CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201820Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Acting Division Director Decisional Memo
NDA #	201,820
Applicant Name	Chiesi Pharmaceuticals, Inc.
Date of Submission	Received April 13, 2012
PDUFA Goal Date	October 13, 2012
Proprietary Name / Established (USAN) Name	Bethkis/ Tobramycin Inhalation Solution
Dosage Forms / Strength	300 mg/4mL Inhalation Solution
Proposed Indication	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Reviews	Dr. Shrimant Mishra, Dr. Ariel Ramirez Porcalla
Pulmonary Consultation	Dr. Robert Lim
Statistical Review	Dr. M. Amper Gamalo
Pharmacology Toxicology Review	Dr. Amy Ellis
CMC Review	Dr. Shrikant N. Pagay
Product Quality Microbiology Review	Dr. Robert J. Mello
Device Consultation	Mr. Sugato De
Microbiology Review	Dr. Frederick Marsik
Clinical Pharmacology Review	Dr. Yongheng Zhang, Dr. Ryan Owen
OSI	Dr. Kassa Ayalew
Labeling Reviews	Dr. Adora Ndu, Ms. Shawna Hutchins, Dr. Christine Corser, Dr. Aleksander Winiarski
Proprietary Name Review	Dr. Aleksander Winiarski
CDTL Reviews	Dr. John Alexander, Dr. Eileen Navarro-Almario

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

1. Introduction

Tobramycin is an aminoglycoside antibacterial approved in a parenteral formulation for treatment of bacterial infections since 1975. A 300 mg/5 mL inhalation solution of tobramycin (TOBI®) was approved for management of cystic fibrosis patients with *Pseudomonas aeruginosa* in 1997. The applicant has submitted NDA 201,820 to obtain marketing approval for a 300 mg/4 mL inhalation solution of tobramycin (referred to as CHF 1538 and the proprietary name Bethkis in this review) for management of cystic fibrosis patients.

Three clinical trials were submitted as evidence of efficacy of CHF 1538 for the indication proposed:

- Trial CT01 was a randomized, double-blind, placebo-controlled trial of 28 days of CHF 1538 or placebo with a 28-day follow-up period.
- Trial CT02 was a randomized, double-blind, placebo-controlled trial of three cycles (28 days on-/28 days off-treatment) of CHF1538 or placebo.
- Trial CT03 was a randomized, open-label, comparative trial of CHF1538 or TOBI® given for 28 days with a 28-day follow-up period.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of CHF 1538 for the indication proposed. For a detailed discussion of NDA 201,820, the reader is referred to individual discipline specific reviews and the Cross-Discipline Team Leader Reviews.

2. Background/Regulatory

This is a 505 (b)(2) application that relies, in part, on previous findings of safety and effectiveness for TOBI®, a 300 mg/5 mL tobramycin inhalation solution, approved for the proposed indication. CHF 1538 has received marketing approval in a number of countries in Europe and South America.

The NDA was originally submitted on October 25, 2010 and a Complete Response Letter was issued on August 25, 2011.

The first deficiency in the original submission was that the applicant proposed labeling to instruct patients to use either the PARI LC PLUS® or [redacted] (b) (4) ® nebulizers with the PARI Vios® Compressor for drug treatment. However, the clinical trials submitted in the NDA were conducted using the PARI LC PLUS® nebulizer in combination with either the PARI TurboBoy N or S compressor. Data to bridge this difference was deemed inadequate. The following were requested of the applicant in the Complete Response Letter:

- Provide an adequate description of the proposed devices
- Provide adequate comparative particle characterization data for review for the proposed to-be-marketed combination product and the product tested in the clinical trials

- Provide sufficient data 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 same data should be provided for the reference drug, TOBI®, delivered using the PARI LC PLUS nebulizer® and De Vilbiss® Pulmo-Aide® compressor. When comparing the aerosol characteristics of CHF1538 in the different nebulizer compressor combinations, the aerosol characteristics of the reference drug TOBI® with the nebulizer and compressor labeled for use with the reference drug may provide a useful reference mark for the proposed comparisons.

In the course of discussions with the applicant following the Complete Response action, the applicant chose to modify the proposed labeling in the resubmission. In the resubmission, the applicant is proposing labeling to instruct patients to use the PARI LC PLUS® nebulizer with the PARI Vios® Compressor for drug treatment. Thus, the labeled compressor would differ from the compressor used in the clinical trials, but the nebulizer would be the same. The Division agreed that the applicant could simplify the in-vitro particle characterization studies to focus on the difference in compressor between the clinical trials and the device configuration proposed to be labeled.

The second deficiency was a clinical site inspection deficiency. In Trial CT02, inspection found that the FEV_1 % predicted measurements were not corrected for changes in height and weight over the course of the trial at one of the inspection sites. Based on the corrections to the pulmonary function test measurements from this site, the changes were unlikely to alter the conclusions regarding the primary endpoint. However, the applicant was asked to provide corrected results for the PFT measurements at any other sites where a similar problem with stored height and weight data occurred as a deficiency in the Complete Response letter.

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

There are no CMC, product quality microbiology, or device issues which preclude approval.

The CMC reviewer recommended approval. The reviewer concluded that this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product, and I concur with this conclusion. The reviewer also noted that an "Acceptable" site recommendation from the Office of Compliance has been made.

The Product Quality Microbiology reviewer recommended approval noting that there were no deficiencies with respect to manufacturing processes that relate to product quality microbiology.

The Device reviewer recommended approval. In the resubmission, the applicant submitted a range of descriptive information and data from in vitro studies intended to

establish relative equivalence in terms of particle size, delivered dose, and respirable dose between the clinical trial device configurations and the proposed to be labeled devices. The Device reviewer examined this information and concluded that the overall differences in particle specifications between the clinical trial and to be labeled configurations are minimal from a statistical perspective. He stated that, "…it is unlikely that the subtle differences in particle characterization and dose delivery observed during in vitro studies when CHF 1538 is delivered by the TurboBoy (used in clinical studies) compared to the proposed Vios compressor would impart any clinical impact in terms of decreased efficacy for patients with CF". The Device reviewer also reviewed a comparative particle characterization analysis comparing CHF 1538 and TOBI® delivered by the LC Plus Nebulizer with different compressors submitted by the applicant. The disposition profiles were comparable.

The osmolality of the test product was changed late in the course of the development program. The osmolalities of the planned to be marketed product and the product used in clinical trials are as follows:
Planned to be marketed product: (b) (4) mOsmoles/kg
Studies CT01 and 02: (b) (4) mOsmoles/kg
Study CT03: (b) (4) mOsmoles/kg
The Pulmonary Consultant recommended further clinical testing. This difference in osmolality was also noted by the CMC reviewer. The CMC reviewer stated that, "On 4 November 2009, FDA agreed that clinical trial CT03 would be acceptable as a bridging study."

I conclude that the difference in osmolality does not raise safety or efficacy concerns and that no additional clinical testing is required. 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 lower than the product tested in trials CT01 and CT02 and was quite similar to the to-be-marketed product. There was an improvement in FEV_1 % predicted in the CHF1538 arm of trial CT03 which was similar to the improvement observed in the CHF1538 arms of trials CT01 and CT02 (see Section 7 of this review).

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology reviewer had no objections to approval of the NDA. While there are differences in tobramycin concentration, sodium chloride concentration and pH between the proposed product and TOBI®, the reviewer stated that appropriate 7-day and 28-day repeat dose toxicity studies were carried out to "bridge" to the reference product. I agree that there are no outstanding Pharmacology Toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer stated that the information provided by the applicant in the NDA submission is acceptable. I agree that there are no outstanding Clinical Pharmacology issues. 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 CHF 1538 in comparison to TOBI®. In addition, the CT01 efficacy trial included a PK sub-study that evaluated peak sputum concentrations of tobramycin on days 1 and 28. The CP01 trial showed comparable low plasma concentration-time profiles for the proposed and reference product, but high variability of sputum concentrations of tobramycin following inhalation of both products. The CT01 sub-study demonstrated similar mean sputum concentrations of tobramycin on days 1 and 28.

6. Clinical Microbiology

The reviewer concluded that "there is no evidence in the data from the treatment trial groups (CHF1538 and TOBI®) that suggest that CHF 1538 is inferior to TOBI® for the treatment of Pseudomonas aeruginosa infection in the lungs of cystic fibrosis patients." I agree that there are no outstanding microbiology issues. Although no interpretive criteria have been established for inhaled tobramycin and *P. aeruginosa*, the reviewer noted that *in vitro* susceptibility (as defined by the breakpoint for systemic tobramycin treatment of ≥16 mcg/mL) was similar between U.S. *P. aeruginosa* isolates (2007-2009) and the baseline isolates from the clinical trials performed by the applicant. The reviewer also noted that the susceptibility profiles of baseline isolates were similar between treatment groups in the clinical trials. Both CHF 1538 and TOBI® in the clinical trials reduced baseline bacterial load in the sputum samples obtained from patients. 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.

7. Clinical/Statistical Efficacy

The Clinical reviewer, Statistical reviewer, and the CDTL recommended approval and I concur. In two clinical trials CT01 and CT02, the applicant has demonstrated superiority of CHF 1538 over placebo for the primary endpoint of change from baseline in FEV_1 % predicted (absolute) at week 4. There was supportive data in trial CT02 for the secondary clinical endpoints of unplanned hospitalizations and use of anti-pseudomonal antibiotics. There was also supportive data from Trial CT03, comparing the test drug with TOBI® for a single cycle of treatment.

Three clinical trials were submitted as evidence of efficacy of CHF 1538 for the indication proposed. The primary endpoint in all three clinical trials was change from baseline in FEV_1 % predicted, though the timing of the endpoint differed:

- Trial CT01 was a randomized, double-blind, placebo-controlled trial of 28 days of CHF 1538 (29 subjects) or placebo (30 subjects) with a 28-day follow-up period. Trial drug was administered using the PARI LC plus nebulizer and the PARI TurboBOY compressor (an early version of the Turbo BOY S compressor). At the end of 4 weeks of treatment, the change from baseline in FEV_1 % predicted was 15.9% for the CHF1538 arm and 4.9% for the placebo arm. The treatment difference was 11% with a 95% confidence interval of (3.0, 18.9).
- Trial CT02 was a randomized, double-blind, placebo-controlled trial of three cycles (28 days on-/28 days off-treatment) of CHF1538 (161 patients) or placebo (85

patients). The change from baseline to week 20 in FEV_1 % predicted was 6.88% for the CHF 1538 arm and 0.64% for the placebo arm. At week 4, the same time point as the primary outcome for the CT01 and CT03 trials, the change from baseline in FEV_1 % predicted was 7.82% for the CHF 1538 arm and 0.51% for the placebo arm. Secondary endpoints including the rate of disease-related unplanned hospitalizations and the receipt of at least one dose of parenteral anti-pseudomonal antibacterials favored CHF 1538.

- Trial CT03 was a randomized, open-label, comparative trial of CHF1538 (155 patients) or TOBI®(166 patients) given for 28 days with a 28-day follow-up period. The PARI LC plus nebulizer and PARI TurboBOY N compressor was used for drug delivery in both treatment arms; so TOBI® was delivered using the labeled nebulizer, but not the labeled compressor (DeVilbiss Pulmo-Aide). At week 4, the change from baseline in FEV_1 % predicted was 7.01% in the CHF 1538 group and 7.50% in the TOBI® group. The difference and 95% CI were -0.49 (-2.58, 1.62); the results met the applicant's predefined non-inferiority margin of 4%; however, there was no justification provided for the non-inferiority margin in the clinical trial.

The Statistical reviewer noted that the change in FEV_1 % predicted in study CT01 was not consistent with the results in studies CT02 and CT03. I note that the greater change in FEV_1 % predicted observed in study CT01 in the CHF 1538 arm may be related to an increased proportion of younger patients in that arm. The Statistical reviewer also concluded that study CT03 should be viewed as supportive due to the lack of an adequate non-inferiority margin justification. I agree with this conclusion.

Both the Statistical review and Clinical reviewer assessed the adequacy of the applicant's response in the resubmission regarding inaccurate recording of height and age at clinical trial sites and impact on pulmonary function results. The inaccurate recording was related to a particular version of spirometry software. The applicant conducted source data verification for the CT02 clinical sites that used this version of spirometry software. Nearly all identified discrepancies were related to height, and the impact of this inaccurate recording was evaluated through three sensitivity analyses. The results of these sensitivity analyses corroborated the findings for the clinical trial summarized above. Both reviewers concluded that this deficiency has been adequately addressed.

8. Safety

Both the Clinical reviewer and CDTL concluded that the reported adverse reactions for CHF 1538 are consistent with FDA's previous findings for safety of TOBI®. I concur with this conclusion.

The safety database included 346 patients treated with CHF 1538 in phase 3 clinical trials, though only 161 patients received treatment for more than one 28-day course. There was 1 death in a CHF 1538 patient in the clinical trials, and this was attributed to cardiomyopathy of unclear etiology and considered unlikely related to drug treatment. Most serious adverse reactions seemed related to pulmonary exacerbations. Common

adverse reactions included dysphonia, pharyngitis, epistaxis and headache. There was no evidence of ototoxicity or nephrotoxicity in the clinical trials.

9. Advisory Committee Meeting

There was no advisory committee meeting held for this product.

10. Pediatrics

The applicant requested a waiver for pediatric patients 0-6 years of age. I agree with the waiver based on the small number of children in this age group with *P.aeruginosa* chronic colonization limiting the feasibility of conducting studies in this age group.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

Labeling was modified and finalized based upon Agency reviews and discussions with the applicant. The labeling including Patient Information is acceptable to provide for acceptable risk benefit of the product.

The proposed proprietary name of Bethkis was reviewed and deemed acceptable.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
I recommend approval for this NDA. The product Bethkis is an inhalational tobramycin product with a higher tobramycin concentration and a higher osmolality compared to the approved product TOBI®. As a 505(b)(2) application, the application relies in part upon the previous findings of safety and efficacy for TOBI®. The NDA provides substantial evidence of efficacy of Behtkis for the management of cystic fibrosis patients with *Pseudomonas aeruginosa.* Safety data from clinical trials and postmarketing data from outside the United States supports a favorable risk benefit for Bethkis.

Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies:
None

Recommendation for Postmarketing Requirement:
Spontaneous post-marketing surveillance reporting will not be sufficient to identify a serious risk of upper airway and bronchial hypersensitivity/irritation (including the risk for acute decreases in FEV1, bronchospasm, wheezing, dyspnea, cough, etc.) that could result from the high osmolality of Bethkis (tobramycin 300 mg/4mL inhalation solution) in patients with low FEV1. The product was not evaluated in patients with a stable FEV1 $\geq$ 25 to <40% predicted. I recommend a post-marketing requirement to conduct a long

term (over 24 weeks or 3 on/off 28-day cycles) postmarketing observational study in 50 patients describing the safety and tolerability of Bethkis® in patients with a stable FEV1 ≥ 25 to <40% predicted. The following efficacy outcomes should also be collected: sustained FEV improvement, number of exacerbations, anti-pseudomonal use, and planned and unplanned hospitalization and death.

Final Protocol Submission: June 30, 2013
First Interim Report: March 31, 2015
Study Completion Date: September 30, 2015
Final Report Submission: December 31, 2015

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/s/

JOHN J FARLEY
10/12/2012