review of the original application by this Medical Officer) of this application, as well as the fact that the CR was not predicated upon clinical issues, this document will summarize in abbreviated fashion the safety update provided by the sponsor and comment upon whether any labeling changes are warranted. Labeling had been extensively discussed internally and with the sponsor and was in final draft form before the CR was issued.

Documents Reviewed

The primary documents examined include:

1. **Summary of Clinical Safety (Safety Update):** This document covers the safety period from Feb. 1st 2012 through Oct. 19th, 2012. This period reflects the time between submission of the 120 Day Safety update with the original application until receipt of the CR. The document summarizes:
 - **Study C2303E2:** This is the second extension from Study C2303. After the completion of Study C2303, all participants were offered the opportunity to participate in a three cycle extension (each cycle consisting of 28 days on drug followed by 28 days off of drug) of open label TIP (Study C2303E1). At the end of this extension period, subjects were allowed to enter into a second three cycle extension period (Study C2303E2). This second extension has now been completed and a study report submitted.
 - **Study C2401:** This is an open label, single arm, multiple center, six cycle long term safety study that is ongoing. Only SAEs and deaths are evaluated in this update. This study is being conducted as part of a post authorization commitment for the European Medicines Agency (EMA).
 - **PSUR:** This PSUR covers Jan. 2012 to June 2012)
 - **Spontaneous safety reports:** To cover the period from July 2012 to Oct. 19th, 2012
2. **Legacy Study Report for study C2303E2:** Finalized full study report
3. **PSUR 2 (covering Jan. 2012 to June 2012):** Finalized full safety report

Additionally case report forms, etc. were examined as necessary.

Exposure to Study Drug: Clinical Trials

As noted above, the safety update includes 2 new clinical trials, one of which has been completed and one of which is ongoing. Please note the sponsor table below:

Table 1: Summary of clinical trials contributing new safety data

Study	Study design and objectives	Patients treated	Treatment duration	Treatment/dose (mg)
Completed study				
C2303E2	Open-label extension to Study C2303E1 for safety and efficacy	49	3 cycles, each with 28 days on-treatment and 28 days off-treatment	TIP: b.i.d. 4x28 mg capsules
Ongoing study				
C2401	Long-term safety in targeted population	115*	6 cycles, each with 28 days on-treatment and 28 days off-treatment	TIP: b.i.d. 4x28 mg capsules

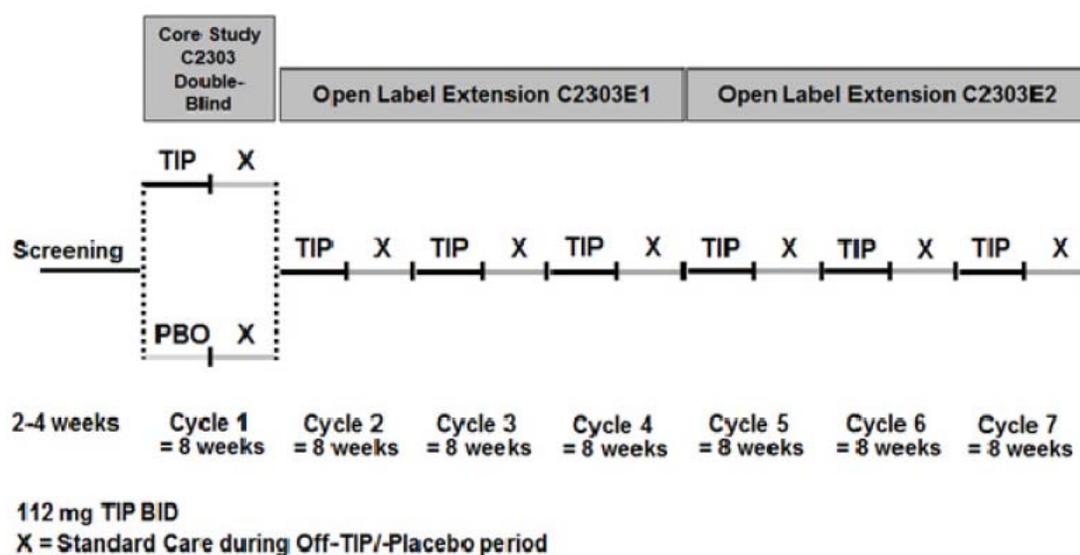
- Summary of Clinical Safety, pg. 7

* As of Oct. 19, 2012 cutoff date; 150 planned

Study C2303E2

The following sponsor figure displays the trial design of C2303, C2303E1, and C2303E2

Figure 2: Trial Design of Core Study C2303 and Extension Studies C2303E1 and C2303E2:



Summary of Clinical Safety, pg. 7

In Study C2302E2, the mean exposure for each cycle was 29 days with a range of 26-35. 46 of 49 subjects (94%) completed the study. Two subjects withdrew consent, and one subject discontinued due to an adverse event

The study population characteristics of C2302E2 are displayed in the table below.

Table 2: C2303E2 Demographics at start of Extension Study

Sex: (n=49)	
Male	17 (35%)
Female	32 (65%)
Age (n=49)	
Mean	13.3 years
Range	6-21 years
Weight (n=49)	
Mean	39.0 kg
Median	36.2 kg
BMI (n=49)	
Mean	17.0 kg/m ²
Median	16.8 kg/m ²
FEV 1 % Predicted (n=47)	
Mean	67.2%
Median	71.8%
Sputum Density of <i>Pseudomonas aeruginosa</i> (log ₁₀ cfu/gm sputum) (n=39)	
Mean	6.0
Median	7.6

Of the 49 subjects, 24 were originally core study TIP subjects while 25 were original placebo subjects. The study population was predominantly adolescent with moderate pulmonary function at baseline. When comparing these subjects to their baseline values in the core study, the median FEV1% predicted had improved from 65.4% to 71.8% (all subjects had had at least 3 cycles of TIP by the time of the start of study C2303E2). Median BMI had improved from 16.1 kg/m² to 16.8 kg/m². It is also of note that only 1 of these subjects had a *Pseudomonas aeruginosa* (*Pa*) tobramycin MIC > 8 µg/ml at core baseline. By the start of C2303E2, 6 subjects had such values while data from 13 subjects was missing. 14 subjects (29%) had a prior history of antipseudomonal antibiotic usage; ceftazidime had been used most frequently.

Compliance:

Overall mean compliance for the 3 cycles (n=49) was 96.9%. Cycle compliance was based on a capsule count of 228 capsules (28.5 day cycle). Only 2/49 (4.1%) subjects had compliance < 80%. However, these numbers should be viewed with caution given potential underlying self selection bias in terms of subjects willing to participate in the extension studies.

Adverse events

23 subjects (47%) had an adverse event (AE) during Study C2303E2. The number of subjects who had AEs did not markedly vary from cycle to cycle and was 12, 10, and 11 subjects in Cycles 5,6,7 respectively. 11 (46%) of core study TIP and 12 (48%) of core study placebo subjects had AEs during C2303E2.

The following sponsor table lists AE by preferred term (PT).

Table 3: AEs by PT, study C2303E2

	Total N=49 n (%)
Patients with AE(s)	23 (46.9)
Preferred term	
Respiratory tract infection	5 (10.2)
Respiratory tract infection viral	4 (8.2)
Bronchitis	3 (6.1)
Cough	3 (6.1)
Infective pulmonary exacerbation of cystic fibrosis	3 (6.1)
Acute sinusitis	2 (4.1)
Dysphonia	2 (4.1)
Hypoacusis	2 (4.1)
Non-cardiac chest pain	2 (4.1)
Alcaligenes infection	1 (2.0)
Antibiotic resistant Staphylococcus test positive	1 (2.0)
Asthenia	1 (2.0)
Bronchospasm	1 (2.0)
Burkholderia cepacia complex infection	1 (2.0)
Constipation	1 (2.0)
Diarrhoea	1 (2.0)
Haemoptysis	1 (2.0)
Influenza	1 (2.0)
Nasopharyngitis	1 (2.0)
Pneumonia	1 (2.0)
Productive cough	1 (2.0)
Protein urine present	1 (2.0)
Pyrexia	1 (2.0)

Preferred terms are sorted in descending order of frequency.

A patient with multiple occurrences of the same preferred term is counted only once in the preferred term.

-Table 12-4, C2303E2 Clinical Study Report; pg. 86

Many of the AEs seen are similar to those noted in the main safety trial C2302 and reflect either known adverse events associated with TIP or underlying disease. However, any such comparisons are limited by the marked differences in sample size, demographics, and trial design between the two studies.

Only 6 subjects had AEs considered to be treatment related. The AEs were 'protein urine present,' 'cough,' 'dysphonia,' 'hypoacusis,' and 'antibiotic resistant staphylococcus test positive.' Only one such event was considered to be severe ('protein urine present'). 'Cough' and 'dysphonia' occurred most frequently (3 and 2 subjects, respectively).

Two subjects had study drug temporarily interrupted, in both instances due to cough.

No deaths occurred in this study. Two subjects had an SAE. One subject discontinued study drug due to an adverse event.

The first SAE involved a 7 year old female who had a history of pneumonia requiring hospitalization and antipseudomonal treatment during both the core (randomized to placebo) and C2303E1 study. This subject had pneumonia/ pulmonary exacerbation events during the on treatment periods of Cycles 5 and 6 of the (Cycles 1 and 2 the second extension study) study C2303E2 study requiring hospitalization and antipseudomonal treatment. The events were considered unrelated to treatment and the subject was able to complete the treatment.

The second SAE event involved a 12 year old female who had a history of rash on her forearm during the core study (patient randomized to TIP) and C2303E1 study. The rash that occurred during the C2303E1 study was considered to be related to TIP. During off cycle of Cycle 7 (Cycle 3 of study C2303E2 subject was hospitalized with signs and symptoms consistent with a pulmonary exacerbation (increased cough, leukocytosis, tachypnea, radiograph consistent with pneumonia, and decrease in FEV 1 % predicted). The subject received antipseudomonals, steroids, and chest physiotherapy and was discharged 3 weeks after admission. The subject was able to complete the study.

The subject who discontinued involved an 11 year old female who had essentially normal renal function at baseline and no proteinuria. The subject was randomized to TIP during the core study and at the end of the on cycle was noted to have proteinuria and hypoacusis. This was noted to be ongoing at the end of the core study. During the C2303E1 study she was noted to have 2+ proteinuria. Her hypoacusis resolved. At the end of the off cycle of Cycle 6 in study C2303E2 (cycle 2 of the second extension study) she was noted to have proteinuria of 3+ (500mg/dL). She finished her last cycle of study drug (cycle 7) and then discontinued from the study. Serum creatinine did not increase by any more than .06mg/dl from baseline during the course of all three studies. Serum BUN did not increase from baseline at any point during all 3 studies. Current proposed labeling describes 'nephrotoxicity' in the *Warnings* section as something not seen with TIP in clinical trials but known to occur with parenteral aminoglycosides. At this point this is likely adequate given the uncertainty about whether TIP in and of itself can lead to nephrotoxicity in subjects without other risk factors such as concomitant nephrotoxic medications or baseline history of renal disease.

Labs were not reviewed extensively given the small sample size and lack of control arm. However no real meaningful changes were noted in renal parameters over the course of the study. As noted above, one subject did discontinue due study due to

proteinuria. As concerns liver function no subject met Hy's law and no subjects had AST or ALT elevations > 3x ULN

5 subjects were noted to have a decrease in FEV1 % predicted from predose to 30 minutes post dose of $\geq 20\%$. Please note the sponsor table below.

Table 4: Airway reactivity: $\geq 20\%$ decrease in FEV1% predicted from predose to 30 minutes post dose (safety population)

Cycle	Scheduled week - day	Total N=49 n/total (%)
Any		5/ 49 (10.2)
Cycle 5	Week 33 - Day 1	1/ 44 (2.3)
	Week 37 - Day 29	0/ 45 (0.0)
Cycle 6	Week 41 - Day 1	1/ 40 (2.5)
	Week 45 - Day 29	2/ 46 (4.3)
Cycle 7	Week 49 - Day 1	3/ 45 (6.7)
	Week 53 - Day 29	0/ 45 (0.0)

Relative change = $100 * (30\text{-m-post-dose} - \text{pre-dose})/\text{pre-dose}$
n is number of patients with event, total is number patients with values at the visit.

Table 12-10, C2303E2 Clinical Study Report; pg.95

Only one subject had a PT of 'bronchospasm.' This occurred in a 20 year old male; the event was considered mild and occurred in the off cycle. Currently, bronchospasm appears in the *Warnings* section of the proposed label as an adverse event that can occur with TIP. This appears adequate.

20 subjects had an audiology test at core study baseline, but one subject had missing values so the audiology subset population consisted of 19 subjects. Only 3 subjects had significant changes on audiometry (defined by ≥ 10 dB decrease in hearing from baseline in 2 consecutive frequencies or a ≥ 20 dB decrease in 1 frequency).

Four subjects reported an adverse event PT of 'hypoacusis' either continuing from prior study or newly occurring. None of these subjects had accompanying hearing complaints. In two of these subjects, the accompanying audiometry did not show significant changes. In another subject, the changes on audiometry were transient. In a third subject the accompanying did show significant and continued decreases on audiometry by end of study. In the current proposed label, ototoxicity appears in the *Warnings* section and is described as having occurred with TIP during clinical trials. Given what is known about parenteral aminoglycosides as well as the above findings, this is likely adequate.

Four subjects were noted to have an adverse event of cough. Three of these subjects had events that were considered possibly related to study drug, moderate in severity, and occurring during the on cycle.

One subject had an adverse event of hemoptysis. This was not considered to be related to study drug and occurred in a 7 year old subject who also had an SAE of pneumonia. Please see earlier SAE narrative.

7 (14%) of subjects had new antipseudomonal usage during the study. The median duration of use was 21 days. As noted earlier, two subjects were hospitalized. By way of comparison, in study C2301, the rate of antipseudomonal usage in the TIP arm after 3 cycles was 28% for the all randomized safety population. This, however, is a

crude comparison given that although some baseline demographics between study C2301 and core study C2303 may have been similar, there appeared to be some indication that the core study C2303 population may have been healthier at baseline.

One subject was noted to *B. cepacia* in her sputum during the off cycle of Cycle 7. She was not reported to have had a previous history of this.

Note: The sponsor comments on multiple analyses comparing core TIP and placebo subjects. It is unclear how relevant such analyses are given that by the end of the C2303E2 study most subjects would have received multiple cycles of TOBI Podhaler. Such analyses are not commented upon in this review.

Study C2401

No deaths were noted in the ongoing study. Most SAEs represented hospitalizations for pulmonary exacerbations. There was one case of bronchospasm for which study drug needed to be discontinued.

Exposure outside of clinical trials

Assuming a daily dose of 112mg and a sales volume of (b) (4) the estimated exposure to study drug is 2076.3 patient treatment years

PSUR-2; Spontaneous Reports from July 2012 to Oct. 19, 2012

These reports were reviewed and found to contain similar safety data as that contained in the clinical study reports. Of note, these reports continued to highlight problems of sometimes significant cough occurring with TOBI Podhaler as well as errors in administration of study drug.

Several instances were noted of subjects who discontinued the medication due to cough. One cough narrative is as follows:

“The poly-medicated elderly patient commenced TOBI Podhaler for pseudomonas infection at a dose of 4 capsules twice daily. The patient suffered from cough, dyspnea and increase of sputum a few days after starting TOBI Podhaler. The events were assessed as severe and serious by the nurse practitioner. It was reported that the patient had to visit the emergency room several times. TOBI Podhaler treatment was stopped after 13 days and the complaints decreased. The complaints decreased after TOBI Podhaler was withdrawn. When TOBI (tobramycin) nebulization was reintroduced to the patient 40 days after stopping TOBI Podhaler, the patient recovered”

Currently, labeling describes cough in detail in the *Adverse Reactions* section of labeling. However, a clear statement noting that significant cough can occur with use of study drug and result in discontinuation of the drug is not present. Thus, proposed changes to the label reflecting this have been sent to the sponsor.

The PSUR also noted cases where it was unclear whether the device was being used correctly or functioning properly. Please note the following narrative illustrating such a case with a 15 year old male:

“The patient coughed a little after receiving first TOBI Podhaler dose probably because he inhaled too quickly. Inside the capsule, the medicine was stuck. The reporter was wondering if it was significant that there was powder remaining in the capsule. It looked like it was just stuck to the inside edges around the top (same after all four capsules).”

Current proposed labeling recommends more intensive monitoring of children 10 years old and younger for proper use of the drug/device. However, it is unclear from the current PSUR whether improper usage occurs with young children only. Accordingly, it is likely of benefit to recommend intensive monitoring of all patients for proper usage of the drug/device, at least during the initial period of use. Proposed labeling changes reflecting this view have been sent to the sponsor for consideration.

Hemoptysis was again noted in this PSUR. Hemoptysis is currently listed in the table under the ‘Adverse Reactions’ section of the proposed labeling and is also part of the sponsor’s Risk Management Plan (RMP). It is difficult to discern in many of the cases whether hemoptysis is occurring independently of a pulmonary exacerbation. As more data accumulates, if a signal emerges of a direct causation between TIP inhalation and hemoptysis, then consideration can be given to either provide more discussion of this adverse event in the *Adverse Reactions* section or possibly elevate this adverse event to the *Warnings* section of labeling.

Conclusions:

Overall, the submitted safety update is in line with what had been seen in the original application. Ototoxicity, bronchospasm, and nephrotoxicity, all of which have been reported in this safety update, had been previously placed in the *Warnings* section of the proposed label. Moreover, cough is discussed in the *Adverse Reactions* section of the proposed labeling. Because continued problems with cough and use of the device/medication were noted in this safety update, comments have been sent by DAIP to the sponsor to strengthen labeling language related to both issues.

Lastly, there are lingering questions about TIP’s overall efficacy on antipseudomonal usage as well as its effect on *Pa* tobramycin resistance. However, these issues cannot be clarified by this safety update. Rather, they are more adequately addressed with the proposed post marketing requirements.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHRIMANT MISHRA
02/14/2013
CR Review TOBi Podhaler

EILEEN E NAVARRO ALMARIO
02/15/2013

Division Director Summary Review

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Acting Division Director Decisional Memorandum
NDA #	201,688
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	12/21/11
PDUFA Goal Date	10/19/12
Proprietary Name / Established (USAN) Name	TOBI Podhaler / tobramycin inhalation powder
Dosage Forms / Strength	Inhalation powder hard capsules / 28 mg
Proposed Indication	TOBI Podhaler is indicated for the management of cystic fibrosis patients with <i>Pseudomonas</i> <i>aeruginosa</i> .
Action:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Dr. Shrimant Mishra
Statistical Review	Dr. Christopher Kadoorie
Pharmacology Toxicology Review	Dr. Amy Ellis
CMC Review	Dr. Mark Seggel, Dr. Stephen Langille
Device Review	Mr. Sugato De
Clinical Microbiology Review	Dr. Peter Coderre
Clinical Pharmacology Review	Dr. Ryan Owen
Device Human Factors	Dr. Aleksander Winiarski, Ms. QuynhNhu Nhuyen
OSI	Dr. Janice Pohlman
Labeling Reviews	Ms. Shawna Hutchins, Dr. Christine Corser, Dr. Adora Ndu
Proprietary Name Review	Dr. Aleksander Winiarski
CDTL Review	Dr. Eileen Navarro
Other – Pulmonary Consultation	Dr. Robert Lim

OND=Office of New Drugs
OSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

The applicant of this New Drug Application (NDA) presents two placebo-controlled trials (Studies C2301 and C2303) and one comparative safety trial (Study C2302) to provide evidence of the safety and efficacy of Tobramycin Inhalation Powder, referred to by the approved proprietary name, TOBI Podhaler, in this review. The TOBI Podhaler is a powder formulation of tobramycin with the proposed indication, “the management of cystic fibrosis patients with *Pseudomonas aeruginosa*”. The active ingredient, tobramycin, is identical to the active ingredient in the intravenous formulation of tobramycin (approved since 1976 for the treatment of lower respiratory tract infections caused by *Pseudomonas aeruginosa*) and the inhaled tobramycin solution TOBI® (approved since 1997 for the same indication proposed for TOBI Podhaler) and also owned by the applicant.

TOBI Podhaler is a dry powder formulation of tobramycin packaged in a hard capsule and accompanied by the T-326 dry powder inhaler device. Drug delivery for this new powder formulation of tobramycin is via the handheld, manually operated, breath-activated T-326 dry powder inhaler. The T-326 inhaler is not an FDA-cleared device. The inhaler device is intended for replacement every 7 days. TOBI Podhaler is to be administered as four capsules equaling 112 mg of tobramycin twice daily for repeated cycles of 28 days on drug and 28 days off drug.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of TOBI Podhaler for the indication proposed. For a detailed discussion of NDA 201,688, the reader is referred to individual discipline specific reviews and the Cross-Discipline Team Leader (CDTL) review.

2. Background/Regulatory

The key clinical trials and their role in the drug development for the TOBI Podhaler are:

Study INH 007 was designed to assess the suitability of the TOBI Podhaler T-326 Inhaler drug-device combination for the inhaled administration of tobramycin.

Study TPI 001 was a dose-ranging study to identify a TOBI Podhaler dose that achieves comparable tobramycin serum and lung exposures to those achieved with TOBI®.

Study C2301 was designed to demonstrate superior efficacy of TOBI Podhaler to placebo in FEV1 (primary), microbiological activity, and clinical outcomes. Study C2301 was a double-blind, placebo-controlled trial over a 56 day period (1 cycle) consisting of 28 days on-therapy (Podhaler vs. Placebo) followed by 28 days off-therapy in CF patients ≥ 6 years of age with screening FEV1 % predicted between 25% and 80%. The initial placebo-controlled cycle was followed by an open-label extension period of 2 cycles (or 16 weeks) where all patients received 4 weeks of Podhaler therapy followed by 4 weeks off-Podhaler therapy in each cycle.

Study C2302 was designed to demonstrate “clinical comparability” of TOBI Podhaler to nebulized tobramycin solution (TOBI®) with respect to safety, microbiological activity, pharmacokinetics, clinical outcomes (lung function, Cystic Fibrosis Questionnaire - Revised [CFQ-R]), administration time, Treatment Satisfaction Questionnaire for Medication [TSQM] EuroQol Questionnaire [EQ-5D]). Study C2302 was an open-label, comparative study over a 24 week period (3 cycles) consisting of 4 weeks of on-therapy (Podhaler vs. TOBI®) followed by 4 weeks of off-therapy.

Study C2303 was designed to demonstrate superior efficacy of TOBI Podhaler to placebo in FEV1 (primary), microbiological activity, and clinical outcomes. Study C2303 was a double-blind, placebo-controlled trial over a 8 week period (1 cycle) consisted of 4 weeks of on-therapy (Podhaler vs. placebo) followed by 4 weeks of off-therapy.

Two formulations were used in the course of clinical development. The first formulation TS-001 was used in early clinical development whereas CN1-002 was used in later phase studies (C2301 and C2302). The manufacturing process for CN1-002 was further modified to reduce variability in powder characteristics (the product evaluated in study C2303 was produced using the new manufacturing process). The change in manufacturing process is further discussed in Section 6 of this review.

TOBI Podhaler is currently marketed in Canada and a number of European nations.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology / Device and Human Factors

Drug and Device Product Quality

The CMC Reviewer concluded that the applicant had provided sufficient information regarding raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The NDA provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the expiration dating period.

An Overall Recommendation of Withhold has been made by CDER Office of Compliance. Deficiencies were noted during the (b) (4) inspection of (b) (4)

The CDRH Office of Compliance has evaluated the report and has recommended Withhold. The deficiencies are related to inadequate procedures to control environmental conditions which could reasonably be expected to adversely impact product quality. Therefore this NDA was not recommended for approval by the CMC reviewer. I concur that this deficiency precludes approval.

The Product Quality Microbiology Reviewer recommended approval from the quality microbiology perspective.

Human Factors

The Human Factors reviewers recommended disapproval on the basis of an inadequate Human Factors Study and no formal evaluation of the draft Instructions for Use. The applicant carried out the major Human Factors study using empty capsules in a patient population primarily composed of asthmatics. The study consisted of three parts:

- A First Use Assessment during which participants were interviewed and trained, but were not required to use the draft Instructions for Use.
- A portion of the participants evaluated the device in a 5 day home use simulation where morning and evening doses were simulated.
- A portion of the participants returned for a Post One Week Assessment Study which included a final observed simulation of dosing.

In the assessments, there were five critical tasks (remove capsules from the blister pack, pierce the capsules, inhale from 4 capsules, inhale twice from each capsule, after inhaling twice – remove and check capsule to determine if pierced and empty). In the First Use Assessment, 33 of 62 participants made at least one error. I note that nearly half of the errors recorded were failure to check the capsule to determine if pierced and empty. In the Post One Week Assessment, 19 of 34 subjects made at least one error.

I do not agree that these concerns would preclude approval. There are study design issues that limit interpretability of the results of the study. The participants chosen were largely not composed of CF patients who are cared for in a health care setting with extensive patient education and who are accustomed to technical medication administration tasks such as use of a nebulizer. Some of the errors (such as failure to check the capsule) may have been artifacts of the design of the study as empty capsules were used. Participants were not required to use the draft Instructions for Use during the First Use Assessment. As described in Section 12 of this review, the applicant and Agency have extensively revised the Instructions for Use. It is my opinion that the Instructions for Use would now be adequate to provide for safe and correct use of the product among CF patients who will receive care in settings that provide extensive patient education. In addition, once the product is approved, the Instructions for Use will need to be formally evaluated as a Post-Marketing Requirement and the applicant has agreed to a Post-Marketing Commitment to produce an instructional video.

The Advisory Committee discussed the results of the Human Factors study and testimony from patients regarding device useability was presented at the Advisory Committee meeting. Advisory Committee members indicated that the Human Factors study results did not alter their opinion that adequate evidence of safety and efficacy had been demonstrated (see Section 9 of this review). Several recommended that the Instructions for Use should be revised.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology Reviewer concluded that there was no objection to approval from her perspective. I concur that there are no outstanding pharmacology toxicology issues that would preclude approval.

Repeat dose toxicity studies were conducted in rats and dogs. Based on a review of these studies, the Reviewer concluded that TOBI Podhaler is unlikely to cause greater systemic or pulmonary toxicity related to tobramycin than the currently marketed drug TOBI®.

The Reviewer recommended that the Pregnancy and Carcinogenesis, Mutagenesis, Impairment of Fertility sections of the label for this product follow the TOBI® label. This is appropriate because both products contain the same active ingredient given by the same route of administration using the same schedule. Clinical exposure appears similar between the products when they are used as described in the label. Aminoglycoside antibacterial drugs, such as tobramycin, have been assigned Pregnancy Category D.

This appears to be the first product for inhalation to contain the excipients 1, 2-distearoyl-SN-glycero-3-phosphocholine (DSPC) and calcium chloride. S-lyso-PC is a lyso-lecithin and a degradation product of DSPC that forms spontaneously during storage. It was of concern because lyso-lecithins can induce bronchoconstriction. The applicant provided data from guinea pigs demonstrating that S-lyso-PC had a similar potency for inducing bronchoconstriction as the better characterized P-lyso-PC (an endogenous substance) and there was a no-effect level for this activity.

Genetic toxicology studies, carcinogenicity studies, and reproductive/developmental toxicity studies for tobramycin are described in the TOBI® label and were negative. Genotoxicity tests for DSPC conducted to support this NDA were negative.

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer concluded that the NDA was acceptable from a Clinical Pharmacology perspective. I concur that there are no Clinical Pharmacology issues that would preclude approval. The Reviewer addressed a number of issues from the Clinical Pharmacology perspective.

With respect to the issue of whether the chosen dose was appropriate, the applicant conducted Study TPI-001 which was a single dose, six-arm trial in CF patients. The trial arms evaluated in TPI-001 were 300 mg TOBI® (control), two 14 mg TOBI Podhaler capsules, four 14 mg TOBI Podhaler capsules, two 28 mg TOBI Podhaler capsules, three 28 mg TOBI Podhaler capsules, and four 28 mg TOBI Podhaler capsules. Pharmacokinetic parameters were calculated in both serum and sputum for all trial arms. Based on the review of Study TPI-001, the Reviewer concluded that the selection of the 112 mg dose of TOBI Podhaler is appropriate.

During late stage development, the applicant changed the manufacturing process (but not the formulation) for TOBI Podhaler between the conduct of studies C2302 and C2303. To address the issue of whether the new manufacturing process changed tobramycin pharmacokinetics, a population pharmacokinetic modeling approach was used by the applicant, using data and a model developed from studies TPI-001, C2301, and C2302 to predict observed serum tobramycin concentrations from C2303. The Reviewer confirmed the modeling and analyses. Based on these analyses as well as the relatively

similar tobramycin serum concentrations between C2303 and the earlier studies, the Reviewer concluded that the manufacturing process change did not result in any significant differences in serum tobramycin concentrations.

The Reviewer also evaluated whether there was sufficient PK information collected in Study C2302 to assess change in MIC (see Section 6 of this review). The Reviewer concluded that the PK data that was collected during Study C2302, after accounting for storage, was not sufficient to determine whether the increase in baseline MIC was due to sub-therapeutic exposures of tobramycin (serum or sputum) in the TOBI Podhaler arm.

6. Clinical Microbiology

The Clinical Microbiology Reviewer recommended against approval. The reviewer cited a number of concerns, with the major concern related to differences in changes in drug susceptibility in Study C2302 for the TOBI Podhaler arm compared with the TOBI® arm. I carefully considered these concerns as did the CDTL; we both agree that these concerns would not preclude approval. However, post-marketing requirements would be necessary to provide for a longer period of follow-up and assess clinical implications for patients.

The Microbiology Reviewer observed that there were large increases in tobramycin MICs for *P. aeruginosa* clinical isolates during therapy with TOBI Podhaler in the pivotal studies, noting that in some instances, the MICs increased three or more dilution steps and as high as > 512 mg/ml in the TOBI Podhaler treatment arm. He noted that these large increases in tobramycin MICs were not present in either the placebo/Podhaler/Podhaler arm of Study C2301 or the TOBI® comparator arm of Study C2302.

The Statistical Reviewer performed an analysis of increases in MIC as fold increase from baseline in Study C2302 which provides a useful perspective. This is shown in TABLE 1.

Table 1: Categorical Change in Tobramycin MIC from Baseline to the Termination Visit (C2302 ITT)

MIC Shift (Baseline to Termination Visit)	Podhaler (N=308) n=298 ¹	TOBI® (N=209) n=202 ¹	Difference
% of Patients with MIC² 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 TOBI Podhaler 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: Statistical Review for NDA 201688 Table 25

The clinical implications of these data are unclear at this time. MIC breakpoints are based upon achievable serum concentrations of the antibacterial drug. Data submitted in the NDA demonstrate that peak sputum levels achieved with the TOBI Podhaler exceed the achievable serum concentration used to establish the tobramycin MIC breakpoints; 95% of patients assessed had sputum concentrations of tobramycin exceeding the MIC₉₀ twenty-five fold. In clinical trials for the TOBI Podhaler, increases in MIC over baseline were not associated with clinical outcomes such as new antipseudomonal antibacterial drug use or hospitalization. There were no patient characteristics identified (for example, FEV₁% predicted at baseline or age) that were associated with an increase in MIC.

A specific Discussion Question was posed to the Advisory Committee regarding these concerns. Most members opined that the clinical relevance was unclear, and some posited that the observation may be due to efficacy of the drug reducing the colony count of lower MIC organisms. The Advisory Committee recommended long-term follow-up and indicated that they felt adequate evidence of safety and efficacy had been demonstrated (see Section 9 of this review).

7. Clinical/Statistical Efficacy

The Clinical Reviewer and CDTL concluded that substantial evidence of efficacy had been provided. The Statistical Reviewer considered the submission to be “potentially approvable depending on the recommendations from the other review disciplines”. The Pulmonary Consultant felt that the evidence of efficacy was equivocal.

I conclude that substantial evidence of efficacy has been demonstrated based upon the robust demonstration of superiority over placebo in Study C2301 and supportive evidence from Studies C2302 and C2303. I note that this is a new mechanism of delivery of a drug which has been previously demonstrated to be efficacious for the proposed indication.

Study C2301

The design of this study is described in Section 2 of this review; the placebo controlled part of the study is cycle 1 and all subjects were changed to the TOBI Podhaler for cycles 2 and 3. The study sought to enroll “TOBI® naïve” subjects with inclusion/exclusion criteria requiring no prior inhaled antipseudomonal drugs during the four months prior to enrollment. The study was stopped early by the DSMB based on an interim analysis for efficacy, and some patients were excluded from the efficacy analysis due to unacceptable spirometry data. The FDA primary analysis population consisted of 61 patients (29 Podhaler, 32 Placebo). The primary endpoint for this trial was change from baseline in the relative change in FEV₁ % predicted from baseline (Day 1 of drug treatment) to the end of study drug treatment (Day 28) of the first cycle. Treatment with TOBI Podhaler and placebo resulted in relative increases in FEV₁ % predicted of 12.54 % and 0.09%, respectively (LS mean difference = 12.44%; 95% CI: 4.89, 20.00; p=0.002). Analyses of secondary endpoints were consistent with the analysis of the primary endpoint. Analysis of absolute changes in FEV₁ % predicted showed LS means of 6.38% for TOBI Podhaler

and -0.52% for placebo with a difference of 6.90% (95% CI: 2.40%, 11.40%). The percentage of patients using new antipseudomonal antibacterials in Cycle 1 was greater in the placebo treatment group (18.4%) compared with the TOBI Podhaler treatment group (13.1%). During the first cycle, 8.7% of TOBI Podhaler patients and 10.2% of placebo patients were treated with parenteral antipseudomonal antibacterials. In Cycle 1, two patients (4.4%) in the TOBI Podhaler treatment group required respiratory-related hospitalizations, compared with six patients (12.2%) in the placebo treatment group.

Study C2302

The design of this study is described in Section 2 of this review. This study was designed to assess the safety of TOBI Podhaler compared with TOBI® over 3 cycles and enrolled largely TOBI® experienced patients. The ITT population included 308 subjects in the TOBI Podhaler arm and 209 subjects in the TOBI® arm. Due to dropouts, there was a high rate of missing data, with 27.9% of ITT patients in the TOBI Podhaler arm and 19.1% of ITT patients in the TOBI® arm missing data for FEV₁% predicted at Week 25. While study C2302 is not appropriate to establish noninferiority due to the missing data, open-label design, hypothesis testing for a number of secondary endpoints, and the absence of a clearly defined M1 or treatment effect in this TOBI® experienced population, there is data supportive of treatment benefit for TOBI Podhaler. For the 227 patients with observed data in the TOBI Podhaler arm, the mean relative change in FEV₁% predicted from baseline was 3.1% compared with 2.3% for the 171 patients with observed data in the TOBI® arm. Using imputation of the missing data, the mean differences (TOBI Podhaler minus TOBI®) in the percent relative change from baseline in FEV₁% predicted at Weeks 5 and 25 were -0.87 (95% CI: -3.80, 2.07) and 1.62 (95% CI: -0.90, 4.14), respectively.

Study C2303

The design of this study is described in Section 2 of this review. It was carried out at the request of the Agency due to the change in manufacturing process following the completion of study C2302. The study sought to enroll “TOBI® naïve” subjects with inclusion/exclusion criteria requiring no prior inhaled antipseudomonal drugs during the four months prior to enrollment. Study C2303 had originally planned to enroll 100 subjects, but due to challenges with enrolling TOBI® naïve patients, enrollment was terminated early. This study enrolled 62 patients in the ITT population who received study drug treatment, 32 in the Podhaler arm and 30 in the placebo arm. The primary endpoint for this trial was change from baseline in the relative change in FEV₁ % predicted from baseline (Day 1 of drug treatment) to the end of study drug treatment (Day 28) of the first cycle. Adjusting for the covariates of age (<13 years, ≥13 years) and FEV₁ % predicted at screening (<50%, ≥50%) and imputing for missing data, TOBI Podhaler (8.19%) compared to placebo (2.27%) failed to achieve statistical significance for relative change in FEV₁ % predicted (LS mean difference = 5.91%; 95% CI: -2.54, 14.37; p=0.167). Analyses of absolute changes in FEV₁ % predicted showed LS means of 4.86% for TOBI Podhaler and 0.48% for placebo with a difference of 4.38% (95% CI: -0.17%, 8.94%).

8. Safety

Both the Clinical Reviewer and the CDTL concluded that the risk benefit is favorable. Based on the imbalance in discontinuations in the TOBI Podhaler arm of Study C2302, it is expected that some patients will discontinue TOBI Podhaler due to adverse effects likely attributable to the dry powder formulation and elect for TOBI® treatment by nebulizer. Physicians will need to monitor patients who initiate treatment with TOBI Podhaler carefully for adverse effects and offer alternative treatment by nebulizer if warranted. I concur that there are no safety issues that would preclude approval.

Subjects in Study C2302 serve as the primary safety population in the safety analysis. The C2302 trial had a much larger safety database than either of the placebo-controlled trials; allowing detection of serious adverse events occurring at a rate of 1% or higher per treatment arm. In addition, the C2302 trial compared TOBI Podhaler to TOBI® over three successive on/off cycles while comparisons with placebo took place over only one on/off cycle. The All Randomized Safety population was 517 subjects, 308 in the TOBI Podhaler arm and 209 in the TOBI® arm.

There were 3 deaths that occurred on the TOBI Podhaler arm compared to none in the TOBI® arm; 2 of the deaths were likely related to a pulmonary exacerbation. The deaths were not assessed by the applicant or the Clinical reviewer as drug related. As described in Section 7 of this review, there were significant numbers of discontinuations in both arms, particularly in the TOBI Podhaler arm (27% vs 18%). The disparity in discontinuations was driven by imbalances in discontinuations due to adverse events (TOBI Podhaler 14% vs. TOBI® 8.1%) and withdrawal of consent (TOBI Podhaler 7.8% and TOBI® 4.3%). The incidence of serious adverse events in the TOBI Podhaler and TOBI® arms were similar (Podhaler 27% and TOBI® 29%). No SAE occurred in the TOBI Podhaler arm at a rate 2% higher than the TOBI® arm.

Using keywords that would have indicated a respiratory illness, the rate of respiratory related hospitalization was 25% in both arms. There was an increased new usage of antipseudomonal medication in the TOBI Podhaler arm (65% TOBI Podhaler vs 55% TOBI®), but this was primarily orally administered as new usage of intravenous antipseudomonal medication was similar between arms. Median time to first antipseudomonal usage was 89 days in the TOBI Podhaler arm and 112 days in the TOBI® arm.

Overall, 51.0% of subjects in the TOBI Podhaler arm and 20.1% of subjects in the TOBI® arm had adverse events categorized as treatment-related. Preferred terms which occurred in the TOBI Podhaler arm at a rate $\geq 2\%$ higher than that of the TOBI® arm were ‘chest discomfort’ (3.2% versus 1.0%), ‘dysgeusia’ (3.9% versus 0.5%), ‘dysphonia’ (12.7% versus 3.3%), ‘dyspnea’ (5.5% versus 1.4%), ‘oropharyngeal pain’ and ‘productive cough’ (both 4.5% versus 1.0%), and ‘throat irritation’ (3.2% versus 1.0%).

The preferred term ‘cough’ occurred at a rate of 25.3% in the TOBI Podhaler arm versus 4.3% in the TOBI® arm. In general, cough was not accompanied by signs of

bronchospasm. Approximately one-third of subjects reporting 'cough' eventually discontinued from the study, but whether the discontinuations were related to 'cough' is not clear. 'Cough' was reported more commonly in cycle 1 (70 subjects) than cycle 2 (22 subjects) or cycle 3 (13 subjects).

There were no apparent differences in ototoxicity or nephrotoxicity, and these adverse events were rare in Study C2302.

9. Advisory Committee Meeting

The Anti-Infectives Drug Advisory Committee discussed the application on September 5, 2012. In addition to discussing the Microbiology issues described in Section 6 of this review, the Committee voted 13 to 1 that the applicant had demonstrated adequate evidence of safety and efficacy for the indication proposed. As described above, Advisory Committee members specifically discussed the increases in MIC observed and opined that the clinical relevance was not clear. Several recommended long term follow-up post-marketing to assess the clinical relevance. The Advisory Committee members also discussed the Human Factors study and opined that while the Instructions for Use should be revised, the results of the Human Factors study did not impact their opinion that safety and efficacy had been demonstrated.

10. Pediatrics

The product will be labeled down to 6 years of age. This orphan product is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

Several clinical site investigators received an FDA Form 483, but the OSI recommendation based upon inspectional findings at these sites was that the efficacy and safety data from these sites could be considered reliable.

12. Labeling

In discussions with the applicant, the Instructions for Use were extensively revised with input from Agency Human Factors and Labeling reviewers. Based on the findings of the Human Factors Study discussed in Section 3 of this review and input from patients obtained by the sponsor, the Instructions for Use were rewritten for clarity and an illustration was added to each step required to administer the dose and insure that the capsule is properly punctured and empty. The revised Instructions for Use will need to be formally evaluated as a Post-Marketing Requirement.

The proposed proprietary name TOBI Podhaler was reviewed and deemed acceptable.

13. Decision/Action/Risk Benefit Assessment

TOBI Podhaler is a new mechanism of delivery of a drug which has been previously demonstrated to be efficacious for the proposed indication. Cystic fibrosis is an orphan disease and the application highlights some of the challenges conducting clinical trials in this population. For example, the infeasibility of adequate accrual of patients in Study C2303 illustrates that a placebo-controlled trial in cystic fibrosis patients chronically colonized with *P. aeruginosa* is no longer considered acceptable to patients or physicians. Alternatives to reduce the burden of treatment in this population are needed. TOBI Podhaler would offer an important alternative to patients that may improve compliance as the time to administer treatment is considerably shorter than TOBI® by nebulizer.

The applicant has provided substantial evidence of efficacy consisting of a robust demonstration of superiority over placebo in Study C2301 and supportive data from Study C2302 and Study 2303. The safety findings in Study C2302 suggest that some patients may elect to discontinue TOBI Podhaler due to adverse effects such as cough. Patients would need to be monitored carefully as they initiate therapy and be switched to TOBI® by nebulizer if necessary. The increase in MIC and clinical implications of this finding would need to be evaluated in a post-marketing requirement. The Instructions for Use have been extensively revised during this cycle, but would also need to be evaluated in a post-marketing requirement.

Based on the findings of inadequate procedures to control environmental conditions which could reasonably be expected to adversely impact product quality at the device manufacturing facility, the regulatory action is Complete Response. The deficiency to be communicated is as follows:

During a recent inspection of the [REDACTED] (b) (4) [REDACTED] manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
10/19/2012

CLINICAL REVIEW

Application Type	NDA 505(b)1
Application Number(s)	201688
Priority or Standard	Standard
Submit Date(s)	Dec. 20, 2011
Received Date(s)	Dec. 21, 2011
PDUFA Goal Date	Oct. 19, 2012
Division / Office	OND/OAP/DAIP
Reviewer Name(s)	Shrimant Mishra, M.D., M.P.H.
Review Completion Date	
Established Name	Tobramycin Inhalation Powder
(Proposed) Trade Name	TOBI® Podhaler™
Therapeutic Class	Aminoglycoside
Applicant	Novartis

Formulation(s)	Powder
Dosing Regimen	28mg capsule x4 BID
Indication(s)	Management of Cystic Fibrosis patients with <i>Pseudomonas aeruginosa</i>
Intended Population(s)	Cystic fibrosis patients with <i>Pseudomonas aeruginosa</i> \geq 6 years old, \geq 25% and \leq 80% FEV 1 % predicted, not colonized with <i>Burkholderia cepacia</i>

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	9
1.1	Recommendation on Regulatory Action	9
1.2	Risk Benefit Assessment.....	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	11
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND	13
2.1	Product Information	13
2.2	Tables of Currently Available Treatments for Proposed Indications	14
2.3	Availability of Proposed Active Ingredient in the United States	14
2.4	Important Safety Issues With Consideration to Related Drugs.....	14
2.5	Summary of Presubmission Regulatory Activity Related to Submission	15
2.6	Other Relevant Background Information	15
3	ETHICS AND GOOD CLINICAL PRACTICES.....	15
3.1	Submission Quality and Integrity	15
3.2	Compliance with Good Clinical Practices	16
3.3	Financial Disclosures.....	17
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	17
4.1	Chemistry Manufacturing and Controls	17
4.2	Clinical Microbiology.....	17
4.3	Preclinical Pharmacology/Toxicology	18
4.4	Clinical Pharmacology	18
4.4.1	Mechanism of Action.....	18
4.4.2	Pharmacodynamics.....	18
4.4.3	Pharmacokinetics.....	18
5	SOURCES OF CLINICAL DATA.....	18
5.1	Tables of Studies/Clinical Trials	18
5.2	Review Strategy	20
5.3	Discussion of Individual Studies/Clinical Trials.....	20
6	REVIEW OF EFFICACY	21
	Efficacy Summary.....	21
6.1	Indication	22
6.1.1	Methods	22
6.1.2	Demographics	26
6.1.3	Subject Disposition.....	31
6.1.4	Analysis of Primary Endpoint(s)	32
6.1.5	Analysis of Secondary Endpoints(s)	45

6.1.6	Other Endpoints	56
6.1.7	Subpopulations	56
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ...	56
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	57
6.1.10	Additional Efficacy Issues/Analyses	57
7	REVIEW OF SAFETY.....	57
	Safety Summary	57
7.1	Methods.....	58
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	58
7.1.2	Categorization of Adverse Events.....	59
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	59
7.2	Adequacy of Safety Assessments	59
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	60
7.2.2	Explorations for Dose Response.....	61
7.2.3	Special Animal and/or In Vitro Testing	61
7.2.4	Routine Clinical Testing	62
7.2.5	Metabolic, Clearance, and Interaction Workup	62
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	62
7.3	Major Safety Results	62
7.3.1	Deaths.....	62
7.3.2	Nonfatal Serious Adverse Events	65
7.3.3	Dropouts and/or Discontinuations	68
7.3.4	Significant Adverse Events	70
7.3.5	Submission Specific Primary Safety Concerns	70
7.4	Supportive Safety Results	78
7.4.1	Common Adverse Events	78
7.4.2	Laboratory Findings	85
7.4.3	Vital Signs	85
7.4.4	Electrocardiograms (ECGs)	87
7.4.5	Special Safety Studies/Clinical Trials	87
7.4.6	Immunogenicity	87
7.5	Other Safety Explorations.....	87
7.5.1	Dose Dependency for Adverse Events	87
7.5.2	Time Dependency for Adverse Events.....	88
7.5.3	Drug-Demographic Interactions	88
7.5.4	Drug-Disease Interactions.....	89
7.5.5	Drug-Drug Interactions.....	90
7.6	Additional Safety Evaluations	90
7.6.1	Human Carcinogenicity	90
7.6.2	Human Reproduction and Pregnancy Data.....	90
7.6.3	Pediatrics and Assessment of Effects on Growth	91

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	91
7.7	Additional Submissions / Safety Issues	91
8	POSTMARKET EXPERIENCE.....	92
9	APPENDICES	98
9.1	Literature Review/References	98
9.2	Labeling Recommendations	98
9.3	Advisory Committee Meeting.....	98

Table of Tables

Table 1: Currently Approved Agents for Indications Similar to that Sought by Tobramycin Inhalation Powder	14
Table 2: Phase 1 and 3 Trials for NDA 201688	18
Table 3: C2301 Trial Design.....	22
Table 4: C2303 Visit Schedule	26
Table 5: C2301 Demographics- All Randomized Safety Population	27
Table 6: C2302 Demographics- All Randomized Safety Population	29
Table 7: C2303 Demographics- Safety Population	30
Table 8: Subject Disposition, All Randomized Safety Population, C2301	31
Table 9: Subject Disposition- 2301.....	32
Table 10: Randomized But Not Included in Safety Populations C2302, Etiology	33
Table 11: Patient Disposition, All Randomized Safety Population, C2302	34
Table 12: Subject Disposition Study C2303	34
Table 13: Relative Change from Baseline in FEV1% Predicted, by Cycle and Treatment Group, C2301.....	37
Table 14: Relative change in FEV1% Predicted from baseline to Day 28, by demographic subgroup; SIA population, C2301	37
Table 15: Mean difference of relative change in FEV1 percent predicted from	38
Table 16: Levels of Compliance as a Function Spirometric Quality, C2301	39
Table 17: Levels of Compliance Cycles 2 and Cycles 3, C2301	40
Table 18: Comparison of Low Compliance (<80% Compliance) By Cycle and Treatment Arm, C2302	41
Table 19: Low Compliance (<80% Compliance), by baseline demographic characteristics, C2302.....	41
Table 20: Relative Change in FEV 1 % predicted from baseline to Day 29, ITT, C2303	42
Table 21: Absolute Change in FEV1% Predicted from Baseline to day 29, ITT , C2303	43
Table 22: Safety population- Relative Change in FEV1% Predicted from Baseline to Day 29, C2303.....	43
Table 23: Relative Change in FEV1% Predicted from Baseline to Day 29, with Outlier Excluded, C2303.....	44
Table 24: Relative Change from Baseline in FEV1 % Predicted at Day 29 Using Imputed Data (ITT/Primary Analysis Population), C2303.....	45
Table 25: Relative Change in FEV1% Predicted from Baseline to Day 29, Subgroup Analysis, C2303	46
Table 26: Change in <i>Pa</i> Sputum Colony Counts (log 10 CFU per gm sputum) from Baseline,	47
Table 27: C2301 Antipseudomonal Usage.....	48
Table 28: C2301 Respiratory Related Hospitalization	49
Table 29: Mean Relative Change in FEV 1 % Predicted from Baseline to End of On Cycle 3,	50

Table 30: Mean Relative Change in FEV 1 % Predicted from Baseline to End of On Cycle 3,	51
Table 31: Median Relative Change in FEV 1 % Predicted from Baseline	52
Table 32: Change in <i>Pseudomonas aeruginosa</i> (log 10 cfu/gm sputum), by treatment arm and timepoint, C2302	53
Table 33: Demographics of New Ciprofloxacin Usage During C2302 Study Period, By Treatment Arm	54
Table 34: Relative change from baseline to day 29 in FVC % Predicted and FEF25%-75% Predicted, ITT population, C2303.....	55
Table 35: Drug Exposure: C2301, C2302, C2303, Safety Populations	60
Table 36: Patient exposure to study drug by treatment cycle (controlled Phase III studies).....	61
Table 37: C2301 Serious Adverse Events, Cycle 1.....	66
Table 38: Serious adverse events (at least 2 patients in total), regardless of study drug relationship, by preferred term and treatment group (Safety population), C2301	67
Table 39: Subgroup Analysis of Study C2302 Discontinuations by Treatment Arm	69
Table 40: Subgroup Analysis of C2302 Study Drug Discontinuations by Treatment Arm	69
Table 41: Number of Subjects with a Relative Decline From Baseline in FEV 1% Predicted of ≥ 10 %, By Visit, SIA population, C2301	76
Table 42: Number of Subjects with a Relative Decline from Baseline in FEV1 % Predicted of ≥ 10 %, by Treatment Group and Visit	77
Table 43: Number of Subjects with a Relative Decline from Baseline of ≥ 10 % in FEV1 % Predicted By Treatment Group and Visit,.....	78
Table 44: Adverse Events, C2302, By Treatment and Cycle	80
Table 45: Adverse Events by SOC and Treatment Group, All Randomized Safety population, C2302	80
Table 46: Cough by Age and Pulmonary Function Subgroups and Treatment Arm, C2302.....	83
Table 47: Cough (Possibly or Probably Related) As a Function of Demographic Subgroups and Treatment Arm, C2302.....	84
Table 48: Rate of TEAEs in CTPI001, by dose cohort	87
Table 49: C2302 Adverse Events by Subgroup, Safety Population	88
Table 50: C2301 and 2303 Adverse Events by Subgroup, Safety Population.....	89
Table 51: Treatment Emergent Adverse Events, C2303E1.....	94

Table of Figures

Figure 1: C2302 Study Design..... page 25

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on upon my review of the safety and efficacy data contained in the New Drug Application, I am recommending approval of the Tobramycin Inhalation Powder (TIP) for the claimed indication. This decision is based not only on my review but also takes into account this orphan disease population for which treatment options are somewhat limited and particularly burdensome, the input of patients and committee members at the recently held Advisory Committee meeting, as well as the valuable input of other disciplines/consultants. Though significant safety issues will need to be followed and labeling improved, overall there is enough data to support approval. Though the application does not meet the traditional requirement for two adequate and well-controlled trials, it does meet the evidentiary standard for one adequate and well controlled trial as outlined in the 1998 Guidance "*Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products.*" There is a positive finding in one placebo controlled trial and enough supportive data from the two other phase 3 trials to conclude that efficacy has been established, particularly in light of the challenges of doing clinical trials in this patient population. Though there have been strong arguments for nonapproval from various corners, in the view of this reviewer there is not enough of a demonstrable efficacy and safety concern to deny a potentially satisfactory treatment option to this vulnerable population. However, this viewpoint may change pending results of postmarketing studies designed to answer key safety and efficacy questions.

1.2 Risk Benefit Assessment

The risk benefit calculus for this application is complex and somewhat dependent on issues external to the application itself.

The study drug appears to show benefit on the primary endpoint in at least one placebo controlled study (C2301). This endpoint, relative change from baseline in FEV1% predicted, was the same one used in the reference listed drug application (TOBI, NDA 050753) and has been shown to be correlated with mortality in cystic fibrosis patients. Moreover, there is modest supportive evidence, though not necessarily clinically significant, on the primary endpoint in the two other phase 3 trials, C2302 and C2303. There is also supportive data in the form of reduced antipseudomonal usage and respiratory-related hospitalizations relative to placebo. Beyond these clinical measures, the drug provides a third treatment option for an inhaled antipseudomonal for a broad segment of cystic fibrosis patients. This treatment option would potentially have advantages of decreased administration times and portability, though improved compliance was not demonstrated in the pivotal studies. In

the setting of very burdensome treatment regimens for such patients, even such small advantages may improve their quality of life. There are concerns over the persistence of beneficial effects over the long term as well as in older populations, however, this can be explored further in post-marketing studies.

The study drug risks that have emerged from this application are primarily related to safety. In particular, there are prominent concerns about increasing *Pseudomonas aeruginosa* tobramycin MICs while on TIP therapy relative to TOBI and increased usage of antipseudomonals in the TIP arm relative to TOBI in the main safety study (C2302). The clinical implications of both issues are unclear. It is unclear whether MICs will continue to increase or will stabilize over time and whether this has short/long term clinical implications for cystic fibrosis patients (who rely on aminoglycoside therapy particularly with pulmonary exacerbations) or the general population (risk of transmission of resistant organisms to vulnerable populations, etc.). Currently, further data are being gathered to clarify the MIC risk and to see if a subset of CF patients emerges as at risk for MIC increases. However, that data is still not available at the time of this review. Similarly, the clinical implications of increased antipseudomonal usage are unclear as well; there was no difference between TIP and TOBI in terms of Serious Adverse Events (SAEs) and respiratory-related hospitalizations. However, there were more deaths in the TIP arm. Compared to TOBI, there are higher rates of “local” airway adverse events such as cough, dysphonia, and oropharyngeal pain with TIP but these appear to abate over time (though they could hinder potential effective use of the drug). Indeed, higher discontinuations were noted in the TIP arm relative to TOBI, though this is not of huge concern given the other treatment options available (e.g. – a subject can always switch back to TOBI® or Cayston®).

Another area of concern is the ability of patients to use this drug device combination properly. The human factors study conducted was inadequate but still showed potential use error signals across the study population. Moreover, the Instructions For Use might be confusing to interpret.

Though these safety issues are alarming, procedures exist to both evaluate and minimize their impact. Properly designed post marketing studies evaluating resistance patterns and clinical outcomes in subjects would be of significant benefit; a prospective cohort study could be considered. Moreover, labeling and electronic media can be enhanced to improve proper use of the drug. Finally, in this closely monitored clinical population, one would hope that worse clinical outcomes or difficulties in use would limit use of the drug on the open market, though this is certainly not guaranteed.

Finally, the difficulties and unwillingness of subjects and drug companies to participate in lengthy, randomized, placebo –controlled trials for this indication cannot be ignored. Furthermore, active controlled study designs have not been clearly delineated, particularly as regards endpoints and noninferiority margins, though certainly valuable safety information could be obtained.

Taken together, there is a general, albeit modest favorable risk benefit calculus that essentially arises from demonstration of efficacy and ways to mitigate and monitor risk.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket REMS strategies are being recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Currently, several pre-post marketing studies are ongoing/being proposed by the sponsor for evaluation of adverse effects related to long term use, device usability in young pediatric patients, and comparison of clinical outcomes with similar class drugs in a real world setting.

C2303E1 and C2303E2 are two back to back open label, single arm 6 month phase 3 extension studies of C2303 to obtain further safety information in this study population. C2303E1 has already been completed and a report issued. C2302E2 is ongoing.

C2401: a single arm, open label phase 4 year long observational study to evaluate TIP safety in CF adults. 150 subjects planned, over half greater than 18 years of age. Look at safety endpoints such as airway reactivity, time to and rate of antipseudomonal usage and respiratory-related hospitalization, change in *Pseudomonas aeruginosa* tobramycin MIC over study period, laboratory results, etc. Study population similar to C2302. This study has not been initiated yet.

C2407: Prospective Observational Study of effectiveness and safety of TIP in CF patients with chronic respiratory *Pseudomonas aeruginosa* infection. US-based study looking two CF cohorts of 500 patients- one cohort using TP and another cohort using another approved inhaled antipseudomonal for this indication. Subjects followed for one year (quarterly visits). Subjects will be 6 years and older, have chronic respiratory *Pseudomonas aeruginosa* infection, be treated with an FDA approved inhaled antipseudomonal be treated at a CFF-accredited care center, and be a part of the Port CF database, a Cystic Fibrosis Foundation database that collects information related to care provided to participating CF patients and outcomes in these patients, including such information as demographics, diagnosis and treatment information, medical history, medication use, clinical practice patterns, pulmonary and nutritional outcomes, and survival. As of 2008, 95% of US CF patients were a part of the registry. Subjects will be followed for SAEs, use of antipseudomonals for pulmonary exacerbations and respiratory-related hospitalizations, pulmonary function measures, adverse events of special interest (bronchospasm, local tolerability, nephrotoxicity, ototoxicity) and quality of life measures. Most information is expected to be collected as part of routine clinical care.

Of note, there is no formal microbiological surveillance study other than what has been proposed as part of the above safety studies.

Most of the sponsor's proposed post marketing safety monitoring involves typical pharmacovigilance for certain prespecified risks and in populations excluded from phase 1-3 studies: cough, bronchospasm, hemoptysis, ototoxicity, fetal harm, decreased *Pseudomonas aeruginosa* susceptibility to tobramycin (MIC), potential drug drug interaction with diuretics and other drugs affecting renal clearance, nephrotoxic/neurotoxic/ototoxic drugs, patients with moderate and severe renal failure not included in clinical trials, and pregnant or lactating females.

Routine pharmacovigilance activities include:

A validated global electronic database for permanent retention and retrieval of all spontaneous adverse event reports (SRs) and all SAEs from phase 1-4 clinical trials and post-marketing studies (e.g. registries, safety studies).

- A validated global electronic tracking system that allows affiliate companies to forward SRs and SAEs collected locally to a centralized data processing unit.
- A validated data mining tool and hypothesis generator for identifying potential safety signals based on pre-defined criteria and methodologies.
- A validated global electronic system for maintaining and providing access to pharmacovigilance Standard Operating Procedures.

The following list summarizes the sponsor's activities for conducting routine pharmacovigilance for multi-national products:

- Daily single case review of serious listed and unlisted spontaneous reports (SR)
- Daily single case review of all Serious Adverse Events (SAEs) from clinical trials (regardless of expectedness and suspectedness)
- Weekly review of line listings for all non-serious spontaneous reports
- Review of cases with at least 2 minimum criteria at annual safety profile review
- Preparation of reports for health authorities, including PSURs, Annual Safety Reports, and equivalent safety summaries required by individual health authorities
- Automated signal detection for statistical disproportionality and designated medical events using the Empirica Signal System (ESS) at least 3 times per year
- Automated signal detection for increased frequency and increased severity using the ESS Annually
- Formal review of drug safety profile every 6 months for priority 1 drugs and annually for priority 2 drugs
- Evaluation of product relevant literature or information from other external sources (e.g. media, prescribing information, of competitor products) at least 3 times per year
- Evaluation of competitor(s) drugs/class effects through the medical literature and/or external safety databases at least 3 times per year
- Evaluation of relevant epidemiological findings as required

In the case of decreased *Pseudomonas aeruginosa* susceptibility to tobramycin (MIC), hemoptysis and ototoxicity, a targeted follow up questionnaire has been devised for all serious and nonserious spontaneous cases. In the case of hemoptysis and ototoxicity events, the questionnaire would investigate things like medical history, concomitant medications, laboratory studies, and diagnostic tests. In the cases of decreased *Pseudomonas aeruginosa* susceptibility to tobramycin (MIC), the questionnaire would gather follow up data on *P. aeruginosa* (*Pa*) tobramycin minimum inhibitory concentration (MIC) susceptibility, usage/duration of intravenous and inhaled antipseudomonal antibiotics, *Pa* colony forming units (CFU), spirometry (FEV1), concomitant medications, concomitant illnesses, and medical history.

These planned studies/pharmacovigilance activities are acceptable as a framework for post marketing requirements/commitments. In particular, a study similar to C2407 might help answer (albeit in limited fashion) safety and usability issues noted in the review process. However, protocol specifics and design issues will need to be discussed with the Agency prior to initiating these studies. Also, a formal microbiology surveillance PMR study will need to be designed in order to address the issue of potentially accelerated increase in *Pseudomonas aeruginosa* tobramycin MICs with TIP.

2 Introduction and Regulatory Background

2.1 Product Information

The study drug is a tobramycin inhalation powder with the proposed trade name of TOBI® Podhaler™. Tobramycin is a part of the aminoglycoside antimicrobial class and is currently available in parenteral and nebulized forms, however this represents the first formulation as an approved powder. The proposed indication for this drug is for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. It is to be administered twice a day through a handheld inhaler device. During each administration, four 28 mg capsules will be sequentially loaded into the inhaler, punctured, and inhaled so that the actual dosing regimen will be 112mg twice a day (bid). The drug is proposed for cystic fibrosis patients with *Pseudomonas aeruginosa*, ≥ 6 years old, FEV1 % predicted ≥ 25% and ≤ 80% , and not concomitantly colonized with *Burkholderia cepacia*. The active ingredient of the drug, tobramycin, acts by interfering with bacterial ribosomal function though its exact mechanism of action is unclear. It is a bactericidal drug that is concentration dependent and has a post antibiotic effect. The spectrum of activity primarily includes gram negative aerobic bacilli but also includes some mycobacteria and protozoa. Aminoglycosides, if given

parenterally, do not penetrate into lung secretions; they achieve much higher bronchial secretions if delivered by aerosol. Because of this characteristic, it is hypothesized that inhaled aminoglycosides will benefit cystic fibrosis patients frequently colonized/infected in the lung with *Pseudomonas aeruginosa*.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Approved Agents for Indications Similar to that Sought by Tobramycin Inhalation Powder

Drug	Indication	Dose	Device	Dosing Regimen
TOBI®	Management of cystic fibrosis patients with <i>Pseudomonas aeruginosa</i>	Nebulized: 300 mg tobramycin/5ml solution bid	Compressor: De Vilbiss® Pulmo-Aide® compressor Nebulizer: PARI LC Plus™	28 Days On Cycle 28 Days Off Cycle
Cayston®	Improve respiratory symptoms in cystic fibrosis patients with <i>Pseudomonas aeruginosa</i>	Nebulized: 75 mg aztreonam mixed with 1ml diluent tid	Altera nebulizer and compressor system	28 Days On Cycle 28 Days Off Cycle

2.3 Availability of Proposed Active Ingredient in the United States

Tobramycin is readily available in the United States; it is already used in parenteral and approved nebulized formulations.

2.4 Important Safety Issues With Consideration to Related Drugs

Primary safety issues related to the active ingredient/aminoglycoside class include nephrotoxicity, ototoxicity, and neuromuscular blockade; these safety issues are dose and duration dependent. Nebulized formulations of tobramycin and aztreonam

have also had route of administration-related safety issues including bronchospasm, voice alteration, wheezing, and pyrexia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant major presubmission activities include the following

A. The choice of primary endpoint for the phase 3 trials, relative change in FEV₁ % predicted from baseline, was chosen based on the primary endpoint used in the pivotal trials for the reference drug - TOBI®.

B. During the conduct of the C 2301 placebo-controlled study, a protocol-planned interim efficacy analysis conducted by the sponsor found that several sites from Latin America had spirometry data of unacceptable quality. A sensitivity interim analysis was performed which excluded such patients, and this analysis was used for the primary efficacy analysis (see section 6.1 for further details).

C. A different manufacturing process was introduced for TIP between the C2302 and C2303 trials. Comparability of drug substance from the prior and current process is the subject of both CMC and Clinical Pharmacology review.

D. The C2303 trial was prematurely stopped due to difficulty in enrollment.

2.6 Other Relevant Background Information

Currently, this drug is approved in the EU, Canada, Colombia, and Chile. It has been launched thus far in Canada, Germany, The Netherlands, UK, Norway, Denmark, and Ireland

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission quality was fair. Multiple information requests needed to be made, some of which were due to lack of information provided in the initial submission. The way information was collected and presented in C2303 differed to a significant degree from the earlier studies, primarily due to the use of digital case report forms. These forms were not user friendly to navigate. Also, rather than creating special sections in EDR for areas such as discontinuations, protocol deviations, etc., information for each study was primarily presented as very large clinical study reports;

this required some time to familiarize oneself with the various sections of the document. In many cases, excessive information was submitted which made trying to find key points of interest/tables difficult. Case report forms did not contain detailed eligibility or laboratory information so this data was difficult to verify. Also, pulmonary function data was not presented as % predicted on CRFs which made verification of such data difficult. Several issues had to do with data interpretation/coding and are discussed further in relevant safety and efficacy sections.

3.2 Compliance with Good Clinical Practices

A Division of Scientific Investigation (DSI) has been conducted and the final report is currently being prepared. Site selection was made based on importance of the particular trial to safety and efficacy, sample size at a study site, logistical planning with regards to inspections, etc. Preliminary discussions with DSI seem to indicate that most findings will fall under a category of VAI (Voluntary Action Indicated). Preliminary findings at inspected sites include inaccurate documentation of spirometry results, inappropriate enrollment into trial, improper informed consent procedures, instances of lack of human subjects protection, incorrect randomization, poor record keeping and mistimed or lack of performance of particular visit procedures. However, taken as a whole, the data was generally considered reliable.

It should be noted that there were significant amounts of missing or unacceptable spirometric and safety data in all three studies, limiting efficacy and safety interpretations. This was particularly disruptive in small trials where missing or faulty data might lead to markedly different outcomes.

In C2301, 73% of subjects had a protocol violation. Frequent violations included failing to take complete dose at any study dosing (48%- *use in compliance discussion*), use of short acting- bronchodilators improperly (21%) prior to study medication, and interruption of study medication during on cycle (17%).

In C2302, 99% of subjects had protocol violations (99% in both arms). The most common violations were 'did not take either morning or evening dose (95% TIP subjects, 95% TOBI subjects) and 'subject that interrupted study medication during any on treatment cycle throughout the study' (95% TIP subjects, 94% TOBI subjects) *put in compliance discussion*. Most protocol violations were well matched. Mild discrepancies occurred with 'subject did not take 28 days of either TIP or TOBI in any cycle' (23% TIP, 17% TOBI), 'subjects used macrolides (chronic use) which has not been initiated more than 28 days before the first dose of study drug (6% TIP, 2% TOBI) and subject took less than 80% of study drug (18% TIP, 9% TOBI).

In C2303, 52% of subjects had a protocol violation (59% TIP, 43% placebo). Significantly, 2 patients in the TIP arm were mistakenly given placebo. 1 subject was enrolled who did not have Pa within 6 month. The most frequent protocol violation was "other evaluation not done as per protocol." Most violations dealt with patient safety issues, such as not doing scheduled pregnancy tests, enrolling subjects with signs of renal impairment, not stopping drug despite signs of renal impairment.

3.3 Financial Disclosures

Novartis submitted inquiries to study staff regarding financial disclosures. It had a poor response rate from non-US sites in study C2301 (<40%), but otherwise had good a response rate from the US sites in C2301 (79%) and from all sites in studies C2302 and C2303 (>90%). It found only one PI who reported a significant financial disclosure. This was an investigator from (b) (6) who enrolled only (b) (6) patients in C2302; he had received honoraria and grants for research in excess of \$25,000 from Novartis. This disclosure is unlikely to be of significant consequence. Overall, there is unlikely to be a significant financial conflict of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Currently approval has not been recommended strictly because GMP inspections are ongoing, including for certain drug manufacturing sites. However, the applicant was felt to have provided “sufficient information on raw material controls, manufacturing processes and process controls, adequate specifications for assuring consistent product quality of the drug product, and sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the expiration dating period.” The product was considered approvable from a CMC Microbiology perspective. Please note the full reviews by Drs. Seggel (CMC) and Langille (CMC Micro.) for further details.

4.2 Clinical Microbiology

The microbiology reviewer noted several significant safety concerns with TIP. Foremost was increasing *Pseudomonas aeruginosa* (*Pa*) tobramycin resistance while on TIP therapy. Increases of three or more dilution steps were noted in some cases as were MICs > 512 mcg/ml. Such changes were not noted to the same degree in comparator arms. Other concerns included lower than anticipated *Pa* sputum log 10 reduction rates, increased resistance to other antibiotics during TIP therapy, and increased emergence of other pathogens while on TIP therapy. Please note the review by Dr. Peter Coderre. Also, please note that these safety concerns are the subject of a current information request.

4.3 Preclinical Pharmacology/Toxicology

Repeat dose inhalation studies in dogs (4 weeks) and rats (26 weeks) were performed by the applicant. Overall, these studies demonstrated that systemic and pulmonary toxicity with TIP was likely to be equivalent to that seen with TOBI, particularly as concerns airway inflammation and nephropathy. Also, nonclinical tests were performed to demonstrate the safety of the DSPC excipient degradation product. The safety of DSPC, its degradant (S-lyso-PC), and calcium chloride were demonstrated by genotoxicity studies and repeat dose rat/dog studies to be safe for repeated inhalation at the levels used in TIP. S- Lyso-PC was not noted to have increased bronchoconstrictive properties in guinea pig studies. Please note the complete review done by Dr. Amy Ellis for further details.

4.4 Clinical Pharmacology

The clinical pharmacology findings confirm that the PK parameters of study drug did not differ from the old to the new manufacturing process. The review also affirmed the chosen dose of TIP (112 mg tobramycin taken as 4 x 28mg inhaled capsules) as having similar serum PK parameters as 300mg nebulized TOBI, though more variability was noted in sputum concentrations. Please note the review by Dr. Ryan Owen

4.4.1 Mechanism of Action

Please note above section 2.1 as well as the Clinical Pharmacology review (section 2.1.2) and Clinical Microbiology review for further information.

4.4.2 Pharmacodynamics

Please note the Clinical Microbiology review

4.4.3 Pharmacokinetics

Please note the Clinical Pharmacology review for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Phase 1 and 3 Trials for NDA 201688

Trial	Study Type	Primary Purpose	Countries Participating	Randomized patients	Dosing Regimen	ITT	Safety	Primary Endpoint
C2301	Randomized, double-blind,	Efficacy/supportive safety	US, Argentina, Brazil, Chile,	102	1st Cycle of 28 days on/off: TIP	Sensitivity Interim Analysis:	TIP: 46 Placebo:	Relative change in FEV1 %

Clinical Review
Shrimant Mishra
NDA 201688
TOBI Podhaler/Inhaled Tobramycin

	placebo controlled with open label follow on		Mexico, Serbia and Montenegro, Bulgaria, Lithuania 32 sites total		BID or Placebo BID 2 nd and 3 rd cycle of 28 days on/off: TIP BID only in both arms	TIP: 29 Placebo: 32 Includes patients only from interim analysis sites not excluded due to poor quality spirometry	49 Pediatric:: TIP: 35 Placebo: 40	predicted from baseline to Day 28
C2302	Randomized, Open-Label, Active Controlled	Safety	US, Australia, Canada, Chile, Colombia, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Netherlands, Spain, Switzerland, United Kingdom 127 sites total	553	3 cycles of 28 Day on/off: TIP BID or TOBI BID	Same as safety	TIP: 308 TOBI: 209 Pediatric: TIP:73 Placebo: 46	Safety
C2303	Randomized, Double-Blind, Placebo Controlled	Efficacy/ Supportive safety	Estonia, Latvia, Lithuania, Bulgaria, Romania, Russia, India, Egypt 18 sites total	62	1 cycle 28 day on/off: TIP BID or Placebo BID	TIP: 32 Placebo: 30 TIP arm includes 2 patients who actually received placebo	TIP: 30 Placebo: 32 Pediatric: TIP:25 Placebo: 25	Relative change in FEV1 % predicted from baseline to Day 28
TPI001	Randomized, Open Label, Active Controlled , Single Dose, Dose Escalation	Dose Finding	USA 15 sites total	86	Single dose of either TOBI or TIP (2x14 mg, 4x 14 mg, 2 x28mg, 3x28mg, or 4x 28 mg TIP)		TIP: 66 TOBI: 20 Pediatric: 36	Safety PK
INH007	Open label, crossover	PK Pulmonary deposition	UK 1 center	14	Each subject sequentially administered 3 single dose inhalations of 13.3 mg TIP		TIP/TOBI: 14 Pediatric: 0	PK Pulmonary deposition

					separated by 4 days per dose, then given dose of TOBI 300mg, followed 7 days later by one dose inhaled 80mg TIP			
--	--	--	--	--	---	--	--	--

5.2 Review Strategy

The clinical review of safety and efficacy for this NDA submission was done by one reviewer only, Dr. Shrimant Mishra. However, as part of this review, relevant areas of the review have been deferred to discipline specific reviewers, such as Clinical Pharmacology, Microbiology, Pharmacology/Toxicology, and CMC. Significant assistance for the efficacy review was provided by the statistical reviewer, Dr. Christopher Kadoorie. Consultations included DPARP (pulmonology assistance on clinical issues), DSI (site inspections), CDRH (device and human factors evaluation in conjunction with CMC), and DMEPA (human factors evaluation).

5.3 Discussion of Individual Studies/Clinical Trials

There were three phase 3 trials, though only two were designed to evaluate efficacy. They are described in further detail in section xxx. Each of these trials differed from each other in significant ways such that an integrated evaluation of safety and efficacy only seems modestly logical. Study C2302 was a much larger and longer (compared to the placebo-controlled portions of C2301 and C2303) open label, active controlled trial that was designed to evaluate safety and thus should be evaluated in isolation. Studies C2301 and C2303 were small, randomized, double blind placebo-controlled trials designed for efficacy (both had the same primary endpoint), and on the surface it would appear to make sense to evaluate them collectively. However, study C2301 was of a longer duration than C2303; it consisted of one placebo controlled cycle followed by two open label cycles. Study C2303 consisted of just one placebo controlled cycle. Also, though it demonstrated significance on the primary endpoint, study C2301 had significant trial conduct issues including marked amounts of invalidated spirometric data. This resulted in an analysis population that did not have the general bias protections of randomization. Similarly, C2303 had significant amounts of missing data and two subjects were given the wrong medication. The study was stopped prematurely due to recruitment issues and failed to meet significance on the primary endpoint. Both trials had only modest overlap in site locations (by country), and C2301 took place from 2005-2007 while study C2303 took place from 2009-2011. Lastly, the

TIP product in study C2303 was created through a different manufacturing process from that used in C2301, though from a formulation standpoint the study drug is equivalent. Thus, it is best to evaluate these studies in isolation lest an integrative analysis overshadow pertinent study characteristics and outcomes, particularly as concerns efficacy. However, some integrated safety data from the placebo controlled portions of studies C2301 and C2303 will be presented later in the review.

C2302 will be used primarily to analyze safety issues, though it also can be used for some descriptive efficacy comparisons (such as compliance between TIP and TOBI and relative comparisons of pulmonary function measures). Please note the table in section 5.1 for further discussion of the various trial designs

6 Review of Efficacy

The review of efficacy will follow this basic format for each relevant section:

Discussion of C2301 efficacy results.

Discussion of C2302 efficacy results (primarily descriptive).

Discussion of C2303 efficacy results.

Efficacy Summary

There was a demonstration of efficacy on the primary endpoint of relative change in FEV1% predicted from baseline to Day 28 in the randomized, placebo-controlled study 2301. Despite significant trial conduct errors such as missing or poor quality spirometry data and less than ideal statistical methods, a statistically significant effect favoring TIP on this measure was shown using different imputation methods. However, a similar result could not be replicated in the randomized, placebo controlled study C2303 though there was a numerical suggestion favoring TIP. This study suffered from recruitment difficulties, missing data, and may have been influenced by outlier data. Though it cannot be viewed as providing strong supportive evidence, it is minimal evidence nonetheless. The open label, active controlled safety study C2302 can only be evaluated on changes in FEV1% predicted from purely descriptive standpoint. However, there is no marked difference noted on this measure between TIP and TOBI.

The secondary/exploratory endpoints provide a somewhat more mixed picture. There was modest decrease in non study drug antipseudomonal usage in studies C2301 and C2303 in the TIP arm relative to placebo, but in C2302 there was actually higher such usage in the TIP arm compared to TOBI (as well

as decreased time to antipsuedomonal usage with TIP). Respiratory-related hospitalizations, also seemed to show a modest decrease in studies C2301 and C2303 relative to placebo, but there was no real difference noted between TIP and TOBI in study C2302.

If one considers compliance a marker efficacy, surprisingly in C2302 (the only study to provide useful information on this measure), there was no improved, and maybe even slightly decreased, compliance with TIP compared to TOBI. However, it should be noted, that compliance was measured somewhat crudely with only returned capsules and dosing logs. If one considers compliance as including proper use of a device/drug, then this was not captured in any granular detail in any of the three studies. Treatment satisfaction and decreased administration times did appear to be noted with TIP though the clinical significance of this is unclear.

Overall, though the picture is quite mixed, the general view is one of TIP appearing to be an improvement over placebo and not substantially worse than TOBI. It is interesting to note that though overall benefit can reasonably be suspected with TIP, the magnitude of benefit, particularly on the primary endpoint, is unclear. In C2302 where there was primarily an older population enrolled, there was a very modest benefit on this measure. More marked benefit was seen in the placebo-controlled trials which had primarily younger patients. However, even between C2301 and C2303, the amount of benefit on this measure differed. Finally, whether beneficial effects on the primary endpoint can be maintained is unclear and will need to be evaluated with long term studies.

6.1 Indication

The stated indication for this drug is “management of cystic fibrosis patients with *Pseudomonas aeruginosa*.” This is the same indication as the reference drug TOBI®.

6.1.1 Methods

C2301

C2301 was a randomized, double blind, placebo-controlled trial with open label follow on. Tabular outline of the trial design is as follows:

Table 3: C2301 Trial Design

Days 1-28	Days 29-56	Days 57-84	Days 85-112	Days 113-140	Days 141-168	
-----------	------------	------------	-------------	--------------	--------------	--

Cycle 1		Cycle 2		Cycle 3		
TIP	Off drug	TIP	Off drug	TIP	Off drug	
Placebo	Off drug	TIP	Off drug	TIP	Off drug	
Visit 2: Day 1 Visit 3: Day 8 Visit 5: Day 28		Visit 7: Day 57 Visit 8: Day 84		Visit 9: Day 113 Visit 10: Day 140	Visit 11/FU: Day 168	

*-visit 1 was screening visit

As noted above, the last two 28 day on/off cycles were open label; all subjects received TIP. Thus the two arms can be designated as the TIP/TIP/TIP arm and the placebo/TIP/TIP arm, respectively. Placebo in this trial was simply the dry powder containing excipients only (1,2-distearoyl–sn-glycerol-3-phosphocholine [DSPC] and calcium chloride [CaCl₂]). The safety of the placebo powder for inhalation was demonstrated in nonclinical studies upon recommendation from the Agency.

The primary objective of this study was to demonstrate the efficacy of a 28 day regimen of bid TIP versus placebo using a similar primary endpoint as the original TOBI trials - relative change in FEV₁ % predicted from baseline (Day 1 predose measurements) to Day 28 (end of study drug dosing for first cycle). In order to facilitate comparisons with the original TOBI trials, the study population was designed to be TOBI “naïve” – subjects had to have been off of an inhaled antipseudomonal for at least four months prior to study. Important planned secondary endpoints included time to first antipseudomonal (other than study drug) use, change in *Pa* sputum density from baseline, and change in *Pa* tobramycin MIC from baseline. Exploratory endpoints included time to first hospitalization and incidence and duration of hospitalization.

Notable inclusion criteria included

- diagnosis of CF based on prespecified criteria (one or more clinical features of CF in addition to either positive sweat chloride test, presence of well characterized mutations in CFTR gene, or abnormal transepithelial difference).
- age ≥6 years old and ≤ 21 years old
- baseline FEV₁ % Predicted ≥ 25% and ≤ 80%
- presence of *Pa* in sputum culture at screening and also within the 6 months prior to screening

Notable exclusion criteria included:

- sputum culture yielding *B. cepacia* within the 2 years prior to screening
- predefined measures for renal insufficiency (creatinine ≥ 2 mg/dl, BUN ≥ 40mg/dl, or urinalysis with 2+ or more proteinuria)
- pregnancy

- use of inhaled antipseudomonal antibiotics in 4 months prior to screening
- use of systemic antipseudomonal antibiotics in the 28 days prior to study drug administration
- could take macrolides, DNase, and inhaled steroids if initiated 28 days before first study drug administration

These criteria allowed for some similarity between this study population and the study populations of the original TOBI trials. These criteria also allowed for enrollment of somewhat medically stable CF subject who were not at the extremes of disease severity.

The protocol for this trial was originally submitted in Jan. 2006 and was amended in Nov. 2006. A preplanned interim analysis was planned after randomization of the 80th subject. However, after this analysis had been performed, the sponsor had concerns about the quality of spirometric data at several sites. After auditing and an independent assessment, several Latin American sites were found to have unacceptable spirometry readings for a variety of reasons (please see section 6.1.4 for further details). As a result, the population analyzed for the primary efficacy endpoint was significantly reduced. The various study populations are defined as follows:

- *Randomized population*: included all randomized patients.

-*All Randomized Safety population*: included all randomized patients who received at least one capsule of study drug.

-*SIA Safety and SIA ITT population*: included all patients in the Sensitivity Interim Analysis (61 subjects). It included all patients from North America and Europe whose data were available at the interim analysis database lock. In addition, it included 8 patients from Latin America who met the spirometry quality review criteria set by an external review panel. 18 Latin American subjects were excluded from this population due to poor quality spirometric data.

-*All ITT and All Safety population*: included all patients from the SIA population (61 subjects) and an additional 8 patients from North America and Europe since SIA. The additional Latin American patients since SIA were not included in the All ITT and All Safety population since they did not go through a quality review of pulmonary function testing by an independent external expert review panel.

It should be noted that the duration of the blinded portion of this trial was only 56 days (one 28 day on/off cycle), which was less than the original TOBI trials (three 28 day on/off cycles), limiting assessment of duration of effect. However, ethical concerns regarding the use of placebo in these subjects in an era when inhaled antipseudomonals have essentially been established as standard CF care led to the decision to shorten the duration of placebo to one cycle only.

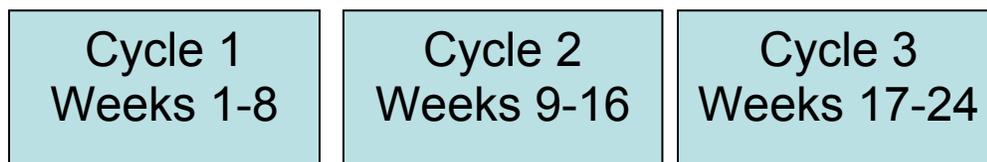
C2302

The C2302 trial was a randomized, active controlled, open label trial comparing TIP to standard nebulized tobramycin (TOBI) over three 28 day on/off cycles in a patient population that differed in some key characteristics from the placebo-controlled trials. Patients in this trial needed only to have been off of an inhaled antipseudomonal for 28 days prior to the study and allowed for enrollment of subjects > 20 years old; in the placebo-controlled trials, subjects were to not have taken an inhaled antipseudomonal four months prior to study and generally had an age limit of 21.

While all three trials provide some information on safety, the vast majority of such information is derived from the C2302 trial. This is for several reasons. First, the C2302 trial had a much larger safety database than either of the placebo controlled trials. Secondly, the C2302 trial compared TIP to TOBI over three successive on/off cycles while comparisons with placebo took place over only one on/off cycle. This longer duration allowed for looking at safety trends and signals over time to better characterize their significance. Third, the placebo used in both C2301 and C2303 was a powder containing the same excipients present in the TIP powder minus the active ingredient- tobramycin sulfate. Thus, this did not provide insight into important safety information, particularly safety considerations related to the use of an inhaled powder rather than a nebulized solution; this is clinically relevant given the current approved usage of only nebulized tobramycin (TOBI®) and nebulized aztreonam (Cayston®) for similar indications in the United States. This information is summarized in the figure below. The visit structure was essentially identical to that of C2301.

Figure 1: C2302 Study Design

TIP N=308	28 Days TIP	28 Days Off	28 Days TIP	28 Days Off	28 Days TIP	28 Days Off
	Open Label					
TOBI N=209	28 Days TOBI	28 Days Off	28 Days TOBI	28 Days Off	28 Days TOBI	28 Days Off



C2303

C2303 was a randomized, double-blind, placebo-controlled trial of TIP vs. placebo in a 28 day on/ 28 day off cycle. The inclusion criteria were similar to those used in C2301, and the primary efficacy endpoint was again relative change in FEV1% predicted from baseline to Day 28. The study was stopped prematurely due to significant difficulties in patient recruitment. Initially, 62 subjects were randomized- 32 to the TIP arm and 30 to the placebo arm. However, in reality, two patients in the TIP arm mistakenly received placebo and so the safety population is actually 30 subjects in the TIP arm and 32 subjects in the placebo arm. Notably, the TIP formulation used in this study was produced by a different manufacturing process from that used in the earlier studies. Similar to study C2301, the placebo consisted of excipients only; individual TIP capsules contained 28 mg of active ingredient while the placebo capsules contained 20 mg of powder. The study visits were as follows:

Table 4: C2303 Visit Schedule

Days	1-28	29-56
TIP	On Drug	Off Drug
Placebo	On Drug	Off Drug
	Visit 2: Day 1 Visit 3: day 28	Visit 4: Day 56

* Visit 1 – Screening Visit

6.1.2 Demographics

C2301

In terms of mean age, height, weight, FEV1% predicted at baseline, gender, and race distributions there was general comparability between the TIP and placebo arm for the all randomized safety population. The mean age for both arms was quite young at 13 years old. There were slightly more females and Hispanic subjects in the TIP arm, and slightly more Caucasian subjects in the placebo arm. There was a slightly increased percentage of patients in the TIP arm who had FEV 1% predicted at baseline < 50% predicted and a slightly decreased percentage of subjects with FEV1% predicted > 80%. Please note Table 5 below. The number of subjects with respiratory symptoms from the 'Respiratory, mediastinal and, thoracic disorders' system organ class (SOC) at baseline was equivalent between the two arms but there was a slightly increased number of subjects with symptoms from the 'Infections and infestations' SOC in the TIP arm (5 subjects TIP vs. 1 subject placebo). Both arms had equivalent proportions of subjects with a medical history involving the 'Infections and infestations' SOC at baseline, but more placebo subjects had a medical history involving the Respiratory, mediastinal, and thoracic SOC at baseline (9 subjects TIP, 16 subjects placebo). Prior antibiotic exposure was high and equivalent between both arms (89% of TIP subjects vs. 88% of Placebo subjects). During the study itself, the placebo arm had higher concomitant use of mucolytics including dornase alfa, beta agonists, glucocorticoids, macrolides, and sodium chloride.

Table 5: C2301 Demographics- All Randomized Safety Population

	TIP N= 46	Placebo N=49
Age Group		
≥ 6 and <13	21 (46%)	24 (49.0%)
≥ 13 and < 22	25 (54%)	25 (51%)
Sex		
Male	19 (41%)	23 (47%)
Female	27 (59%)	26 (53%)
Race		
Caucasian	37 (80%)	43 (88%)
Hispanic	8 (17%)	4 (8%)
Baseline pulmonary		

function ^{1,2}		
< 25% Predicted	1 (3%)	2 (6%)
≥25 to < 50%	11 (38%)	10 (31%)
≥50 to ≤ 80%	15 (52%)	16 (50.0%)
>80%	2 (7%)	4 (13%)

1-Baseline was defined as the last measurement prior to the first dosing of study medication (screening or predose day 1 of cycle 1); for example, if predose day 1 was missing, the non-missing screening value was used

2-numbers and percentages represents SIA Population; TIP: 29 Placebo: 32; cannot assess baseline pulmonary function of All Randomized Safety Population because several subjects with poor quality spirometry

In terms of the SIA population, there was a predominance of females in the TIP arm relative to placebo (55 vs. 43%, respectively) but was well matched in terms of age and pulmonary function. The mean age was 14 years for both arms. Compared to the All Randomized safety population, the SIA population was older, had proportionally more males, and proportionally more Caucasians. Pulmonary function between these two populations cannot be compared due to poor quality spirometry in several subjects of the All Randomized Safety Population.

C2302

Subjects were well matched for age, sex, region, and race in the All Randomized Safety population. There was a slightly higher proportion of individuals in the TIP arm with baseline FEV1 % predicted ≥ 50%. The mean age in both arms was 25-26 years old (significantly older than study C2301), and it should be noted that fully 20% of patients in the TIP arm and 19% of patients in the TOBI arm were greater than 35 years old. Though the life expectancy of CF has increased, the large proportion of older patients raises concerns about whether subjects had a verified diagnosis of CF. Unfortunately no database of verified sweat chloride tests/gene mutations was provided though the sponsor states that only 3 subjects did not have a confirmed diagnosis of CF. Mean baseline pulmonary function in both arms was 53%. There was a slightly increased proportion of subjects reporting symptoms from the 'Respiratory, thoracic, and mediastinal' SOC at baseline in the TOBI arm (69% of TOBI subjects, 64% of TIP subjects). A slightly increased proportion of subjects in the TOBI arm had a baseline medical condition from the Infections and infestations SOC (57% TIP, 61% TOBI) while a slightly increased proportion of TIP subjects had baseline medical conditions from the Respiratory, thoracic, and mediastinal SOC (63% TIP 58% TOBI). There was a slightly increased percentage of patients in the TOBI arm who had never used antipseudomonal antibiotics prior to first study dose (4.9% of subjects TIP vs. 8.6% of subjects TOBI). The treatment arms were well matched in terms of previous antibiotics used, although a slight increased number of subjects in the TIP arm had used ceftazidime and levofloxacin (around 6-7% more subjects in both cases). The demographics of the Latin American region differed from that of Europe and North America but because this region made up only 3% of the population in both arms, this is not discussed in further detail. Please note the table below.

Table 6: C2302 Demographics- All Randomized Safety Population

	TIP N= 308	TOBI N=209
Age Group		
≥ 6 and <13	28 (9%)	18 (9%)
≥ 13 and < 20	66 (21%)	48 (23%)
≥ 20	214 (60%)	143 (68%)
Sex		
Male	171 (55%)	115 (55%)
Female	137 (45%)	94 (45%)
Race		
Caucasian	279 (91%)	189 (90%)
Hispanic	20 (7%)	17 (8%)
Baseline FEV1 % Predicted₁		
< 25%	5 (2%)	10 (5%)
≥25 to < 50%	117 (38%)	85 (41%)
≥50 to ≤ 80%	173 (56%)	93 (44%)
>80%	13 (4%)	21 (10%)

1- Baseline FEV₁ was defined as the last measurement prior to the first dose of study drug.

C2303

Given the inappropriate dispensation of placebo to two patients randomized to TIP, it is reasonable to evaluate the demographics of the as treated Safety population. The two arms were matched for age but there was a higher proportion of females in the TIP arm; the mean age was 13 years old for both arms. There was a slightly decreased

proportion of subjects in the placebo arm with baseline FEV1% predicted < 50% (TIP 30% of subjects vs. Placebo 25% of subjects). The mean baseline FEV1% predicted appeared similar between the two arms (TIP 59.1% vs. Placebo 59.3%). Mean *Pa* sputum colony density was high and equivalent between both arms. There appeared to be a slightly higher percentage of subjects in the placebo arm with *Pa* tobramycin MIC > 8 µg/ml at baseline (3% TIP vs. 9% placebo). 20% of TIP and 34% of placebo subjects had a history of antipseudomonal and macrolide usage (though certain 'antipseudomonal' medications listed, such as cefotaxime, may be considered quite poor for treatment of *Pa*). During the study, there was a higher use of short and long acting b-agonists and macrolides in the placebo arm. More subjects in the placebo arm had baseline complaints from the Respiratory, thoracic, and mediastinal disorders SOC (70% TIP vs. 84% placebo), but more subjects in the TIP arm had baseline complaints from the Infections and infestations SOC (43% TIP vs. 34% placebo). More subjects in the placebo arm had baseline medical histories derived from the Respiratory, thoracic, and mediastinal disorders (6% TIP vs. 13% placebo), but an equal proportion of subjects had medical histories derived from the Infections and infestations SOC. All comparisons should be taken with caution given the small sample size.

Table 7: C2303 Demographics- Safety Population

	TIP N= 30	Placebo N=32
Age Group		
<13	15 (50%)	15 (47%)
≥ 13	15 (50%)	17 (53%)
Sex		
Male	9 (30%)	13 (41%)
Female	21 (70%)	19 (59%)
Race		
Caucasian	29% (97%)	32% (100%)
Baseline FEV1 % Predicted₁		
< 25%	0 (0%)	0 (0%)
≥25 to < 50%	9 (30%)	8 (25%)
≥50 to ≤ 80%	20 (67%)	21 (66%)
>80%	0 (0%)	1 (3%)

missing	1 (3%)	2 (6%)
---------	--------	--------

C2301 and C2303 Comparison

The All Randomized Safety Population of C2301 and Safety Population of C2303 did not markedly differ in terms of baseline age and pulmonary function distributions (comparison made with SIA population of C2301 on this measure) between the TIP and placebo arms but there was comparatively higher distribution of females and Caucasians in the TIP arm in C2303 compared to C2301. It should be noted that antipseudomonal and macrolide exposure in the TIP and placebo arms of C2301 were much lower than prior antibiotic exposure in C2301, though these are somewhat different sets of data being compared (antipseudomonal vs. antibiotic usage). However, considerably higher percentages of subjects in both the TIP and placebo arms of C2303 had baseline medical symptom complaints from the ‘Respiratory, mediastinal, and thoracic’ and ‘Infections and infestations’ SOC compared to C2301. Conversely, considerably higher percentages of subjects in both the TIP and placebo arms of C2301 had baseline medical histories from the ‘Respiratory, mediastinal, and thoracic’ and ‘Infections and infestations’ SOC compared to C2303.

6.1.3 Subject Disposition

C2301

The subject disposition in this study is confusing. 102 subjects were randomized into the study, but 3 were screen failures and 4 subjects were discontinued prior to receiving study drug. 3 of the discontinuations were in the placebo arm and were the result of loss to follow up, inappropriate enrollment, and ‘unable to classify.’ 1 subject in the TIP arm discontinued due to administrative reasons.

The randomized safety population (had at least one dose of study drug) consisted of 95 patients, 46 in the TIP arm and 49 in the placebo arm. At least 15% of subjects in both arms discontinued. Please note the following sponsor table.

Table 8: Subject Disposition, All Randomized Safety Population, C2301

	TIP N=46 n (%)	Placebo N=49 n (%)	Total N=95 n (%)
Completed prior to final lock	39 (84.8)	40 (81.6)	79 (83.2)
Discontinuations	7 (15.2)	9 (18.4)	16 (16.8)
AE or death	0	1 (2.0)	1 (1.1)
Withdrawal of consent	0	5 (10.2)	5 (5.3)
Inappropriate enrollment	2 (4.3)	1 (2.0)	3 (3.2)
Protocol violation	1 (2.2)	1 (2.0)	2 (2.1)
Unable to classify	4 (8.7)	1 (2.0)	5 (5.3)

Unable to classify includes e.g. move out of area, intolerant of inhaler, non-compliance, and self discontinued from study drug.

Subjects categorized into ‘unable to classify’ or ‘withdrawal of consent’ may in some cases imply an adverse event, dissatisfaction with, or noncompliance with study drug.

As noted earlier, a separate population involves the SIA population. This population is comprised of 61 subjects who were found to have valid spirometric measurements at the time of the preplanned interim analysis (which took place after randomization of 79 subjects; 18 of these subjects were excluded from SIA due to poor quality spirometry).

Among the SIA population, there was a similar rate of study completion (both arms > 85%; TIP 86% vs. Placebo 91%). Please not the table below which highlights disposition from Randomized population to SIA Safety population

Table 9: Subject Disposition- 2301

	TIP	Placebo	Total	
Randomized	48	54	102	
Screen Failure	1	2	3	
Discontinuation	1	3	4	
All Randomized Safety	46	49	95	
Non Latin American Patients With Data Available after OIA/SIA	3	5	8	Included in ‘All Safety Population’ as defined by sponsor
Latin American Subjects With Data Available after OIA/SIA	4	4	8	Not Included in ‘All Safety Population’ as defined by

				sponsor
Original Interim Analysis	39	40	79	
Poor Quality Spirometry	10	8	18	
SIA Population	29	32	61	

Clearly the amount of missing data, hinders any true assessment of both primary efficacy information (where there is a loss of at least 20% from the Original Interim Analysis to Sensitivity Interim Analysis) and safety information (where at least 15% of subjects did not complete the trial). Though it's possible to perform various sensitivity analyses to account for missing data, these may over or underestimate outcomes and cannot fully account for a loss of randomization.

C2302

553 subjects were randomized into the study, 329 in TIP arm and 224 into the TOBI arm. The Randomized population did not differ markedly from the All Randomized Safety population in terms of screening age, FEV1% predicted, and regional distributions.

Table 10: Randomized But Not Included in Safety Populations C2302, Etiology

	TIP N=21	TOBI N=15	Total
Adverse Event or Death	1	3	4
Inappropriate Enrollment	4	1	5
Protocol Violation	6	1	7
Unable to Classify	6	3	9
Withdrawal of Consent	4	3	7
Loss to Follow Up	0	3	3
Administrative Reasons	0	1	1
Total	21	15	36

517 subjects were part of the All Randomized Safety Population (this was the same as the ITT population), 308 subjects in the TIP arm and 209 subjects in the TOBI arm.

There was a significant number of discontinuations in the study, particularly in the TIP arm (especially when compared to TOBI in the later cycles). Moreover, more discontinuations in the TIP arm were related to adverse events and withdrawal of consents. Discontinuations are discussed in further detail in section 7.3.3. Please note the following sponsor table:

Table 11: Patient Disposition, All Randomized Safety Population, C2302

	TIP N=308 n (%)	TOBI N=209 n (%)
Completed	225 (73.1)	171 (81.8)
Discontinued	83 (26.9)	38 (18.2)
Adverse Event or Death	43 (14.0)	17 (8.1)
Withdrawal of consent	24 (7.8)	9 (4.3)
Lost to follow-up	5 (1.6)	3 (1.4)
Inappropriate Enrollment	0 (0.0)	1 (0.5)
Administrative Reason	1 (0.3)	0 (0.0)
Protocol violation	6 (1.9)	5 (2.4)
Unable to classify	4 (1.3)	3 (1.4)
Discontinuations by cycle		
Cycle 1	44 (14.3)	28 (13.4)
Cycle 2	30 (9.7)	9 (4.3)
Cycle 3	9 (2.9)	1 (0.5)

C2303

A total of 62 subjects were randomized into the study, of which 59 completed the study. 3 subjects discontinued from the study, all 3 of which were randomized into the TIP arm. However one of these subjects mistakenly actually received placebo. As noted earlier, the safety population, accounting for the two mis-dispensation errors, consisted of 30 TIP patients and 32 placebo patients. Please note the sponsor table below.

Table 12: Subject Disposition Study C2303

	TIP N=32 n (%)	Placebo N=30 n (%)	Total N=62 n (%)
Completed	29 (90.6)	30 (100.0)	59 (95.2)
Discontinued	3 (9.4)	0 (0.0)	3 (4.8)
Adverse event(s)	2 (6.3)	0 (0.0)	2 (3.2)
Abnormal lab value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)
Patient's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	1 (3.1)	0 (0.0)	1 (1.6)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)

Owing to the mis-dispensation of placebo treatment to 2 patients (PID C2303-0231-00001 and PID C2303-0231-00003) randomized to the TIP group, the safety population contained 30 patients who were treated with TIP and 32 patients who were treated with placebo. Patient PID C2303-0231-00003 who was randomized to TIP and discontinued due to AEs was actually treated with placebo.

6.1.4 Analysis of Primary Endpoint(s)

For the two pivotal trials C2301 and C2303, the primary endpoint chosen was relative change from baseline in FEV₁ % predicted. This endpoint has long been recognized by the CF community as representing an adequate surrogate for clinical benefit, particularly in trials of inhaled antimicrobials. Indeed, decline in FEV₁ % predicted levels has been correlated with increased mortality. However, it should also be noted that recently there has been a shift toward more obvious clinical endpoints such as time to predefined pulmonary exacerbation/use of antipseudomonals (other than study drug). The reason for this shift has been increasing concern about whether the effects of inhaled antimicrobials on FEV₁ % predicted have been attenuated over time as well as concern over how to interpret the clinical benefit of relatively small changes in FEV₁% predicted. For this reason, in this review significant supportive weight is also given to secondary endpoints, such as time to use of antipseudomonal antibiotics, that theoretically should mimic and bolster the primary endpoint results.

C2301

The study population of interest for the primary efficacy variable in C2301 is the SIA safety population (see definition noted in section 6.1.1). Originally a preplanned, prespecified interim analysis had been planned after the randomization of the 80th subject had taken place. This analysis was to have been conducted and interpreted by an independent DMC and had 3 objectives: to focus on the standard deviation calculation for sample size reestimation, to analyze key safety findings, and to evaluate efficacy of TIP relative to placebo for potential early stopping of study. Based on an initial review of results, early stopping of study was recommended. However, it was noted during the review that some pulmonary function tests appeared to not meet quality standards, particularly those from Latin American sites. Thus, an external blinded committee of pulmonologists was convened to look at spirometry quality from all Latin American sites for all visits related to the primary endpoint. Criteria used to decide acceptability included evidence of proper calibration of the spirometer and FEV1 quality adherence to strict standards. Calibration criteria included use in proper temperature settings, checking for leaking tubes, etc. Once calibration and equipment quality had been verified then tracing quality was evaluated by the external panel and designated as “interpretable” or “unacceptable” based on multiple predetermined age-specific criteria. At the end of this process, it was found that only 8 of 26 Latin American subjects had acceptable spirometry data. These subjects were combined with the North American and European subjects to give a sample size of 61 “evaluable” subjects. These 61 subjects were analyzed under the original interim analysis plan but were termed the Sensitivity Interim Analysis (SIA) population.

There was a difference of 13.8% (p value 0.0010) between TIP and placebo in the mean relative change in FEV 1 % predicted from baseline to predose Day 28 for the SIA population; the difference in mean absolute change in FEV1 % predicted was 7.3% at day 28. It should be noted that these values reflect observed values only and do not include any subjects with missing data at visit 5. Baseline data was considered to be Visit 2 predose measurements unless Visit 2 data was missing in which case screening data was used. Looking at the primary endpoint through a least squares analysis taking into account baseline FEV1 % predicted, age, region, and treatment, the difference in relative change is similar and also statistically significant (13.29% in favor of TIP [p value .0016]). The statistical reviewer has noted that the distribution of relative changes in the TIP arm is positively skewed. The reviewer also notes that TIP appears to show the strongest benefit in a small subgroup of subjects (very positive outliers, minimally negative outliers). The review notes that:

“when comparing the most favorable relative changes, changes in the TIP vs. Placebo arm strongly favored TIP (e.g. TIP: 56.1%, 48.4% vs. Placebo 25.3%, 23.9%). Similarly, when comparing the least favorable relative changes, changes in the TIP vs. Placebo arm also strongly favored TIP (e.g. TIP: -10.1%, -6.1% vs. Placebo: -28.3%, -23.6%).”

However, nonparametric analyses should control for this to some degree and in such analyses a statistically significant difference in relative change was still noted; if a

similarly adjusted analysis based on non parametric tests is used, the difference in the relative change is 12.4% in favor of TIP (p=0.0061).

Using the sponsor’s initial unadjusted, parametric analysis, TIP appears to maintain a relative increase from baseline during the successive on cycles (end of on Cycle 2– relative change of 10.6% in favor of TIP, end of on cycle 3- relative change of 11.4% in favor of TIP) and to a lesser degree during the off cycle (end of off Cycle 1 relative change of 7.6%, end of off Cycle 2 relative change of 8.4%, end of off Cycle 3 relative change of 10.5% all in favor of TIP. However, these calculations take into account observed data only, and considering that there was missing data for 3-24% of subjects at various time points in the TIP arm and 6-19% in the placebo arm, ignoring missing data can alter results markedly. The statistical reviewer attempted to account for missing data using conservative methods and in this sensitivity analysis, the relative change at the end of the on cycle of Cycles 2 and 3 never went above 10%.

When placebo was switched to TIP in the second and third cycles, this arm showed a relative increase of 11.7% and 12.9% from baseline to the end of the 2nd and 3rd on cycles, respectively, and 13.5% and 6.7% at the end of the 2nd and 3rd off cycles. However, these values are limited by missing data as discussed above. Under the statistical reviewer’s sensitivity analysis conservatively accounting for missing data, the relative change is roughly 10% at the end of the on cycle of Cycles 2 and 3. Please note the table below showing the unadjusted sponsor analysis:

Table 13 Relative Change from Baseline in FEV1% Predicted, by Cycle and Treatment Group, C2301

Cycle	TIP	Placebo	Difference
Cycle 1 End of On Cycle	13.2%	-0.6%	13.8%
End of Off cycle	7.6%	0.1%	7.5%
Cycle 2 End of On cycle	10.6%	11.7%	-1.1%
End of Off cycle	8.4%	13.5%	-5.1%
Cycle 3 End of On Cycle	11.4%	12.9%	-1.5%
End of Off Cycle	10.5%	6.7%	3.8%

-unadjusted sponsor analysis

In terms of subgroup analyses, no differences in outcome were noted by baseline FEV 1 % predicted category or sex at Visit 5. However, there was a trend toward better improvement in the younger age group at Visit 5. However, if the statistical reviewer’s conservative assumptions are used, no difference by age, gender, or pulmonary function subgroup is noted (data not shown). Please note the following table:

Table 14: Relative change in FEV1% Predicted from baseline to Day 28, by demographic subgroup; SIA population, C2301

Subgroup	TIP	Placebo	Difference
----------	-----	---------	------------

Sex	9.8%	-2.4%	12.2%
Male			
Female	15.5%	1.7%	13.8%
Age	14.5%	-2.0%	16.5%
≥6 - ≤13			
≥13 - ≤22	12.6%	0.5%	12.1%
Baseline FEV1 % Predicted	11.6%	-1.6%	13.2%
≥25% - <50%			
≥50% - ≤80%	14.2%	-0.2%	14.4%
Region			
North America	1.5%	-2.6%	4.1%
Latin America	26.6%	3.3%	23.3%
Europe	17.2%	-0.3%	17.5%

- unadjusted sponsor analysis

There was concern whether subjects with very low baseline FEV1% predicted (\leq 40% predicted) would have worse outcomes on the primary endpoint, particularly in younger patients with already small lung volumes. However, in all three studies, such an outcome was noted though admittedly there were few young patients (6-13 year old patients) with low baseline pulmonary function enrolled into the trial. For example in C2301, the mean relative change in FEV1% predicted for subjects whose baseline FEV1% predicted was \leq 40% was 12% (observed data only). For such subjects 6-13 years old, the mean relative change was 19%. Similarly, in C2302 the findings were 11.7% and 62.3% (3 young subjects only), respectively. Thus, no restriction on use should be proposed strictly due to concerns of limited effectiveness in subjects with very poor lung function.

In both the sponsor's and statistical reviewer's analyses, there are differences in outcome by region. Of particular concern is the discrepancy between Europe and North America (Latin America was a very small sample size so results there must be viewed with caution). The sponsor notes that there was not a statistically significant treatment interaction by region and also notes that North America had the largest increase in FEV1% predicted from screening to Visit 2 in the TIP arm. If FEV1% predicted from the screening visit is used as baseline, there is less discrepancy between the regions (see table below- page 63 CSR2301); a similar trend is seen for the SIA population (relative change in Europe 6.8%, LA 4.5%, NA 6.3%).

Table 15: Mean difference of relative change in FEV1 percent predicted from screening to Day 28 of Cycle 1 (All ITT population), C2301

Region		N	n	Relative change
North America	TIP - Placebo	23	19	10.9
EU	TIP - Placebo	38	36	14.7
Latin America	TIP - Placebo	8	4	6.2

N is total # of subjects.

n is # of subjects with measurements at both visits. Note there are only 4 subjects in Latin America with values at both visits, the interpretation of Latin America results need to be cautious.

Looking at the demographics of the 3 regions for the SIA population does not provide clear reasons for this discrepancy. Males, older subjects, and subjects with lower baseline pulmonary function were proportionally overrepresented in the placebo arm of North America relative to Europe so it is unclear what is driving the regional differences. It is unclear whether treatment of CF differs enough by region that more dramatic treatment effects are seen in Europe.

The sponsor also presented data on the primary endpoint for the ITT population (which as stated earlier included several more subjects from the non- latin American sites evaluated after the interim analysis). These analyses were similar to, though slightly more improved than, those of the SIA population for both the TIP and placebo arms. However, the data suffers from the same statistical issues as those outlined above, namely the use of parametric analyses and significant amounts of missing data.

Compliance

Assessment of compliance with the TIP and placebo dosing schedule was based on completed subject dosing logs, number of used and unused capsules returned per patient, and percentage of completion of scheduled study visits.

For Cycle 1, compliance for the TIP and placebo arms for the All Randomized Safety population was 91% and 88.9%, respectively. However, since placebo was also an inhaled powder, this was a limited gauge of compliance in terms of comparisons to currently approved therapies. One particular difficulty in trying to connect compliance data with efficacy on the primary endpoint is that a disproportionate amount of patients who had low compliance (arbitrarily defined as < 80% compliance) had spirometry that was considered to be “unacceptable” for evaluation. Please note the table below.

Table 16: Levels of Compliance as a Function Spirometric Quality, C2301

Cycle 1	Low Compliance	Low Compliance	High Compliance (>	High compliance and
---------	----------------	----------------	--------------------	---------------------

	(<80%) (# of subjects)	and unacceptable spirometry (# of subjects)	80%) (# of subjects)	unacceptable spirometry
TIP	6/45=13%	4/6= 67%	39/45=87%	12/39= 31%
Placebo	8/49= 16%	7/8= 88%	41/49=84%	10/41= 24%

-Randomized Safety population; one subject with missing compliance data in TIP arm

-denominators represent subjects without missing data

Of the two subjects in the TIP arm for which there was low compliance and an acceptable spirometry at day 28, one subject was noted to have a relative change in FEV₁ % predicted of -6.06% at day 28 and the other subject had missing data at the day 28 visit. For the one subject in the placebo arm for which there was low compliance and an acceptable spirometry at day 28, the subject had missing data at day 28. Of the 27 subjects in the TIP arm with high compliance and acceptable spirometric quality, only 26% had a negative relative change in FEV₁ % predicted at Day 28 (for one subject there was missing spirometry data at day 28). For Cycles 2 and 3, the placebo arm switched to TIP. Please note the table below evaluating compliance in these 2 cycles.

Table 17: Levels of Compliance Cycles 2 and Cycles 3, C2301

	Cycle 2 Low Compliance (<80%)	Cycle 2 High Compliance (>80%)	Cycle 3 Low Compliance (<80%)	Cycle 3 High Compliance (>80%)
TIP/TIP/TIP	2/41= 5%	39/41= 95%	1/39=3 %	38/39=97%
Placebo/TIP/TIP	2/40= 5%	38/40= 95%	1/40=2%	39/40=98%

-Cycle 2 missing data for one subject in placebo arm

-Denominators represent subjects without missing data who were present at start of each cycle

The two arms mirror each other for cycles 2 and 3

C2302

There were no primary efficacy endpoints in this study (safety was the primary objective); all efficacy endpoints are secondary and are described further in section 6.1.5

Compliance

As noted earlier, there were more discontinuations overall in the TIP arm, including more discontinuations due to adverse events, compared to TOBI.

Compliance was measured through methods similar to those used in study C2301. Cycle compliance was defined as the number of doses taken during the on

treatment period/56 possible doses. Of note, the dosing period used for these calculations was 30 days because patients received an extra 2 day supply of medication in case a capsule was damaged, study visits were delayed, etc. A TIP dose was defined as 4 TIP capsules so each capsule was .25 of a full dose; a TOBI dose was one ampoule of solution. Thus compliance could range from 0% to 107%. Overall compliance was the mean compliance of all 3 cycles (or however many cycles data was available for the patient).

Overall compliance was 90% in the TIP arm and 94% in the TOBI arm. The following table evaluates low compliance (arbitrarily set as < 80% compliance).

Table 18: Comparison of Low Compliance (<80% Compliance) By Cycle and Treatment Arm, C2302

	1st Cycle	2nd Cycle	3rd Cycle
TIP	36/308 (12)	35/264 (13)	38/234 (16)
TOBI	14/209 (7)	17/181 (9)	14/172 (8)

- denominator based on the numbers of subjects available at the beginning of that cycle

The following table looks at low compliance by baseline demographics

Table 19: Low Compliance (<80% Compliance), by baseline demographic characteristics, C2302

	TIP < 80% compliance	TOBI < 80% compliance	Age Category TIP	TOBI	Sex TIP	TOBI	Screening FEV1 TIP	TOBI
Cycle 1	36/305=11.8%	14/206=6.8%	≥13 to < 20= 6 (6/66)= 9.1% ≥20= 30 (30/211)= 14.2%	≥13 to < 20= 2 (2/45)= 4.4% ≥20= 12 (12/142)= 8.4%	F= 14 (14/137)= 10.2% M=22 (22/168)= 13.1%	F= 5 (5/91)=5.5% M=9 (9/115)= 7.8%	≥25 to <50= 18 (18/126)= 14.3% ≥50 to ≤75= 18 (18/179)= 10.1%	≥25 to <50= 4 (4/88)= 4.5% ≥50 to ≤75=10 (10/118)= 8.5%
Cycle 2	35/263=13.3%	17/175=9.7%	≥ 6 to 13= 3 (3/28)= 10.7% ≥13 to < 20= 9 (9/59)= 15.3% ≥20= 23 (23/176)= 13.1%	≥ 6 to 13= 1 (1/17)= 5.9% ≥13 to < 20= 3 (3/38)= 7.9% ≥20= 13 (13/120)= 10.8%	F= 17 (17/116)= 14.6% M=18 (18/147)= 12.2%	F= 4 (4/74)= 5.4% M=13 (13/101)= 12.9%	≥25 to <50= 13 (13/102)= 12.7% ≥50 to ≤75= 22 (22/161)= 13.7%	≥25 to <50= 8 (8/71)= 11.3% ≥50 to ≤75= 9 (9/104)= 8.7%
Cycle 3	38/233=16.3%	14/169=8.3%	≥ 6 to 13= 4 (4/28)= 14.3% ≥13 to < 20= 11 (11/55)= 20% ≥20= 23 (23/150)= 15.3%	≥ 6 to 13= 1 (1/16)= 6.3% ≥20= 13 (13/115)= 11.3%	F= 18 (18/105)= 17.1% M=20 (20/128)= 15.6%	F= 5 (5/71)= 7.0% M=9 (9/98)= 9.2%	≥25 to <50= 14 (14/83)= 16.9% ≥50 to ≤75= 24 (24/150)= 16%	≥25 to <50= 6 (6/70)= 8.6% ≥50 to ≤75= 8 (8/99)= 8.0%

% based on number patients available in each cycle without missing data

No clear conclusions can be drawn about TIP subgroups with higher rates of low compliance from the above table. Please note that the amount of missing data limits assessment of compliance for later cycles.

C2303

The primary endpoint for this study was the same as in study C2301- relative change in FEV1% predicted from baseline to Day 29 (end of on cycle). As discussed earlier, two subjects were randomized to the TIP group but actually received placebo, one of whom discontinued from the study due to adverse events. Three subjects had no baseline FEV1% predicted measurements. Seven subjects did not have acceptable spirometry measurements on Day 29. Two of these seven patients had missing data because they discontinued from the study early, while in 5 of these patients the missing data was due to poor quality spirometry at Day 29. Taken together, there is a significant amount of missing or inaccurate data, and it is unclear what the best analysis method is. An analysis that only accounts for observed data may overestimate effect by ignoring subjects that discontinued study drug due to adverse effects/poor response. Imputing an effect of zero for missing data may underestimate effect of study drug, especially in subjects who had missing data for purely technical reasons (such as poor quality spirometry data). Looking at the randomized population does not account for misdistribution of study drug, which could have an effect on endpoints due to the small sample size of the study. Thus, it is useful to evaluate this endpoint using several different analyses, though primary importance should be given to prespecified analyses.

According to the latest protocol amendment for this study, the primary analysis population was the ITT population (patients must have received one dose of study drug and were analyzed according to their randomization). The primary analysis was to be based on an ANOVA analysis which factored in categorical variables for age (< 13 and ≥13 years old) and screening FEV1% predicted (<50% and ≥ 50% FEV1% predicted). If no post-baseline FEV1 values prior to the day 29 visit were available, 0 was imputed for the relative change in FEV 1 % predicted.

Using these prespecified criteria, there was a trend toward improvement on the primary endpoint in the TIP arm relative to placebo, but this was not statistically significant. See the sponsor table below:

Table 20: Relative Change in FEV 1 % predicted from baseline to Day 29, ITT, C2303

Treatment	n	--- Treatment ---		Comparison	----- Treatment difference -----			
		LS Mean [#]	SE		LS Mean [#]	SE	95% CI	p-value
FEV1 % predicted, ITT population (adjusted analysis: ANOVA)¹								
TIP	31	8.2	2.93	TIP-Placebo	5.9	4.03	(-2.2, 14.0)	0.148
Placebo	28	2.3	3.13					

In the adjusted analysis, analysis model: response (% change) = treatment + Screening FEV₁ % predicted (<50 and >=50) + age (<13 and >=13) + error.
 In the unadjusted analysis, analysis model: response (% change) = treatment + error.
 In ITT population, patients with missing or unacceptable Day 29 spirometry measurements have relative change from baseline of FEV₁ % predicted imputed using last available post-baseline value or zero.

When looking at the change in absolute FEV 1 % predicted for the same prespecified criteria, there was a marginally statistically significant trend in favor of the TIP arm, though it's clinical importance may be underwhelming. Please note the sponsor table below:

Table 21: Absolute Change in FEV1% Predicted from Baseline to day 29, ITT , C2303

Treatment	n	--- Treatment ---		Comparison	----- Treatment difference -----			
		LS Mean [#]	SE		LS Mean	SE	95% CI	p-value
FEV1 % predicted, ITT population (adjusted analysis: ANOVA)¹								
TIP	31	4.9	1.59	TIP-Placebo	4.4	2.18	(0.0, 8.8)	0.050*
Placebo	28	0.5	1.70					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
 In the adjusted analysis, analysis model: response = treatment + Screening FEV₁ % predicted (<50 and >=50) + age (<13 and >=13) + error.
 * denotes a statistically significant difference between TIP and Placebo.
 Significance for the FEV₁ % predicted is reached for p-values <= 0.05.
¹ Pre-planned analysis

It is useful to look at the primary endpoint according to the treatment actually received and through the lens of different analyses that likely overstate and understate the effect of the study drug. Please note the table below:

Table 22: Safety population- Relative Change in FEV1% Predicted from Baseline to Day 29, C2303

Treatment	N	Mean Change	Mean Difference	P value	
ITT Analysis					
TIP	29	8.8	6.7	.098	
Placebo	30	2.1			
Observed Analysis					
TIP	24	11.1	8.8	.056	
Placebo	28	2.3			
mITT					

Analysis					
TIP	25	10.6	8.2	.064	
Placebo	29	2.4			

- all analyses involve actual treatment received
- means displayed are LS (adjusted means)
- ITT population handled Day 29 missing data for primary endpoint as follows: last post baseline measurement imputed or, if none available, given a value of 0 (no change from baseline)
- mITT population handled Day 29 missing data for primary endpoint as follows: last post baseline measurement imputed or, if none available, given a value of 0 (no change from baseline). Subjects who had missing data on day 29 due to poor quality spirometry were excluded from analysis
- Observed population handled Day 29 missing data for primary endpoint as follows: they were excluded from the analysis.

It is notable that the difference between TIP and placebo in relative change in FEV1% predicted in this study (comparing the adjusted observed analysis in C2303 with a similar analysis in C2301) was less than that achieved in 2301 (comparing the adjusted observed analysis in C2303 with a similar analysis in C2301). In C2301 the difference in relative change was slightly greater that 13% whereas in C2303 it is close to 9%. It is unclear why there is this variability in response. Though enrollment criteria was similar, as noted earlier, the TIP and placebo subjects in C2303 may have been healthier overall than those in C2301

In the above analysis, there is a suggestion of a positive effect of TIP, however, this does not reach statistical significance. The sponsor asserts that one subject in the TIP arm may have accounted for the inability to demonstrate a statistically significant effect of TIP over placebo. This subject had a relative decrease of 37% from baseline to Day 29. The sponsor performed a detailed analysis of the subject’s inhaler device, used capsules, sputum and serum PK data and medical data. This subject was a 7 year old boy with marked growth retardation who appeared to have difficulty using the inhaler and/or had a faulty device. This is supported by analysis of the inhaler which appeared to have residual powder, low serum and sputum tobramycin concentrations at Day 29 and inappropriately pierced capsules. The sponsor also suggests that the subject’s baseline spirometry was an outlier and subsequent spirometry measurements were more likely to represent the norm. The sponsor performed sensitivity analyses on the primary endpoint excluding this subject which appeared to show statistical significance in some analyses, though not in the prespecified analysis preferred by the Agency. Please note the following sponsor table; pg. 96.

Table 23: Relative Change in FEV1% Predicted from Baseline to Day 29, with Outlier Excluded, C2303

Treatment	n	— Treatment —		Comparison	----- Treatment difference -----			p-value
		LS Mean ^a	SE		LS Mean	SE	95% CI	
FEV1 % predicted, ITT population excluding outlier (adjusted analysis: ANOVA)								
TIP	30	10.4	2.81	TIP-Placebo	7.3	3.77	(-0.3, 14.8)	0.058
Placebo	28	3.1	2.92					
FEV1 % predicted, observed cases population excluding outlier (adjusted analysis: ANOVA)								
TIP	24	13.1	3.25	TIP-Placebo	9.8	4.15	(1.4, 18.1)	0.023*
Placebo	27	3.4	3.08					
FEV1 % predicted, modified ITT population excluding outlier (adjusted analysis: ANOVA)								
TIP	28	12.4	3.14	TIP-Placebo	8.9	4.03	(0.8, 17.0)	0.032*
Placebo	27	3.5	3.05					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
 Model: response (% change) = treatment + Screening FEV₁ % predicted (<50 and ≥50) + age (<13 and ≥13) + error.
 * denotes a statistically significant difference between TIP and Placebo.
 Significance for the FEV₁ % predicted is reached for p-values ≤ 0.05.
 Source: PT-Table 14.2-1.18, PT-Table 14.2-1.20, PT-Table 14.2-1.38

While there appears to be some evidence to support the sponsor’s assertions concerning this particular subject, it is questionable to look at one subject in isolation. Other subjects did not appear to have received this level of scrutiny. For example, would placebo subjects with decreases in FEV1% predicted over the same time period be evaluated thoroughly to see whether their baseline spirometry represented an “outlier” measurement? Moreover, the sponsor asserts that this subject should not have been randomized into the study yet appears to have met inclusion/exclusion criteria. Lastly, the device use errors made by this patient points to a potentially larger issue of whether the device can be used as intended, particularly within the younger population (please see the Human Factors analysis for further details).

The statistical reviewer attempted to evaluate the data taking into account positive skewness of results (similar to C2301), yet also failed to show statistical significance on the primary endpoint. Please note the statistical reviewer table below:

Table 24: Relative Change from Baseline in FEV1 % Predicted at Day 29 Using Imputed Data (ITT/Primary Analysis Population), C2303

	TIP N=32	Placebo N=30	Mean Treatment Difference (SE)	95% CI for Mean Difference	P-value
Adjusted Mean	8.19	2.27	5.91	(-2.54, 14.37)	p=.167 p=.233 ¹
Unadjusted Mean Median	8.27 3.17	2.45 2.71	5.82 (4.19)	(-2.56, 14.20)	p=.170 p=.244 ²

¹ Reviewer’s primary analysis- non-parametric test based on ranks adjusted for screening FEV1 % predicted (<50% and ≥50%) and age (<13 years and ≥13 years).

² Sensitivity analysis- Unadjusted non-parametric test (Wilcoxon Rank Sum test)

It should be noted that the range of relative changes in FEV1% predicted from baseline to Day 28 were positively skewed in the TIP arm; there appeared to be heavy negative tail in the placebo arm. This suggests benefit of the drug however given the significant amounts of missing data this must be viewed with caution.

Most subgroup analyses were hampered with small size of subgroups. There appeared to be significant benefit for subjects > 13 years old or baseline FEV1% predicted $\geq 50\%$. However, due to the small sample size in the study, outliers may have undue influence, particularly the TIP subject who was 7 years old with baseline FEV1% predicted 33% who had a relative change of -37% from baseline to Day 28. Please note the following table for the prespecified ITT population.

Table 25: Relative Change in FEV1% Predicted from Baseline to Day 29, Subgroup Analysis, C2303

Subgroup	Subgroup Division	Adjusted Mean Change*		
		TIP	Placebo	Treatment Diff. (95% CI), p-value
Disease Severity	FEV1 < 50% pred. (n=16)	4.6 (n=9)	8.8 (n=7)	-4.2 (-29.6, 21.1), p=0.722
	FEV1 $\geq 50\%$ pred. (n=43)	12.5 (n=22)	0.3 (n=21)	12.1 (3.2, 21.0), p=0.009
Age Group	< 13 (n=28)	3.8 (n=15)	2.7 (n=13)	1.2 (-11.9, 14.3), p=0.855
	≥ 13 (n=31)	12.4 (n=16)	2.2 (n=15)	10.2 (-0.4, 20.8), p=0.059
Gender	Male (n=21)	7.4 (n=9)	3.4 (n=12)	4.0 (-16.1, 24.1), p=0.677
	Female (n=38)	8.7 (n=22)	2.4 (n=16)	6.3 (-2.4, 15.0), p=0.148

-In the adjusted case the LS mean

-Calculated from an ANOVA model (Response = treatment + Age (< 13 and ≥ 13) + screening FEV1 % predicted (< 50 and ≥ 50)).

- Two sided two sample t-test.

-Baseline is defined as the latest measurement prior to the first dosing of study medication.

- If day 29 measurement is missing, it will be imputed by the last post-baseline measurement if available. If there is no post-baseline measurement, it will be imputed by the baseline value (relative change from baseline is then 0).

- If screening FEV1 % predicted is missing, it will be imputed by the baseline value.

*- [Disease severity not represented by adjusted means](#)

Compliance

Mean compliance was virtually the same between the two groups. Compliance was measured as $100 \times [\text{number of doses taken over on cycle}/228 \text{ capsules}]$. 228 capsules represented 28 days of twice a day dosing plus a morning dose on Day 29.

Several subjects returned late for clinic visits, took reserve medication, and thus had compliance >100%. If compliance was analyzed according to treatment taken and with a value of 100% given for any subject with $\geq 100\%$ compliance, the TIP arm had a mean compliance of 95.5% and the placebo arm had a mean compliance of 97.2%.

6.1.5 Analysis of Secondary Endpoints(s)

C2301

Though initially several secondary endpoints were prespecified for analysis, due to the small sample size available after the DMC recommended early stopping of the study, statistical analyses of these endpoints were not performed; only descriptive secondary and exploratory analyses are available. These include analyses of changes in *Pseudomonas aeruginosa* colony counts in sputum over the course of the study in both treatment arms, changes in *Pa* sputum tobramycin MICs over the course of the study, time to and frequency of antipseudomonal use (other than study drug), and frequency of hospitalization.

Change in sputum *Pa* colony forming units (cfu) from baseline

Pa colony counts were evaluated by biotype, including dry and mucoid biotypes. For the All Randomized Safety population, there was a decrease in *Pa* sputum log₁₀ cfu's from baseline to all end of on cycle time points in the TIP arm with some rebound in the counts at the end of the off cycles. Please note the following table. The placebo arm paralleled these finding once subjects had switched over to TIP. However, any interpretation must be made with caution giving the significant amounts of missing data

Table 26: Change in *Pa* Sputum Colony Counts (log₁₀ CFU per gm sputum) from Baseline, All Randomized Safety Population, C2301

	TIP N= 46	Placebo N= 49
Mucoid		
Cycle 1 Day 28	N=22 - 2.61	N=33 -0.43
Cycle 2 Day 1	N=28 -0.48	N=31 -0.30
Day 28	N=23 -2.13	N=21 -2.41
Cycle 3 Day 1	N=26 -0.30	N=26 -0.65
Day 28	N=22	N=22

	-1.72	-2.56
Dry		
Cycle 1 Day 28	N=13 -1.91	N=21 -0.15
Cycle 2 Day 1	N=15 -.40	N=22 -.17
Day 28	N=9 -1.72	N=8 -1.76
Cycle 3 Day 1	N=15 -1.14	N=14 -1.15
Day 28	N=11 -2.58	N==6 -2.57

N= subjects with data at baseline and at timepoint

Worse increases in *Pa* tobramycin MIC occurred in the TIP arm from baseline to Day 28 relative to placebo; please see the formal microbiology review by Dr. Peter Coderre for further information.

Relative Change in FVC % and FEF 25-75% predicted

When looking at the ITT population, the TIP arm had an improvement in FVC % predicted at the end of the on Cycle 1 while the placebo arm did not (TIP mean relative change 8.2%, placebo mean relative change -2.8%). Thereafter (after placebo switch to TIP) both arms had improvement at the end of on Cycles 2 and 3. For FEF 25-75% predicted, the TIP arm had an improvement at the end of on Cycle 1 while placebo did not (TIP mean relative change 34.8%, placebo mean relative change -4.2%). Thereafter both arms had improvement at the ends of on Cycles 2 and 3, however improvement was less robust in the placebo arm.

Antipseudomonal Usage

For cycle 1, the sponsor reported a placebo and TIP arm antipseudomonal usage rate of 33% and 20%, respectively, for the All Randomized Safety population. This could not be verified upon reviewer analysis; in contrast, only a slight difference in usage was noted between study arms (see Table 2 below). This appeared to be due to the fact that some subjects using azithromycin and cefotaxime (drugs with questionable antipseudomonal activity) were classified as antipseudomonals by the sponsor but were not counted in analyses performed by this reviewer.

Table 27: C2301 Antipseudomonal Usage

All Randomized Safety Population	Antipseudomonal Usage	
	Cycle 1	By Cycle 3
TIP/TIP/TIP	6/46= 13%	13/46= 28%
Placebo/TIP/TIP	9/49= 18%	18/49= 37%

-all numbers reflect individual subjects

-denominators reflect starting All Randomized Safety populations in each arm; some subjects discontinued so interpretation may be limited

Hospitalization

When looking at hospitalizations, the results obtained from Agency review slightly differed from that of the sponsor, primarily due to discrepancies in how events were classified. For example, subjects with hospitalizations due to 'cystic fibrosis exacerbation' were at times not classified as respiratory related illnesses. For cycle 1, 6.1% (3 subjects) and 15.2% (7 subjects) of subjects in the TIP and placebo arm, respectively, were hospitalized. When looking at respiratory-related hospitalizations for the same cycle, the rate is 4.3% (2 subjects) and 12.2% (6 subjects) respectively. The average length of stay for the Cycle 1 respiratory-related hospitalizations was 21 days and 16 days for the TIP and placebo arms, respectively, though caution must be used in interpreting these numbers given the small number of events. The TIP arm had a total of 6 subjects who were hospitalized by the end of Cycle 3 (13%), 4 of which were related to a respiratory illness.

Table 28: C2301 Respiratory Related Hospitalization

All Randomized Safety Population	Respiratory Related Hospitalization	
	Cycle 1	By Cycle 3
TIP/TIP/TIP	2/46= 4.3%	4/46= 8.7%
Placebo/TIP/TIP	6/49= 12.2%	11/49= 22%

-all numbers reflect individual subjects

-denominators reflect starting All Randomized Safety populations in each arm; some subjects discontinued so interpretation may be limited

For both of the above clinical endpoints, note that values may be somewhat underestimated due to the amount of discontinuations in both arms (15%)

discontinuation in TIP arm and 18 % discontinuation in placebo arm over course of entire study).

C2302

As discussed earlier, there were no primary efficacy endpoints in this study as it was designed for safety. Important secondary endpoints included time to and proportion of antipseudomonal usage in both arms, time to and proportion of respiratory related hospitalization, relative change in FEV1% predicted from baseline, and changes in *P. aeruginosa* log 10 cfu/gm sputum and susceptibility from baseline.

Relative Change in FEV1% Predicted

There was virtually no difference between the TIP and TOBI arm in the amount of relative change in FEV1% predicted from baseline to the end of on Cycle 3. However, this analysis took into account only observed data even though there was a significant amount of missing data in both arms (26% of subjects with missing data in TIP arm vs. 18% of subjects with missing data in the TOBI arm). The statistical reviewer used the method of least favorable mean to account for missing data. In that calculation, results in both arms were essentially the same. Please note the table below:

Table 29: Mean Relative Change in FEV 1 % Predicted from Baseline to End of On Cycle 3, All Randomized Safety Population, C2302

Method	TIP N _o =227 N _m =308	TOBI N _o =171 N _m =209	Difference
Observed Data (Unadjusted)	3.1%	2.3%	0.8%
Observed Data (Least squares method)	5.8%	4.7%	1.1%
Least Favorable Mean	2.9%	2.3%	0.6%

N_o= number of subjects with values at baseline and Day 28 (end of on cycle) of cycle 3

N_m= All Randomized safety population with missing values imputed using least favorable means method

Least squares= calculated from ANCOVA with treatment, baseline FEV1 % predicted, age, chronic macrolide use, and region in model

The absolute change in FEV1% predicted from baseline to end of on cycle 3 was minimal in both arms: 0.92% for TIP and 0.47% for TOBI (observed data only). The

clinical significance of this is unclear though an argument could be made that a lack of decrease in this measure still provides benefit for patients.

The following table looks at this endpoint by subgroups (observed data only).

Table 30: Mean Relative Change in FEV 1 % Predicted from Baseline to End of On Cycle 3, All Randomized Safety Population, Subgroup Analysis, C2302

Subgroup	TIP	TOBI	Difference (TIP-TOBI)
Overall	3.1%	2.3%	0.8%
Sex			
Male	5.2%	3.6%	1.6%
Female	0.6%	0.6%	0%
Age			
≥6 to <13 years old	10.4%	10.4%	0%
≥13 to <20 years old	6.8%	3.4%	3.4%
≥20 years old	0.3%	0.9%	-0.6%
Screening FEV1% Predicted			
≥25 to <50 % Predicted	6.7%	3.9%	2.8%
≥50 to ≤75 % Predicted	3.9%	1.2%	2.7%
Region			
North America	0.6%	-0.4%	1.0%
Europe/ROW	5.5%	6.3%	-0.8%
Latin America	24.9%	7.8%	17.1%

-only subjects with observed values are used in calculations

Compared to the overall population, more improvement was seen in the youngest age group, Latin America, the TIP arm of the adolescent age group and lowest screening FEV1% predicted category, and the TOBI arm of Europe. Decreased improvement was seen in females, the oldest age group, and in North America. The middle age group and Latin America showed a slight advantage for TIP compared to TOBI.

There was little difference in relative change between the two arms at the end of on Cycles 2 and 3. However, it is also notable that the relative change did not differ markedly between off and on cycle and was, in general, very modest. Please note the following table for difference in median relative change from baseline:

**Table 31: Median Relative Change in FEV 1 % Predicted from Baseline
 All Randomized Safety Population (Observed Values Only), C2302**

Timepoint	TIP	TOBI	Difference (TIP-TOBI)
Cycle 1 Day 28	1.1%	2.7%	-1.6%
Cycle 2 Day 1	-0.9%	0.5%	-1.4%
Cycle 2 Day 28	0.0%	2.6%	-2.6%
Cycle 3 Day 1	0.0%	0.5%	-0.5%
Cycle 3 Day 28	0.5%	1.8%	-1.3%

These values seem to show little to no increase in FEV1% predicted with either drug in inhaled antipseudomonal- experienced subjects, particularly in the case of TIP. These calculations, however, are plagued by significant levels of missing data. When looking at absolute changes in FEV1% predicted from baseline, the changes in this variable are also miniscule for both arms.

FVC % Predicted and FEF 25-75% Predicted

Only at the end of on cycle 1, was there a positive median relative change from baseline in FVC % predicted – this was a median relative change of 0.3% in the TOBI arm (a modest decrease of 1.4% was seen in the TIP arm). At all other end of on cycle timepoints the median relative change was modestly negative for both arms.

The median relative change from baseline in FEF 25-75% predicted was 4.9%, 6.0%, and 6.1% for end of on Cycles 1,2,and 3, respectively, in the TIP arm and 4.0%, 4.8%, and 2.8% for the TOBI arm.

Treatment Satisfaction – C2302

The sponsor administered a Treatment Satisfaction Questionnaire for Medication (TSQM) to evaluate and compare patient opinions of TIP vs. TOBI in four broad categories - effectiveness, side effects, convenience, and global satisfaction. This survey was comprised of 18 questions that were completed by subjects at the end of each on cycle period. Each question had a range of possible answers which varied slightly in detail and number from question to question (answers might range from not at all certain to extremely certain, extremely difficult to extremely easy, a great deal to not at all, etc.), and each subject was asked to reflect on each question as related to use of the study drug/device in the previous four weeks. A scoring system was used to provide a score between 0-100 for each of the four broad categories, higher numbers indicating higher satisfaction in that domain. The questionnaire was not validated in its current iteration.

The score for a particular category did not markedly differ from on cycle to on cycle within a particular arm. However, the results of this survey showed a trend toward improved satisfaction in the TIP arm vs. TOBI, particularly in the areas of convenience,

effectiveness, and global satisfaction. There was no real difference in side effects between the two arms. It is unclear how to interpret the results of this survey. For example, the sponsor reports that in the area of global satisfaction there is a five point difference between TIP and TOBI in overall score for all on cycles (76.2 and 71.0, respectively); this is statistically significant with a p value of .0018. Clinically, the meaning of this difference is unclear. Moreover, it is difficult to draw a relationship between treatment satisfaction and clinical results. An example of this is illustrated below with question 13 of the questionnaire:

Question 13: How certain are you that the good things about your medication outweigh the bad things?

1. Not at all certain 2. A little certain 3. Somewhat certain 4. Very Certain 5. Extremely certain

In the TIP arm, 229 subjects (74%) reported a score of 4 or above on the above question at any point in the study. 69 (30%) of these 229 subjects had an SAE. 69 subjects (22%) ever reported a score of 2 or below. 19 (28%) of these 69 subjects had an SAE.

In the TOBI arm, 166 subjects (79%) reported a score of 4 or above on this question at any point in the study. 48 (29%) of these 166 subjects had an SAE. In the TOBI arm 27 subjects (13%) ever reported a score of 2 or below. 6 (22%) of these 27 subjects had an SAE.

Thus, though the survey may indeed point to increased satisfaction with TIP compared to TOBI, this cannot be assumed or interpreted with any clarity.

Pa log₁₀ cfu sputum density and tobramycin resistance

Extensive review of the microbiological data for all 3 studies was performed by the microbiology reviewer – Dr. Peter Coderre - and is not discussed in detail here. Notably, TIP had a slightly greater log₁₀ decrease in *Pseudomonas aeruginosa* cfu/gm sputum at the end of each on cycle than TOBI. Please note the following table:

Table 32: Change in *Pseudomonas aeruginosa* (log₁₀ cfu/gm sputum), by treatment arm and timepoint, C2302

Timepoint	TIP	TOBI
End of 1 st On Cycle	-1.76	-1.32
End of 2 nd On Cycle	-1.54	-1.11
End of 3 rd On Cycle	-1.61	-0.77

Baseline was defined as the latest measurement prior to the first dosing of study medication.

Change = change from baseline.

Overall density is used, and it is defined as the sum of bio-types (mucoid, dry and small colony variant). The log₁₀ is taken on the sum.

Also notable from Dr. Coderre’s review is that *Pa* tobramycin MIC’s increased at a faster pace for TIP than for TOBI over the course of the study, particularly as regards dry and mucoid colony types. The etiology and significance of this MIC increase is unclear. In a very limited analysis of TIP subjects at the end of the third on cycle with a ≥ 4 fold increase in *Pa* (maximum MIC of all biotypes) tobramycin MIC’s, no real difference in either compliance or SAE was noted in this population as compared to the overall TIP safety population.

Antipseudomonal Usage

More patients in the TIP arm had new usage of antipseudomonal antimicrobials during the study period (65% TIP arm vs. 55% TOBI arm; All Randomized Safety Population). The time to first antipseudomonal usage was also decreased in the TIP arm (89 days TIP arm vs. 112 days TOBI arm). Most of the difference in new usage of antipseudomonals was due to non-inhaled uses (64% new non-inhaled use TIP vs. 53.% new non-inhaled use TOBI). This was driven largely by differences in ciprofloxacin usage as described by Table 7.

Table 33: Demographics of New Ciprofloxacin Usage During C2302 Study Period, By Treatment Arm

Arm	New Usage	Sex		Age (y)			FEV1 (% predicted)	
		M	F	≥ 6 to <13	≥ 13 to <20	≥ 20	≥ 25 to <50	≥ 50 to ≤ 75
TIP	146 (47%)	75 (44%)	71 (52%)	9 (32%)	31 (47%)	106 (50%)	63 (49%)	83 (46%)
TOBI	74 (35%)	40 (35%)	34 (36%)	10 (56%)	16 (33%)	48 (34%)	32 (36%)	42 (35%)

-percentages based on All Randomized Safety demographics

There was increased use of ciprofloxacin in virtually all TIP subgroups except in the youngest age group. Females also appeared to have increased usage of ciprofloxacin relative to males.

Hospitalizations

According to the sponsor there was a roughly equivalent number of subjects in each arm that were hospitalized due to a respiratory-related event (TIP 24% and TOBI 22%; All Randomized Safety Population). Similar results were found upon Agency review. In that analysis, using keywords that would have indicated a respiratory illness, the rate of respiratory related hospitalization was found to be 25% in both the TIP and TOBI arms. Using the sponsor analysis, the time to hospitalization was noted to be 199 days in the TIP arm and 190 days in the TOBI arm.

C2303

Secondary endpoints in this study were similar to those of the prior phase 3 studies.

Relative Change in FVC % Predicted and FEF 25-75% Predicted from Baseline to Day 28

Similar to the primary analysis, there was a trend toward improvement in these measures for the TIP arm relative to placebo but this was not statistically significant. Interestingly, the placebo arm had a mildly positive effect over this period as well. Please note the sponsor table below.

Table 34: Relative change from baseline to day 29 in FVC % Predicted and FEF25%-75% Predicted, ITT population, C2303

Treatment	n	-- Treatment --		Comparison	----- Treatment difference -----			
		Mean	SE		Mean	SE	95% CI	p-value
FVC % predicted								
TIP	31	5.8	2.33	TIP-Placebo	4.2	3.19	(-2.22, 10.58)	0.196
Placebo	28	1.6	2.48					
FEF25-75 % predicted								
TIP	31	16.5	5.88	TIP-Placebo	9.8	8.08	(-6.41, 25.96)	0.231
Placebo	28	6.7	6.28					

Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
 Model: response (% change) = treatment + Screening FEV₁ % predicted (<50 and >=50) + age (<13 and >=13) + error.

Reduction in Pa sputum colony count from baseline to Day 28

In the ITT population, there appeared to be a 1.2 log reduction Pa in the TIP arm at Day 29 compared to no reduction in the placebo arm. This was statistically significant. Further discussion of microbiology efficacy variables, including changes in MIC, is deferred to the primary microbiology reviewer, Dr. Peter Coderre.

Antipseudomonal Usage

There were 4 (12.5%) subjects in the placebo arm and 2 (6.7%) subjects in the TIP arm who used antipseudomonal medication during the course of the study. While the majority of antipseudomonal usage in the placebo arm happened during the on cycle, in the TIP arm all such usage happened during the off cycle. All such usage in the placebo arm were related to respiratory-related AEs. In the TIP arm, such usage was listed due to 'wet cough' in one subject and as pre-planned IV antimicrobial prophylaxis in another. It is again notable that both the TIP and placebo arms had less antipseudomonal usage than in 2301. The reason for this is unclear, though the 2301 population may have been healthier at baseline.

Respiratory - related Hospitalizations

There were no hospitalizations in the TIP arm. In the placebo arm, there was one respiratory-related hospitalization (pneumonia) and one non respiratory related hospitalization (leg fracture). Similar to antipseudomonal usage, the level of respiratory related hospitalizations in both arms was less than what was seen in study 2301.

6.1.6 Other Endpoints

The endpoints of interest have been already discussed

6.1.7 Subpopulations

Subpopulation studies, particularly as relates to the primary endpoint have already been discussed in sections 6.1.4. In particular, differences in comparative effect by age group were noted in C2301 and C2302 (favoring younger age groups), and regional differences were noted in C2301 (less effect in North America than Europe). It should be noted that decreased effect on FEV1 % predicted in older patients has also been noted with other inhaled antipseudomonals. However, the conclusions that can be drawn from subpopulations in small trials with significant missing data is limited.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The TIP 112mg dose was chosen to be equivalent to the approved 300mg TOBI dose. The Clinical Pharmacology colleagues have concluded that both doses are equivalent from a serum PK perspective. There appears to be some variability between TIP and TOBI in the sputum concentrations. Please see Dr. Ryan Owen's Clinical Pharmacology review for further details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This has already been discussed in section 6.1.4. There are suggestions of slightly decreased effectiveness of TIP on the primary endpoint over the 3 cycles in the 2301 and 2302 studies, but this is not definitive, especially given the study designs (open label/lack of placebo) and the amount of missing data. However, as noted earlier, several long term studies are ongoing or have been planned by the sponsor to further evaluate this issue. Please see Dr. Christopher Kadoorie's statistical review for further evaluation of this issue.

The first extension study of C2303 (termed C2303E1) has just been completed. In this study, willing and eligible subjects from both arms of C2303 could go on to receive three 28 day on/off cycles of TIP. 55 subjects enrolled in the study and 52 completed it; demographics resembled those of the core C2303 study. At the end of the third on cycle, the relative change in FEV1% predicted from the core C2303 baseline was 17%. However, within each of the subsequent three cycles the mean relative change from beginning to the end of the on cycle decreased markedly with each subsequent cycle (Cycle 2 mean relative change 8.4%, Cycle 3 4.7%, Cycle 4 1.9%). How much the findings of this study can be generalized to studies C2301 and C2302 is unclear given differences in age and overall health in this study population compared to those studies. 5 subjects had new antipseudomonal usage and 2 subjects had respiratory-related hospitalizations. *Pa* tobramycin MIC increases from core study baseline were noted.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety profile of TIP reveals issues of major and minor concern.

The increased usage of antipseudomonals in the TIP arm relative to TOBI poses a particular safety worry. Though the increased usage is driven primarily by ciprofloxacin use and respiratory hospitalizations did not differ between the two arms, at the very least increased patient exposure to the side effects of an antimicrobial warrants concern. Whether this increased usage is also a marker of more devastating consequences on mortality and hospitalization (ie. decreased effectiveness of TIP) over the long term is unclear but can in part be evaluated by a well-designed long term post marketing study. Indeed, even in the relatively short C2302 study, three deaths were noted in the TIP arm while none were noted in the TOBI arm.

Also of major concern, is the possible increased rate of *Pseudomonas aeruginosa* resistance to tobramycin as noted in the Clinical Microbiology review (not discussed in this review). The etiology of this is unclear however an assumption can be made that, despite comments made at the Advisory Committee, this might have potentially negative long-term clinical consequences (decreased treatment options during exacerbations, etc.). This will also need to be evaluated over the a longer study period as part of a post marketing requirement to decipher whether this trend in increased resistance is reproducible, is prevalent within certain subpopulations, and leads to poor clinical outcomes. Ideally, this could be studied in conjunction with the post marketing study designed to evaluate increased antipseudomonal usage.

Despite the above safety concerns, there is less worry about some of the more traditional side effects associated aminoglycosides. There did not appear to be any increased nephrotoxicity or ototoxicity with TIP relative to TOBI or placebo. This is unsurprising given the low rate of systemic absorption of inhaled tobramycin. However, it is possible that such consequences may not be seen over the short term of these studies and may instead become more prominent after years of usage. Indeed current labeling for TOBI cites postmarketing ototoxic events. Moreover, subjects with baseline renal or hearing dysfunction were not enrolled in the study and undoubtedly, such cystic fibrosis subjects will be using TIP upon approval. Similar to TOBI, labeling for TIP will likely have to reflect the potential for these class adverse events.

The use of a dry powder for inhalation of tobramycin, as opposed to a nebulized solution, appears to make particular local airway side effects more prominent. Adverse effects such as cough, dysphonia, oropharyngeal pain, and dysgeusia were more frequent with TIP compared to TOBI. Such side effects could limit use/compliance with the drug. Indeed, increased discontinuations from study were noted with TIP relative to TOBI. Though, most of these adverse effects are relatively benign, the potential for more bronchospasm with TIP compared to TOBI is a more serious clinical concern. However, there was only a small, if any, increase in airway reactivity with TIP relative to TOBI. Nonetheless, TIP labeling will need to reflect the potential for bronchospasm.

It should be noted that the evaluation of safety was limited by the amount of missing data, part of which was due to discontinuations. Thus, though an overall TIP safety picture may emerge from this evaluation, rates of particular adverse events and laboratory analyses should be viewed with caution.

7.1 Methods

The basic structure of the safety evaluation is described in the following sections

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety study was C2302 with supportive safety information provided by C2301 and C2303; please see Table 2 for further details on the size of the safety database in these studies. Minimal safety information was provided by the two phase 1 studies- CTPI001 and INH007. Beyond the information provided in the NDA, safety

information was also gathered from a recently completed extension study (C2303E1), PSUR, scientific literature, and usability study reports.

Safety information was evaluated by this reviewer on a trial by trial basis, primarily because of their differences in trial design (open label, partially open label, placebo-controlled), demographics (C2302 primarily with older patients while C2301 and C2303 primarily with younger patients), and duration (1 cycle vs. 3 cycle). Only pooling of the first cycle of C2303 and C2301 (the placebo-controlled portion) was appropriate given similar demographics.

7.1.2 Categorization of Adverse Events

Adverse events were categorized according to the latest MedDRA version available.; a newer version of MedDRA was used for the Summary of Clinical Safety (version 14.0) than was used for the original C2302 trial (version 11.0) which may have led to some differences in coding particular events, such as coding 'cystic fibrosis lung' as 'infective pulmonary exacerbation of CF.' Adverse events were categorized and described by in terms of its seriousness, severity, cycle of occurrence, its relationship to study drug, and actions taken to address it.\

Though this method of categorization of adverse events is common, there are particular pitfalls in interpreting safety information for this indication. First, when trying to assess levels of pulmonary exacerbations in the two arms, 'splitting' is encountered. A pulmonary exacerbation might be described by many different preferred terms in 2 different system organ classes (Respiratory, thoracic, and mediastinal' SOC and 'Infections and Infestations' SOC). In this review, lumping was often done in order to accurately assess the frequency of related adverse events of special interest. Secondly, in a setting where typical underlying disease symptoms mimic adverse events, it is also difficult to sort of true adverse events, though assessing relatedness certainly helped. However, oftentimes, multiple adverse events are related to study drug so that trying to sort out which adverse event is truly responsible for an effect on study drug (if at all) is difficult.

Overall, categorization of adverse events for this NDA were adequate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As noted earlier, pooling of safety data will generally not be performed due to differences in trial design, duration, and study demographics. There will be modest pooling of the Cycle 1 data from C2301 and C2303.

7.2 Adequacy of Safety Assessments

Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Assessment of adequate safety exposure for TIP reveals a somewhat mixed picture. There was a large safety database, especially considering the limited patient pool for this indication. For the phase 3 studies, the studies that provided the most pertinent safety information, 425 patients received at least one dose of TIP. There was generally equivalent number of males (218) and females (207) in this population and unsurprisingly the vast majority of patients were Caucasian (383). The 2302 study was comprised primarily of patients ≥ 20 years old (over 200 subjects). The adolescent (13- <20 years old) population of all phase three studies was comprised of roughly 121 subjects. However, there were fewer young (6-13 years old) children enrolled in these studies (roughly 83 subjects). There were over 200 subjects with baseline FEV1% predicted $\geq 50\%$ predicted and over 100 subjects with baseline FEV1% < 50% predicted. 93 subjects had baseline FEV1% predicted $\leq 40\%$ predicted, only 12 of those individuals were ≤ 13 years old. (Please note that the above demographic breakdowns include C2301 placebo subjects who were switched to TIP after cycle 1; baseline FEV1% predicted for these patients was considered to be visit 7 [start of cycle 2]).

Table 35: Drug Exposure: C2301, C2302, C2303, Safety Populations

	Cycle 1: >21 days exposure	Cycle 2: >21 days exposure	Cycle 3: ≤ 21 days exposure
C2302 TIP	92%	81%	74%
TOBI	97%	84%	80%
C2301 TIP/TIP/TIP	87%	85%	85%
PIb/TIP/TIP	86%	84%	82%
C2303 TIP	97%	-----	-----
Placebo	97%	-----	-----

-Percentages reflect total safety populations for each arm

-Duration = last dosing date of study medication in on-treatment cycle - first dosing date of study medication in on-treatment cycle+1 day

In the C2302 study, TIP exposure decreases over time and is less than in the corresponding TOBI arm, primarily due to discontinuations. In C2301, TIP exposures are consistent from cycle to cycle but lower than in C2302. C2303 exposures were high for the lone cycle. These exposure totals do not account for potential occasional missed doses between first and last days of dosing.

The durations studied in the trial reflect what was considered to be ethical and also replicated what had been done with the original TOBI trials. Placebo controlled trials were only one on/off cycle long due to ethical considerations of giving patients longer durations of placebo. The C2302 study was designed similarly to the original TOBI trials. The TIP dose chosen for the phase 3 studies was shown to be equivalent to the currently approved 300mg TOBI dose.

However, the study designs did have significant limitations, particularly the open label format of C2302 and lack of placebo control in cycles 2 and 3 of C2301 and large amounts of missing data.. Moreover, exclusion criteria excluded subjects with significant renal or hepatic dysfunction at baseline so no real recommendations can be made for this population. Still, many of the safety issues related to tobramycin and powders are already known and assessments were built into the phase 3 trials for evaluating ototoxicity (in a subset population), nephrotoxicity. and bronchoreactivitiy.

7.2.2 Explorations for Dose Response

The following sponsor table looks at mean TIP dose exposure per cycle (SCS, pg. 20)

Table 36: Patient exposure to study drug by treatment cycle (controlled Phase III studies)

Number of cycles on-treatment	Number of patients	Mean dose (mg) of treatment per cycle		Mean duration of treatment (days) per cycle	
		n	Mean (SD)	n	Mean (SD)
TIP (1-cycle)	425	420	5839 (1111.2)	425	27.6 (4.72)
TIP (2-cycle)	345	342	5939 (706.6)	345	28.3 (2.38)
TIP (3-cycle)	273	271	5937 (621.7)	273	28.7 (1.78)
TOBI (1-cycle)	209	206	16009 (2364.6)	209	28.4 (3.41)
TOBI (2-cycle)	180	175	16090 (1713.8)	178	28.7 (1.43)
TOBI (3-cycle)	171	165	16125 (1573.2)	169	28.9 (1.07)
Placebo (1-cycle)	81	-	-	81	27.2 (5.89)

Based on studies C2301, C2302 and C2303

1-cycle: exposed to 1 cycle of treatment with at least one dose of study drug in the cycle

2-cycle: exposed to 2 cycles of treatment with at least one dose of study drug in each of the 2 cycles

3-cycle: exposed to 3 cycles of treatment with at least one dose of study drug in each of the 3 cycles

n - number of patients with relevant measurements

The above model does not take into account subjects who discontinued during off cycles. For patients exposed to drug, TIP mean dose was between 104 and 106 mg and the mean TOBI dose was 286 and 288 mg.

7.2.3 Special Animal and/or In Vitro Testing

Inhaled nonclinical studies were performed for this NDA, and prior nonclinical studies done for TOBI were relied upon as well. Please note Dr. Amy Ellis's Pharmacology/Toxicology review for further details.

7.2.4 Routine Clinical Testing

Overall, clinical safety testing was acceptable. Adverse events, laboratory data, and vital signs data were all collected in typical fashion. Also, class/drug specific issues were also evaluated including bronchoreactivity (through post dose spirometry) ototoxicity hearing loss (patient report and audiometry), though such assessments were limited in scope and depth.

7.2.5 Metabolic, Clearance, and Interaction Workup

Because tobramycin is primarily excreted by glomerular filtration and undergoes no hepatic metabolism, no real drug interaction studies were performed. Also, this drug is expected to have minimal systemic absorption. Within the current TOBI labeling exists a statement warning about concurrent use of TOBI with diuretics that might increase serum tobramycin levels; similar proposed labeling has been included. Though not a prototypical drug interaction consideration, given the amount of chronic inhaled medications cystic fibrosis patients take, it would be of interest to know whether such combinations improve efficacy or worsen safety, but that is more the scope of general scientific investigation and not necessarily the specific purview of this application

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Aminoglycosides are a well understood drug class. Major class toxicities include nephrotoxicity, ototoxicity and neuromuscular weakness (particularly in cases of overdose). As has been already stated, the safety evaluation did include monitoring for nephrotoxicity (serum creatinine and BUN) and ototoxicity (patient reports of hearing loss and tinnitus, subset of patients with audiometry).

7.3 Major Safety Results

7.3.1 Deaths

C2301

There was only one death in this study. This occurred in a 10 year old female placebo patient with a history of complications of CF including cor pulmonale and pulmonary hypertension and multiple pulmonary exacerbations requiring antipseudomonal treatment. The patient developed pulmonary exacerbation soon after enrollment (Day 5), was hospitalized, started on antibiotics, and was discontinued on Day 9. At this point, she was tachypneic and her predose FEV 1 value had dropped almost in half. She received amikacin, ceftazidime, meropenem, and vancomycin and was discharged 22 days after discontinuation. 18 days after discharge she was readmitted with cardiopulmonary complications of CF and died the same day due to decompensated cor pulmonale and respiratory insufficiency.

There were no deaths in the TIP arm

C2302

There were 3 deaths in this study, all in the TIP arm. Another patient was screened but never dosed and died due to progression of cystic fibrosis lung disorder.

TIP

24 y/o Caucasian female with history of cystic fibrosis, diabetes mellitus, repeated pulmonary exacerbations (had used vancomycin and meropenem prior to starting study), zosyn and iodine allergy, depression, pancreatic insufficiency, and hypothyroidism with extensive prior use of inhaled tobramycin. At visit 2, the patient had a baseline FEV 1 % predicted of 31.6% and had an elevated sputum counts of both MRSA and *Pseudomonas aeruginosa*. By the end of the first cycle, the patient had very little improvement in FEV1 % predicted (35.7%) and had only a modest reduction in *Pa* sputum counts. The patient had been compliant with her medication and appeared to be very satisfied with TIP according to her responses on TSQM. After her second cycle of drug, she continued to have no improvement in pulmonary function (FEV1% predicted 32.2%) with moderate reduction in *Pa*. Again, the patient had very good medication compliance and appeared quite satisfied with TIP. It should be noted that prior to starting both her first and second cycles of study drug, elevated tobramycin MIC's of 8 and 32, respectively were noted for *Pa*. During the 2nd on cycle, the patient was noted to have an upper respiratory infection which required treatment with 3 weeks of IV meropenem and vancomycin. 1 month later the patient again developed signs and symptoms of pneumonia and was discontinued from study. She was initially started on vancomycin and meropenem again but was then hospitalized after showing signs of hypoxemia, svt, hyperglycemia, and fluid overload. She was maintained on vancomycin and meropenem and also started on aztreonam, inhaled tobramycin, levofloxacin, and adenosine. Her sputum culture grew out MRSA and *Pa*. The patient was intubated, but

continued to deteriorate. Three weeks later she had continued respiratory deterioration, went into asystole and died. A culture done 6 days prior to death showed *Pa* and *Stenotrophomonas maltophilia* (which had also been present in prior cultures).

While no direct link can be made between TIP and death, the study drug did not appear to provide adequate protection against the development of a pulmonary exacerbation despite good compliance. However, the patient may have also had tobramycin resistant organisms and did not fare any better with the use of TOBI (albeit in an acute rather than preventative setting).

21 year old Hispanic male with a history of cholecystectomy, chronic sinusitis, and two year history of inhaled tobramycin use. His last usage was two months prior to screening. The patient had a predose FEV 1 % predicted of 39.2% at baseline and had elevated levels of *Pa* in the sputum with a tobramycin MIC of 1. After the 1st cycle, there was no improvement in pulmonary function (FEV 1 % predicted 38%) or *Pa* counts and tobramycin MIC had increased to 512 ug/ml. The patient was compliant with the medication and also appeared to be satisfied with TIP according to the TSQM. At the start of the second cycle, the patient was noted to have *Pa* in sputum with MICs of 128 ug/ml. At the end of the second cycle, he again was compliant with drug but had no improvement in pulmonary function (FEV 1% predicted 34.3%) or *Pa* counts and tobramycin MIC was again 512 ug/ml. During the second off cycle, the patient had clinical signs of a pulmonary exacerbation (increased dyspnea, cough, sputum production) and was hospitalized and treated with multiple antipseudomonals including ciprofloxacin (pre hospitalization), imipenem, and piperacillin-tazobactam. He was hospitalized for six days, discharged but then readmitted again with similar symptoms four days later and again treated with multiple antipseudomonals including meropenem, and piperacillin-tazobactam. However, the patient continued to deteriorate and died two weeks later.

TIP did not appear to prevent the development of pulmonary exacerbation in this case. Also, it is concerning that *Pa* tobramycin resistance may have increased while on treatment and could have contributed to failure of drug.

25 year old Caucasian male with history of diabetes, hydrocephalus with nonfunctioning CSF shunt, asthma, and a history of multiple antipseudomonal courses in the year prior to study initiation. At visit 2 (pre dose), patient had baseline FEV 1 % predicted of 38.4% and elevated sputum *Pa* counts with MIC of 2 ug/ml. By the end of the first cycle, the patient had a modest improvement in FEV 1 % predicted (44.1%) and a modest reduction of *Pa* counts but the tobramycin MIC was 512 ug/ml. He was compliant with his medications and was somewhat satisfied according to the TSQM. In the 2 weeks after the last dose of cycle 1, patient started exhibiting signs and symptoms of pulmonary exacerbation (dyspnea, cough, etc.) and eventually was hospitalized for

10 days and treated with ciprofloxacin and colistin. By the beginning of cycle 2, patient's FEV1% predicted was close to baseline (39%) and he again had elevated levels of sputum *Pa* with elevated tobramycin MIC levels (512 ug/ml). He was compliant with his medications though by the end of this cycle he displayed dissatisfaction with drug according to the TSQM. Four days after finishing study drug, patient again started having symptoms of pulmonary exacerbation and was hospitalized (FEV1% predicted 26.7% and sputum showed *Pa* with tobramycin MIC of 256 ug/ml). He was treated with colistin, meropenem, and ciprofloxacin and was eventually discharged after 10 days though showing only modest improvement in pulmonary function and continued elevated *Pa* counts. It is unclear if the patient was restarted on study drug after this but did have a Visit 9 (Start of 3rd On cycle) and FEV1% predicted at that time was 28.8% with elevated *Pa* sputum counts (tobramycin MIC of 16 ug/ml). Three weeks after this visit the patient overdosed on a recreational drug (CRF does not state what the drug was) and remained unconscious for a prolonged period. This led to an ischemic brain injury, mechanical ventilation, and aspiration pneumonia. He eventually succumbed to these clinical events and died 3 weeks after overdose. Though the cause of death here is likely unrelated to TIP, it is again notable that the use of TIP did not prevent the occurrence of pulmonary exacerbations and in fact may have led to increased *Pa* tobramycin resistance.

TOBI

There were no deaths in the TOBI arm

C2303

There were no deaths in this study

7.3.2 Nonfatal Serious Adverse Events

C2301

During Cycle 1, 3 (6.5%) subjects in the TIP arm and 7 (14.3%) subjects in the placebo arm had an SAE. The vast majority of these events were described by preferred terms that represent a pulmonary exacerbation, including 'lung disorder' and pneumonia.' For all 3 cycles, the TIP arm had 5 (10.9%) subjects with SAEs, almost all signifying pulmonary exacerbation events. A similar finding was seen in the placebo arm after switch to TIP - 6 subjects had SAEs over 2 cycles with a profile similar to the TIP arm. It is useful to note that 3 cycles of TIP in study C2301 had comparatively fewer SAEs than 3 cycles of TIP in study C2302 (discussed later). However, these studies

varied significantly in sample size. Also, the TIP arm in C2301 was much younger than the TIP arm in C2302 (mean age 13 years old vs. 26 years old in C2301 and C2302, respectively) and was off of an inhaled antipseudomonal for 4 months prior to study as opposed to only 1 month in C2302. Thus, it is possible that the TIP patients in C2301 were generally healthier at baseline than the TIP subjects in C2302. Please note the following sponsor table highlighting cycle 1 SAEs.

Table 37: C2301 Serious Adverse Events, Cycle 1

MedDRA system organ class Preferred term	TIP (N=46) n (%)	Placebo (N=49) n (%)	Total (N=95) n (%)
-Any MedDRA system organ class			
-Total	3 (6.5)	7 (14.3)	10 (10.5)
infections and infestations			
-Total	0 (0.0)	2 (4.1)	2 (2.1)
Hepatitis B	0 (0.0)	1 (2.0)	1 (1.1)
Pneumonia	0 (0.0)	1 (2.0)	1 (1.1)
Investigations			
-Total	0 (0.0)	2 (4.1)	2 (2.1)
Pulmonary function test decreased	0 (0.0)	1 (2.0)	1 (1.1)
Sputum abnormal	0 (0.0)	1 (2.0)	1 (1.1)
Respiratory, thoracic and mediastinal disorders			
-Total	3 (6.5)	4 (8.2)	7 (7.4)
Lung disorder	3 (6.5)	4 (8.2)	7 (7.4)
Cough	0 (0.0)	1 (2.0)	1 (1.1)
Dyspnoea exertional	0 (0.0)	1 (2.0)	1 (1.1)
Haemoptysis	0 (0.0)	1 (2.0)	1 (1.1)
Productive cough	0 (0.0)	1 (2.0)	1 (1.1)
Sputum discoloured	0 (0.0)	1 (2.0)	1 (1.1)

MedDRA system organ classes are presented alphabetically; preferred terms are sorted within MedDRA system organ class in descending order of frequency in the Total column.

- A subject with multiple occurrences of the same AE is counted only once in the AE category.

- A subject with multiple adverse events within a MedDRA system organ class is counted only once in the Total row.

C2302

The incidence of serious adverse events between the TIP and TOBI arms were similar (TIP 27% and TOBI 29%). No SAE occurred in the TIP arm at a rate 2% higher than the TOBI arm. The SAE-associated PT with the largest incidence was 'lung disorder' (a surrogate term for pulmonary exacerbation), and this was essentially equivalent between the two arms (TIP 19.5% vs. TOBI 18.7%). It should be noted that the vast majority of SAE-associated PTs could also have a link with a pulmonary

exacerbation/background disease ('cough,' 'hemoptysis,' 'bronchitis,' 'dyspnea,' etc.), and thus a better analysis of the risk of a pulmonary exacerbation- associated SAE would be to look at secondary efficacy endpoints such as rates of hospitalization for respiratory-related illness and use of antipseudomonals between treatment arms (discussed earlier in section 6.1.5). No other SAE preferred term had an incidence of 3%. 11 subjects in the TIP arm had SAEs considered related to study drug vs. only 1 in the TOBI arm. The vast majority of such events were likely associated with a pulmonary exacerbation. Please note the following sponsor table.

Table 38: Serious adverse events (at least 2 patients in total), regardless of study drug relationship, by preferred term and treatment group (Safety population), C2301

Preferred term	TIP N=308 n (%)	TOBI N=209 n (%)	Total N=517 n (%)
Patients with SAE(s)	85 (27.4)	61 (29.2)	146 (28.2)
Lung disorder	60 (19.5)	39 (18.7)	99 (19.1)
Haemoptysis	8 (2.6)	4 (1.9)	12 (2.3)
Cough	7 (2.3)	5 (2.4)	12 (2.3)
Bronchitis	6 (1.9)	1 (0.5)	7 (1.4)
Dyspnoea	5 (1.6)	4 (1.9)	9 (1.7)
Productive cough	5 (1.6)	2 (1.0)	7 (1.4)
Pulmonary function test decreased	4 (1.3)	3 (1.4)	7 (1.4)
Fatigue	3 (1.0)	0 (0.0)	3 (0.6)
Cystic fibrosis lung	2 (0.6)	2 (1.0)	4 (0.8)
Dyspnoea exertional	2 (0.6)	0 (0.0)	2 (0.4)
Epistaxis	2 (0.6)	1 (0.5)	3 (0.6)
Lower respiratory tract infection	2 (0.6)	2 (1.0)	4 (0.8)
Lung infection pseudomonal	2 (0.6)	1 (0.5)	3 (0.6)
Pneumonia	2 (0.6)	2 (1.0)	4 (0.8)
Pneumonia bacterial	2 (0.6)	2 (1.0)	4 (0.8)
Sinusitis	2 (0.6)	1 (0.5)	3 (0.6)
Abdominal pain	1 (0.3)	1 (0.5)	2 (0.4)
Bronchopneumonia	1 (0.3)	2 (1.0)	3 (0.6)
Distal intestinal obstruction syndrome	1 (0.3)	1 (0.5)	2 (0.4)
Forced expiratory volume decreased	1 (0.3)	1 (0.5)	2 (0.4)
Lung abscess	1 (0.3)	1 (0.5)	2 (0.4)
Pseudomonas infection	1 (0.3)	2 (1.0)	3 (0.6)
Pulmonary congestion	1 (0.3)	1 (0.5)	2 (0.4)
Pyrexia	1 (0.3)	2 (1.0)	3 (0.6)
Respiratory tract infection	1 (0.3)	1 (0.5)	2 (0.4)
Bronchiectasis	0 (0.0)	2 (1.0)	2 (0.4)
Hypoxia	0 (0.0)	2 (1.0)	2 (0.4)
Weight decreased	0 (0.0)	3 (1.4)	3 (0.6)

Preferred terms are sorted in descending order of frequency in the TIP column.

A patient with multiple occurrences of the same preferred term is counted only once in the preferred term.

C2303

Serious Adverse Events (SAE).

Only 2 subjects, both in the placebo arm, were hospitalized and considered to have an SAE. One subject had an SAE of 'lower limb fracture' and another subject had an SAE of 'pneumonia.' Neither event was considered related to study drug.

Please note that for all 3 studies, SAE rates are limited by the significant number of discontinuations.

7.3.3 Dropouts and/or Discontinuations

Discontinuations were somewhat prevalent in all three phase 3 studies

C2301

In the TIP arm, 85% of subjects (39/46 subjects in All Randomized Safety population) completed the protocol. Two subjects were non compliant, two subjects were inappropriately enrolled (lack of *Pa* on culture), and three subjects were 'unable to classify' (may have discontinued due to adverse events but difficult to assess from records). 82% of subject in the placebo arm completed the protocol (40/49). Of the nine subjects who discontinued the study, only one appeared to occur during the open label period with TIP; this subject may have discontinued due to an adverse event though it is difficult to discern from records.

C2302

There were more discontinuations in the TIP arm than TOBI arm (TIP 83 subjects [26.9%] and TOBI 38 subjects [18.2%]). This disparity was driven by imbalances in discontinuations due to adverse events (TIP 14% vs. TOBI 8.1%) and withdrawal of consent (TIP 7.8% and TOBI 4.3%). Preferred terms where TIP arm discontinuation exceeded TOBI arm discontinuation by at least 2 subjects included 'cystic fibrosis lung,' 'chest discomfort,' 'pyrexia,' 'cough,' 'dyspnea,' 'bronchospasm,' 'dysphonia,' and 'throat irritation.' The following table evaluates discontinuations by subgroup; the vast majority of these discontinuations were either due to an adverse event or withdrawal of consent (which in some cases may be due to an adverse event).

Table 39: Subgroup Analysis of Study C2302 Discontinuations by Treatment Arm

	TIP 83 Discontinuations	TOBI 38 Discontinuations
Sex		
Male	47/171=27.5%	17/115=14.8%
Female	36/137=26.3	21/94=22.3%
Age		
≥6 to <13 years old	1/28=3.6%	3/18=16.7%
≥13 to < 20 years old	12/66=18.2%	8/48=16.7%
≥ 20 years old	70/214=32.7%	27/143=18.8%
Baseline pulmonary function		
< 50 % FEV1 % predicted	47/122=38.5%	20/95=21%
≥ 50 FEV1 % predicted	36/186=19.4%	18/114=15.7%
Region		
NA	52/195=26.7%	28/131=21.4%
LA	1/9=11.1%	0/7=0%
Europe	30/104= 28.8%	10/71=14%

- percentages represent percentage of that particular demographic in the All Randomized Safety population

When comparing TIP to TOBI, all analyzed subgroups except for the youngest age group had a higher rate of discontinuation within the TIP arm. Within the TIP arm, higher rates of discontinuation were seen in the eldest age group and in subjects with lower baseline pulmonary function.

It is also useful to look at the profile of subjects who discontinued study drug permanently due to an adverse event (a subject may have discontinued study drug but not discontinued the study and this would not have been counted in the above table). Please note the table below.

Table 40: Subgroup Analysis of C2302 Study Drug Discontinuations by Treatment Arm

	TIP 57 Discontinuations	TOBI 18 Discontinuations
Sex		
Male	31/171=18.1%	8/115=7.0%
Female	26/137=19%	10/94=10.6%%
Age		
≥6 to <13	2/28=7.1%	2/18=11.1%
≥13 to < 20	8/66=12.1%	2/48=4.2%
≥ 20	47/214=22%	14/143=9.8%
Baseline pulmonary		

function		
< 50 % FEV1 % predicted	32/122=26.2%	7/95=7.4%
≥ 50 FEV1 % predicted	25/176=14.2%	11/114=9.6%
Region		
NA	32/195=16.4%	14/131=10.7%%
LA	1/9=11.1%	0/7=0%
Europe	24/104= 23.1%	4/71=5.6%

- percentages represent percentage of that particular demographic in the All Randomized Safety population

Similar to the earlier table, all analyzed subgroups except for the youngest age group had a higher rate of discontinuation in the TIP arm. Within the TIP arm, higher rates of discontinuation were seen in the eldest age group, in subjects with higher baseline pulmonary function, and subjects in the European region.

C2303

One subject in each arm discontinued. In the TIP arm, a 10 year old subject discontinued study drug due to pulmonary hemorrhage on Day 27 and was treated with aminocaproic acid and Vitamin K (unclear whether this event was associated with hemoptysis). The event was considered to be related. Though it was reported that the adverse event resolved by Day 29, the subject discontinued study on Day 55 for unclear reasons. In the placebo arm, a 12 year old female had an exacerbation of chronic bronchitis on Day 13 and study drug was discontinued. The subject started ciprofloxacin and inhaled colistin six days later and was discontinued from the study. The event was considered to be related.

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

Particular safety concerns that arise from this application can be separated into two areas:

- 1) safety concerns specific to an aminoglycoside, particularly nephrotoxicity and ototoxicity
- 2) safety concerns associated with inhalation of a dry powder, such as bronchospasm, cough, and other local airway effects

Nephrotoxicity

Aminoglycosides as a class are known to have nephrotoxic potential, increasing with dose and duration. TIP is not expected to be absorbed to any large degree, however it may be used concomitantly with other nephrotoxic agents including parenteral aminoglycosides. All three phase 3 studies have only limited ability to assess the issue of nephrotoxicity given the exclusion from phase 3 trials of renally impaired subjects.

C2301

No preferred terms directly related to nephrotoxicity were reported in the study.

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. Both the TIP and placebo (after TIP switch) arms showed mild increases in mean creatinine by the end of the third cycle (mean increase of 0.04 mg/dl in the TIP arm at Day 28 of cycle 3 and 0.05 mg/dl at Day 28 of cycle 3 for the placebo/TIP arm). This appears to be clinically insignificant and in the TIP arm, appeared to partially reverse by the end of the 3rd off cycle. 4 subjects in the placebo arm had an increase of 50% in serum creatinine from visit 2 to visit 5; no subjects had such changes in the TIP arm over the same period. The highest post-baseline creatinine level recorded in a subject receiving TIP was 1.6 mg/dl. However, this subject had a baseline level of 1.3 mg/dl which increased to 1.4 while receiving placebo, then decreased to 1.3 mg/dl at Visit 10 after switch to TIP. At follow up the level had increased to 1.6 mg/dl.

Mean changes did not markedly differ between the two arms and were clinically insignificant. No clear trends could be identified from shift tables. Only 2 TIP subjects had an increase of at least 100% in BUN values from Visit 2 to Visit 5; there were no such subjects in the placebo arm over the same time period. In the first TIP subject, the BUN increased from 5 mg/dl to 10 mg/dl from visit 2 to 5 but then decreased over subsequent visits and was 7 mg/dl by visit 10. Another TIP subject had values increase from 8 mg/dl to 20 mg/dl from visit 2 to visit 5, but had dropped to 12 mg/dl by visit 10.

C2302

In the 'Renal and Urinary Disorders' SOC, the preferred terms 'proteinuria,' 'dysuria,' 'polyuria,' 'nephrolithiasis,' were reported. Additionally 'blood in urine,' 'blood creatinine increased,' 'blood urea increased,' and 'protein urine present' were reported. These events were reported in 9 (2.9%) TIP and 5 (2.4%) TOBI subjects. 2 TIP events and 1 TOBI event was considered possibly related to study drug.

Mean and median changes in serum creatinine did not show one agent to be more nephrotoxic than the other; differences appear clinically insignificant. Only 2 subjects in the TIP arm and 2 subjects in the TOBI arm had post baseline serum creatinine levels ≥ 1.5 mg/dl. One TOBI subject is likely to have been laboratory error as it is markedly different from prior and subsequent readings. No real difference in shift tables were noted. Finally, there was no real difference between the two arms in terms

of subjects who had a 50% increase from baseline in serum creatinine; 15 (4.9%) TIP subjects and 8 (3.8%) TOBI subjects had such changes anytime post baseline

No significant differences between treatment arms was noted in terms of mean and median BUN changes over the course of study. Also, no real differences were noted in shift tables. 17 (4.9%) subjects in the TIP arm and 8 (3.8%) subjects in the TOBI arm had a 100% increase from baseline in serum BUN. 18 (5.8%) subjects in the TIP arm and 12 (5.7%) subjects in the TOBI arm had post baseline measurements \geq 25mg/dl.

C2303

Only a PT of 'proteinuria' was reported, and this was in a TIP patient. This subject was an 11 y/o female who was found to have proteinuria at a level of 100mg/dl at the end of on cycle visit. The subject had a negative urinalysis and a serum creatinine of .26mg/dl at baseline. At the end of on cycle, serum creatinine was .31 mg/dl (subject only 24 kg). Proteinuria was ongoing at end of off cycle but serum creatinine had returned to baseline. This event was considered mild but related and nonserious and no action was taken.

No clinically significant differences in median changes in serum creatinine from baseline to Day 28 were seen between the TIP and placebo arm. Median change from baseline to Day 28 in the TIP arm was an increase of 0.06 mg/dl. In the placebo arm, there was a decrease of .006 mg/dl. No clinically significant trends were identified. The highest value noted at Visit 3 was in the TIP arm (0.78 mg/dl). 3 (10%) of TIP subjects and 1 (3%) placebo subject had an increase in serum creatinine of 50% from baseline to Day 28.

No clinically significant differences in median changes in serum BUN from baseline to Day 28 were seen between the TIP and placebo arm. Median change from baseline to Day 28 in the TIP arm was an increase of 2mg/dl. In the placebo arm, there was an increase of .14 mg/dl. No clear trend was identified on shift tables. The highest value noted at visit 3 was in the TIP arm (17.7 mg/dl). 1 (3%) subject in the TIP arm and none in the placebo arm had an increase in serum BUN of 100% from baseline to Day 28.

As with most of the safety assessments, conclusions are limited by the amount of missing data.

Ototoxicity

Ototoxicity is also known to occur with aminoglycosides, particularly with increasing dose and duration. Tobramycin is not expected to be absorbed into the systemic

circulation at a high level. However, tinnitus and hearing loss have been reported with TOBI.

C2301

No AE preferred terms truly corresponded to a typical aminoglycoside-associated ototoxic event (no AEs reported for tinnitus, deafness, etc.). There were three subjects in the placebo arm who had an AE of 'ear pain,' two of which had this complaint during cycle two when they would have been on TIP. One subject in the TIP arm had an AE of 'ear discomfort;' this subject had this symptom in the setting of a pulmonary exacerbation and missed many doses due to inhaler intolerance. None of these events were considered related; all such were mild and nonserious. Two adverse events related to dizziness occurred in the placebo arm during cycle 1.

Pure tone audiometry was performed in a subset of subjects at Visit 2, 5, 8, and 10. This was conventional testing up to 8kHz. Such testing would not test for high frequency hearing loss – the usual target of aminoglycoside mediated toxicity. There were no prespecified criteria for assessing the significance of changes in audiogram measurements over time. For Agency review, criteria set out by the American Academy of Audiology were used to assess significance of changes. These criteria are:

Significant ototoxic change must meet one of the following three criteria: (a) ≥ 20 dB decrease at any one test frequency, (b) ≥ 10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were previously obtained. (provide ref.)

Two subjects in the TIP arm and none in the placebo arm met the above criteria.

One TIP subject had a 10 dB loss at 4 and 8 kHz in the right ear at Visit 5. This patient had a history of hearing loss in the past and otitis media at baseline. The patient was compliant with TIP over the first cycle but was discontinued from study due to 'inappropriate enrollment' (patient did not have Pa isolated at screening).

Another TIP subject had a loss of 10 db at frequencies .13 kHz and .25 kHz at Visit 5 and had a 15 dB loss at .13 kHz and 10 dB loss at .25 kHz at Visit 8. Bone conduction was performed and the hearing loss was thought to be conductive. No decreases were noted at Visit 10. The subject did not have a history of hearing loss but did report complaints of toothache and rhinitis during cycle 1.

One subject who had a complaint of ear pain while on TIP had decreases of 5dB and 10 dB at 4 and 8 kHz respectively though this did not meet criteria for a significant change.

No formal testing for vestibulotoxicity was done.

C2302

When trying to evaluate this issue based on reported adverse events, it is complicated by which preferred terms to use for analysis- i.e. should a broader umbrella of terms or

more specific terms be used? Using the reported preferred terms of 'deafness,' 'tinnitus,' 'hypoacusis,' 'deafness neurosensory,' and 'deafness unilateral,' 11 subjects in the TIP arm (3.6%) (7 related) and 6 subjects in the TOBI arm (2.9%) (4 related) were found. If the preferred term 'dizziness' was added, 16 subjects in the TIP arm (5.2%) (11 related) and 9 subjects in the TOBI arm (4.3%) (4 related) were found to fit this criteria. Nine of these subjects in the TIP arm and 4 of these subjects in the TOBI arm were a part of the subset of subjects that had audiograms done to monitor for ototoxicity (audiology population). Five of these nine subjects in the TIP arm and one of the four subjects in the TOBI arm reported these adverse events and also had a decrease of at least 10 dB at any point in the study. Terms not included in this analysis were 'cerumen impaction,' 'postural dizziness,' 'ear discomfort,' 'ear hemorrhage,' 'ear pain,' 'ear infection,' 'otitis media,' 'middle ear effusion,' 'tympanic membrane perforation,' 'tympanic membrane scarring,' 'tympanosclerosis,' and 'tympanic membrane disorder' because it was either felt they did not describe aminoglycoside mediated ototoxicity well or they occurred during screening. Of note baseline macrolide usage (which can cause ototoxicity) was equivalent for both arms 47% TIP, 45% TOBI.

The procedure for ototoxicity monitoring with audiometry was the same as in study C2301. Audiometry was performed on a subset of 123 subjects (78 subjects in the TIP arm and 45 subjects in the TOBI arm) at visits 2, 5, 8, and 10. The TOBI subset had slightly more adolescents and the TIP group had slightly more patients ≥ 20 years old. Mean age for TIP subset was 24.7 while for TOBI it was 23.9. The TIP arm had more Caucasians and the TOBI arm had more Hispanic subjects.

Using the criteria outlined earlier to monitor for clinically significant changes in hearing levels over time, five subjects in the TIP arm and 3 subjects in the TOBI arm were noted to have such changes. Another two subjects in the TIP arm had a decrease of 15dB in just one frequency. Brief discussions of these subjects are posted below.

One TIP subject had a hearing loss of 15 dB at 8kHz in the left ear at visit 10. The hearing loss was thought to be sensorineural. No ototoxicity-related adverse events were noted.

One subject in the TIP arm had a decrease of 20dB at 6kHz at visit 8. This frequency was not retested at the next visit. The hearing loss was thought to be sensorineural. No ototoxicity-related adverse events were noted.

One TIP subject had a decrease of 15 dB at 8 kHz at visit 10 in the right ear; the hearing loss was thought to be sensorineural. No ototoxicity-related adverse events were noted.

One TIP subject had a hearing loss of 25 dB at 16 kHz in the right ear at visit 8. However at visit 10, no decrease was noted at this frequency. Bone conduction testing was not performed. An adverse event of tinnitus and cerumen impaction were noted at Cycle 1 and hypoacusis was noted in Cycle 2.

One TIP subject had hearing loss of 10 dB at 3 kHz and 8kHz in the right ear at visit 10. No bone conduction testing was performed. No ototoxicity-related adverse events were noted.

One TIP subject had a hearing loss of 20dB at 4 kHz in the right ear at visit 10 and losses of 15dB and 10dB at 4 and 8 kHz, respectively, in the left ear. The hearing loss was thought to be sensorineural. At a follow up visit a month later, the left defect remained and a loss of 20 dB was also noted at 8kHz in this ear. No ototoxicity-related adverse events were noted.

One TIP subject had hearing losses at 6 and 8 kHz bilaterally at visit 8. In the right ear the losses were 15 and 10 dB, respectively, and in the left ear the losses were 10 dB at both frequencies. At visit 10, such decreases were not noted at 6 and 8 kHz bilaterally, however there was a drop of 10 dB at 0.5 and 1 kHz in the right ear. No ototoxicity-related adverse events were noted.

One TOBI subject had losses of 10 dB at 2,4, and 8 kHz of the left ear and 4 and 8 kHz of the right ear at visit 10. No bone conduction testing was performed. No ototoxicity-related adverse events were noted.

One TOBI subject had a loss of 35dB at 12.5 kHz of the left ear at visit 5. This hearing loss was thought to be sensorineural. An adverse event of deafness was reported in cycle 1.

One TOBI subject had a loss of 20dB at 8kHz in the right ear at visit 10. Bone conduction was performed and the hearing loss was thought to be conductive. No ototoxicity-related adverse events were noted.

Based on the above data, no clear evidence is seen of more potential ototoxicity with TIP compared to TOBI, though the data is limited from both a procedural and missing data standpoint. However, a decline in audiometry hearing threshold levels was seen in some TIP subjects and its potential for ototoxicity cannot be ruled out.

C2303

There were 5 reports of 'hypoacusis' in the study, 3 in the TIP arm and 2 in the placebo arm. None of the events were severe or serious. One subject in each arm was considered to have had a related hypoacusis adverse event.

Audiology exams were performed as in prior studies in a subset of 26 subjects, 15 in the TIP arm and 11 in the placebo arm, at visit 2 and visit 3. If an audiological abnormality was noted and was clinically significant or a subject was prematurely withdrawn, testing was done at visit 4. One subject in TIP and one subject in placebo had adjacent frequencies with at least a drop of 10 dB. In the TIP arm this decrease was seen at both visits 3 and 4. In the placebo arm, this was only seen in visit 3. Both subjects had reports of a 'hypoacusis' adverse event as a result of the audiometry findings. Another subject in the placebo arm had a decrease of 10 dB at visit 3 but this was not in adjacent frequencies; this subject also had a hypoacusis adverse event.

Assessment of rates of ototoxicity are limited by missing data.

Bronchoreactivity

There is concern whether an inhaled powder might lead to more bronchospasm than a nebulized solution. All 3 phase 3 studies tried to evaluate study drug-induced bronchoreactivity.

C2301

The sponsor measured FEV1 both predose and up to 30 minutes post dose at Visits 2, 3, 5, 7, 8, 9, and 10. This provides some indication of acute reactions though it does not provide any insight into potential very acute (3-5 minutes post dose) or late stage reactions (occurring 4 to 8 hours after dose). Also, since the placebo comparator is also an inhaled powder, the study does not really allow for testing of the bronchospastic qualities of the powder itself against other formulation types such as nebulized solutions. Table 4 below analyzes the number of subjects in each arm with a relative decline in FEV1 % Predicted from baseline of $\geq 10\%$. Please note that because several subjects were noted by the sponsor to have spirometry readings of poor quality, they were not included in this analysis.

Table 41: Number of Subjects with a Relative Decline From Baseline in FEV 1% Predicted of $\geq 10\%$, By Visit, SIA population, C2301

		V2	V3	V5	V7	V8	V9	V10
TIP	≥ 10 to <20 % decline	4 (13%)	3 (9%)	1 (3%)	4 (13%)	2 (6%)	3 (9%)	5 (16%)
N=32	$\geq 20\%$ decline	1 (3%)	0	0	0	0	0	0
Placebo	≥ 10 to <20 % decline	4 (11%)	5 (14%)	3 (8%)	2 (5%)	3 (8%)	5 (14%)	1 (3%)
N=37	$\geq 20\%$ decline	2 (5%)	0	2 (5%)	0	1 (3%)	0	0

-SIA population is the Sensitivity Interim Analysis population; this includes only those subjects noted to have good quality spirometry readings

-Placebo arm: Placebo 1st cycle, followed by 2 cycles of TIP

-TIP arm: Three cycles of TIP

- Placebo: Missing data: Visit 2: 2 subjects; Visit 3: 1 subject; Visit 5: 3 subjects; Visit 7: 8 subjects; Visit 8: 7 subjects; Visit 9: 9 subjects; Visit 10: 9 subjects

- TIP: Missing Data: Visit 2: 1 subject Visit 3: 5 subjects Visit 5: 6 subjects Visit 7: 5 subjects Visit 8: 8 subjects Visit 9: 8 subjects Visit 10: 8 subject

For Cycle 1, there was more bronchoreactivity in the placebo arm. The implications of this are unclear (were excipient quantities in placebo responsible for this? Is tobramycin protective?). For Cycles 2 and 3, no clear trend was noted between arms. For the TIP arm, the number of events appeared somewhat stable over time. It should be noted that the amount of missing data increased as time went on and, thus, limits interpretation of results, especially in the setting of a small sample size.

C2302

Five subjects had a preferred term of ‘bronchospasm’ in the TIP group (1.6%) versus only one subject in the TOBI (0.5%) arm. All such subjects were in the oldest age group. If one looked at patients who had a related (including possibly or probably related) PT of ‘bronchospasm’ or ‘wheezing,’ 12 (3.9%) such subjects were in the TIP arm and 3 (1.4%) in the TOBI arm, almost all in the oldest age group. No event was considered serious and only one event in the TIP arm was considered severe (subject discussed below). All events in the TOBI arm were considered mild.

Airway reactivity was measured the same way as in C2301 (FEV1 measured both predose and up to 30 minutes post dose at Visits 2, 3, 5, 7, 8, 9, and 10). Table 12 below analyzes the number of subjects with a relative decline from baseline in FEV1 % predicted of $\geq 10\%$.

**Table 42: Number of Subjects with a Relative Decline from Baseline in FEV1 % Predicted of $\geq 10\%$, by Treatment Group and Visit
 All Randomized Safety Population, C2302**

		V2	V3	V5	V7	V8	V9	V10
TIP	≥ 10 to <20 % decline	33 (11%)	12 (4%)	14 (5%)	21 (7%)	19 (6%)	28 (9%)	17 (6%)
N=308	$\geq 20\%$ decline	3 (1%)	3 (1%)	3 (1%)	3 (1%)	2 (0.6%)	4 (1%)	1 (0.3%)
TOBI	≥ 10 to <20 % decline	23 (11%)	10 (5%)	8 (4%)	14 (7%)	8 (4%)	11 (5%)	12 (6%)
N=209	$\geq 20\%$ decline	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (1%)	2 (1%)	2 (1%)	3 (1%)

-TIP: Missing data: Visit 2: 6 subjects; Visit 3: 26 subjects; Visit 5: 50 subjects; Visit 7: 44 subjects; Visit 8: 79 subjects Visit 9: 75 subjects Visit 10: 103 subjects

-TOBI: Missing data: Visit 2: 1 subject; Visit 3: 28 subjects; Visit 5: 30 subjects; Visit 7: 27 subjects; Visit 8: 46 subjects Visit 9: 35 subjects Visit 10: 57 subjects

- percentages represent percent of All Randomized Safety population

Though there are obvious of limitations in interpretation due to the amount of missing data, the two drugs appeared relatively comparable in terms of airway reactivity. The TIP arm showed a modest decrease in airway reactivity over time.

One subject in the TIP arm had a wheezing event that was considered severe and related. This was a 23 year old female with a history of cystic fibrosis, asthma, sinusitis, and bronchiectasis. At visit 2, the subject had a relative decrease of FEV1% predicted of 11% from pre to post dose. Eight days later the subject had symptoms of chest tightness, wheezing, and shortness of breath that were considered moderate (chest tightness) and severe (wheezing, shortness of breath), related and resulted in

discontinuation from study drug and the study itself. The subject's steroid inhaler dose was also increased (budesonide).

In the TOBI arm, one subject was noted to have a related event under the preferred term 'bronchospasm'. However, on the dates the AE was noted, either no spirometry measurements were taken or showed a relative decrease in FEV1% predicted of < 10%. However, on subsequent 3rd on cycle visits, the subject was noted to have pre to post dose relative decreases of 14% and 28% and Visit 9 and Visit 10, respectively.

C2303

Airway reactivity was measured in the same manner in this trial as in the prior studies. As mentioned earlier, placebo in this trial was a powder made up of the excipients in TIP. The TIP powder in this trial was made through a different manufacturing process from earlier trials.

Table 43: Number of Subjects with a Relative Decline from Baseline of ≥ 10 % in FEV1 % Predicted By Treatment Group and Visit, Safety Population, C2303

		Visit 2	Visit 3
TIP N= 30	≥ 10 to <20% decline	3	4
	$\geq 20\%$ decline	1	0
Placebo N = 32	≥ 10 to <20% decline	3	3
	$\geq 20\%$ decline	0	2

-TIP: Missing data: Visit 2: 9 subjects; Visit 3: 6 subjects

-Placebo: Missing Data: Visit 2: 6 subjects Visit 3: 7 subjects

There are significant amounts of missing data so comparisons are limited. However, looking at observed data, there appear to be no real difference in airway reactivity between TIP and placebo.

A discussion of local airway events such as cough, dysphonia, and throat irritation are discussed further in section 7.4.1.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Related and Unrelated common adverse events were frequent. The overall adverse event profile and profile of particular adverse events is discussed in this section.

2301

50 % of subjects in the TIP arm and 76% of subjects in the Placebo arm had an AE during Cycle 1. Using a difference of 3 subjects between study arms to define preferred term adverse events that occurred with greater incidence, only 'pharyngolaryngeal pain' occurred at a higher level in the TIP arm (TIP 5 subjects vs. placebo 0 subjects). In the nonclinical studies, tobramycin was found to irritate the nasal and respiratory epithelium on histopathology and this adverse event may reflect that finding. In the placebo arm, only 'cough,' 'productive cough,' and 'migraines' occurred at a greater incidence. Cough/productive cough may represent symptoms of a pulmonary exacerbation. There did not appear to be any increase in ototoxicity, nephrotoxicity, neuromuscular weakness, allergic reactions, or diarrhea in the TIP arm based on reported adverse events.

Over three cycles, the most frequent adverse events (occurring in 3 or more subjects) in the TIP arm were 'cough,' 'lung disorder,' 'pyrexia,' 'dysgeusia,' 'pharyngolaryngeal pain,' 'upper respiratory tract infection,' 'dysphonia,' 'abdominal pain,' 'nasal congestion,' 'hemoptysis,' 'rhinitis,' and 'aspartate aminotransferase (AST) increased.' With no real placebo comparison over this time period, it is difficult to make any real assessments of this information.

Related Adverse Events

In the TIP arm, the most common related AEs were 'cough' (5 subjects), 'dysgeusia' (4 subjects), 'dysphonia' (2 subjects), and 'pharyngolaryngeal pain' (2 subjects). For the placebo arm, the most common related AEs after switching over to TIP were 'dysgeusia' (4 subjects), 'cough' (3 subjects), and 'dysphonia' (3 subjects). None of these related events in either arm were serious.

C2302

Because this was an open label trial, there is the possibility of bias against the study drug (TIP) in terms of both reporting and relatedness of adverse events. Several symptoms such as cough and dyspnea, though reported individually, are oftentimes likely to be related to concurrent pulmonary exacerbations, and thus their frequency is likely to be somewhat overstated.

There was a higher incidence of adverse events in the TIP group overall and by cycle, particularly in cycles 1 and 3. In the TIP arm, 90.3% of subjects reported an adverse event vs. 84.2% of subjects in the TOBI arm. Please note the sponsor table

below, though keep in mind that the incidences reported in cycles 2 and 3 for both arms would be slightly altered if discontinuations are taken into account and counted as subjects with AEs.

Table 44: Adverse Events, C2302, By Treatment and Cycle

	TIP	TOBI
Cycle 1 - total	308	209
# with AE	240 (78%)	139 (67%)
Cycle 2 - total	264	178
# with AE	177 (67%)	18 (66%)
Cycle 3 - total	234	171
# with AE	154 (66%)	100 (59%)

-Total is the number of patients in each cycle who received study drug
 -% is n/total in the specific cycle

System Organ Classes (SOCs) that had at least a 4% higher incidence of AEs in the TIP arm relative to the TOBI arm were the 'Respiratory, thoracic, and mediastinal disorders SOC,' 'General disorders and administration site conditions SOC,' and 'Nervous system disorders SOC.' Please note the sponsor table below. For the 'Respiratory, thoracic, and mediastinal disorders SOC,' the preferred terms (PTs) of 'cough,' 'lung disorder,' 'dyspnea,' 'oropharyngeal pain,' 'dysphonia,' 'throat irritation,' 'dyspnea exertion,' and 'nasal mucosa disorder' drove the disparity. For the General disorders and administration site conditions SOC, the differences were noted in the PTs 'pyrexia' and 'chest discomfort.' For the Nervous system SOC, the disparity was driven by the PT 'dysgeusia.' There was no real difference in the 'Renal and urinary disorders' SOC or the 'Ear and labyrinth disorders' SOC between treatment arms.

Table 45: Adverse Events by SOC and Treatment Group, All Randomized Safety population, C2302

	TIP N= 308	TOBI N=209
SOC		
Respiratory, thoracic and mediastinal disorders SOC	246 (80%)	141 (68%)
General disorders and administrative site conditions SOC	93 (30%)	45 (22%)
Nervous system disorders SOC	65 (21%)	34 (16%)

-% reflect percentages of all randomized safety population

The preferred terms (PTs) most frequently reported in both arms were 'cough' and 'lung disorder.' When looking at individual PTs, those whose incidence was at least 2% higher in the TIP arm relative to the TOBI arm were 'diarrhea,' 'pyrexia,' 'chest discomfort,' 'forced expiratory volume decreased,' 'blood glucose increased,' 'dysgeusia,' 'cough,' 'lung disorder,' 'oropharyngeal pain,' 'dyspnea,' 'dysphonia,' 'throat irritation,' 'dyspnea exertional,' and 'nasal mucosa disorder'. In the case of 'cough' and 'dysphonia,' the disparity was > 5%. Generally speaking, one could lump most of these PTs into a broad category of either local irritation or possible symptoms of a pulmonary exacerbation. Hemoptysis' was equivalent: 10 subjects (3.2%) TIP, 7 subjects (3.3%) TOBI.

Related Adverse Events

Overall, 51.0% of subjects in the TIP treatment group and 20.1% of subjects in the TOBI group had AEs suspected of being related to the treatment. Preferred terms which occurred in the TIP arm at a rate \geq 2% higher than that of the TOBI arm were 'chest discomfort' (3.2% TIP arm and 1.0% in the TOBI arm), 'dysgeusia' (3.9% versus 0.5% in the TIP and TOBI arms, respectively), 'cough' (25.3% in the TIP arm and 4.3% in the TOBI arm), 'dysphonia' (12.7% in the TIP arm and 3.3% in the TOBI arm), 'dyspnea' (5.5% versus 1.4% in the TIP and TOBI groups, respectively), 'oropharyngeal pain' and 'productive cough' (both 4.5% in the TIP arm and 1.0% in the TOBI arm), and 'throat irritation' (3.2% in the TIP arm and 1.0% in the TOBI arm). This related event profile is quite similar to the general adverse event profile (related or not) discussed above and again fall under the two general categories of local irritation and symptoms associated with a pulmonary exacerbation.

A few selected events of interest from this study are discussed in further detail below:

Neuromuscular weakness

Using the reported preferred terms 'asthenia' and 'muscular weakness,' 5 (1.6%) TIP subjects and 3 (1.4%) TOBI subjects were identified. No event was serious and only one subject in each arm had an event that was considered to be related. No event was severe.

Generalized allergic reactions

Using the reported PTs of 'hypersensitivity,' 'drug hypersensitivity,' 'rash,' 'macular rash,' 'papular rash,' 'erythematous rash,' 'urticaria,' and 'swollen tongue,' 15 (4.9%) subjects in the TIP arm and 8 (3.8%) subjects in the TOBI arm met this criteria. 5 subjects in the TIP arm were considered to have related events; no subjects in the TOBI

arm were considered to have related events. No events in the TIP arm were serious. No events in either arm were severe.

Clostridium difficile associated diarrhea or colitis

Using the reported preferred terms 'clostridial infections,' '*Clostridium difficile* colitis,' and 'diarrhea,' 14 subjects in the TIP arm (4.5%) and 8 subjects in the TOBI arm (3.8%) met such criteria. Only 3 subjects (all in the TIP arm) were thought to have related events. One subject had an event that was considered both serious and related, but this subject could not be fully assessed because of a loss to follow up. No event in the TIP arm was considered severe.

Hepatotoxicity

No preferred terms for a related liver failure event was noted for either arm. When analyzing reported preferred terms as 'ALT increased,' 'AST increased,' 'GGT increased,' 'blood alkaline phosphatase increased,' 'blood bilirubin increased,' 'hepatic enzymes increased,' 'transaminases increased,' and 'liver function test abnormal,' 8 (2.6%) subjects in the TIP arm and 2 (1.0%) subjects in the TOBI arm had such corresponding preferred terms; none of these events were considered serious or severe. Only 2 subjects had related such events, both in the TIP arm, however in both cases confounding factors existed (other medications, etc.). Moreover, inhaled aminoglycosides are modestly absorbed and have virtually no hepatic metabolism and would not be expected to have a profound effect on the liver.

Candidiasis

Using the reported preferred terms of 'vulvovaginal candidiasis,' 'vulvovaginal mycotic infection,' 'oropharyngeal candidiasis,' 'oral fungal infection,' 'oral candidiasis,' 'genital infection fungal,' and 'candidiasis,' 13 (4.2%) subjects in the TIP arm and (3.4%) 7 subjects in the TOBI arm had adverse events corresponding with such terms. 3 or 4 (unclear based on review) events were thought to be related in the TIP arm and only one event was thought to be related in the TOBI arm. The TIP events were a mix of both oral and vaginal infections. If only the preferred terms that specifically mention an oral candidal/fungal infection are used, 6 (1.9%) such subjects were noted in the TIP arm and none in the TOBI arm.

Blood Glucose Increased

There were 9 subjects in the TIP arm and only one in the TOBI arm that had a PT of 'blood glucose increased.' There was no real difference in other PTs such as 'hyperglycemia' or 'blood glucose fluctuation.' Of the 9 subjects in the TIP arm, 2 subjects were thought to have a related event and one of these events was considered serious. In one related nonserious event, the subject had associated diabetes mellitus

and glucose did not consistently elevate with treatment. Moreover, the increases occurred in the setting of possible infection. In the serious, related event a pulmonary exacerbation was occurring at the time of elevation and the subject was also receiving IV tobramycin. Moreover, given the background rate of diabetes in this population and the relative similarity between study drug and TOBI, a link between increased serum glucose and TIP is unlikely.

C2303

Eight subjects (26.7%) in the TIP arm and eleven subjects (34.4%) in the placebo arm reported at least one adverse event. Cough occurred in 3 subjects in the TIP arm and none in the placebo arm. Respiratory tract infection viral occurred in 3 subjects in the placebo arm and none in the TIP arm. No severe cases were reported.

Related adverse events

Five subjects (16.7%) in the TIP arm and two subjects (6.3%) in the placebo arm were felt to have adverse events related to the study drug. In the TIP arm, 3 subjects were noted to assess the adverse event 'cough' as related. Also in this arm, one subject each was noted to assess the adverse events of 'hypoacusis,' 'dysgeusia,' 'dysphonia,' 'infective pulmonary exacerbation of cystic fibrosis,' 'proteinuria,' and 'pulmonary hemorrhage' as related. In the placebo arm, an adverse event of 'hypoacusis' and 'bronchitis' were thought to be related.

Selected Local Airway Adverse Events

Cough (C2302)

Cough was reported as an AE in 48% of TIP patients and 31% of TOBI patients. When analyzing this AE by subgroup, all age and baseline pulmonary function groups had greater cough in the TIP arm relative to TOBI. Within the TIP arm, cough was present in higher numbers in the youngest age group (note: slightly different numbers of cases were found upon agency review; 4 more cases were found in the TOBI arm and 1 more case was found in the TIP arm).

Table 46: Cough by Age and Pulmonary Function Subgroups and Treatment Arm, C2302

	Age ≥6 to <13	≥13 to <20	≥20	Baseline FEV 1% Predicted ≥25 to <50%	≥50% to ≤75%

TIP	18/28= 64%	36/66= 55%	96/214= 45%	61/128= 48%	89/180= 49%
TOBI	4/18= 22%	16/48= 33%	49/143= 34%	29/89= 33%	40/120=33%

- PTs used for analysis were 'cough,' 'productive cough,' 'upper airway cough syndrome,' and 'post-tussive vomiting,'
 -denominators represent subgroups of All Randomized Safety population

Because cough can often be a sign of underlying cystic fibrosis disease or a pulmonary exacerbation, another way to evaluate this adverse event is to look at only those cough events that were thought by the investigator/subject to be related to the study drug. This might help separate instances of cough that may have occurred with drug administration from those cough events that were part of a pulmonary exacerbation. The following table analyzes those results.

Table 47: Cough (Possibly or Probably Related) As a Function of Demographic Subgroups and Treatment Arm, C2302

	Age ≥ 6 to <13 Years old	≥13 to <20	≥ 20	Pulmonary Function ≥25 to < 50% FEV1 % Predicted	≥50 to ≤75%	Sex Female	Male	Region Europe	LA	NA
TIP	11/28=39 %	18/66 = 27%	50/214 = 23%	34/122=28%	45/180= 24%	41/137= 30%	38/171 = 22%	26/104= 25%	1/9= 11%	52/195 = 27%
TOBI	0/18= 0%	1/48= 2%	8/143= 6%	2/95= 2%	7/114= 6%	6/94= 6%	3/115= 3%	2/71= 3%	1/7= 14%	6/131= 5%

-PTs analyzed were 'cough,' 'productive cough,' 'upper airway cough syndrome' and 'post-tussive vomiting'
 -Denominators represent subgroups of All Randomized Safety population
 -Europe includes Isreal and Australia, LA = Latin America, NA= North America

Both within the TIP arm and between both treatment arms, there is a predisposition to more cough in the youngest age group. However, given the small sample size of the youngest age group, these results must be viewed with caution.

There were 79 subjects in the TIP arm who reported a cough event possibly or probably related to study drug. 24 of these subjects eventually discontinued (though this does not necessarily have to be due to cough). 16 of these discontinuations occurred in cycle 1, 6 in Cycle 2, and 2 in Cycle 3. 70 subjects had events occurring in Cycle 1, 22 subjects had events occurring in Cycle 2, 13 subjects had events occurring in Cycle 3. 72 subjects had at least one cough event on treatment. 13 subjects had study drug stopped permanently due to AE; 12 subjects had dose interrupted, reduced, or delayed (though this does not have to necessarily be due to cough).

Of the 24 discontinuations, 19 were in ≥ 20 year old group (9%), 5 in ≥13 to < 20 adolescent group (7%); 8 were female (6%) and 16 male (9%); 6 were from Europe (6%) and 18 from US (9%); 10 had baseline/screening FEV1% predicted ≥ 50% (5%) and 14 had < 50% (11%)

A limited assessment, given missing data in this study, that can be made from the above data is that a quarter of TIP subjects had cough and almost a third of those

subjects eventually discontinued. Cough occurred a lot in the first cycle, but then was reported less frequently over cycles 2 and 3.

Dysphonia/aphonia

Using the PTs 'Dysphonia,' and 'aphonia' PT's, 40 subjects with such related AEs were found in the TIP arm. 34 subjects had such an event in Cycle 1; 11 subjects in Cycle 2; and 6 subjects in Cycle 3. 8 subjects discontinued, almost all in cycle 1, though the discontinuation was not necessarily due to dysphonia/aphonia. Of the 40 subjects, 21 were female (15%) 19 male (11%); 15 had baseline/screening FEV1 % predicted <50% (12%), and 25 had ≥ 50% (14%); 5 were in the ≥ 6 to <13 year old age group (18%), 7 in the ≥ 13 to < 20 year old group (11%), 28 in the ≥ 20 year old age group (13%); and 11 were in the Europe region (11%), 1 in LA (11%), and 28 in the US (14%).

Oropharyngeal pain, throat irritation, larynx irritation

Using the PTs 'oropharyngeal pain,' 'throat irritation,' and 'larynx irritation,' 23 subjects with such related AEs were found in the TIP arm. 19 subjects had such an event in Cycle 1; 7 subjects in Cycle 2; and 1 subjects in Cycle 3. 7 subjects discontinued, 4 subjects in cycle 1, though the discontinuation was not necessarily due to oropharyngeal pain, throat irritation, and larynx irritation. Of the 23 subjects, 14 were female (10%), 9 male (5%); 13 had baseline/screening FEV1 % predicted <50% (10%), and 10 had ≥ 50% (5%); 2 were in the ≥ 6 to <13 year old age group (7%), 4 in the ≥ 13 to < 20 year old group (6%), 17 in the ≥ 20 year old age group (8%); and 8 were in the Europe region (8%) and 15 in the US (8%).

As has been noted earlier, all rates should be interpreted cautiously given the amount of missing data/discontinuations in this study

7.4.2 Laboratory Findings

Please note appendix 2 for full details as well the above discussions of nephrotoxicity

7.4.3 Vital Signs

2301

Pulse: from baseline to end of on cycles, clinically insignificant mean decreases were noted in the TIP arm. No clear trends were noted pre to post dose.

Respiratory Rate: from baseline to end of on cycles, clinically insignificant mean decreases were noted in the TIP arm. No clear trends were noted pre to post dose.

Temperature: from baseline to end of on cycles, clinically insignificant mean increases were noted in the TIP arm. No clear trends were noted pre to post dose.

Systolic Blood Pressure: from baseline to end of on cycles, clinically insignificant mean decreases were noted in the TIP arm. Similar clinically insignificant decreases were noted pre to post dose.

Diastolic Blood Pressure: There was a median increase of 5 mmHg from baseline to the end of the 1st on cycle in the TIP arm but all other mean and median values at the end of on cycles showed either no change or clinically insignificant increases in this arm. No clear trends were noted pre to post dose.

Height: modest increase in mean height was noted from baseline to follow up for the TIP arm.

Weight: no clear trend could be noted from baseline to follow up for the TIP arm.

2302

Mean changes in the TIP arm in pulse, respiratory rate, temperature, systolic blood pressure, and diastolic blood pressure from baseline to a particular visit and from predose to 30 minutes post dose were not clinically significant.

No clear trends were noted with mean changes in the TIP arm in height from baseline to the end of the on cycles. Clinically insignificant mean increases in weight were noted from baseline to the end of on cycles. No clear trends were noted for BMI.

2303

Clinically insignificant decreases in mean pulse were noted from baseline to Day 28 in the TIP arm. A clinically insignificant mean increase was noted pre to 30 minutes post dose for this arm

Clinically insignificant increases in mean systolic and diastolic blood pressure were noted from baseline to Day 28 in the TIP arm. Similar clinically insignificant increases were noted pre to 30 minutes post dose for this arm.

Clinically insignificant increases in mean respiratory rate were noted from baseline to Day 28 in the TIP arm. No clear trends were noted pre to 30 minute post dose

No change was noted in mean temperature from baseline to Day 28 in the TIP arm or from pre dose to 30 minutes post dose.

No real change was seen in mean and median height from baseline to Day 28 for the TIP and placebo arm.

Very modest increases in mean weight (0.3-0.4kg) from baseline to Day 28 were seen in both the and placebo and TIP arms.

7.4.4 Electrocardiograms (Eggs)

Because this is an inhaled product with limited systemic absorption and also because aminoglycosides are not known to have significant ant arrhythmic potential, ECG recordings were not part of the safety evaluation.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted as part of this NDA; safety issues of interest were incorporated into the C2301, C2302, and C2303 phase 3 studies.

7.4.6 Immunogenicity

Immunogenicity studies do not apply to this non-protein compound

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was only one dose finding study (CTPI001) for TIP, and this study was a single dose, dose escalation study. Thus, the information that can be obtained from this study is limited.

In the CTPI001 study, there appeared to be an increasing rate of adverse events with increased dose. Please note the following table:

Table 48: Rate of TEAEs in CTPI001, by dose cohort

TOBI 300mg/5ml	30% (6 of 20 subjects)
----------------	------------------------

TIP 2 x 14mg	45%
TIP 4 x 14mg	54%
TIP 2 x 28mg	64%
TIP 3 x 28mg	67%
TIP 4 x 28mg	69%
TIP total	61% 40 of 66 subjects

Preferred terms that showed possible dose-associated increases in incidence were 'cough/cough aggravated' and 'dysgeusia,' and to a lesser extent 'lacrimation increased,' 'throat irritation,' 'dizziness,' and 'sputum increased.'

7.5.2 Time Dependency for Adverse Events

Please refer to sections 7.4.1 for a discussion of rates of selected adverse events (cough, dysphonia, oropharyngeal pain) over time. Also, please note that several long term studies are being planned to evaluate safety over a longer duration (i.e. > 6 months).

7.5.3 Drug-Demographic Interactions

Please refer to sections 7.4.1 for a discussion rates of selected adverse events (cough, oropharyngeal pain, dysphonia), in common demographic subgroups.

The table below looks at overall adverse events in study C2302 by subgroups

Table 49: C2302 Adverse Events by Subgroup, Safety Population

Subgroup		TIP	TOBI
		Total AEs, n= 278	Total AEs, n= 176
Gender	Male	148/171= 86.5%	100/115= 87%
	Female	130/137= 95%	76/94= 80.9%
Region	NA	180/195= 92.3%	117/131= 89.3
	Europe	91/104= 87.5%	54/71= 76.1%
	LA	7/9= 78%	5/7= 71%
Age	≥ 6 to < 13	25/28= 89.3%	15/18=83.3%
	≥ 13 to < 20	59/66= 89.4%	39/48= 81.3%
	≥ 20	194/214=90.7%	122/143=85.3%
Baseline FEV1% Predicted		112/122=92%	84/95=88%
	<50 % predicted		
	≥ 50 to < 80% predicted	166/186=89%	92/114= 81%

- percentages represent number of subgroup subjects with adverse events/ safety population demographics

Within the TIP arm, increased levels of adverse events were seen in females. A greater difference in adverse events rates between TIP and TOBI was seen in females and Europeans.

The following table looks at the pooled adverse event rates, by subgroup, for placebo portion of Study C2301 and C2303

Table 50: C2301 and 2303 Adverse Events by Subgroup, Safety Population

Subgroup	TIP	Placebo
	Total AEs, n= 31	Total AEs, n= 48
Gender Male	8/28= 29%	23/36= 64%
Female	23/48= 48%	25/45= 56%
Age ≥ 6 to < 13	12/36= 33.3%	25/39=64.1%
≥ 13 to < 20	16/34= 47.1%	23/39= 59%
≥ 20	3/6=50%	0/3=0%
Baseline FEV1% Predicted	12/24=50%	10/22=45%
<50 % predicted		
≥ 50 to < 80% predicted	15/39=38%	26/45= 58%
Missing	4/13=31%	12/14=86%

- percentages represent number of subgroup subjects with adverse events/ safety population demographics
- only represent Cycle 1 of study 2301 and 2303

Within the TIP arm, more AEs were seen in females, older population groups, and subjects with baseline FEV1% predicted < 50%. Differences between TIP and placebo were reduced (or actually worse in the TIP arm) for those same groups.

In the above pooled population adverse events that occurred in the TIP arm at an incidence 2% higher than that of the placebo arm were

- Dysgeusia: TIP 4 subjects (5.2%); 1 placebo subject (1.2%)
- Dysphonia: TIP 3 subjects (3.9%); 1 Placebo subject(1.2%)
- Pharyngolaryngeal Pain: TIP 5 subjects (6.5%); 0 Placebo
- Rash: TIP 2 subjects (only one of these on treatment) (2.6%); 0 Placebo

7.5.4 Drug-Disease Interactions

Patients with renal or hepatic disease were excluded from the phase 3 trials, so no formal examination of adverse event rates/profiles in such patients exists. However, it can generally be assumed that subjects with renal dysfunction may have larger serum

concentrations of tobramycin and have a higher frequency of tobramycin-related adverse events.

Patients with hemoptysis > 60 ml within 30 days prior to study were excluded from the phase 3 studies.

Three TIP patients had lung transplant prior to study drug therapy and all were on immunosuppressive medications. Two of the three completed the study, while another was lost to follow up. None of the three had an ototoxic event but one subject had nephrolithiasis. Renal function was normal. Only one of these subjects had PK measurements; these were within safe peak and trough tobramycin levels.

7.5.5 Drug-Drug Interactions

Please note the comments in section 7.2.5

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not performed for TIP. The sponsor is relying to some degree on nonclinical data gathered for the TOBI application. Please see Dr. Amy Ellis's pharmacology toxicology review for further details.

7.6.2 Human Reproduction and Pregnancy Data

No formal reproductive toxicology studies were performed for TIP. The sponsor is relying in part on nonclinical data gathered in part for the TOBI NDA. Please see Dr. Amy Ellis's pharmacology toxicology review for further details. However, the drug will be categorized as category D because of aminoglycosides' ability to cause fetal harm (congenital deafness) in pregnant patients.

The sponsor notes one subject who became pregnant during the phase 3 studies:

A report of pregnancy was received during the follow-up phase in Study C2302. Patient [PID C2302-0058-00303] was reported to be pregnant, with the estimated date of conception 37 days after last dose of TIP medication. The fetus was diagnosed with congenital

diaphragmatic hernia and congenital cystic lung. The outcome of the pregnancy was a successful delivery by caesarean section. The neonate was male, weighed 5 pounds 13 ounces (about 2.27 kg), 20 inches height (50.8 cm). The investigator did not suspect a relationship between the events (pregnancy, congenital diaphragmatic hernia and congenital cystic lung) and the study medication.

No other cases were noted in the latest PSUR

There were no reports of breast feeding during the phase 3 studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Height and weight measurements were taken during the phase 3 studies (see Vitals Signs Section 7.4.3). However, a formal study evaluating pediatric growth using established methodologies for measuring height and conversion to z scores was not prespecified.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of 'overdose' reported with exposure to TIP for the phase 3 studies and in the PSUR. The sponsor states that, *"the maximum tolerated daily dose of TIP has not been established. No adequate data exists for the impact of overdose with TIP capsules."*

Tobramycin has no known abuse potential.

Specific studies related to withdrawal and rebound effects of inhaled tobramycin have not been performed.

No new information on the above issues was provided in the PSUR.

7.7 Additional Submissions / Safety Issues

Two formal Human Factors Engineering studies were performed to evaluate patients ability to use the inhaler device and deliver a TIP dose properly, one in the US and one in the EU. The US study was formally reviewed by both DMEPA and CDRH, and they had significant concerns about 1) correct use of the drug/device combination and 2) validation of the Instructions For Use. Please see the Human Factors reviews by Alek Winiarski (DMEPA) and Quynh Nguyen (CDRH) for further details.

7 Postmarket Experience

In its 120 day safety update, relevant information included:

- 1) PSUR covering the period from Nov. 25, 2010, to Dec. 31st, 2011
- 2) Clinical Study Report for study C2303E1- a 3 cycle open label extension of study C2303

PSUR

31 events were reported during the reporting period: 10 serious, 21 nonserious. 20 events were unlisted. The vast majority of reactions were in the Respiratory, thoracic, and mediastinal SOC, followed by 'Infections and infestations SOC,' 'General disorders and administration site conditions,' 'Nervous systems disorders,' and 'Injury, poisoning and procedural complications' SOC. The most serious cases were in the Infections and Infestations SOC. Events of interest included a patient who could not tolerate more than 3 capsules at a time

There were several cases of cough reported related to drug (in many cases related to inhalation). Some cases resulted in discontinuation from drug. One case of reduced *Pa* susceptibility noted after TOBI podhaler administration but specifics of the case were sparse; there were 76 cumulative cases noted, but most preferred terms don't strictly deal with increased resistance. There were at least 4 cases of medication errors from spontaneous reports – two cases were related to accidental exposure to the tobramycin powder (a 7 year old got powder on her face; a nurse inhaled some powder after a patient coughed it out). Another case described inappropriate inhalation technique with TIP. There were reports of cough, dysgeusia, and angular cheilitis, but information that might help link drug to adverse event was quite lacking in most cases.

C2303E1

The baseline visit for this visit was visit 5 (visits 1-4 had taken place in the original C2303 trial). Visits took place monthly thereafter for three 28 day on/off cycles (visits 6-11). Subjects who had completed all visits in the original study, did not have acute pulmonary disease, did not have clinically significant laboratory abnormalities at visit 4 could opt to participate in this extension study. As in the original study, the TIP product used in this study was formulated with a new manufacturing process. 55 subjects were enrolled into the study and 52 subjects completed the study. 3 subjects discontinued,

one due to an AE, another due to withdrawal of consent , and a third due to administrative problems. There were 3 major protocol violations involving 3 subjects who did not complete all visits from the original study. Several minor protocol violations were related to missing laboratory data for renal parameters. 23 subjects were in a subset of the safety population that had audiology testing done.

Demographics

The mean age of the study population was 13 years old, with an age range of 6 to 21; two-thirds of the group were female. Median baseline FEV1% predicted was 70.4%. Slightly over a quarter of patients had a history of antipseudomonal use and macrolide usage.

Compliance

All subjects were exposed to study drug for > 21 days and almost all had compliance > 80%.

Antipseudomonal Usage and Hospitalization

5 subjects reported new usage of antipseudomonals in the extension study. There were three hospitalizations for respiratory-related events (discussed in SAEs).

Adverse events

26 subjects (47.3%) had a TEAE during the study. The number of adverse events slightly decreased from cycle to cycle (29.1%, 23.6%, and 23.1% in Cycles 2,3,4 respectively), however, if only the placebo patients from the original core study are analyzed, the percentage of subjects with an AE actually slightly increased from the first to the last cycle (the converse was true for the original TIP subjects from the core study). There is no clear explanation for this. The following sponsor table shows the all TEAEs by PT in descending order of frequency.

Table 51: Treatment Emergent Adverse Events, C2303E1

Preferred terms	Total N=55 n (%)
Patients with AE(s)	26 (47.3)
Cough	5 (9.1)
Respiratory tract infection	5 (9.1)
Dysphonia	3 (5.5)
Hypoacusis	3 (5.5)
Abdominal pain	2 (3.6)
Bronchopulmonary aspergillosis	2 (3.6)
Diarrhoea	2 (3.6)
Headache	2 (3.6)
Protein urine present	2 (3.6)
Pyrexia	2 (3.6)
Sinus polyp	2 (3.6)
Arthralgia	1 (1.8)
Ascariasis	1 (1.8)
Aspergillosis	1 (1.8)
Blood calcium decreased	1 (1.8)
Bronchitis	1 (1.8)
Dyspnoea	1 (1.8)

Preferred terms	Total N=55 n (%)
Gastrointestinal candidiasis	1 (1.8)
Hepatic enzyme increased	1 (1.8)
Hypoglycaemia	1 (1.8)
Lung infection	1 (1.8)
Middle ear effusion	1 (1.8)
Nasopharyngitis	1 (1.8)
Pneumonia	1 (1.8)
Productive cough	1 (1.8)
Protein urine	1 (1.8)
Rash	1 (1.8)
Respiratory tract infection viral	1 (1.8)
Sinusitis	1 (1.8)
Stenotrophomonas infection	1 (1.8)
Upper respiratory tract infection	1 (1.8)
Vaccination complication	1 (1.8)
Viral rhinitis	1 (1.8)
White blood cell count increased	1 (1.8)

Preferred terms are sorted in descending order of frequency

A patient with multiple occurrences of the same preferred term is counted only once in the preferred term

Source: [PT-Table 14.3.1-1.1a](#) to [PT-Table 14.3.1-1.1d](#)

Without a control arm, it is difficult to be able to draw any meaningful conclusions. Many of these TEAEs likely represent underlying disease or a pulmonary exacerbation. Several of the most common TEAEs mirror what was seen in the pivotal trials (cough, dysphonia, etc.). All TEAEs were reported as mild or moderate in severity. It is interesting to note that original placebo subjects reported certain PTs like cough and dysphonia at a higher rate than original TIP subjects. Whether this is a random finding or represents an attenuation of adverse events over time in the TIP arm is unclear (original TIP arm for cough does not bear this theory out).

Related AEs

10 subjects had drug related AEs. PTs where more than one subject reported a related AE included hypoacusis, dysphonia, and protein urine present. Other related AEs were cough, diarrhea, productive cough, pyrexia, and rash.

Deaths

There were no deaths in this study.

SAEs

3 (5.5%) subjects had an SAE, all due to hospitalizations for pulmonary events (moderately severe lung infection, moderately severe pneumonia and, mildly severe aspergillosis).

The first SAE involved 13 year old male with CF who had been on placebo in the initial core study. Nine days after starting TIP in the extension study, he was diagnosed with 'aspergillosis' and hospitalized a month later. During hospitalization he was treated with an antifungal (voriconazole) and antimicrobial (ampicillin-sulbactam). He was discharged 10 days later and went on to complete the study.

The second SAE involved an 8 year old female with a history of cf, bronchiectasis, and percutaneous gastrostomy who had been assigned to placebo in the core study. During the on cycle of the core study, the subject was hospitalized with pneumonia for a week and treated with cefoperazone and netilmicin. The subject was enrolled into the extension study and during the on cycle of Cycle 3, she was again hospitalized with pneumonia and treated with antipseudomonals; she was discharged a week later. It should also be noted that this patient went on to enroll in the second extension study (C2303E2) and during the first on cycle was again hospitalized with pneumonia and treated with antipseudomonals for almost 2 weeks.

The third AE involved an 18 year old female with a history of diabetes, asthma, and mitral valve prolapse, who had been enrolled into the placebo arm of the core study. She enrolled into the TIP extension and had baseline FEV1% predicted of 44.2% at that time. At the end of on cycle 3, FEV1 % predicted was 47.5%. During off cycle 3, the subject was hospitalized for lung infection, treated with ceftazidime, and discharged 18 days later.

Discontinuations

1 subject discontinued due to a TEAE, primarily for the adverse event of hypoacusis. This event involved a 17 year old female who was randomized to placebo for the initial core study. At the end of the on cycle of the core study, the subject was found to have decreased hearing on audiometry (decrease in hearing of 10 dB at 4, 6, and 8 kHz bilaterally). No serum tobramycin was detected as subject was on placebo. At end of off cycle of core study, subject had improved but still had decreased hearing (right ear decrease of 5 and 10 dB at 6 and 8 kHz, respectively; left ear 5 dB, 5 dB, 10 dB decrease at 4, 6, and 8 kHz, respectively). The subject went on to enter into the TIP extension study. At the end of the on cycle 2 of the extension study, the subject was noted to have a decrease in hearing of 20dB bilaterally and the medication was permanently discontinued. The decrease was 20 dB, 10 dB, and 20dB in the 0.25, 0.5, and 1 kHz frequencies in the right ear and in 20 dB, 20 dB, and 10 dB in the 0.25, 0.5, and 1 kHz in the left ear. This adverse event of hypoacusis was thought to be related to study drug, although bone conduction study seemed to show a conductive hearing loss. It should be noted that the subject reported AEs of middle ear effusion and sinus polyps

28 days after discontinuation. At end of study, subject still had decreases in hearing from core study baseline at multiple frequencies.

Airway reactivity

10 (18%) subjects had absolute decreases in FEV1% predicted of at least 10%. From pre dose to 30 minutes post dose (though in many cases the post dose measurement took place beyond 30 minutes). 5 (9%) subjects had a relative decrease in FEV1% predicted of at least 20% from pre to post dose measurements.

Ototoxicity

Twenty two subjects had audiology testing done in the core study at baseline.

One subject had a decrease in hearing of 10dB at the 0.25 and 0.5 kHz of the right ear frequencies at both the end of the on cycle 2 and the end of the on cycle 3 of the extension study. By termination visit this abnormality had resolved. This subject also had hearing complaints.

A second subject has been described above in Discontinuations.

A third subject had decreases of 10dB at 3 adjacent frequencies in the right ear and 4 adjacent frequencies in the left ear at the beginning of the extension study. This continued to end of the on cycle of Cycle 3. The subject had hearing complaints at the time. By the end of cycle 4, all abnormalities had resolved.

Another subject had decreases of 10 dB at 0.25 and 0.5 kHz in the left ear at the end of the third cycle of the extension study. The subject had no hearing complaints.

All adverse events related to ototoxicity stemmed from abnormal audiograms and not from spontaneous report.

Safety Reports

Safety reports of adverse events from the past year were reviewed. They did not provide new information. Events included those already being monitored (such as hemoptysis and hearing loss), could reflect underlying disease (such as hemoptysis and pulmonary exacerbations), reflected known side effects (such as dysphonia, chest tightness, cough/productive cough), or did not have enough information to assess a relationship between an event and TIP.

9 Appendices

9.1 Literature Review/References

American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring

<http://www.audiology.org/resources/documentlibrary/Documents/OtoMonPositionGuideline.pdf>

9.2 Labeling Recommendations

These have been incorporated into the proposed label and is currently being negotiated with the sponsor.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was held to discuss the relevant issues of this application. By a vote of 13 to 1, there was virtually unanimous support for approval of this drug. The lone dissent was the consumer representative. It should be noted that the sponsor was allowed to present copious anecdotal evidence (from clinicians and patients) as well as data from studies not previously evaluated by the Agency. It is the opinion of this reviewer that such evidence strongly swayed committee opinion and did not allow for nuanced discussion of the study drug. Reasons given for approval included:

- the belief that equivalence of TIP and TOBI had been demonstrated and that TIP provided another treatment option for these patients
- this was a treatment population that was difficult to study and needed treatment options
- C2301 showed statistically significant evidence of efficacy, while C2303 provided supportive evidence
- TIP was essentially similar to TOBI; tobramycin was not a novel compound; no real safety issues other than tolerability issues
- No difference noted in nephrotoxicity and ototoxicity between TIP and TOBI; no clear data that resistant organisms can be transmitted to outside population

- Increased treatment options, no compelling safety data, close follow up of patients occurs in clinics
- Demonstrated efficacy over placebo and there was similar pharmacokinetic data
- Suggestion of efficacy in C2302 study; great training in CF centers; difficult to do another study
- No strong safety concerns and comparable efficacy with TOBI; some flaws in study design are unavoidable
- Efficacy similar in the setting of no strong safety signal with TIP
- Vast experience with TOBI gives comfort with approval of TIP
- C2301 was enough to demonstrate efficacy

Reasons for caution and recommendations to improve safety included:

- Provide CD/digital media to enhance training
- Not clear that adherence will be improved
- Poor studies with lots of missing and compromised data; no longitudinal data
- Bronchospasm issue should be followed closely
- Deaths in TIP arm are concerning; dyspnea and wheezing may be issues- can follow closely with peak flows
- Need long term data to see if benefit attenuates with time
- May need formal postmarketing studies to evaluate clinical outcomes

Appendix 1: Full Laboratory Analysis C2301, C2302, C2303

Appendix 2: Brief Discussion of Phase 1 Studies (INH007, CTPI001)

Appendix 2: Laboratory analysis C2301, C2302, and C2303

Note: Rates taken on total safety populations, however these evaluations limited by amount of missing data.

2302

Hematology

Hemoglobin:

No significant difference seen in mean changes from baseline; Shift tables did not show an increased shifts from high to normal, or normal to low in the TIP arm relative to TOBI

Absolute eosinophils:

No real difference in mean or median increases from baseline in eosinophils between TOBI and TIP; no real difference in shift tables;

Absolute neutrophils:

The mean and median differences were not clinically significant between both arms; no real difference in shift tables; 3 (1%) cases in TIP and none in TOBI had postbaseline absolute neutrophil values < 1000 cells/microliter. In these cases, only in one case did decreases have concordance with on cycles. All 3 subjects had normal values by visit 11.

Platelet count:

The mean and median differences were not clinically significant between both arms; no real difference between shift tables. In 3 (1%) cases of TIP and 2 (1%) cases of TOBI were there post-baseline platelet counts of $\leq 100,000$ platelets/microliter. In all 3 TIP cases the decreased levels did not clearly track with on cycles and were $>100,000$ platelets/microliter upon last recorded lab value. 43 (14%) and 34(16%) TOBI had post baseline platelet levels $>500,000$ platelets/microliter.

Leukocyte count:

The mean and median differences between both arms were not clinically significant; no real difference in shift tables. 8 (3%) TIP subjects and 4 (2%) TOBI subjects had postbaseline levels ≤ 3000 cells/microliter. 46 TIP (15%) and 37 (18%) TOBI subjects had post baseline assessments $\geq 15,000$ cells/microliter.

Absolute lymphocytes

Mean changes in serum absolute lymphocytes were clinically insignificant. No clear trends or clinically significant changes could be identified in shift tables. 4 subjects in the TIP arm and 6 in the TPBI arm had a serum post-baseline absolute lymphocyte value count ≤ 500 cells/microliter. 3 subjects in the TIP arm and none in the TOBI arm had a serum post-baseline absolute lymphocyte count ≥ 6000 cells/microliter

Absolute monocytes

Mean changes in serum absolute monocytes were clinically insignificant. No clear trends or clinically significant changes could be identified in shift tables. 23 (7.5%) subjects in the TIP arm and 14 (6.7%) subjects in the TOBI arm had postbaseline serum absolute monocyte counts ≥ 1000 cells/microliter. No value was > 1500 cells/microliter.

Absolute basophils

Mean changes in serum absolute basophils were clinically insignificant. No clear trends or clinically significant changes could be identified in shift tables. 59 (19%) TIP subjects and 49 (24%) TOBI subjects had post-baseline serum absolute basophil counts > 200 cells/microliter.

Serum Chemistry

Creatinine

The mean and median differences do not show one agent to be more nephrotoxic than the other; differences appear clinically insignificant; only 2 subjects in the TIP arm and 2 subjects in the TOBI arm had postbaseline serum creatinine levels ≥ 1.5 mg/dl. One TOBI subject is likely to have been laboratory error as it is markedly different from prior and subsequent readings. No real difference in shift tables. There was no real difference between the two arms in terms of subjects who had a 50% increase from baseline in creatinine.

AST

No clinically significant difference in terms of changes in mean and median values were noted over course of study. No real difference in shift tables. 5 subjects (2%) in the TIP arm and 9 subjects (4%) in the TOBI arm had post baseline values ≥ 100 U/L. The highest value was in a TIP subject with a recorded value of 557 at visit 7, four weeks after last dose of study medication. This subject had a history of chronic pancreatitis and was hospitalized 3 days after abnormal reading for endobronchitis. The patient did not complete study because was started on TOBI while hospitalized. At termination visit, the value had normalized.

ALT

No real differences in shift table. No clinically significant difference in mean and median tables over course of study. 11 (4%) of TIP subjects and 16 (8%) of TOBI subjects had a post baseline ALT value of >100 U/L. The highest value was 352 U/L recorded in a TOBI subject at an unscheduled visit.

Alkaline phosphatase

No clinically significant difference in mean and median tables was noted over the course of the study. No real differences in shift tables. 113 (37%) TIP Subjects and 86 (41%) TOBI subjects had postbaseline values ≥ 150 U/L. A large portion of these individuals (over half in both arms) were subjects ≤ 18 years old who generally have higher levels of alkaline phosphatase normally. Also, CF patients themselves oftentimes have underlying liver disease/biliary sludging.

BUN

No significant differences between treatment arms were noted in terms of mean and median shifts over course of study. No real differences in shift tables. 17 (6%) subjects in the TIP arm and 8 (4%) subjects in

the TOBI arm had a 100% increase from baseline in serum BUN. 18 (6%) subjects in the TIP arm and 12 (6%) subjects in the TOBI arm had postbaseline measurements $\geq 25\text{mg/dl}$.

Sodium

Mean changes in serum sodium were clinically insignificant and also similar between both arms. No significant differences were noted on shift tables. No subjects in either arm had a post-baseline value $> 150\text{ meq/L}$. 5 subjects in each arm had a post-baseline value $\leq 130\text{meq/L}$.

Potassium

Mean changes in serum potassium were clinically insignificant and also similar between both arms. No significant differences were noted on shift tables. No subjects in the TIP arm had values post-baseline values $\leq 3\text{ meq/L}$. 7 (2.3%) subjects in the TIP arm and 3 (1.4%) subjects in the TOBI arm had post-baseline values $\geq 5.5\text{meq/L}$.

Glucose

Mean changes in serum glucose were clinically insignificant and also similar between both arms. No clear trends could be identified in shift tables. 36 (12%) TIP subjects had post-baseline values $\leq 60\text{mg/dl}$; 21 (10%) such subjects were in the TOBI arm. 54 (18%) subjects in the TIP arm and 38 (18%) in the TOBI arm had post-baseline measurements $\geq 200\text{mg/dl}$. However, the highest values were located in the TIP arm including one subject with a value of 1658 mg/dl . This value most likely was lab error (this subject had a history of pancreatic insufficiency and impaired glucose tolerance and was withdrawn from trial due to an adverse event); the lab result is not explained or discussed further in case narrative or CRF.

Bicarbonate

Mean changes in serum bicarbonate were clinically insignificant and also similar between both arms. No clear trends could be identified in shift tables. 127 (41%) TIP subjects and 81 (39%) TOBI subjects had post-baseline serum bicarbonate levels $\leq 21\text{ meq/L}$. 13 (4% TIP and 6% TOBI) subjects in each arm had post-baseline serum bicarbonate levels $\geq 30\text{meq/L}$.

Serum Calcium

Mean changes in serum calcium were clinically insignificant and also similar between both arms. No clear trends could be identified in shift tables. Only one subject in each arm had a post-baseline serum calcium value $\leq 8\text{mg/dl}$. 9 (3%) subjects in the TIP arm and 5 (2%) in the TOBI arm had post-baseline serum calcium values $\geq 10.5\text{ mg/dl}$. The highest value recorded was a value of 37mg/dl in a TIP subject- this is likely lab error (the same subject had a serum glucose of 1658 mg/dl at the same visit). Only 3

pediatric subjects in the TIP arm (none in TOBI arm) had post-baseline serum values ≤ 8.5 mg/dl; pediatric subjects have a slightly higher lower limit for serum calcium than adults.

Serum Chloride

Mean changes in serum chloride were clinically insignificant and also similar between both arms. No clear trends could be identified in shift tables. No subjects in either arm had a post-baseline serum chloride value ≤ 90 meq/L. Only one subject (in the TIP arm) had a post-baseline serum chloride value ≥ 110 meq.

Direct Bilirubin

Mean changes in serum direct bilirubin were clinically insignificant and also similar between both arms. No clear trends or clinically significant changes could be identified in shift tables. Two subjects in the TOBI arm and 1 in the TIP arm had post-baseline serum direct bilirubin values ≥ 0.5 mg/dl.

GGT

Mean changes in serum GGT were clinically insignificant and also similar between both arms. No clear trends or clinically significant changes could be identified in shift tables. 47 (15%) subjects in the TIP arm and 41 (20%) subjects in the TOBI arm had post-baseline serum GGT values ≥ 50 U/L. 19 TIP pediatric subjects and 15 TOBI pediatric subjects had serum GGT post-baseline values ≥ 35 U/L; the upper limit of normal in children is generally lower than in adults.

Phosphate

Mean changes in serum phosphate were clinically insignificant and also similar between both arms. No clear trends or clinically significant changes could be identified in shift tables. 70 TIP (30% of adults) and 45 (27% of adults) TOBI subjects ≥ 18 years old had post-baseline serum phosphate levels ≥ 4.5 mg/dl. 7 (3% of children) TIP and 4 (2% of children) TOBI pediatric subjects had post-baseline serum phosphate levels ≥ 6.0 mg/dl. 12 (16% of children) TIP subjects and 8 (18% of children) TOBI pediatric subjects post-baseline serum phosphate levels ≤ 3.5 mg/dl. 17 (7% adults) TIP and 18 (11% adults) TOBI subjects ≥ 18 years old had post-baseline serum phosphate levels ≤ 2.5 mg/dl. High/low thresholds vary between pediatric and adult patients.

Total Bilirubin

Mean changes in serum total bilirubin were clinically insignificant and also similar between both arms. No clear trends or clinically significant changes could be identified in shift tables. 11 TIP (4%) subjects and 4 (2%) of TIP subjects had post-baseline serum total bilirubin values ≥ 1.5 mg/dl. One individual had total bilirubin levels as high as 10 mg/dl. This appeared to be mostly indirect bilirubin and may have been the result of hemolysis (low hgb levels present, but potassium levels normal; no CRF provided).

Total Protein

Mean changes in serum total protein were clinically insignificant and also similar between both arms. No clear trends or clinically significant changes could be identified in shift tables. 7 TIP (2%) subjects and 2 (1%) TOBI subjects had post-baseline serum total protein levels > 9.0 g/dl. Only one subject (in the TIP arm) had a post-baseline serum total protein value < 5.5 g/dl. This subject had value of 0.7 g/dl at an unscheduled visit, but this is likely to be lab error given considerable abnormalities in other lab values for this subject at this visit, including a serum glucose level of 1658 mg/dl and serum calcium level of 37 mg/dl.

C2301- Only Cycle 1 evaluated (Placebo controlled cycle)

Hematology

Absolute basophils

Differences in mean changes in serum absolute basophils were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Absolute eosinophils

Differences in mean changes in serum absolute eosinophils were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Absolute lymphocytes

Differences in mean changes in serum absolute lymphocytes were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Absolute Monocytes

Differences in mean changes in serum absolute monocytes were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Absolute Neutrophils

Differences in mean changes in serum absolute neutrophils were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Hgb

Differences in mean changes in serum hemoglobin were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Leukocytes

Differences in mean changes in serum leukocytes were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Platelet Count

Differences in mean changes in serum platelet count were clinically insignificant between both arms over the first cycle. No consistent trends were noted on shift tables.

Serum Chemistry

ALT

Mean changes in the TIP arm over the 1st cycle were clinically insignificant; a mean decrease of 25 units occurred in the placebo arm. Median changes did not markedly differ between the two arms and were clinically insignificant. There appeared to be more shifts into the 'high' category for the TIP arm. However, no values exceeded greater 100U/L in either the TIP or placebo arm during the course of the study.

Alakaline Phosphatase

Mean changes did not markedly differ between the two arms over the 1st cycle and were clinically insignificant. No clinically significant differences were noted in the shift table.

AST

Mean changes in the TIP arm over the 1st cycle were clinically insignificant; a mean decrease of 17 units occurred in the placebo arm. Median changes did not markedly differ between the two arms and were clinically insignificant. There appeared to be more shifts into the 'high' category for the TIP arm. However, no values exceeded greater 100 U/L in either the TIP or placebo arm during the course of the study.

Bicarbonate

Mean changes did not markedly differ between the two arms and were clinically insignificant. There appeared to be more shifts in the TIP arm into the 'low' category. 6 (13%) subjects in the TIP arm and 2 (4%) subjects in the placebo arm had values < 20 meq/L at Day 28. Two subjects receiving TIP had a serum bicarbonate post-baseline level of 15 meq/L or less over the course of the study. One subject had improved values of 20 meq/L or greater at subsequent visits. Another subject had fluctuations in levels that did not clearly correspond with treatment.

BUN

Mean changes did not markedly differ between the two arms and were clinically insignificant over the 1st cycle. No clear trends could be identified from shift tables. Only 2 TIP subjects had an increase of at least 100% in BUN values from Visit 2 to Visit 5; there were no such subjects in the placebo arm over the same time period. In the first TIP subject, the BUN increased from 5 mg/dl to 10 mg/dl from visit 2 to 5 but then

decreased over subsequent visits and was 7 mg/dl by visit 10. Another TIP subject had values increase from 8 mg/dl to 20 mg/dl from visit 2 to visit5, but had dropped to 12 mg/dl by visit 10.

Calcium

Mean changes did not markedly differ between the two arms and were clinically insignificant over the 1st cycle. No clear trends were identified by shift tables.

Chloride

Mean changes did not markedly differ between the two arms and were clinically insignificant over the 1st cycle. No clear trends were identified by shift tables.

Creatinine

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. Both the TIP and placebo (after TIP switch) arms showed mild increases in mean creatinine by the end of the third cycle (mean increase of 0.04 mg/dl in the TIP arm at Day 28 of cycle 3 and 0.05 mg/dl at Day 28 of cycle 3 for the placebo/TIP arm). This appears to be clinically insignificant and in the TIP arm, appeared to partially reverse by the end of the 3rd off cycle. 4 subjects in the placebo arm had an increase of 50% in serum creatinine from visit 2 to visit 5; no subjects had such changes in the TIP arm over the same period. The highest post-baseline creatinine level recorded in a subject receiving TIP was 1.6 mg/dl. However, this subject had a baseline level of 1.3 mg/dl which increased to 1.4 while receiving placebo, then decreased to 1.3 mg/dl at Visit 10 after switch to TIP. At follow up the level had increased to 1.6 mg/dl.

Direct Bilirubin

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. No clear trends can be discerned from shift tables. No post-baseline value in the TIP arm was greater than 0.4mg/dl from Visit 2 to Visit 5.

GGT

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. No clear trends could be identified from shift tables.

Glucose

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. Glucose changes during on cycles of TIP (in both arms) was not consistent- at times levels decreased, increased, or did not change from baseline while on therapy with TIP. No clear trends could be identified from shift tables.

Phosphate

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. There appeared to be more shifts into the 'high' category in the TIP arm. 31 subjects in the TIP arm and 29 in the placebo arm had serum Visit 5 values > 4.5 mg/dl. However only 2 such subjects in each of these arms were ≥ 18 years old; serum thresholds for pediatric patients are generally higher.

Potassium

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. No clear trends could be identified on shift tables.

Sodium

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. No clear trends could be identified from shift tables.

Total bilirubin

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle. No clear trends could be identified from shift tables.

Total Protein

Mean changes did not markedly differ between the two arms and were clinically insignificant over the first cycle.

C2303

Hematology

Absolute basophils

There appeared to be a decrease in median serum absolute basophils during the on cycle in the TIP arm relative to placebo; this is unlikely to be clinically significant. No clinically significant differences between the two arms were noted on shift tables.

Absolute Eosinophils

There appeared to be a median increase in serum eosinophils in the on cycle for the TIP arm relative to placebo. No clinically significant differences between the two arms were noted on shift tables.

Absolute Lymphocytes

No clinically significant differences in median changes in serum absolute lymphocytes from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends could be noted on shift tables.

Absolute Monocytes

There appeared to be a median increase in serum absolute monocytes from baseline to Day 28 of the TIP arm relative to placebo. No clear trends could be noted on shift tables.

Absolute Neutrophils

There appeared to be a median decrease in serum absolute neutrophils from baseline to Day 28 of the TIP arm relative to placebo. No clear trends could be noted on shift tables.

Hgb

No clinically significant differences in median changes in serum hemoglobin from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends could be noted on shift tables.

Platelets

There appeared to be a median decrease in serum platelets from baseline to Day 28 of the TIP arm relative to placebo. No clear trends could be noted on shift tables.

Leukocytes

There appeared to be a median decrease in serum platelets from baseline to Day 28 of the TIP arm relative to placebo. No clear trends could be identified on shift tables.

Serum Chemistry

Alkaline phosphatase

No clinically significant differences in median changes in serum alkaline phosphatase from baseline to Day 28 were seen between the TIP and placebo arm. On shift table, there was a slight trend toward more subjects going from the 'normal' to the 'high' category in the TIIP arm compared to placebo. 14 (47%) subjects in the TIP arm and 13 (41%) subjects in the placebo arm had a value > 200 at visit 3. The highest value recorded at this visit was in a placebo patient (598 U/L).

Direct Bilirubin

No clinically significant differences in median changes in serum direct bilirubin from baseline to Day 28 were seen between the TIP and placebo arm. No clinically significant trends were noted on shift tables.

Total Bilirubin

No clinically significant differences in median changes in serum total bilirubin from baseline to Day 28 were seen between the TIP and placebo arm. No clinically significant trends were noted on shift table.

BUN

No clinically significant differences in median changes in serum BUN from baseline to Day 28 were seen between the TIP and placebo arm. Median change from baseline to Day 28 in the TIP arm was an increase of 2mg/dl. In the placebo arm, there was an increase of .14 mg/dl. No clear trend was identified on shift tables. The highest value noted at visit 3 was in the TIP arm (17.7 mg/dl). 1 (3%) subject in the TIP arm and none in the placebo arm had an increase in serum BUN of 100% from baseline to Day 28.

Calcium

No clinically significant differences in median changes in serum calcium from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified on shift tables.

Chloride

No clinically significant differences in median changes in serum chloride from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified on shift tables.

Creatinine

No clinically significant differences in median changes in serum creatinine from baseline to Day 28 were seen between the TIP and placebo arm. Median change from baseline to Day 28 in the TIP arm was an increase of 0.06 mg/dl. In the placebo arm, there was a decrease of .006 mg/dl. No clinically significant trends were identified. The highest value noted at Visit 3 was in the TIP arm (0.78 mg/dl). 3 (10%) of TIP subjects and 1 (3%) placebo subject had an increase in serum creatinine of 50% from baseline to Day 28.

GGT

No clinically significant differences in median changes in serum GGT from baseline to Day 28 were seen between the TIP and placebo arm. No clinically significant trends were identified on shift table.

Glucose

No clinically significant differences in median changes in serum glucose from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified on shift tables.

Phosphate

No clinically significant differences in median changes in serum phosphate from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified on shift tables.

Potassium

No clinically significant differences in median changes in serum potassium from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified on shift tables

AST

No clinically significant differences in median changes in serum AST from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified from shift tables.

ALT

No clinically significant differences in median changes in serum ALT from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were identified from shift tables.

Bicarbonate

No clinically significant differences in median changes in serum bicarbonate from baseline to Day 28 were seen between the TIP and placebo arm. No clinically significant differences were noted on shift tables.

Sodium

No clinically significant differences in median changes in serum sodium from baseline to Day 28 were seen between the TIP and placebo arm. No clinically significant differences were noted on shift tables.

Total protein

No clinically significant differences in median changes in serum total protein from baseline to Day 28 were seen between the TIP and placebo arm. No clinically significant trends were noted on shift tables.

Uric Acid

No clinically significant differences in median changes in serum uric acid from baseline to Day 28 were seen between the TIP and placebo arm. No clear trends were noted on shift tables.

No subject in either arm met Hy's law in any of the phase 3 studies

Urinalysis

2301

3 subjects in the TIP arm had 1+ proteinuria develop during study, 2 of which had trace proteinuria at baseline

3 subjects in the placebo arm had proteinuria of 1+ all after TIP switch. One subject had 2+ proteinuria; this subject had trace proteinuria by cycle 3.

2303

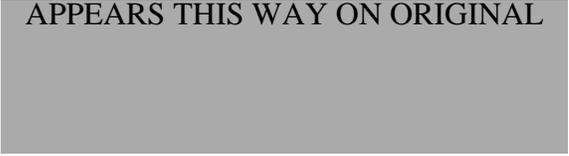
One subject in the TIP arm developed 2+ proteinuria on Day 29 that persisted; this patient also had a mild related AE of proteinuria. The subject was an 11 year old girl who did not have an elevated creatinine or BUN throughout the study.

No placebo subjects developed 1+ proteinuria

2302

In the TIP treatment group, five patients had positive protein (1+ or greater) urinalysis results for at least 2 consecutive visits. Of these patients, four had had positive assessments at screening. In the TOBI treatment group, two patients had two consecutive urinalysis results positive for protein, of whom one had had a positive screening assessment. 12 TIP subjects and 7 TOBI subjects had a postbaseline level of proteinuria \geq 2+ that was also increased from baseline levels.

APPEARS THIS WAY ON ORIGINAL



Appendix 3: Phase 1 Trial Reviews: INH007 and CTPI001

Phase 1 Study: TBM100INH007

The objective of this study was both to assess individual and intrasubject variability in lung deposition of tobramycin powder and to compare the pharmacokinetics of tobramycin powder and TOBI

Study Design

Enrolled healthy volunteers inhaled one capsule of radiolabeled tobramycin powder on 3 separate occasions for the purpose of assessing lung deposition in each instance. Then the enrollees inhaled a dose of radiolabeled nebulized tobramycin at a separate visit followed by an inhalation of 6 capsules of tobramycin powder a week later. At the fourth visit, both PK and lung deposition of TOBI was measured, while at the fifth visit only the PK of six capsules of TIP was measured. Please note the sponsor table below outlining the study design. The six capsule inhalation of tobramycin powder was thought to be equivalent, and thus provide a valid comparison, to a single dose of TOBI.

Safety monitoring included pre and postdose pulmonary function testing, screening and poststudy laboratory measurements, and monitoring of vital signs and adverse events.

Table 1: Study INH007 Trial Design

Treatment	Part I			Part II	
	A	A	A	B	C
Regimen	1 inhalation of Tobramycin PulmoSphere	1 inhalation of Tobramycin PulmoSphere	1 inhalation of Tobramycin PulmoSphere	Inhalation of nebulized tobramycin (TOBI)	6 inhalations of Tobramycin PulmoSphere
Nominal dose* (mg)	13.3	13.3	13.3	300	80
Assessment	Deposition	Deposition	Deposition	Deposition and PK	PK only
Overnight stays	None	None	None	2 night stay	2 night stay
Interdose interval	At least 4 days			At least 7 days between B and C	

*tobramycin free base

Subjects had to be between 18-50 years old, in good health, and have a baseline FEV1 % predicted > 80%. 14 patients were randomized and 12 completed the protocol. One subject discontinued after the first dose of Part A and another discontinued after receiving the Part B dose. Both discontinuations were reportedly due to scheduling conflicts.

Safety Discussion

Adverse Events

8 of 14 subjects had 23 treatment emergent adverse events. All AEs were mild, nonserious, and did not result in discontinuation. In Treatment Period A, 5 of 14 subjects had an AE. In treatment period B 3 of 13 subjects had an AE. In treatment period C, 4 of 12 subjects had an AE. There were no deaths.

There were eleven episodes of cough in six subjects, 10 of which were considered to be treatment related. 5 subjects had cough after treatment period A and 2 after treatment period C. Only 3 other AEs were considered treatment related- headache (treatment B), wheezing (treatment B and C) and fatigue (treatment A). Other AEs occurring after either Treatment A or C included 'blood creatine phosphokinase increased, catarrh, eye injury NOS, lymphadenopathy, pharyngitis NOS, and pharyngolaryngeal pain.

Bronchoreactivity:

One subject had a >10% absolute decrease in FEV1% predicted from pre to 30 minutes post dose at the 3rd treatment visit of period A; no other such changes were noted in the study.

Phase 2 study: TBM100CTPI-001

Study Design:

This was a randomized, open label, sequential cohort, active controlled, dose escalation, single dose study designed to primarily assess the safety of TIP. A secondary objective was find a dose of TIP that would have comparable PK to TOBI based on single-dose PK of tobramycin.

Eligible subjects were randomized to individual cohorts in a 3:1 fashion of TIP to TOBI. The individual cohorts were as follows:

- a. two capsules of TIP (14 mg capsules)
- b. Four capsules of TIP (14mg capsules)

- c. Two capsules of TIP (28mg capsules)
- d. Three capsules of TIP (28mg capsules)
- e. Four capsules of TIP (28 mg capsules)

Subjects could only participate in one cohort. The subjects receiving TOBI received the typical 300mg/5ml nebulized dose. Dose escalation from one cohort to the next occurred after safety data monitoring review by a Data Monitoring Committee (DMC) and if the following conditions were not met:

- a. 3 or more subjects from a TIP treated cohort had a relative drop in FEV1% predicted of $\geq 20\%$ at 30 minutes post dose
- b. Any TIP dosed subject had an SAE.

Subjects had to be cystic fibrosis patients ≥ 6 years old and have a baseline FEV1% predicted $\geq 40\%$. 90 subjects were randomized, but only 87 received study treatment. One subject was found to have taken study drug but did not pierce study capsules. Thus, only 86 individuals can be evaluated for safety. 86 individuals completed the study. One subject in the 4 x 28mg cohort was withdrawn due to a treatment emergent adverse event.

Demographics

The size of the various cohorts ranged from 12 to 20 subjects. Because of these small sizes, demographic trends at baseline must be viewed with caution. The mean ages of the five TIP cohorts ranged from 18- 24 years old. The mean age for the TOBI cohort was 18. Proportionally, the TOBI cohort appeared to have less subjects in the 6 to 12 year old age group and the ≥ 18 year old age group relative to the TIP arms. The baseline median FEV 1 % predicted ranged from 59% -82% in the TIP cohorts and 68% in the TOBI cohort. There were instances of improper dosing in this study. One TIP subject in the 2 x 28 cohort never took a dose from one capsule. Two subjects in the 4x 28 TIP cohort either did not take two inhalations with dosing due to improper training or were found to have high residue of TIP in the inhaler.

Adverse Events

67 subjects in the safety population were in the TIP cohorts. This was spread out among the five dose cohorts (12, 13, 14, 15, and 13 subjects in the 2 x 14mg TIP, 4 x 14mg TIP, 2 x 28mg TIP, 3 x 28mg TIP, 4 x 28mg TIP dose cohorts, respectively). 20 subjects received 300mg/5 ml of TOBI.

More subjects in the TIP cohorts had a TEAE (61% of TIP subjects vs. 30% of TOBI subjects). Within the TIP cohorts, TEAEs seemed to increase in incidence with increasing dose. Please note the following table.

Table 2: Rate of TEAEs in CTPI 001 by Treatment Dose Cohort

TOBI 300mg/5ml	30% (6 of 20 subjects)
TIP 2 x 14mg	45%
TIP 4 x 14mg	54%
TIP 2 x 28mg	64%
TIP 3 x 28mg	67%
TIP 4 x 28mg	69%
TIP total	61% 40 of 66 subjects

All TEAEs were mild to moderate in severity, and only one SAE was noted (in the TIP cohorts). There was one discontinuation due to a TEAE and four subjects had treatment modification due to cough, all in the TIP cohorts.

No more than one TOBI subject experienced any particular TEAE. In contrast, several TEAEs were experienced by more than one subject in the TIP cohorts. Please note the sponsor table below.

Table 3: Treatment Emergent Adverse Events, CTPI 001

MedDRA System Organ Class Preferred Term^a [no. (%) of subjects]	TPI Dosage Regimens					TOBI 300 mg (N = 20)
	2x14 mg (N = 11)	4x14 mg (N = 13)	2x28 mg (N = 14)	3x28 mg (N = 15)	4x28 mg (N = 13)	
Any AE	5 (45)	7 (54)	9 (64)	10 (67)	9 (69)	6 (30)
<u>Respiratory, Thoracic, & Mediastinal System</u>	3 (27)	6 (46)	5 (36)	4 (27)	7 (54)	2 (10)
Cough aggravated	0	2 (15)	2 (14)	0	3 (23)	0
Cough	0	1 (8)	1 (7)	2 (13)	2 (15)	0
Pharyngitis	1 (9)	0	3 (21)	0	0	1 (5)
Crackles lung	1 (9)	0	0	0	2 (15)	1 (5)
Haemoptysis	1 (9)	1 (8)	1 (7)	1 (7)	0	0
Rhinorrhea	0	2 (15)	0	0	2 (15)	0
Sputum increased	0	0	0	1 (7)	2 (15)	1 (5)
Throat irritation	0	1 (8)	0	0	2 (15)	0
<u>Nervous System Disorders</u>	2 (18)	1 (8)	4 (29)	3 (20)	5 (38)	0
Dysgeusia	1 (9)	1 (8)	3 (21)	3 (20)	3 (23)	0
Dizziness	0	0	1 (7)	0	2 (15)	0
Headache NOS	1 (9)	0	1 (7)	1 (8)	0	0
<u>Gastrointestinal Disorders</u>	0	3 (23)	1 (7)	1 (7)	1 (8)	1 (5)
Abdominal pain upper	0	2 (15)	1 (7)	0	0	0
<u>Infections & Infestations</u>	0	0	1 (7)	1 (7)	2 (15)	2 (10)
Upper respiratory tract infection NOS	0	0	1 (7)	0	1 (8)	1 (5)
<u>Musculoskeletal, Connective Tissue, & Bone Disease</u>	1 (9)	1 (8)	1 (7)	0	2 (15)	0
Arthralgia	0	1 (8)	0	0	1 (8)	0
Back pain	1 (9)	0	1 (7)	0	0	0
<u>Eye Disorders</u>	0	0	1 (7)	0	3 (23)	0
Lacrimation increased	0	0	1 (7)	0	2 (15)	0
<u>General Disorders & Administration Site Conditions</u>	1 (9)	0	0	0	1 (8)	1 (5)
<u>Blood & Lymphatic System Disorders</u>	0	0	0	1 (7)	1 (8)	0
Lymphadenopathy	0	0	0	1 (7)	1 (8)	0
<u>Investigations</u>	0	0	0	0	1 (8)	1 (5)

^a **Note:** AEs reported by two or more subjects; if no AEs are listed for a MedDRA class, then AEs were reported by no more than one subject each. Source: Table 14.3.1 1.1; Appendices 16.2.7.1 and 16.2.7.2.

It is difficult to draw many conclusions from such a limited sample size. However, preferred terms dealing with cough did not occur in the TOBI cohort but appeared to increase in incidence with increasing dose in the TIP cohort. A similar conclusion can be drawn for 'dysgeusia' and, to a lesser extent, 'lacrimation increased,' 'dizziness,' 'sputum increased,' and 'throat irritation.' There also appeared to be

increased incidences (though not particularly dose- related) of hemoptysis, rhinorrhea, abdominal pain, arthralgia, back pain, and lymphadenopathy in the TIP cohorts.

Related TEAEs

24 of 66 subjects (36.4%) in the TIP cohorts and 2 of 20 subjects (10%) in the TOBI cohort had related TEAEs. Please note the table below.

Table 4: Related TEAEs by Treatment Dose Cohort

MedDRA System Organ Class Preferred Term [no. (%) of subjects]	TPI Dosage Regimens					TOBI 300 mg (N = 20)
	2x14 mg (N = 11)	4x14 mg (N = 13)	2x28 mg (N = 14)	3x28 mg (N = 15)	4x28 mg (N = 13)	
Any Treatment-Related AE^a	2 (18)	5 (38)	4 (29)	8 (53)	5 (38)	2 (10)
Dysgeusia	1 (9)	1 (8)	3 (21)	3 (20)	3 (23)	0
Cough aggravated	0	2 (15)	1 (7)	0	3 (23)	0
Cough	0	1 (8)	1 (7)	2 (13)	0	0
Haemoptysis	1 (9)	1 (8)	0	1 (7)	0	0
Throat irritation	0	1 (8)	0	0	2 (15)	0
Lacrimation increased	0	0	1 (7)	0	2 (15)	0
Pharyngitis	0	0	1 (7)	0	0	1 (5)
Sputum increased	0	0	0	1 (7)	0	1 (5)
Mouth ulceration	0	1 (8)	0	0	0	0
Vomiting NOS	0	0	0	1 (7)	0	0
Chest tightness	0	0	0	0	0	1 (5)
Herpes simplex	0	0	0	0	0	1 (5)
Eosinophil count increased	0	0	0	0	0	1 (5)
Dizziness	0	0	0	0	1 (8)	0
Dry throat	0	0	0	0	0	1 (5)
Pharyngolaryngeal pain	0	1 (8)	0	0	0	0
Pulmonary congestion	0	0	0	1 (7)	0	0
Rhinorrhea	0	0	0	0	1 (8)	0
Sputum viscosity increased	0	0	0	0	0	1 (5)
Throat tightness	0	0	1 (7)	0	0	0

^a Treatment-Related = considered possibly or probably related to treatment by the investigator.

Source: Table 14 3.1.1.3, Appendices 16 2.7.1 and 16.2.7.2.

Related events in the TIP cohorts were particularly noticeable for ‘cough,’ ‘cough aggravated,’ ‘dysgeusia,’ ‘hemoptysis,’ ‘throat irritation,’ and ‘lacrimation increased.’

Deaths

There were no deaths in this study.

SAE

One subject in the 4 x 28mg TIP cohort had cough and sputum increased on the day after dosing. Then on day 8 the subject was hospitalized for a CF exacerbation. The event was considered unrelated to treatment. This subject also had 3+ proteinuria on urine dipstick at day 6 which was attributed to subject's exacerbation.

Discontinuations due to TEAE

One subject in the 4 x 28mg cohort discontinued from treatment and study due to TEAEs of cough aggravated, dysgeusia, and lacrimation increased. This involved an 8 year old subject who developed the above AEs within a minute of TIP dosing and stopped inhalation. He restarted a few minutes later but stopped again within a minute due to the same symptoms. He withdrew from study, received treatment with albuterol, and had improvement of symptoms in roughly a half hour. The subject did note he forgot to take his usual Advair.

As noted earlier, 4 subjects in the TIP cohorts (in the 4 x 14mg, 3 x 28mg, and 4 x 28mg cohorts) had their dose interrupted or modified due to cough events; they did not discontinue from study. This involved an 11, 13, 25, and 22 year old. In all cases, therapy was not needed (one subject rinsed mouth with water and drank some water before restarting).

Bronchoreactivity

7 subjects in the TIP cohorts (10%) and 2 in the TOBI cohort (10%) had a relative decline in FEV₁ predicted from predose to 30 minutes post dose of at least 10%. Increased incidence was seen with increasing TIP dose, though the largest relative decreases were seen in some of the lowest TIP dose cohorts. It should be noted that one TIP subject with a 21% decrease did not have spirometry performed according to ATS criteria at predose; this decrease may have been inaccurate. 3 of the TIP subjects had symptoms of cough either at 30 minutes post dose or around time of dosing. No TOBI subjects had cough.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHRIMANT MISHRA
10/10/2012

EILEEN E NAVARRO ALMARIO
10/11/2012

DIVISION OF PULMONARY, ALLERGY AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date	7/18/2012
To	Shrimant Mishra MD, Medical Officer Eileen Navarro-Almario, MD, Team Leader Division of Anti-infective Products
From	Robert Lim, MD, Medical Officer Division of Pulmonary, Allergy & Rheumatology Products, HFD-570
Through	Theresa Michele, MD, Medical Team Leader Division of Pulmonary, Allergy & Rheumatology Products, HFD-570
Through	Lydia Gilbert-McClain, MD, Deputy Director Division of Pulmonary, Allergy & Rheumatology Products, HFD-570
Subject	Medical Officer Consultation: DPARP review and comment is requested regarding pulmonary perspective on NDA for TOBI Podhaler

General Information

NDA #	201,688
Sponsor	Novartis
Drug Product	TOBI Podhaler (tobramycin inhaled powder)
Requested from	Shrimant Mishra, MD, Medical Officer Eileen Navarro-Almario, MD, Team Leader Division of Anti-infective Products
Date of Request	12/28/2012
Materials Reviewed	Consultation Request, NDA submission, supportive literature,

1. Executive Summary

The Division of Anti-Infective Products (DAIP) has requested that the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consult on 12/28/2011 for NDA 201,688 for Tobramycin Inhaled Powder (TIP). The requested completion date is 7/20/2012. The proposed indication is for the treatment of pseudomonas colonization in patients with Cystic Fibrosis (CF). The product will be given at a dose of 112mg BID (4 x 28mg) on an alternating 28 day cycle (28 days on, 28 days off) similar to TOBI, which is a nebulized solution of tobramycin indicated for the management of cystic fibrosis patients with *P. aeruginosa*. The dosing for TIP was based on comparable PK to TOBI (systemic). To support this

indication, Novartis has submitted three phase 3 trials, designated 2301, 2302, and 2303.

Trial 2301 was a 3 cycle, placebo controlled trial in CF patients with pseudomonal colonization, but who had not been on inhaled anti-pseudomonal antibiotics for >4 months. These patients were essentially TOBI naïve. This trial used a drug product manufactured by an earlier method that is not the to-be-marketed product. The primary endpoint for 2301 was relative change from baseline in percent predicted FEV-1 after the first 28 days of treatment in the TIP group compared to placebo. Due to ethics concerns, patients remained on placebo for only the first cycle, and were switched to TIP for cycles 2 and 3. The Data Safety Monitoring Board (DSMB) recommended that trial 2301 be stopped after the planned interim analysis. The DSMB felt that it was unethical to continue with placebo as a significant treatment effect for TIP had been demonstrated. During an audit of PFT data from Latin American and European sites in trial 2301, several Latin American sites were found to have unacceptable PFT calibration practices. This prompted a review of PFT data from these sites. As a result, some values were removed and the data were reanalyzed. This was performed in a blinded fashion. The DSMB re-evaluated the data and again concluded that there was significant treatment effect and that the trial 2301 should be stopped.

Trial 2303 was similar in design to 2301, but was for only a single cycle. This trial was performed due to a manufacturing change for the dry powder. Per Novartis, *in vitro* testing implied that deposition and lung delivery is comparable to the product used in 2301 and 2302; however, DAIP requested another clinical trial. The product used in 2303 is the to-be-marketed product. Trial 2303 was stopped early due to difficulties in enrolling patients with Pseudomonas colonization, but who had not been on an inhaled anti-pseudomonal antibiotic for >4 months. In trial 2303, TIP did not demonstrate a significant treatment effect compared to placebo. Multiple *post-hoc* statistical analyses were performed with similar results.

Trial 2302 was a 3-cycle safety and non-inferiority trial comparing TOBI to TIP. The non-inferiority margin was 6% (relative change from baseline in FEV1 percent predicted). This trial used the same TIP formulation as 2301, which is not the to-be-marketed formulation. To be included in the trial, patients had to be colonized with *P. aeruginosa* and not have been on an inhaled anti-pseudomonal drug for >28 days. Results from this trial demonstrated that while the NI margin was met, TIP had a less favorable safety profile compared to TOBI. This is primarily based on increased new anti-pseudomonal antibiotic use and hearing loss in the TIP patients versus TOBI patients.

We note the following issues with this development program:

- Efficacy of the TIP product is equivocal.

- A significant treatment effect was only demonstrated in one trial (2301) that did not use the to-be-marketed formulation of TIP.
- The trial that used the to-be-marketed formulation did not demonstrate any treatment benefit (2303); however, this trial was halted early due to enrollment issues.
- Efficacy cannot be extrapolated from the TOBI program because tobramycin is a locally acting drug for this indication and the formulations and drug delivery methods are entirely different.
- Given current standard of care and the current CF population, it is unlikely that another placebo controlled trial similar in design to trial 2301 could be performed.
- TIP may have a worse safety profile compared to TOBI based on the following parameters:
 - Increased frequency of cough, dysphonia, dysgeusia, and pharyngolaryngeal pain
 - Increased use of anti-pseudomonal antibiotics
 - Increased hearing loss
 - Increased development of drug resistance
- With regard to ease of use and administration time, TIP may represent a clinically meaningful benefit over TOBI.
- Given the issues regarding the safety and efficacy of TIP and the difficulty in performing another placebo controlled trial we concur with the need for an Advisory Committee meeting.

2. DPARP Comments and Response to Questions

Comments on dry powder inhaler (DPI) drug products:

TIP is delivered via a single dose dry powder inhaler, and the product's mode of action is local rather than systemic. As such, some general concepts about DPIs apply to the development program.

- In general, DPARP considers products containing the same drug substance but different formulations or different delivery devices to be different products. This is pertinent to the TIP program in that dose, efficacy and safety cannot be extrapolated from TOBI or from systemic exposure. In the case of CF in particular, a dry powder may have very different lung dispersion characteristics than a liquid nebulized solution since a major problem with the disease is thick, viscid secretions. A dry powder may be unable to penetrate the mucous layer to reach the site of action where bacteria live. Also, cough generated by a dry powder may cause increased drug distribution in the upper airways including penetration of the eustachian tubes, possibly leading to the different safety profile observed with TIP compared to TOBI (increased hearing loss).

- The development program must generate data that support not only the efficacy and safety of the drug substance, but also the efficacy, safety, and performance of the entire product (drug+DPI device). The podhaler device requires inhalation of 4 separate capsules, which is unique compared to other single dose DPI devices on the market that only use one capsule per dose. The human factors study demonstrated that approximately 15% of patients were unable to inhale all 4 capsules correctly, which may ultimately result in underdosing. This may be particularly problematic for an antibiotic product.
- Changes in the DPI device or drug substance formulation can substantially affect local deposition. For the TIP program, the sponsors changed the drug formulation after the first Phase 3 trial. We concur with DAIP that additional clinical data (including efficacy data) with the new formulation are needed.

We also have specific considerations related to the single dose dry powder inhaler (SDDPI) products:

- Patients may mistakenly use a non-matching SDDPI with a medication capsule, which could affect local deposition, affecting efficacy and local safety. Other products currently on the market using a SDDPI include Spiriva HandiHaler, Foradil Aerolizer, and Arcapta Neohaler. We recommend that sponsors employ strategies to minimize this risk (e.g. color matching the capsules and SDDPI device). In addition, in vitro studies to evaluate delivery if the TIP capsules are inadvertently used with another device may be beneficial to quantify risk.
- Patients may ingest the dry powder capsules, rather than loading them into the device for oral inhalation. Product labeling proposed by the sponsor includes specific instructions about not swallowing capsules. In the case of tobramycin systemic bioavailability of orally ingested tobramycin is known to be very low, and a substantial amount of oral ingestion is occurring even with inhalation. Therefore, the major impact of swallowing capsules is likely to be lack of efficacy, and possible development of resistance (if the inhaled route is used for some doses but not others).

During the course of this consult, DAIP noted that aerodynamic particle size testing was performed using a next generation impactor at a flow rate of 60 liters per minute (LPM). Because of this, DAIP asked if the 60 LPM inspiratory flow rate was clinically relevant (i.e. can CF patients with severe lung disease generate this flow rate using this device?). Based on work done by Tiddens et al (2006), the majority of adult and pediatric CF patients should be able to generate 60LPM of flow using the TIP delivery device (T-326). While theoretically a very young CF patient with severe lung disease may have difficulty generating this flow rate, severe lung disease (FEV1<40% predicted) is rare in pediatric patients. More than 85% percent of pediatric CF patients have normal/near normal lung

function (FEV1>70% predicted). Adult CF patients generally have lower FEV1% predicted values than children, but due to larger absolute lung volumes most adult patients should still be able to generate 60 LPM flow rate.

Questions and Responses:

1) Device: Are claims regarding delivered dose, mean particle size accurate? We have consulted CDRH but also welcome your input.

*DPARP response:
We defer to CMC.*

2) Is there a specific way compliance is measured within DPARP for inhaled/nebulized therapies? Should the improvement in administration times and ease of use with TIP still be viewed as a clinically meaningful improvement over TOBI or CAYSTON?

*DPARP response:
In general DPARP measures compliance based on patient logs, returned medications, canister weight and dose counter information (in the case of metered-dose-inhalers), and PK measurements. Efficacy can also be used as a surrogate for compliance in cases where efficacy is known. Since the TIP product is a single-dose dry powder inhaler, traditional methods of measuring compliance such as pill counts and diaries can be used. Novartis' method of measuring compliance was appropriate.*

With regard to administration times, TIP represents a clinically meaningful improvement over TOBI and to a lesser degree Cayston. Based on sponsor data, TIP represents a time savings of approximately 22 minutes/day compared to TOBI and 3 minutes/day compared to Cayston. Taking into account that the average time spent with daily therapies in adult CF patients is approximately 108 minutes/day (Sawicki GS et al, 2009), TIP likely represent a meaningful benefit compared to TOBI. However, the time savings compared to Cayston is marginal. In addition to shorter administration times, TIP does not require a nebulizer, compressor, or power source for administration, theoretically making it easier to use than TOBI or Cayston, particularly for travel. In terms of ease of use and administration times, TIP may demonstrate a clinically meaningful benefit over TOBI, and a marginal benefit over Cayston. However, it is worth noting that due to the post-inhalational cough and bronchoreactivity following TIP administration (trial 2302), a subset of CF patients may be unable see this benefit due to an inability to tolerate TIP.

It should be noted that a single TIP treatment requires 4 capsules to be individually loaded and unloaded into the DPI device (T-326). While the administration time is still shorter compared to TOBI or Cayston, the need to load and unload capsules introduces a layer of complexity for administration,

potentially affecting appropriate use. This concern was confirmed in a human factors study, where only 85% of participants correctly loaded all four capsules. These results imply that in actual use, up to 15% of patients may under dose TIP. Chronic under dosing may result in increased antibiotic resistance in patients receiving TIP, which was seen in trial 2302.

In the question it was noted that compliance between TIP and TOBI in trial 2302 was essentially the same. However there is reason to believe that in a 'real world' CF population TIP may have better compliance compared to TOBI. Available evidence suggests treatment burden and compliance are inversely related (review Kettler et al 2002). In study by Dziuban EJ et al (2010), CF patients predominantly reported time management issues as the specific issue that decreased compliance. This would imply that decreased time of administration would improve compliance.

Whether or not the decreased treatment burden for TIP outweighs the equivocal efficacy and possible safety signal is debatable.

3) Assuming no further supportive information is found to show effectiveness of TIP over placebo in this trial, should another trial be recommended given the difficulty in recruiting patients for these placebo-controlled studies? Is demonstration of effectiveness in one trial in this case sufficient given the extenuating circumstances?

DPARP response:

We acknowledge the difficulty in recruiting patients and that it is unlikely that another trial similar to 2301/2303 could be performed. However, demonstration of efficacy in a single trial is problematic given that efficacy from TOBI cannot be extrapolated to this formulation (see general comments). This is especially true as the only trial (2301) that demonstrated a treatment effect did not use the to-be marketed TIP formulation. Given that this drug acts locally and that changes in formulation can significantly affect local delivery, using the efficacy data from trial 2301 as the sole support for efficacy of the to-be marketed formulation is extremely difficult.

However, exactly what type of trial is appropriate for further study of TIP is questionable. A placebo controlled trial would likely not be feasible. A non-inferiority trial (TIP v. TOBI) would potentially be an option; however, it would have to be longer in duration and have a smaller non-inferiority (NI) margin compared to trial 2302. As FEV-1 in CF patients infected with Pseudomonas decreases by ~1.6% annually (Que C, et al 2006), the NI margin would have to be narrow, and a trial duration of 1 year or more may be necessary. An extended NI trial as described may also pose ethical issues, as it would necessitate placing patients on a potentially ineffective therapy. Another potential option is a trial similar to the one used to support the approval of Cayston. In that trial patients were only required to have been off anti-pseudomonal antibiotics for 28 days and

the primary endpoint was improvement in symptoms, although the trial also demonstrated improvement in FEV-1. This trial would be feasible and would likely not raise ethical concerns given the short duration. However, it is unclear if such a trial would be able to demonstrate a treatment effect given the results from the current TIP trials. Additionally, because of the subjective nature of symptom improvement, it is a suboptimal primary endpoint and a more objective measure would be preferred. We concur with DAIP's plan to discuss this issue at a public advisory committee meeting.

4) There are some signs that TIP may be less safe than TOBI as regards small AEs like cough and dysphonias and larger AEs such as additional use of antipseudomonal antibiotics. However, the drug may be judged to be more effective than placebo. Should concerns of worse safety vs. TOBI preclude its approval if it is shown to demonstrate safety and effectiveness over placebo, especially given the alternatives already present on the market?

DPARP response:

As there are alternatives on the market, concerns about TIP's safety profile versus TOBI may be sufficient to preclude approval. Many of the AE imbalances between TIP and TOBI are likely related to the dry powder formulation (e.g. cough, dysphonia, dysgeusia, oropharyngeal pain). These types of AEs are clinically monitorable and would not likely cause permanent harm, although they may limit patient tolerance and acceptability of use. As such, while of some concern, these would not preclude approval.

However, two potential safety signals that could more significantly affect approval are increased anti-pseudomonal antibiotic use and increased hearing loss in TIP patients compared to TOBI patients. Increased anti-pseudomonal antibiotic use is a concern as it implies more frequent pulmonary exacerbations, which can lead to decrements in respiratory status. Increased anti-pseudomonal antibiotic use in the TIP patients also implies decreased efficacy compared to TOBI. It is also concerning that in trial 2302, there was a greater increase in antimicrobial resistance in TIP versus TOBI patients (based on minimum inhibitory concentrations). These two issues may or may not be related given the short duration of the trial. If the increase in antibiotic resistance were to continue with chronic use of TIP, this may affect future antibiotic treatment options for CF patients in TIP.

The imbalance in hearing loss is also a significant concern in CF patients for several reasons. First, CF patients are inherently at greater risk for hearing loss due to frequent aminoglycoside exposure. Second, TIP would be chronically administered. Third, based on trial data (2302) the hearing loss frequently did not resolve. It is also of concern that in the majority of cases the hearing loss was only noted in audiology testing and was not reported by the patient, making this AE more difficult to follow clinically. The reason for this imbalance in hearing is

unclear, but may be related to local toxicity as in general the systemic exposure to tobramycin was similar between TOBI and TIP patients.

Even if TIP demonstrates efficacy and safety over placebo, its increased risk compared to TOBI may preclude its approval. Given this fact, we agree with DAIP that an AC is necessary.

3. Background

*Treatment of *P. aeruginosa* in Cystic Fibrosis:*

The Cystic Fibrosis Foundation (CFF) guidelines recommend that CF patients have at least 4 respiratory cultures per year. When *P. aeruginosa* is detected in a respiratory culture for the first time, eradication is usually attempted. However, there is currently no consensus on the optimal eradication regimen. Depending on the care center, the eradication protocol may include inhaled antibiotics, oral antibiotics, or IV antibiotics for varying durations of therapy. Although eradication can be often achieved, in most cases, patients will eventually develop chronic *P. aeruginosa* colonization. CFF guidelines strongly recommend chronic use of inhaled tobramycin in CF patients 6 years and older with moderate to severe lung disease and persistent *P. aeruginosa* in airway cultures. The CFF also recommends inhaled tobramycin use in asymptomatic CF patients 6 year older; however, the strength of this recommendation is weaker. The duration of 'chronic' therapy is not defined. In clinical practice, patients generally stay on inhaled antibiotics indefinitely.

Indication:

The proposed indication for TIP is for the treatment of pseudomonal colonization in patients with Cystic Fibrosis. The proposed treatment regimen is 112mg (4 capsules) for oral inhalation delivered via the T-326 delivery device twice daily. It is to be given for repeated cycles of 28 days on drug and 28 day off drug. There is currently one other approved product with the same indication: TOBI. TOBI is a tobramycin solution formulated for inhalation via a nebulizer and compressor. It is specifically indicated for use with the Pari LC Plus nebulizer and Pulmo-aide air compressor. The treatment dose is 300mg inhaled delivered twice daily. TOBI is taken for repeated cycles of 28 days on drug and 28 days off drug.

It should be noted that while Cayston has as similar indication to TOBI, the drug and the indication are not the same. Cayston is aztreonam formulated for inhalation via the Altera nebulizer (75mg TID). It is indicated to improve respiratory symptoms in CF patients with *P. aeruginosa*, however, it is only approved for 28 days of therapy. It is not approved for chronic cycled therapy. However, in the clinical setting, it is often used in a manner similar to TOBI.

4. Drug/Device

TIP is a dry powder packaged in a hard capsule. It is delivered for oral inhalation via the T-326 DPI device (Figure 1). The T-326 is a hand held manually

operated, breath activated, single dose dry powder inhaler. To administer the medication, the patient must remove the mouthpiece of the T-326, load a single TIP capsule into the inhaler chamber, screw the mouthpiece back on, pierce the capsule by pressing down on the blue button, and then inhale. These steps must be repeated again 3 times to administer the full dose (4 TIP capsules).

Figure 1. T-326 single dose dry powder inhaler



5. Clinical Development Program

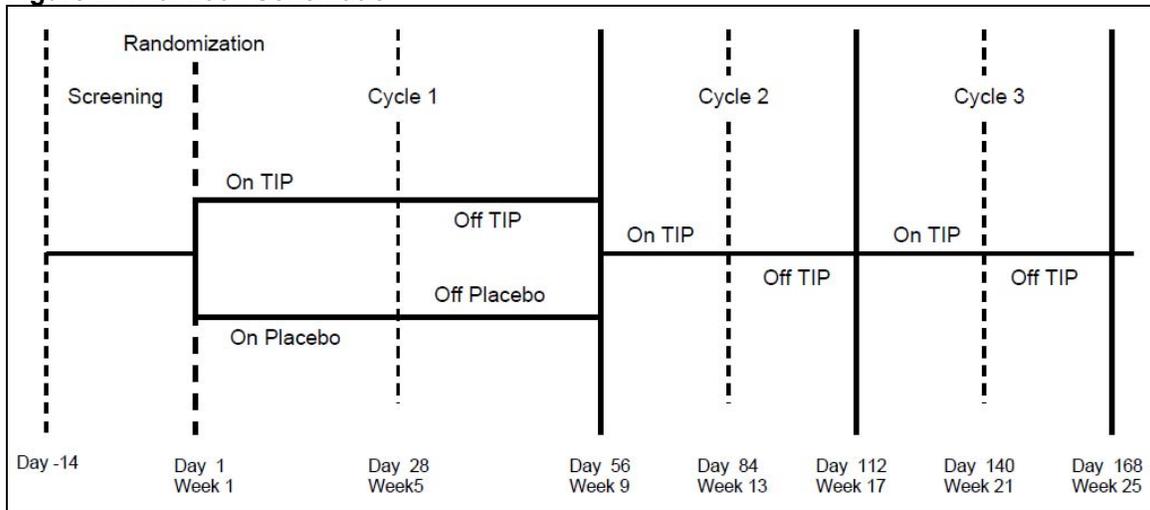
To support the proposed indication, Novartis has submitted two placebo controlled trials (2301, 2303) and one comparative safety and non-inferiority trial (2303). These are briefly reviewed with an emphasis on pulmonary issues. For a complete clinical review of these trials, see review by Dr. Shrimant Mishra, MD, DAIP.

Trial 2301:

Design:

This was a randomized, double-blind placebo controlled, multicenter phase 3 trial to assess the safety and efficacy of TIP in patients with CF. Patients received TIP at 112mg (28mg capsules x 4) twice daily for 3 cycles. Each cycle consisted of 28 days on treatment and 28 day off treatment. For ethical reasons, the placebo group receive placebo for only the first cycle. For the other 2 cycles, the placebo group received TIP. The TIP group received TIP for all three cycles. Sixteen (16) study centers were located in the U.S., 4 in Eastern Europe, 11 in South America, and 2 in Mexico. One hundred two (102) patients were randomized. The first patient was enrolled in 9/22/2005, and the trial was completed 2/28/2007. The study schedule is summarized in Figure 2.

Figure 2. Trial 2301 Schematic



Objectives:

The primary objective was to demonstrate efficacy of TIP when given BID (4 x 28mg) for 28 day alternating cycles versus placebo. The primary efficacy endpoint was relative change from baseline in FEV-1 percent predicted (cycle 1, day 1) to end of cycle 1 (day 28). Secondary objectives were to assess for safety and efficacy when administered for more than 1 cycle.

Population:

Key Inclusion Criteria

- Clinically stable CF patients ≥ 6 to ≤ 21 years with and FEV-1 between $\geq 25\%$ and $\leq 80\%$ predicted.
- *P. aeruginosa* positive sputum culture within the past 6 months

Key Exclusion Criteria

- History of *B. cepacia* within 2 years prior to screening
- Hemoptysis $>60\text{mL}$ at any time within 30 days prior to study drug
- Any inhaled anti-pseudomonal antibiotics within 4 months prior to screening
- Any systemic anti-pseudomonal antibiotics within 28 days prior to study drug. Their use was allowed after study drug began.
- Initiation of a macrolide, dornase alpha, or inhaled corticosteroids within 28 days prior to study drug. Their use was allowed during the study if started prior to 28 days before study drug.
- Use of loop diuretics within 7 days of drug administration

Key Removal Criteria (including, but no limited to)

- Development of proteinuria ($>2+$) or above normal BUN following earlier normal BUN, or an elevated creatinine
- Treatment with excluded therapy

- Sensi-neural hearing loss >20dB at one or more frequencies in one or both ears.

Treatments:

- 1) Tobramycin Inhaled Powder (TIP) 112mg delivered by T-326 inhaler BID for 3 treatment cycles (28 days on, 28 days off)
- 2) Placebo delivered by T-326 inhaler BID for 1 cycle, then TIP for the 2 subsequent cycles (dosing the same as in item 1)

Inhaled treatments were given in the following order:

- 1) Bronchodilator (15-60 minutes prior to inhalation)
- 2) Chest Physiotherapy
- 3) Other inhaled medications
- 4) Trial medication

Assessments:

Compliance:

Patient compliance was based on subject dosing logs, number of used and unused capsules, and percentage of completed scheduled study visits.

Efficacy:

Study efficacy was assessed using FEV-1, *P. aeruginosa* colony forming units (CFU), *P. aeruginosa* antibiotic susceptibility based on minimum inhibitory concentrations (MIC), time to first anti-pseudomonal antibiotic use, first hospitalization, and incidence/length of hospitalization. Spirometry was performed after bronchodilator, but prior to study drug administration.

Safety:

Safety assessments included SAEs, AEs, clinical labs, hearing, airway reactivity, vital signs, physical exam, and serum tobramycin levels.

Reviewer comment:

The study design was reasonable. Although a longer treatment period would have been ideal, given the ethical concerns a 28 day treatment period is understandable. Given current standard of care, it is unlikely that the study population exists today. CF patients are generally seen every 3-4 months and when first time pseudomonas colonization is detected, patients are started on some combination of IV, oral, and inhaled antibiotics. Once started on an inhaled anti-pseudomonal antibiotic, patients generally remain on them, even if subsequent throat cultures are negative. Therefore, it would be unlikely to find patients who had a positive pseudomonas throat culture in the past 6 months, but who have not been on inhaled anti-pseudomonal antibiotics in the past 4 months. As such, the treatment effect seen in this trial is likely greater than what would be found in today's CF population.

The order of treatment is reasonable, as are the compliance, efficacy, and safety assessments.

Results:**Disposition:**

A total of 102 patients were randomized. Of these patients 95 (93%) completed the study. Overall, similar numbers of patients discontinued from each group. Only one patient discontinued due to an AE (placebo). More TIP patients (4, 8.7%) discontinued due to 'unable to classify' compared to placebo patients (1, 2%). 'Unable to classify' included reasons such as 'move out of area,' intolerant of inhaler,' 'non-compliance,' and 'self discontinued.'

A pre-specified interim analysis was performed after the 80th patient completed the trial(original interim analysis, OIA). The database was locked on 11/2/06 for the OIA. Based on this analysis, the CF Foundation's standing DSMB concluded that TIP demonstrated a conclusive benefit, and that Novartis should halt the study.

Shortly prior to OIA database lock, a Novartis audit of Latin American study sites revealed compliance issues with PFT calibration practices. A blinded panel of Pulmonologists reviewed PFT data from these sites. The panel excluded patients with invalid PFTs. Validity of results was based on current assessment of spirometry hardware and review of data from PFTs logs. Data reviewed from logs included 'was temperature recorded', 'was calibration done on the day of testing prior to patient testing,' and 'was calibration performed with multiple flow rate'. These parameters were assessed for day 1 and 28 of each cycle. The subpopulation of the OIA population with 'valid' PFT results was designated the sensitivity interim analysis (SIA) population. The SIA data was again reviewed by the DSMB, and the conclusion was the same. A total of 61 patients (TIP=29, placebo=32) were included in this analysis (versus 79 in the OIA analysis).

The baseline demographic, disease characteristics, and concomitant medications for the OIA and SIA populations were similar when comparing placebo to TIP groups. Discontinuations were similar between treatment groups in the OIA and SIA populations.

Compliance:

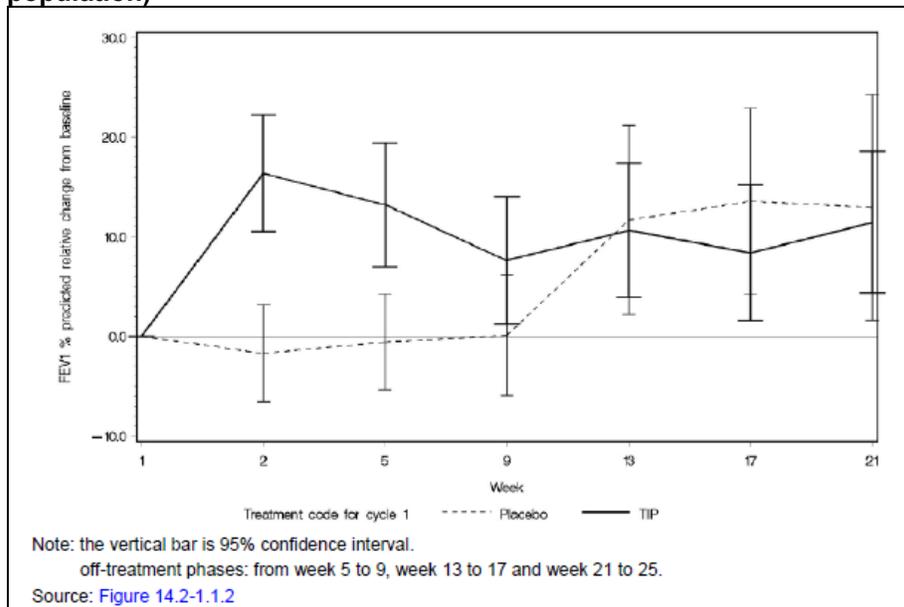
Treatment compliance for cycle 1 was 91% and 88.9% percent for the TIP and placebo groups, respectively. In cycles 2 and 3, compliance was >95% for both groups.

Efficacy:

In terms of the primary endpoint, in the SIA population, relative change from baseline in percent predicted FEV-1, was greater in the TIP group versus placebo (13.97 and 0.68 for TIP and placebo, respectively). The TIP-Placebo

difference was 13.79 (95% confidence interval=5.87, 21.7) with a p-value of 0.001. This data is expressed graphically in Figure 3. Note that in cycles 2 and 3 (week 9-21), the placebo group received TIP.

Figure 3. Relative change in FEV-1 % predicted from baseline in cycles 1-3 (SIA population)



Source: Trial 2301 CSR, Figure 11-11, pp64

When the placebo group was started on TIP (cycle 2), an increase in FEV-1 percent predicted similar to the TIP group in cycle 1 was demonstrated. Similar results were seen when sub-dividing the populations by region, though the treatment effect in North America was less than Europe and Latin America.

Compared to placebo patients, TIP patients also had less anti-pseudomonal antibiotic usage (TIP=32.7%, placebo=19.6%) and fewer respiratory related hospitalizations during cycle 1 (TIP=0, placebo=12.2%).

Reviewer comment:

TIP demonstrated efficacy in terms of their primary endpoint compare to placebo. The improvement in FEV-1 seen in the placebo group after starting TIP is also supportive of efficacy. The treatment effect seen here is similar in magnitude to that seen in the original TOBI trials.

Safety:

While the primary efficacy analysis was based on the SIA population only, the safety analysis was based on the entire intent to treat population. A total of 46 patients received TIP (cycle 1), and a total of 49 received placebo (cycle 1).

Deaths, SAEs, discontinuations due to AEs

There were no deaths in the TIP group during this trial. A total of 17 patients reported SAEs. During cycle 1, fewer SAEs were reported by TIP patients (6.5%) compared to placebo (14.3%). Additionally, every SAE classified by preferred term was more frequent in placebo patients. Results were similar when considering SAEs over all 3 cycles. More patients in the placebo group (1) discontinued due to AEs compared to the TIP group (0).

AEs of special interest (bronchoreactivity, hearing):

Bronchoreactivity following TIP administration was less in the TIP group compared to the placebo group in cycle 1. With regard to audiology testing performed on day 28 of cycle 1, a total of 5 patients (3 TIP, 2 placebo) demonstrated hearing loss. For 2 of the 3 TIP patients audiologic exam normalized by the end of cycle 3. No AEs of tinnitus, ear pressure, or hearing loss were reported.

Common Adverse events:

When comparing AEs during cycle 1, the most common AEs more frequent in the TIP group compared to placebo were pharyngolaryngeal pain, dysgeusia, pyrexia, and dysphonia. A summary of cycle 1 AEs that occurred more frequently in TIP patients is presented in Table 1. All other AEs were more common in the placebo group, including cough (TIP=13%, placebo=26.5%).

Table 1. AEs in first cycle (on/off) all randomize safety population.

AEs by preferred term	TIP N=46	Placebo N=41
Total Reported AEs	23 (50)	37 (75.5)
Pharyngolaryngeal Pain	5 (10.9)	0
Pyrexia	3 (6.5)	2 (4.1)
Dygeusia	3 (6.5)	1 (2.0)
Dysphonia	2 (4.3)	0
Rhinitis	2 (4.3)	2 (4.1)
Sinusitis	2 (4.3)	2 (4.1)
URI	2 (4.3)	2 (4.1)
Migraine	2 (4.3)	1 (2.0)
Ear Discomfort	1 (2.2)	1 (2.0)
Thirst	1 (2.2)	1 (2.0)
Arthralgia	1 (2.2)	1 (2.0)
Hemoptysis	1 (2.2)	1 (2.0)
Nasal Congestion	1 (2.2)	1 (2.0)
Increased AP	1 (2.2)	1 (2.0)
Increase Glucose	1 (2.2)	1 (2.0)
Increased GGT	1 (2.2)	1 (2.0)
Increased PMN	1 (2.2)	1 (2.0)
Increased AST	1 (2.2)	1 (2.0)
Lacrimation increased	1 (2.2)	0
Vulvovaginitis	1 (2.2)	0
Metrorrhagia	1 (2.2)	0
Pulmonary Congestion	1 (2.2)	0
Rash	1 (2.2)	0

Source: Trial 2301 CSR, Table 12-2, pp69

Reviewer comment:

With regard to deaths, SAEs, and discontinuations due to AEs, there were no imbalances. The same is true for bronchoreactivity and hearing loss. The most common AEs that demonstrated an imbalance compared to placebo are likely attributable to the dry powder formulation. Those AEs are also clinically monitorable and not likely to cause permanent harm to patients receiving TIP.

Overall comment on trial 2301:

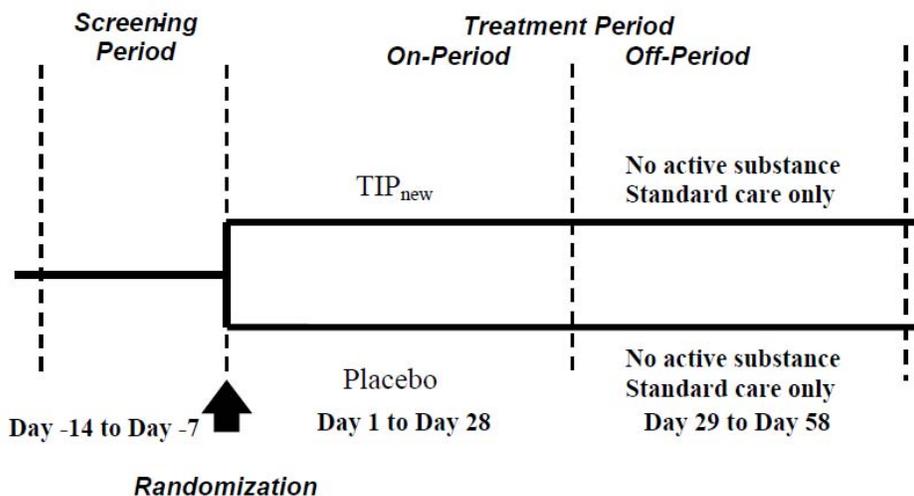
This trial demonstrated that based on the primary endpoint, TIP is effective in treating CF. However, as this study population may differ from the current CF population, the treatment effect seen may be exaggerated. With regard to AEs, pharyngeolaryngeal pain, dysphonia, and dysgeusia were more common in the TIP group than in placebo. These AEs are likely related to the DPI formulation, but do not represent important safety concerns that would necessarily preclude approval.

Trial 2303:

Design:

This was a randomized, double-blind placebo controlled, multicenter phase 3 trial to assess the safety and efficacy of TIP in TOBI naïve CF patients. This trial was similar in design to trial 2301. However, in this trial, patients received either TIP or placebo for one cycle only, after which they returned to their region’s standard of care.

Figure 4. Trial 2303 Schematic



Source: Trial 2303 CSR, Figure 9-1, pp48

All trial sites were located in Eastern Europe (Bulgaria, Estonia, Latvia, Lithuania, Romania, and Russia). Per Novartis, other countries with more experienced research centers did not participate due to widespread use of TOBI. Additionally, many centers had ethical concerns with use of a placebo arm. Sites

in Latin America were excluded due to issues with PFTs raised in trial 2301. The first patient enrolled in this trial on 6/4/09, and the trial was completed on 5/6/11.

This trial was performed because Novartis altered their manufacturing process for the dry powder. Although Novartis argued that the *in vitro* characteristics were similar enough to imply similar lung deposition and delivery, DAIP requested a clinical trial.

The objectives, inclusion/exclusion criteria, withdrawal criteria, and study assessments were essentially the same as trial 2301. However, as this trial involved only a single treatment cycle (28 days on treatment, 28 days off treatment), assessments did not go beyond study day 58.

Reviewer Comment:

Given the increased clinical use of TOBI (and other inhaled anti-pseudomonal antibiotics) and ethical concerns with a placebo arm, the difficulty in finding and enrolling patients is not surprising. As stated in a previous reviewer comment, in current western clinical practice, CF patients are seen every 3-4 month and sputum cultures taken. If P. aeruginosa is found, in general, patients are started on anti-pseudomonal antibiotics (oral, IV, inhalational). Inhalational antibiotics are often continued indefinitely. As such, in the US and Western Europe, it would be virtually impossible to enroll patients. However, it is somewhat surprising that they were unable to complete enrollment in Eastern Europe. The use of less experienced trial sites is concerning with regard to interpretability of results.

Results:

Disposition:

Due to difficulties enrolling patients, Novartis halted the trial after only 62 of the targeted 100 patients were randomized. Of these, 59 patients completed the trial. All 3 discontinuations were in the TIP group. One patient withdrew consent, and 2 withdrew due to AEs. Baseline demographics were similar between TIP and placebo groups, as were baseline mean FEV-1 and maintenance medication use. However, a higher percentage of TIP patients had FEV-1 between 25-50% percent predicted compared to placebo (23.3% vs. 12.5%). Fewer patients in the TIP group had a history of anti-pseudomonal antibiotic and macrolide use compared to placebo (20% vs. 34.4%).

Efficacy:

Based on the pre-specified primary endpoint and analysis, TIP did not demonstrate efficacy. The primary pre-specified endpoint was relative change from baseline in FEV-1 percent predicted at day 29 in the ITT population. In this analysis, patients missing FEV-1 values at day 29 were assigned to have a relative change from baseline of 0 if no post-baseline values were available. If post-baseline values were available, then that value was used to calculate relative change in FEV-1. There was no statistically significant difference between TIP and placebo patients (8.2% and 2.3%, respectively). The TIP-

placebo difference was 5.9 (95% confidence interval=-2.2, 14) with a non-significant p-value. Analysis was also performed using a variety of other imputation approaches, including no imputation (observed cases), imputation of missing data with mean values, baseline observation carried forward, and last observation carried forward. Similar methods were used to analyze a modified ITT population (those with valid spirometry) and per protocol population. There were no statistically significant differences with any of these approaches.

The sponsor also analyzed FEV-1 percent predicted in terms of absolute change from baseline to day 29. Results of this analysis demonstrated a statistically significant difference between TIP and placebo of 4.4 (0, 8.8) when analyzing the intent to treat population.

The sponsor also performed analysis of the primary endpoint excluding an 'outlier.' This 7 year old patient had a 36.7% decrease in FEV-1 from screening to day 29, but did not report any AEs. The sponsor argued that this patient should be excluded because 1) the lack of AEs with such a large drop in FEV-1 suggests an erroneous initial reading, 2) the patient was likely not receiving the appropriate TIP dose. Assessment of this patient's inhaler demonstrated a large amount of residual powder in the capsule chamber, suggesting to the sponsor that the patient had poor technique and did not inhale the full dose. Tobramycin concentrations in sputum and plasma were also lower compared to the rest of the group.

When excluding this patient and using the same analytical method as in the pre-specified primary endpoint, the TIP-placebo difference was 7.3 (-0.3, 14.8) with a p-value of 0.06. However, when using no imputation or the modified ITT population a p-value of less than 0.05 was attained.

With regard to use of new anti-pseudomonal antibiotics, numbers were small and there were no differences overall. However, number of days used was overall greater for placebo. In examining duration of use based on route, TIP patients were on IV antibiotics longer compared to placebo patients (16 days vs. 10 days), but on oral antibiotics for a shorter duration than placebo (8.3 days vs. 13 days). Note that only 2 TIP patients and 2 placebo patients received oral anti-pseudomonal antibiotics. Only one patient from each group received IV antibiotics. Only one patient (placebo) was hospitalized for respiratory reasons.

Reviewer Comment:

Based on these results, TIP is not effective in treating CF. This conclusion is further bolstered by the lack of statistically significant improvement in FEV-1 despite multiple post-hoc analysis strategies. This result is somewhat surprising given the results from trial 2301. It is possible that the lack of significant effect is in part reflective of the difficulties with enrollment, use of less experienced research centers, and the higher percentage of TIP patients with an FEV1 between 25-50% compared to placebo.

Safety:

Deaths, SAEs, discontinuations due to AEs

No patients died during this trial, and SAEs occurred only in the placebo group. One TIP patient discontinued due to an AE of pulmonary hemorrhage and one placebo patients discontinued due to bronchitis. The pulmonary hemorrhage was reported on day 27 of TIP treatment. TIP was discontinued. Spirometry measurement performed that day were of inadequate quality (ATS criteria). Symptoms resolved after 2 days.

Common AEs:

Total reported AEs were higher in placebo patients compared to TIP patients (34.4% vs. 26.7%). However, AEs in the Respiratory, Mediastinal, and Thoracic disorder SOC were higher in the TIP patients compared to placebo (10% vs. 6.3%). For Ear and Labyrinth disorder SOC, the same was true with 6.3% in the placebo patients compared to 10% in TIP patients. When examining AEs by preferred term (PT), notable AEs that demonstrated an imbalance between TIP and placebo were cough (10% TIP, 0% PBO), hypoacusis (10% TIP, PBO 6.3%), and dysgeusia (3.3% TIP, 0% PBO). Table 2 shows all AEs that were more frequent in TIP patients compared to placebo.

Table 2. Trial 2303. Adverse event more frequent in TIP patients compared to placebo

Trial 2303- AEs by preferred term	TIP N=30 N(%)	Placebo N=32 N(%)
Total	8 (26.7)	11(34.4)
Cough	3 (10.0)	0 (0.0)
Hypoacusis	3 (10.0)	2 (6.3)
Ascariasis	1 (3.3)	0 (0.0)
Diabetes mellitus	1 (3.3)	0 (0.0)
Diarrhoea	1 (3.3)	1 (3.1)
Dysgeusia	1 (3.3)	0 (0.0)
Dysphonia	1 (3.3)	1 (3.1)
Giardiasis	1 (3.3)	0 (0.0)
Infective pulmonary exacerbation of cystic fibrosis	1 (3.3)	0 (0.0)
Proteinuria	1 (3.3)	0 (0.0)
Pulmonary hemorrhage	1 (3.3)	0 (0.0)
Rash	1 (3.3)	0 (0.0)

Source: Trial 2303 CSR, Table 12-3, pp118

AEs of special interest (bronchoreactivity, hearing)

Bronchoreactivity following TIP administration was less compared to the placebo group. With regard to hearing, a sub-group of patients receive audiology testing at baseline (TIP=15 patients, placebo=11), at day 29 (TIP=14, placebo=11), and at day 57 (TIP=9, placebo=7) . Of these patients, 3 TIP patients and 2 placebo patients had hearing loss from baseline at day 29. At day 57, one patient from each group had hearing loss had sustained hearing loss. These 2 patients also

had hearing deficits at the day 29 assessment. Of the patients with hearing loss based on audiology testing, one from each group also reported subjective hearing loss.

Reviewer comment:

With regard to deaths, SAEs, and AEs leading to discontinuation, there were no imbalances between treatment groups. With regard to bronchoreactivity, the results were favorable for the TIP group. With regard to hearing, the percentage of patients with hearing loss was similar between TIP and placebo groups. For common AEs while there were imbalances, the total numbers were low.

Overall Reviewer comment:

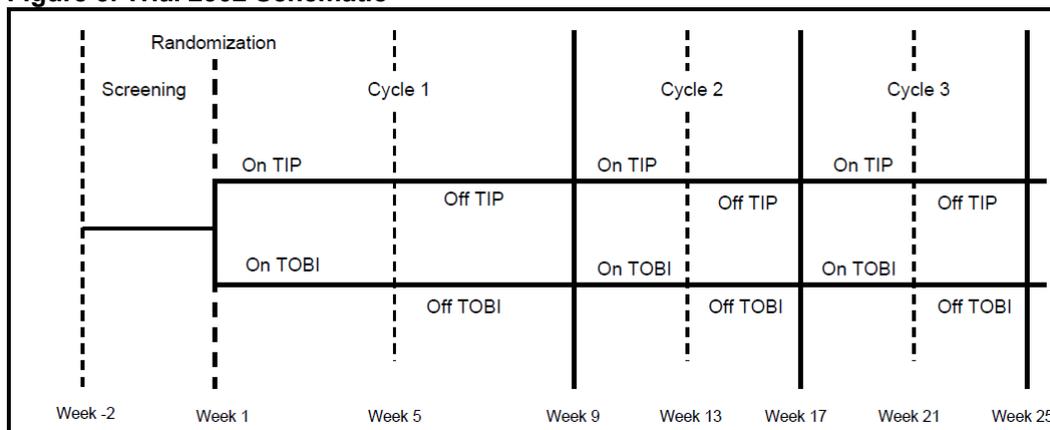
Based on the primary efficacy endpoint, TIP did not demonstrate efficacy. Even when employing multiple post-hoc analyses, a significant effect was not seen, except when removing an ‘outlier.’ The negative results are robust. This result is surprising given the treatment effect seen in trial 2301. The lack of efficacy in this trial may be related to the difficulties in enrollment, inexperienced research site, different patient population (though similar inclusion/exclusion criteria), and change in formulation. With regard to safety, for the most part, the data was balanced between treatment groups, but the number of patients treated was small.

Trial 2302:

Design:

This was a randomized, open-label, multicenter phase 3 trial to compare the safety of TIP compared to TOBI in patients with CF. Patients received either TOBI 300mg BID or TIP (4 x 28mg) BID for 3 cycles. Seventy eight (78) study centers were located in the U.S., 31 in Europe, 5 in the UK, 3 in South America, 4 in Australia, 4 in Israel, and 1 in Mexico. The first patient was enrolled in 2/6/06, and the trial was completed 3/12/09.

Figure 5. Trial 2302 Schematic



Objectives:

The primary objective was to compare the safety of TIP to TOBI. The secondary objective was to assess the efficacy of TIP compared to TOBI based on relative change in FEV-1 percent predicted at the end of cycle 3.

Population:

Key Inclusion Criteria

- Clinically stable CF patients ≥ 6 to years with and FEV-1 between $\geq 25\%$ and $\leq 75\%$ predicted.
- *P. aeruginosa* positive sputum culture within the past 6 months
- ≥ 6 years old

Key Exclusion Criteria

- Similar to trial 2301, except that anti-pseudomonal antibiotics were allowed within 28 days of study drug administration (versus 4 months in trial 2301)

Key Removal Criteria (including, but no limited to)

- The same as Trial 2301

Assessments:**Compliance:**

Patient compliance was based on subject dosing logs, number of used and unused capsules, and percentage of completed scheduled study visits.

Efficacy:

For the secondary objective, efficacy was assessed using FEV-1, *P. aeruginosa* colony forming units and susceptibility, time to first anti-pseudomonal antibiotic use, first hospitalization, and incidence and length of hospitalization. For FEV-1 at the end of cycle 3, the non-inferiority margin was of 6%. This was based on the treatment effect in trial 2301 (relative change from baseline in FEV-1 percent predicted after the first 28 day treatment cycle)

Safety:

Safety assessments included SAEs, AEs, clinical labs, hearing, airway reactivity, vital signs, physical exam, and serum tobramycin levels.

Patient Satisfaction:

To assess patient satisfaction, the sponsor used the Treatment Satisfaction Questionnaire (TSQM). This TSQM consists of 14 questions with responses rated on a 5 or 7 point scale. These questions were divided into four domains described as side effects, convenience, and global satisfaction. The TSQM has been validated in the scientific literature; however, the sponsor added 4 questions to the original 14 questions and also adjusted some wording. The TSQM with these modifications was not re-validated.

Reviewer Comments:

As compared to 2301 and 2303, this trial allowed for inclusion of non-TOBI naïve patients, and only limited anti-pseudomonal antibiotic usage to the previous 28

days. This may have allowed for inclusion of patients on an alternating schedule of inhaled TOBI, or those who had relatively recently been on oral or IV antibiotics. As a result, it is likely that any treatment effect seen in this trial would be less than that seen in trials 2301 and 2303. However, the sponsor based their NI margin on the treatment effect seen in 2301. Given the differences in the patient populations, the NI-margin is likely too large and should not be used as the basis to determine non-inferiority. Additionally, the length of this trial was insufficient. Given the patient population in 2302, addition of TOBI or TIP would not likely significantly increase FEV-1. It is more likely that either could have slowed the rate of decrease in FEV-1. As such, for a non-inferiority trial, a longer duration would have been more informative. While non-inferiority conclusions should not be made from this trial, this trial still has important utility as a comparative safety trial.

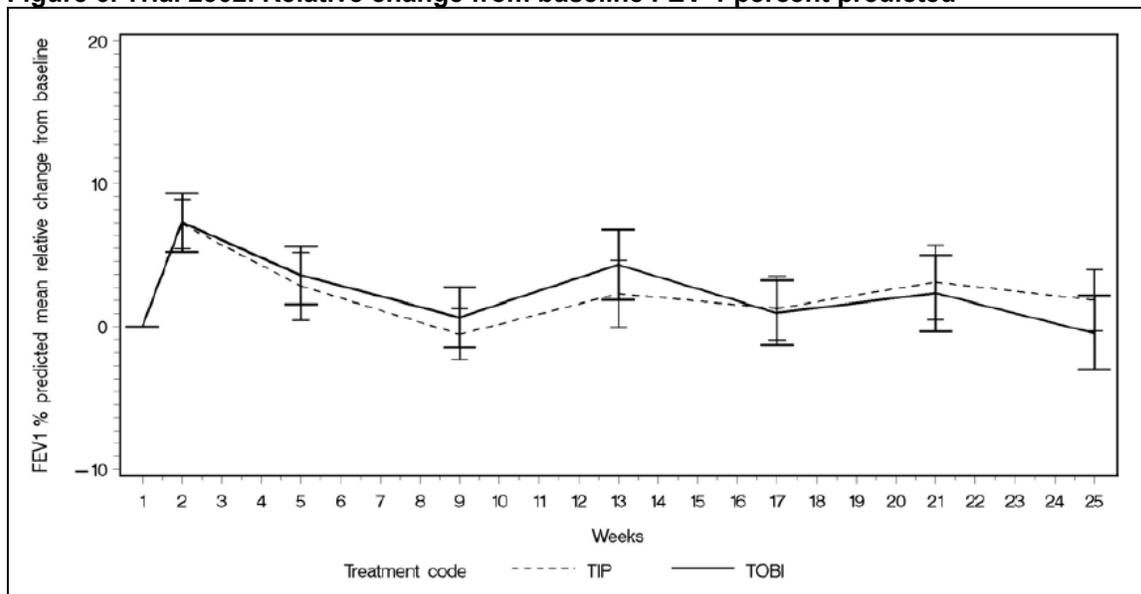
Results:**Disposition:**

A total of 553 patients were randomized, of whom 517 were included in the analysis populations, and 396 completed the study (73% of TIP patients and 82 of TOBI patients). The ITT population used for analysis (safety and efficacy) consisted of 309 patients in the TIP group and 209 in the TOBI group. Baseline demographic characteristics were generally similar between groups. Baseline FEV-1 and concomitant/previous medications were also similar. Last use of anti-pseudomonal antibiotics was also similar between groups; however, more patients in the TOBI group were naïve to anti-pseudomonals compared to the TIP group (4.87% vs. 8.61%). Over all three cycles, 27% (83) of TIP patients withdrew versus 18% (38) of the TOBI patients. More patients in the TIP group withdrew due to AEs or withdrawal of consent (14% and 7.8%, respectively) as compared to TOBI (8.1% and 4.3%).

Efficacy:

Relative change from baseline in FEV-1 percent predicted from pre-dose to day 28 of cycle 3 were similar between TIP and TOBI groups (5.8% and 4.7%, respectively). The TIP-TOBI difference was 1.1% (-0.67, 2.96). This was within the sponsor's pre-specified NI margin (6%). The improvement in FEV-1 seen in the initial cycle for TOBI and TIP was not maintained in subsequent cycles. The relative change from baseline in FEV-1 % predicted over the entire course of the trial is summarized in Figure 6.

Figure 6. Trial 2302. Relative change from baseline FEV-1 percent predicted



Source: Trial 2302 CSR, Figure 11-1, pp70

Changes in *P. aeruginosa* colony density and CFUs were also similar between TIP and TOBI at the end of cycle 3. However, the TIP group for all pseudomonal colony subtypes had a greater increase in MICs by the end of the 3rd cycle compared to TOBI (Table 3).

Table 3. Shift in maximum tobramycin MIC values from baseline to weeks 21 and 25 (ITT)

Shift from baseline	TIP N=308		TOBI N=209	
	Week 21 n (%)	Week 25 n (%)	Week 21 n (%)	Week 25 n (%)
Total	199	201	154	155
≥ 4-fold increase	67 (33.7)	63 (31.3)	42 (27.3)	28 (18.1)
≥ 2-fold increase	97 (48.7)	93 (46.3)	61 (39.6)	52 (33.5)
No change ¹	42 (21.1)	43 (21.4)	41 (26.6)	47 (30.3)
> 2-fold decrease	60 (30.2)	65 (32.3)	52 (33.8)	56 (36.1)

Source: Trial 2302 CSR, Table 11-6, pp75

The TIP group also demonstrated higher frequency of new anti-pseudomonal antibiotic use compared to TOBI (64.9% and 54.5% respectively). Mean duration of use was similar. Historical use of anti-pseudomonal antibiotics (prior to screening) was also similar between TIP and TOBI patients. Hospitalization rates and duration of hospitalization were marginally higher in TIP patients.

In this trial, administration times for TIP ranged from 3.5 to 6 minutes per treatment. Treatment times for TOBI ranged from 18 to 20 minutes.

Results from the TSQM demonstrated that in the effectiveness, convenience, and global satisfaction domains, TIP had statistically more favorable scores

compared to TOBI. The least square mean differences for effectiveness, convenience, and global satisfaction were 9.36 (1.46), 24.35 (1.547), and 5.2 (1.655), respectively.

Despite differences in those TSQM domains, compliance was slightly lower in the TIP group versus TOBI (90.30% versus 94.32% overall). Additionally, the major protocol deviation of taking <80% study drug was higher markedly higher in the TIP (17.9%) compared to TOBI (9.1%) groups.

Reviewer Comment:

The relative change from baseline in FEV-1 percent predicted is similar between the TIP and TOBI groups. Both TIP and TOBI had minimal effect on FEV-1 percent predicted. In comparing the treatment effect to trial 2301, it is much more modest; however, given that over half the patients in both groups had had anti-pseudomonal antibiotics within 1-3 months and a quarter within 30 days prior to the first dose of study drug, this is not surprising. Recent previous exposure to anti-pseudomonal antibiotics could have diluted the treatment effect in both groups. Because of this, non-inferiority conclusions based on the sponsor NI-margin are not likely valid.

With regard to the microbiology results, the increase seen in MICs for the TIP versus TOBI group may imply that usage of TIP encourages antibiotic resistance more so than TOBI. It is also concerning that TIP patients more frequently received other anti-pseudomonal antibiotics during the trial compared to TOBI patients. Anti-pseudomonal antibiotics (oral, IV, or inhaled) are generally given in response to increased symptoms or pulmonary exacerbations. This finding may imply that TIP is less effective than TOBI. Results of the TSQM are difficult to interpret as the questionnaire was significantly modified for use in this trial. Although compliance was similar in the trial, it is unclear what the 'real world,' long term compliance would be.

Safety:

There were 3 deaths in this study, all in the TIP group. One death was due to a drug overdose (recreational), the other 2 (21 year old male and 24 year old female) were related to pulmonary exacerbations and respiratory failure. The latter 2 deaths were both in patients with severe lung disease (based on FEV-1) and likely represented normal disease progression. All were over 30 days after study drug. SAE frequency was similar between TIP and TOBI groups (27.4% and 29.2% respectively). The most common were 'lung disorders,' 'hemoptysis,' and 'cough.' With each successive cycle the frequency of SAEs for both groups decreased. This may have been related to patient drop out.

Adverse events leading to discontinuations were higher in the TIP group (14.9%) as compared to TOBI (8.1%). Across all three cycles, AEs in the Respiratory, Thoracic, and Mediastinal system organ class were the most frequent cause (11% TIP, 5.7% TOBI). By preferred term, cough (3.9% TIP, 1% TOBI). dyspnea

(2.6% TIP, 1.9% TOBI), chest discomfort (1.6% TIP, 0% TOBI), bronchospasm (1% TIP, 0% TOBI), and dysphonia (1% TIP, 0% TOBI) most frequently lead to discontinuation and demonstrated an imbalance. Discontinuations due to AEs decreased with each subsequent cycle.

Over all three treatment cycles, common AEs ($\geq 2\%$) were more frequent in the TIP group (90.3%) as compared to TOBI group (84.2%). This difference was most noticeable in the first cycle (77.9% vs. 66.5%); in cycles 2 and 3 the differences were similar. Overall, the SOC with the most frequent reported AEs was Respiratory, Mediastinal, and Thoracic (79.9% TIP, 67.5% TOBI). Common AEs that demonstrated an imbalance between TIP and TOBI groups are summarized in Table 4.

Table 4. Common AEs ($\geq 2\%$) that demonstrated and imbalance

AEs by Preferred Term	TIP N=308 n(%)	TOBI N=209 n(%)
Total	278 (90.3%)	176 (84.2)
Cough	149 (48.4)	65 (31.1)
Lung disorder	104 (33.8)	63 (30.1)
Dyspnoea	48 (15.6)	26 (12.4)
Pyrexia	48 (15.6)	26 (12.4)
Oropharyngeal pain	43 (14.0)	22 (10.5)
Dysphonia	42 (13.6)	8 (3.8)
Haemoptysis	40 (13.0)	26 (12.4)
Rales	22 (7.1)	13 (6.2)
Wheezing	21 (6.8)	13 (6.2)
Chest discomfort	20 (6.5)	6 (2.9)
Fatigue	20 (6.5)	10 (4.8)
Vomiting	19 (6.2)	12 (5.7)
Pulmonary congestion	17 (5.5)	9 (4.3)
Weight decreased	15 (4.9)	8 (3.8)
Throat irritation	14 (4.5)	4 (1.9)
Decreased appetite	13 (4.2)	7 (3.3)
Diarrhea	13 (4.2)	4 (1.9)
Sinus headache	13 (4.2)	6 (2.9)
Dysgeusia	12 (3.9)	1 (0.5)
Forced expiratory volume decreased	12 (3.9)	2 (1.0)
Blood glucose increased	9 (2.9)	1 (0.5)
Insomnia	9 (2.9)	5 (2.4)
Rhinitis	9 (2.9)	5 (2.4)
Arthralgia	8 (2.6)	4 (1.9)
Epistaxis	8 (2.6)	4 (1.9)
Pain	8 (2.6)	2 (1.0)
Dyspnoea exertional	7 (2.3)	0 (0.0)
Lower respiratory tract infection	7 (2.3)	2 (1.0)
Lymphadenopathy	7 (2.3)	1 (0.5)
Nasal mucosal disorder	7 (2.3)	0 (0.0)

Source: Trial 2302 CSR, Table 12-4, pp89

Reviewer comment:

Overall, deaths and SAEs were similar between groups. The most common imbalanced AEs leading to discontinuation (cough, dyspnea, chest discomfort, bronchospasm, and dysphonia) may be in part related to known reactions to dry powder formulations. Though the formulation may have contributed, these events were significant enough to warrant discontinuation. As such, they cannot be disregarded. The decrease in discontinuations seen with successive cycles is likely related to selection for tolerant patients.

Common AEs (≥2%) were more common in TIP patients compared to TOBI. This appeared to be driven primarily by AEs partially attributable to the dry powder formulation (e.g. cough, dysphonia, chest discomfort, throat irritation, dygeusia). These AEs while notable are clinically monitorable, and do not lead to permanent impairment. In clinical practice, patients who exhibit these AEs could easily be switched to another inhaled antibiotic, with minimal detrimental effect. More concerning than the common AEs is the imbalance in anti-pseudomonal antibiotic use.

AEs of special interest:

Cough:

Cough was more frequent in the TIP versus TOBI groups overall. For TIP, cough was almost twice as frequent when on TIP (28 day on-cycle) versus when off TIP (28 day off cycle). The difference was minimal in the TOBI groups. Based on this, increased cough may have been related to TIP usage. This data is summarized in Table 5.

Table 5. Cough by cycle

Cycle	Treatment Period	TIP N=308 N(%)	TOBI N=209 N(%)
1	On	82 (26.6)	24 (11.5)
	Off	45 (14.6)	23 (11.1)
	On and Off	116 (37.7)	45 (21.5)
2	On	30 (11.4)	18 (10.1)
	Off	20 (7.6)	11 (6.1)
	On and Off	47 (17.8)	28 (15.7)
3	On	14 (17.5)	10 (5.8)
	Off	22 (9.4)	13 (7.6)
	On and Off	55 (23.5)	20 (11.7)

Source: Trial 2302 CSR, Table 12-9, pp108

Bronchoreactivity:

In cycle 1, bronchospasm (FEV-1 decrease >20%) following TIP administration was more frequent compared to following TOBI administration (1.2% v. 0.6%). However in cycles 2 and 3 there was no clear imbalance. It should be noted that drop out was higher for the TIP group versus TOBI, which could explain why in cycle 2 and 3 there was no clear imbalance.

Hearing:

A subset of 78 (25.3%) TIP patients and 45 (21.5%) TOBI patients had formal hearing assessments. In both groups, approximately 79% had normal baseline hearing assessments. Over the entire study, 25.6% (20) of TIP patients and 15.6% (7) of TOBI patients had hearing loss based on audiologic testing. Of these patients, 18% (14) of TIP patients and 13% (6) TOBI patients had decreases in their final audiology assessment.

With regard to PK parameters, systemic exposure to Tobramycin trended higher compared to TOBI, however, confidence intervals were widely overlapping.

Reviewer comment:

Based on these results, TIP administration likely results in cough and bronchoreactivity in a subset of CF patients. However, these reactions are easily monitored and patients can be screened after initial dosing. This is routinely done by many practicing pediatric pulmonologist for certain inhalational medications. As such, while the cough and bronchoreactivity seen shortly after TIP administration may limit which patients can receive TIP, it is not a significant safety concern. However, the hearing loss is a significant concern. Unlike cough and bronchoreactivity, the increased frequency of hearing loss is not likely related to the dry powder formulation. The increased frequency of hearing loss is especially concerning as CF patients are already at risk of hearing loss due to a lifetime of aminoglycoside exposure and would likely be on TIP chronically. Additionally, in most the patients, the hearing loss persisted at their final audiology assessment. While there was recovery of hearing in 2301, the patient population in 2302 is more representative of those who would use TIP (i.e. patients who have received inhaled anti-pseudomonal antibiotics).

Overall Comment on Trial 2302:

No non-inferiority conclusions can made based on the data and NI margin provided by the sponsor. However, it is relatively clear that based on multiple parameters, the safety profile of TIP is less favorable than TOBI. Additionally, TIP patients were more likely to require anti-pseudomonal antibiotics and have more resistant pseudomonas.

REFERENCES

Dziuban EJ, Saab-Abazeed L, Chaudhry SR, Streetman DS, Nasr SZ. Identifying barriers to treatment adherence and related attitudinal patterns in adolescents with cystic fibrosis. *Pediatr Pulmonol.* 2010 May;45(5):450-8.

Kettler LJ, Sawyer SM, Winefield HR, Greville HW. Determinants of adherence in adults with cystic fibrosis. *Thorax.* 2002 May;57(5):459-64.

Que C, Cullinan P, Geddes D. Improving rate of decline of FEV1 in young adults with cystic fibrosis. *Thorax.* 2006 Feb;61(2):155-7.

Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros*. 2009 Mar;8(2):91-6.

Tiddens HA, Geller DE, Challoner P, Speirs RJ, Kesser KC, Overbeek SE, Humble D, Shrewsbury SB, Standaert TA. Effect of dry powder inhaler resistance of teh inspiratory flow rates and volumes of Cystic Fibrosis patients of six years and older. *Journal of Aerosol Medicine* 2006. 19(4):454-465.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT H LIM
07/18/2012

THERESA M MICHELE
07/19/2012

LYDIA I GILBERT MCCLAIN
07/19/2012
I concur