CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 20, 2012
From	Eileen Navarro, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 201, 820 (S 0037) Class 2 Resubmission
Applicant	Chiesi Pharmaceuticals, Inc
Date of Submission	13 April 2012
PDUFA Goal Date	12-OCT-2012
GRMP Goal Date	16-SEP-2012
Proprietary Name / Established (USAN) names	Bethkis® TIS (Tobramycin) Inhalation Solution 300 mg/4mL
Dosage forms / Strength	one ampule (300 mg tobramycin in 4 ml) twice daily by oral inhalation in repeated cycles of 28 days on drug, followed by 28 days off drug
Proposed Indication(s)	For the management of cystic fibrosis patients with *P. aeruginosa*. Safety and efficacy have not been demonstrated in patients under the age of six years, patients with FEV_1 less than 40% or greater than 80% predicted, or patients colonized with *Burkholderia cepacia*.
Recommended:	*Approval with postmarketing commitments*

Summary:
This NDA is a class II resubmission of a 505 (b)(2) NDA that relies, in part, on previous findings of safety and effectiveness for TOBI®, a 300 mg/5 mL tobramycin inhalation solution, approved for the treatment of CF patients with *Pseudomonas aeruginosa* infection. The proposed new drug, Bethkis® (Tobramycin) Inhalation Solution available as a 300mg/4 ml product (also referred to as TIS or CHF1538 in pre NDA communication) is marketed in 23 countries with various trade names (Bramitob®, Actitob® and Tobrineb®).
The initial NDA submission received a CR letter dated 8/25/2011 for the following unresolved issues, as discussed in the Division Director's Decisional memo:
1. "*In Trial CT02, ..the FEV1 % predicted measurements were not corrected for changes in height and weight over the course of the trial at one of the inspection sites. (T)he changes are highly unlikely to alter the conclusions regarding the primary endpoint. However, the applicant will be asked to provide corrected results…. There are no other unresolved relevant regulatory issues.*"
2. "*While trials CT01 and CT02 demonstrate efficacy of CHF1538 for the indication proposed and the safety profile of the CHF1538 is similar to TOBI®, the applicant proposes labeling the product to be used with either the PARI LC Plus or* (b) (4) *nebulizer with the PARI Vios compressor, and this drug device combination is not the same as that evaluated in clinical trials. The applicant has not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination.*"
3. "*(T)here is a difference in osmolality between the to-be-marketed product and the product tested in trials CT01 and CT02. The higher osmolality product tested in trials CT01 and CT02 did not raise safety concerns. The osmolality of the product tested in trials CT03 was quite similar to the to-be-marketed product. There was an improvement in FEV1 % predicted in the CHF1538 arm of trial CT03 which was similar to the improvement observed in trials CT01*

Reference ID: 3202921

and CT02. ***Whether the data from trial CT03 and additional in vitro data to be obtained by the applicant would be an adequate "bridge" in terms of efficacy will be a review issue in the next cycle."***

This NDA resubmission will review the adequacy of the applicant's response to the Division's recommendations to address the deficiencies summarized in Dr. Farley's review:

1. "*Pulmonary function test results should be revised for all trial CT02 individuals at all sites that were affected by inaccurate recording of/loss of source input data including height and age. The primary and secondary outcomes (such as other pulmonary function variables and weight/BMI/height changes over time) that may have been affected by the above issues should also be recalculated and submitted. The methodology and formula for the above recalculations should be submitted. In addition, the applicant should provide an explanation of exactly what documentation/calculation errors occurred at various sites and how such errors were remedied, as well as a reassessment of trial CT02's results given the new data*.
2. "*Comparative particle characterization data should be obtained for CHF1538 with an osmolality of* (b) (4) *mOsmoles/kg and* (b) (4) *mOsmoles/kg."*
3. "*The applicant should provide comprehensive drug device combination bridging data based on the in vitro studies recommended by the CDRH reviewer. (*P*)article characterization data (*should be*) obtained (*to*) include data …. for TIS with the Pari LC Plus Nebulizer and the DeVilbiss PulmoAide Compressor and the TurboBoy N Compressor.* ***If the device data provided are not adequate to bridge the clinical trial and to-be-marketed drug device configurations, then additional clinical trial data will be required.*** *The applicant should consider conducting a placebo-controlled trial similar in design to trial CT01 using the to-be-marketed drug device combination."*

The CDTL, Dr. John Alexander further recommended that

4. *"the in vitro aerosol characteristics of TOBI, the market standard, be assessed when delivered using the labeled nebulizer / compressor (PARI LC plus nebulizer/DeVilbiss Pulmo-Aide compressor)*
5. *the applicant be asked to provide additional documentation of audiometry testing, and laboratory test results for the CT03 trial."*

The review team has determined that the responses to the issues laid out in the CR letter have either been satisfactory or the issue infeasible to address and the recommendation for approval is unanimous in this second review cycle.

1. Dr. Gamalo finds that the revised pulmonary function test data for CT02 was appropriately verified, the methodology and formulae for the recalculation are sound and while minimally altered, the FEV1 outcomes measures do not change the study conclusions of superior efficacy over placebo.
2. Upon review of the in vitro bridging data Mr. Sugato De concluded that the dose of the to-be-marketed Bethkis drug product delivered by the to-be- marketed device configuration was equivalent when delivered through the devices used in the clinical trials and that no additional clinical trial data was needed for successful labeling.
3. These invitro tests could be perfomed on the high osmolality drug product used in CT01 and CT02. Due to the interval in time from the conduct of these trials to the NDA resubmission, no remaining lots of the high osmolality CT product could be recovered and comparative particle characterization could not be performed. FDA did not deem an invitro bridge essential as clinical findings from study CT03 enable

Reference ID: 3202921

bridging of the to-be-marketed Bethkis product to the efficacy and safety demonstrated in studies CT01 and CT02.

4. Mr. De likewise concluded that the particle size distribution of the RLD TOBI delivered using the device in CT03 was equivalent to that delivered by the labeled device for TOBI. This provides external validation that the comparator performed as expected in the bridging study and that study CT03's finding of similar efficacy for the to be marketed product is reliable.
5. Dr. Porcalla reviewed the safety endpoints of interest for inhaled tobramycin and determined that clinically patent cases of ototoxicity were similar to TOBI and that Chiesi's inability to provide source data verification for the requested audiometry test verification and laboratory testing for trial CT03 would not be required to make an assessment of the safety of Bethkis®. The considerable postmarketing safety experience with the to-be-marketed drug-device combination supports a favorable risk/benefit.

The drug products and drug product characteristics, device configurations and studies conducted in the drug development program for Bethkis are summarized in the Table below. A product currently consulted to DAIP by the Office of Generic Products is also referenced, as the action in this NDA informs the advice to be provided by DAIP.

Table 1 Drug Attributes, Device Configurations & Outcomes for TobiPodhaler, TOBI & proposed ANDA

	NDA 50-753	NDA 201820			ANDA (b) (4) (b) (4)
	TOBI	CT01, CT02 TIS vs placebo	CT03 TIS vs. TOBI	Bethkis To be marketed	
Tobramycin (mg/ml)	300 /5 60	300 /4	300/4	300/4	
pH	6 (5.5-6.5)	(b) (4)			
NaCl (% wt/vol)	11.25 mg (.225)				
mOsmol/kg	(b) (4)				
Compressor * Flow rate (L/min)	De Vilbis PulmoAide 9	TurboBOY CT01 4.5 TurboBOYN CT02 5.1	TurboBOY N 5.1	VIOS 4.5	
In vitro data	Tested	Not tested	(TOBI tested)	Tested	
Clinical data	By B2 reference	Trial Conducted	Trial Conducted	None	
Serum concentration (ug/mL)	0.95			0.55 (0.06-1.89)	
Sputum concentration (ug/g)	1237 (35 -7414)			814 (23 - 2843)	
Difference in Primary endpoint	12.5 (28d)002 11.4 (28d)003 Relative change@	13.3 (28d) CT01 11 (28 d) CT02 6.6 (140d)	7.5 (28d) TIS 7.01 (28d)TOBI		
Log CFU reduction	1.7-1.8 log	1.7 log CT02	2.14 TIS 2.08 TOBI		
Adverse Events of interest	Deaths 0 Cough (46.1%) FEV decrease (16%)	Death 1 Cough (53%) FEV decreased (37%)	Death 0 Cough (6%) FEV decrease not reported		

* nebulizer Pari LC Plus common to all +includes "decreased lung function" @TNDS 002/003

Reference ID: 3202921

The clinical and statistical criteria for acceptance of the invitro measures of drug distribution intended to bridge the device-compressor differences in the studies were clearly laid out in the submission. What is less clear is if the same in vitro criteria can serve as the sole criterion for bridging the differences in drug products amongst the trial formulations that varied in their physiochemical attributes (pH, osmolality, NaCl content, tobramycin concentration).

In a consult by the Office of Generic products (for a product that had intermediate physiochemical attributes between TOBI® and Bethkis®), OGD opined that the formulation pH, osmolarity, and sodium chloride content of an inhaled product, are all attributes that contribute to the distribution, efficacy, and safety of an inhaled antibiotic and that in vivo testing is necessary to ensure therapeutic equivalence for a generic product. OGD further opined that comparison of microbial kill rate is not sufficient to compare the efficacy of the test and reference product and that equivalence of the droplet size of the nebulized product (with use of the recommended nebulizer) must be demonstrated to ensure that the active drug reaches the site of action in the small bronchioles and that equivalent serum and sputum concentrations of tobramycin be achieved. Were the pH, osmolarity, and saline content of a proposed product appear to remain within a generally acceptable physiologic range (not defined), OGD considers the generic formulation unlikely to present a serious safety risk. However, if in vitro attributes sufficiently differ (found to be not bioequivalent per OGD) and thus safety or efficacy determination be deemed necessary, clinical trials would be needed. These trials will be powered for efficacy as a controlled trial; trials adequately powered to detect a meaningful safety difference may be challenging to conduct in an CF.

The difference in safety observed between TOBI and CT01 and CT02 may indicate that the large osmolality difference is meaningful. Acute reduction in lung function (measured as reduced FEV1 immediately post dose) with the higher osmolality product tested in CT01 and CT02 resulted in a adverse reaction rate double that observed for the low osmolality product TOBI. However, differences in study design and populations limit this cross-study comparison.

Mr. Sugato De concludes that Bethkis and TOBI doses delivered by the various device configurations used in for TOBI and Bethkis (in the trials or per the label) did not differ in particle size and lung distribution. The limitation of these in vitro comparisons is that the highest osmolality product was not tested in vitro; thus the studies that serve to anchor the efficacy of the new drug are not bridged to the to-be marketed product using the invitro bridge.

Clinical efficacy testing across the formulations studied (summarized in the Table above) shows some differences in the magnitude of the treatment effect from ~12 in CT01 and CT02, to a more modest 7 in the bridging study. Whether this is attributable to formulation attributes is hard to discern. Comparison to TOBI in the bridging study is limited in that the constancy assumption about TOBI efficacy is limited due to the widespread use of this standard of care such that naïve populations are no longer readily enrolled in CF trials. While efficacy testing in CF may be feasible in an add-on superiority study (i.e. 28 days on standard of care, 28 days on new molecular entity), noninferiority studies that detect small effect sizes from drugs with identical active substances (i.e. tobramycin formulations) are unlikely to be feasible. The pathway to a generic formulation for tobramycin will likely require (b) (5) [redacted].

Table 2 Populations Studied and Outcomes in Patients that Received TIS in the Besthkis NDA

	CTO1 (N=29)	CT02 (N=161	CT03 (N=158)
Sex			
Male	15 (51.7%)	89 (55.3 %)	72 (45.6%)
Female	14 (48.3%)	72 (44.7 %)	86 (54.4%)
Age (years) (in classes)			
Mean (SD)	11.0	14.8 (5.7)	15.89 (6.25)
6-12	19 (65.5%)	63 (39.1%)	47 (29.7%)
13-17	7 (24.1%)	47 (29.2%)	54 (34.2%)
> 17	3 (10.3%)	51 (31.7%)	57 (36.1%)
BMI (kg/m²)[2]			
Mean (SD)	15 (2.7)	17.70 (3.32)	17.56 (3.01)
Colonization of *P. aeruginosa* (years)[3]			
Chronic	22 (75.9%)	145 (90.1 %)	Time from 1st colonization (years) 11.99 (SD 6.34)
First or intermittent	7(24%)	16 (9.9 %)	
Time from first CF diagnosis (years)[4]			
Mean (SD)	9.15 (5.9)	12.1years (5.6)	12.36 (y)(6.18)
FEV1 (% predicted) (in classes)			
< 50		38 (23.3%)	74 (23.1%)
≥ 50		125 (76.7%)	247 (76.9%)
Mean absolute change in FEV1% predicted over baseline by Week 4 (greatest difference)			
All ages	15.9	7.82	6.99
6-12	12.98	8.93	8.97
13 and older	16.98	7.71	13-17 5.44
			>17 2.46

Age (and chronicity of CF and Pseudomonas colonization) appears to modify the observed treatment effect as measured by the absolute change in FEV1 at week 4 as shown in the table above. Thus, as trial differences in patient characteristics, concomitant medications, access to care may influence the effect size observed, clinical studies are unlikely to be discriminate small differences in product attributes. Notwithstanding these limitations, the review team find that studies CT01 –CT02 and the original TOBI studies do show a measurable benefit over placebo that although varied in the effect size, persists throughout the many years despite obvious change in experience with Tobramycin over time, using an objective, reliably measured endpoint of pulmonary function. We take this to mean that the FEV endpoint allows us to determine benefit despite variation in tobramycin product.

As to the regulatory requirement that adequate and well controlled studies serve as the basis for marketing a specific drug product, the data from CT03, while not acknowledged to be sufficient for noninferiority testing, serves as a necessary bridge to the efficacy studies that used a product with different characteristics from the to-be-marketed Bethkis. The results of study 2303 provides supportive evidence that a formulation with intermediate osmolal characteristics between TOBI and the product in the placebo controlled studies, provides similar benefit consistent with the RLD and the pivotal studies, although not designed for inferential testing of efficacy.

The review team concludes that the clinical trial data submitted in this 505b2 submission provides adequate and well controlled evidence of effectiveness and that the particle size distribution is sufficiently similar that no additional clinical safety and efficacy evidence is needed to assure equivalence across the drug formulations and device configurations used in the trials. In this CDTL review, we summarize the conclusions from the discipline reviews that assessed the invitro particle size distribution, PK, microbiology, efficacy and safety outcomes between the various drug/device products studied and summarize the review teams' conclusions as to the evidence that the to be marketed product has efficacy and safety for the intended indication. We also draw on reviews of other inhaled products, the published literature and physiologic or in vitro studies to understand the ranges of these attributes (pH, osmolality) where differences in safety have been reported, against which to benchmark our conclusions of no significant difference in safety across these formulations. We also describe the postmarketing safety experience with Bethkis that is comparable to that of the RLD, TOBI.

Based on this review, we conclude that the difference in attributes of pH, osmolality, sodium chloride content, tobramycin concentration and dose volume, do not differ sufficiently to alter efficacy or safety materially across the products used in the marketing studies.

A limitation in the drug development for Bethkis, however is that only patients with moderate CF baseline FEV1 >40 % predicted were studied, whereas the comparator, TOBI, is approved for patients with moderate to severe CF, consistent with the current treatment recommendation for chronic inhaled antibiotic therapy in CF[1]. It is unclear whether patients with severe CF may respond differentially to formulations that vary in certain physiochemical attributes and I recommend that this would need to be studied as a postmarketing requirement. As well, given remaining issue about the relevance of short term benefits of FEV increments, this study should also document sustained FEV improvement, number of exacerbations, antipseudomonal use and planned and unplanned hospitalization and death in patients with a stable FEV1 <40% predicted for up to 6 months. Until efficacy and safety is shown in this study, I recommend that the product be restricted in its indicated use to the severity strata of patients studied with Bethkis® and that pharmacovigilance focus on reporting of outcomes in patients with severe disease who may receive this drug off-label.

[1] 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 2007;176:957-969.

Reference ID: 3202921

Cross Discipline Team Leader Review Template

1. Introduction

At issue in this NDA resubmission is whether the proposed to be marketed new drug Bethkis® (also referred to as TIS [tobramycin inhalation solution] or CHF1538) sufficiently differs from the reference drug (TOBI) and the clinical trial (CT) product in composition and delivery, as to render the original studies insufficient for approval of a new drug. While TIS contains the same active product as TOBI, it was formulated differently so as not to infringe on the TOBI patent and allow marketing as a new drug and also is designed for delivery using a different nebulizer and compressor than TOBI. As such, although the original NDA concluded that TIS was active over placebo and similar to TOBI in safety and efficacy, differences in product attributes required additional in vitro characterization to detect a difference between the to-be-marketed (TBM-TIS) product and the CT product and between the TBM TIS and TOBI.

In performing this review FDA needs to determine whether differences in product attributes and delivery device configurations translated into differences in invitro tests of drug delivery as to render the previous findings of efficacy, safety and tolerability insufficient such that new clinical studies are needed to demonstrate safety and efficacy of the to be marketed drug when delivered with its labeled device. In so doing, FDA would also have had to consider what degree of in vitro difference in critical product attributes would not require new clinical trials for either safety or efficacy and thus define the relevant bioequivalence limits for a generic product.

Table3. Clinical Trials reviewed in first and 2nd cycle, with differences in formulation, drug delivery configurations, efficacy and safety

Trial No.	Design Study Sites Number exposed Dose/Duration	TIS Formulation mOsm/kg Nebulizer/ Compressor	FDA Efficacy** Mean FEV1 % difference (95% CI)		Exposure Safety in TIS	Exposure Safety in Placebo or TOBI
			Cycle 1	Cycle 2		
CT01	R, DB, vs placebo Moldova, Italy, France, Spain 29 TIS 30 placebo 1 cycle*	(b) (4) PARI LCplus PARI TurboBOY^	15.9% TIS 4.9% placebo difference 11% (3.0, 18.9)		29 days Death 0/29 All SAE 1/29 3.4% Discontinuation 1/29 3.4%	29.2 days Death 1/30 All SAE 3/30 6.7% Discontinuation 7/30 2.3%
CT02^^	R, DB, vs placebo Hungary, Poland, Russia 161 TIS 85 placebo 3 cycles		7.82% TIS 0.51% placebo difference 7.3% (3.0, 18.9)	6.36% TIS 0.06% placebo difference 5.95% (2.24, 9.65)	87.5 days Death 1/176 All SAE 17/161 10.6% Discontinuation 7/161 4.3%	85.8 days Death 2/161 All SAE 17/161 11.2% Discontinuation 8/85 9.4%
CT03	R, OL, vs TOBI As above + France Ukraine, Germany, Czech Rep, Spain 155 TIS 166 placebo 1 cycle	(b) (4) PARI LCplus PARI TurboBOY N	7.01% TIS 7.50% TOBI® difference -0.49 (-2.58, 1.62)		29 days Death 0/156 All SAEs 6/156 3.8% Discontinuation 4/156 2.6%	28.7days Death 0/156 All SAE 2/168 1.2% Discontinuation 6/168 3.6%

Reference ID: 3202921

2. Background

TOBI® (NDA 50 753) was approved in 1975 for the treatment cystic fibrosis patients with *P. aeruginosa* infections specifically for use with the Pari LC Plus nebulizer and De Vilbiss Pulmo-aide air compressor. The treatment dose is 300 mg in 5 ml saline by inhalation delivered in 15 minutes twice daily for repeated cycles of 28 days on drug and 28 days off drug. The intravenous formulations of both drugs are also used off-label to treat acute exacerbations of CF.

Two pivotal safety and efficacy Phase 3 trials, PC-TNDS-002 and PC-TNDS-003 served as the basis for the TOBI NDA based on 1) a treatment difference between the TOBI and placebo groups in the mean relative change from baseline to Visit 10 in FEV1 % predicted; and 2) the difference between the TOBI and placebo groups in the mean change from baseline to Visit 10 in log 10 CFU/g of sputum. From this initial submission, therefore, lung function and microbiologic endpoints were shown to be sensitive indicators of an antibiotic treatment effect.

TOBI Treatment Outcomes in NDA 50, 753.

RELATIVE CHANGES IN PRIMARY ENDPOINTS

	Protocol 002			Protocol 003		
	Mean Change		P-value	Mean Change		P-value
Endpoint	TOBI	Placebo	for Diff	TOBI	Placebo	for Diff
FEV_1 %Pred	12.02	-.52	<.001	8.70	-2.72	<.001
FVC %Pred	8.72	-.89	.001	7.07	-1.55	<.001
log_{10}(CFU)	-.87	.30	<.001	-.62	.37	<.001

Source: NDA 50753. Clinical Review for TOBI. 1997. p. 30.

As this study is a 505b2 that relies on the FDA's previous finding of efficacy for tobramycin in the TOBI NDA, the placebo studies should have been sufficient for approval. However, as the product used in these initial studies had an osmolality double that of TOBI and diffred significantly from the to-be-marketed product, [redacted] (b) (4) required a bridging study for a product with intermediate product attributes between the placebo controlled studies and the to-be marketed TIS product. As no studies were to be undertaken for the to be marketed product, much of the "bridging" depended on study 2303, which was open label and could not be relied upon for inference testing of noninferiority, per the statistical reviewer. As such, much was dependent on the TOBI outcomes as an anchor for external validity of Study 2303. However, TOBI was delivered using a different compressor in Study 2303 and DAIP required an assessment of the invitro characteristics of the product when delivered by the clinical trial (CT) and the labeled device.

3. CMC/Device

The original CMC review of the NDA (dated 6/24/2011) recommended NDA approval pending satisfactory resolution of the device USP specifications versus the Proposed TIS

Reference ID: 3202921

Specifications for the following Product Quality Attributes: Absorbance, pH, Osmolality and Impurities

The TIS label specifies that the product does not comply with USP in pH, osmolality and absorbance, to avoid patent infringement and enable regulatory submission as a new drug rather than a generic product.

Label	**TOBI**	**TIS**
Concentrations	300mg/5 ml 60 mg/ml	300 mg/4mL 75 mg/ml
Nebulizer	Pari LC Plus	PARI LC PLUS
Compressor	De Vilbiss Pulmo-Aide	PARI VIOS
Package	4 ampoules /pouch 14 pouches /carton	4 ampoules
Sputum PK	1237 µg/g (35 -7414)	814 ug/g (23- 2843)
Serum PK	0.95 µg/mL	0.549 ug/mL (0.06-1.89)
Test Attribute	**USP Specification**	**Proposed specification**
Absorbance	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)
Osmolality	(b) (4)	(b) (4)
Specified Unidentified Impurity	NMT (b) (4)	NMT (b) (4)
(b) (4)	NMT	NMT
	NMT	NMT
Any unspecified individual impurity	NMT	NMT
Total impurities	NMT	NMT

- General product quality considerations

Drug Substance: The drug substance, tobramycin (b) (4) to that used to manufacture the approved TOBI (NDA 50-753). Tobramycin is freely soluble in water ((b) (4) amino groups is highly basic, with an aqueous solution pH of (b) (4). (b) (4), (b) (4) is the drug substance manufacturer. The drug substance is (b) (4). Chiesi referenced the DMF of the two drug substance manufacturers, (b) (4). (DMF (b) (4)) and (b) (4) (DMF (b) (4)).

Drug Product:

The CMC and microbiology reviewers Drs.Shrikant Pagay and Robert Mello finds no deficiencies in the drug product manufacture. The drug product contains sterile water as a vehicle, sulfuric acid to (b) (4) pH adjustment, sodium hydroxide as a pH adjuster, and sodium chloride (b) (4). The solution underwent sterile (b) (4). The sterile (b) (4)

The submission clarifies that "The formulation of the inhalation solution in the nonclinical toxicology batches, the clinical batches and the to-be-marketed drug product is identical. No changes in the formulation have been made from the time of pivotal GLP nonclinical studies and clinical

development, through production of the three primary stability batches. Differences in the drug product throughout development are limited to the manufacturers of the finished product, the suppliers of drug substance, the manufactures of the low-density polyethylene, and the manufacturer of the foil (b) (4) pouch." As with TOBI, Production of tobramycin solution and packaging occurs in Woodstock Ill (Automated Liquid packaging, Inc for TOBI and Catalent Pharma Solutions for TIS) is responsible for drug product manufacturing, in process controls, packaging and storage.

Table 2. Differences in TIS Drug Product throughout Drug Development

	Clinical Trial Material (CTM) Batches	**To-Be-Marketed (TBM) Product**	**TOBI**
Drug Substance Supplier	(b) (4)		
Drug Product Manufacturer	(b) (4)	Catalent Pharma Solutions, Woodstock, Illinois	Automated Liquid packaging , Inc Woodstock, Illinois

Dr. Shrikant Pagay similarly recommends approval following review of the updated CMC information summarized below:
1. Leachable data from the stability samples stored for 24 months at 5°C.
2. Stability data of samples stored for 24 months at 5°C.
3. Stability data of In-use study for 1 month at 25°C/60% RH after storage for 24 months at 5°C.
4. Label
5. EER (OC report)

1. Leachable data from the stability samples stored for 24 months at 5°C
A leachable study of the samples stored will continue for 36 months, but the NDA provides data for 24 months at 5°C to support the proposed shelf life of 24 months.

The level of leachable compounds ranged from (b) (4) with most of the 14 identified compounds falling below (b) (4) g/mL, the limit of safety concern. The majority (10) of those compounds are (b) (4) whereas 4 are (b) (4) . The (b) (4) leachable were analyzed by HPLC-Mass spectroscopy. The CMC review states: The proposed limits are based on (b) (4) µg/day (without structural alert) or based on known toxicological information.

2. Stability data of samples stored for 24 months at 5°C (Long term)
Dr. Pagay previously reviewed the pH stability evaluation conducted over a pH range of (b) (4) to (b) (4) for TIS over a storage period of six months. He found no significant differences in product attributes between the five pH preparations ((b) (4)) under long-term (5 ± 3 °C), accelerated (25 ± 2 °C/60 ± 5% RH) and stressed (40 ± 2 °C/75 ± 5% RH) storage conditions. Table 3 below, copied from the NDA submission summarizes the batch analysis and product stability data.

Table 3: Batch Analysis Data for Drug Product Used in Clinical Studies and Primary Stability Program

Use	CP01, CT01, CT02			CT03				US Stability		
Batch Number	0105012[1]	0111035[2]	0303019[3]	HI226	IB061	IG020	KB287	05909B	05909D	05909E
Manufac. Date	04/2001	10/2001	02/2003	09/2007	02/2008	07/2008	02/2009	11/2009	11/2009	11/2009
Tobramycin Assay (mg/4mL)	(b) (4)									
Total Related Substances[4]										
NaCl (mg/4mL)										
Osmolality (mOsmol/kg)										
pH										
Drug Product Manufacturer			(b) (4)					Catalent		
API Manufacturer								(b) (4)		

[1] Batch used in CP01 and CT01
[2] Batch used in CT01 and CT02
[3] Batch used in CT01 and CT02
4 Batches used in CP01, CT01 and CT02 were analyzed by a different method than subsequent batches. NQ=not quantifiable, ND=none detected.

(b) (4)

In this resubmission, stability data for all 3 primary batches stored for 24 months are within the proposed limit and all test attributes (assay, particulate matter, weight loss and related substances) remain within specifications. (b) (4)

CDTL comment: The CT product used in CT01/CT02 had a slightly higher tobramycin content (>300 mg/4mL) compared to the product used in the bridging study CT03 but similar sodium content; whereas the 2303 CT product and the TBM (lowest osmolality), have similar tobramycin content (<300) although the latter has more variable sodium content. It appears that the Bethkis® product attributes across the CTM and TBM (pH, osmolality and concentration) could be altered both through reduced sodium or active drug concentration and modified such that the specifications that would not infringe the TOBI patent. Study 2303 was conducted for the French authorities for the formulation approved in Europe to bridge the placebo controlled studies to that of TOBI, which has an osmolality approximately half of that studied for TIS in 2301 and 2302. Dr. Pagay considers the manufacturing of Bethkis to be straightforward and it should be feasible for all manufactured product to have osmolal characteristics fall within the stated range for the to be marketed product, and unlikely to stray to the 300 range tested in the efficacy studies.

3. In-Use Study Results
Testing for product attributes under simulated in-use conditions for one month finds all test results including sterility and endotoxin test results satisfactory.

4. The compliance status of manufacturing facilities was found satisfactory as of June 1, 2012.

Delivery Device:

Bethkis® is intended to be market for use with a novel nebulizer (PARI LC PLUS®) - compressor (PARI Vios® Compressor) configuration. This configuration was not studied in the drug development program for Bethkis® and this resubmission provides the in vitro evidence that allows the FDA to bridge from the clinical evidence of efficacy and safety in the trials supporting Bethkis® to the anticipated safety and effectiveness of the product that is eventually marketed for use, as delivered by the labeled device configuration. Dr. Sugato De concludes that the invitro evidence establishes that the to-be-marketed device configuration is equivalent (well within the (b) (4)% margin of expected particle delivery) to that of the other clinical trial device configurations on which efficacy and safety conclusions of Bethkis® are based.

Table 4. The delivery devices used in the clinical development program are shown below:

Study /PRODUCT	Phase and Design	NEBULIZER COMPRESSOR	Duration	# of Subjects per Arm	Study Population (Label population)
CP01	Randomized, double-blind, 2-way crossover vs TOBI		Single dose	11/9	Cystic Fibrosis
CT01	Randomized, double-blind, parallel group, placebo controlled	PARI LC PARI TurboBOY (nolonger available but identical to PARI TurboBOY-S)	One, 4-week treatment followed by one 4-week washout	CHF 1538: 29/28 Placebo: 30/23	Cystic Fibrosis with *P. aeruginosa* infection FEV1≥ 40 % and ≤ 80 % predicted
CT02	Randomized, double-blind, parallel group, placebo controlled	PARI LC PARI TurboBOY-N	Three cycles of 4-week treatment followed by 4- week washout	CHF 1538: 161/154 Placebo: 86/78	Cystic Fibrosis with *P. aeruginosa* infection FEV1≥ 40 % and ≤ 80 % predicted
CT03	Randomized, open-label, parallel group vs TOBI	PARI LC PARI TurboBOY-N	One, 4- week treatment followed by one, 4-week washout	CHF 1538: 159/155 TOBI: 165/159	Cystic Fibrosis with *P. aeruginosa* infection FEV1≥ 40 % and ≤ 80 % predicted
TIS		VIOS			FEV1≥ 40 % and ≤ 80 % predicted
TOBI		DeVilbiss PulmoAide			FEV1 ≥25% or ≤ 75% predicted

The clinical trials were conducted using the PARI LC PLUS® nebulizer in combination with either the PARI TurboBoy N or S compressor. In the comparative study CT03, TIS and the reference product TOBI were delivered with PARI LC Plus nebulizer with the PARI TurboBoy N compressor, and not using the TOBI labeled De Vilbiss Pulmoaide compressor. To verify that the comparative study is valid as a bridging study to earlier Bethkis® CTM products tested, FDA also required that the constancy of effect of the comparator TOBI be tested by evaluating its delivery from the trial device configuration vs the labeled device by cascade impaction studies.

An early model of PARI TurboBOY compressor, currently no longer marketed, used in the CT01 trial had identical specifications to the PARI TurboBOY S model. The PARI TB- N compressor was used in the CT02 and CT03 trials. The specifications for the PARI TurboBOY and TB- S compressors are identical; the TB-N compressor differs from the others, for all specifications except voltage and frequency as shown in the table below.

Table 5 Compressor Specifications for TOBI, TIS Clinical Trials and Bethkis

Compressor (Study/Drug)	Intended Use	Performance Pressure	Flow Rate	Materials / Filters	Operating Principles	Power Supply V/HZ/A/W	Target Population
Vios **TIS TBM**	[redacted]					(b) (4)	Adult and ediatric atients
TurboBOY N **CT02 CT03**							atients ages and older
TurboBOY S							atients ages and older
TurboBOY[1] **CT01**							atients ages and older
DeVilbiss Pulmo-Aide[2] **TOBI**							Adult & ediatric atients

[1] TurboBOY no longer available from PARI and replaced by the TurboBOY S

[2] Information on the Pulmo-Aide compressor taken from http://www.phc-online.com/Pulmo-Aide Nebulizer p/devilbiss-5650.htm, accessed 15 December 2011. The procedure and apparatus used by DeVilbiss to measure operating pressure and flow rate is unknown by Chiesi. The flow and pressure will be dependent on any restriction that the testing method uses at the end of the tubing.

In his review of the original submission, CDRH reviewer Sugato De identified the following deficiencies that needed to be addressed:

1. An adequate description of the proposed devices was not provided for review
2. Adequate comparative particle characterization data has not been provided for review for the proposed to-be-marketed combination product and the product tested in the clinical trials.
3. Sufficient data must be provided to assess potential sources of variability in terms of particle size, total emitted mass, and respirable mass that may be attributable to the device and demonstrate that the dosing specifications in labeling are validated.
4. To provide a reference mark when comparing the aerosol characteristics of TIS in the different nebulizer compressor combinations, the aerosol characteristics of TOBI® were also requested to be assessed when delivered using the labeled PARI LC PLUS nebulizer® and De Vilbiss® Pulmo-Aide® compressor.

Dr. De's original CDRH consult notes "*limitations of relying on aerosol characteristics for drawing conclusions of the comparability of drug delivery to patients, since many factors may affect individual breathing patterns in patients*" thus "*the in vitro data provided for aerosol `characterization is not sufficient*" to assess the substantial equivalence of the drug delivery systems (nebulizer and compressor) for delivery of CHF1538.

CDTL comment: Vios is an approved general device (jet nebulizer-compressor configuration) found substantially equivalent to two other marketed devices. Since VIOS is used for Bethkis®, coupled with an already marketed PARI LC PLUS jet nebulizer, this configuration is novel for tobramycin delivery, and for purposes of Bethkis® labeling, in vitro evidence was needed to fulfill the equivalence standard as defined by CDRH. On the basis of Mr. De's finding of no difference in dose of Bethkis delivered between the to be marketed and the clinical trial device configurations, DAIP concludes that no additional clinical studies are needed to label delivery with the VIOS device configuration. The DPARP considers the need for additional clinical trials when the delivery device is a high efficiency device or when nebulizer performance is altered by a high flow compressor such that the nebulizer performs like a "high efficiency" device. The Pari LC nebulizer is a jet nebulizer and not considered high efficiency. The VIOS compressor has a low flow rate of 4.5 L/min, exactly half of the flow rate of the DeVilbiss Pulmo-Aide compressor (9L) and is unlikely to dramatically alter the performance of the jet nebulizer, based on prior studies looking at the impact of compressors on various nebulization efficiencies for the aminoglycoside gentamicin (shown in the Figure below)[2].

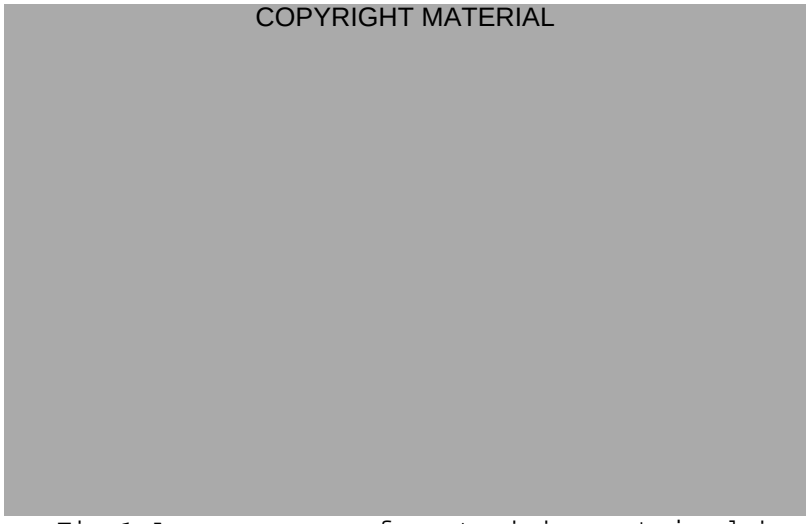

Fig 1 Average mass of gentamicin contained in droplets of less than 5 um diameter plotted as a function of compressed air flow rate for 2 and 4 ml volume fills.(copied from Newman et al)

In the experiment shown above, the flow rate of 4.5 L/min is at the foot of the slope (compared to 6,8,10 and 12 L/min) in terms of the change in nebulized drug delivery of inhaled gentamicin, a solution with similar tonicity as tobramycin. Furthermore, Mr. De reportedly reviewed the information regarding particle size distribution with TOBI and found no difference in drug delivery between the labeled and the novel device configuration, supporting the conclusion that no clinical studies are needed for the device delivery configuration (PARI LC PLUS/VIOS).

The responses to the CR device issues are summarized in Mr. De's review and in brief below:
1. Adequate description of the proposed device: In the Complete Response Letter, FDA requested the submission of a device module containing descriptive information about each device referenced in the NDA.

[2] Newman SP, Peter F et al. Effect of compressed gas flow rate on the efficiency of the devilbiss nebulizer. Evaluation of jet nebulisers for use with gentamicin solution Thorax 19al85;40:671-676

On October 17, 2011 Chiesi provided letters of reference from the device manufacturer (PARI respiratory equipment) authorizing cross-reference to the 510(k) applications for the to-be-marketed device combination (PARI LC Plus nebulizer/PARI Vios compressor).

PARI Vios compressor 510(k) K092918, FDA decision date February 4, 2010
PARI LC Plus nebulizer 510(k) K935540, FDA decision date March 17, 1995

Pari Vios is a class II nebulizer-compressor found substantially equivalent to predicate devices [redacted] (b) (4). PAri Trek S, in terms of the toal output rate, MMD, Volume %<5uM and operating pressure. It has a normal operating flow rate of 4.5 LPM and requires a prescription.

Beyond obtaining the right to reference to the relevant compressor and the technological specifications provided by CHIESI at the preNDA and reproduced below, Chiesi is unable to provide detailed comparison of the technological features and materials between the device delivery systems as the predicate device manufacturer is unwilling to provide details on design differences or a summary analysis of the effect of each design difference on the output specifications for each device. Chiesi contends that providing the invitro aerodynamic particle size distribution (APSD) between the compressors (following), the reference to the 510 K applications and technological specification [intended use, performance pressure/flow, materials (housing, cylinders and seals), filters, operating principles (piston pump, etc.), power supply, and target population] should allow FDA to assess whether the noted differences impact the APSD from the device, even if the proprietary information (engineering drawings etc) is not released by the device manufacturer.

2. Adequate comparative particle characterization data has not been provided for review for the proposed to-be-marketed combination product and the product tested in the clinical trials. Sufficient data must be provided to assess potential sources of variability in terms of particle size, total emitted mass, and respirable mass that may be attributable to the device and demonstrate that the dosing specifications in labeling are validated.

The device configuration proposed for marketing is a novel nebulizer-compressor not tested in the development program.
Compressor: Clinical studies have exclusively used the PARI TurboBOY compressors and the PARI LC Plus nebulizer. The TurboBOY compressors are not available in the US, the TBM product must be administered using a different compressor than TurboBOY. Therefore, *in vitro* performance study presented in this module compare the dose distribution of CHF 1538 delivered by the various compressors used in clinical trials and the to-be-marketed compressor, Vios. The studies demonstrate that the performance characteristics of the different compressors are substantially equivalent, and that the choice of the compressor does not impact the dose delivery of CHF 1538 and TOBI.
Nebulizer: All clinical studies used the PARI LC Plus nebulizer, and this nebulizer will be recommended in the label for delivery of CHF 1538. Based on the supporting data, the recommended nebulizer for administering CHF 1538 will be PARI LC Plus and the recommended compressor will be PARI Vios

In response to FDA requests in the CRL, the following product-device configurations (Table 6) were assessed for equivalence using both a statistical and clinical approaches.

Table 6 Comparison of In vitro Characterization for Bethkis and TOBI in this NDA resubmission

	CHF 1538		TOBI	
Compressor/Test	NGI*	Delivered Dose	NGI	Delivered Dose
PARI Vios®,	X	X		
PARI TurboBOY N (TB-N)	X	X	X	
PARI TurboBOY S (TB-S);	X	X		
DeVilbiss PulmoAide			X	

*Cascade impaction

Mr Sugato De's review of the statistical and clinical conclusions from these collective studies demonstrate that the to-be-marketed device configuration (Pari LC Plus Nebulizer and Pari Vios Compressor) reliably administers a delivered dose of (b) (4) mg of Tobramycin with an median particle size of approximately (b) (4) µm. The reader is referred to his review for details beyond those summarized below.

Statistical Equivalence:

FDA agreed with the proposed statistical approaches for testing and analysis of the in vitro results modified for brevity from the CSR (Section 3.2.P.7 Device Module) below:

"A comparison of the Vios to TurboBOY S and TurboBOY N was performed with a two-sided 90% confidence interval (CI) for the ratio of Test/Reference (Vios/TurboBOY S or Vios/TurboBOY N) for each of the key APSD parameters (N=15 data points for each configuration). The ratios of the Test/Reference were determined for the different compressor units used with the same LC Plus nebulizer unit and means of those Test/Reference ratios were used for the analysis. For all six key aerosol performance parameters, the confidence intervals are well within the acceptance criteria of (b) (4) (see Table); moreover, the largest observed difference is 7% in FPD between Vios and TurboBOY N. Therefore, the compared combinations are concluded to be substantially equivalent."

Table 7 Summary of Results from *in vitro* Studies with the To-Be-Marketed and the Clinical Trial Device Configurations (N=15)

In Vitro Parameter	To-Be-Marketed	Clinical Trial Units		Ratio of Test/Reference (CI)[1]	
	Vios	TB-N	TB-S	Vios/TB-N	Vios/TB-S
MMAD NGI (µm)	(b) (4)				
GSD NGI					
FPD, < 5 µm NGI (mg)					
FPF NGI (%)					
TEM NGI (mg)					
DD (mg)					

Reference ID: 3202921

CDTL comment. The finding that the *in vitro* total delivered dose for Vios/TurboBOY N (as used in CT03) is close to unity and the confidence interval lies entirely between (b) (4) representing at the very most a 10% difference between device configurations is reassuring. Also reassuring is that coherence in effect is seen for the other 5 measures of dose uniformity; multiplicity adjustments notwithstanding.

Invitro Testing of the RLD TOBI
The stage-by-stage data of the APSD for TOBI and CHF 1538, with the different compressor-nebulizer configurations demonstrates the comparable deposition profiles

Table 8. Comparison of CHF 1538 and TOBI Dose Delivery and Cascade Impaction Delivered by LC Plus Nebulizer with Different Compressors

Parameter	CHF 1538 Tobramycin 300 mg/4 mL		TOBI Tobramycin 300 mg/5 mL	
	Vios	TurboBOY-N	TurboBOY-N	PulmoAide
TEMNGI(mg)	(b) (4)			
FPDNGI(mg)				
FPFNGI(%)				
MMADNGI(μm)				
GSDNGI				
SputterPoint(min)				

[1] In ( ) is the %RSD

From the CSR

Clinical Equivalence
The following is summarized from the CSR, in the absence of a review from CDRH at the time of this CDTL report. All nebulized tobramycin formulations must comply with USP <905>, Uniformity of Dosage Units[3] harmonized standards, whose acceptance criteria (mean content deviating up to (b) (4)% from target) are established with regard to inherent variability due to the manufacturing and filling process. This implies that batches of TOBI, for example, must certifiably deliver up to (b) (4) of the expected dose of TOBI. On this basis, CHIESI proposed (b) (4) dose variability as the threshold for clinical equivalence. FDA noted that because these data are intended to provide an in vitro bridge between the device configurations used in the clinical study and the to-be-marketed device configuration in lieu of a new clinical study, differences in tobramycin dose uniformity specifications approaching (b) (4)% may not be acceptable. However, the differences fall within a range of 4-5% for APSD specifications, well within the (b) (4)% margin and bridging is supported from the invitro studies.

To support the clinical relevance of the statistical conclusion, Chiesi further states:
"Chiesi is holding the in vitro data to a higher standard than that set by USP <905> by setting statistical equivalence criteria to (b) (4)%, which is slightly more rigorous than the criteria

[3] USP <905> Uniformity of Dosage Units harmonized Standard, accessed September 24, 2012 from http://www.usp.org/usp-nf/harmonization/stage-6/uniformity-dosage-units

reported in FDA's guidance regarding population bioequivalence for nasally-inhaled products[4]. Such differences within an approved product specification, or even for smaller quantitative differences in delivered dose or aspects of in vitro particle size distribution analyses, especially if they are statistically not significant, are not considered to be clinically relevant. In fact, the relatively small variability in these in vitro data could be considered in the context of the larger, inherent and well-established variability of patient use of nebulizer devices in the routine clinical setting[5]"

The sponsor states that no PK/PD benchmarks are established for CF and that the 300 mg dose for tobramycin was not established by dose ranging, rather chosen to delivery sputum concentration at the site of infection (defined as > 128 µg tobramycin/g sputum at peak, or at least 10 fold an MIC 90≤ 16 µg/mL for P aeruginosa obtained from a historical cohort of cystic fibrosis patients). The PK data for Bethkis®s reviewed in the original NDA exceed this historical MIC several fold.
CDTL comment Based on the data presented in the above table, labeling of Bethkis® with the Vios compressor would be expected to provide the effectiveness observed in the clinical Studies CT01 and CT02, that used the TurboBOY S and TurboBOY N compressors for delivery. The reference to a historical cohort of patietns with the cited mIC distribution may be dated and need to be updated due to changes in TOBI use and the rise of high tobramycin MICs in P aeruginosa isolates in CF patients. Dr. De proposed labeling modifications that cite the device configuration to be used for Bethkis®, the basis for its designation as equivalent to the CT delivery device configuration, and appropriate citations on the instructions for use.

4. Nonclinical Pharmacology/Toxicology

Dr. Amy Ellis finds that the language for label sections 8.1 Pregnancy and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility that were based on the TOBI label are appropriate for TIS because both products contain the same active ingredient to be given via the same route of administration and dosing schedule. Appropriate 7-day and 28-day repeat dose toxicity studies carried out to "bridge" to the reference product in the original submission as reviewed by Dr. Ellis provides reassuring toxicity profiles despite differences in tobramycin concentration, pH and osmolality between the proposed product and TOBI®. No labeling changes are proposed by her discipline. As well, she does not find the reported leachables in the resubmission (described in the CMC section) concerning for the conditions under which the nebulizers are designed for use.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer for the original NDA submission Dr. Yongheng Zhang recommended approval of the NDA. The resubmission contains no new information profiles for the proposed and the reference product; demonstrating the low systemic exposure after inhalation of either formulation. The Cmax for tobramycin was 0.549 mcg/mL after inhalation of one dose of TIS. In addition, the CT01 efficacy trial included a PK sub-study that evaluated peak sputum concentrations of tobramycin on days 1 and 28. The CT01 sub-study demonstrated similar mean sputum concentrations of tobramycin on days 1 and 28 suggesting no accumulation of trial drug.

The CDTL memo states *"The similar, low systemic exposure after inhalation of CHF1538 or TOBI provides reassurance that the change in formulation would not alter the low risk of tobramycin*

[4] Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action accessed September 24, 2012 from http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070111.pdf
[5] Heijerman H, Westerman E, Conway S, Touw D, Doring G. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus. J Cyst Fibros. 2009 Sep;8(5):295-315.

Reference ID: 3202921

systemic toxicity identified in studies of TOBI. The similar sputum PK suggests that similar efficacy may be expected, but the high variability of sputum concentrations do not allow for conclusions of "bioequivalence" between the inhaled products. Since tobramycin in the inhaled product is acting locally within the lung, evidence of efficacy is needed to demonstrate that the change in formulation does not alter the effect

The applicant carried out a Phase 1 bioavailability and pharmacokinetic study (CP01) to evaluate tobramycin PK in plasma and sputum of CF patients after a single administration by nebulization of TIS in comparison to TOBI®. The CP-01 findings are thus summarized in the drug label based on Dr. Owen's review:

12.3. Pharmacokinetics

Sputum Concentrations: Thirty minutes after inhalation of the first 300 mg dose of Tobramycin Inhalation Solution, the maximum geometric mean concentration of tobramycin was 814 mcg/g (ranging from 23 to 2843 mcg/g) in sputum. High variability of tobramycin concentration in sputum was observed. Three hours after inhalation started, sputum tobramycin concentrations declined to approximately 15% of those observed at 30 minutes. After four weeks of therapy with Tobramycin Inhalation Solution average mean sputum tobramycin concentrations obtaine 10 minutes following administration were 717 mcg/g.

Serum Concentrations: In patients with normal renal function treated with Tobramycin Inhalation Solution, serum tobramycin concentrations are approximately (b) (4) mcg/mL one hour after dose administration and do not require routine monitoring

Elimination: The elimination half-life of tobramycin from serum is approximately two hours after intravenous (IV) administration. The elimination half-life following the inhalation of Tobramycin. Inhalation Solution is approximately 4.4 hours. Assuming tobramycin absorbed following inhalation behaves similarly to tobramycin following intravenous administration, systemically absorbed tobramycin is eliminated principally by glomerular filtration. Unabsorbed tobramycin following inhalation is likely eliminated in expectorated sputum.

6. Clinical Microbiology

Dr. Fred Marsik concluded in 4/12/12 that both TIS and TOBI® reduced baseline bacterial load in the sputum samples obtained from patients after treatment, that bacterial load increased once treatment was stopped in both groups in the trials, and there was no significant difference in the bacterial load between groups after cessation of treatment. He also concludes that the susceptibility profiles of baseline isolates were similar between treatment groups in the clinical trials. No new information was submitted for review in this resubmission, and his conclusions are unchanged.

7. Clinical Efficacy

The following studies, coupled with the Agency's previous finding of safety and efficacy for the reference product TOBI, consist the primary evidence of efficacy supporting this NDA:

Table 9 Efficacy Outcomes in Clinical Trials Supporting Bethkis efficacy

Trial No.	Design Study Sites Number exposed Dose/Duration	TIS Formulation mOsm/kg Nebulizer/ Compressor	FDA Efficacy** Mean FEV1 % difference (95% CI)		Exposure Safety in TIS	Exposure Safety in Placebo or TOBI
			Cycle 1	Cycle 2		
CT01	R, DB, vs placebo Moldova, Italy, France, Spain 29 TIS 30 placebo 1 cycle*	(b) (4) PARI LCplus PARI TurboBOY^	15.9% TIS 4.9% placebo difference 11% (3.0, 18.9)		29 days Death 0/29 All SAE 1/29 3.4% Discontinuation 1/29 3.4%	29.2 days Death 1/30 All SAE 3/30 6.7% Discontinuation 7/30 2.3%
CT02^^	R, DB, vs placebo Hungary, Poland, Russia 161 TIS 85 placebo 3 cycles		7.82% TIS 0.51% placebo difference 7.3% (3.0, 18.9)	6.36% TIS 0.06% placebo difference 5.95% (2.24, 9.65)	87.5 days Death 1/176 All SAE 17/161 10.6% Discontinuation 7/161 4.3%	85.8 days Death 2/161 All SAE 17/161 11.2% Discontinuation 8/85 9.4%
CT03	R, OL, vs TOBI As above + France Ukraine, Germany, Czech Rep, Spain 155 TIS 166 placebo 1 cycle	(b) (4) PARI LCplus PARI TurboBOY N	7.01% TIS 7.50% TOBI® difference -0.49 (-2.58, 1.62)		29 days Death 0/156 All SAEs 6/156 3.8% Discontinuation 4/156 2.6%	28.7days Death 0/156 All SAE 2/168 1.2% Discontinuation 6/168 3.6%

* 28 days on, 28 days off
** change from baseline in FEV1% predicted
^ early model of TurboBOY S
^^ Secondary endpoints including the rate of disease-related unplanned hospitalizations and the receipt of at least one dose of parenteral anti-pseudomonal antibacterials favored TIS.
TOBI not used with the approved compressor as labeled DeVilbiss Pulmo-Aide

In their review of the original submission, the Clinical and Statistical reviewers recommended a CR based on the following main deficiencies reflected in the CR letter:

> *"1. You propose labeling the product to be used with either the PARI LC Plus or* (b) (4) *nebulizer with the PARI Vios compressor, and this drug device combination is not the same as that evaluated in clinical trials. You have not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination. In addition, we note that the osmolality of the test drug used in trials CT-01 and CT-02 was higher than the osmolality of the to-be-marketed product. You should provide comprehensive drug device combination bridging data as recommended in the CLINICAL/DELIVERY DEVICES section below. The data submitted should allow the Agency to make a proper evaluation of the comparability of the various drug-device combinations used in clinical trials and proposed for marketing. If the device data provided are not adequate to bridge the clinical trial and to-be-marketed drug device configurations, then additional clinical trial data will be required. We recommend that you consider conducting a placebo-controlled trial similar in design to trial CT-01 using the to-be-marketed drug device combination.*
>
> *2. The primary and secondary endpoint results (pulmonary function tests) for the CT-02 trial are not correct as submitted. Pulmonary function test results should be revised for all trial CT-02 individuals at all sites that were affected by inaccurate recording of/loss of source input data including height and age. The primary and secondary outcomes (such as other pulmonary function variables and weight/BMI/height changes over time) that may have been affected by the above issues should also be recalculated and submitted. The methodology and formula for the above recalculations should be submitted. In addition, provide an explanation of exactly what documentation/calculation errors occurred at various sites and how such errors were remedied, as well as a reassessment of trial CT-02 results given the new data".*

Reference ID: 3202921

The Medical Officer review addresses the first of these two deficiencies whereas the Statistical review does the second issue.

Dr. Ariel Procalla's review was based on the initial assessment made by Dr. Shrimant Mishra and M Amper Gamalo's review. Efficacy data from Studies CT01 and CT02 were analyzed based on the statistical plan and imputing outcomes to missing data in multiple sensitivity analyses. All analyses showed that the mean change from baseline to Visit 8 (or Week 20 ON cycle) in FEV1 % predicted normal was significantly higher in the CHF-treated group compared to the placebo treated group, with the p-value being <0.001 for the comparisons.

Dr. Gamalo analysed the change from baseline in Forced Expiratory Volume in one second (FEV1) expressed as percentage of predicted normal at the end of the third "ON" cycle (Visit 8, Week 20) or when data was missing at week 8, the *prior FEV1 values which were lower than they are at baseline was used and implies that a patient had an exacerbation*. Multiple endpoint analyses performed in the orginal submission are not reviewed in this cycle, which is limited to the following: (FEV1) expressed as percentage of predicted normal, absolute change in FEV1, FVC % of predicted normal, and FEF25-75% (L/sec and % of predicted normal) at Baseline (Visit 2) and the end of the third "ON" cycle (Visit 8, Week 20) were provided. Source data verification for the disputed data from site 26 was then extended to all clinical sites that participated in study CT02. Height was measured twice during study visits: 1) during the physical examination and 2) by the spirometry technician at the time of pulmonary function testing leading tro discrepancy of about ~1cm in 14.7% of total measurements. The sponsor presented the formulae for calculation of the FEV1, FVC and FEF25-79%The statistical reviewer verified that the resubmitted data based on these formulae are accurate as calculated by the sponsor. The statistical reviewer then verified the primary analysis and sensitivity analyses conducted by the applicant as follows:

- Sensitivity A: In 100% of patients, re-calculate predicted normal values and % predicted values from the clinical database submitted to FDA in the original NDA applying the above formulae for the determination of percent predicted values across all clinical sites;
- Sensitivity B: In 87-89% of patients, input data from the spirometer printouts were used for the calculation of the predicted normal values and % predicted values using the above formulae
- Sensitivity C: Input data from the clinical database have been used to re-calculate predicted normal values and percent predicted values, but in the same subset of patients used in Sensitivity Analysis B. using the same formulae.

Table 10 FEV1 % Predicted Mean Baseline & Mean Change From Baseline with Multiple Imputation

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	161	84	
		Mean	60.7	63.6	0.145
3	2	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	8.02	1.91	< 0.001
		Difference (95% CI)	6.11 (3.08, 9.15)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	7.82	0.51	< 0.001
		Difference (95% CI)	7.32 (4.24, 10.40)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	4.84	1.85	
		Difference	3.00 (-0.09, 6.09)		0.057
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	7.28	2.26	
		Difference (95% CI)	5.02 (1.70, 8.33)		0.003
		N imputed	3	4	
7	16 "OFF" Drug	Mean Change from Baseline1,2	6.14	0.74	
		Difference (95% CI)	5.40 (1.95, 8.85)		0.002
	20 "ON" Drug	N imputed	4	5	
8	(1° endpoint)	Mean Change from Baseline1,2	6.88	0.64	
		Difference (95% CI)	6.24 (2.71, 9.77)		0.001
		N imputed	7	6	
9	24 "OFF" Drug	Mean Change from Baseline1,2	6.94	0.67	0.001
		Difference (95% CI)	6.27 (2.74, 9.81)		

Reference ID: 3202921

TIS produced significantly higher change in FEV1 % from baseline compared to placebo, with a stable effect size varying from 5.95 to 6.56 consistently found for all timepoints, all sensitivity analyses and despite inaccurate recording of/loss of source input data. The review team thus concludes that the results of the CT02 trial as submitted and reviewed originally are robust. In particular, it was concluded in the original statistical review that the change in FEV1 % predicted normal from baseline was significantly greater in the CHF 1538 group than in the Placebo group at Visit 8, Week 20 (at the end of the third "ON" cycle of randomized treatment). The results of the sensitivity analysis provide a mean change from baseline to Visit 8 in FEV1 % predicted normal in the CHF 1538 group ranging from 5.93 to 6.55 compared to the Placebo group which ranges from -0.64 to 0.21. The difference in mean change from baseline ranges from 6.21 to 6.34 and all are statistically significant and corroborates the result presented in the original statistical review

As the formulation in Study 2301 and 2302 was not assessed in the invitro studies of drug delivery and particle size distribution, Study 2303 was requested by the French autorhirites, to bridge between the placebo controlled studies and the to-be marketed formulation.
Dr. Gamalo characterizes this study, which served as the bridging study, in his label proposal:

"A third study was also conducted and was designed as a bridging study for the marketed drug-device configuration to rely upon equivalent efficacy and safety established in the clinical trials CT01 and CT02. Study CT03 was an open-label, randomized (1:1), two-arm, non-inferiority study comparing the efficacy and tolerability of aerosolized Tobramycin Inhalation Solution and the reference product TOBI, both administered via a nebulizer (PARI LC Plus with the PARI Boy N compressor, Pari, Germany), over a 4-week treatment in 324 patients with CF and P. aeruginosa chronic infection and with $FEV_1 \geq 40\%$ and $\leq 80\%$ of the predicted normal value. Results of this study showed that Tobramycin Inhalation Solution and the reference product TOBI have comparable efficacy, albeit, inconclusive due to the characteristics of the trial design. "

CDTL comment: The findings of the in vitro studies aside, the review team that assessed the original submission was concerned that the variation in the size of the observed treatment effect in change in FEV1% predicted between studies reflected tobramycin physiochemical or device configuration differences.
As pointed out by John Alexander in his CDTL memo, difference in outcomes between the placebo controlled studies may be attributable to difference in populations, and timing of endpoint assessment and that similar variation in the effect size have been observed in the placebo controlled studies for TOBI, TIP, and Cayston.
The Statistical reviewer concluded that study CT03 should be viewed as supportive given the inadequate justification of the non-inferiority margin. The CDTL concluded that the efficacy findings for TIS on pulmonary function tests and sputum microbiology are consistent with efficacy findings for TOBI®, the secondary outcomes from the CT02 trial support a similar treatment effect on clinically meaningful endpoints, and therefore the data are sufficient to demonstrate that TIS treatment results in a similar treatment effect to the reference product, and that difference in drug product characteristics do not translate into a meaningful difference in efficacy. However, what is not certain is whether the reference product would have performed similarly were it used with the approved nebulizer/compressor delivery device. Invitro studies indicate that equivalent doses of TOBI are delivered with the different device configurations, thus the same efficacy and safety are expected of the RLD as seen in the bridging study.

As stated in the Division Director's Decisional Memorandum, there is a need to determine whether the change in osmolality from the formulation used in the two pivotal Phase 3 trials to the formulation used in Trial CT03, with a lower osmolality similar to the proposed to-be-marketed product, would have any potential impact on the product's efficacy and safety.

Reference ID: 3202921

In his review of the original submission, Dr. Mishra writes: In CT02, "*endpoints such as proportion of subjects with a predefined pulmonary exacerbation, time to pulmonary exacerbation, proportion of subjects hospitalized, and time to hospitalization were analyzed. Though these results should be viewed with a certain amount of caution because this trial was not specifically designed to track these endpoints, overall there did seem to be some benefit in these more clinically relevant measures. For example, there was an absolute reduction of 10% in the proportion of TIS subjects with a pulmonary exacerbation (though the effect might be less using a broader definition of exacerbations). Moreover, there was a trend toward prolonged time to pulmonary exacerbation in the TIS arm, though the median difference between the two arms was nonsignificant. Similarly, the absolute difference in hospitalization was 15% in favor of TIS. The combination of these modest improvements in both pulmonary function and clinical endpoints provides more assurance that the study drug is indeed efficacious for this indication.*"

Dr. Porcalla finds that compared to the Bethkis® trials, TOBI efficacy was studied in older patients (> 18 years old), at different time points and using slightly different endpoints, thus some slight differences might be seen between the Bethkis and the TOBI pivotal trials
- TOBI trials: difference between the treatment groups in the mean **relative** change of FEV1 % predicted from baseline to Visit 10;
- Bethkis® trials difference between the treatment groups in the mean **absolute** change of FEV1 % predicted from baseline to time of evaluation (after 1 cycle for CT01 and CT03 and after 3 cycles for CT02)

Nontheless, as shown in the Table below, the study drug remains highly superior to placebo and Dr. Porcalla believes that the osmolality change in the formulation used in Trial CT03 and in the proposed to-be-marketed product, compared to the formulation used in the two pivotal trials, does not significantly impact the efficacy profile of CHF 1538 .

Table 11 Comparative Primary Efficacy Results

Product and Treatment Groups	**Difference in Mean Change (or Mean Relative Change - TOBI) of FEV1 % Predicted between Treatment Groups**	**Confidence Interval and/or p-value**
TOBI (pH6, [redacted])		
PC-TNDS-002 (placebo)	12.54	<0.001
PC-TNDS-003 (placebo)	11.42	<0.001
CHF 1538 trials		
CT01 (placebo) (pH [redacted]%)	13.3	(4.7, 21.8), p=0.003
CT02 (placebo) (pH [redacted]%)	6.56	(2.35, 10.78), p= 0.0024
CT03		
CHF-1538 (pH [redacted] osm [redacted] Na%)	7.50	
TOBI (pH [redacted] osm [redacted] Na%)	7.01	

8. Safety

In their review of the original submission, Dr. Shrimant Mishra and his Cross Discipline Team Leader Dr. John Alexander concluded that the safety profile for TIS is consistent with FDA's previous findings for safety of TOBI® based on their review of the aggregate safety database of 346 patients treated with TIS in phase 3 clinical trials, of whom 161 patients received treatment for more than one 28-day course. Most serious adverse reactions were related to pulmonary exacerbations whereas common adverse reactions (dysphonia, pharyngitis, epistaxis and headache) were non serious. Full audiometric results for all trials and complete laboratory data for trial CT03 were not provided; ototoxicity or nephrotoxicity was not reported in the clinical trials.

Table 12 Comparison of Exposure and Safety in the Trials Conducted for Bethkis

Study	Exposure Safety in TIS	Exposure Safety in Placebo or TOBI
CT01	29 days Death 0/29 All SAE 1/29 3.4% Discontinuation 1/29 3.4%	29.2 days Death 1/30 All SAE 3/30 6.7% Discontinuation 7/30 2.3%
CT02	87.5 days Death 1/176 All SAE 17/161 10.6% Discontinuation 7/161 4.3%	85.8 days Death 2/161 All SAE 17/161 11.2% Discontinuation 8/85 9.4%
CT03	29 days Death 0/156 All SAEs 6/156 3.8% Discontinuation 4/156 2.6%	28.7days Death 0/156 All SAE 2/168 1.2% Discontinuation 6/168 3.6%
All Studies	361	191 placebo, 168 TOBI

To address these deficiencies in information Dr. Mishra writes in his review and in the CRL:
1." Provid(e) full audiometric results if available. This would include decibel thresholds recorded at every frequency at every visit for every patient in every trial. This will help to better understand what changes in hearing threshold were occurring during the course of treatment. If such data is unavailable, then any future assessments of otoxicity (including in labeling) will be based on what has been provided in this NDA.
2. Complete statistical tables describing more fully laboratory data in trial CT03.
Tables describing mean and median changes in values over the course of the study should be provided, as well as a reference guide to help understand the shift tables provided in the current NDA submission (e.g., what values fall under the parameters of clinically significant, normal, and nonclinically significant for hemoglobin?)."
In his safety review of this resubmission, Dr. Porcalla recounts the regulatory history of interaction between the FDA and the applicant regarding these two additional comments. In brief, it appears that in a preNDA meeting held on 16 December 2011, FDA agreed to the following:

1. the assessment of ototoxicity of CHF 1538 would be based on information already submitted in the NDA and reviewed in the initial cycle, because the full audiometric results are not available for rubmission.
2. Likewise, it appears that the information requested in item #2 were submitted in the original submission.

As no new safety data relevant to the safety database originally reviewed by Dr. Shrimant is submitted for this review cycle, the reader is referred to Dr. Mishra's original review for detail.

In his review, Dr. Porcalla comments on the relative safety of the various formulations used in the CT program for TIS, compares the safety profile with that observed in the comparative study with TOBI and the original findings of safety in the trials that supported TOBI, as a means to discern differences in safety between products with varying attributes in terms of concentration, pH, osmolality (and sodium content).

Dr. Porcalla reviews the available postmarketing data and safety labeling submitted for review in this review cycle from the following sources:

1. spontaneous reports of adverse drug reactions (ADRs)
2. review of published literature on tobramycin,
3. reports to FDA Adverse Events Reporting System (AERS).

The adverse reactions of bronchospasm, cough, dyspnea and oropharyngeal are more frequently reported from these aggregate sources and are felt to potentially represent airway hypersensitivity. The data is limited in that absolute rates cannot be calculated and comparison to TOBI is infeasible.

From AERS, its is notable that class-related toxicities such as vestibular disorder and nephrotoxicity are reported, as are supratherapeutic blood levels – these adverse reactions are listed in the TOBI label. Causality could not be attributed to solely to TIS based on the limited information accompanying these reports. Dr. Porcalla concludes that the postmarketing experience of CHF 1538 provided in the submission does not provide sufficient information to identify specific safety signals associated with TIS use. At the most, the information in this submission informs the Medical Officer of several AEs that would require close monitoring.

Effect of variance in physiochemical product attributes (pH, tonicity)

Tobramycin is a basic molecule and sulfuric acid is often added to alter its pH. Bronchial provocation studies conducted in patients with asthma, demonstrate acute bronchoconstriction over that expected of histamine alone, when the inhaled solution pH falls below 5, as measured by a fall in FEV1 by 20 % or more 60 and 90 minutes after inhalation of unbuffered relative to buffered histamine phosphate.[6],[7] It appears therefore that pH changes have important safety effects on safety measures such as cough and bronchoconstriction though this may only be of clinical consequence at extremes of deviation from neutral pH (for e.g. pH<5). While the to be marketed product has a pH of 5, the range may extend below 5 and this may need to be monitored in routine pharmacovigilance and strict periodic product quality assessment.

Hypertonic saline and mannitol as hyperosmotic products have been used in CF patients as a means to osmotically pull liquid into the mucosal surface. However, these hypertonic products are also known to induce acute bronchial reactivity[8], so it is clear that tonicity or osmolality may affect tolerability of an inhaled drug. In the dog, for example, relative to 0.9% saline, hypertonic saline (14.4% NaCl) induced acute bronchoreactivity[9]. These findings are borne out in a comparative study of mannitol as a bronchial provocation test where ARIDOL (mannitol), an approved testing substance for asthma, caused similar reductions in FEV as hypertonic saline[10]. Tonicity could also alter the amount of drug and particle size delivered by a specific nebulizer, adding to the concern regarding the variation in the compressor used in the studies and the proposed delivery device in the product label.

CDTL comment: The drug product with the highest osmolality was used in the placebo controlled studies that provide the evidence of efficacy for this NDA. The rule of three states that if no major adverse events occurred in a group of 190 people, then the interval

[6] DW COCKCROFT, BA BERSCHEID Effect of pH on bronchial response to inhaled histamine. Thorax 1982;37:133-136

[7] Mirić M, Plavec D. Risk of acute bronchospasm and bronchial hyperreactivity from inhaled acid aerosol in healthy subjects: randomized, double-blind controlled trial. Croat Med J. 2004 Dec;45(6):709-14.

[8] Aridol NDA 22368 Complete Study Report Study 301

[9] RYOICHI SUZUKI AND ARTHUR N. FREED Hypertonic saline aerosol increases airway reactivity in the canine lung periphery. J Appl Physiol 89: 2139–2146, 2000.

[10] Medical Officer review of NDA 022368, October 5, 2010

from 0 to 3/190 or 0 to 1 in 64 people is a 95% confidence interval for the rate of adverse events, assuming a binomial distribution. "*This rule of three states that if none of n patients showed the event about which we are concerned, we can be 95% confident that the chance of this event is at most 3 in n (i.e. 3/n). In other words, the upper 95% confidence limit of a 0/n rate is approximately 3/n. One can therefore determine the maximum risk of an event, with a 5% error, that is compatible with n observations of non-occurrence: (1-maximum risk)n=0.05, equal to 1-maximum risk=(n root 0.05), equal to 1-maximum risk=(0.05)1/n. For n>30 this can be approximated by 1-maximum risk=1-(3/n), equal to maximum risk=3/n.* [11]" If 190 people have taken the drug in placebo controlled trials and no deaths are seen, the chance of another patient from the same sample dying from the drug used in CT01 and CT02 is likely to be less than 1 in 63; thus one has "ruled out" an event occurring at or greater than a rate of 1 in 63. However, one death occurred in CT01, attributed to cardiomyopathy and not due to the drug product. However, the safety of the drug product to be marketed is more likely to be reflective of Study 2303, where no deaths were observed. Likewise, Bethkis has been marketed in 23 countries with an estimated 2.3 million patient-treatment-day exposures and the large postmarketing safety summarized by Dr. Porcalla, is reassuring, as is the chemists' conclusion that the manufacture of Bethkis assures osmolality variation within the 50 osm ((b) (4)) range specified for this new drug.

Conclusion Safety and Efficacy:

Differences in the product attributes across the Bethkis® (aka TIS NDA, CHF 1538), TOBI and a generic TIS product evaluated by DIP in consult, and the findings from the drug development programs completed or proposed, are shown below. Based on a cross-study comparison, there was no large difference in the effect size on the primary endpoint between the products with the widest osmolality difference (TOBI vs CT01 and CT02). As well, there was no large difference in the point estimate of treatment effect between TIS and TOBI in study 2303. As well, differences in the reduction of bacterial counts were not striking for these two comparisons. Both these endpoints are objective, measurable and reproducible, with accepted methods and standards. On the other hand, there was a wide variation in the rate of reported cough; this event is subjective, passively reported and not systematically captured in these studies. Differences based on the most serious AE, death, are too unstable to draw safety conclusions, although acute decreases in FEV could be meaningful and varied between TOBI and CT01/CT02.

Table 13 – Reproduction of Table 1 Comparison of Product Attributes, device configuration and Efficacy and Safety from the TOBI and Bethkis trials and to a putative ANDA product

	NDA 50-753	NDA 201820			(b) (4)
	TOBI	CT01, CT02 TIS vs placebo	CT03 TIS vs. TOBI	Bethkis To be marketed	
Tobramycin (mg/ml)	300 /5 60	(b) (4)			
pH	6 (5.5-6.5)				
NaCl (% wt/vol)	11.25 mg (.225)				
mOsmol/kg	(b) (4)				
Compressor * Flow rate (L/min)	De Vilbis PulmoAide 9	TurboBOY CT01 4.5 TurboBOYN CT02 5.1	TurboBOY N 5.1	VIOS 4.5	

[11] Hanley, JA; Lippman-Hand A (1983). "If nothing goes wrong, is everything alright?". JAMA 249 (13): 1743–5.

Reference ID: 3202921

In vitro data	Tested	Not tested	(TOBI tested)	Tested	To be tested
Clinical data	By B2 reference	Trial Conducted	Trial Conducted	None	Consult question
Serum concentration (ug/mL)	0.95			0.55 (0.06-1.89)	Not studied
Sputum concentration (ug/g)	1237 (35 -7414)			814 (23 - 2843)	Not studied
Difference in Primary endpoint	12.5 (28d)002 11.4 (28d)003 Relative change@	13.3 (28d) CT01 11 (28 d) CT02 6.6 (140d)	7.5 (28d) TIS 7.01 (28d)TOBI		Not studied
Log CFU reduction	1.7-1.8 log	1.7 log CT02	2.14 TIS 2.08 TOBI		Not studied
Adverse Events of interest	Deaths 0 Cough (46.1%) FEV decrease (16%)	Death 1 Cough (53%) FEV decreased (37%)	Death 0 Cough (6%) FEV decrease not reported		Not studied

*Relative Change in FEV 1 % Predicted after 28 days of treatment

**relative to normal saline (physiological salt solution) which contains (b) (4)% w/v of NaCl, about (b) (4)

+ existing patent 5,508,269, as this patent claims for the use of pH range of 5.5 to 6.5 and a sodium chloride concentration of 0.225%.

There was no efficacy and safety characterization of the to-be-marketed product in this NDA. The Statistical colleagues refer to indirect evidence assuming that Bethkis will have intermediate efficacy between that provided by TOBI (referenced by a b2 mechanism) and the placebo controlled studies (studies conducted by the sponsor) since the osmolality of Bethkis falls between the osmolality of these 2 products. As well, Study CT03 provided similar efficacy as the RLD, TOBI.

Thus differences in physiochemical characteristics between formulations and the differences in drug delivery devices employed to deliver the drug were bridged by invitro and clinical data and did not appear to significantly alter the efficacy or safety of the approved products beyond the expected variation based on the populations studied.

9. Advisory Committee Meeting

No Advisory Committee discussion was held for this NDA.

10. Pediatrics

P. aeruginosa colonization in pediatric patients under 6 years of age makes studies in this age group infeasible and a waiver is recommended. The submitted information for TIS in conjunction with FDA's findings of safety and effectiveness for the reference drug, TOBI, is sufficient basis for pediatric use labeling for pediatric patients >6 years.

11. Other Relevant Regulatory Issues

~ This resubmission required a reinspection and was therefore classified as a Class 2 resubmission.[12]

Two other studies are ongoing to fulfill EU requirements:
Study CP02- open-label clinical pharmacology study comparing the bioavailability of TIS when delivered via the PARI LC Plus nebulizer versus the PARI eFlow® rapid electronic nebulizer
Ct03 Extension - an open-label extension study to Study CT03.

12. Labeling

- The label for this product was harmonized to a label (NDA 201 688, TOBIPodhaler) under concurrent negotiation.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval with PMC
- Risk Benefit Assessment: The evidence for efficacy for this product relies on part on the TOBI NDA as the product has the same active and is manufactured in an identical process. This product expands the choice of compressors for use with tobramycin but affords no additional advantages over the marketed RLD and other alternative therapies exist. However, differences in physiochemical attributes between the clinical trial lots and the RLD TOBI, and in the compressor for use necessitated that the sponsor conduct studies beyond the placebo controlled clinical trials that provide efficacy, and included a bridging safety and efficacy study with a product similar to the to-be-marketed, in vitro bridging studies for both the new drug and TOBI, assurance of quality manufacturing within specifications and review of the postmarketing safety database from the marketing history in 23 countries to assure safety and efficacy.
- Recommendation for Postmarketing Risk Evaluation and Management Strategies: none are recommended
- Recommendation for other Postmarketing Commitments

Due to a concern that Bethkis will be used in patients with more severe CF who were not studied in the clinical trials of efficacy and safety, I recommend a 6 month postmarketing study assessing safety and tolerability in patients with a stable FEV1 <40% predicted. Until efficacy and safety is shown in this study, I recommend that the product be restricted in its indicated use to the severity strata of patients studied with Bethkis® . To expand upon the databse assessing correlation of FEV to clinical endpoints, I also recommend assessment of the following efficacy I endpoints in this study: sustained FEV improvement, number of exacerbations, antipseudomonal use and planned and unplanned hospitalization and death. Routine pharmacovigilance should allow assessment of outcomes in patients with severe disease who may receive this drug off-label.

Eileen Navarro, MD

[12] MAPP 6020.4 Rev. 1Classifying Resubmissions of Original NDAs, BLAs, and Efficacy Supplements in Response to Action Letters (recertified 3/6/12) available at http://www fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082002.pdf

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10/12/2012