CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201,820
Priority or Standard	Class 2 Resubmission
Submit Date(s)	12 April 2012
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Division / Office	Division of Anti-Infective Products/Office of Antimicrobial Products
Reviewer Name	Ariel Ramirez Porcalla, MD, MPH
Review Completion Date	1 October 2012
Medical Team Leader	Eileen Navarro-Almario, MD
Established Name	Tobramycin 300 mg/4 mL Inhalation Solution (CHF 1538)
(Proposed) Trade Name	Bethkis®
Therapeutic Class	Aminoglycoside
Applicant	Chiesi Pharmaceuticals, Inc. 9605 Medical Center Drive, Suite 380 Rockville, MD 20850
Formulation(s)	Inhalation Solution
Dosing Regimen	300 mg of tobramycin/4 mL by

	nebulization twice daily
Indication(s)	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Intended Population(s)	Cystic Fibrosis patients with *Pseudomonas aeruginosa*; age ≥ 6 years; FEV1 % predicted ≥ 40% and ≤ 80%; no lung colonization with *Burkholderia cepacia*

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends marketing approval for CHF 1538 (Bethkis®). The decision is based on efficacy and safety data submitted in the original NDA submission and the Applicant's response to the Division's Complete Response Letter. This recommendation, however, is dependent on the recommendation of the Center for Devices and Radiological Health Consultant on the adequacy of the evidence presented to demonstrate the comparability of the nebulizer-compressor combination used in clinical trials to the to-be-marketed combination on the drug-device efficacy and safety characteristics. Furthermore, this recommendation should be taken in the context of continued monitoring for AEs associated with systemic aminoglycosides (i.e. ototoxicity, nephrotoxicity, and neuromuscular weakness) and AEs indicative of airway hypersensitivity/irritation (i.e. bronchospasm, dysphonia, wheezing, and epistaxis).

1.2 Risk Benefit Assessment

CHF 1538 is an inhalational tobramycin product with a higher tobramycin concentration and a higher osmolality compared to the reference drug TOBI®. The original NDA for this drug product presented safety and efficacy data consistent with the reference drug. The resubmission provides efficacy data indicating the negligible impact of source data errors in the original submission.

Safety data from clinical trials and postmarketing sources do not identify any new safety signals for CHF 1538. Except for the AEs of dysphonia, wheezing, and epistaxis occurring more frequently in the CHF 1538 group, the safety profile of CHF 1538 does not indicate a greater potential for airway hypersensitivity/irritation. Moreover, the greater frequencies of major safety events reflecting worse outcomes in placebo-treated patients from the underlying CF/pulmonary exacerbation may be related to the relative effectiveness of CHF 1538 in preventing these major AEs. Therefore, it appears that the risk associated with CHF 1538 use is minimal and is consistent with that ascribed to the use of the reference drug TOBI®.

Based on this evaluation, the Medical Officer believes that the benefit provided by the use of CHF 1538 by the intended CF patients outweigh the risk of its use. This assessment should be taken in the context of continued monitoring for AEs typically associated with systemic aminoglycosides (i.e. ototoxicity, nephrotoxicity, and neuromuscular weakness) and AEs indicative of airway hypersensitivity/irritation (i.e. bronchospasm, dysphonia, wheezing, and epistaxis).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

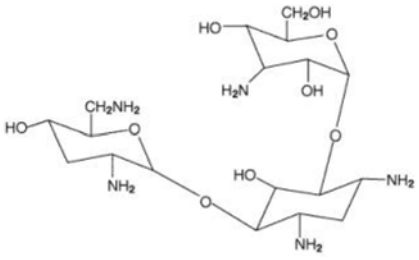
None.

2 Introduction and Regulatory Background

2.1 Product Information

Chiesi Pharmaceuticals, Inc. is seeking approval to market tobramycin 300 mg/4 mL inhalation solution, also known by its code number CHF 1538 and by its approved trade name Bethkis®, in the United States for the management of cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*. The submission, NDA 201 820, is a 505(b)(2) application that relies, in part, on prior findings of safety and efficacy for TOBI®, a 300 mg/5 mL tobramycin inhalation solution approved for the same indication in 1997.

The chemical formula for tobramycin is C18H37N5O9 and its molecular weight is 467.52. Its structural formula is:



Tobramycin is an aminoglycoside bactericidal antibacterial that is one of several components of an aminoglycoside complex (nebramycin) that is produced by *Streptomyces tenebrarius*. Tobramycin's bactericidal activity and its post-antibiotic effect are concentration-dependent. Once tobramycin diffuse through channels formed by porin proteins in the bacterial outer membrane and by electron transport across the cytoplasmic (inner) membrane, tobramycin binds to the 30s ribosomal subunit of the bacteria to interfere with the initiation of protein synthesis. This leads to altered cell membrane permeability and eventual cell death. Transport of aminoglycosides across the inner bacterial membrane is oxygen- and pH-dependent. The activity of aminoglycosides is consequently reduced markedly in an anaerobic environment (i.e. abscess) and in an acidic medium (i.e. urine). In addition, stricly anaerobic bacteria and

facultative bacteria grown under anaerobic conditions are intrinsically resistant to aminoglycosides. [1]

Tobramycin is active against Gram negative bacteria, including *Pseudomonas aeruginosa*.

2.2 Tables of Currently Available Treatments for Proposed Indications

For the indication proposed for CHF 1538, two drugs are available:

1. TOBI® - labeled for the management of CF patients with *P. aeruginosa*. Safety and efficacy have not been demonstrated in patients under 6 years of age, patients with FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.
2. Cayston® - labeled to improve respiratory symptoms in CF patients with *P. aeruginosa*. Safety and effectiveness have not been demonstrated in patients younger than 7 years, patients with FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.

2.3 Availability of Proposed Active Ingredient in the United States

Tobramycin is a parenteral aminoglycoside approved in the United States for the treatment of bacterial infections since 1975.

2.4 Important Safety Issues with Consideration to Related Drugs

Parenteral aminoglycosides have been associated with the following:

- Ototoxicity – measured by symptoms of hearing loss or tinnitus or by audiometry. This is manifested as both auditory (hearing loss) and/or vestibular toxicity (vertigo, ataxia, dizziness).
- Nephrotoxicity
- Neuromuscular dysfunction with aggravation of muscle weakness in pre-existing muscular disorders such as myasthenia gravis or Parkinson's disease.

Postmarketing reports of hearing loss in patients receiving TOBI® with previous or concomitant treatment with systemic aminoglycosides were noted. With these, physicians are recommended to exercise caution when prescribing TOBI® to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients should also be monitored for these antibacterial class adverse reactions.

Bronchospasm was noted to occur with inhalation of TOBI®, though in clinical trials, changes in FEV_1 measured after the inhaled doses were similar between treatment groups. Thus, patients treated with tobramycin inhalation solution should be closely monitored for bronchospasm and if bronchospasm develops, patients should be treated as medically appropriate.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

2.5.1. Regulatory History Prior to Original New Drug Application (NDA) Submission

Since 2010, several countries in Europe and South America have granted marketing approval for CHF 1538 for the management of CF patients older than 6 years of age with *P. aeruginosa*.

Clinical trials have been previously conducted in Europe. In 2005, the Applicant initiated discussion of its plans to obtain marketing approval in the United States using data from these trials, in conjunction with a 505(b)(2) application. During this time, to address the issue of a compressor (TurboBoy) used in the clinical trials that is unavailable in the United States, the Agency recommended finding a comparable compressor in the US with sufficient evaluable specifications and with possible plans for bridging studies.

In 2007, the Chemistry, Manufacturing, and Controls (CMC) reviewer evaluated a compressor the Applicant suggested (b) (4) and decided that the TurboBoy and (b) (4) were equivalent. At that time, the CMC reviewer considered that a bridging study may not be necessary at that time. However, in 2009, the Agency decided that a bridging study was necessary, given the different osmolality of the to-be-marketed product ((b) (4) mOsmoles/kg) when compared to the osmolality of the drug product used in the clinical trials (Studies CT01 and CTO02: (b) (4) mOsmoles/kg; Study CTO3: (b) (4) mOsmoles/kg) and when compared to the reference product TOBI ((b) (4) mOsmoles/kg). The Applicant proposed that Study CT03 could be used as a bridging study as this trial compares a formulation approximating the to-be-marketed product and TOBI. The Applicant also notified the Agency that the Applicant would be submitting an NDA for CHF 1538 in the second quarter of 2010. The Division concurred with this proposal.

Prior to the submission of the original NDA, the Sponsor reported that CHF 1538 has been given marketing approval in 23 countries for the management of pulmonary infections caused by *Pseudomonas aeruginosa* in CF patients age six years and older.

2.5.2. Regulatory Issues Identified in the Original NDA Submission

The initial NDA submission for CHF 1538, submitted October 22, 2010, received a Complete Response decision from the Division on August 25, 2011.[2]

2.5.2.1. Chemistry, Manufacturing and Controls/Product Quality Microbiology/ Device

The Regulatory Device Consult provided by the Center for Devices and Radiological Health (CDRH) identified deficiencies as "Clinical Hold Issues". These deficiencies center on the issue that the labeling proposes that CHF 1538 be administered using a nebulizer and a compressor, the PARI LC PLUS or (b) (4) nebulizers with the PARI Vios Compressor, different from the nebulizer and compressor used in the clinical trials, PARI LC PLUS nebulizer with either the PARI TurboBoy N or S compressor. The deficiencies listed by the CDRH reviewer are:

- An adequate description of the proposed devices was not provided for review.
- Adequate comparative particle characterization data for the proposed to-be-marketed combination product/s and the product/s tested in the clinical trials was not provided for review.
- 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 the labeling are validated.

The previous Cross-Disciplinary Team Leader (CDTL), Dr. John Alexander, also recommended that the Sponsor should provide the same data required by the CDRH reviewer for the reference drug, TOBI, delivered using the PARI LC PLUS nebulizer and the De Vilbiss Pulmo-Aide compressor, as this may provide a reference parameter for the proposed comparisons.

The Agency was concerned that clinical studies may need to be conducted to sufficiently justify the use of the to-be-marketed devices instead of the devices used in clinical trials, even when *in-vitro* bridging data is provided. The Pulmonary Division Reviewer/Consultant shared this concern, stating that *in vitro* studies alone are not acceptable in bridging clinical safety and efficacy findings from one drug-device combination to another. The Consultant stated that changing the compressor/jet nebulizer system for an inhaled drug/device combination may significantly affect the dosing, delivery, and absorption of the drug. These differences may not be predicted by in vitro studies alone, specially in patients with chronic lung disease.

Both the CMC Reviewer and the Pulmonary Consultant noted that the Applicant modified the osmolality of the drug product late in the course of the development progam:

- Trials CT01 and CT02: (b) (4) mOsmoles/kg
- Trial CT03: (b) (4) mOsmoles/kg
- Proposed To-be-marketed product: (b) (4) mOsmoles/kg.

As previously stated, the Applicant had intended to use Trial CT03 as a bridging clinical study that may address the safety and efficacy concerns of a to-be-marketed drug with a lower osmolality. According to the Acting Division Director's Decisional Memo, the

Division would determine the adequacy of data from Trial CT03 and additional in vitro data submitted in bridging safety and efficacy concerns with the use of the to-be-marketed drug-device combination to safety and efficacy data from the drug-device combinations used in clinical trials during this review cycle.

Prior review of safety data of Trials CT01 and CT02 using the higher osmolality drug product did not raise safety concerns. With a comparable osmolality to the to-be-marketed product, the drug product used in Trial CT03 likewise did not raise any safety concern. Regarding efficacy of the drug product with comparable osmolality to the to-be-marketed drug, the previous Medical Reviewer noted similar degrees of improvement in FEV_1% predicted in the CHF 1538 group of Trial CT03 compared to the improvement in FEV_1% in Trials CT01 and CT02. This may indicate comparable efficacy between the to-be-marketed drug product with the drug products used in the clinical trials. Using additional data submitted for this review cycle, these observed comparability in safety and efficacy between the to-be-marketed drug-device combination and the ones used in clinical trials will be verified.

2.5.2.2. Non-Clinical Pharmacology Toxicology, Clinical Pharmacology/Biopharmaceutics, and Clinical Microbiology

The Pharmacology Toxicology Reviewer, Dr. Amy Ellis, had no objections to the approval of the original NDA submission. The Reviewer noted the differences in the tobramycin concentration, sodium chloride concentration, and pH between the drug product and TOBI®. She did not identify any Pharmacology Toxicology issues as she believes that the 7-day and 28-day repeat dose toxicity studies conducted sufficiently "bridges" the drug product to TOBI®.

The Clinical Pharmacology Reviewer, Dr. Yongheng Zhang, determined that there were no outstanding Clinical Pharmacology issues in the original NDA submission. The Applicant conducted a Phase 1 bioavailability and pharmacokinetic study (CP01) to evaluate plasma and sputum levels after a single administration of nebulized CHF 1538 in comparison to TOBI®. The study showed comparable low plasma concentration-time profiles for the both the study drug and TOBI®, but highly variable sputum concentrations of both products. Trial CT01 included a PK substudy that evaluated peak sputum concentrations on Study Days 1 and 28. The substudy showed similar mean sputum concentrations of tobramycin on Days 1 and 28 in patients treated with CHF 1538.

The Clinical Microbiology Reviewer, Dr. Frederick Marsik, determined that there are no outstanding Clinical Microbiology issues. No interpretative criteria have been established for inhaled tobramycin and *P. aeruginosa*. However, Dr. Marsik noted the similarity in the *in vitro* susceptibility (defined by the breakpoint of ≥ 16 mcg/mL) between the baseline isolates from the clinical trials and the US *P. aeruginosa* isolates from 2007 to 2009. Between the two treatment groups in the clinical trials, Dr. Marsik

also noted the similarity between the susceptibility profiles of the baseline isolates. Lastly, the Dr. Marsik noted that while on a treatment cycle, both CHF 1538 and TOBI® similarly reduced baseline bacterial loads in sputum samples. However, once treatment stopped, no significant difference in bacterial loads between groups was noted.

2.5.2.3. Clinical and Statistical Assessment of Efficacy

The Cross-Discipline Team Leader, Medical Reviewer, and Statistical Reviewer all recommended a Complete Response for the original NDA submission because the Applicant did not provide adequate data to justify and evaluate the change in nebulizer and compressor to be used with CHF 1538, compared to the combination used in the clinical trials.

The Clinical Reviewer, Dr. Shrimant Mishra, and the Statistical Reviewer, Dr. M. Amper Gamalo, both raised the following concerns:

- The observed degree of improvement in FEV_1 % predicted in Trial CT01 when the CHF 1538 group is compared to placebo (i.e. 12.8% at Week 2 and 11.0% at Week 4) is inconsistent with the that in Trial CT02 (6.1% at Week 2 and 7.3% at Week 4) and CT03 (5.81% at Week 2 and 5.53% at Week 4). The Reviewers conducted multiple analyses to determine the cause of these inconsistent results may be due to the following:
    - Study design and protocol differences (inclusion of patients with exacerbation during baseline and during the study in CT02, inclusion of patients with tobramycin-susceptible strains of P. aeruginosa in CT01)
    - Differences between the baseline characteristics of the populations of the trials (i.e. enrollment of a significantly younger set patients in the CHF 1538 group in CT01 compared to CT02, differences in chronic colonization status with *P. aeruginosa* between the trials
    - Differences in use of concomitant medications between treatment groups in each trial (i.e. increased use of mucolytics and steroids in the placebo arm of CT01 and increased use of ß-agonist drugs in the CHF 1538 arm in CT02).
    - Geographic differences with each trial being conducted in different regions of Europe

  However, the reviewers were unable to determine a definite etiology for the observed inconsistencies between the degrees of improvement observed in trials.

  Medical Officer Comment:
  The only significant difference that may explain the inconsistent results between trials is the significant difference in the age of enrolled patients between the two treatment groups in Trial CTO1, with the CHF 1538 patients being younger (11.0 years compared to the mean age of the placebo-treated patients [14.2 years]

[p=0.024]). Related to this age difference between treatment groups is the significantly higher weight and height of the placebo group (27.4 kg and 132.2 cm of the CHF 1538 group compared to 40.7 kg and 151.4 cm of the placebo group). These significant differences in age, weight, and height between the two treatment groups in Trial CT01 were not seen in Trial CT02 and CT03. The current Medical Reviewer concurs with Dr. John Farley that the younger patients in the CHF 1538 group in Trial CT01 may have better response rates; thereby, partly explaining the inconsistent treatment differences between the treatment groups among the trials.

- Data Integrity Issues

  - The Division of Scientific Investigations (DSI) identified two sites from which data may not be reliable. One site in Study CT02 (Poland, Site # 26, Dr. Maria Trawinska Barnicka, n=29), the changes in age and/or height of patients were not incorporated in the calculation of the predicted FEV_1, FVC, and FEF. In some cases, changes in the FEV_1, FVC, and FEF were recorded without changes in age and/or height. These would lead to erroneous calculations of FEV1 % predicted. Based on these findings, the data for the primary and secondary endpoint variables are incorrect for Trial CT02. This issue was cited as one of the major deficiencies the Applicant is required to address in the Complete Response Letter. The Applicant must submit recalculated values for the primary and secondary variables that may have been affected by the incorrect height and weight data.

    Medical Officer Comment:
    The Medical Officer concurs with prior reviewers in citing this as an issue that needs to be addressed in the Applicant's resubmission. In Trial CT02, The mean ages of enrollees in the CHF-1538 and placebo groups are 14.8 years (6.0 to 31.0 years) and 14.7 years (6.0 to 45 years), respectively. Moreover, majority of enrollees are < 17 years old in both treatment groups (68.3% in the CHF-1538 group and 73.8% in the placebo group). Thus, changes in height in these age groups may impact the primary and secondary outcome variables. The Applicant must ensure that the correct height is used to determine the FEV_1 % predicted.

  - DSI inspection of another site (Russia, Site # 32, Dr. Nikolai Kapranov, n=24) found regulatory violations, subsequently being classified as VAE (voluntary action indicated). The site had issues with drug distribution and accountability, with the Inspectors having difficulty deciphering which patients received what medication. The Investigator, however, was able to provide other documentation of the trial drug given to patients. Also,

clinical inspection summary (CIS) indicates that observations at this site do not appear to significantly impact data integrity or subject protection.

- The previous Medical Reviewer noted that audiometric test results in Site 17 in CT01 may have repeated thresholds for every patient while other sites have their own pattern of results (i.e. 0-10 dB range or 10-20 dB range in a site). This observation could potentially be fabricated data and could be potentially related to the inconsistent degrees of improvement noted between CT01, CT02, and CT03.

- FEV_1 vs Time to First Exacerbation

The primary endpoint variable investigated in the trials, the % improvement in predicted FEV_1 above baseline does not directly translate to a clinically meaningful benefit for the patients, such as time to first pulmonary exacerbation, decrease in days of hospitalization, etc. The Statistical Reviewer cites this issue as a concern. In Trial CT02, the following secondary endpoints were investigated:

- Clinical symptoms (wheezing, cough)
- Pulmonary exacerbations
- Hospitalizations due to the disease
- Loss of school/working days due to disease
- Use of parenteral anti-Pseudomonal antibacterial (and parenteral tobramycin).

According to the Statistical Reviewer, while the trial did not show a significant difference on the timing of pulmonary exacerbations in both CHF-1538 and the placebo-treated groups, the trial was not designed to detect such differences.

Medical Officer Comment:
The primary endpoint in the three trials, defined as the percentage change from baseline in Forced Expiratory Volume in one second (FEV_1) from the predicted normal FEV_1, was compared between treatment groups. Analyses of data indicate that there is a significant difference between the two groups. The Medical Officer concurs with previous reviewers that the trial does not address how differences in percentage improvement or percentage deterioration, whether statistically significant or not, translate to clinically relevant parameters to a patient with cystic fibrosis (i.e. how a patient feels, functions, and survives). While this is not a major issue for this Complete Response, the Medical Officer believes that future trials have to ensure that endpoints reflect clinically relevant parameters.

- Noninferiority Trial

  The noninferiority margin identified for Trial CT03 was not clearly established and was not adequately justified. Prior reviewers considered results from Trial CT03 as supportive information.

2.6 Other Relevant Background Information

Based on the discussion above of the major deficiencies in the application, the reviewers and the consultants have determined that the application could not be approved in its present form. The Division issued a Complete Response Letter in 25 August 2011, citing the reasons for non-approval and the recommendations to address these issues in the subsequent review cycle.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the Complete Response eCTD submission appears acceptable.

3.2 Compliance with Good Clinical Practices

During FDA inspection of Site 26, inaccurate recording/loss of source input data that included height and age was identified. Since absolute and predicted values for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and forced expiratory flow (FEF25-75%) are functionally linked to height, age, and sex, verification of the accuracy in transcribing printouts of these parameters from the spirometer to the case report forms, and subsequently in the clinical database was important. The Sponsor attributed the loss of source data to a software modification used in the MES Lung Test 1000 Spirometer that calculated predicted pulmonary function parameters based on source input data. The Applicant determined that four clinical sites used the MES Lung Test 1000 Spirometer and in effect, experienced difficulty with retrieval of source input data. These sites are as follows: Site 13 (Investigator: Gonczi), Site 23 (Investigator: Stetmach), Site 26 (Investigators: Trawinska, Bartnicka), and Site 29 (Investigator: Kaczmarski). This issue was the basis for the Clinical Reason No. 2 cited in the Complete Response Letter.

The previous Medical Reviewer, Dr. Shrimant Mishra, has enumerated several aspects of trial conduct he deemed to marginally impact the efficacy and safety results. These include poor physical examination performance or poor documentation of physical examination performance, improperly performed or documented audiometric tests, protocol violations in applying the inclusion and exclusion criteria, protocol violations in

allowing the administration of a number of minor excluded concomitant medications, and the administration of the study drug opposite to the randomized treatment arm in 15 patients.

Medical Officer Comment:
The Medical Officer concurs with Dr. Mishra that the protocol violations and study conduct irregularities minimally impact the ability of the trials to demonstrate the safety and efficacy of CHF-1538.

However, in concurrence with the Complete Response letter, the Medical Officer believes that the Applicant must demonstrate that the discrepancies between the absolute and predicted values of pulmonary function parameters from the clinical database used in the efficacy analysis in the original submission and those from the retrieved spirometry source input data do not significantly impact the evidence of efficacy presented in the original submission. To do this, the Applicant must recalculate the pulmonary function parameters using the retrieved spritometry source input data and compare the resultant primary efficacy outcome measures with those in the original submission.

3.3 Financial Disclosures

None.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Microbiology Product Quality Reviewer, Robert J. Mello, has reviewed the Applicant's Response to the Division's Complete Response. He has determined that there are no new microbiology product quality information that would impact his initial recommendation of approval.

4.2 Clinical Microbiology

Tobramycin has in vitro activity against a spectrum of Gram negative bacteria that includes Pseudomonas aeruginosa. Tobramycin is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. For more details, please refer to the reviews of the original NDA submission of the Clinical Microbiology reviewer, Dr. Frederick Marsik, and the Medical Reviewer, Dr. Shrimant Mishra.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewer, Dr. Amy L. Ellis, has reviewed the Applicant's submission in response to the Division's Complete Response letter. The current submission does not contain any new nonclinical data. As with the original NDA submission, Dr. Ellis has not identified any nonclinical issues in the current submission that would preclude approval of CHF-1538.

4.4 Clinical Pharmacology

The current Clinical Pharmacology Reviewer, Dr. Ryan Owen, has reviewed the Applicant's response to the Division's Complete Response letter. Dr. Owen has not identified any Clinical Pharmacology issues that would preclude approval of CHF 1538.

4.4.1 Mechanism of Action

Tobramycin is an aminoglycoside produced by *Streptomyces tenebrius*. The mechanism of action of tobramycin is the disruption of protein synthesis resulting from the binding of the drug molecule to the 30s subunit of the bacterial RNA. Disruption of protein synthesis leads to altered cell membrane permeability, progressive disruption of the cell envelope, and cell death.

4.4.2 Pharmacodynamics

Please refer to the review of the original NDA submission of the previous Clinical Pharmacology Reviewer, Dr. Yongheng Zhang.

4.4.3 Pharmacokinetics

Dr. Zhang also reviewed PK data from Study CP01, which is a randomized, double-blind, 2-way crossover study to determine the PK of CHF 1538 compared to TOBI after a single dose. The study demonstrated that the concentration-time profiles of tobramycin after one dose of CHF 1538 or TOBI® were superimposable, indicating similar systemic exposure. While tobramycin sputum concentrations were highly variable, the study showed that sputum concentrartions for both formulations declined to around 15% of tobramycin levels at 30 minutes, indicating minimal sputum accumulation. Dr. Zhang concluded that data from this study adequately described and compared the PK of tobramycin in plasma and sputum for both products. From this comparison, Dr. Zhang expects that the systemic safety profile of both formulations should also be similar.

Using PK data obtained from a sample of patients enrolled in Trial CT01, Dr. Zhang concurred with the Applicant that tobramycin did not accumulate in the sputum following repeated dosing of CHF 1538 for a 28-day treatment period.

Medical Officer Comment:
The Medical Officer believes that the comparative PK data in Table 1 *demonstrates that both formulations have similar PK profiles. The data show that tobramycin from either formulations do not get significantly absorbed systemically. Moreover, the PK data are important in providing a potential rationale for the similar efficacy and safety profile that could be observed between CHF 1538 and TOBI, despite the differences in concentration and osmolalities of the two drug formulation.*

Table 1. Comparison of Tobramycin Plasma and Sputum PK Parameters after a Single Dose of CHF or TOBI

PLASMA				
	CHF 1538	**TOBI**	**Point Estimate**	**Statistical Comparison [90% CI]**
C_{max} (ng/mL)	549.10	540.42	1.02	NS (p=0.950) [0.64-1.62]
T_{max} (h)	1.5 (1.0-2.0)	1.0 (0.5-3.0)		NS (p=0.531) [-]
AUC_t (ng×h/mL)	3349.05	3323.88	1.01	NS (p = 0.979)
AUC_∞ (ng×h/mL)	3470.40	3454.35	1.00[1]	NS (p=0.987) [0.61-1.66]
$T_{½}$ (h)	4.4	4.7	-	- [-]
MRT (h)	5.8	6.1	-	- [-]
SPUTUM				
C_{max} (µg/g)	813.94	543.11	-	NS (p=0.300)
T_{max} (h)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	-	NS (p=0.875)

[1] relative bioavailability

Note: C_{max} shown as geometric means

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. List of studies/trials included in the analysis

Study	Phase and Design	Study and Control drugs Dose, Route and Regimen	Duration	# of Subjects per Arm	Study Population
CP01	Randomized, double-blind, 2-way crossover Active-controlled	CHF 1538 300 mg BID by inhalation vs. TOBI	Single dose	11/9	Cystic Fibrosis
CT01	Randomized, double-blind, parallel group, placebo controlled	CHF 1538 300 mg BID by inhalation vs. Placebo	One, 4-week treatment followed by one 4-week	CHF 1538: 29/28 Placebo: 30/23	Cystic Fibrosis with *P. aeruginosa* infection

			washout		FEV1≥ 40 % and ≤ 80 % predicted normal
CT02	Randomized, double-blind, parallel group, placebo controlled	CHF 1538 300 mg BID by inhalation vs. Placebo	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 normal
CT03	Randomized, open-label, parallel group, Active-controlled	CHF 1538 300 mg BID by inhalation vs. TOBI	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 normal

5.2 Review Strategy

The current Medical Reviewer will determine the efficacy and safety of CHF-1538 to treat the proposed indication by reviewing the Applicant's response to the Division's Complete Response. The Medical Reviewer would determine the adequacy of the Applicant's response to each of the reasons/points the Division specified in the Complete Response letter and evaluate the additional efficacy and safety data submitted during the current review cycle.

While the Medical Officer would rely more on the safety data from the pivotal clinical trials previously reviewed by Dr. Mishra, the Medical Reviewer would evaluate the submitted postmarketing safety data from the use of CHF-1539 in countries where the drug product approved as supportive evidence of the safety of CHF-1538.

5.3 Discussion of Individual Studies/Clinical Trials

The NDA submission utilized data from the following studies/trials in the analysis to demonstrate the efficacy of CHF-1538 for the proposed indication.

Study CT01

Study CT01 is a randomized, double-blind, placebo controlled, parallel-group, multicenter trial designed as a superiority trial. The trial was conducted in Moldavia, Italy, France, the Ukraine, and Spain. The primary objective of the study was to evaluate the efficacy and safety of a 4-week treatment regimen of CHF 1538 compared to placebo in patients with CF and *P. aeruginosa* infection. Twenty-nine patients were randomized to CHF 1538 while 30 patients were randomized to placebo. The following are the major trial components:

- Primary Efficacy Variable: Change from baseline in Forced Expiratory Volume in one second (FEV_1)

- Primary Endpoint: Change from baseline to Visit 4 in the percentage of observed FEV_1 of the predicted normal FEV_1 , after four weeks of treatment with the study drug vs. placebo (at Visit 4)
- Secondary Endpoints:
    - Changes from baseline to Visit 8 or to the last ON cycle visit in the following pulmonary function parameters: FEV_1 (L), Forced Vital Capacity [FVC] expressed in liters (L) and as a percentage of predicted normal; Forced Expiratory Flow at 25-75% of FVC ($FEF_{25-75\%}$) expressed in L/second (sec) and as a percentage of predicted normal; Respiratory Volume (RV) (L); Total Lung Capacity (TLC) (L); and RV/TLC ratio (RV/TLC, %)
    - Change in microbiological indices;
    - Changes in body measurements (body weight, height, and body mass index).
- Inclusion: Moderate pulmonary function impairment with an FEV_1 % predicted normal ≥ 40% and ≤ 80%, and susceptibility of isolated *P. aeruginosa* strains to tobramycin based upon tobramycin systemic breakpoints and local laboratory methods.

FEV_1 % predicted normal at study entry was 58.2% in the CHF 1538 group and 62.3% in the placebo group, with the difference not statistically significant. Patients in this trial used the PARI TurboBOY compressor and a PARI LC Plus® nebulizer for use during the trial.

Study CT02

Study CT02 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter superiority trial conducted in Hungary, Poland, and Russia. The following are the major study parameters:

- Primary Objective: To demonstrate the efficacy and safety/tolerability of inhaled aerosolized intermittent administration of CHF 1538 (300 mg BID) compared to inhaled aerosolized placebo saline solution following three 4-week treatment periods ("ON" cycles), each followed by one of three, 4-week periods without treatment ("OFF" cycles) in CF patients infected with *P. aeruginosa* infection
- Primary Efficacy Variable: Change from baseline in FEV_1
- Primary Endpoint: Change in FEV_1 % of predicted normal from baseline visit to Visit 8 (end of 3rd treatment cycle) or to the last "ON" cycle visit for patients terminating the study prematurely.
- Secondary Endpoints:
    - Changes from baseline to Visit 8 or to the last ON cycle visit in the following pulmonary function parameters: FEV_1 (L), Forced Vital Capacity [FVC] expressed in liters (L) and as a % of predicted normal; Forced Expiratory Flow at 25-75% of FVC ($FEF_{25-75\%}$) (L/ sec) and as a percentage of predicted normal; Respiratory Volume (RV) (L); Total Lung Capacity (TLC) (L); RV/TLC ratio (RV/TLC, %); and respiratory rates (RR)

- Changes in microbiological indices: bacterial load of P. aeruginosa in sputum; tobramycin susceptibility (MIC, MIC50, and MIC90 values); categorical results (eradication, morphotype analysis)
- Changes in clinical symptoms (wheezing, cough)
- Changes in pulmonary exacerbations
- Hospitalizations due to the disease
- Loss of school or/and working days due to the disease
- Use of parenteral antipseudomonal drug (including parenteral tobramycin)
- Changes in body measurements (body weight, height, and body mass index).

Study CT03

Study CT03 is an open-label, multinational, multicenter, randomized, active controlled (with the reference product TOBI®), parallel group study designed as a noninferiority study between CHF 1538 and TOBI®. This study was conducted in Russia, the Ukraines, Poland, Hungary, Germany, Czech Republic, Spain, and France. While an outpatient study, a maximum of 320 patients were were recruited from inpatient and outpatient settings to obtain 286 evaluable patients. The following are the major study parameters:

- Primary Objective: To compare the efficacy and safety of CHF 1538 and TOBI® administered over a 4-week treatment period using a twice-daily regimen in patients with CF and *P. aeruginosa* chronic infection.
- Primary Efficacy Variable: Change from baseline of FEV_1
- Primary Endpoint: Change in FEV_1 % of predicted normal from baseline visit to the end of treatment phase (Visit 4)
- Secondary Endpoints: Pulmonary function tests (FEV_1 % of predicted normal at Visits 3 and 5; FEV_1 % (L) measured at Visits 3, 4, and 5; FVC (L) and % predicted normal at Visits 3, 4, and 5; and $FEF_{25-75\%}$ (L/sec) and % predicted normal measured at Visits 3, 4, and 5.

6 Review of Efficacy

Efficacy Summary

The Medical Officer concludes that CHF 1538 (Bethkis®) is effective in significantly improving the change from baseline in the FEV1 % predicted after either 28 days of CHF 1538 with a 28 day follow-up period or after three cycles (28 days on-/28 days off-treatment) compared to placebo. This conclusion is based on efficacy evidence from three clinical trials submitted in the original NDA submission and on the supplemental efficacy information in the Applicant's response to the Division's Complete Response Letter.

The NDA was submitted to obtain marketing approval for a 300 mg/4 mL tobramycin inhalation solution given twice daily for the management of cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*. The Applicant intends to administer the inhalation solution using the PARI LC Plus nebulizer and the PARI Vios compressor. This application is a 505(b)(2) application that relies on previous findings of safety and efficacy for TOBI®, an inhalation product with a slightly different formulation approved in 1997. The objective of this application is to demonstrate that the efficacy findings for CHF 1538 (pulmonary function tests and secondary outcomes) from the three clinical trials are consistent with the efficacy findings for TOBI®.

The Applicant provided efficacy data from three clinical trials with differing study designs but with the same primary endpoint: mean change from baseline in FEV1 % predicted after a specified treatment cycle. The trials are:

- Trial CT01 was a randomized, double-blind, placebo-controlled trial of a 28-day course of CHF 1538 (formulation with osmolality of (b) (4) mOsmol/kg) in 29 patients or placebo in 30 patients, administered using the PARI LC Plus nebulizer and the PARI TurboBoy compressor, with a 28-day follow-up period.
- Trial CT02 was a randomized, double-blind, placebo-controlled trial comprising of three cycles (28 days On/28 days OFF treatment) of CHF 1537 (formulation with osmolality of (b) (4) mOsmol/kg) in 161 patients or placebo in 85 patients, using the PARI LC Plus nebulizer and the PARI TurboBoy compressor. The trial evaluated several secondary endpoints that include microbiologic endpoints, changes in other pulmonary function tests, proportion of disease-related unplanned hospitalizations, and proportion of patients who received at least one dose of parenteral anti-pseudomonal antibacterials.
- Trial CT03 was an open-label, multinational, multicenter, randomized, active controlled, parallel group study designed as a noninferiority study between CHF 1538 (formulation with osmolality of (b) (4) mOsmol/kg) in 155 patients and TOBI® (formulation with osmolality of (b) (4) mOsmoles/kg) in 166 patients given for 28 days with a 28-day follow-up period using the PARI LC Plus nebulizer and the PARI TurboBoyN compressor.

The Statistical Reviewer, Dr. M. Amper Gamalo, verified the Applicant's efficacy analysis from Trials CT01 and CT02 (Table 3). The primary efficacy analyses using data from the original NDA submission demonstrated a significant increase in the mean change from baseline in the FEV1 % predicted in patients treated with CHF 1538 compared to patients given placebo. Results from Trial CT03 are considered supportive because the proposed noninferiority margin of -4.5% was not adequately justified. The results of CT03 further indicate that patients treated with CHF 1538 appear to have a similar trend in improvement of the FEV1 % from baseline values when compared with patients treated with TOBI.

Table 3. Summary of Primary Efficacy Analyses Results from Trials CT01 and CT02 Using the Multiple Imputation Method

Trial	Week		CHF 1538 (%)	Placebo (%)	P-Value
CT01	4 "ON" Drug	Mean change from Baseline	15.9	4.9	**0.003**
		Difference (95% CI)	**11.0 (3.0, 18.9)**		
CT02	20 "ON" Drug	Mean Change from Baseline	6.88	0.64	**0.001**
		Difference (95% CI)	**6.24 (2.71, 9.77)**		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

The previous Medical Reviewer, Dr. Shrimant Mishra, and the previous Cross-Discipline Team Leader, Dr. John Alexander, concurred with Dr. Gamalo that the efficacy data from these trials are consistent with the efficacy findings for TOBI®.

The Division, however, issued a Complete Response to the initial NDA submission based on two main issues. One issue was the lack of ample data to evaluate the impact of the following changes on the efficacy of the product: 1. the proposed change in compressor or nebulizer-compressor combination proposed to administer the to-be-marketed product; and 2. the change in osmolality of the to-be-marketed drug formulation compared to formulations used in clinical trials.

The Applicant provided drug-device combination bridging data in their resubmission that is being evaluated by the Devices Consultant from the Center for Devices and Radiologic Health. The impact of the osmolality change will be discussed later.

The second issue was the inaccurate recording of/loss of source input data in 4 study sites in Trial CT02, including data on patient age and height during the study duration. To resolve this issue, the Applicant conducted source data verification in all clinical sites. The Applicant submitted a modified primary endpoint analysis using recalculated predicted pulmonary function tests from retrieved data from all Trial CT02 sites. Dr. M. Amper Gamalo verified the Applicant's sensitivity analyses using verified data from the clinical database, from the spirometry printouts, and from the clinical database in the subset of patients with spirometry printouts. (Table 4)

Table 4. Sensitivity Analyses Conducted Using Retrieved and Verified Efficacy Data from Trial CT02: FEV1 % Predicted – Visit 8 (Week 20) – ITT Population – Baseline Observation Carried Forward

Source of Data	Week		CHF 1538	Placebo	P-Value
Clinical Database	20 "ON" Drug	N	161	84	
		Mean Change from Baseline	6.01	0.06	

		Difference (95% CI)	**5.95 (2.24, 9.65)**		0.0018
Spirometry Printouts	20 "ON" Drug	N	142	73	
		Mean Change from Baseline	6.36	0.33	
		Difference (95% CI)	**6.03 (2.20, 9.86)**		0.0022
Clinical Database (patients with printouts)	20 "ON" Drug	N	142	73	
		Mean Change from Baseline	5.84	-.62	
		Difference (95% CI)	**6.47 (2.38, 10.55)**		0.0021

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

The sensitivity analyses demonstrated that the impact of the height and age adjustments with source data verification from both the clinical database and the spirometry printouts were negligible. Both sensitivity analyses demonstrate that patients given CHF 1538 experience a significant improvement from baseline of their FEV1 % predicted compared to patients with placebo. While the TOBI pivotal trials have a slightly different primary endpoint (mean **relative** change from baseline in the FEV1 % predicted), the Medical Officer concludes that the primary efficacy analyses results are consistent with the efficacy findings of TOBI®.

Furthermore, the consistency between the efficacy findings between the three CHF 1538 trials and the TOBI pivotal trials using different formulations with different osmolalities indicates that the variation in concentration and osmolality between the evaluated formulation, the reference product, and the to-be-marketed product has minimal impact on the drug product's efficacy.

All in all, based on the efficacy data submitted in the original NDA submission and the resubmission, the Medical Officer concludes that CHF 1538 is efficacious in significantly improving FEV1 % predicted of CF patients with *P. aeruginosa*, in a manner consistent with the reference drug, TOBI®.

6.1 Indication

6.1.1 Methods

Important details of the three Phase 3 trials and the 2 PK studies included in the original submission are summarized in Table 5. The table describes pertinent design information and identified issues that may affect the purported demonstration of efficacy and safety for CHF 1538.

Table 5. Overview of Clinical Studies in the Original NDA Submission

Trial	Design/Location	Duration/ITT population	Dose/Drug /Device	Relevant Inclusion/Exclusion criteria	Primary Endpoint	Important secondary endpoints	Issues of relevance
CT01	Placebo Controlled, Randomized, Double Blind, Multicenter Superiority study Foreign (Italy, France, Ukraine,and Moldavia)	1 cycle- 28 days on treatment cycle followed by 28 day off treatment cycle ITT Population: CHF1538: 29 Placebo: 29 Safety: CHF1538: 29 Placebo: 30 Pediatric Population: 26 subjects received CHF1538 and were < 17years of age	300 mg of inhaled CHF 1538 bid or inhaled placebo bid CHF 1538: Osmolality (b) (4) mOsmol/kg Device: PARI LC Plus nebulizer, PARI TurboBOY compressor	Inclusion Criteria 1.Age ≥ 6 years 2. FEV1 % Predicted ≥40% and ≤80% 3. Sputum containing *Pa* susceptible to tobramycin Exclusion Criteria 1.Administration of antipseudomonal therapy by any route in the previous 4 weeks 2. Impaired renal function 3. Impaired auditory function. 4.Pt. with sputum colonized with *Burkholderia cepacia*	Change in FEV1% Predicted from baseline to visit 4 (end of On treatment cycle)	1. Change in other pulmonary function parameters 2. Change in microbiological indices 3. Change in body weight and body mass index	Exclusion criteria limited participation of individuals who may have been having a pulmonary exacerbation at start of study Patients could not receive antipseudomonal ant biotics during course of study other than study drug Most common concomitant CF medications allowed if had been using at steady dose for previous four weeks Study did not use TBM compressor or nebulizer
CT02	Placebo Controlled, Randomized, Double Blind, Multicenter Superiority study Foreign (Hungary, Poland, Russia)	3 cycles of 28 days On treatment followed by 28 days Off treatment ITT Population: CHF1538:161 Placebo: 84 Safety Population: CHF1538:161 Placebo: 85 Pediatric Population: 110 subjects received CHF1538 and were < 17years of age	300 mg of inhaled CHF1538 bid or inhaled placebo bid CHF1538: Osmolality (b) (4) mOsmol/kg Device: PARI LC Plus nebulizer, PARI TurboBOY compressor	Inclusion Criteria 1.Age ≥ 6yo 2. FEV1 % Predicted ≥ 40 and ≤80% 3. Sputum containing *Pa* Exclusion Criteria 1.Administration of aminoglycosides by any route and nebulised antibiotic therapy in the previous 4 weeks 2. Impaired renal function 3. Impaired auditory function. 4.Pt. with sputum colonized with *Burkholderia cepacia*	Change in FEV1% predicted from baseline to visit 8 (end of 3rd On treatment cycle)	1. Change in other pulmonary function parameters 2. Change in microbiological indices 3.Change in body weight and body mass index 4.Incidence of prespecified pulmonary exacerbations 5.Incidence and length of hospitalizations 6. Incidence and length of IV antipseudomonal use	Exclusion criteria allowed for participation of individuals who may have been having a pulmonary exacerbation at baseline. Patients could receive other antipseudomonal medications during the course of the study Most common concomitant CF medications allowed if had been using at steady dose for previous four weeks Patients were allowed into study regardless of whether of *Pa* resistant to tobramycin Study did not use TBM compressor or nebulizer

Trial	Design/Location	Duration/ITT population	Dose/Drug /Device	Relevant Inclusion/Exclusion criteria	Primary Endpoint	Important secondary endpoints	Issues of relevance
CT03	Active controlled, Open label, Randomized, Multicenter study Noninferiority study Foreign (Russia, Ukraine, Poland, Hungary, Germany, Czech Republic, Spain, France)	One cycle of 28 days On treatment and 28 days Off treatment ITT[1]: CHF1538: 155 Placebo: 166 Safety Population: CHF1538: 156 Placebo: 168 Pediatric Population: 99 subjects received CHF1538 and were < 17 years of age	CHF 1538: 300 mg inhaled bid TOBI: 300mg inhaled bid CHF1538 Osmolality: (b) (4) mOsmol/kg Device: PARI LC Plus nebulizer, PARI TurboBOY N compressor	1.Age ≥ 6yo 2. FEV1 % Predicted ≥ 40 and ≤80% 3. Sputum containing *Pa* susceptible to tobramycin 4. Chronic colonization of sputum with *Pa* defined as two positive cultures within the last year Exclusion Criteria: 1.Administration of antipseudomonal therapy by any route in the previous 4 weeks 2. Impaired renal function 3. Impaired auditory function. 4.Pt. with sputum colonized with *Burkholderia cepacia*	Change in FEV1% Predicted from baseline to visit 4 of study (end of On Treatment cycle)	1.Change in other pulmonary function parameters throughout the course of study 2.Changes in microbiological indices (*Pa* CFU, *Pa* tobramycin MIC) over the course of the study 3. Change in body weight and body mass index over the course of the study 4. Categorical microbiological tests for sputum Pa (eradication, superinfection, reinfection, etc.) over the course of the study	Patients with pulmonary exacerbation at baseline limited by exclusion criteria Patients could not receive antipseudomonal ant biotics during course of study other than study drug Most common concomitant CF medications allowed if had been using at steady dose for previous four weeks Study did not use TBM compressor or nebulizer
CP01	Single Center, Single Dose, Randomized, Double Blind, Two Way Crossover Foreign (Austria)	19 Subjects CHF1538 given first: 10 TOBI given first: 9	Crossover Study: Single dose of CHF1538 (300mg/4ml) or TOBI (300mg/5ml) followed by single dose of crossover medication; washout period of 3 to 7 days Pari TurboBoy /LC Plus Nebulizer		CHF 1538 concentration and PK parameters in plasma and sputum		
CT01 PK Subs tudy	Same as CT01				CHF 1538 concentration in sputum		Sputum obtained 10 minutes after 1st and last dose and on Day 565

Source: Clinical Review NDA 201820 of Dr. Shrimant Mishra, pp 19-21. 19 August 2011.

6.1.2 Demographics

The demographic information for the ITT population enrolled in the three trials are summarized in the following table:

Table 6. Comparative Demographic Data for the ITT Population in Studies CT01, CT02, and CT03

	CT01		CT02		CT03	
	CHF 1538 (%)	**Placebo (%)**	**CHF 1538 (%)**	**Placebo (%)**	**CHF 1538 (%)**	**TOBI (%)**
Gender						
Male	15 (51.7%)	17 (56.7%)	89 (55.3 %)	46 (54.8 %)	72 (45.6%)	84 (51.5%)
Female	14 (48.3%)	13 (43.3%)	72 (44.7 %)	38 (45.2 %)	86 (54.4%)	79 (48.5%)
Age (years)	11 (5 %)	14.2 (5.5)	14.8 (5.7)	14.7 (6.6)	15.9 (6.3)	15.6 (7.3)
6-12 years	19 (65.5%)	12 (40.1%)	63 (39.1%)	37 (44.0%)	47 (29.7%)	56 (34.4%)
13-17 years	7 (24.1%)	11 (36.7%)	47 (29.2%)	25 (29.8%)	54 (34.2%)	57 (35.0%)
> 17 years	3 (10.3%)	7 (23.3%)	51 (31.7%)	22 (26.2%)	57 (36.1%)	50 (30.7%)
BMI (kg/m2)	15.0 (2.7)	16.7 (4.1)			17.6 (3.0)	17.70 (3.3)
Colonization with *P. aeruginosa*						
Chronic	22 (75.9%)	25 (83.3%)	145 (90.1%)	68 (81.0 %)		
First or intermittent	7 (24.1%)	5 (16.7%)	16 (9.9 %)	16 (19.0 %)		
Time from First CF4 Diagnosis (years)	9.16 (5.90)	9.77 (6.28)	12.1 (5.6)	11.8 (5.8)		
Number of Patients with At Least One Medical Condition	17 (58.6%)	19 (63.3%)			117 (74.1%)	123 (75.5%)
Number (%) of Patients with At Least One Concomitant Medication	26 (89.7%)	28 (93.3%)	161(100.0%)	84(100.0%)		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

6.1.3 Subject Disposition

The previous Statistical and Medical Reviewers, Dr. M. Amper Gamalo and Dr. Shrimant Mishra, respectively, comprehensively discussed the disposition of subjects enrolled in Studies CT01, CT02, and CT03, salient points of which the Medical Reviewer will briefly discuss.

Study CT01

Fifty-nine patients were randomized, with 29 patients randomized to CHF 1538 and 30 patients randomized to placebo. Twenty eight patients in the CHF 1538 group completed the run-out period while 23 patients in the placebo group completed the run-out period. The final composition of the analysis populations is summarized in Table 7.

Table 7. Analysis Populations for Study CT01

Population	CHF 1538	Placebo
Safety	29	30

Intent-to-Treat	29	30*
Per Protocol	28	28

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Study CT02

A total of 247 patients out of 312 screened patients were randomized in 21 centers (8 centers in Hungary, 9 centers in Poland, and 4 centers in Russia. One hundred sixty one (161) patients were randomized to CHF 1538 and 86 patients were randomized to placebo. Out of these randomized patients, 154 patients completed treatment with CHF 1538 and 78 patients completed treatment with placebo. Of the patients initially randomized, a total of 30 patients had at least one major protocol deviation during the study (17 [10.6%] in the CHF 1538 group and 13 (15.1%) in the placebo group. As can be seen from Table 8, the most frequent protocol deviation is the inappropriate timing or use of permitted medication, followed by the administration of non-allowed medication, and by poor compliance.

Table 8. Major Deviations from Protocol for Study CT02

Major Deviations From Protocol	**CHF 1538 N=161**	**Placebo N=86**	**Total N=247**
Patients with at least one major deviation	**17 (10.6%)**	**13 (15.1%)**	**30 (12.1%)**
Inappropriate timing or use of permitted medication	**14 (8.7%)**	**8 (9.3%)**	**22 (8.9%)**
Inhaled bronchodilators started after V1 > seven days	7 (4.3%)	2 (2.3%)	9 (3.6%)
Mucolytics started after V1 > 14 days	6 (3.7%)	3 (3.5%)	9 (3.6%)
Oral steroids > ten days	2 (1.2%)	2 (2.3%)	4 (1.6%)
Intravenous steroids > three days	1 (0.6%)	2 (2.3%)	3 (1.2%)
Non-steroidal anti-inflammatory > two weeks	2 (1.2%)	1 (1.2%)	3 (1.2%)
Inhaled steroids > 14 days (4)	0 (0.0%)	1 (1.2%)	1 (0.4%)
Mucolytics with unstable dosage	1 (0.6%)	0 (0.0%)	1 (0.4%)
Non-permitted medication	**3 (1.9%)**	**4 (4.7%)**	**7 (2.8%)**
Tobramycin after Visit 6 (after 12 weeks)	1 (0.6%)	2 (2.3%)	3 (1.2%)
Amikacin > 14 days	1 (0.6%)	1 (1.2%)	2 (0.8%)
Nebulized antibiotic active on *P. aeruginosa*	1 (0.6%)	1 (1.2%)	2 (0.8%)
Poor compliance (<70%)	**0 (0.0%)**	**2 (2.3%)**	**2 (0.8%)**

The analysis populations for Study CT02 are summarized in Table 9.

Table 9. Analysis Populations

Population	**CHF 1538**	**Placebo**
Total	312	
Randomized	247	
Safety	161	85
Intent-to-Treat	161	84
Per Protocol	144	71

Study CT03

Four hundred six patients were screened, of whom 324 patients were randomized. Of the 159 randomized to the CHF 1538 group, four patients withdrew due to an adverse event (AE), a protocol violation and consent withdrawal. Of the 165 randomized to the TOBI group, six withdrew due to an AE or a protocol violation. Table 10 summarizes patient disposition and analysis populations for Study CT03.

Table 10. Patient Disposition for Study CT03

	CHF 1538	TOBI	TOTAL (N=324)
Randomized Population	159	165	324 (100%)
ITT Population	158	163	321 (99.1%)
Safety Population	156	168	324 (100%)
Reason for exclusion from As Treated Population: No baseline or post-baseline FEV1	1	2	3 (0.9%)
As Treated Population	155	166	321 (99.1%)

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

6.1.4 Analysis of Primary Endpoint(s)

The Medical Reviewer will present the primary efficacy results and analyses conducted by Dr. M. Amper Gamalo and Dr. Shrimant Mishra using efficacy data from the original NDA submission. After discussing the results of the orginal submission, the Medical Reviewer would present the amended efficacy results in the current NDA resubmission in response to the Clinical Comment 2 in the Complete Response letter.

6.1.4.1. Primary Efficacy Results from Study CT01

Dr. Gamalo's analyses of the primary efficacy data utilized several methods in replacing missing data. The primary analysis constituted of replacing missing pulmonary function data by using the Last Observation Carried Forward (LOCF) method that was only applied to data measured at Visit 3 and carried forward to Visit 4. Table 11 shows the results of the analysis using this method.

Table 11. FEV1 % Predicted Normal Mean Baseline with the LOCF Method: ITT Population

Visit	Week		CHF 1538 (%)	Placebo (%)	P-Value
2	Baseline	N	29	29	
		Mean	57.7	59.8	0.580
3	2 "ON" Drug	N	29	27	
		Mean Change from Baseline	13.5	0.1	0.003
		Difference (95% CI)	13.2 (4.9, 21.5)		
4	4 "ON" Drug (1° endpoint)	N imputed	0	3	
		Mean change from Baseline	16.0	2.7	0.003
		Difference (95% CI)	13.3 (4.7, 21.8)		
5	8 "OFF" Drug	N	27	22	
		Mean Change from Baseline	5.8	7.7	0.709
		Difference	-1.8 (-11.6, 7.9)		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Results from Study CT01 show that patients treated with CHF 1538 experienced an increase in FEV1 % predicted normal by 13.5% at Week 2 and by 16% at Week 4 above baseline values, compared to patients treated with placebo who experienced minimal changes in FEV1 % predicted normal. Thus, patients treated with CHF 1538 experienced a significant increase in FEV1 % predicted normal from baseline to either Week 2 or Week 4, compared to patients treated with placebo.

However, data obtained 4 weeks after CHF 1538 was discontinued showed that the mean FEV1 % predicted normal decreased to near baseline values, so that differences in the FEV1 % predicted normal between the CHF 1538 and the placebo groups were not significant.

Dr. Gamalo performed two additional sensitivity analyses. One analysis used Multiple Imputation procedure in SAS by generating five observations using change from baseline in Visit 3 and 4 to impute missing data in these visits (Table 12). Another analysis using the worst change from baseline observed from Visits 3, 4, and 5 to replace missing values (imputation by worst observation). Both sensitivity analyses demonstrated that patients treated with CHF 1538 experienced increases in the mean FEV1 % predicted normal from baseline that were significantly higher than patients treated with placebo. Analysis using imputation by worst observation attenuates the differences between the mean FEV1 % predicted normal from baseline of the CHF-treated group compared to the placebo-treated group because most of the missing data are in the placebo-treated group.

Table 12. FEV1 % Predicted Normal Mean Baseline Using Multiple Imputation: ITT Population

Visit	Week		CHF 1538 (%)	Placebo (%)	P-Value
2	Baseline	N	29	29	
		Mean	57.7	59.8	0.580
3	2 "ON" Drug	N imputed	0	2	
		Mean Change from Baseline	13.3	0.5	0.002
		Difference (95% CI)	12.8 (4.3, 21.2)		
4	4 "ON" Drug (1° endpoint)	N imputed	0	3	
		Mean change from Baseline	15.9	4.9	0.003
		Difference (95% CI)	11.0 (3.0, 18.9)		
5	8 "OFF" Drug	N imputed	2	7	
		Mean Change from Baseline	7.1	8.3	0.700
		Difference	-1.2 (-10.2, 7.7)		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Medical Officer Comment:
The multiple analyses of Study CT01 efficacy results using different methods to impute missing data consistently demonstrate that CHF 1538, when administered by nebulization for 4 weeks, can significantly improve the FEV1 % predicted normal at Week 4 from baseline values, compared to placebo.

6.1.4.2. Primary Efficacy Results from Study CT02

Dr. Gamalo performed the primary analysis for the efficacy results of Study CT02 using the LOCF method. The analysis can be seen in Table 13.

Table 13. FEV1 % Predicted Normal Mean Baseline and Mean Change from Baseline with LOCF: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	161	84	
		Mean	60.7	63.6	0.145
3	2 "ON" Drug	N			
		Mean Change from Baseline	8.02	1.91	< 0.001
		Difference (95% CI)	6.11 (3.08, 9.15)		
4	4 "ON" Drug	N imputed			
		Mean change from Baseline	7.82	0.51	< 0.001
		Difference (95% CI)	7.32 (4 24, 10.40)		
5	8 "OFF" Drug	N	159	83	
		Mean Change from Baseline	4.69	1.90	0.077
		Difference	2.79 (-0.30, 5.88)		
6	12 "ON" Drug	N			
		Mean Change from Baseline1,2	7.33	2.27	0.003
		Difference (95% CI)	5.06 (1.73, 8.39)		
7	16 "OFF" Drug	N	160	83	
		Mean Change from Baseline1,2	6.16	0.68	0.002
		Difference (95% CI)	5.48 (2.03, 8.92)		
8	20 "ON" Drug (1° endpoint)	N	161	84	
		Mean Change from Baseline1,2	6.97	0.59	< 0.001
		Difference (95% CI)	6.38 (2.92, 9.84)		
9	24 "OFF" Drug	N	160	83	
		Mean Change from Baseline1,2	5.92	-1.19	< 0.001
		Difference (95% CI)	7.11 (3.59, 10.62)		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

The analysis demonstrates that in the ITT population, the changes in FEV1 % of predicted normal from baseline were significantly greater in the CHF 1538 group than in the Placebo group at all visits except Visit 5, end of the first "OFF" cycle. The mean change from baseline to the primary efficacy timepoint (Visit 8) in FEV1 % of predicted normal was significantly higher in the CHF 1538 group (6.97%) than in the placebo group (0.59%) ($p < 0.001$). CHF 1538 efficacy on FEV1 % of predicted normal was significantly superior compared to that of the placebo in all visits, except at Visit 5 (end of the first "OFF" cycle).

As was done in the efficacy results for Study CT01, efficacy data from Study CT02 were analyzed using two other methods used in replacing missing data. Both 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. Table 14 shows the primary efficacy analysis Dr. Gamalo performed using the Multiple Imputation method.

Table 14. FEV1 % Predicted Normal Mean Baseline and Mean Change From Baseline with Multiple Imputation: ITT Population

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

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Medical Officer Comment:
Analyses of the efficacy data from Study CT02 demonstrate that patients treated with CHF 1538 experience a significantly higher increase in the mean FEV1 % of predicted normal from baseline to Visit 8, when compared to placebo. The analysis shows that CHF 1538 is efficacious in terms of significantly increasing FEV1 % of predicted normal from baseline to Week 20 ON cycle.

With the identification of two problematic sites by the Office of Scientific Investigations (Site 26, Dr. Maria Trawinska Barnicka, n=29 and Site 32, Dr. Nikolai Kapranov, n=24), Dr. Gamalo conducted a sensitivity analysis of the Study CT02 results excluding these sites. The results are shown in Table 15.

Table 15. FEV1 % Predicted Normal Mean Baseline and Mean Change from Baseline with LOCF: ITT Population (excluding Sites 26 and 32)

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	126	67	
		Mean	60.27	62.75	0.281
3	2 "ON" Drug	N imputed	0	0	
		Mean Change from Baseline	7.88	2.02	0.002
		Difference (95% CI)	5.87 (2.26, 9.48)		
4	4 "ON" Drug	N imputed	0	0	
		Mean change from Baseline	7.65	0.76	<0.001

		Difference (95% CI)	6.89 (3 24, 10.54)		
5	8 "OFF" Drug	N imputed	2	1	
		Mean Change from Baseline	4.84	1.47	0.069
		Difference	3 37 (-0.26, 7.01)		
6	12 "ON" Drug	N imputed	3	3	
		Mean Change from Baseline1,2	6.81	2.91	0.045
		Difference (95% CI)	3.90 (0.09, 7.72)		
7	16 "OFF" Drug	N imputed	3	4	
		Mean Change from Baseline1,2	5.96	0.94	0.017
		Difference (95% CI)	5.01 (0.87, 9.16)		
8	20 "ON" Drug (1° endpoint)	N imputed	3	4	
		Mean Change from Baseline1,2	6.71	1.27	0.009
		Difference (95% CI)	5.45 (1.34, 9.56)		
9	24 "OFF" Drug	N imputed	6	5	
		Mean Change from Baseline1,2	6.74	1.22	0.009
		Difference (95% CI)	5.52 (1.37, 9.67)		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Using multiple imputations for missing observations, FEV_1 % predicted normal had increased by 7.88% at Week 2 and 7.65 % at Week 4, 6.81% at Week 12 and 6.71% at Week 20 above baseline values for CHF 1538-treated patients (see Table 3.15). In contrast, changes in FEV_1 % predicted normal were 2.02% in Week 2, 0.76% in Week 4, 2.91% in Week 12, and 1.27% in Week 20 in the Placebo group. Therefore, comparison of mean changes from baseline between the CHF 1538 and placebo groups were still significant in all the "ON" periods, even with the exclusion of these two sites.

6.1.4.3. Primary Efficacy Results from Study CT03

Because the noninferiority (NI) margin proposed in the analysis (-4.5%) of the efficacy data from Study CT03 was not adequately justified by the Sponsor, data from this reference drug-controlled study were considered supportive.

From the Applicant's analysis which adjusts for baseline and country of origin, the mean change from baseline in FEV_1 % predicted normal was 6.99% in the CHF 1538 group and 7.51% in the TOBI group (see Table 16). Using the ANCOVA model, the least squares (LS) means of the change from baseline in FEV_1 % predicted normal were 4.66% in the CHF 1538 group and 5.16% in the TOBI group with a difference of -0.50 (95% CI: -2.58 to 1.59). Based on the proposed prespecified NI margin, CHF 1538 may not be inferior to TOBI because the lower limit of the 95% CI (-2.58%) is within the pre-specified non inferiority margin of -4.5%.

Table 16. FEV1 % Predicted Normal1 Mean Baseline and Mean Change From Baseline with LOCF Used for "ON" Drug Visits While Accounting for Baseline and Country: ITT Population

Visit	Week		TOBI (%)	CHF 1538 (%)	P-Value
2	Baseline	N	163	158	
		Mean	61.68	61.32	0.792
3	2	N imputed	0	0	

	"ON" Drug	Mean Change from Baseline	5.81	5.53	0.796
		Difference (95% CI)	-0.28 (-2.42, 1.86)		
4	4	N imputed	2	3	
	"ON" Drug	Mean change from Baseline	5.16	4.66	0.640
	(1° endpoint)	Difference (95% CI)	-0.50 (-2.58, 1.59)		
5	8	N	159	155	
	"OFF" Drug	Mean Change from Baseline	1.99	2.05	0.967
		Difference	0.05 (-2.49, 2.60)		

Note: The shaded row indicates the primary endpoint
Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Dr. Gamalo performed an additional statistical analysis based on the original prespecified model that also adjusts for baseline FEV% and country but using the Multiple Imputation method. Results of this prespecified analysis, shown in Table 17, demonstrate that the impact of the country of origin is significant. The least squares (LS) means of the change from baseline in FEV1 % predicted normal were 5.27% in the CHF 1538 group and 4.75% in the TOBI group with a difference of -0.51 (95% CI: -2.60 to 1.57).

Table 17. FEV1 % Predicted Normal1 Mean Baseline and Mean Change From Baseline with Multiple Imputation Used for "ON" Drug Visits while accounting for baseline and country: ITT Population

Visit	Week		TOBI	CHF 1538	P-Value
2	Baseline	N	163	158	
		Mean	61.68	61.32	0.792
3	2	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	5.81	5.53	0.796
		Difference (95% CI)	-0.28 (-2.42, 1.86)		
4	4	N imputed	2	3	
	"ON" Drug	Mean change from Baseline	5.27	4.75	0.627
	(1° endpoint)	Difference (95% CI)	-0.51 (-2.60, 1.57)		
5	8	N imputed	4	3	
	"OFF" Drug	Mean Change from Baseline	1.92	2.09	0.890
		Difference	0.17 (-2.36, 2.71)		

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

From the analyses of the primary endpoints of the three trials, the efficacy data from Studies CT01 and CT02 in the original submission appears to demonstrate that CHF 1538 is superior to placebo in significantly increasing the FEV1 % predicted normal from baseline to the timepoint assessed in the primary endpoint.

6.1.5 Analysis of Secondary Endpoints(s)

Please refer to Dr. Shrimant Mishra and Dr. M. Amper Gamalo's previous Clinical and Statistical Reviews, respectively.

6.1.6 Other Endpoints

Please refer to Dr. Shrimant Mishra and Dr. M. Amper Gamalo's previous Clinical and Statistical Reviews, respectively.

6.1.7 Subpopulations

Please refer to Dr. Shrimant Mishra and Dr. M. Amper Gamalo's previous Clinical and Statistical Reviews, respectively.

Medical Officer Comment:
Dr. Mishra and Dr. Gamalo's prior analyses of subpopulations showed no significant treatment interactions noted, in terms of gender, age, baseline FEV1 % predicted, baseline rhDNAse use, baseline MIC, and countries of treatment sites. Dr. Mishra observed a nonsignificant trend of decreasing efficacy of CHF 1538 compared to placebo when the country of the site is considered, with increasing age, and baseline rhDNase use. Reanalysis of the retrieved source input data would most unlikely significantly impact prior subpopulation efficacy analyses results.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please refer to Dr. Shrimant Mishra and Dr. M. Amper Gamalo's previous Clinical and Statistical Reviews, respectively.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please refer to Dr. Shrimant Mishra and Dr. M. Amper Gamalo's previous Clinical and Statistical Reviews, respectively.

6.1.10 Additional Efficacy Issues/Analyses: Secondary Endpoints

6.1.10.1. Pulmonary Exacerbation Analysis

Table 18. Number of Patients with Pulmonary Exacerbations in the ITT Population

Visit	Week	CHF 1538 n/N (%)	Placebo n/N (%)	P-Value[2]
2	Baseline	11/161 (6.8%)	5/84 (6.0%)	1.0
3	2 "ON" Drug	13/161 (8.1%)	13/84 (15.5%)	0.064
4	4 "ON" Drug	7/161 (4.3%)	12/84 (14.3%)	0.006
5	8 "OFF" Drug	34/160 (21.3%)	16/83 (19.3%)	0.739
6	12 "ON" Drug	18/159 (11.3%)	13/82 (15.9%)	0.315
7	16 "OFF" Drug	16/158 (10.1%)	13/81 (16.0%)	0.186
8	20 "ON" Drug	13/157 (8.3%)	11/79 (13.9%)	0.172
9	24 "OFF" Drug	17/154 (11.0%)	10/78 (12.8%)	0.660

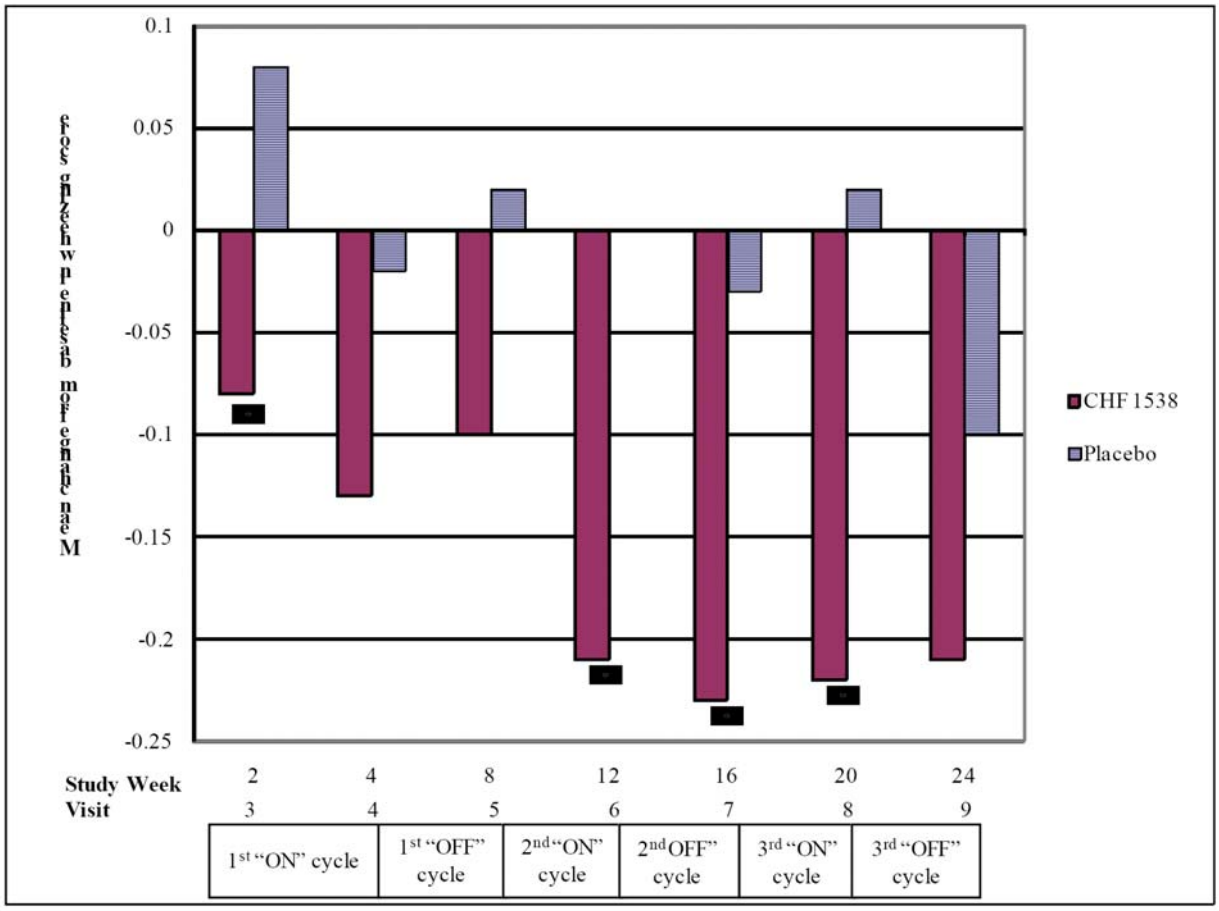
[1] At least three of eleven pre-defined findings (see 9.5.4.3)
[2] Fisher's Exact Test for baseline comparison and Cochran-Mantel-Haenszel procedure stratified by baseline result for all others.
Source: Table 55, Table 225, Table 226, Table 227, Table 228, Table 229, Table 230, Table 231, Table 232 and Table 233.

Source: NDA 201820, SD No. 0. 5.3.5.1.3 CT02 Study Report Body. Table 19, p 99

Medical Officer Comment:
This secondary endpoint evaluated for any significant differences on the number of patients with pulmonary exacerbations at specific Visits during the study. Dr. Mishra has enumerated the limitations of the efficacy data, including the non-inclusion of cases treated with antibacterials but not diagnosed as pulmonary exacerbation and the fact that these rates may reflect more the prevalence, rather than the incidence of pulmonary exacerbations, at each timepoint. In any case, at the end of the study, the differences between the two groups are not significant.

6.1.10.2. Clinical Symptom Analysis

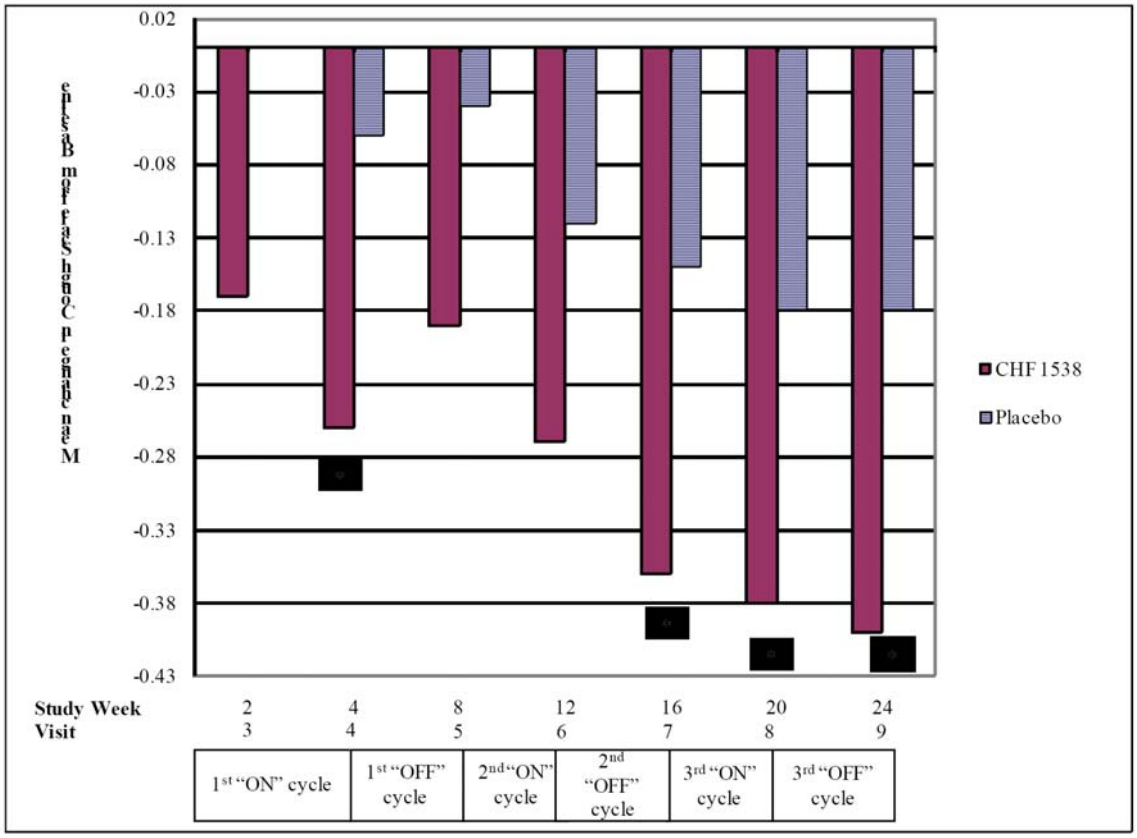
Figure 1. Mean Change in Wheezing Score from Baseline to Each Visit: ITT Population



* There are statically significant differences ($p < 0.05$) between the CHF 1538 and Placebo groups.
Note: The mean change from baseline at Visit 6 for Placebo group is 0.
Source: Table 52

Source: NDA 201820, SD No. 0. 5.3.5.1.3 CT02 Study Report Body. Figure 15, p 100

Figure 2. Mean Change in Cough Score from Baseline to Each VisitL ITT Population



* There are statically significant differences ($p < 0.05$) between the CHF 1538 and Placebo groups.
Note: The mean change from baseline at Visit 3 for the Placebo group is 0.
Source: Table 54

Source: NDA 201820, SD No. 0. 5.3.5.1.3 CT02 Study Report Body. Figure 15, p 101.

Medical Officer Comment:
The descriptive data illustrated in these figures demonstrate the relative decrease in the cough and wheezing scores of patients in the two groups compared to the placebo group. However, the Applicant has not presented information on whether the scoring systems used to evaluate these endpoints have been standardized and have been validated for their reliability. Thus, the results presented here should be mainly descriptive and exploratory, rather than definitive.

6.1.10.3. Disease-Related, Unplanned Hospitalization

Table 19. Patients with Disease-Related, Unplanned Hospitalization and the Number of Days Hospitalized: Safety Population

	CHF 1538 (N=161)	Placebo (N=85)
n (%) with one or more hospitalizations	16 (9.9%)	21 (24.7%)
Hazard Ratio (95% CI)	0.359 (0.187 – 0.688)	
P-Value	0.001	
Total number of days[1] hospitalized		
Mean	1.6	4.4
Range	0 – 28	0 – 42

[1] Patients who were missing a discharge date had the median number of days for hospitalized patients (15 days) imputed.
Source: Table 180, Table 182, Table 184 , Table 185, Table 186 and Table 198.

Source: NDA 201820, SD No. 0. 5.3.5.1.3 CT02 Study Report Body. Figure 15, p 102.

Medical Officer Comment:
The significant difference between the CHF 1538 group and the placebo group in the proportion of patients with disease related unplanned hospitalizations and the trend of shorter hospital days should be treated as descriptive and supportive trends in favor of CHF 1538 as the groups were not controlled for anti-PA use and pulmonary exacerbation. The Medical Officer believes that these statistically significant differences should be interpreted cautiously.

6.1.10.4. Use of Antibacterials

6.1.10.4.a. Use of IM/IV Tobramycin

Table 20. IM or IV Tobramycin Use and the Number of Days Using IM or IV Tobramycin

	CHF 1538 (N=161)	Placebo (N=85)
n (%) with at least one dose	10 (6.2%)	14 (16.5%)
Hazard Ratio (95% CI)	0.355 (0.158 – 0.799)	
P-Value	0.009	
Total number of days[1] using tobramycin		
Mean	0.9	2.5
Range	0 – 36	0 – 31

[1] Patients who were missing an end date had the median value of 14 days imputed.
Source: Table 298, Table 300, Table 302, Table 304 and Table 305

Source: NDA 201820, SD No. 0. 5.3.5.1.3 CT02 Study Report Body. Figure 15, p 102.

6.1.10.4.b. Use of IM/IV Anti-Pseudomonal Antibacterial (Anti-PA)

Table 21. Use of IM or IV Anti-PA Use and Number of Days Using Anti-PA

	CHF 1538 (N=161)	Placebo (N=85)
n (%) with at least one dose	37 (23.0%)	30 (35.3%)
Hazard Ratio (95% CI)	0.576 (0.356 – 0.933)	
P-Value	0.023	
Total number of days[1] using Anti-PA		
Mean	4.9	7.5
Range	0 – 46	0 – 85

[1] Patients who were missing an end date had the median value of 14 days imputed.
Source: Table 199, Table 201, Table 203, Table 204 and Table 217.

Source: NDA 201820, SD No. 0. 5.3.5.1.3 CT02 Study Report Body. Figure 15, p 102.

Medical Officer Comment:
The positive trend in favor of CHF 1538 on the use of IM or IV tobramycin and other anti-pseudomonal antibacterial, while significant, should be treated, as an encouraging trend since other factors were not controlled for in the analysis.

Overall Medical Officer Comment on Secondary Endpoints:
The Medical Officer believes that the secondary endpoints evaluated in the two trials may be useful in providing the clinician with clinically-relevant endpoints. However, limitations in evaluating and studying these endpoints exist.

- *Definitions of disease conditions may vary by clinicians.*
- *Estimation of the frequencies of the secondary endpoints may not be optimal (i.e. incidence vs. prevalence).*

- *Secondary endpoints were evaluated independent of the interaction of other secondary endpoints.*
- *Lastly, analyses of the secondary endpoints were performed by simultaneous multiple comparisons. However, the p-values of each secondary endpoint were not adjusted for the inflation of type-1 error resulting from the simultaneous multiple comparisons.*

Multiple, univariate comparisons between the CHF 1538 group and the placebo group were conducted and yielded statistically significant differences favoring the CHF 1538 group, these differences should be interpreted cautiously.

The Medical Officer realizes that these endpoints are clinically relevant and would assist clinicians in putting the primary endpoint results in perspective. However, the comparisons were not adjusted for simultaneous multiple comparisons. Non-adjustment of the p values increases the Type 1 error; thereby increasing the probability that these significant differences were actually false positive results. Therefore, while these secondary endpoints provide physicians clinically relevant information, the secondary endpoints evaluated in Trial CT01 and CT02 should be considered exploratory and descriptive. Efficacy data and analyses from these endpoints should be interpreted cautiously.

6.1.10.5. Response to the FDA Clinical Request 1

The Complete Response (CR) Letter cited the following deficiency:

Quote from CRL: "*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. We recommend that you meet with the review division to discuss your plans for providing a complete response.*"

A Type A Meeting was held between the Applicant and the Division during which options to address this comment were discussed. Table 22 summarizes the devices used in the three studies in the submission.

Table 22. Devices Utilized in Clinical Studies and Proposed for Delivery of the To-Be Marketed Product

Device	Clinical Study CT01	Clinical Studies CT02 CT03	To-Be-Marketed
Nebulizers	PARI LC Plus	PARI LC Plus	PARI LC Plus
Compressors	PARI TurboBOY[1]	PARI TurboBOY N	PARI Vios

[1] The TurboBOY compressor is no longer available from the manufacturer, PARI GmbH, but is identical to the TurboBOY S compressor.

Source: Type A Meeting Package. Serial No. 33 (SD 35). Submitted 1/9/2012. p. 40

The Applicant contended that the pivotal trials account for variability between patients and for device usability. Furthermore, the proposed compressor to be used with the to-be-marketed product, PARI Vios™ is a general purpose compressor cleared by the Agency, with the consistency of the flow rate and operating pressure acknowledged and confirmed by the Agency through the 510(k) process. The Applicant and the Division agreed that the Applicant's proposal to provide data on the Total Drug Substance Delivered from one CF breathing pattern and to provide data from the compressors used in the studies and the to-be marketed product in the NDA resubmission is appropriate.

To respond to the Clinical Request 1, the Applicant provided comprehensive drug device combination bridging data.

Medical Officer Comment:
The Medical Officer defers to the Center for Devices and Radiologic Health Reviewer to determine the adequacy of the submitted bridging data in evaluating the acceptability of changing the compressor and/or the nebulizer-compressor combination in drug delivery.

6.1.10.6. Response to the FDA Clinical Request 2: Study CT02 Cited in the Complete Response Letter

The CR Letter further cited the following deficiency in the efficacy data from the original submission that has to be addressed:

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.

In the original submission, data in the clinical database (for absolute and % predicted values for FEV_1, FVC, and $FEF_{24-75\%}$) came from spirometer printouts that were transcribed to case report froms (CRFs). Inaccurate recording of/loss of source input data was identified from Site 26 during FDA inspections. Since input data for height and age are functionally linked to the predicted values, the impact of inaccurate recording and/or loss of source input data on the predicted lung function parameters in sites using the same version of spirometer software and subsequently in all clinical sites has to be clarified. Initially, aside from Site 26, the Applicant identified three other similarly-affected sites (Site 13, 23, and 29), from which FEV1 predicted normal and FEV1 % predicted normal values were corrected, reanalyzed and submitted on 28 June 2011 (Serial No. 0026). The Applicant then extended the source data verification to all clinical sites that participated in the study.

The verification resulted in the determination of corrected FEV1 predicted normal and FEV1 % predicted normal values of patients in all clinical sites. After the Complete Response Letter was received, the Applicant submitted the recalculated FEV1 predicted normal and FEV1 % predicted normal for all patients at all sites for which input data was available on 21 November 2011 (SN 0032) as part of a Type A meeting package. The submission included several re-analyses and sensitivity analyses using corrected data from patients from all clinical sites with available source data. The Division indicated during the Type A Meeting held on 16 December 2011 that the method of recalculation of the newly acquired data appeared appropriate but that full datasets and a detailed methodology of the recalculations have to be provided to the Division, including a summary of the data errors that occurred at each site.

6.1.10.6.1. Source Data Discrepancies

Source data (gender, birth date or age, height, and FEV_1, FVC, $FEF_{25-75\%}$) were available for 83.3% to 84.9% of patients compared to the original number of patients with data available in the database. Applying Last Observation Carried Forward (LOCF) increased this proportion to 87.3% to 88.7%. The Applicant compared the values from the retrieved input source spirometry data (i.e. height, gender, date of birth or age, and FEV_1, FVC, $FEF_{25-75\%}$) recorded in the clinical database to the spirometry printouts. The Applicant noted that nearly all identified discrepancies were from height measurements.

The Applicant explains this by the fact that height was measured twice during study visits. These measurements apparently did not match in all instances. In all, the Applicant states that height discrepancies between the spirometry source input and values in the clinical database were detected on 14.7% of total measurements, with most discrepancies being small (≤ 1 cm).

Table 23 summarizes the discrepancies between the values in the database and the spirometry printouts.

Medical Officer Comment:
The discrepancies observed were predominantly due to inaccuracies in height measurements, of which majority of these (10% of total number of measurements) are less than 1 cm. From these, the Medical Reviewer estimates that the impact of these inaccuracies on the overall results/conclusions of the study may be insignificant.

Table 23. Summary of Discrepancies between Database and Source Input Data for Study CT02

Variable	Total No. of Measurements in Database	Available No. of Measurements from Printouts	Frequency of Discrepancies	Percentage of Discrepancies[1]	Height Discrepancy Details
AGE	245	239	1	0.4	
SEX	245	216	0	0.0	
HEIGHT	490	441	49	10.0	Discrepancy less or equal to 1 cm
			16	3.3	Discrepancy equal to 2 cm
			7	1.4	Discrepancy more than 2 cm
FEV_1	490	488	7	1.4	
FVC	490	488	6	1.2	
$FEF_{25-75\%}$	488	484	9	1.8	

[1]Percentages of discrepancies are based on total number of measurements by variable at baseline and endpoint visit

Source: Resubmission Class 2. Serial Number 0035 (SD 38). Submitted 4/13/2012.Efficacy Information Amendment. Response to Complete Response Letter. p. 8.

6.1.10.6.2. Methodology and Recalculations of Pulmonary Function Results

The Applicant performed several sensitivity analyses using corrected pulmonary function results based on retrieved source input data comparing the change in previously specified absolute values of pulmonary function parameters (FEV_1, FVC, $FEF_{25-75\%}$) from baseline (Visit 2) to the endpoint visit (Visit 8 – after completion of the 3rd "ON" cycle). The formulae to calculate the predicted normal values for these pulmonary function parameters can be found in Appendix D.

The Applicant conducted sensitivity analyses of pulmonary function parameters in the proportion of the ITT population with available spirometry input data. The number and proportion of patients in the sensitivity analyses are summarized in Table 24.

Table 24. Proportion of Patients Included in the Sensitivity Analyses based on the Original ITT Population

Change from Baseline to Visit 8 End of 3rd On Cycle	Treatment	Patients included in the SN 0000 Submission	Patients included in the Sensitivity Analyses
		n	n (%)[1]
FEV_1 % predicted (Primary endpoint)	CHF 1538	161	142 (88.2%)
	Placebo	84	72 (85.7%)
	Total	245	214 (87.3%)
FVC % predicted	CHF 1538	161	142 (88.2%)
	Placebo	84	72 (85.7%)
	Total	245	214 (87.3%)
$FEF_{25-75\%}$ % predicted	CHF 1538	158	139 (88.0%)
	Placebo	80	72 (90.0%)
	Total	238	211 (88.7%)

[1] Percent of patients is based on the number of patients included in the original analysis (SN 0000, Section 11.1 of the CT02 Study Report Body)

Source: Resubmission Class 2. Serial Number 0035 (SD 38). Submitted 4/13/2012.Efficacy Information Amendment. Response to Complete Response Letter. p. 12.

6.1.10.6.3. Sensitivity Analyses

To respond to the FDA Clinical Request 2, the Applicant conducted several sensitivity analyses using pulmonary function parameter values from the original submission and from retrieved source outcome data.

From the original submission, the Applicant presented the following analyses:

- Original Analysis from the Clinical Study Report (CSR) – This analysis was submitted in the original NDA submission and is presented for comparison. The pulmonary function test predicted normal values in this analysis were calculated by each site's spirometer using formulae programmed into each spirometer.
- Sensitivity Analysis A – This analysis uses pulmonary function test predicted normal values and % predicted values recalculated data from the clinical database submitted in the original NDA submission using the same formulae across all clinical sites.
- Sensitivity Analysis B – This analysis uses recalculated predicted normal values and % predicted values from the retrieved source input data from spirometer printouts in 87 to 89% of the total patient database. The same formulae to determine the % predicted values were applied across all clinical sites.

- Sensitivity Analysis C – This analysis uses predicted normal values and % predicted values recalculated from the input data from the clinical database in 87-89% of the total patient database, using the same formulae applied across all clinical sites.

The following table summarizes the results from these sensitivity analyses of the primary endpoint (change in FEV_1 % Predicted on Visit 8 from Visit 2).

Visit	Week		CHF 1538 (N=161)	Placebo (N=84)	p-value
Original results from CSR – Table 12					
2	0 Baseline	n	161	84	
		Mean	60.67	63.60	
8	20 "ON" Drug (1° endpoint)	n	161	84	
		Mean Change from Baseline[1]	6.97	0.59	
		Difference (95% CI[2])	**6.38 (2.92, 9.84)**		**0.0003**
Sensitivity A: ***Re-calculated % predicted values using data from clinical database***[3,4]					
2	0 Baseline	n	161	84	
		Mean	60.79	64.36	
8	20 "ON" Drug (1° endpoint)	n	161	84	
		Mean Change from Baseline[1]	6.10	-0.11	
		Difference (95% CI[2])	**6.21 (2.40, 10.02)**		**0.0015**
Sensitivity B: ***Re-calculated % predicted values using data from available spirometry printouts***[4]					
2	0 Baseline	n	142	73	
		Mean	60.41	65.20	
8	20 "ON" Drug (1° endpoint)	n	142	72	
		Mean Change from Baseline[1]	6.55	0.21	
		Difference (95% CI[2])	**6.34 (2.37, 10.31)**		**0.0019**
Sensitivity C: ***Re-calculated % predicted values using data from clinical database,*** [3,4] ***in the same subset of patients used in the analysis B***					
2	0 Baseline	n	142	73	
		Mean	60.33	65.58	
8	20 "ON" Drug (1° endpoint)	n	142	72	
		Mean Change from Baseline[1]	5.93	-0.64	
		Difference (95% CI[2])	**6.56 (2.35, 10.78)**		**0.0024**

[1] LOCF data; adjusted for baseline value
[2] Confidence Interval
[3] For Patient 23-009, the spirometry height has been used.
[4] According to Quanjer's formula [3] and MES spirometer user manual [1, 2].

Source: Resubmission Class 2. Serial Number 0035 (SD 38). Submitted 4/13/2012.Efficacy Information Amendment. Response to Complete Response Letter. p. 14.

The sensitivity analyses B and C above demonstrate that using the retrieved available source input data from 87 to 89% of the total patient ITT population, the change in FEV_1 % predicted normal from baseline to Visit 8 (Week 20) in the CHF 1538 group is

significantly greater than in the placebo group (Sensitivity B: 6.34% difference [2.37 to 10.31 CI with p=0.0019] and Sensitivity C: 6.56 % [2.35 to 10.78 CI with p=.0024). This demonstrates the efficacy of CHF 1538 in significantly improving the % of observed FEV_1 compared to predicted FEV_1 from baseline to the end of the third "ON" cycle of treatment, when compared to placebo.

Medical Officer Comment:
The results of the sensitivity analyses B and C are consistent with previous results of the analysis conducted by the Applicant using data submitted in the original submission. The Medical Officer therefore concludes that the impact of the exclusion of patients with unretrievable source input data on the evidence of efficacy of CHF 1538 using the primary endpoint is insignificant.

The Applicant also conducted sensitivity analyses on secondary lung function parameters (FVC and FEF $_{25-75\%}$) using the same analyses methods. The analyses can be found in the resubmission.[3] The results of the analyses on the effect of CHF 1538 compared to placebo demonstrate that patients treated with CHF 1538 experienced a statistically significant increase/improvement of the % of observed values over predicted normal from baseline to the end of the treatment duration (Visit 8 or Week 20). This provides corroborative supportive evidence that CHF 1538 is efficacious.

The Statistical Reviewer, Dr. M. Amper Gamalo, conducted sensitivity analyses similar to the Applicant's sensitivity analyses where patients from the ITT population with verifiable source input data were included in the analysis population. Based on the revised datasets provided by the Applicant, the analyses verified the % FEV1 predicted normal changes, confidence intervals, and p-values obtained by the Applicant. The results of Dr.Gamalo's re-analyses are summarized in Table 25 *and* Table 26*. The Applicant used the Last-Observation-Carried Forward (LOCF) method in populating missing values for pulmonary function parameters in the resubmitted datasets. Dr. Gamalo conducted the analysis by using both the LOCF and Baseline Observation Carried Forward (BOCF) methods to populate missing values. Dr. Gamalo did not perform the Multiple Imputation method as the Applicant only provided revised source input data and revised pulmonary function parameter data calculated using the same formulae for predicted normal and % predicted normal from Visits 2 and 8 (baseline and end-of-treatment visits).*

The slight deviations in the mean change of FEV1 % predicted normal from baseline to end of therapy in the three sensitivity analyses and the statistical signficance of the % difference between the two treatment groups imply that the evidence of efficacy is robust, despite the inaccurate recording of or loss of source input data cited in the original submission. The Medical Officer therefore agrees with Dr. Gamalo's overall conclusion that "the findings for FEV1 % predicted are numerically consistent, statistically significant, and corroborate the analyses found in the original NDA".

Table 25. Sensitivity Analyses Conducted by Dr. Gamalo Using Efficacy Data from the Resubmission Using the Baseline Observation Carried Forward Method.

Visit	Week		CHF 1538	Placebo	P-Value
Sensitivity A: Re-calculated % predicted values using data from clinical database					
2	Baseline	N	161	84	
		Mean	60. 79	64.36	
8	20 "ON" Drug	N	161	84	
		Mean Change from Baseline	6.01	0.06	
		Difference	5.95 (2.24, 9.65)		0.0018
Sensitivity B: Re-calculated % predicted values using data from Spirometry printouts					
2	Baseline	N	142	73	
		Mean	60.41	65.20	
8	20 "ON" Drug	N	142	73	
		Mean Change from Baseline	6.36	0.33	
		Difference (95% CI)	6.03 (2.20, 9.86)		0.0022
Sensitivity C: Re-calculated % predicted values using data from clinical database, in the same subset of patients used in analysis B					
2	Baseline	N	142	73	
		Mean	60.33	65.58	
8	20 "ON" Drug	N	142	73	
		Mean Change from Baseline	5.84	-0.62	
		Difference (95% CI)	6.47 (2.38, 10.55)		0.0021

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

Table 26. Sensitivity Analyses Conducted by Dr. Gamalo Using Efficacy Data from the Resubmission Using the LOCF Method.

Visit	Week		CHF 1538	Placebo	P-Value
Original results from previous review					
2	Baseline	N	161	84	
		Mean	60.7	63.6	
8	20 "ON" Drug	N	161	84	
		Mean Change from Baseline	6.88	0.64	
		Difference (95% CI)	6.24 (2.71, 9.77)		0.001
Sensitivity A: Re-calculated % predicted values using data from clinical database					
2	Baseline	N	161	84	
		Mean	60. 79	64.36	
8	20 "ON" Drug	N	161	84	
		Mean Change from Baseline	6 10	-0.11	
		Difference	6.21(2.40, 10.02)		0.0015
Sensitivity B: Re-calculated % predicted values using data from Spirometry printouts					
2	Baseline	N	142	73	
		Mean	60.41	65.20	
8	20 "ON" Drug	N	142	72	
		Mean Change from Baseline	6.55	0.21	
		Difference (95% CI)	6.34 (2 37, 10.31)		0.0019
Sensitivity C: Re-calculated % predicted values using data from clinical database, in the same subset of patients used in analysis B					
2	Baseline	N	142	73	
		Mean	60.33	65.58	
8	20 "ON" Drug	N	142	72	
		Mean Change from Baseline	5.93	-0.64	
		Difference (95% CI)	6.56 (2.35, 10.78)		0.0024

Source: Statistical Review for NDA 201820 of Dr. M. Amper Gamalo.

6.1.10.6.4. Efficacy Comparison with TOBI

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. The Medical Reviewer will discuss the impact of the osmolality change in efficacy in this section.

As background, TOBI® was approved in 1997 based on efficacy and safety findings from two pivotal Phase 3 trials, PC-TNDS-002 and PC-TNDS-003. The USP specification limits for TOBI is (b) (4) mOsmol/kg. The number of patients enrolled and who completed the study are as follows:

Table 27. Patient Enrollment in the TOBI® Phase 3 Pivotal Trials

	PC-TNDS-002			PC-TNDS-003		
	TOBI	**Placebo**	**Total**	**TOBI**	**Placebo**	**Total**
Enrolled	109	114	223	149	148	297
Completed	96	100	196	136	132	268

Source: NDA 50753. Clinical Review for TOBI. 1997. p. 28.

The demographic information of the patients enrolled in the TOBI® pivotal trials can be found in Appendix E.

The TOBI trials evaluated the efficacy of TOBI® using the following primary endpoints: 1) the 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.

Using the first primary endpoint, the following summarize the TOBI® pivotal trials' efficacy data:

Table 28. Primary Efficacy Results of the TOBI® Pivotal Trials

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.

Medical Officer Comment:
Comparing the pivotal trials for TOBI®*I and the pivotal trials for CHF-1538, the Medical Reviewer has the following observations:*

- *The number of the patient population for the* TOBI® *pivotal trials were similar to the number of patients enrolled to CT02. The population enrolled in the* TOBI® *trials differed slightly with the enrollment of a greater proportion of older patients (> 18 years old) compared to CT01 and CT02.*
- *The time of assessment of the primary endpoint for the pivotal TOBI trials was different from CT01 and CT03 wherein the endpoint was assessed after one cycle of 28 days on therapy and one cycle of 28 days on therapy and one cycle of 28 days off therapy, respectively, and was similar to CT02 where the endpoint was assessed after three cycles.*
- *A slight difference between the primary endpoint evaluated in the TOBI pivotal trials and the CHF 1538 CT01, CT02, and CT03 trials is noted.*
    - *TOBI trials: difference between the treatment groups in the mean **relative** change of FEV1 % predicted from baseline to Visit 10;*
    - *CHF 1538 trials difference between the treatment groups in the mean change of FEV1 % predicted from baseline to time of evaluation (after 1 cycle for CT01 and CT03 and after 3 cycles for CT02)*
- *The comparative results of the trials are as follows:*

Table 29. Comparative Primary Efficacy Results

Product and Treatment Groups	Difference in Mean Change (or Mean Relative Change for TOB trials) of FEV1 % Predicted between Treatment Groups	Confidence Interval and/or p-value
TOBI*		
PC-TNDS-002 (placebo)	12.54 (mean rel change); 11.0% (mean change)	<0.001
PC-TNDS-003 (placebo)	11.42 (mean rel change); 8.05% (mean change)	<0.001
CHF 1538 trials		
CT01 (placebo)	13.3 (mean change)	(4.7, 21.8), p=0.003
CT02 (placebo)	6.56 (mean change)	(2.35, 10.78), p= 0.0024
CT03		
CHF-1538	7.50 (mean change)	
TOBI	7.01 (mean change)	

**Source: NDA 50753 Clinical Review of Efficacy and Safety of TOBI. 1997. p.29-32.*

- *The Medical Officer believes that the primary efficacy results from the CHF 1538-placebo trials provide adequate evidence that CHF 1538 is efficacious in improving FEV1 in patients with CF and* P. aeruginosa*. Such improvement may be more dramatic in the first month of treatment with CHF 1538, as the greater difference observed in the mean change in CT01 compared to CT02 could only be partly explained by the younger patient cohort in CT01.*
- *The results of Trial CT03, which can be considered as a bridging study comparing the efficacy of CHF 1538 to the reference drug TOBI, indicate a*

similar trend of efficacy for both the CHF 1538 and TOBI® *groups (7.50% vs 7.01%).*

- *The degree of improvement in the primary efficacy variable in Trial CT03 appears similar to the degree of improvement in Trial CT02, indicating similar efficacy trends, despite the changes in the osmolality of the formulation used in Trials CT02 and and CT03.*
- *While the degree of improvement from the pivotal* TOBI® *trials appear to be greater than what was observed in two of the three CHF 1538 trials (Trials CT01 and CT03), the primary efficacy variable evaluated in the* TOBI® *trials, the difference in mean relative change in FEV1 % predicted between baseline and Visit 10 is slightly different from that evaluated in the CHF 1538 trials (i.e. mean change in FEV1 % predicted). This difference may partly explain the differences.*

In conclusion, the Medical Officer 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 appear to significantly impact the efficacy profile of CHF 1538.

7 Review of Safety

Safety Summary

The drug development program for CHF 1538 includes a safety database of 346 patients in Phase 3 clinical trials: 29 patients in Trial CT01 (mean exposure of 29.9 days), 161 patients in Trial CT02 (mean exposure of 87.5 days), and 156 patients in Trial CT03 (mean exposure of 29.1 days). As the submission is a 505(b)(2) application relying partly on prior safety data of TOBI®, the safety exposure for CHF 1538 appears acceptable. The safety data of CHF 1538 is based on integrated safety data from Trials CT01 and CT02 which were double-blinded and placebo-controlled. As with efficacy, safety findings from Trial CT03 are considered supportive and informative on the issue of the comparability of CHF 1538 and TOBI®.

More major safety events (deaths, nonfatal serious adverse events, discontinuation rates) were reported in the placebo group than in the CHF 1538 group in the three clinical trials. Assessment of the association of these safety events to the study drug is complicated by the need to delineate events related to the underlying CF.

An imbalance of death was observed in Trials CT01 and CT02, with more deaths in the placebo group (3/115 [2.6%]) than in the CHF 1538 group (1/190 [0.5%]). No deaths were reported in Trial CT03. The death in the CHF 1538 was from cardiomyopathy of unknown origin unlikely to be related to the study drug while the deaths in the placebo group were probably related to pulmonary exacerbations. This trend is comparable to the safety data from the original TOBI® trials.

More nonfatal serious adverse events were reported in the placebo group (17/190 [8.9%]) compared to the CHF 1538 group (23/115 [20%]). Most of the reported NSAEs were secondary to the underlying CF/pulmonary exacerbation. In Trial CT03, the frequency of NSAEs in the CHF 1538 (6/156 [3.8%]) and the TOBI® group (2/168 [1.2%]) were low but similar between groups. Discontinuations were also higher in the placebo group than in the CHF 1538 group in the three trials. Most of the discontinuations were related to the underlying CF or pulmonary exacerbation. The trends observed in the frequencies of these major safety events may indicate the relative effectiveness of CHF 1538 in preventing worse outcomes from the underlying cystic fibrosis (i.e. pulmonary exacerbation, etc.).

The trends observed in the CHF 1538 trials appear to be consistent with the trends observed in the original TOBI® trials.

Limited safety data demonstrate that AEs associated with systemic aminoglycoside treatment (ototoxicity/vestibulotoxicity, nephrotoxicity, neuromuscular weakness) do not appear to be related to the administration of CHF. Possible deafness was reported only in 2 patients in the CHF 1538 group and 1 in the placebo group, though monitoring and documentation of audiometric tests were limited. Safety data on nephrotoxicity and neuromuscular weakness are extremely limited. Lastly, bronchospasm was reported in only one patient.

The most common treatment-emergent adverse events occurring in >5 % of patients, reported in greater frequency in the CHF 1538 group, and evaluated as possibly associated with the study drug are: forced expiratory volume decreased, rales, red blood cell sedimentation rate increase, dysphonia, pharyngitis, wheezing, and epistaxis. Except for dysphonia, wheezing, and epistaxis, most of the TEAEs indicative of airway hypersensitivity of airway irritation were more markedly reported in the placebo group. This trend is reassuring considering that the proposed CHF 1538 formulation has a higher tobramycin concentration and a higher osmolality than the TOBI® reference drug. However, monitoring of the frequencies of dysphonia, wheezing, and epistaxis, together with monitoring for AEs associated with systemic aminoglycosides, must be conducted

In conclusion, safety data from the integrated safety population (Trials CT01 and CT02) and Trial CT03 indicate that no new safety signals are noted. The safety profile of CHF 1538 appears to be consistent with the safety profile of the reference drug TOBI®.

7.1 Methods

The Applicant modified the osmolality of the drug product late in the course of the development progam so that the formulation of the study drug used for Trials CT01 and CT02 had a higher osmolality than the formulation used for Trial CT03 and the proposed To-be-marketed formulation and the reference drug TOBI®. The differences are as follows:

- Trials CT01 and CT02: (b) (4) mOsmoles/kg
- Trial CT03: (b) (4) mOsmoles/kg
- Proposed To-be-marketed product: (b) (4) mOsmoles/kg.
- TOBI®I: (b) (4) mOsmoles/kg.

As previously stated, the Applicant had intended to use Trial CT03 as a bridging clinical study that may address the safety and efficacy concerns of a to-be-marketed drug with a lower osmolality. Referring to Dr. Mishra's review and Dr. Farley's Division Decisional Memorandum, evaluation of the original NDA submission's safety data from Trials CT01 and CT02 using the higher osmolality drug product did not raise safety concerns. With a comparable osmolality to the To-be-marketed product, evaluation of safety data from Trial CT03 likewise did not raise any safety concerns.

This review of safety therefore has the following objectives:

- To compare the safety profile of the drug formulation used for Trials CT01 and CT02 to the drug formulation used for Trial CT03 and to the reference drug TOBI®;
- To verify the previous reviewers' safety conclusions; and
- To evaluate the postmarketing safety data provided by the Applicant in the current submission for potential safety signals that may be incompatible with the safety profile of the reference drug TOBI®.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The three primary sources of safety data for this review:

a. Trial CT01 – *Double-Blind, Multicenter, Randomized, Placebo-Controlled, Parallel Groups, Clinical Trial of CHF1538 Tobramycin 300 mg/4 mL Inhalation Solution (300 mg BID) in the 4-Week Treatment (Plus 4 Weeks of Run-Out) of Patients With Cystic Fibrosis and a Positive Culture for Pseudomonas aeruginosa.*
b. Trial CT02 – *Double-Blind, Multinational, Multicenter, Randomized, Placebo-Controlled, Parallel Groups, Clinical Trial of Intermittent CHF1538 Tobramycin (300 mg/4 mL Inhalation Solution) or Placebo in Three 4-Week Cycles of Treatment, Given In Addition to Other Antipseudomonal Treatments, in Patients With Cystic Fibrosis and a Positive Culture for Pseudomonas aeruginosa.*
c. Trial CT03- *A Multicentre, Multinational, Open-Label, Randomised, Parallel Group Clinical Trial of Bethkis® (Tobramycin Solution for Nebulisation, 300 mg Twice Daily in 4 mL Unit Dose Vials) Compared to* TOBI® *in the Treatment of Patients With Cystic Fibrosis and Chronic Pseudomonas Infection*.

A brief description of the trials is found in Table 5.

7.1.2 Categorization of Adverse Events

Dr. Mishra previously described problematic issues encountered in the classification of and coding of adverse events, particularly the coding of cystic fibrosis-related pulmonary exacerbations.

Splitting one AE to a number of Preferred Terms (PT) could make the reported frequency of a condition/AE typically comprised of different conditions/AEs less accurate and result in a reportedly lower frequency. Pulmonary exacerbations were typically coded to the Preferred Term (PT) 'condition aggravated'. However, the use of this PT depended on the investigator and there were instances when a pulmonary exacerbation symptom/PT such as "dyspnea," "obstructive airways disorder" and "worsening of respiratory failure," was used to describe an AE. In another instance the investigator term 'febrile dyspnea' was split into the two PT 'pyrexia' and 'dyspnea.' Lastly, the PTs"bronchitis bacterial" or "respiratory tract infection" may or may not represent pulmonary exacerbation as many of these patients were treated with non-antipseudomonal antibiotics such as amoxicillin.

Instances of possible miscoding were also present. For instance, an investigator term of "increase of body temperature" was coded under the preferred term "body temperature increased" rather than "pyrexia". In addition, the term "giddiness" reported by the invetigator may not necessarily reflect the complaint of "dizziness" by the patient.

Trial CT02 demonstrated the difficulty of accurately coding CF-related pulmonary exacerbations as an AE to a specific PT. The difficulties could be from the design of the trial itself but could also be inherent to the complexity of coding this condition. In this study, investigators went through a checklist of symptoms at each post-baseline visit to assess for the presence of a pulmonary exacerbation. This checklist included questions such as:

- increased cough,
- increased sputum or change in appearance of expectorated sputum,
- fever (≥38° C for at least 4 hours in a 24-hour period) on more than one occasion in the previous week,
- weight loss ≥1 kg or 5% of body weight associated with anorexia and decreased dietary intake or growth failure in an infant or child,
- school or work absenteeism (due to illness) in the previous week,
- increased respiratory rate and/or work of breathing,
- new findings on chest examination (e.g. rales, wheezing, crackles),
- decreased exercise tolerance, decrease in forced expiratory volume in one second (FEV_1) ≥10% from previous baseline study within the past 3 months,
- decrease in oxygen saturation (as measured by oximetry) from baseline value within past three months of ≥10%; and
- new findings on chest radiography.

With the checklist, investigators either coded the individual criteria for pulmonary exacerbation as individual AEs, code the AE as a pulmonary exacerbation, or both. This resulted in the difficulty of differentiating the etiology and association of AEs in the Respiratory SOC with the study drug (i.e. whether the AE was due to a pulmonary exacerbation or whether the AE may be associated with study drug use).

In addition to the inaccuracy in estimating AE/PT incidences from coding pulmonary exacerbation symptoms individually or as a whole, exacerbations could also be coded under other PTs that include tracheobronchitis, pneumonia, bronchopneumonia, bronchitis, respiratory failure, and hemoptysis.

Medical Officer Comment:
The Medical Reviewer agrees with the concerns Dr. Shrimant Mishra identified caused by either lumping different AEs into one AE or splitting one AE and reporting individual symptoms of a disease condition as individual AEs. As pointed out, this causes difficulty in determining the causality and association of each AE to the the study drug. However, from the following safety data (SAEs causing deaths and non-fatal SAEs), the placebo group experienced more deaths and more nonfatal SAEs than the CHF 1538 group. Among the fatal and nonfatal SAEs, majority of the cases were classified under the SOC Respiratory Disorders. The Medical Reviewer believes that these respiratory SAEs could be episodes of pulmonary exacerbations developing in the absence of prophylactic antibacterial therapy in the placebo group.

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

Medical Officer Comment:
The Medical Officer agrees with the Applicant's method of pooling safety data from Trials CT01 and CT02 despite the inherent differences in study design (i.e. longer duration of study drug therapy in Trial CT02) and CF patients enrolled (i.e. prior anti-pseudomonal antibacterial was allowed in the last 4 weeks in CT02 and patients were required to have P. aeruginosa strain susceptibility to tobramycin in CT01). These two trials are placebo-controlled and pooling could increase the safety database for CHF 1538. However, based on the Rule of 3s, the pooled safety data from CT01 and CT02, by themselves, may still be inadequate to detect AEs that could occur with a frequency of 1% in exposed patients (1:100) since there are only 190 patients exposed to CHF 1538. However, because the application is a 505(b)(2) application that relies partly on safety data from the reference drug TOBI and because CF is a relatively rare disease, the Medical Officer considers the safety database in CHF 1538's drug development program to be acceptable.

The safety data obtained from these trials may reflect the safety experience of patients during the initial month of treatment with CHF 1538 and the accumulated safety

experience of patients at the end of the recommended dosing regimen (6 months) compared to placebo. Therefore, safety data from each trial may also need to be evaluated individually to provide a more descriptive safety experience of patients given CHF 1538. The Medical Officer concurs with the safety evaluation performed by Dr. Mishra wherein the safety data from each trial were evaluated both independently and as a whole.

7.2 Adequacy of Safety Assessments

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

The safety population exposed to CHF 1538 in Trials CT01, CT02, and CT03 was 29 subjects, 161 subjects, and 156 subjects, respectively for a total safety database of 346 patients.

Table 30 provides a summary of patients exposed to the study medications in Trial CT01 and CT02. In CT01, the mean exposure for the 29 patients given CHF 1538 was 29.9 days while that for the 30 patients given placebo was 29.2 days. In CT02, the mean exposure to CHF 1538 in 161 patients was 87.5 days while the mean exposure to placebo in 85 patients was 85.8 days.

Table 30. Exposure of Patients to the Study Drugs by Time Intervals from Trial CT01 and CT02

Patients	≥ 1 Day		≥ 30 Days		≥ 60 Days		≥ 90 Days	
	CHF 1538	Placebo	CHF 1538	Placebo	CHF 1538	Placebo	CHF 1538	Placebo
Total	190	115	172	98	158	80	35	24
Gender								
Males	104	63	95	54	87	44	22	16
Females	86	52	77	44	71	36	13	8
Age								
6-12 years	82	50	69	45	62	35	16	9
13-17 years	54	36	50	31	46	24	11	10
> 17 years	54	29	53	22	50	21	8	5

Source: NDA 201820, SD No. 0. Original Submission. 2010

In Trial CT03, the mean days of exposure to CHF 1538 in 156 patients was 29 days and the mean days of exposure to TOBI in 168 patients was 29 days. Table 31 summarizes the exposure data for patients enrolled in Trial CT03.

Table 31. Exposure of Patients to CHF 1538 or TOBI in Trial CT03

	CHF 1538 (N=156)	TOBI (N=168)
Extent of Exposure (days)		
N	156	168
Mean (SD)	29.08 (2.91)	28.67 (4.33)
Median	29.00	29.00
Min / Max	4.00/34.00	1.00/35.00
Extent of Exposure (in classes)		
≤ 7 days	1 (0.6%)	3 (1.8%)
8-14 days	1 (0.6%)	1 (0.6%)
15-21 days	0	2 (1.2%)
22-28 days	39 (25.0%)	46 (27.4%)
29-35 days	115 (73.7%)	116 (69.0%)
> 35 days	0	0

Source data: Appendix 16.2.5.1
Extent of exposure calculated as (date of last intake of study drug - date of first intake of study drug) + 1.
Source: NDA 201820, SD No. 0. Original Submission. 2010

Medical Officer Comment:
The Medical Officer considers the exposure of patients to CHF 1538 in the three trials as acceptable and similar to patients treated with placebo or TOBI. This is based on the fact that CF is a rare disease and that the evaluation of safety for CHF 1538 is partly based on prior safety data from the TOBI® *experience. For more details, the Medical Reviewer refers the reader to the review by Dr. Shrimant Mishra evaluating the adequacy of the overall exposure of the safety population at appropriate doses and duration of CHF 1538.*

7.2.2 Explorations for Dose Response

No dose-response studies were conducted as this is a 505(b)2 application relying on the prior dose-response studies conducted to determine the dosing regimen of 300 mg twice daily for the reference drug TOBI.

7.2.3 Special Animal and/or In Vitro Testing

Please see Dr. Mishra's review.

7.2.4 Routine Clinical Testing

Please see Dr. Mishra's review.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Dr. Mishra's review.

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

The following are adverse events of specific interest based on AEs of antibacterials of the same drug class that should be monitored. These include nephrotoxicity, oto-/vestibular toxicity, and neuromuscular blockade. Bronchospasm should be included as this is a potential AE from use of an inhaled product.

Ototoxicity

The Applicant conducted audiometric tests in each of the Phase 3 trials. The tests covered the 250-8000 Hz frequency range and included both bone and air conduction tests. No specific tests were done to assess vestibular toxicity, but rather relied on patient report of symptoms such as dizziness.

Nephrotoxicity

Serum Creatinine (Cr) and blood urea nitrogen (BUN) were regularly monitored during the trials to monitor for nephrotoxicity. Urinalysis and serum electrolyte measurements such as magnesium and calcium levels were also monitored as supportive data to identify nephrotoxicity.

Neuromuscular Blockade

No specific test was done to assess neuromuscular blockade other than patient report and physician assessment of reported adverse events

Bronchospasm

No post-study drug administration spirometric tests were performed to assess bronchospasm. Evaluation for bronchospasm was based on patient/clinician reported adverse events (i.e. wheezing) that may have been verified by physical examination findings.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1. Trials CT01 and CT02

During the course of the three trials, four deaths were reported: three in the placebo group and one in the CHF 1538 group. One patient given placebo was enrolled in Trial CT01. The remaining three patients who died were enrolled in Trial CT02, with one treated with CHF 1538 and two treated with placebo.

Table 32. Mortality Rate for the Safety Population of Trial CT01 and CT02

Group	Mortality Rate in Trials CT01 and CT02 Combined
Placebo	3/115= 2.6%
CHF 1538	1/190= 0.5%

Source: NDA 201820, SD No. 0. Original Submission. 2010

Table 33. Summary Information of Reported Deaths

Trial	Center	Subject	Age	Sex	Drug[1]	Cycles completed[2]	Baseline FEV1 (% Predicted)	Description	Study Drug-Related
CT01	21	21-002	11	F	placebo	N/A	59.3%	Respiratory failure	N/A[3]
CT02	24	24-018	14	F	placebo	N/A	40.6%	Pulmonary Exacerbation	N/A
CT02	34	34-008	11	F	placebo	N/A	45.3%	Pulmonary Exacerbation	N/A
CT02	29	29-001	22	M	CHF1538-off treatment	3 On/Off cycles completed[4]	56%	Cardiomyopathy	29

1 Dose at time of death if on study drug;
2 Drug On/Off cycles completed at time of death
3 Not applicable; relationship of adverse events to subjects on placebo not assessed by reviewer
4 Technically discontinued from study at end of 3rd on cycle but did not pass away until several weeks after discontinued so for all intents and purposes completed a 3rd Off cycle

Source: Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

Death Narratives

CT01/ Patient 21-002:

This is an 11 year-old female with a history of sinusitis and cardiomyopathy who received placebo. Around 2 to 3 weeks from Visit 2, she experienced worsening respiratory failure/sinusitis not responding to antimicrobials, steroids, ipatropium, and supportive care in the ICU. She passed away 18 days after visit 2.

CT02/ Patient 34-008:

This is an 11 year-old female treated with placebo with a history of malabsorption, cirrhosis, GERD, hypoplasia of gallbladder, chronic gastroduodenitis, and CF. She experienced three episodes of pulmonary exacerbation: once prior to and during the run-in stage of the study and another during around Visit 2. She received antibacterial treatment for these episodes. She improved with treatment. However, during her 1st Off cycle, patient developed signs and symptoms of another episode of pulmonary exacerbation, with a decrease in her FEV1 % predicted (49.1%). She received ofloxacin and TMP-SMX for a brief period, then was off antimicrobial therapy for 2 weeks, then restarted ofloxacin before eventually getting hospitalized. Once hospitalized, she received antimicrobials including cefepime, meropenem, ceftriaxone, and amikacin (this is a protocol violation). Forty days after being hospitalized, the patient passed away despite steroids, oxygen therapy, antimicrobials, and ICU admission. Death was attributed to a protracted single course or multiple epsiodes of recurrent pulmonary exacerbations.

CT02/ Patient 24-018:

This is a 14 year-old female, treated with placebo, with pancreatic insufficiency and a pulmonary exacerbation that resolved prior to the study. After 2 weeks on placebo, the patient was diagnosed to have another episode of pulmonary exacerbation with a decrease in FEV1 %. She was hospitalized for 2 weeks and given IV tobramycin, ceftazidime, and cotrimoxazole. She slightly improved but experienced another exacerbation during the 1st Off cycle and the 2nd On cycle. She was started on oral steroids and was withdrawn from the study. Patient subsequently received ceftazidime, amikacin, and IV steroids, with hospitalization. Patient rapidly deteriorated. Within 2-3 days, patient had acidosis, hypercapnea, and hypoxia and required pressor, inotropes, beta agonists, and mechanical ventialtion. She passed away after 5 days of hospitalization. Death was attributed to an episode of CF pulmonary exacerbation.

CT02/ Patient 29-001

This is a 22 year-old male with GERD, depression, hepatitis B, and “distal intestinal obstruction syndrome” who was treated with CHF 1538. He was colonized with *Pseudomonas aeruginosa* and MRSA at baseline. Concomitant medications at baseline include Pancreatin, trimebutine, dornase alfa, ipratropium, fenoterol, formoterol, ambroxol, retinol, phytonadione, ergocalciferol, tocopherol, ursodeoxycholic acid, budesonide, lactulose, and tianeptine. He had a baseline FEV1 % predicted of 56%. The patient experienced a progressive decline in his FEV1 % predicted save for some improvement during the 2nd On cycle.

At the end of the 3rd On cycle, the subject had a pulmonary exacerbation with *Pseudomonas aeruginosa* and MRSA treated with a 3 week course of oral ciprofloxacin.

At the end of treatment, the patient was hospitalized for "bronchitis" and treated with IV ciprofloxacin, imipenem, vancomycin, and fluconazole. Concomitantly, the subject was diagnosed with cardiomyopathy and received treatment with diuretics, inotropes, pressors, beta blocker, colloid, amiodarone, and ACE inhibitor. The patient died 3 weeks after admission. The Investigator did not provide the patient's cause of death.

To elucidate the etiology of the patient's demise, the Division requested for more information on this patient. The Applicant could not verify from the investigator an autopsy was performed. Moreover the investigator stated that the patient had no signs of cardiomyopathy or circulatory insufficiency prior to the AE. The investigator did not consider the cardiomyopathy related to drug. The Applicant performed its own review and stated that "while rare cardiomyopathy is a known complication of CF, it is generally found in younger children." The Applicant also reviewed AERS for CHF 1538 and found one report of cardiomyopathy after exposure to inhaled tobramycin.

Medical Officer Comment:
The Medical Officer does not believe that the cardiomyopathy the patient experienced can be attributed to inhaled tobramycin. Given the minimal systemic absorption of CHF 1538, it is unlikely that inhaled tobramycin could cause cardiomyopathy. Dr. Mishra conducted a brief review of the AERS database and concluded that the two cases of cardiomyopathy with intake of inhaled tobramycin were confounded and therefore may not be related to tobramycin intake.

A plausible cause of cardiac dysfunction could be cystic fibrosis itself. Cardiac dysfunction in cystic fibrosis could potentially manifest as either cor pulmonale or as a myocardial fibrosis leading to asystole/circulatory failure in infants [4] [5]. In another series, a group of 18 CF patients with sudden unexpected cardiac arrest were evaluated and generally had profound ECG changes, early onset pancreatic insufficiency, limited respiratory disease, and death in infancy[6]. These patients experience signs and symptoms of chronic heart failure. However, the Medical officer believe that it is still difficult to attribute the patient's cardiomyopathy to CF as the patient did not exhibit sigs and symptoms of chronic cardiac failure.

7.3.1.2. Trial CT03

There were no deaths in the CT03 trial.

Medical Officer Comment:
The Medical Officer did not observe an increase in mortality rates in patients treated with CHF 1538 relative to placebo or active control. Three of the four deaths were seen in the placebo group and all the three deaths were caused by respiratory failure or pulmonary exacerbation. The only death in a patient treated with CHF 1538 was possibly from cardiomyopathy or cardiac failure and the Medical Officer could not definitively attribute this death to CHF 1538 as the patient did not have prior signs and

symptoms of cardiomyopathy, as reported, and his underlying disease (i.e. CF) has been reported to rarely cause cardiomyopathy that typically manifests with signs and symptoms of chronic heart failure. Therefore, the Medical Officer believes that the only case of death in the CHF 1538 group could not be attributed to CHF 1538.

In relation to the objective of this safety review, the NDA 50753 Safety Review for TOBI indicated that there were 4 deaths in the pivotal trials for TOBI, all occurring in the placebo group.[7] Two deaths reportedly occurred while on study while one withdrew from the study and subsequently dies, and the final patient died after completing the study.

Table 34 *compares the death rates of the three trials for CHF 1538 and TOBI.*

Table 34. Comparative Mortality Rates for CHF 1538 and TOBI

Trial	**CHF 1538**	**Placebo/TOBI for CT03**
CT01 and CT02 (higher osmolality)*	1/190= 0.5%	3/115= 2.6%
CT03 (lower osmolality)*	0	0
Trial (1997	**TOBI**	**Placebo**
TOBI (lower osmolality)#	0	4/120= 3.33%

*Source: Source: NDA 201820, SD No. 0. Original Submission. 2010
Source: NDA 50753. Clinical Review of Efficacy and Safety of TOBI. December 1997.

The death rates obseved in the placebo groups of CT01/CT02 and of the TOBI® *pivotal trials appear to be comparable. As discussed previously, the placebo group has a greater number of deaths compared to the CHF 1538 group. With the etiologies in the placebo group reported to be pulmonary exacerbations, the Medical Officer believes that this may reflect the effectiveness of inhaled tobramycin in preventing pulmonary exacerbations.*

7.3.2 Nonfatal Serious Adverse Events (NSAEs)

7.3.2.1. Trial CT01

Three SAEs were reported, one in the CHF 1538 group and two in the placebo group. Table 35 provides the rates of SAEs in both arms while Table 36 provides a descriptive tabular summary of the SAEs reported.

Table 35. Incidence Rates of Nonfatal SAEs in Trial CT01

Treatment Group	Patients Reporting Nonfatal SAEs
CHF 1538	1/29 = 3.4%
Placebo	2/30 = 6.7%

Source: NDA 201820, SD No. 0. Original Submission. 2010

Table 36. Tabular Summary of Nonfatal SAEs in Trial CT01

Center	Age	FEV1 % Predicted at baseline	Drug	SOC[2]	PT[3]	Investigator Term	Withdrawal /Did not complete study	Outcome	Causality Assessment[4]
17	11	61.8%	CHF 1538	Gastrointestinal Disorder	Intestinal Obstruction	Cys ic Fibrosis, Mixed Form, Coprostasis	No	Recovered	Likely Not Related
17	15	49.8%	Placebo	General Disorders and Administration Site Conditions	Condi ion Aggravated	Cys ic Fibrosis, Exacerbation Coprogram	Yes	Recovered with Sequelae	Not Applicable[5]
10	17	49%	Placebo	Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea	Febrile Dyspnea	Yes	Recovered	Not Applicable

1- At time of NSAE
2- System Organ Class
3- Preferred Term
4- In the opinion of this reviewer
5- If occurred in placebo then relationship of event to study drug not assessed

Source: NDA 201820, SD No. 0. Original Submission. 2010

Medical Officer Comment: The size of the trial makes it difficult to make a valid comparison on the incidence of SAEs between groups. However, the Medical Officer does not think that the intestinal obstruction caused by fecal impaction is related to CHF 1538. Rather, this SAE may be related to the underlying condition itself. The two SAEs reported for the placebo group are related to pulmonary exacerbations.

7.3.2.2. Trial CT02

In Trial CT02, the placebo group appears to have a greater frequency of SAEs reported. As Dr. Mishra has reported, most of the SAEs occurred during the Off cycle. More females were reported to have an SAE compared to males and more SAEs occurred in children (6-12 y.o.), followed by adolescents, then adults. Dr. Mishra believes that the slight increase in SAEs in age groups follow the demographics of the enrolled population.

Table 37. Incidence of NSAEs in Trial CT02

Treatment Group	Number of Patients with NSAEs (%)
CHF 1538	16/161 = 9.9%
Placebo	21/85 = 24.7%

Source: NDA 201820, SD No. 0. Original Submission. 2010

The following table provides a tabular summary of all the SAEs reported in Trial CT02. All the reported SAEs led to hospitalization.

Table 38. Tabular summary of SAEs Reported in Trial CT02

Site	Age	Sex	FEV1 % Predicted at baseline	Drug	SOC[2]	PT[3]	Investigator Term	Withdrawal	Outcome	Causality Assessment[4]
12	9	M	63%	CHF 1538	Surgical and Medical Procedures	Polypectomy	Polypectomy wit Hospitalization	No	Recovered	Not related

Site	Age	Sex	FEV1 % Predicted at baseline	Drug	SOC[2]	PT[3]	Investigator Term	With drawal	Outcome	Causality Assessment[4]
13	10	F	45%	CHF 1538	Infections and Infestations	Pneumonia	Pneumonia	No	Recovered	Likely Not Related
13	10	F	45%	CHF 1538	Infections and Infestations	Pneumonia	Pneumonia	No	Recovered	Likely not related
13	10	F	45%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
15	19	F	62%	CHF 1538	Respiratory, Thoracic, and Mediastinal Site Disorders	Hemoptysis	Hemoptae with Hospitalization	No	Recovered	Possibly Related
15	16	M	45%	CHF 1538	Infections and Infestations	Bronchopneumonia	Bronchopneumonia with hospitalization	No	Recovered	Likely Not Related
21	7	F	62 9%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
21	7	F	62 9%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
21	22	M	51 2%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
22	18	F	31.4%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	Yes	Recovered	Likely Not Related
24	16	F	56 3%	CHF1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
24	7	F	69%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	Yes	Recovered	Likely Not Related
26	20	F	45%	CHF 1538	Gastrointestinal Disorders	Pancreatitis Acute	Acute Pancreatitis	No	Recovered	Likely Not Related [5]
27	18	M	58%	CHF 1538	Gastrointestinal Disorders	Abdominal Pain	Abdominal Pain (Note: really constipation/fecal impaction/	No	Recovered	Likely not related
29	8	M	60%	CHF 1538	Infections and Infestations	Bronchitis	Bronchitis	No	Recovered with Sequelae	Likely not related
31	19	F	51 3%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
32	14	M	44%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
32	14	M	41%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
34	7	M	40 2%	CHF 1538	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Likely Not Related
12	8	F	84%	Placebo	Surgical and medical Procedures	Polypectomy	Polypectomy	No	Recovered	Not applicable[6]
15	9	F	63%	Placebo	Infections and Infestations	Tracheobronchitis	Tracheobronchitis	No	Recovered	Not Applicable
15	9	F	60%	Placebo	Infections and Infestations	Bronchopneumonia	Bronchopneumonia	No	Recovered	Not Applicable
SS15	9	F	60%	Placebo	Infections and Infestations	Bronchopneumonia	Bronchopneumonia	No	Recovered	Not Applicable
16	9	F	54%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
21	16	M	69 6%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable

Site	Age	Sex	FEV1 % Predicted at baseline	Drug	SOC[2]	PT[3]	Investigator Term	Withdrawal	Outcome	Causality Assessment[4]
21	13	F	63 9%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
21	11	M	70.1%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
21	11	M	70.1%	Placebo	Infections and Infestations	Bronchopneumonia	Bronchopneumonia	No	Recovered	Not Applicable
21	6	F	37 9%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
22	25	M	55 8%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	Yes	Recovered	Not Applicable
22	21	F	76 9%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
23	11	F	42%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
24	17	M	48 5%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
24	13	M	34.1%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
24	13	M	34.1%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
24	14	F	40 6%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	Yes	Recovered	Not Applicable
24	13	F	77%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	No	Recovered	Not Applicable
24	12	F	77%	Placebo	Infections and Infestations	Laryngitis	Acute laryngitis	No	Recovered	Not Applicable
27	11	F	75%	Placebo	General Disorders and Administration Site Conditions	Condition Aggravated	Pulmonary exacerbation	Yes	Recovered	Not Applicable
29	15	F	51%	Placebo	Infections and Infestations	Acute bronchitis	Acute Bronchitis	No	Recovered	Not Applicable
29	23	M	43%	Placebo	Respiratory, Thoracic, and mediastinal Disorders	Hemoptysis Note: possibly could be coded as PExac.	Hemoptysis	No	Recovered	Not Applicable
29	23	M	43%	Placebo	Respiratory, Thoracic, and mediastinal Disorders	Hemoptysis Note: possibly should be coded as PExac.	Hemoptysis	No	Recovered	Not Applicable
29	16	M	79%	Placebo	Cardiac Disorders	Tachycardia; Note: Could have had Bronchitis or Cough code as well	Tachycardia	Yes	Recovered	Not Applicable
32	32-019	17	F	36%	Placebo	Beginning of 2nd Off Cycle	General Disorders and Administration Site Conditions	Condition Aggravated[7]	Hospitalization	No

Source: Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

Medical Officer Comment:
Majority of the SAEs reported in both groups appear to represent pulmonary exacerbation-related PTs (79.5%). The Medical Officer believes that since more AEs requiring hospitalization occurred in the placebo group, this pattern may represent the effectiveness of CHF 1538 in preventing episodes of pulmonary exacerbation and related illnesses.

As can be seen in Table 38*, the SAEs reported for CHF 1538 can be classified as related to a pulmonary exacerbation except for the following: polypectomy, hemoptysis, acute pancreatitis, and abdominal pain.* Table 39 *further separates the different PTs coded that are likely episodes of pulmonary exacerbations.*

The Medical Officer agrees with the investigator and the Applicant that the SAE of polypectomy is not related to the study drug. The SAEs of acute pancreatitis and abdominal pain appear to be more related to the underlying condition of CF, rather than related to the study drug. When further examined, the patient who experienced hemoptysis during the 1st ON cycle did have an episode of hemoptysis six months prior to the initiation of CHF 1538 treatment. Thus, the Medical Officer considers the SAE of hemoptysis as likely not related to the study drug. Therefore, in agreement with Dr. Mishra, the Medical Officer concludes that the SAEs reported in both treatment arms of Trial CT02 are related to episodes of pulmonary exacerbation or to the underlying disease, rather than to CHF 1538.

Table 39. Preferred Terms (PTs) Likely to Represent Pulmonary Exacerbations

NSAE by PT	CHF1538 - # of events /# of individuals/ % of safety population	Placebo - # of events /# of individuals/ % of safety population
Condition Aggravated	11/10 /6.2%	15/14/16.4%
Bronchopneumonia	1/1/0.6%	3/2/2.3%
Bronchitis	1/1/0.6%	1/1/1.2%
Tracheobronchitis	0	1/1/1.2%
Pneumonia	2/1/0.6%	0
Total	15/13/8.1%	20/18/21.2%

Source: Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

7.3.2.3. Trial CT03

In Trial CT03, 9 SAEs occurred in 8 patients, with 7 SAEs occurring in 6 patients given CHF 1538 and 2 SAEs occurring in 2 patients given TOBI. The table below gives the frequencies of SAEs in the treatment arms.

Table 40. Rate of SAEs in CT03 Safety Population

Treatment Group	Number of Patients with NSAEs (%)
CHF 1538	6/156= 3.8%

TOBI	2/168 = 1.2%

Source: NDA 201820, SD No. 0. Original Submission. 2010

Table 41 provides a tabular summary of the SAEs/PTs reported in Trial CT03. Most of the SAEs represent an episode of pulmonary exacerbation that required hospitalization. Four SAEs reported in 3 patients can possibly, but highly unlikely, to be related to CHF 1538.

Table 41. Summary of SAEs reported in Trial CT03

Center	Age	Sex	FEV1 % Predicted at baseline	Drug	SOC[2]	PT[3]	Inv. Term	Withdrawal/Lack of Completion of Study	Outcome	Causality Assessment[4]
104	14	M	50.4%	CHF 1538	Infections and Infestations	Lung Infection	Exacerbation of Lung Infection in CF	No	Recovered/resolved	Likely not Related
109	19	F	69.4%	CHF 1538	Infections and Infestations	Bronchitis	Exacerbation of Chronic Bronchitis in CF	No	Recovered/resolved	Likely not Related
203	10	F	75.1%	CHF 1538	Congential Familial and genetic Disorders	Cystic Fibrosis Lung	Exacerbation of CF	No	Recovered/resolved	Likely Not Related
209	17	F	56.5%	CHF 1538	Infections and Infestations	Appendicitis	Acute Appendicitis	No	Recovered/resolved	Possible though unlikely
302	14	F	62.6%	CHF 1538	Nervous System Disorders	Syncope	Syncope	No	Recovered/resolved	Possible though unlikely
302	14	F	62.6%	CHF 1538	Injury, Poisoning, and Procedural Complications	Head Injury	Contusion of the Head	No	Recovered/resolved	Possible though unlikely
305	7	M	76.7%	CHF 1538	Infections and Infestations	Laryngitis	Acute laryngitis	No	Recovered/resolved	Possible
109	11	M	49.0%	TOBI	Infections and Infestations	Bronchitis	Exacerbation of Chronic Bronchitis due to CF	No	Recovered/resolved	Likely Not Related
301	26	M	42.4%	TOBI	Congenital, familial, and genetic disorders	CF Lung	CF Exacerbation	Yes	Recovered/resolved	Likely Not Related

Source: NDA 201820, SD No. 0. Original Submission. 2010

Medical Officer Comment:
The Medical Officer interprets the rates of SAEs reported in this trial with caution as this is an open-label trial that could be prone to over-reporting of SAEs. As for the individual SAEs reported, the Medical Officer does not consider the SAE Acute Appendicitis as related to the study drug. Syncope and the resulting head injury was discussed by Dr. Mishra. The Medical Officer concurs that the syncopal episode, whether or not the episode may be vestibular in origin, could possibly be related to the study drug. Similarly, laryngitis, based on prior experience with TOBI with which patients experienced more episodes of pharyngitis and voice alteration compared to placebo, may be related to the study drug.

In general, the Medical Officer concurs with Dr. Shrimant's conclusion that from the analysis of NSAEs reported in Trials CT01, CT02, and CT03, no new safety signals were noted with the use of CHF 1538. In fact, the greater number of SAEs related to pulmonary exacerbations in the placebo group may reflect the effectiveness of inhaled tobramycin in preventing exacerbations.

In order to determine if any variations in osmolality in the different formulations used for the CHF 1538 trials resulted in any safety signals or in a different safety profile, the Medical Officer compared the frequencies of SAEs reported in theCHF 1538 trials using differrent osmolalities and the original TOBI pivotal trials, Table 42 *provides this overall summary information.*

Table 42. Comparative Number of Patients Reporting SAEs in Trials for Inhaled Tobramycin (CHF 1538 and TOBI)

Trial	CHF 1538	Placebo/ TOBI for CT03
CT01 and CT02 (higher osmolality)*	17/190 (8.9%)	23/115 (20%)
CT03 (lower osmolality)*	6/156= 3.8%	2/168 = 1.2%
Trial (1997 trials)	**TOBI**	**Placebo**
TOBI (lower osmolality)#	96/256 (37.5%)	120/262 (45.8%)

* Source: NDA 201820, SD No. 0. Original Submission. 2010
\# Source: NDA 50753. Clinical Review of Efficacy and Safety of TOBI. December 1997.

Grossly, in all the inhaled tobramycin-placebo trials enumerated (pooled CT01 and CT02 results and TOBI 1997 trial results), the rate of SAEs reported appears to be higher in the placebo group compared to the CHF 1538 group. The Medical officer believes that this trend is consistent between the CHF 1538 trials and the original TOBI trials.

The rate of SAEs in the original pivotal trials for TOBI appeared significantly higher However, comparing the rates of SAEs reported between the CHF 1538 and original TOBI trials and making definitive conclusions from the comparison would be difficult and challenging. This is because the CHF 1538 trials and TOBI trials were conducted in different trial settings with different patient populations (i.e. younger population for the CHF 1538 cohort vs older population for the TOBI cohort), different concurrent and supportive therapy (i.e. different use of adjunctive therapies), different reporting threshold and mechanisms during the time the trials were conducted, and different trial designs.

As a bridging study, Trial CT03 appears to demonstrate that the rate of SAEs in the CHF 1538 group is comparable, albeit higher, to the rate of SAEs in the TOBI group. The Medical Officer therefore concludes that the safety profile of CHF 1538 is similar to and consistent with the safety profile of the reference product TOBI, as far as reported NSAEs are concerned.

7.3.3 Dropouts and/or Discontinuations

Of the eight patients who discontinued Trial CT01, five discontinued due to a treatment emergent adverse event (TEAE) or change in concomitant medication. Three patients were lost to follow-up. The placebo group experienced more discontinuations than the CHF 1538 group.

Table 43. Discontinuation Rates in Trial CT01

Treatment Group	Number of Patients who Discontinued the Study (%)
CHF 1538	1/29 = 3.4%
Placebo	7/30 = 23%

Source: NDA 201820, SD No. 0. Original Submission. 2010

Table 44 describes the TEAEs leading to discontinuations, which include worsening underlying conditions, fever, and respiratory disorders. These may reflect that worsening of the underlying condition or a pulmonary exacerbation that would require a change in concomitant medications.

Table 44. TEAEs Leading to Discontinuation in Trial CT01

Table 33: Treatment-Emergent Adverse Events (by SOC[1] and PT[2]) Leading to Discontinuation from the Study: Safety Population

Treatment-Emergent Adverse Event Leading to Discontinuation From Study (by SOC and PT)	CHF 1538 (N[3] = 29)	Placebo (N = 30)
Total number of TEAEs[4] leading to discontinuation from study	0	6
Number of patients with any TEAE[4, 5] leading to discontinuation from study	0 (0.0%)	5 (16.7%)
General Disorders and Administration Site Conditions	0 (0.0%)	4 (13.3%)
Condition aggravated	0 (0.0%)	3 (10.0%)
Pyrexia	0 (0.0%)	1 (3.3%)
Respiratory, Thoracic and Mediastinal Disorders	0 (0.0%)	2 (6.7%)
Dyspnoea	0 (0.0%)	1 (3.3%)
Respiratory failure	0 (0.0%)	1 (3.3%)

[1] system organ class
[2] preferred term
[3] total number of patients
[4] treatment-emergent adverse event(s)
[5] A patient may have been withdrawn from the study because of more than one AE.
Source: Appendix 16.2.1.1 and Appendix 16.2.7.1

Source: NDA 201820, SD No. 0. Original Submission. 2010

For Trial CT02, the discontinuation rate of the placebo group exceeded the discontinuation of the CHF 1538 group as seen in Table 45.

Table 45. Discontinuation Rates in Trial CT02

Treatment Group	Number of Patients who Discontinued the Study (%)
CHF 1538	7/161= 4.3%
Placebo	8/85 = 9.4%

Source: NDA 201820, SD No. 0. Original Submission. 2010

By demographics, the discontinuations are greater in younger patients (patients 6.12 years of age) and adults in the CHF 1538 group. However, when comparing to the

placebo group, the discontinuation rates appear to be higher in the patients > 17 years of age in the CHF 1538 group compared to the placebo group (42.9% vs. 25%, respectively). As far as baseline FEV1 % Predicted is concerned, the discontinuations, while similar in both CHF 1538 and placebo groups, are more frequent in patients with baseline FEV1 % of > 50% of predicted.

Table 46. Discontinuation Rates by Patient Demographics in Trial CT02

Demographic	CHF 1538		Placebo		Total (ITT)
Age	ITT	Discont.	ITT	Discont.	
6-12	63 (39.1%)	3(42.9%)	37 (44%)	3 (37.5%)	100 (40.8%)
13-17	47 (29.2%)	1 (14.3%)	25(29.8%)	3 (37.5%)	72 (29.4%)
>17	51 (31.7%)	3(42.9%)	22 (26.2%)	2 (25%)	73 (29.8%)
Sex	ITT	Disc.	ITT	Disc.	
M	89 (55.3%)	4 (57.1%)	46 (54.8%)	4 (50%)	135 (55.1%)
F	72 (44.7%)	3 (42.9%)	38 (45.2%)	4 (50%)	110 (44.9%)
Baseline FEV1 % Predicted	ITT	Disc.	ITT	Disc.*	
>50%	113 (70.2%)	5 (71.4%)	66 (78.5%)	5 (62.5%)	179 (73.1%)
≤ 50%	48 (29.8%)	2 (28.6%)	18 (21.4%)	2 (25%)	66 (26.9%)

Source: Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

As observed in Trial CT01, most of the discontinuations were due to pulmonary exacerbation manifestations as shown in Table 47.

Table 47. Possible Etiologies of Discontinuations in Trial CT02

Possible Etiology	CHF 1538	Placebo
Possible Pulmonary Exacerbation-like manifestations	4	4
Withdrawal of consent	1	2
Loss to Follow-up	1	0
Dry cough related to drug	1	1
Vomiting/bitter taste related to drug	0	1 (same as dry cough event)
Other		1

Source: Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

For Trial CT03, the rate of discontinuations in the CHF 1538 group appear to be similar to the discontinuation rate in the TOBI group as shown in Table 48.

Table 48. Discontinuation Rates in Trial CT03

Treatment Group	Number of Patients who Discontinued the Study (%)
CHF 1538	4/156 = 2.6%
TOBI	6/168 = 3.6%

Source: NDA 201820, SD No. 0. Original Submission. 2010

By demographics, the rate of discontinuation was observed to be highest in adults given CHF 1538 compared to the other age groups given CHF 1538. For the TOBI group, more adults discontinued treatment compared to the younger age groups.

Table 49. Discontinuation Rates by Demographics of Patients in Trial CT03

Demographic	CHF 1538		TOBI		Total (ITT)
Age	ITT	Disc.	ITT	Disc.	

6-12	47 (29.7%)	0 (0%)	56 (34.4%)	1 (16.7%)	103 (32.1%)
13-17	54 (34.2%)	0 (0%)	57(35.0%)	2 (33.3%)	111 (34.6%)
>17	57 (36.1%)	4(100%)	50 (30.7%)	3 (50%)	107 (33.3%)
Sex	ITT	Disc.	ITT	Disc.	
M	72 (45.6%)	3 (75.0%)	84 (51.5%)	3 (50%)	156 (48.6%)
F	86 (55.4%)	1 (25.0%)	79 (48.5%)	3 (50%)	165 (51.4%)
Baseline FEV1 % Predicted	ITT	Disc.	ITT	Disc.	
≥50%	122 (77.2%)	2 (50%)	125 (76.7%)	5 (83.3%)	247 (76.9%)
<50%	36 (22.8%)	2 (50%)	38 (23.3%)	1 (16.7%)	74 (23.1%)

Source: NDA 201820, SD No. 0. Original Submission. 2010

Majority of discontinuations in both the CHF 1538 and TOBI groups were from adverse events. In particular, two patients discontinued CHF 1538 because of an episode of hemoptysis that was evaluated as associated with CHF 1538 use. None in the TOBI group experienced hemoptysis.

Table 50. Possible Etiologies of Discontinuations in Trial CT03

Association	CHF 1538	TOBI
Pulmonary Exacerbation-like manifestation	0	1
Protocol Violation	1	2
Adverse Event		
Cough	1	2
Hemoptysis	2	0
Hoarseness	0	1
Bronchospasm	0	1
Withdrawal of Consent	1	0

Source: Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

Medical Officer Comment:
For the placebo-controlled trials (CT01 and CT02), discontinuations are more frequent in the placebo group, possibly from an imbalance of AEs that represent pulmonary exacerbations or worsening of the patient's CF. The rate of discontinuation in the CHF 1538 group appear to be similar to the rate of discontinuation in the TOBI group. When demographics of the patient population in CT02 and CT03 are considered, the Medical Officer noted a higher discontinuation rate in adults (>17 years of age) in both trials. Lastly, in Trial CT03, the two cases of hemoptysis were evaluated to be associated to CHF 1538 treatment, with no episodes of hemoptysis occurring in the TOBI group. The Medical Officer believes that these observations could, at best, be considered trends as the relatively low frequencies of discontinuations in the three trials preclude the Medical Officer from making a valid conclusion.

The Medical Officer does not identify any safety signals from analysis of data on discontinuations from the three trials.

Table 51. Summary Table of Discontinuation Rates in Trials CT01, CT02, and CT03

Trial	Discontinuation Rates	
	CHF 1538	Placebo/TOBI^
CT01	1/29 = 3.4%	7/30 = 23%

CT02	7/161= 4.3%	8/85 = 9.4%
CT03*	4/156 = 2.6%	6/168 = 3.6%

Source: Adapted from Mishra, Shrimant. Clinical Review for NDA 201820 Original submission. 2010

The Medical Officer believes that the discontinuation rates for CHF 1538 are similar between the three trials and and between the TOBI group in CT03, indicating a similar safety profile in terms of discontinuation between the CHF 1538 formulations with different osmolalities.

7.3.4 Significant Adverse Events

Please refer to Dr. Shrimant Mishra' review.

7.3.5 Submission Specific Primary Safety Concerns

The Clinical Review of Safety previously conducted by Dr. Shrimant Mishra focused on four primary safety concerns that could potentially develop with the use of inhaled tobramycin. These safety concerns are the following: ototoxicity, nephrotoxicity, bronchospasm, and neuromuscular weakness.

Ototoxicity

No clear signs of ototoxicity or vestibular toxicity were observed from safety data from these trials. In CT01, two TEAEs, vertigo and giddiness, that may indicate vestibular or otoxocity were reported. In CT02, while bone and air conduction tests were performed, documentation was poor and inconsistent. Moreover, standardization of testing procedures and consistent monitoring and reporting were limited. Safety data from CT02 and CT03 do not suggest a signal of ototoxicity for CHF 1538. In the original TOBI trials, seven patients reported deafness (4 given TOBI and 3 given placebo). None of the three patients given TOBI and evaluated for ototoxicity with audiology exam revealed ototoxicity. Tinnitus appeared to be more significantly common in the TOBI-treated patients in the original TOBI trials conducted in the 1990s.

Medical Officer Comment:
The Medical Officer agrees that no definite signal of ototoxicity and vestibular toxicity is identified, consistent with the TOBI experience. While there are more reports of patients reporting signs and symptoms of oto- or vestibulotoxicity as seen in Table 52*, the frequencies and the safety database is small to make definitive conclusions about the association between CHF 1538 use and ototoxicity. The Medical Officer believes that further monitoring for these auditory events need to be done.*

As one of the Clinical Comments in the Complete Response issued to the Applicant pertains to the submission of the full audiometric results/data from the trials, this issue will be discussed in a later Section.

Table 52. TEAEs Indicative of Ototoxicity or Vestibular Toxicity

TEAE (Oto- or Vestibulotoxicity	CHF 1538 (N=190) (%)	Placebo (N=115) (%)
Dizziness	*2 (1.1%)*	*1 (1%)*
Vertigo	*2 (1.1%)*	*0*
Audiogram abnormal	*1 (0.5%)*	*1 (0.9%)*
Acoustic stimulation tests abnormal	*1 (0.5%)*	*0*

Source: Adapted from NDA 201820. SD No. 0. Section 5.3.5.3 Reports of Analyses of Data from More than One Study – ISS Tables. 2010. Table 2. p. 11-16.

Nephrotoxicity

No relationship between inhaled tobramycin and worsened renal laboratory parameters was noted from the Dr. Shrimant Mishra's review on changes in serum creatinine and blood urea nitrogen (BUN) observed in the three trials.

Neuromuscular Weakness

No safety signals related to neuromuscular weakness were observed from the safety data. Safety data that may reflect AEs (weakness, asthenia, general weakness) related to neuromuscular weakness is extremely limited and prone to investigator error and reporting preference. Only the 1 case (0.5%) of asthenia was reported in the CHF 1538 group and 3 cases (3%) were reported in the placebo group.

Bronchospasm

Only one case of bronchospasm was reported in a 15 year old male receiving CHF 1538 in the pooled safety data from the three trials. However, in all three trials, monitoring for bronchospasm, whether through subjective report or through pulmonary function test verification, was not specified. Therefore, while the limited data indicates no clear signal for bronchospasm, this observation may not be conclusive.

Medical Officer Comment:
The Medical Officer believe that safety data from the three trials do not reveal any safety signal related to the four primary safety concerns. The concern for these potential safety concerns were based on safety concerns from systemic administration of aminoglycosides, including tobramycin. With minimal systemic absorption of inhaled tobramycin, the Medical Officer believes that these concerns are, at best, theoretical.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 53 lists adverse reactions occurring more in and reported in >5% of the patients in the CHF 1538 group compared to placebo in the safety population. Table 48 lists all the TEAEs reported in the integrated safety population. Appendix F organizes these reported TEAEs by SOC. Overall there were more patients in the placebo arm (88%) reporting at least one TEAE compared to the CHF 1538 arm (79%).

As can be seen in Appendix F, a significant proportion of the reported TEAEs in both groups are classified under the SOC Respiratory, Thoracic and Mediastinal Disorders (63.5% in the placebo group vs 58% in the CHF 1538 group). The most common TEAEs reported under these SOC are cough (placebo (P) 53.9% vs. CHF 1538 (C) 45.3%), productive cough (P 35% vs C 33%) and rales (P 16% vs C 19%).

The next SOC most TEAEs are reported under is General Disorders and Administration Site Conditions, with more TEAEs reported in the placebo group (47%) compared to the CHF 1538 group (36.3%). This SOC includes TEAEs reflecting the general state of the patient's CF (i.e. condition aggravated, exercise tolerance, hyperthermia).

The next most common SOC under which TEAEs are classified is the Infections and Infestations SOC, more common in the placebo group (43.5%) vs the CHF 1538 group (30.5%). The most frequently reported TEAEs in this SOC are rhinitis (13% (P) vs 7% (C)), nasopharyngitis (7% vs 4%) and pharyngitis (5.2% vs 5.3%).

Table 53. Treatment Emergent Adverse Events (TEAEs) Occurring in > 5% of Patients in Trials CT01 and CT02 : Integrated Safety Population

Treatment-Emergent Adverse Event (by PT[1])	CHF 1538 N=190	PLACEBO N=115
Number (and %) of Patients with at least one TEAE	**150 (79%)**	**101 (88%)**
Forced expiratory volume decreased	59 (31%)	33 (29%)
Rales	36 (19%)	18 (16%)
Red blood cell sedimentation rate increased	16 (8%)	6 (5%)
Dysphonia	11 (6%)	2 (2%)

[1] Preferred Term
Source: Module 5.3.5.3, ISS Tables, Table 2

Medical Officer Comment:
The imbalance in the number of TEAEs reported in these three SOCs likely implies that the placebo group experiences either an overall worsening status of their underlying CF

and/or a higher number of pulmonary exacerbations. The Medical Officer believes that this trend appears to reflect the relative effectiveness of CHF 1538 in improving the overall status of the underlying CF.

The Medical Officer notes that most of the TEAEs indicative of airway hypersensitivity or irritation to the study drug were not more significantly reported in the CHF 1538 group compared to the placebo group as can be seen in the following table:

Table 54. TEAEs Indicative of Hypersensitivity or Irritation

TEAE (Airway Hypersensitivity/Irritation)	***CHF 1538 (N=190) (%)***	***Placebo (N=115)***
Cough	*86 (45%)*	*62 (54%)*
Productive Cough	*62 (33%)*	*40 (35%)*
Rhinitis	*13 (7%)*	*15 (13%)*
Dysphonia	*11 (6%)*	*2 (2%)*
Pharyngitis	*10 (5%)*	*6 (5%)*
Wheezing	*10 (5%)*	*4 (3.5%)*
Nasopharyngitis	*8 (4)*	*8 (7%)*
Dyspnoea	*6 (3%)*	*8 (7%)*
Epistaxis	*6 (3%)*	*0*
Pharyngolaryngeal Pain	*5 (3%)*	*1(1%)*
Bronchospasm	*1 (0.5%)*	*0*

Source: Adapted from NDA 201820. SD No. 0. Section 5.3.5.3 Reports of Analyses of Data from More than One Study – ISS Tables. 2010. Table 2. p. 11-16.

Except for dysphonia, wheezing and epistaxis, most of these TEAEs were more markedly reported in the placebo group. The Medical Officer is reassured by this trend considering that CHF 1538 has a higher tobramycin concentration and a higher osmolality (for formulations used in the trials and the to-be-marketed product) compared to the reference drug TOBI.

Regarding TEAEs indicating airway hypersensitivity/airway irritation, the Medical Officer notes that the TEAEs of dysphonia and epistaxis are more markedly reported in the CHF 1538 group, warranting closer monitoring for these TEAEs during the postmarketing stage.

As relates to labeling, the Medical Officer, with the Review Team, would select TEAEs likely associated with the use of CHF 1538, reflecting its safety profile demonstrated in the trials.

Table 55. TEAEs Reported in the Integrated Safety Population

Treatment-Emergent Adverse Event (TEAE) (by PT[1])	CHF 1538 N=190	PLACEBO N=115
Total number of TEAEs	791	607
Number of Patients with at least one TEAE	150 (78.9%)	101 (87.8%)
Cough	86 (45.3%)	62 (53.9%)
Productive cough	62 (32.6%)	40 (34.8%)
Forced expiratory volume decreased	59 (31.1%)	33 (28.7%)
Rales	36 (18.9%)	18 (15.7%)
Exercise tolerance decreased	33 (17.4%)	24 (20.9%)
Pyrexia	31 (16.3%)	23 (20.0%)
Condition aggravated	25 (13.2%)	25 (21.7%)
Respiratory rate increased	20 (10.5%)	15 (13.0%)
Weight decreased	19 (10.0%)	12 (10.4%)
Red blood cell sedimentation rate increased	16 (8.4%)	6 (5.2%)
Rhinitis	13 (6.8%)	15 (13.0%)
Dysphonia	11 (5.8%)	2 (1.7%)
Crepitations	10 (5.3%)	11 (9.6%)
Pharyngitis	10 (5.3%)	6 (5.2%)
Viral infection	10 (5.3%)	5 (4.3%)
Wheezing	10 (5.3%)	4 (3.5%)
Haemoptysis	9 (4.7%)	6 (5.2%)
Nasopharyngitis	8 (4.2%)	8 (7.0%)
Dyspnoea	6 (3.2%)	8 (7.0%)
Sputum abnormal	6 (3.2%)	4 (3.5%)
Epistaxis	6 (3.2%)	0 (0.0%)
Influenza	5 (2.6%)	2 (1.7%)
Pharyngolaryngeal pain	5 (2.6%)	2 (1.7%)
Bronchitis	5 (2.6%)	1 (0.9%)
Leukocytosis	4 (2.1%)	3 (2.6%)
Tonsillitis	4 (2.1%)	0 (0.0%)

Treatment-Emergent Adverse Event (TEAE) (by PT)	CHF 1538 N=190	PLACEBO N=115
Hyperthermia	3 (1.6%)	3 (2.6%)
Vomiting	3 (1.6%)	3 (2.6%)
Herpes simplex	3 (1.6%)	2 (1.7%)
White blood cell count increased	3 (1.6%)	2 (1.7%)
Diarrhoea	3 (1.6%)	1 (0.9%)
Respiratory tract infection	3 (1.6%)	1 (0.9%)
Eosinophilia	3 (1.6%)	0 (0.0%)
Immunoglobulins increased	3 (1.6%)	0 (0.0%)
Headache	2 (1.1%)	6 (5.2%)
Abdominal pain	2 (1.1%)	3 (2.6%)
Sinusitis	2 (1.1%)	3 (2.6%)
Nausea	2 (1.1%)	2 (1.7%)
Transaminases increased	2 (1.1%)	2 (1.7%)
Aspartate aminotransferase increased	2 (1.1%)	1 (0.9%)
Body temperature increased	2 (1.1%)	1 (0.9%)
Chest pain	2 (1.1%)	1 (0.9%)
Dizziness	2 (1.1%)	1 (0.9%)
Oxygen saturation decreased	2 (1.1%)	1 (0.9%)
Urticaria	2 (1.1%)	1 (0.9%)
Abdominal pain upper	2 (1.1%)	0 (0.0%)
Liver function test abnormal	2 (1.1%)	0 (0.0%)
Varicella	2 (1.1%)	0 (0.0%)
Vertigo	2 (1.1%)	0 (0.0%)
Tachycardia	1 (0.5%)	4 (3.5%)
Asthenia	1 (0.5%)	3 (2.6%)
Blood glucose increased	1 (0.5%)	2 (1.7%)
Bronchopneumonia	1 (0.5%)	2 (1.7%)
Conjunctivitis	1 (0.5%)	2 (1.7%)
Hyperglycaemia	1 (0.5%)	2 (1.7%)

Treatment-Emergent Adverse Event (TEAE) (by PT)	CHF 1538 N=190	PLACEBO N=115
Increased viscosity of bronchial secretion	1 (0.5%)	2 (1.7%)
Neutrophil count increased	1 (0.5%)	2 (1.7%)
Acute tonsillitis	1 (0.5%)	1 (0.9%)
Alanine aminotransferase increased	1 (0.5%)	1 (0.9%)
Anaemia	1 (0.5%)	1 (0.9%)
Audiogram abnormal	1 (0.5%)	1 (0.9%)
Blood creatinine increased	1 (0.5%)	1 (0.9%)
Drug hypersensitivity	1 (0.5%)	1 (0.9%)
Electrophoresis protein abnormal	1 (0.5%)	1 (0.9%)
Lymphadenitis	1 (0.5%)	1 (0.9%)
Polypectomy	1 (0.5%)	1 (0.9%)
Respiratory tract infection viral	1 (0.5%)	1 (0.9%)
Stomatitis	1 (0.5%)	1 (0.9%)
Throat irritation	1 (0.5%)	1 (0.9%)
Upper respiratory tract infection	1 (0.5%)	1 (0.9%)
Acoustic stimulation tests abnormal	1 (0.5%)	0 (0.0%)
Arthralgia	1 (0.5%)	0 (0.0%)
Aspergillosis	1 (0.5%)	0 (0.0%)
Back pain	1 (0.5%)	0 (0.0%)
Blood albumin decreased	1 (0.5%)	0 (0.0%)
Bronchospasm	1 (0.5%)	0 (0.0%)
Burkholderia cepacia infection	1 (0.5%)	0 (0.0%)
Cardiomyopathy	1 (0.5%)	0 (0.0%)
Cheilosis	1 (0.5%)	0 (0.0%)
Conjunctivitis infective	1 (0.5%)	0 (0.0%)
Cor pulmonale chronic	1 (0.5%)	0 (0.0%)
Culture urine positive	1 (0.5%)	0 (0.0%)
Dermatitis allergic	1 (0.5%)	0 (0.0%)
Diabetes mellitus inadequate control	1 (0.5%)	0 (0.0%)

Treatment-Emergent Adverse Event (TEAE) (by PT)	CHF 1538 N=190	PLACEBO N=115
Dyspepsia	1 (0.5%)	0 (0.0%)
Dysphagia	1 (0.5%)	0 (0.0%)
Eczema	1 (0.5%)	0 (0.0%)
Enterovirus infection	1 (0.5%)	0 (0.0%)
Eosinophil count abnormal	1 (0.5%)	0 (0.0%)
Flatulence	1 (0.5%)	0 (0.0%)
Gastritis	1 (0.5%)	0 (0.0%)
Glossitis	1 (0.5%)	0 (0.0%)
Gynaecomastia	1 (0.5%)	0 (0.0%)
Haemolytic anaemia	1 (0.5%)	0 (0.0%)
Hand fracture	1 (0.5%)	0 (0.0%)
Hepatitis C	1 (0.5%)	0 (0.0%)
Hepatosplenomegaly	1 (0.5%)	0 (0.0%)
Intestinal obstruction	1 (0.5%)	0 (0.0%)
Leukopenia	1 (0.5%)	0 (0.0%)
Migraine	1 (0.5%)	0 (0.0%)
Nasal congestion	1 (0.5%)	0 (0.0%)
Oral candidiasis	1 (0.5%)	0 (0.0%)
Palpitations	1 (0.5%)	0 (0.0%)
Pancreatitis acute	1 (0.5%)	0 (0.0%)
Platelet count decreased	1 (0.5%)	0 (0.0%)
Pneumonia	1 (0.5%)	0 (0.0%)
Pneumonia mycoplasmal	1 (0.5%)	0 (0.0%)
Radius fracture	1 (0.5%)	0 (0.0%)
Rash	1 (0.5%)	0 (0.0%)
Red blood cell sedimentation rate abnormal	1 (0.5%)	0 (0.0%)
Red blood cell sedimentation rate decreased	1 (0.5%)	0 (0.0%)
Rhinitis allergic	1 (0.5%)	0 (0.0%)
Rhinorrhoea	1 (0.5%)	0 (0.0%)

Treatment-Emergent Adverse Event (TEAE) (by PT)	CHF 1538 N=190	PLACEBO N=115
Salivary hypersecretion	1 (0.5%)	0 (0.0%)
Seasonal allergy	1 (0.5%)	0 (0.0%)
Seborrhoeic dermatitis	1 (0.5%)	0 (0.0%)
Sputum discoloured	1 (0.5%)	0 (0.0%)
Urinary tract infection	1 (0.5%)	0 (0.0%)
Viral sinusitis	1 (0.5%)	0 (0.0%)
Herpangina	0 (0.0%)	3 (2.6%)
Candidiasis	0 (0.0%)	2 (1.7%)
Ear infection	0 (0.0%)	2 (1.7%)
Haematuria	0 (0.0%)	2 (1.7%)
Mumps	0 (0.0%)	2 (1.7%)
Nasal polyps	0 (0.0%)	2 (1.7%)
Platelet count increased	0 (0.0%)	2 (1.7%)
Respiratory failure	0 (0.0%)	2 (1.7%)
Anorexia	0 (0.0%)	1 (0.9%)
Bronchitis acute	0 (0.0%)	1 (0.9%)
Bronchitis bacterial	0 (0.0%)	1 (0.9%)
Cholelithiasis	0 (0.0%)	1 (0.9%)
Chronic sinusitis	0 (0.0%)	1 (0.9%)
Constipation	0 (0.0%)	1 (0.9%)
Depression	0 (0.0%)	1 (0.9%)
Distal intestinal obstruction syndrome	0 (0.0%)	1 (0.9%)
Dysgeusia	0 (0.0%)	1 (0.9%)
Fungal skin infection	0 (0.0%)	1 (0.9%)
Giardiasis	0 (0.0%)	1 (0.9%)
Heat stroke	0 (0.0%)	1 (0.9%)
Hospitalization	0 (0.0%)	1 (0.9%)
Hypochromic anaemia	0 (0.0%)	1 (0.9%)
Laryngitis	0 (0.0%)	1 (0.9%)
Lower respiratory tract inflammation	0 (0.0%)	1 (0.9%)
Nasal vestibulitis	0 (0.0%)	1 (0.9%)
Obstructive airways disorder	0 (0.0%)	1 (0.9%)
Oesophagitis	0 (0.0%)	1 (0.9%)
Otitis media	0 (0.0%)	1 (0.9%)
Pain in extremity	0 (0.0%)	1 (0.9%)
Petechiae	0 (0.0%)	1 (0.9%)
Post procedural haemorrhage	0 (0.0%)	1 (0.9%)
Pruritus	0 (0.0%)	1 (0.9%)
Rhonchi	0 (0.0%)	1 (0.9%)
Somnolence	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
Tinea versicolour	0 (0.0%)	1 (0.9%)
Tracheobronchitis	0 (0.0%)	1 (0.9%)
Vulvovaginal mycotic infection	0 (0.0%)	1 (0.9%)
White blood cell count abnormal	0 (0.0%)	1 (0.9%)

[1] preferred term
Source: Module 5.3.5.1, CT01 Study Report Body, Table 131 and Module 5.3.5.1, CT02 Study Report Body, Table 280

Source: NDA 201820. SD No. 0. Section 5.3.5.3 Reports of Analyses of Data from More than One Study – ISS Tables. 2010. Table 2. p. 11-16.

7.4.2 Laboratory Findings

Please refer to Dr. Shrimant Mishra's review.

7.4.3 Vital Signs

Please refer to Dr. Shrimant Mishra's review.

7.4.4 Electrocardiograms (ECGs)

Please refer to Dr. Shrimant Mishra's review.

7.4.5 Special Safety Studies/Clinical Trials

The Complete Response Letter includes two Clinical Comments to which the Applicant has responded through communications and a meeting with the Division.

7.4.5.1. First Additional Clinical Comment

Quote from CRL: *Provide full audiometric results, if available, for trials CT-01, CT-02, and CT-03. If full audiometric results are not available for all sites, we request that you provide such information for the sites from which the data can be obtained. This would include decibel thresholds recorded at every frequency tested for both ears 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 are unavailable, then any future assessments of ototoxicity (including labeling for ototoxicity) will be based on what has already been provided in the NDA.*

Table 56. Regulatory History for the First Additional Clinical Comment

Date	Description
25 August 2011	Complete Response Letter received by Chiesi
21 November 2011 (SN 0032)	Sponsor submission: Type A Meeting Package
14 December 2011	Type A Meeting responses received by Chiesi (via email)
16 December 2011	Type A Meeting held between Chiesi and FDA
09 February 2012	Official minutes received by Chiesi from FDA, in which FDA accepted that the assessment of ototoxicity will be based on previously-submitted data.

Ototoxicity is recognized as a systemic toxicity of tobramycin. Pharmacokinetic profiles of CHF 1538 and TOBI® indicate comparable systemic exposure and relative bioavailability, and the link between these two profiles was presented clearly in the NDA (reference Module 5.3.1.2, Study Report Body CP01). Additionally, Chiesi's proposed label warns of the potential risk of ototoxicity even though it was not evidenced in clinical studies. The proposed label for CHF 1538 is therefore consistent with the label for TOBI and the class effect concerning the potential risk of ototoxicity known for aminoglycosides.

During the Type A Meeting held between Chiesi and FDA on 16 December 2011 it was agreed that the assessment of ototoxicity of CHF 1538 would be based on what has already been submitted in the NDA, especially in light of the fact that the clinical studies were performed several years ago and full audiometric results are not available.

Medical Officer Comment:
The Medical Officer finds that the difficulty in obtaining source data for the audiometric tests conducted during the trials, as specified in the Complete Response letter, expressed by the Applicant is acceptable.

As demonstrated by the number of TEAEs reported under ototoxicity or vestibulotoxicity (see Table 52*), no clear signs of ototoxicity or vestibulotoxicity were observed from safety data from these trials. However, this data is limited by the fact that while bone and air conduction tests were performed, documentation was poor and inconsistent. Moreover, standardization of testing procedures and consistent monitoring and reporting were limited. Therefore, the Medical Officer believes that the limited safety data from the integrated safety population do not suggest a signal for ototoxicity when CHF 1538 is used.*

The Medical Officer, however, recommends postmarketing monitoring for ototoxicity as there appears to have a nonsignificant trend of increased reporting of auditory-related TEAEs (i.e. deafness, vertigo, dizziness) in the CHF 1538-treated group.

7.4.5.2. Second Additional Clinical Comment

Quote from CRL: *For trial CT-03, provide tables describing mean and median changes in values over the course of the study, 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 not clinically significant for each of the laboratory measurements?).*

Table 57. Regulatory History for the Second Additional Clinical Comment

Date	Description
25 August 2011	Complete Response Letter received by Chiesi
21 November 2011 (SN 0032)	Sponsor submission: Type A Meeting Package
14 December 2011	Type A Meeting responses received by Chiesi (via email)
16 December 2011	Type A Meeting held between Chiesi and FDA
09 February 2012	Official minutes received by Chiesi from FDA, in which FDA

The requested tables and guide to interpretation were provided in the Type A Meeting Package (See Module 1.6.2.11.3 [SN 0032]).

During the 16 December 2011 Type A Meeting it was further explained that the reference values for each local laboratory were submitted as part of the original NDA submission SDTM lb and supplb datasets and in the Study CT03 CSR Appendix 16.2.8.3 and 16.2.8.4.

Medical Officer Comments:
The Medical Officer finds that the concern expressed by the Division is sufficiently addressed by previous communications with the Division and by this submission.

7.4.6 Immunogenicity

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.5.2 Time Dependency for Adverse Events

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.5.3 Drug-Demographic Interactions

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.5.4 Drug-Disease Interactions

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.5.5 Drug-Drug Interactions

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please refer to Dr. Shrimant Mishra's review. No new information was submitted in the Applicant's Complete Response submission discussing this issue.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

8.1. Postmarketing Safety Experience

The Applicant submitted a summary of the postmarketing safety experience for CHF 1538 outside the United States and the postmarketing safety experience for TOBI in the US that is available to the general public. Information regarding the postmarketing safety of CHF 1538 and the reference listed drug, TOBI®, was obtained from different sources that include spontaneous reports of adverse drug reactions (ADRs) received by the Applicant and its parent company, Chiesi Farmaceutici S.p.A.-Italy, review of published literature on tobramycin, and a search of the FDA Adverse Events Reporting System (AERS).

According to the Applicant, since approval, there have been changes to the TOBI label that classifies tinnitus as a sentinel symptom associated with ototoxicity. The labeling revisions include a warning regarding hearing loss and the recommendation for physicians to consider audiograms for patients at risk.

8.1.1. Spontaneous Reports of Adverse Drug Reactions (ADRs)

Chiesi Farmaceutici S.p.A.-Italy has been receiving spontaneous reports of ADRs from several countries where CHF 1538 has been approved. The following information has been collected during the period covering 09 April 2006 to 31 December 2011. From Table 58, a total of 45 ADRs have been reported to Chiesi and is summarized in the following table. These ADRs were passively reported to the Applicant following an estimated exposure of 2.3 million patient-treatment days to CHF 1538 at the proposed dose of 300 mg. The exposure was calculated from the number of unit drug sold in countries where CHF 1538 is already marketed.

Table 58. ADRs Reported to the Applicant

System Organ Class PT	Serious ADRs		Non-Serious ADRs		Total
	U[1]	L[2]	U	L	
Infections and infestations					
Candidiasis	-	-	-	1	1
Nasopharyngitis	-	-	1	-	1
Psychiatric disorders					
Illusion	1	-	-	-	1
Nervous system disorders					
Dysgeusia	-	-	-	1	1
Loss of consciousness	-	-	1	-	1
Ear and labyrinth disorders					
Tinnitus	-	-	-	1	1
Vertigo	-	-	-	1	1
Vascular disorders					
Pallor	-	-	1	-	1
Respiratory, thoracic and mediastinal disorders					
Bronchospasm	-	6	-	-	6
Cough	-	1	-	4	5
Dysphonia	-	-	-	1	1
Dyspnoea	-	3	-	2	5
Oropharyngeal pain	-	1	1[3]	-	2
Respiratory failure	-	1	-	-	1
Throat irritation	-	-	1	-	1
Wheezing	1	-	-	-	1
Gastrointestinal disorders					
Mouth ulceration	-	-	-	1	1
Nausea	-	-	-	3	3
Retching	-	-	1	-	1
Salivary hypersecretion	-	-	-	1	1
Vomiting	-	-	-	1	1
Skin and subcutaneous tissue disorders					
Dermatitis	-	-	1	-	1
Pruritus	-	-	-	1	1
Rash	-	1	-	-	1
General disorders and administration site conditions					
Asthenia	-	-	-	1	1
Face oedema	1	-	-	-	1
Malaise	-	-	1	-	1
Investigations					
Creatinine urine increased	1	-	-	-	1
Drug level increased	1	-	-	-	1
Total	5	12	8	20	45

[1] unlabeled
[2] labeled
[3] "Oropharyngeal pain" considered unlisted due to its specificity as the reporter described "Sore throat".

Medical Officer Comment:
Among the ADRs reported to the Applicant, most of the ADRs reported are classified in the Respiratory, Thoracic, and Mediastinal Disorders SOC. In particular, bronchospasm, cough, dyspnea, and oropharngeal pain were most frequently reported. These ADRs

may represent airway hypersensitivity/irritation. However, the incidence of these ADRs could not be estimated well because of the lack of information on the exposed population. More importantly, the data from this data is non- comparative, limiting their utility in comparing safety between CHF 1538 and TOBI.

8.1.2. Adverse Events Reported to the AERS Database

A search of the AERS database was conducted for the duration between the fourth quarter of 1997 through the third quarter of 2011 using the search terms "TOBI" or "Tobramycin" and having the route of administration coded as "Resp". The Applicant assumes that the AEs reported in the database related to the reference listed drug, TOBI®, which is the only inhaled tobramycin marketed in the US.

The following table (Table 59) summarizes AEs reported 5 or more times in the AERS database.

Table 59. Unlabeled Adverse Events Reported 5 or More Times in the AERS Database

AE Term[1]	Number of Reports
ANTIBIOTIC LEVEL ABOVE THERAPEUTIC	5
BLOOD CREATININE INCREASED	16
BLOOD UREA INCREASED	5
BRONCHIECTASIS	7
C-REACTIVE PROTEIN INCREASED	5
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	6
CLOSTRIDIUM DIFFICILE COLITIS	7
CONDITION AGGRAVATED	17
DEATH	33
DEHYDRATION	11
DERMATITIS NOS	5
DISEASE PROGRESSION	6
DRUG INEFFECTIVE	10
DRUG INTERACTION	6
DRUG LEVEL INCREASED	12
DRUG MALADMINISTRATION	5
EOSINOPHILIA	5
FATIGUE	14
FEELING ABNORMAL	5
HEART RATE INCREASED	8
HYPONATRAEMIA	5
HYPOTENSION	10
HYPOXIA	6
INFECTION	9
MEDICATION ERROR	7
OXYGEN SATURATION DECREASED	8
PHARMACEUTICAL PRODUCT COMPLAINT	5
PNEUMONIA	5
PNEUMONIA NOS	7
POLLAKIURIA	5
PSEUDOMEMBRANOUS COLITIS	7
PSEUDOMONAS INFECTION	13
RENAL FAILURE	7

AE Term[1]	Number of Reports
RENAL FAILURE ACUTE	10
RENAL IMPAIRMENT	8
RESPIRATORY FAILURE	11
SEPSIS	5
SPUTUM CULTURE POSITIVE	5
STAPHYLOCOCCAL INFECTION	7
TACHYCARDIA	9
VESTIBULAR DISORDER	7
WHEEZING	8

[1] The AE terms presented represent the MedDRA coding of the verbatim term.

The search identified 1705 AEs between the fourth quarter of 1997 through the third quarter of 2011. The Applicant states that almost all AEs have been previously identified and are either labeled as possible side effects in the TOBI label or in the summary of product characteristics for CHF 1538.

Medical Officer Comment:
The AERS database includes reports from the public (physicians, healthcare providers, other concerned individuals who may want to file a complaint) of 15-day safety reports, unlabeled events and serious adverse events, regardless of assessment of causation. The most common AEs reported in the AERS that occurred with CHF 1538 intake were

- *deaths (33),*
- *condition aggravated (17),*
- *blood creatinine increased (16),*
- *pseudomonas infection (13),*
- *drug level increased (12).*

In particular, seven reports of psedomembranous colitis and seven reports of Clostridium difficile *colitis were received. While these cases could potentially be from the inadvertent ingestion of inhaled tobramycin, information on concomitant medications, in particular concomitant antibacterials, received by the patients with pseudomembranous or C. dificile colitis is lacking. The lack of this information precludes the Medical Officer in definitively attributing these AEs to CHF 1538 use. More information is needed to define causality. Therefore, analysis of the data from the AERS database is inconclusive unless additional information is provided.*

Overall, the postmarketing experience of CHF 1538 provided in the submission does not provide sufficient information to identify specific safety signals associated with CHF 1538 use. Information on CHF 1538's postmarketing safety experience informs the Medical Officer of several AEs that would require close monitoring.

9 Appendices

9.1 Literature Review/References

See Endnotes.

9.2 Labeling Recommendations

Please see Labeling and Product Information and Patient Information recommendations sent to the Applicant.

9.3 Advisory Committee Meeting

As this NDA is, in part, a 505(b)(2) application relying on information for TOBI, the reference drug, no Advisory Committee meeting was or will be held.

9.4 Baseline Demographic Characteristics of Patients Enrolled in Trials CT01, CT02, and CT03

Appendix A. Baseline Demographic Characteristics of Patients in Trial CT01

	CHF 1538 (n=29)	Placebo (n=30)
Gender		
Male	15 (51.7%)	17 (56.7%)
Female	14 (48.3%)	13 (43.3%)
p value	0.703	
Age (years)		
mean	11.0	14.2
Range	6.0-28.0	6.0-30.0
p value	0.024	
Age Group		
6-12 Years	19 (65.5%)	12 (40.0%)
13-17 Years	7 (24.1%)	11 (36.7%)
> 17 Years	3 (10.3%)	7 (23.3%)
p- value	0.132	
Weight (kg)		
mean	27.4	40.7
Range	15.0-69.0	18.0-99.0
p value	0.003	
Height (cm)		
mean	132.2	151.4
Range	102.0-172.0	113.0-118.0
p value	0.001	
BMI (kg/m^2)[2]		
mean	15	16.7
Range	10.9-23.9	11.5-31.6
p value	0.069	
Colonization with P. aeruginosa		
Chronic	22 (75.9%)	25 (83.3%)

	CHF 1538 (n=29)	Placebo (n=30)
First or Intermittent	7 (24.1%)	5 (16.7%)
p value	0.476	
Time from first CF[3] diagnosis (days)	29	30
N	29	30
mean	3343	3565
Range	103.0-10126.0	96.0-9240.0
p value	0.704	

Source: NDA 201820 SDN 0, Section 5.3.5.1.3, CT01 Study Report Body, Table 6

Appendix B. Baseline Demographic Characteristics of Patients in Trial CT02

Demographic Data	CHF 1538 (n=161)	Placebo (n=84)	Total: 245
Gender			
Male	89 (55.3%)	46 (54.8%)	135 (55.1%)
Female	72 (44.7%)	38 (45.2%)	110 (44.9%)
Total	161 (100%)	84 (100.0%)	245 (100.0%)
Chi Square	p= 0.938		
Age (years)			
Mean	14.8	14.7	14.8
Min/Max	6.0/31.0	6.0/45.0	6.0/45.0
Age in Classes (years)			
6-12	63 (39.1%)	37 (44%)	100 (40.8%)
13-17	47 (29.2%)	25 (29.8%)	72 (29.4%)
>17 yo	51 (31.7%)	22 (26.2%)	73 (29.8%)
Total	161 (100%)	84 (100%)	245 (100%)
Chi Square	P=.641		
Colonization with P. Aeruginosa			
Chronic	145 (90.1%)	68 (81.0%)	213 (86.9%)
First or Intermittent	16 (9.9%)	16 (19.0%)	32 (13.1%)
Total	161 (100.0%)	84 (100.0%)	245 (100.0%)
Time from Diagnosis (years)			
Mean	12.1	11.8	12.0
Min/max	1.0/27.0	1.0/27.0	1.0/27.0
Missing	0	0	0
Height (cm)			
Mean	151.7	150.9	151.4
Median	156.0	154.5	156.0
Range	107.0-188.0	115.0-191.0	107.0-191.0
Weight (kg)			
Mean	40.7	39.9	40.4
Median	41.4	37.0	40.5
Range	16.0-84.0	15.5-72.0	15.5-84.0
BMI (kg/m^2)			
Mean	16.9	16.8	16.9
Median	16.8	16.2	16.3
Range	11.8-24.3	11.7-24.9	11.7-24.9

Appendix C. Baseline Demographic Characteristics of Patients in Trial CT03

	CHF 1538 (N=158)	TOBI (N=163)	Total (N=321)
Sex			
Male	72 (45.6%)	84 (51.5%)	156 (48.6%)
Female	86 (54.4%)	79 (48.5%)	165 (51.4%)
Age (years)[1]			
Mean	15.89	15.58	15.73
Median	15.00	14.00	15.00
Min/Max	6.00/37.00	6.00/46.00	6.00/46.00
Age (years) (in classes)			
6-12	47 (29.7%)	56 (34.4%)	103 (32.1%)
13-17	54 (34.2%)	57 (35.0%)	111 (34.6%)
>17	57 (36.1%)	50 (30.7%)	107 (33.3%)
Height (cm)			
Mean	153.59	152.72	153.15
Median	157.00	158.00	157.00
Min/Max	111.00/195.00	104.00/190.00	104.00/195.00
Weight (kg)			
Mean	42.89	43.27	43.08
Median	44.40	43.00	44.00
Min/Max	16.00/87.00	15.00/97.00	15.00/97.00
BMI (kg/m^2)[2]			
Mean	17.56	17.70	17.63
Median	17.55	17.30	17.40
Min/Max	12.00/28.40	11.50/28.40	11.50/28.40
Time from diagnosis of chronic colonization of *P. aeruginosa* (years)[3]			
Mean	2.35	2.18	2.27
Median	0.31	0.36	0.33
Min/Max	0.02/20.15	0.02/22.04	0.02/22.04
Time from first CF diagnosis (years)[4]			
Mean	12.36	11.63	11.99
Median	11.80	10.90	11.40
Min/Max	1.10/32.80	1.10/32.00	1.10/32.80
Tobramycin MIC value (mcg/ml) (in classes)			
<16	145 (91.8%)	154 (94.5%)	299 (93.1%)
≥ 16	13 (8.2%)	8 (4.9%)	21 (6.5%)
Missing	0	1 (0.6%)	1 (0.3%)
FEV_1 % Predicted (in classes)			
<50	36 (22.8%)	38 (23.3%)	74 (23.1%)
≥50	122 (77.2%)	125 (76.7%)	247 (76.9%)
Use of RH Dnase[5]			
Yes	112 (70.9%)	114 (69.9%)	226 (70.4%)
No	46 (29.1%)	49 (30.1%)	95 (29.6%)

Appendix D. Formulae to Determine the Predicted Normal Values for Pulmonary Function Parameters in the Reanalysis of Study CT02

Pulmonary Function Parameters	Gender	Age (years)	Formulae to Determine Predicted Normal Values	Notes
FEV_1	Male	4-18[1]	FEV_1 predicted=$10^{-(5.86521-2.87294p)}$	p=$\log_{10}$h h=height in centimeters. if h is > 180cm, then h=180 cm if h is < 115 cm, then h=115cm
	Female	4-18[1]	FEV_1 predicted=$10^{-(5.60565-2.74136p)}$	
	Male	≥ 19[2,3]	FEV_1 predicted= 4.30H-0.029A-2.49	H=height in meters A=age in years For ages between 19 and 25 years, A=25 was used.
	Female	≥ 19[3]	FEV_1 predicted=3.95H-0.025A-2.60	
FVC[4]	Male	N/A	FVC predicted=exp [-12.2209155+ 2.6121724* log(ht) + 0.0908706*log(age)+ cubic spline for age]	
	Female	N/A	FVC predicted=exp [-11.20585589 + 2.43233063 * log(ht) + 0.02404024 *($age^{0.25}$)+ cubic spline for age]	
$FEF_{25-75\%}$[4]	Male	N/A	$FEF_{25-75\%}$=exp [-8.740202545+1.970003241* log(ht) -0.005123813*(age)+ cubic spline for age]	
	Female	N/A	$FEF_{25-75\%}$=exp [-8.052504398+1.848024261* log(ht) -0.008277853*(age)+ cubic spline for age]	

[1] The formula for FEV_1 for patients between 4 and 18 years of age was obtained from Appendices A and B of the MES LUNGTEST 1000 Spirometer User Manual [1, 2]
[2] N.B. Please refer to SN 0028, 02Aug11 CT02 Follow Up to 483 Response for the corrected version of the formula for males aged 19 to 70 years old.
[3] The formula for FEV_1 for patients 19 years of age and older was obtained from a paper by Quanjer, et al. [3]
[4] The formulas for both FVC and $FEF_{25-75\%}$ were obtained from a paper by Stanojevic, et al. [4].

Source: Resubmission Class 2. Serial Number 0035 (SD 38). Submitted 4/13/2012.Efficacy Information Amendment. Response to Complete Response Letter. p. 10

Appendix E. Patient Demographic Information for the Pivotal Phase 3 Trials for the Reference Drug TOBI

Patient Demographic and Stratification Data at Screening(ITT)

	PC-TNDS-002		PC-TNDS-003		Pooled(002/003)	
Number (%) of Patients	TOBI 109	Placebo 114	TOBI 149	Placebo 148	TOBI 258	Placebo 262
Gender:						
Male	63 (57.8)	59 (51.8)	86 (57.7)	73 (49.3)	149 (57.8)	132 (50.4)
Female	46 (42.2)	55 (48.2)	63 (42.3)	75 (50.7)	109 (42.2)	130 (49.6)
Mean Age in Years (STD)	20.5 (9.33)	19.8 (10.16)	21.0 (9.59)	21.2 (9.84)	20.8 (9.46)	20.6 (9.98)
Age Group:						
6 - < 13 years	26 (23.9)	30 (26.3)	29 (19.5)	31 (20.9)	55 (21.3)	61 (23.3)
13 - < 18 years	24 (22.0)	32 (28.1)	39 (26.2)	35 (23.6)	63 (24.4)	67 (25.6)
≥ 18 years	59 (54.1)	52 (45.6)	81 (54.4)	82 (55.4)	140 (54.3)	134 (51.1)
FEV_1 % Predicted:						
< 50%	50 (45.9)	56 (49.1)	72 (48.3)	72 (48.6)	122 (47.3)	128 (48.9)
≥ 50%	59 (54.1)	58 (50.9)	77 (51.7)	76 (51.4)	136 (52.7)	134 (51.1)
rhDNase Therapy						
No	24 (22.0)	28 (24.6)	36 (24.2)	30 (20.3)	60 (23.3)	58 (22.1)
Yes	85 (78.0)	86 (75.4)	113 (75.8)	118 (79.7)	198 (76.7)	204 (77.9)
Tobramycin baseline MIC (*P. aerug*)						
< 8 g/mL	95 (87.2)	98 (87.5)	123 (82.6)	125 (84.5)	218 (84.5)	223 (85.8)
≥ 8 g/mL	14 (12.8)	14 (12.5)	26 (17.4)	23 (15.5)	40 (15.5)	37 (14.2)

Appendix F. Summary of TEAEs by SOC: Integrated Safety Population

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	CHF 1538 (N=190)	PLACEBO (N=115)
Total number of TEAEs	791	607
Number of patients with at least one TEAE	150 (78.9%)	101 (87.8%)
Blood and Lymphatic System Disorders	**11 (5.8%)**	**6 (5.2%)**
Anaemia	1 (0.5%)	1 (0.9%)
Eosinophilia	3 (1.6%)	0 (0.0%)
Haemolytic anaemia	1 (0.5%)	0 (0.0%)
Hypochromic anaemia	0 (0.0%)	1 (0.9%)
Leukocytosis	4 (2.1%)	3 (2.6%)
Leukopenia	1 (0.5%)	0 (0.0%)
Lymphadenitis	1 (0.5%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
Cardiac Disorders	**4 (2.1%)**	**4 (3.5%)**
Cardiomyopathy	1 (0.5%)	0 (0.0%)
Cor pulmonale chronic	1 (0.5%)	0 (0.0%)
Palpitations	1 (0.5%)	0 (0.0%)
Tachycardia	1 (0.5%)	4 (3.5%)
Ear and Labyrinth Disorders	**2 (1.1%)**	**0 (0.0%)**
Vertigo	2 (1.1%)	0 (0.0%)
Eye Disorders	**1 (0.5%)**	**2 (1.7%)**
Conjunctivitis	1 (0.5%)	2 (1.7%)
Gastrointestinal Disorders	**18 (9.5%)**	**13 (11.3%)**
Abdominal pain	2 (1.1%)	3 (2.6%)
Abdominal pain upper	2 (1.1%)	0 (0.0%)
Cheilosis	1 (0.5%)	0 (0.0%)
Constipation	0 (0.0%)	1 (0.9%)
Diarrhoea	3 (1.6%)	1 (0.9%)
Distal intestinal obstruction syndrome	0 (0.0%)	1 (0.9%)
Dyspepsia	1 (0.5%)	0 (0.0%)

Treatment-Emergent Adverse Event (TEAE) (by SOC and PT)	CHF 1538 (N=190)	PLACEBO (N=115)
Dysphagia	1 (0.5%)	0 (0.0%)
Flatulence	1 (0.5%)	0 (0.0%)
Gastritis	1 (0.5%)	0 (0.0%)
Glossitis	1 (0.5%)	0 (0.0%)
Intestinal obstruction	1 (0.5%)	0 (0.0%)
Nausea	2 (1.1%)	2 (1.7%)
Oesophagitis	0 (0.0%)	1 (0.9%)
Pancreatitis acute	1 (0.5%)	0 (0.0%)
Salivary hypersecretion	1 (0.5%)	0 (0.0%)
Stomatitis	1 (0.5%)	1 (0.9%)
Vomiting	3 (1.6%)	3 (2.6%)
General Disorders and Administration Site Conditions	**69 (36.3%)**	**54 (47.0%)**
Asthenia	1 (0.5%)	3 (2.6%)
Chest pain	2 (1.1%)	1 (0.9%)
Condition aggravated	25 (13.2%)	25 (21.7%)
Crepitations	10 (5.3%)	11 (9.6%)
Exercise tolerance decreased	33 (17.4%)	24 (20.9%)
Hyperthermia	3 (1.6%)	3 (2.6%)
Pyrexia	31 (16.3%)	23 (20.0%)
Hepatobiliary Disorders	**1 (0.5%)**	**1 (0.9%)**
Cholelithiasis	0 (0.0%)	1 (0.9%)
Hepatosplenomegaly	1 (0.5%)	0 (0.0%)
Immune System Disorders	**2 (1.1%)**	**1 (0.9%)**
Drug hypersensitivity	1 (0.5%)	1 (0.9%)
Seasonal allergy	1 (0.5%)	0 (0.0%)
Infections and Infestations	**58 (30.5%)**	**50 (43.5%)**
Acute tonsillitis	1 (0.5%)	1 (0.9%)
Aspergillosis	1 (0.5%)	0 (0.0%)
Bronchitis	5 (2.6%)	1 (0.9%)

Treatment-Emergent Adverse Event (TEAE) (by SOC and PT)	CHF 1538 (N=190)	PLACEBO (N=115)
Bronchitis acute	0 (0.0%)	1 (0.9%)
Bronchitis bacterial	0 (0.0%)	1 (0.9%)
Bronchopneumonia	1 (0.5%)	2 (1.7%)
Burkholderia cepacia infection	1 (0.5%)	0 (0.0%)
Candidiasis	0 (0.0%)	2 (1.7%)
Chronic sinusitis	0 (0.0%)	1 (0.9%)
Conjunctivitis infective	1 (0.5%)	0 (0.0%)
Ear infection	0 (0.0%)	2 (1.7%)
Enterovirus infection	1 (0.5%)	0 (0.0%)
Fungal skin infection	0 (0.0%)	1 (0.9%)
Giardiasis	0 (0.0%)	1 (0.9%)
Hepatitis C	1 (0.5%)	0 (0.0%)
Herpangina	0 (0.0%)	3 (2.6%)
Herpes simplex	3 (1.6%)	2 (1.7%)
Influenza	5 (2.6%)	2 (1.7%)
Laryngitis	0 (0.0%)	1 (0.9%)
Mumps	0 (0.0%)	2 (1.7%)
Nasal vestibulitis	0 (0.0%)	1 (0.9%)
Nasopharyngitis	8 (4.2%)	8 (7.0%)
Oral candidiasis	1 (0.5%)	0 (0.0%)
Otitis media	0 (0.0%)	1 (0.9%)
Pharyngitis	10 (5.3%)	6 (5.2%)
Pneumonia	1 (0.5%)	0 (0.0%)
Pneumonia mycoplasmal	1 (0.5%)	0 (0.0%)
Respiratory tract infection	3 (1.6%)	1 (0.9%)
Respiratory tract infection viral	1 (0.5%)	1 (0.9%)
Rhinitis	13 (6.8%)	15 (13.0%)
Sinusitis	2 (1.1%)	3 (2.6%)
Tinea versicolour	0 (0.0%)	1 (0.9%)

Treatment-Emergent Adverse Event (TEAE) (by SOC and PT)	CHF 1538 (N=190)	PLACEBO (N=115)
Tonsillitis	4 (2.1%)	0 (0.0%)
Tracheobronchitis	0 (0.0%)	1 (0.9%)
Upper respiratory tract infection	1 (0.5%)	1 (0.9%)
Urinary tract infection	1 (0.5%)	0 (0.0%)
Varicella	2 (1.1%)	0 (0.0%)
Viral infection	10 (5.3%)	5 (4.3%)
Viral sinusitis	1 (0.5%)	0 (0.0%)
Vulvovaginal mycotic infection	0 (0.0%)	1 (0.9%)
Injury, Poisoning and Procedural Complications	**2 (1.1%)**	**2 (1.7%)**
Hand fracture	1 (0.5%)	0 (0.0%)
Heat stroke	0 (0.0%)	1 (0.9%)
Post procedural haemorrhage	0 (0.0%)	1 (0.9%)
Radius fracture	1 (0.5%)	0 (0.0%)
Investigations	**90 (47.4%)**	**56 (48.7%)**
Acoustic stimulation tests abnormal	1 (0.5%)	0 (0.0%)
Alanine aminotransferase increased	1 (0.5%)	1 (0.9%)
Aspartate aminotransferase increased	2 (1.1%)	1 (0.9%)
Audiogram abnormal	1 (0.5%)	1 (0.9%)
Blood albumin decreased	1 (0.5%)	0 (0.0%)
Blood creatinine increased	1 (0.5%)	1 (0.9%)
Blood glucose increased	1 (0.5%)	2 (1.7%)
Body temperature increased	2 (1.1%)	1 (0.9%)
Culture urine positive	1 (0.5%)	0 (0.0%)
Electrophoresis protein abnormal	1 (0.5%)	1 (0.9%)
Eosinophil count abnormal	1 (0.5%)	0 (0.0%)
Forced expiratory volume decreased	59 (31.1%)	33 (28.7%)
Immunoglobulins increased	3 (1.6%)	0 (0.0%)
Liver function test abnormal	2 (1.1%)	0 (0.0%)
Neutrophil count increased	1 (0.5%)	2 (1.7%)

Treatment-Emergent Adverse Event (TEAE) (by SOC and PT)	CHF 1538 (N=190)	PLACEBO (N=115)
Oxygen saturation decreased	2 (1.1%)	1 (0.9%)
Platelet count decreased	1 (0.5%)	0 (0.0%)
Platelet count increased	0 (0.0%)	2 (1.7%)
Red blood cell sedimentation rate abnormal	1 (0.5%)	0 (0.0%)
Red blood cell sedimentation rate decreased	1 (0.5%)	0 (0.0%)
Red blood cell sedimentation rate increased	16 (8.4%)	6 (5.2%)
Respiratory rate increased	20 (10.5%)	15 (13.0%)
Sputum abnormal	6 (3.2%)	4 (3.5%)
Transaminases increased	2 (1.1%)	2 (1.7%)
Weight decreased	19 (10.0%)	12 (10.4%)
White blood cell count abnormal	0 (0.0%)	1 (0.9%)
White blood cell count increased	3 (1.6%)	2 (1.7%)
Metabolism and Nutrition Disorders	**2 (1.1%)**	**2 (1.7%)**
Anorexia	0 (0.0%)	1 (0.9%)
Diabetes mellitus inadequate control	1 (0.5%)	0 (0.0%)
Hyperglycaemia	1 (0.5%)	2 (1.7%)
Musculoskeletal and Connective Tissue Disorders	**2 (1.1%)**	**1 (0.9%)**
Arthralgia	1 (0.5%)	0 (0.0%)
Back pain	1 (0.5%)	0 (0.0%)
Pain in extremity	0 (0.0%)	1 (0.9%)
Nervous System Disorders	**5 (2.6%)**	**9 (7.8%)**
Dizziness	2 (1.1%)	1 (0.9%)
Dysgeusia	0 (0.0%)	1 (0.9%)
Headache	2 (1.1%)	6 (5.2%)
Migraine	1 (0.5%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (0.9%)
Psychiatric Disorders	**0 (0.0%)**	**1 (0.9%)**
Depression	0 (0.0%)	1 (0.9%)

Treatment-Emergent Adverse Event (TEAE) (by SOC and PT)	CHF 1538 (N=190)	PLACEBO (N=115)
Renal and Urinary Disorders	**0 (0.0%)**	**2 (1.7%)**
Haematuria	0 (0.0%)	2 (1.7%)
Reproductive System and Breast Disorders	**1 (0.5%)**	**0 (0.0%)**
Gynaecomastia	1 (0.5%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	**110 (57.9%)**	**73 (63.5%)**
Bronchospasm	1 (0.5%)	0 (0.0%)
Cough	86 (45.3%)	62 (53.9%)
Dysphonia	11 (5.8%)	2 (1.7%)
Dyspnoea	6 (3.2%)	8 (7.0%)
Epistaxis	6 (3.2%)	0 (0.0%)
Haemoptysis	9 (4.7%)	6 (5.2%)
Increased viscosity of bronchial secretion	1 (0.5%)	2 (1.7%)
Lower respiratory tract inflammation	0 (0.0%)	1 (0.9%)
Nasal congestion	1 (0.5%)	0 (0.0%)
Nasal polyps	0 (0.0%)	2 (1.7%)
Obstructive airways disorder	0 (0.0%)	1 (0.9%)
Pharyngolaryngeal pain	5 (2.6%)	2 (1.7%)
Productive cough	62 (32.6%)	40 (34.8%)
Rales	36 (18.9%)	18 (15.7%)
Respiratory failure	0 (0.0%)	2 (1.7%)
Rhinitis allergic	1 (0.5%)	0 (0.0%)
Rhinorrhoea	1 (0.5%)	0 (0.0%)
Rhonchi	0 (0.0%)	1 (0.9%)
Sputum discoloured	1 (0.5%)	0 (0.0%)
Throat irritation	1 (0.5%)	1 (0.9%)
Wheezing	10 (5.3%)	4 (3.5%)

Treatment-Emergent Adverse Event (TEAE) (by SOC and PT)	CHF 1538 (N=190)	PLACEBO (N=115)
Skin and Subcutaneous Tissue Disorders	**6 (3.2%)**	**2 (1.7%)**
Dermatitis allergic	1 (0.5%)	0 (0.0%)
Eczema	1 (0.5%)	0 (0.0%)
Petechiae	0 (0.0%)	1 (0.9%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	1 (0.5%)	0 (0.0%)
Seborrhoeic dermatitis	1 (0.5%)	0 (0.0%)
Urticaria	2 (1.1%)	1 (0.9%)
Surgical and Medical Procedures	**1 (0.5%)**	**2 (1.7%)**
Hospitalization	0 (0.0%)	1 (0.9%)
Polypectomy	1 (0.5%)	1 (0.9%)

[1] system organ class
[2] preferred term
Source: Module 5.3.5.1, CT01 Study Report Body, Table 130 and Module 5.3.5.1, CT02 Study Report Body, Table 279

Source: NDA 201820. SD No. 0. Section 5.3.5.3 Reports of Analyses of Data from More than One Study – ISS Tables. 2010. Table 2. p. 4-10.

[1] MacDougall C. Chapter 54. Aminoglycosides. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011.
<http://www.accessmedicine.com/content.aspx?aID=16677657. Accessed May 21, 2012.>
[2] <http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80240935>
[3] Resubmission Class 2. Serial Number 0035 (SD 38). Submitted 4/13/2012.Efficacy Information Amendment. Response to Complete Response Letter. p. 13-17.
[4] Pediatr Pathol Mol Med.2002 May-Jun;21(3):343-52
[5] Pediatrics Vol. 70 No. 5 November 1, 1982 pp. 728 -741
[6] *Clin Genet 2000: 57: 56–60*
[7] NDA 50753. Clinical Review of Efficacy and Safety of TOBI. December 1997.

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/s/

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