

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201688s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 20, 2012
From	Eileen Navarro, MD
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 201, 688 (IND 64409)
Supplement#	S000
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	21-DEC-2011
PDUFA Goal Date	19-OCT-2012
GRMP Goal Date	16-SEP-2012
Proprietary / Established (USAN) names	TOBI Podhaler™ Tobramycin
Dosage forms / Strength	Four - 28 mg capsules administered twice daily, in two inhalations per tablet for a total of 4 capsules (8 inhalations) per dose in a 28 day cycle of treatment followed by 28 days off treatment.
Proposed Indication(s)	Treatment of CF patients with chronic <i>P. aeruginosa</i> infections.
Recommended:	<i>Approval with Postmarketing Requirements</i>

- **Summary:**

The drug product proposed in this NDA505b(1) submission, TOBI® Podhaler™ (tobramycin inhalation powder), is a dry powder formulation, intended as alternative to the currently marketed product tobramycin solution in saline. It is the first antimicrobial powder developed for any respiratory indication. At issue is whether the this alternative formulation, delivered via a novel device, affords similar benefits and assures similar safety as the identical drug substance marketed as a liquid solution, so as to serve as a treatment alternative for cystic fibrosis in patients ages 6 and older, who are chronically colonized with *Pseudomonas aeruginosa*. One of two placebo controlled trials concludes significant benefit using the FEV1 increment endpoint at 1 month, whereas the other trial failed recruitment goals and the difference favoring the new drug was not statistically conclusive of a benefit. In a large comparative safety study, cough and upper airway adverse reactions, none serious, were seen with TIP compared to TOBI. A similar increment in FEV1 was seen with TIP compared to the standard of care, and notwithstanding a greater need for rescue oral antimicrobial, rates of hospitalization and intravenous antibiotic therapy were similar between the two study arms. Three deaths, all in the TIP arm are attributed to breakthrough infectious exacerbation of CF. Following treatment, more resistant *P. aeruginosa* isolates were seen in the TIP arm; the increment in MIC for this small number of isolates was disproportionately higher than seen with TOBI. There are no minimum inhibitory concentrations (MIC) standards established for resistance in *P aeruginosa* airway infections; resistance as defined by MICs for systemic infections has not been shown to correlate with treatment failures in CF and other airway infections. Increased adherence was not seen with TIP, compared to TOBI, despite the shorter drug administration time, and the portability and simplified maintenance of the inhaler. A single placebo-controlled (2301) study provides a direct measure of treatment effect in this drug development program, for an endpoint demonstrated to correlate in the long term with increased survival. The applicant also concludes noninferior efficacy of TIP relative to TOBI,

using the same pulmonary function endpoint, in a comparative trial (2302) although the margin of benefit was not justified sufficiently *apriori*. The Agency, however, has adequate experience in placebo controlled trials for this endpoint in this indication, to put this proposed margin for a treatment effect in context, as it has in the past¹. Nonetheless, data from the NDA provides little information on pulmonary drug delivery from the inhaler in patients with limited pulmonary flows (such as in pediatric patients with FEV1 <40% of predicted or the frail elderly). As well there is limited long term follow up to assess impact of resistance development, no instructions for use demonstrated to predictably limit errors of use, limited long terms outcome assessment for clinically relevant endpoints such as exacerbation rate, hospitalization, rescue antimicrobial use and death. Given the limits of information in the drug development program, the Division should require postmarketing studies that fill the gap in information, and craft a label that conveys these gaps. Foreign regulators in the EU required a postmarketing study in pediatric patients that would assess usability in the younger age group and assess long term efficacy of the product over 48 weeks (6 cycles). The applicant plans a “real world study in the US (Study C2407), contingent upon US approval that would compare safety ((b)(4)) and other clinical efficacy endpoints (b)(4) with an approved inhaled product”. I recommend that the (b)(4) also be assessed in this study and that the comparator be TOBI .

¹ Response to GAO inquiry – NI margins for antifungal agents

Cross Discipline Team Leader Review Template

1. Introduction

The drug product proposed in this NDA505b(1) submission, TOBI® Podhaler™ (tobramycin inhalation powder), is a dry powder formulation is intended as an alternative to the currently marketed inhalation solution TOBI® with the same active ingredient, tobramycin. The applicant of this New Drug Application (NDA) presents two placebo controlled trials conducted mainly in pediatric patients and one comparative safety trial largely in adults, to provide evidence of the safety and efficacy of TOBI Podhaler (referred to as TIP in the rest of this document), a powder formulation of tobramycin for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. TIP is a dry powder packaged in a hard capsule. Drug delivery for this new powder formulation of tobramycin is via a handheld, manually operated, breath-activated T-326 dry powder inhaler (DPI). The inhaler is intended for replacement every 7 days. TIP 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. TIP is marketed in Canada, Chile, Colombia, Germany, The Netherlands, Norway, Denmark, Ireland, and the UK countries.

2. Background

CF is an orphan disease, there are 30 000 patients in the US with this autosomal recessive disease. The ion transport defects in cystic fibrosis (CF) lead to low volumes of fluids essential to the function of mucosal surfaces and secretory organs. In the lung, the small volumes of thick viscid mucus predispose to chronic infections with *Pseudomonas aeruginosa*. Antibiotics to treat *P. aeruginosa* pulmonary infections have resulted in improved pulmonary function (as measured by FEV1) and a corollary increase in survival in patients with CF. As treatment of episodic exacerbations of CF with antipseudomonal antibiotics has proven beneficial, the chronic intermittent use of antibiotics for chronic suppression of *P. aeruginosa* is standard of care. CFF guidelines strongly recommend chronic use of inhaled tobramycin in CF patients 6 years and older with FEV1% predicted <40 to 69² and persistent *P. aeruginosa* in airway cultures. The CFF also recommends inhaled tobramycin use in asymptomatic CF patients 6 year older; however, the evidence supporting this recommendation is weaker. The duration of 'chronic' therapy is not defined. In clinical practice, patients generally remain on cycled inhaled antibacterial drugs indefinitely.

Three drugs, belonging to three different antimicrobial classes, are approved for the treatment of *Pseudomonas aeruginosa* in CF.

Ciprofloxacin, a fluoroquinolone antimicrobial, is approved for the treatment of acute pulmonary exacerbations in CF patients 5-17 years, based on a comparative study demonstrating improved symptoms of exacerbation in 67 patients who receive d ciprofloxacin 10mg/kg/dose q8h IV for one week followed by ciprofloxacin tablets 20mg/kg/dose q12h to

² Flume PA, O'Sullivan BP, Robinson KA, et al Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health Am J Respir Crit Care Med 176:957-969, 2007

complete 10-21 days treatment. Concerns regarding chondrotoxicity limit long term use of this drug class in pediatric patients.

For the chronic suppression of *P. aeruginosa*, liquid formulations of the aminoglycoside tobramycin (TOBI®) and the monobactam aztreonam (Cayston®) are approved for use by inhalation with nebulizers. TOBI® (NDA 50 753) is specifically indicated for use with the Pari LC Plus nebulizer and Pulmo-aide air compressor. The treatment dose is 300 mg inhaled delivered in 15 minutes twice daily for repeated cycles of 28 days on drug and 28 days off drug. Cayston® (NDA 50814) is formulated for inhalation via the Altera nebulizer (75mg delivered in 2-3 minutes per dose TID). Although the indication of use for Cayston differs from TOBI^c (to improve respiratory symptoms in CF patients with *P. aeruginosa* for a single 28 day cycle of therapy), in the clinical setting, it is often used in a manner similar to TOBI®. The intravenous formulations of both drugs are also used off-label to treat acute exacerbations of CF. Cayston was filed as a 505b2, allowing FDA to rely in part on the finding of effectiveness of the parenteral formulation aztreonam; in the EU, the drug is labeled for use only in patients 18 and older. In the current NDA, the applicant similarly references the effectiveness of TOBI although studies supporting TIP efficacy were conducted and stand on their own.

Given the microenvironment in thick dry mucus secretions of the CF patient, the chronic use of inhaled hypertonic saline is recommended by the CF foundation to improve lung function and to reduce exacerbations (^{ibid Flume}). A concern regarding the use of this tobramycin powder formulation, is that the powder may be less efficacious than TOBI® which is a liquid solution in saline. While the serum pharmacokinetic studies indicate that absorption of the powder TIP is more efficient than that of the inhaled solution, activity at the endobronchial and peripheral airways is not known to correlate with serum PK of topically acting products in CF (^{ibid Flume}).

3. CMC/Device

TIP is the first antimicrobial powder formulation developed for inhalation and similar to TOBI, is intended for chronic use. Dr. Mark Seggel finds that sufficient information is provided in the NDA to assure the identity, strength, quality, purity, and potency of the drug product and that the labels have provide requisite information (e.g., description, how supplied, storage statements). He recommends approval pending favorable GMP inspections as reflected in a recommendation from the Office of Compliance. The quality product microbiology reviewer Stephen E. Langille, Ph.D. likewise recommends approval.

Drug Substance: The drug substance, tobramycin, is identical to that used to manufacture the approved TOBI (NDA 50-753, referenced by the applicant, who also provides references the DMF of the two drug substance manufacturers, (b)(4) (DMF (b)(4)) and (b)(4) (DMF (b)(4)). There are no inspectional issues related to the drug substance.

Drug Product: The API Tobramycin is a (b)(4) antibiotic mixed (b)(4) with sulfuric acid (salt forming and pH adjustment), DSPC and calcium chloride (wall forming) and perflubron (poreforming agent (b)(4)). Spray drying yields (b)(4) particles with porous structure which is dispensed into capsules. TOBI® Podhalertm capsules each contain 28 mg of tobramycin powder (corresponds to a target delivered dose of 25.5 mg tobramycin per capsule).

Two powder formulations were used in the drug development of TIP. The first formulation TS-001 was used in the normal volunteer phase 1 study 000INH-007 whereas CN1-002 was used in the dose ranging phase 1 and in all phase 3 studies (C2301, C2302 and 2303). Due to the (b) (4) Dr. Seggel raised early concern that (b) (4) could contribute to product (u) (4), reducing overall efficacy of the product. The manufacturing process for CN1-002 was further modified to reduce variability in powder characteristics as the sponsor prepared to scale up manufacturing; FDA required an additional placebo controlled study (C2303) to bridge the safety and efficacy of this final product with that seen in the two other phase 3 studies. Dr. Seggel concludes that the final product addresses previous concerns about stability and product quality attributes. Further, the bridging serum pharmacokinetics of tobramycin was shown to be unaltered due to the change in manufacturing process (see Dr. Ryan’s Clinical Pharmacology review for details).

Mr. Sugato De, consultant reviewer from CDRH for the Podhaler device, concludes that the device engineering is adequate. Other CDRH colleagues, Dr. Quynh Nguyen and the DMEPA reviewer, Dr. Alex Winiarski, who reviewed the Human Factors study, likewise do not recommend device approval. The issues raised in the course of the development of TIP are summarized below:

Delivery Device: The inhaler device Podhaler™, referred to as T-326 preapproval, is a hand held, breath-actuated oral inhaler replaced every 7 days.

To administer a TIP dose, 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, inhale twice (counting to 5 after each inhalation) and check the capsule to determine if the capsule was emptied. These 5 steps must be repeated an 4 times to administer a full dose (4 TIP capsules=112 mg). Two such doses are administered daily for one 28-day on-therapy cycle.

To assess suitability of the device and its ability to deliver TIP, the applicant conducted a study in normal volunteers (Study IN-007) and in CF patients (TIP001) comparing the systemic exposure, sputum exposure and the lung deposition between TIP and TOBI formulations as the parameters of interest to aid in dose selection. Study IN-007 is not summarized in any of the CDRH reviews and the sponsor’s characterization of the study is abridged below:

- Study IN-007 assessed lung distribution, pharmacokinetics and safety of ascending doses of radiolabeled TIP and TOBI® in healthy adults volunteers who were not receiving bronchodilators or other medications. While a greater distribution of tobramycin (measured as

Table 1 Percent of total radioactivity in normal volunteers

	TIP (N=13)	TOBI (N=13)
Central lung	9.3 ± 3.0	1.4 ± 0.8
Peripheral lung	13.7 ± 2.5	1.9 ± 0.7
Total lung	34.3 ± 5.8	5.0 ± 2.0
Mouth, esophagus, stomach	43.7 ± 8.4	8.2 ± 3.6

%

radioactivity)

was seen in the lung and mouth with TIP compared to TOBI® (table), it required more than a single inhalation to deliver the required dose (data not shown). The reported lung deposition for TOBI in this study was about half that predicted from published data and the TOBI NDA. The sponsor concluded that better lung distribution could be achieved with >1 inhalation per capsule and that 4 capsules should constitute the dose for TIP. The AE rate from these exposures is shown in Table 2, reproduced from the sponsor’s complete study report and provides early indication of the relative rates of adverse reactions between the two drug formulations.

Table 2 Adverse Events by Treatment

	Number (%) AE by subject	AE Incidence
TIP 1 inhalation (18 mg)	5/14 (35.7)	12
TIP inhalation (18 x 6 =72 mg)	4/12 (33.3)	8
TOBI (300 mg)	3/13 (23.0)	3

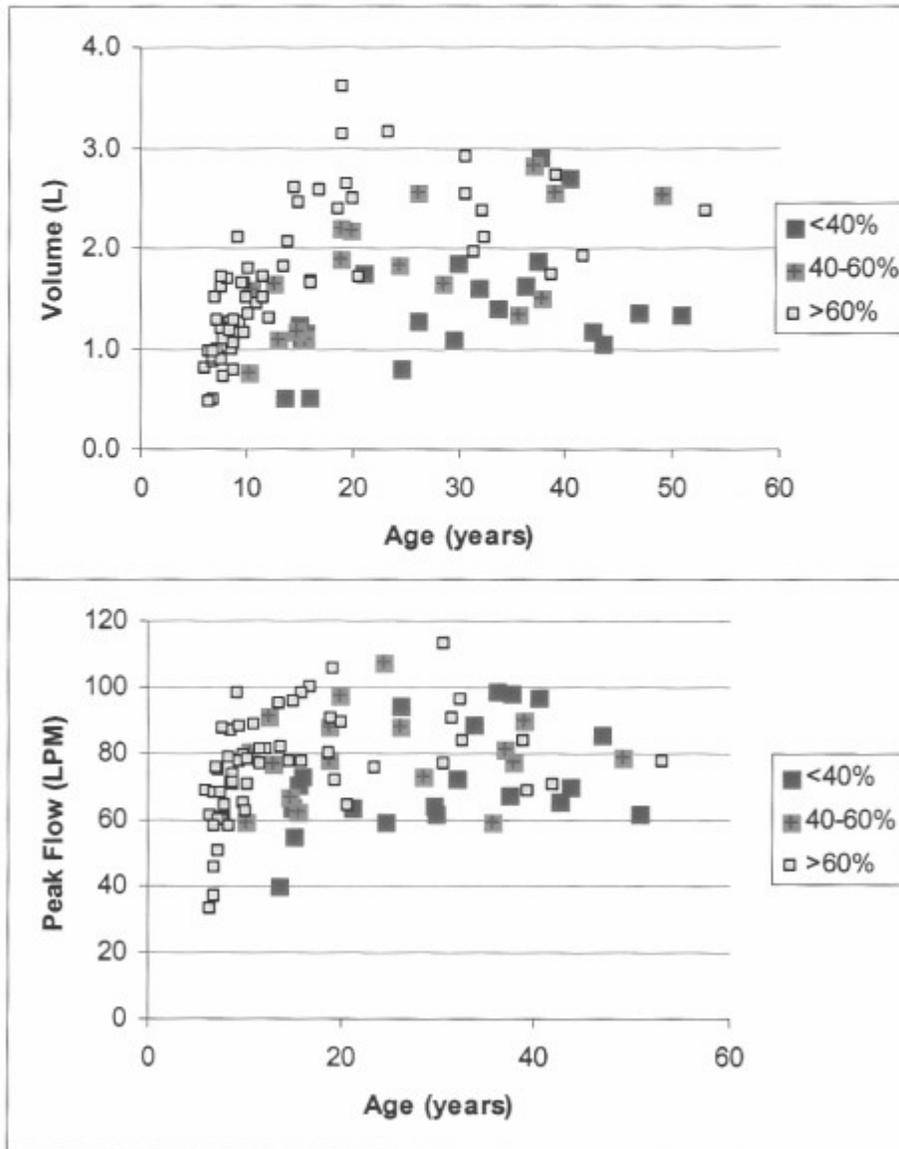
- Study TSB-001 was designed to derive optimal flow and performance characteristics of the simulated device in delivery of TIP to smaller subjects and/or subjects with more restrictive lung disease. CF patients aged 6 to 53 years, (mean age 20 years, 20% of whom had FEV< 40% of predicted) were enrolled, of whom only 27% of patients were capable of inspiratory volumes of 2 liters. While all patients achieved a peak flow rate of (b) (4) the minimum peak flow rate required to utilize the device, the lowest values approaching this limit were seen in the youngest age group. The study did not include pediatric CF patients with the full range of inspiratory flow profiles, 2 patient 6-10 years had an FEV1 <60% predicted, and none had an FEV1<40% predicted. This study was not described in the review by Mr. Sugato De and portions relevant to understanding device use are reproduced below. The study report (Page 30 CSR TBM100ctsb001) concludes:

“The 6-10 year old age group is representative of both the youngest age group currently approved for the therapeutic use of Tobramycin (TOBI®) and the lower volumes and flows attained by the CF population. In order to be certain that virtually all CF patients can effectively use the T-326 inhaler, future in-vitro performance tests should utilize both the pediatric inspiratory flow profiles and volumes and flows common to this age group.”

The team raised concerns about the performance of the inhaler for patients incapable of inspiratory volumes of 2 liters or peak flow rates of (b) (4). The Pulmonary consultants consider this limitation less meaningful for US CF pediatric patients, who are likely to be healthier and to have FEV1 > 40% predicted.

Plots of the inspired volumes and peak flows against age were made (Figure 3). Beyond the age of 15, there does not appear to be a clear trend of either volume or flow with age. Adults with severe lung disease are within the range of the 6-10 year olds for both inspired volume and flow.

Figure 3. Inspired volume (top panel) and peak flow (bottom panel) plotted against age.



- **CDTL comment:**
Studies INH-001 and TSB-001 assess drug delivery through the device and the clinical data need to be viewed with an understanding of the limitations of the device delivery

system to appreciate its labeling implications. Study INH-001 concludes that more than one inhalation is needed to deliver the drug – instructions for use should clarify that a full dose consists of 4 capsules and that each capsule should be emptied by effective inhalation. Study TSB-001 assessed delivery in only 2 pediatric patients with FEV1<60% predicted and none below FEV1<40% predicted. Note that the CF foundation strongly recommends use of inhaled antibiotics in patients with severe (<40% predicted) to moderately severe disease (<70%), based on their FEV1. Although it is probably true that most US cystic fibrosis pediatric patients would have mild to moderately severe CF, some patients with severe CF or those that are poorly nourished with low BMI, may not derive full benefit. I requested Drs. Mishra and Kadoorie to perform an analysis of the primary endpoint stratified by age and severity of lung function to determine the proportions of patients with limited pulmonary reserve as well as the benefit derived from TIP inhalation in these patient subgroups. Dr. Mishra looked at the mean and range of change in FEV1 in 2301 and 2302 and found 3 TIP treated subjects in 2301, all of whom derived benefit and in 2302 where the mean FEV1 increased was ~12% over baseline, thus no concerns are raised regarding limited benefit in patients with diminished pulmonary reserve. Dr. Kadoorie's analysis is pending at the time of this review.

To extend labeling to pediatric patients with FEV1 <40% predicted, I recommend either an in-vitro study (as per the study INH-007 conclusions) or restricted labeling until efficacy and safety is established in such patients.

In his review of the descriptive information for the proposed inhaler and the data characterizing its performance, Mr. Sugato De, M.S., Biomedical engineer (ODE/DAGID/ARDB) concludes that the applicant has demonstrated the ability of the device to deliver the respirable product from an engineering standpoint. Based on both the simulated flow rate study and the results of the Phase I clinical study, he concludes that the information is adequate to assess delivery delivers of the target dose (with a mass-median aerosol diameter between (b) (4) over the batches of products studied) and assess the device for mechanical safety and reliability. However he concludes that the biocompatibility testing is insufficient and that approval cannot be recommended; the device is categorized as an externally communicating device with tissue contact and that there is a potential for chemical leachants entering the patients airway. They consider the information submitted to be minimally acceptable testing and not sufficient to validate biocompatibility for an externally communicating device with tissue contact. If CDER agrees with the device categorization, subchronic toxicity, genotoxicity and implantation tests would be conducted by the sponsor. If the leachables and extractables are shown to be below a threshold known to be associated with toxicity, then additional testing may not be necessary. He recommended that the biocompatibility testing be selected in accordance with ISO 10993 with attention to appropriate duration and level of contact of the device and that cumulative duration of use be considered in determining patient contact. The Pulmonary (Dr. Peri Prasad) and DAIP (Dr. Mark Seggel) chemists, do not agree with this categorization. Consistent with the Pulmonary drug product review team viewpoint, classification of the dry powder inhaler as an “externally communicating” is not warranted. Dr. Seggel writes” *The gas path and [dry] drug product contact surfaces are the same material. ..(L)ow levels of extractables (were) observed*

in controlled extraction studies. ..Assessment of extracts per ISO 10993 (cytotoxicity, sensitization, and irritation) and USP <88> (acute systemic toxicity) is routinely considered sufficient for demonstrating biocompatibility of dry powder inhalers and other inhalation devices. The results of these tests on T-326 components were negative”. Dr. Amy Ellis, toxicologist agrees with their assessment.

Mr. De concludes

*“The Center for Devices and Radiological Health (CDRH) recognizes that there are a range of human factors and clinical efficacy concerns with the proposed product. Specifically, the human factors study results demonstrate patterns of failures, use errors and operational difficulties. These issues are expected to lead to **modifications to product labeling** and also **user training**. In addition, a number of these issues may reasonably lead to **design changes that may affect the performance of the proposed device.**”*

CDTL comment: I agree with the CDER reviewers for the following reasons:

- a) total time of exposure to the device is brief per dose**
- b) the device does require contact with the pseudostratified epithelium in the lips during the process of inhalation. This is not analogous to the mucosal exposures to the buccal , nasopharyngeal, laryngeal and tracheal epithelium that occurs with an endotracheal tube or to the endovascular exposure seen with intravenous catheters, for which such studies are required.**
- c) device is discarded after 7 days and formulation is a dry powder, so possibility of breakdown and leaching /extracting of device plastic components is anticipated to be minimal**
- d) potential for inhalation of fragments is minimal given the filter**
- e) the product has been marketed worldwide for a total of 83.15 patient treatment years and Dr. Shrimant Mishra’s review of the postmarketing experience finds no unusual adverse events implying mucosal incompatibility with the device (lip swelling, pain etc). Local tolerability issues (dysphonia and dysgeusia) are attributed to the drug rather than the device and although more frequent with TIP compared to TOBI, have been reported with other inhaled antibiotic products as well.**

At the time of this review, DAIP has not been in receipt of the labeling modifications, user training and design changes from CDRH referred to in Dr. Sugato De’s review.

Table 3 Human Factors, Usability and Comprehension of Instructions for Use

The applicant sites the following device usability evaluation studies in their NDA:

Study No.	Study Title
TBM100 Formative adult usability report	Adult usability study
TBM100 EU Readability report	TBM100C Consultation w/ patients target groups
TBM100 Formative child usability report	Child CF study Report
TBM100 EU summative child usability report	T-326 Inhaler usability evaluation in children
TBM100 US summative usability report	TOBI Podhaler (T-326 inhaler) usability evaluation final report
TBM100 Packaging evolution report	Packaging and IFU evolution - technical memo
TBM100 Usability summary report	TOBI Podhaler Human Factors Engineering/ Usability Engineering report

The studies were designed to assess the ability of different subgroups to properly use the combination of drug and device, to demonstrate successful performance of all essential and critical tasks associated with complete drug delivery per dose by representative users, to obtain subjective measures using rating scales/questionnaires and assess comprehension of the instructions for use of the drug- device product.

Dr. Quynh Nguyen, who reviewed the human factors and usability of the device T326 (TBM100 US summative usability report) with Dr. Aleksander Winiarski , DMEPA reviewer

recommend against approval due to the unacceptable error rate for several individual steps in dosing TIP, the limitations of the study assessing instructions for use, the inability to provide assurance regarding safe and effective drug-device use. In this study, patients and their adult caregivers, in the case of pediatric patients, were provided the instructions for use, interviewed and trained by a representative, and their initial use observed for errors. A 5-day at home use was then conducted, with commercial weekly patients packs containing empty capsules. This was followed by a post 1 week dosing observation, followed by a second interview. More patients in this study (N=50) had a diagnosis of asthma than cystic fibrosis (N=12). This is notable in that patients with asthma often use powder formulations (such as corticosteroids)³, some using similar dry powder inhalers; whereas CF patients have not.

Initial Training and Use

The applicant reports that 85% of subjects followed the correct dosing procedures on the first attempt, and the FDA reviewers disagree as the study assessed only 3 of the 5 dosing steps and the tasks of “inhaling twice from each capsule” and “removing and visually inspecting the capsule to ensure the capsule is pierced and empty” were not tested. In the FDA review, over half of subjects did not correctly administer the dose (53%, 33/62), despite the fact that all participants were trained on the use of the product and received the IFU immediately prior to commencing the study. IFU use was not formally observed. The types of errors observed within the various age groups on the first attempt is shown below:

Table 4 Age-Related Frequency of Various Types of Dosing Errors

Age group (years)	Number of subjects with at least one error	Not Removing Capsules	Not Completely Piercing Capsules	Not Inhaling from 4 Capsules*	Not Inhaling Twice from Each Capsule	Not Checking Capsule	Total number of critical errors**
6 to 8	11/15 (73%)	0	2	2	8	3	15
9 to 12	10/15 (67%)	0	2	3	4	5	14
13 to 17	4/15 (27%)	0	0	0	3	5	8
Over 18	8/16 (50%)	0	0	1	2	7	10
Total	33/64 (52%)	0	4	6	17	20	47

The error rate was highest in the youngest age groups, with errors leading to incomplete dosing predominating. While certain use errors increased in incidence from initial assessment to post one week, the error that could lead to incomplete dosing, i.e. checking that capsule was pierced was of most concern (initial test 17% to 34%). In a separate study, testing whether patients would re-inhale a capsule that was partially full, 11% of subjects did not re-inhale, so examining a capsule may not result in a full dose.

CDTL comment:

The instructions for use that could limit such errors were not considered adequate and not formally tested. At the advisory committee meeting, the sponsor showed an instructional video that I considered effective in providing instructions, and could potentially address the limitations of the IFU. I discussed this with Dr. Winiarski and his supervisor Dr. Carol Holquist, who are open to reviewing other instructional materials. Similar such materials are already widely available as YouTube videos on the internet although their attribution is not known. A PMC is recommended to develop digital

³ <http://www.mayoclinic.com/health/asthma-inhalers/HQ01081>, accessed August 22, 2012.

media that supports the training needs of patients on the use of this drug-device combination. In the interim, the review team has proposed changes to the IFU in concert with DMEPA, CDRH, DPDP, DCDP, DMPP.

Facilities review/inspection and other issues

The product quality microbiology reviewer recommends approval of the NDA. The clinical inspections for the drug product have been completed (see review by Dr. Janice K. Pohlman, DGCP, OSI). Dr. Pohlman finds no violations that alter the conclusions of efficacy and safety. A US investigator, Dr. David E. Geller, who enrolled patients into the safety trial 2302, is cited for violations regarding human subject protection in a study unrelated to this submission; this finding do not alter the ability to rely on the data from this site. The device inspection, which the OC has recently required, will likely not be completed as of the PDUFA date.

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the toxicology review by Dr. Amy Ellis who concludes that the toxicology studies suggest that repeated dosing with TIP will not cause greater systemic or pulmonary toxicity related to tobramycin than the currently marketed drug TOBI®. In the toxicology studies, rats were dosed using nose-only inhalation and the dogs were dosed using a face mask. The animals received drug by breathing a test atmosphere containing the suspended TIP for up to 3 hours (rats) or 45 minutes (dogs) rather than by oral rapid inhalation of the total dose in two breaths as humans would. The concentration of TIP in the test atmosphere in the rat study was about 1 mg/L and the concentration of TIP in the test atmospheres in the dog study ranged from about 2.5-3.0 mg/L. The highest inhaled dose of tobramycin base used in the 26-week rat study was approximately 38 mg/kg/day and the highest inhaled dose of tobramycin base used in the 4-week dog study was approximately 28 mg/kg/day. The pulmonary deposited doses for rats and dogs are assumed to be 10% and 20% of the inhaled dose, respectively. There were no clinical signs of tobramycin toxicity in either species in any of the inhalation toxicity studies conducted with TIP. Histopathologic findings in the respiratory tissues of the rats dosed with TIP for up to 26 weeks were similar to those observed following chronic treatment with TOBI® solution given by nebulization. Kidney changes identical to those observed in older rats as age-related nephropathy were observed at a greater incidence in TIP treated rats than controls. There were fewer findings in dogs dosed with TIP for up to 4 weeks. Nonclinical issues with the DSPC excipient and its degradant (S-Lyso-PC) have been addressed to the clinical pharmacologist's satisfaction through the conduct of appropriate in vivo and in vitro studies.

CDTL comment: In humans, the dose regimen is to inhale the contents of 4 capsules of TIP twice daily, for a total of 224 mg tobramycin powder. This is an inhaled dose of 11.2 mg/kg in a child weighing 20 kg. The high particle volume delivered in 2 breaths is not similar to that of inhaling powder in the ambient atmosphere for 30 minutes to one hour. However, feasibility limits the conduct of testing oral inhalation in the animal models.

5. Clinical Pharmacology/Biopharmaceutics

The pharmacology of TIP was described in 5 clinical studies, the first in normal adults (INH 007) and the rest in patients with CF (TPI 001, C2301, C2303, C2302). Dr. Ryan Owen recommends approval based on his review of these studies. He finds the dose ranging study TPI-001 adequate in that the range of tobramycin concentrations following the administration

of the identified clinical dose of 112 mg of TIP delivers comparable to, or higher than, the range of tobramycin serum and sputum concentrations throughout the 12 hour time course, following the administration of 300 mg TOBI. Since the pharmacokinetics and ADME of tobramycin are well known, the focus of the clinical pharmacology program was to show comparability of the pharmacokinetics achieved with the drug powder relative to the approved liquid tobramycin solution (shown in the table below).

Table 5 Study TPI001 Selected Pharmacokinetic Parameters of Tobramycin in Serum and Sputum Following TOBI® (300 mg) and TIP (28, 56, 84, and 112 mg)

Parameter	TOBI® 300 mg (n = 20)	TIP 2 × 14 mg (n = 11)	TIP 4 × 14 mg (n = 13)	TIP 2 × 28 mg (n = 13)	TIP 3 × 28 mg (n = 15)	TIP 4 × 28 mg (n = 12)
SerumC _{max} (µg/mL)	1.04 ± 0.58	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53
Serum AUC _{inf} (µg·hr/mL)	5.3 ± 2.6	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0
SerumAUC ₀₋₁₂ (µg·hr/mL)	4.8 ± 2.5	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0
SerumHalf-life (hr)	3.0 ± 0.8	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4
Sputum C _{max} (µg/mL)	737 ± 1028	258 ± 194	515 ± 421	574 ± 527	1092 ± 1052	1048 ± 1080
SputumAUC _{inf} (µg·hr/mL)	1302 ± 1127	390 ± 139	1741 ± 1173	855 ± 469	2044 ± 1334	1740 ± 809
SputumAUC ₀₋₁₂ (µg·hr/mL)	974 ± 1143	261 ± 168	1195 ± 1224	652 ± 421	1340 ± 1320	1307 ± 978
Sputum Half-life (hr)	1.7 ± 1.6	0.9 ± 0.8	1.8 ± 0.9	1.3 ± 1.5	0.8 ± 0.8	2.2 ± 1.7

^a Presented as median (range)

To demonstrate that the pharmacokinetics of tobramycin were not altered with the change in the manufacturing process, the applicant developed a population pharmacokinetic model for serum tobramycin based on the pharmacokinetic data from Studies TPI001 and C2301 and C2302, conducted with the CN1-002 formulation using the initial manufacturing process for TIP. Dr. Owen agrees that the applicant's population pharmacokinetic model is valid, and that the serum pharmacokinetics of tobramycin were not altered due to the new manufacturing process.

Assessment of PK/PD relationships between achieved serum and sputum concentrations to treatment success and adverse reactions were attempted. However, the applicant reports that the subset of specimens were mishandled, resulting in insufficient data upon which to draw any conclusions regarding these relationships.

6. Clinical Microbiology

Dr. Peter Coderre finds the short term decrease from baseline in *P. aeruginosa* sputum concentration for TIP superior to placebo and similar to TOBI®. These findings are similar to the microbiologic outcomes for other antibiotic products evaluated in FDA. He also finds low log 10 reduction rates, increased resistance to other antibiotics and increased emergence of other pathogens - The reader is referred to Dr. Coderre's review for greater detail for these analyses.

However, as Dr. Coderre is appropriately concerned regarding the development of resistance in patients receiving TIP relative to TOBI and its potential implications for untreatable infections, he recommends non-approval of the NDA. He cites the greater than 85% increase in tobramycin resistance rate in *P. aeruginosa* isolates from CF patients since 1999 to substantiate his concern and argues for prudent use of antimicrobials in this population⁴.

In study 2302, where treatment experienced patients were enrolled, the MIC90s of the baseline organisms in the TIP arm (64 µg/mL) and the TOBI arm (128 µg/mL) are resistant by the accepted CLSI systemic breakpoints for tobramycin. CLSI systemic interpretive criteria define tobramycin resistance as an MIC ≥ 16 µg/ml for *P. aeruginosa* isolates; the Spanish Antibiogram Committee defines ≥ 128 µg/ml as resistant for inhaled tobramycin. Dr. Coderre also finds greater increases in MIC during therapy for TIP treated patients compared to TOBI as shown in the MIC shift table below.

Table 6 Study C2302 MIC shifts, maximum of *P. aeruginosa* types -1,-2,-3 (ITT population)

Range	N	Tobramycin MIC (mcg/mL)				N	TOBI®	
		Range	MIC50	MIC90	Range		MIC50	MIC90
Baseline	308	≤0.12->512	2	64	208	≤0.12->512	2	128
Week 5	239	≤0.12->512	2	512	173	≤0.12->512	4	64
Week 21	199	≤0.12->512	4	256	154	≤0.12->512	4	256
Week 25	201	≤0.12->512	2	256	155	≤0.12->512	2	64
Termination	298	≤0.12->512	2	512	202	≤0.12->512	2	64

Legend: light grey= two dilution step increase over baseline; dark gray =three or more dilution step increase over baseline

Source: Table 4-18, Clinical Pharmacology Summary, NDA submission

Patients with resistant isolates did not fail therapy; there is no information on the susceptibility of isolates for patients who developed breakthrough exacerbations, as only surveillance cultures were evaluated systematically for MIC shifts. A request for information regarding essential patient attributes that may be associated with resistance development is pending, but was unavailable at the time this CDTL review was completed.

CDTL Comment:

There is a biologically plausible explanation of the resistance seen in the trials reviewed. However, the MIC breakpoints referred to here are based on achievable serum concentrations; which do not relate to topically achievable concentrations, much more so with a drug such as tobramycin. Moreover, there are no in vitro susceptibility test interpretive criteria for isolates of *P. aeruginosa* obtained from the sputum of patients for tobramycin, or aztreonam, which is similarly labeled. Peak sputum levels achieved with TIP exceed the MIC breakpoint concentrations several fold (10 times the MIC90) and fully 95% of patients assessed had sputum concentrations exceeding the MIC90 25 fold. As well, a single sputum sample from a cystic fibrosis patient may contain multiple morphotypes of *Pseudomonas aeruginosa* and each morphotype may have a different level of in vitro susceptibility to tobramycin. The clinical significance of bacterial resistance has not been clearly established in the treatment of cystic fibrosis patients. The lack of correlation between pathogen resistance and clinical failure is also seen with exacerbations of COPD, another endobronchial infection. Whether this is due to limited information, lack of long term follow-up, a pathophysiologic rationale (inflammatory vs infectious disease etc) or lack of assay sensitivity is unclear. The emergence of resistance in

⁴ Shawar et al (1999);

surveillance cultures and in episodic exacerbation episodes should be part of a postmarketing requirement should the drug be approved.

7. Clinical/Statistical- Efficacy

Dr. Christopher Kadoorie concludes “*This submission provided some persuasive evidence of a treatment benefit for patients with cystic fibrosis due to PA using TIP. Study C2301 provided adequate evidence of a TIP treatment benefit, while Study C2303 provided only weak evidence since the primary endpoint was not met. Additionally, Study C2302, an open-label comparative safety study, provided some weak supportive evidence towards the overall risk/benefit assessment.*”

The sponsor also referenced the effectiveness of TOBI and summarized the studies that served to support the original NDA for that tobramycin formulation. As this NDA is a 505b(1) submission, the FDA did not rely on the findings of efficacy of TOBI and considers the evidence from studies conducted by the applicant for NDA 201 688, as the basis for its conclusions.

Placebo Controlled Studies: The sponsor concludes superiority of TIP to placebo for the primary endpoint change in predicted FEV1% from baseline in a single treatment cycle from a pooled analysis of studies 2301 and 2301. The challenge of conducting placebo controlled studies in CF patients with P aeruginosa is reflected in the study limitations of Study 2301 and 2303. Although similar in study design (endpoints, inclusion criteria for age, CF severity, previous use of TOBI etc) the FDA reviewed the efficacy from these two studies individually given important differences in study formulation, differences in outcome and execution, as well as unexplained differences in performance of the placebo group between the two studies. A highly significant treatment effect of 13.8% (5.9, 21.9) was seen in 2301 compared to a modest numerical difference of 5.9% in 2303 (-2.2, 14). Study 2303, conducted on advice of FDA, with a conservative primary endpoint imputing failures to missing data, was conducted in Russia and Eastern Europe and used the to-be-marketed TIP formulation. Study 2303 conducted in 16 centers, fell short of its recruitment targets and is underpowered for its intended superiority analysis. Notable is that despite having enrolled more (N=103) than its planned (N=100) population, only 31 were judged evaluable in the TIP arm. FDA’s review of this failed study agrees with the applicant’s conclusion and is not presented here. Notable as well is that 2303 suffered from imbalance in missing data (greater in TIP), better than expected outcomes in the placebo group, errors in drug dispensation and an outlier response in a 7 year old patient on TIP who had a much lower FEV1 % change than the rest of the TIP patients. This Egyptian male had failure to thrive (11 kg weight, 110 cm height, BMI of 9 kg/m²), a baseline FEV1 of 0.33 L (33% predicted), and a -36.7% relative change from baseline in FEV1 % predicted at Day 29 without any evidence of a severe exacerbation. Technical evaluation of his device and capsules indicated inappropriate use of the device and study medication, borne out by his low, outlying PK values. Study 2301 (n=27 TIP arm) provides evidence that TIP is efficacious in the treatment of CR. The study met its prespecified stopping criterion when the DMC found superiority over placebo in the interim analysis; however, despite the exclusion of data from inexperienced sites with unreliable spirometry, treatment benefit was preserved. The applicants’ primary analysis of Study 2301 (parametric ANCOVA) and the FDA primary analysis (non

parametric ANCOVA) both indicate a statistically different increase in FEV1% predicted over baseline at 28 days for TIP over placebo; please see Dr. Kadoorie’s review for details.

Table 7 Applicant and FDA Analysis of Primary Endpoint: Relative Change from Baseline in FEV1 % Predicted at Day 28 (Study C2301 SIA Population)

	TIP (N=29)	Placebo (N=32)	Mean Treatment Difference (SE)	95% CI for Difference	P-value
Applicant Analysis					
Adjusted Mean (%)	13.97	0.68	13.29 (3.98)	(5.31, 21.28)	p=.0016¹
Unadjusted Mean (%)	13.21	-0.57	13.79 (3.95)	(5.87, 21.70)	p=.0010
FDA Analysis					
Adjusted Mean (%)	12.54	0.09	12.44 (3.77)	(4.89, 20.00)	p=.0017 p=.0061²
Unadjusted Mean (Median) (%)	12.26 (9.52)	-0.57 (-0.29)	12.83 (3.80)	(5.23, 20.44)	p=.0013 p=.0070 ³

1 Applicant’s primary analysis- parametric ANCOVA test adjusted for age, region and baseline FEV1 % predicted using observed data in 58 patients (27 TIP, 31 Placebo)

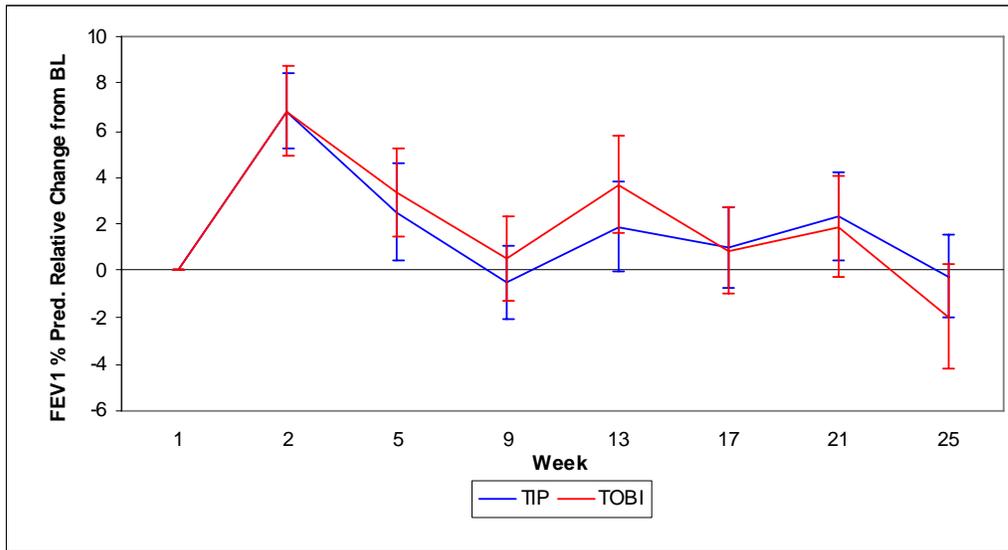
2 FDA’s primary analysis- non-parametric ANCOVA based on ranks adjusted for age, region and baseline FEV1 % predicted, using imputed data

3 FDA’s sensitivity analysis- Unadjusted non-parametric test (Wilcoxon Rank Sum test) using imputed data

Active controlled study: This study does not have a primary efficacy analysis and secondary efficacy analyses are presented here. It is important to note that this study consisted largely of adults, with 69% of the population at least 20 years of age, and with a mean age of 24 years old. In the FDA analysis of efficacy, Dr. Kadoorie notes a larger percentage of discontinuations observed in the TIP, of which a greater proportion were attributed to adverse events (13.0% TIP vs. 8.1% TOBI®). In his analysis, FEV1 % predicted comparisons generally favored TOBI® and approached statistical significance at the end of Cycle 2 (Week 25), (p=0.055), Wilcoxon Rank Sum test. Rates of use of rescue antipseudomonal antibacterial drugs significantly favored TOBI® over TIP (i.e. 64.9% for TIP vs. 54.5% for TOBI®, p=0.018), although the hospitalization rate was similar between the 2 arms (24% TIP vs 22% TOBI). There were 3 deaths in the TIP arm (2 respiratory deaths) and none in the TOBI arm; these deaths appear to be related to respiratory infections and are discussed in detail in Dr. Mishra’s review.

A smaller proportion (73%) of patients completed treatment with TIP compared to TOBI (82%). This is consistent with the fact that the study did not demonstrate improved compliance for TIP vs. TOBI®. As well, while the applicant notes a statistically higher patient satisfaction assessed by questionnaire for TIP in patients that completed treatment, this is a select population, as patients that were dissatisfied and withdrew or discontinued were not available for assessment at the end of treatment. Nonetheless, the FEV1 change in this study throughout the three treatment cycles is shown below and is similar for TIP and OTBI patients that remained on treatment for 3 cycles.

Table 8 Study C2302- Mean FEV1 % Predicted Relative Changes from Baseline with 95% Confidence Limits by Visit (ITT)



In summary, one of two placebo controlled trials concludes benefit based on a change in FEV1% predicted after 1 treatment cycle. Study 2301 with 31 TIP treated patients, half of whom were under 13 years of age, constitutes the efficacy evidence for TIP. A large comparative safety study, conducted mainly in adults, provides insight as to the difference between the new powder formulation and the marketed standard of care, TOBI inhaled solution. Withdrawals and drug discontinuation due to adverse events were seen with the study drug over the inhaled solution and the rate of discontinuations of the powder formulation continued to exceed those seen with the inhaled solution over all 3 cycles. However, patients who are able to tolerate the drug through 3 treated cycles appeared to continue to derive benefit based on the FEV1 improvement over baseline. No benefit was demonstrated in increased adherence with use of the dry powder with a handheld delivery device, compared to the inhaled solution, despite the benefits of shorter administration time, portability, simplified maintenance of the powder inhaler and overall patient satisfaction. A concern the dry powder formulation, delivered via a novel unapproved device entirely reliant on patients’ ability to fully inhale the dry powder, affords similar benefits and assures similar safety as the marketed product, so as to serve as a treatment alternative for cystic fibrosis patients ages 6 and older, who are chronically colonized with *Pseudomonas aeruginosa*.

Emergence or resistance in *P. aeruginosa* was more frequent with the powder formulation. The powder formulation produces similar FEV1 benefit as the inhaler in the exploratory secondary short term analyses. Epidemiologic evidence demonstrating prolonged survival with preserved lung function supports the importance of the FEV1 function endpoint; the clinical benefit from short term FEV1 improvement is brought into question by an increased need for anti Pseudomonal antimicrobial use in the study drug arm relative to placebo and the larger number of missing data for the study drug arm.

CDTL comment:

Based on 1 placebo controlled study with definitive statistical evidence of benefit and one supportive comparative study, the statutory requirement for adequate and well controlled studies has been met for a disease that is ultimately fatal and for which significant morbidity exists. A non-inferiority margin of $\Delta = 6\%$ was pre-specified for the secondary efficacy endpoint, but as the margin was not justified in the submission, the statistical review considers evidence form the

2302 study supportive, but not definitive evidence. The effect size that was proposed to be excluded is not outside the realm of studies that the agency has reviewed and that have served as the basis for the approval of antibiotics and other therapies in this disease. The difference in change in FEV1% predicted relative to baseline in the placebo controlled registrational trials for TOBI was 11 and 8% (NDA 50, 753, see drug label) respectively, for Cayston (NDA 50, 814, see drug label) 10%, for TIS 23 and 11% (NDA 201 820, see statistical review of the NDA) respectively. Similar effect sizes are reported for non antibiotic therapies approved by the FDA, Ivacaftor 10.6 % (Study 102), 12.5% (Study103B), and for Pulmozyme 7.9% once daily, 9% twice daily at 1 week, and 5.6% at 24 weeks, lending external validity to the effect seen with antimicrobials in this indication. Notwithstanding the differences in trial design and populations studied, a consistent effect is seen over placebo and the proposed 4% margin is suitably conservative. As well, I believe that describing the effect in adults over a longer period (beyond the one month endpoint in 2301), as shown in 2302, is important information for clinicians, for what has become, in the majority of patients, a chronic disease in surviving CF patients older than 18 years. As well, leaving out any discussion on efficacy outcomes from this study in the product label precludes a balanced discussion on the limits of correlation between short term FEV1 outcomes and other clinically relevant outcomes in CF such as antipseudomonal use, hospitalizations and exacerbation rates.

8. Safety

The safety experience with TIP in the drug development program is summarized below
 Table 8 Summary of Safety Exposures in the NDA 201688

Study	TIP Safety Population* N	Age mean and range (y)	TIP		TOBI Exposure	
			Exposure (mg)	AE Rate n/N (%)	Exposure	AE Rate n/N (%)
INH 007	14	34 (23-47)	13 mg 1 inhalation	5/14 (35)	300 mg+	3/13 (23)
			80 mg 6 inhalations	4/12 (33)		
TPI 001	66	18-24 TIP cohorts 18 TOBI (7-50)	All doses	40/66 (61)	300 mg	6/20 (30)
			28mg	5/11 (45)		
			56 mg	7/13 (54)		
			56 mg	9/14 (64)		
			84 mg	10/15 (67)		
		112mg	9/13 (69)			
2301	46	12.9	224 mg/dayx3cycles	23/46 (50)	-	
2303	30	12.9 (6-21)	224 mg/day x1 cycle	8/30 (27)	-	
2302	308	25.6 (6-66)	224mg/day x3 cycles	278/309 (90)	300 mg	176 (84.2)

* at least one dose +less than full dose per label instructions

The safety experience in studies 2301 and 2302 best represent the expected safety for the dose and duration of use of TIP, whereas safety in 2303 is likely to best represent the safety for a population analogous to that in the US, i.e. with a large population of adults, highly treatment experienced with chronic antipseudomonal therapy. The sponsor has appropriately analysed Study 2302 as their primary safety population, compared to TOBI.

Safety in comparative Phase 3 Study (C2302)

The mean age of patients in 2302 was 25.6 years, with the oldest patient enrolled being 74, and the oldest treated patient, 66years. This study shows a greater frequency of all adverse events, treatment related adverse events, and discontinuations due to adverse events in the TIP arm relative to TOBI. . Local upper airway adverse events of dysphonia and dysgeusia were seen with greater frequency with TIP compared to TOBI®. Cough was reported as an AE in 48% of TIP patients and 31% of TOBI® patients. When analyzing the AE of cough by subgroup, all age and baseline pulmonary function subgroups had more cough in the TIP arm relative to the TOBI® arm, with the greatest difference seen in the youngest age group. 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 attributed to adverse events (TIP 14% vs. TOBI® 8.1%) and withdrawal of consent (TIP 7.8% and TOBI® 4.3%).EAs that are related to efficacy were mixed, with more patients in TIP requiring antipseudomonal antibiotic rescue (please see Dr. Shrimant Mishra’s review for details), whereas the hospitalization rate did not differ between study arms. Three deaths occurred on the TIP arm compared to none in the TOBI® arm, two of these deaths are attributable to pulmonary exacerbations. However, these deaths occurred late in the off period and are unlikely to reflect direct toxicity of TIP. The number of exposures in this study would allow the exclusion of a serious adverse events occurring at a rate of 1 in 100.

The applicant notes that patients ≥ 6-<13 years of age had overall a low discontinuation rate due to AEs, [TIP arm 3.6% vs TOBI arm 11.1%]; patients ≥13-<20 years of age had slightly higher discontinuation rates due to AEs [TIP 7.6% vs. TOBI 4.2%] and patients above 20 years of age had the greatest discontinuation in TIP relative to TOBI [TIP 17.3% vs TOBI 9.1%. However, as the >20 years constituted the majority of the subjects in the study, this is not unexpected. A breakdown of AEs by decade shown the AE rate to be higher in the younger age groups and persistently reported through the three cycles of treatment for the upper airway events of dysphonia and dysgeusia, possibly related to the use of the device leading to deposition I the oral airway. Whereas the AE rate of cough was seen similarly in all age groups, the AEs of bronchospasm and dyspnea were more common reported in the older age groups, likely representing the severity of disease in this population. The number of events that are a class effect (ototoxicity, nephrotoxicity) are not convincingly different for TIP compared to TOBI, although numerical differences (described in Dr. Mishra’s review) are seen that slightly favor TIP.

Nonetheless, the finding in this comparative phase 3 study were predicted from the AE rates in the two comparative phase 1 studies, both of which showed a greater number of total AEs with the powder formulation relative to the liquid inhaled product TOBI. The reader is referred to Dr. Shrimant’s review for details.

Table 9, Comparative Summary of Safety between TIP and TOBI in NDA 201, 688

Adverse Event (AE) Category	Adverse Event Rate n/N (%)					
	INH 007		TIP 001		2302	
	TIP All doses (N=26)	TOBI® 300 mg (N=13)	TIP All doses (N=66)	TOBI® 300 mg (N=20)	TIP 224 mg (N=308)	TOBI® 300 mg (N=208)
Any AE	34	23	60.6	30	90.3	84.2
Discontinuation due to AE	-	-	1.5	0	14.9	8.1
Serious AE	0	0	1.5	0	27.4	29.2
Treatment related AE	34	15.4	37.8	10	51	20.1

Deaths	0	0	0	0	3	0
Upper airway AE (Dysgeusia)	0	0	6.6	0	3.9	0.5
Lower airway AE (Decreased FEV)	3.8	0	10.6	10	1.2	0.6

CDTL Comment:

In the population tested in the safety database for this NDA, TIP was tolerated by many patients up to a total of 3 cycles of treatment. However, patients who could not tolerate TIP discontinued drug or withdrew early. As well, AEs were more frequent with TIP compared to TOBI although most were mild and severe AEs represented exacerbations and did not require hospitalization. Nonetheless, there are important limitations to the safety characterization of TIP in the NDA relative to the label indication sought and the anticipated use of the drug. Labeling is for “CF patients with *P aeruginosa*” and the standard of care is to use inhaled antibiotics for patients with severe to moderate pulmonary function. Pediatric patients comprised ~10 % of the entire database, and pediatric patients with moderate to severe CF were under represented, consistent with the majority of US pediatric patients. Although adults were represented in the study in proportions that represent the changing epidemiology of the disease, Study 2302 enrolled relatively healthy adults, over half of whom had a mean FEV1 >50%. Duration of exposure is limited to 3 cycles and the safety of chronic treatment is not described. Thus there is a gap in understanding how TIP would be safe (and efficacious) in pediatric patients with moderate disease and older adults with more severe disease. It is also these populations whose flows and volumes were not adequately represented in the distribution and PK studies assessing the device-drug combination in Studies INH-007 and TSB-001.

A relevant concern expressed by Dr. Shrimant at the Advisory Committee meeting is whether benefit is seen in patients with limited pulmonary reserve (FEV1 increment seen in patients with an FEV1 < 30% predicted). This concern was raised due to the two deaths in 2302 attributed to CF exacerbation in patients with ~30 FEV1% predicted, and the 7 year old patient in 2303 who was an extreme outlier with severe declines in FEV1% predicted on treatment. Due to this concern, Dr. Kadoorie performed an additional analysis evaluating the 28 day endpoint across the range of CF severity pooling across the placebo controlled studies and in the comparative study, shown in Table 10 below:

FEV1 % Predicted at Baseline	Mean Relative Change in FEV1 % Predicted at Day 28 (TIP Patients)	
	Study 2301 & 2303 (Pooled)	Study 2302
< 30%	10.98 (N=8)	17.59 (N=20)
[30%, 40%)	2.85 (N=9)	7.28 (N=45)
[40%, 50%)	25.06 (N=5)	3.49 (N=57)
[50%, 60%)	19.31 (N=6)	-0.24 (N=85)
[60%, 70%)	10.89 (N=10)	-0.10 (N=63)
≥ 70%	6.75 (N=22)	-2.50 (N=38)

In Studies 2301 and 2303 (pooled), mean relative changes were highly variable and did not appear to depend much on FEV1 % predicted at baseline. The small number of 2.85% in the [30%, 40%) was heavily influenced by the outlier (Egyptian boy in Study 2303) with a -36.7% relative change. Without this patient, the mean relative change would have been ~ 7.8% in the [30%, 40%) group.

In Study 2302, TIP patients with greater disease severity (FEV1 % predicted < 50%) at baseline tended to show larger mean relative changes, especially those with extremely low FEV1 % predicted at baseline. There was an extreme outlier in the < 30% group, one patient had a relative change of 107.1%, without this patient the mean drops to ~ 12.9% in the < 30% group.

This analysis does not support limitation of the label relative to TOBI which is indicated down to an FEV1 \geq 25% predicted. However, as only 8 pediatric patients and 20 adult patients with an FEV1 < 30% predicted, patients should be counseled regarding the limitation of information in this group of patients.

9. Advisory Committee Meeting

The Advisory Committee (in a meeting held September 5 at White Oak, Silver Spring) voted favorably for the approval of TIP, with one negative vote from the consumer representative. The AC opined that the clinical relevance of the resistance reported needs further characterization but that it should not preclude market availability of the product. There were no labeling limitations proposed.

10. Pediatrics

TIP will be labeled for use in pediatric patients down to age 6. As CF is an orphan disease, the NDA is not subject to PREA requirements. Further, chronic P aeruginosa infections are rare in CF patients under 6 years of age.

11. Other Relevant Regulatory Issues

EES Establishment evaluation requests pending.

12. Labeling

- Proprietary name – TOBI Podhaler approved by OSE reviewer Dr. Winiarski (DMEPA) from a safety and promotional perspective. DMEPA also recommended proposed label and labeling to improve the readability and prominence of important information on the label to promote safe use of the product.
- Instructions for Use – LaShawn Griffiths, MSHS-PH, BSN, RN, Associate Director for Patient Labeling in the Division of Medical Policy Programs (DMPP) stated that the PPI and IFU are at the target reading level of at or below an 8th grade level and in the format that is adherent to the font size needed. DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU provided advice on the product label, IFU, and Patient Labeling.
- Christine Corser, PharmD, Regulatory Review Officer from the Division of Professional Drug Promotion provided labeling comments that were considered by the team in labeling, specially as pertains pregnancy, lactation and teratogenic risk. The issue regarding whether class labeling regarding aminoglycosides is relevant to a product that is poorly absorbed was discussed at length and the accommodation made to the concerns regarding minimization of risk is reflected in the product label.
- Another issue discussed is whether drugs for which drug-drug interactions are known to occur should be listed in patient labeling as “should not take” as has been the

practice employed for patient instructions, per OSE. The Division expressed concern as drug interactions may only require dose adjustment and do not rise to the level of a contraindication, as implied in the proposed patient labeling. The compromise language was “*If you are using TOBI Podhaler, you should discuss with your healthcare provider if you should take:*” followed by the list of interacting medications.

- The following product characteristics that have a labeling impact are summarized from Sugato De’s review:

Product Characterization Summary and Labeling Impact

Study	Section	Conclusions	Impact on Labeling
Determination of appropriate storage conditions	4.3.1	Drug product is stable under the proposed storage conditions. The primary packaging adequately protects the drug product from moisture.	Expiry dating
Stability of primary (unprotected) package	4.3.2	In-use stability data support the proposed drug product instructions for use.	Patients instructed to dose immediately after removing capsules from blister
Effect of storage of the drug product on the particle size distribution	4.3.5	No impact on aerosol performance	Expiry dating
Dose build-up and flow resistance	4.3.6	No impact on aerosol performance through-inhaler life	T-326 Inhaler use life 7 days
Effect of orientation	4.3.8	Orientation of the inhaler during dosing does not affect aerosol performance. Dropping and shaking the inhaler after capsule piercing has no impact to performance.	No specific statements in the labeling however patient is instructed to not use a dropped or damaged inhaler
Effect of patient use	4.3.9	Drug product performance after use is acceptable and limited product performance complaints received	No specific statement in the labeling however patient is instructed to not use a dropped or damaged device, and to store inhaler in case and keep away from moisture.
Effect of moisture	4.3.10	Aerosol performance is affected at high humidity conditions	Store inhaler in case, keep away from moisture. Use capsule as soon as removed from the blister card.
Cleaning instructions	4.3.12	Cleaning procedure adequate	Use a dry clean cloth to wipe exterior mouth piece.

Labeling discussions with the sponsor were ongoing at the time of the completion of this review. The reader is referred to the final PI and the revised IFU.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of this NDA consistent with the clinical, statistical, clinical pharmacology, and pharmaco-toxicology reviewer’s recommendations. The consultant reviewers from CDRH do not recommend approval based on an inadequate instructions for use (IFU), and recommend an alternative IFU which needs to be tested postmarket. The pulmonary consult defers to the Division but share the concerns regarding the finding of transient benefit in lung function in patients who remain on the drug, the findings of greater need for oral antibiotic rescue, more frequent drug withdrawals, more frequent adverse events, increased Pseudomonas resistance, high error rates in dosing and limitations of the instructions for use (especially in pediatric populations unable to draw in the volumes and flow rates required to deliver the expected benefit).

I do not see the product as a viable alternative to the available saline formulation for all CF patients, as the trials show that many patients are clearly unable to maintain use of the powder and discontinue therapy due to adverse events or fail and require rescue antibiotic therapy. The device issues cause concern that some patients (such as the emaciated 7 year old with outlier FEV1 responses in 2303) may be unable to derive benefit from the inhaled drug, due to

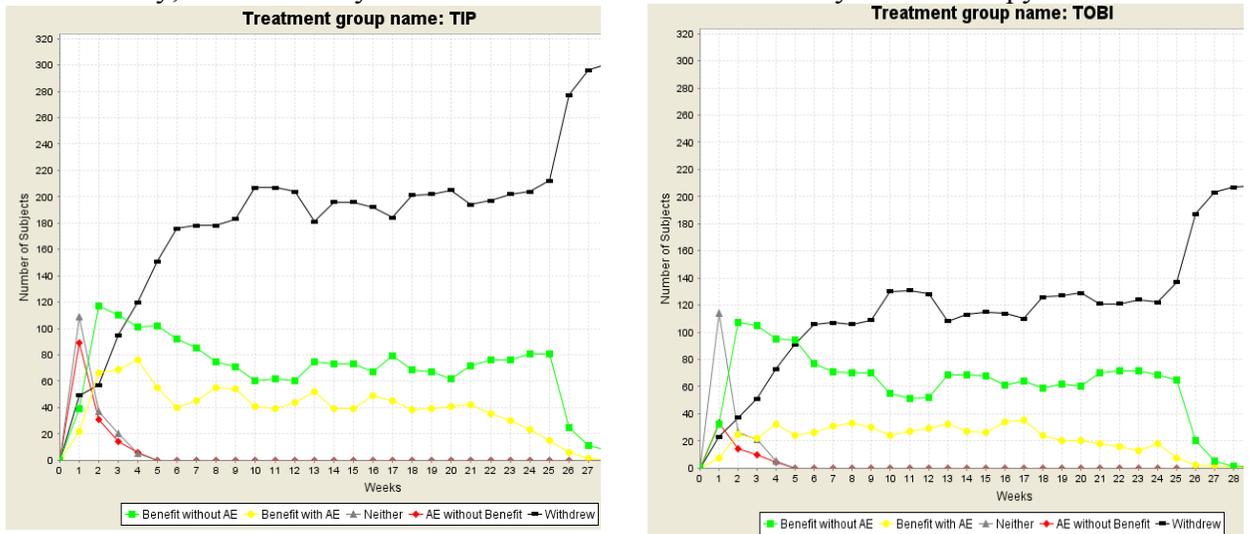
delivery issues with DPI, as is known for many asthma inhalers. These issues have been remedied by the use of spacers, but the studies on human factors are not revealing of ways to mitigate the errors observed. Additionally I have concern that the 3 deaths represent failure to treat a patient early due to the reliance on the efficacy of the powder formulation.

I do, however, recommend approval of the product for short term use in adults CF patients who demonstrate the ability to draw the flows and volumes that allow use of the product and are able to tolerate the dry powder formulation and thus derive potential benefit of portability of the device and ease of dosing.

- Risk Benefit Assessment

Population based analyses in the placebo controlled study 2301 confirmed effect and the failed study 2303 showed favorable trends, but is inconclusive. The efficacy findings in 2302 are relevant to the majority of CF patients in the US and I recommend their inclusion in the label. Further, while risk benefit is assessed on a population basis, a patient level risk –assessment shown below in the comparative study 2302 indicates that similar proportion of patients derive benefit with TIP relative to TOBI, even if they develop an AE, and that these patients are likely to self select over time. This context is relevant within the optimal practice setting of CF in the US, but may not be relevant in other practice settings.

A patient-level risk benefit assessment conducted by this reviewer indicates that patients who are able to receive TIP for the entire 3 cycles of therapy, have a favorable risk-benefit similar to those who received TOBI. In this analysis that used an increase in FEV1 % predicted for efficacy and any bronchoreactive and local airway AE representing an AE, many patients unable to continue treatment with a powder formulation of TOBI withdraw or discontinue treatment early, whereas many continue to do so over the entire 3 cycles of therapy.



The lines in black indicates that a higher rate of withdrawal occurred with TIP and persisted through the 24 week cycle – patients who withdrew could not derive benefit and their safety is not captured. The red line (higher for tip) shows the early onset of AEs that precluded continued therapy and is greater for TIP than TOBI, thus patients unable to continue (black and red lines) with inhaled powder are a large proportion of the enrolled population. The lines

in green shows similar proportions of patients who derived benefit and did not develop an AE, whereas the line in yellow (greater AUC for TIP) showed that more TIP patients derived benefit but also had an adverse event. Note that for the latter, the rates exceeded those for TOBI from the start of treatment up till completion of the third cycle. Patients will therefore likely self select to continue treatment based on tolerance of the product.

More patients with CF are living longer well into their adulthood. While generally considered to be a disease in children, in 2010, the mean age of patients with CF is 20 years, the predicted median age of survival in 2010 was 38.3 years (95%CI 35.5-41.1 y) of age⁵ and approximately half of patients are 18 and older. Likewise, since 2009, for the first time CF adults have made up the majority of patients in the German CF registry⁶. Pediatric patients are often healthier, given the access to care, training and support available in the US health care system. In these patient populations, TIP may have a place in therapy for patients who are able to tolerate the drug over time, as the convenience of portability is most valuable to an active healthy population. However, whether patients eventually develop more exacerbations, more hospitalizations or if resistance emerges as a clinically relevant concern, cannot be predicted based on studies of relatively healthy patients and is likely to emerge only in postmarket use over time. Given the orphan nature of the disease and the already demonstrated failure in recruitment to a placebo control study, the likelihood of another placebo controlled study with long term follow-up for clinical endpoints is infeasible to conduct.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The sponsor's program includes the following elements:

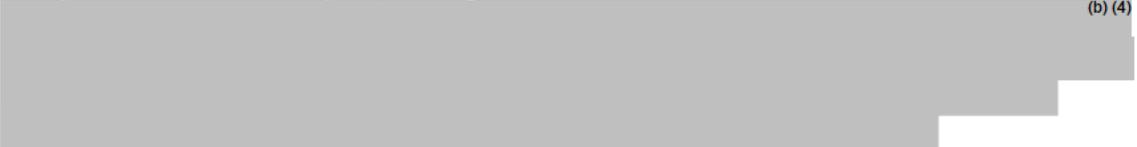
1. Routine pharmacovigilance is planned for the individual events of cough, bronchospasm, hemoptysis, nephrotoxicity, ototoxicity, fetal harm, drug-drug interactions and resistance.
2. In addition targeted followup with questionnaires or check list are planned for bronchospasm, hemoptysis, ototoxicity and resistance.
3. For the missing information on patients with renal failure, patients on diuretics, post lung transplant, long term use, use in pregnancy, disease severity other than studied, premedications with steroids, demographics of deafness and device use in younger patients, the applicant also intends to perform routine pharmacovigilance to evaluate the risk.
4. Additionally, 2 sequential open-label extension studies (CTBM100C2303E1 and CTBM100C2303E2) of the ongoing CTBM100C2303 study and an open-label study (CTBM100C2401) are planned to address long term safety.
5. The applicant also recommends usability evaluation of the T-326 Inhaler in children (TBM100C_HANDP_T-326_USABILITY STUDY_01) to understand handling of the device in younger patients. The protocol for this study should specify that patients with more limited pulmonary reserve or those with low BMIs should be enrolled as well.

⁵ <http://www.cff.org/UploadedFiles/LivingWithCF/CareCenterNetwork/PatientRegistry/2010-Patient-Registry-Report.pdf> accessed August 31, 2012

⁶ Adults with cystic fibrosis. It's not just about longevity.von der Hardt H, Schwarz C, Ullrich G. Gesundheitsschutz. 2012

The following 4 PMRs and a single PMC have been transmitted to the sponsor.

PMRs

1. A prospective study in the United States which includes the five year period of time after introduction of the TOBI Podhaler to the market to determine if decreased susceptibility to tobramycin is increasing in *Pseudomonas aeruginosa* from cystic fibrosis patients. These studies should also monitor resistance to these additional antibacterial drugs: meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin. Provide a detailed protocol to the Agency for review and comment prior to commencing the study. Interim reports of changes in *P. aeruginosa* susceptibility from CF patients should be submitted annually for five years. After the first year, the report should be cumulative.
2.  (b) (4)
3. A one year, randomized, prospective cohort study in the United States of CF patients chronically colonized with *P. aeruginosa* who use TOBI Podhaler as part of their regular care compared to similar patients using other approved inhaled antipseudomonal antibacterial drugs to assess clinical outcomes, particularly among patients with increased *P. aeruginosa* minimum inhibitory concentrations to tobramycin at baseline and on therapy, use of other antipseudomonal antibacterial drugs, respiratory and respiratory-related hospitalizations, mortality, changes in *P. aeruginosa* sputum log₁₀ cfu/g, and changes in FEV1% predicted from baseline.
4. An actual use human factors study to assess errors using the approved Instructions for Use.

PMC

1. Create adjunct instructions for use using alternative media and validate these instructions for use to ensure the patient can safely and effectively perform the critical tasks for the intended use of this product.

- Recommended Comments to Applicant
Labeling comments are currently being drafted.

Eileen Navarro, MD
Cross-Discipline Team Leader

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/s/

EILEEN E NAVARRO ALMARIO
10/05/2012