CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

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*

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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

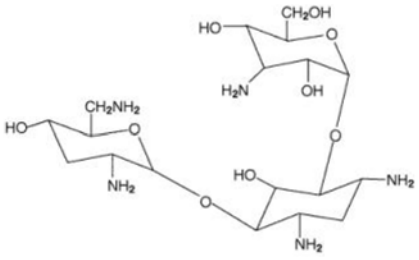
None.

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

	CHF 1538	TOBI	Point Estimate	Statistical Comparison [90% CI]
PLASMA				
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

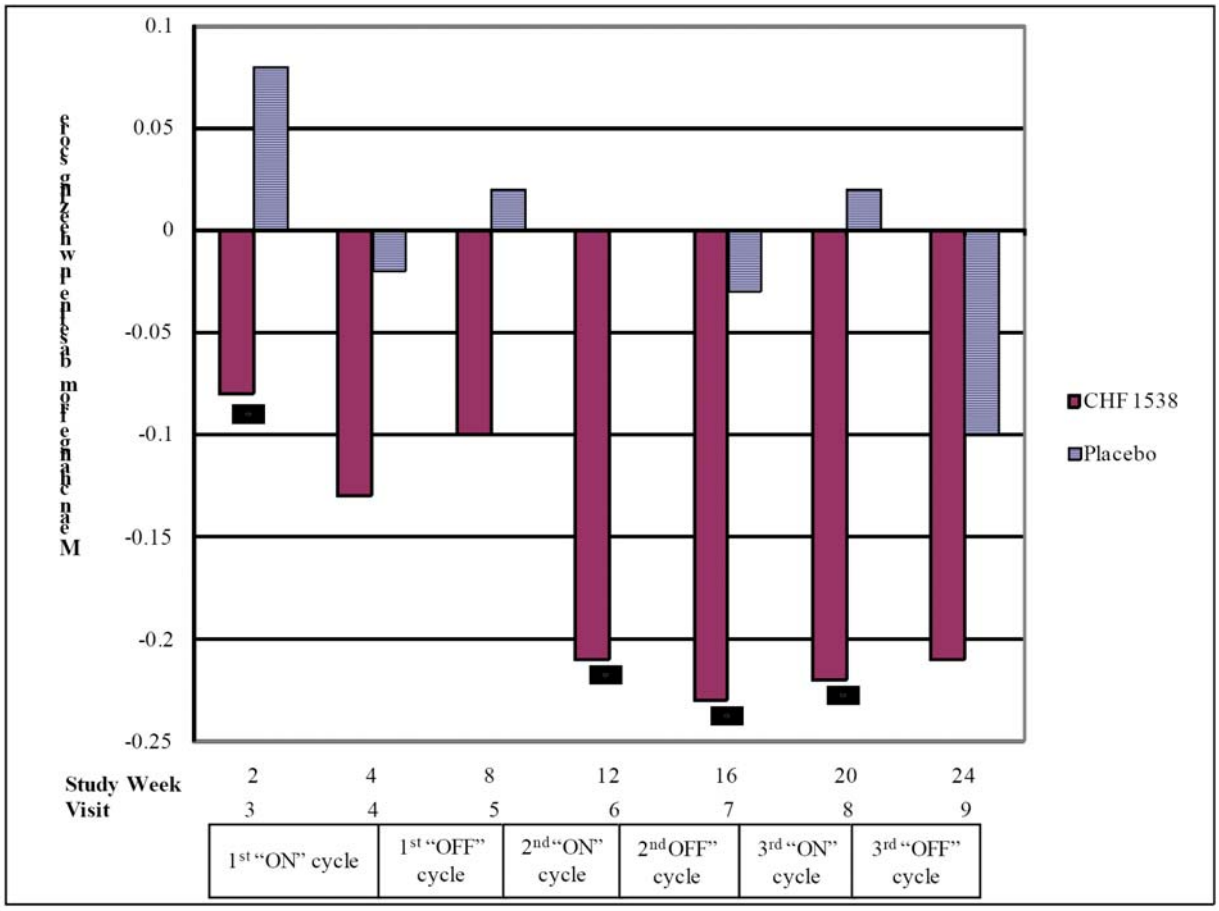
[1] At least three of eleven pre-defined findings (see 9.5.4.3)
[2] Fisher's Exact Test for baseline comparison and Cochran-Mantel-Haenszel procedure stratified by baseline result for all others.
Source: Table 55, Table 225, Table 226, Table 227, Table 228, Table 229, Table 230, Table 231, Table 232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

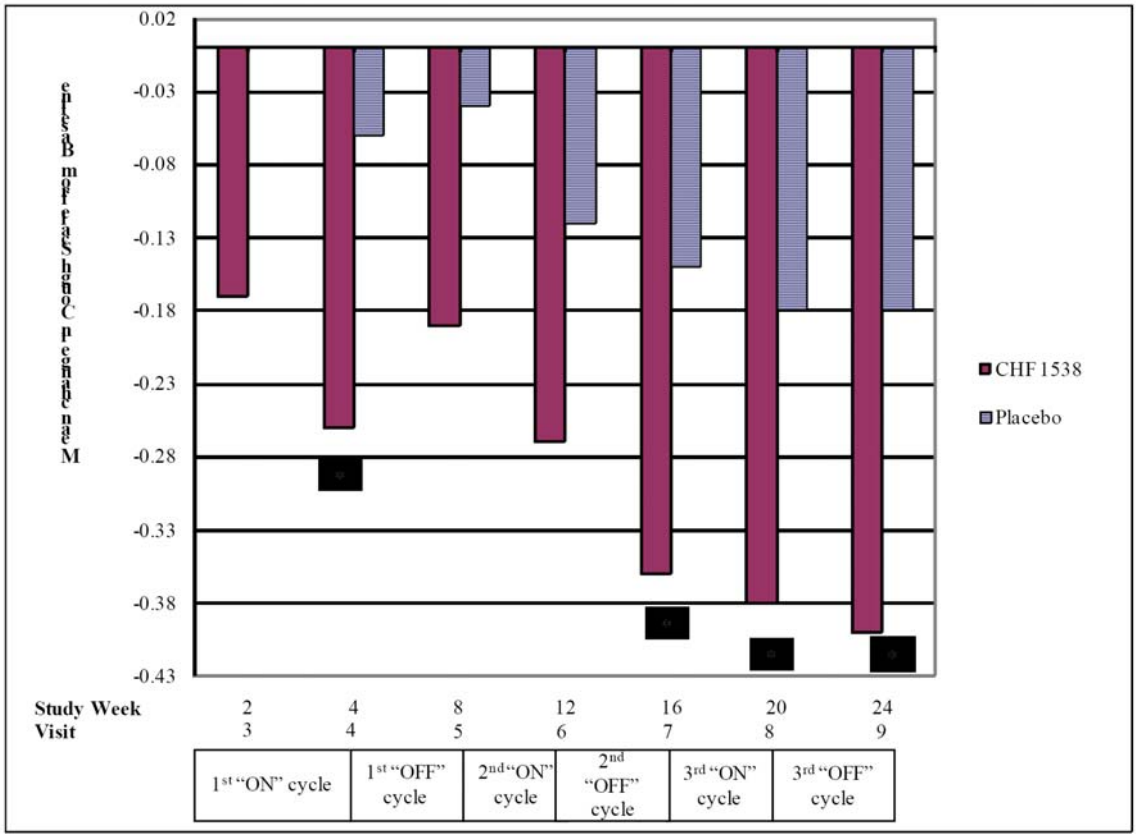
Figure 1. Mean Change in Wheezing Score from Baseline to Each Visit: ITT Population



* 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/

ARIEL R PORCALLA
10/02/2012

EILEEN E NAVARRO ALMARIO
10/02/2012

Division Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Acting Division Director Decisional Memo
NDA #	201,820
Applicant Name	Chiesi Pharmaceuticals, Inc.
Date of Submission	Received October 25, 2010
PDUFA Goal Date	August 25, 2011
Proprietary Name / Established (USAN) Name	No Proprietary Name Accepted/ Tobramycin Inhalation Solution
Dosage Forms / Strength	300 mg/4mL Inhalation Solution
Proposed Indication	Management of Cystic Fibrosis Patient with *Pseudomonas aeruginosa*
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Dr. Shrimant Mishra
Pulmonary Consultation	Dr. Robert Lim
Statistical Review	Dr. Mark Gamalo
Pharmacology Toxicology Review	Dr. Amy Ellis
CMC Review	Dr. Shrikant N. Pagay
Product Quality Microbiology Review	Dr. Robert J. Mello
Device Consultation	Mr. Sugato De
Microbiology Review	Dr. Frederick Marsik
Clinical Pharmacology Review	Dr. Yongheng Zhang
DSI	Dr. Kassa Ayalew
CDTL Review	Dr. John Alexander

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

1. Introduction

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

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

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

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

2. Background/Regulatory

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

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

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

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

The Regulatory Device Consult provided by the CDRH reviewer identified deficiencies in the NDA precluding approval, and I concur. These centered around the fact that the

applicant has proposed labeling to instruct patients to use either the PARI LC PLUS® or (b) (4) ® nebulizers with the PARI Vios® Compressor for drug treatment. However, the clinical trials submitted in the NDA were conducted using the PARI LC PLUS® nebulizer in combination with either the PARI TurboBoy N or S compressor. These deficiencies are listed as "Clinical Hold Issues" in the Regulatory Device Consult. The deficiencies include:

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

In addition, the CDTL recommended:

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

I concur with this recommendation.

The CDRH reviewer noted that it is unclear whether *in-vitro* bridging data between the to-be-marketed combination product and the product tested in clinical studies will be sufficient to justify not providing additional clinical data for the to be marketed combination product. I share this concern.

The Pulmonary Consultant opined that *in vitro* studies alone are not an acceptable means to bridge clinical safety and efficacy findings from one drug-device combination to another, noting that changing the compressor/jet nebulizer system for an inhaled drug/device combination can significantly affect the dosing, delivery, and absorption of the drug and these differences cannot be predicted by *in vitro* testing alone, particularly in patients with chronic lung disease.

The Pulmonary Consultant also noted that the applicant changed the osmolality of the test product late in the course of the development program. The osmolalities of the planned to be marketed product and the product used in clinical trials are as follows:
Planned to be marketed product: (b) (4) mOsmoles/kg
Studies CT01 and 02: (b) (4) mOsmoles/kg
Study CT03: (b) (4) mOsmoles/kg
The Pulmonary Consultant stated that this further underscores the need for further clinical testing.

This difference in osmolality was also noted by the CMC reviewer. The CMC reviewer noted that the batches used in Study CT03 did meet the proposed osmolality specification of (b) (4) mOsmoles/kg. The specification of the product to be marketed is (b) (4)

mOsmoles/kg. The CMC reviewer states that, "On 4 November 2009, FDA agreed that clinical trial CT03 would be acceptable as a bridging study."

I further discuss the osmolality differences in Section 13 of this review.

4. Non-Clinical Pharmacology Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

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

6. Clinical Microbiology

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

7. Clinical/Statistical Efficacy

The Clinical reviewer, Statistical reviewer, and the CDTL recommended a CR citing the deficiencies described in Section 3 of this review that the applicant has not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination. The Statistical reviewer also raised concern that the change in FEV_1 % predicted in study CT01 was not consistent with the results in studies CT02 and CT03. I note that the greater change in FEV_1 % predicted observed in study CT01 in the CHF 1538 arm may be related to an increased proportion of younger patients in that arm. The Statistical reviewer also concluded that study CT03 should be viewed as supportive due to the lack of an adequate non-inferiority margin justification. I agree with this conclusion.

The CDTL concluded that: the efficacy findings for CHF 1538 show results on pulmonary function tests, and sputum microbiology that are consistent with efficacy findings for TOBI®, the secondary outcomes from the CT02 trial support a similar treatment effect on clinically meaningful endpoints, and therefore the data are sufficient to demonstrate that a more concentrated tobramycin formulation shows a similar treatment effect to the reference product. I agree with the CDTL conclusions.

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

- Trial CT01 was a randomized, double-blind, placebo-controlled trial of 28 days of CHF 1538 (29 subjects) or placebo (30 subjects) with a 28-day follow-up period. Trial drug was administered using the PARI LC plus nebulizer and the PARI TurboBOY compressor (an early version of the Turbo BOY S compressor). At the end of 4 weeks of treatment, the change from baseline in FEV_1 % predicted was 15.9% for the CHF1538 arm and 4.9% for the placebo arm. The treatment difference was 11% with a 95% confidence interval of (3.0, 18.9).
- Trial CT02 was a randomized, double-blind, placebo-controlled trial of three cycles (28 days on-/28 days off-treatment) of CHF1538 (161 patients) or placebo (85 patients). The change from baseline to week 20 in FEV_1 % predicted was 6.88% for the CHF 1538 arm and 0.64% for the placebo arm. At week 4, the same time point as the primary outcome for the CT01 and CT03 trials, the change from baseline in FEV_1 % predicted was 7.82% for the CHF 1538 arm and 0.51% for the placebo arm. Secondary endpoints including the rate of disease-related unplanned hospitalizations and the receipt of at least one dose of parenteral anti-pseudomonal antibacterials favored CHF 1538.
- Trial CT03 was a randomized, open-label, comparative trial of CHF1538 (155 patients) or TOBI®(166 patients) given for 28 days with a 28-day follow-up period. The PARI LC plus nebulizer and PARI TurboBOY N compressor was used for drug delivery in both treatment arms; so TOBI® was delivered using the labeled nebulizer, but not the labeled compressor (DeVilbiss Pulmo-Aide). At week 4, the change from baseline in FEV_1 % predicted was 7.01% in the CHF 1538 group and 7.50% in the TOBI® group. The difference and 95% CI were -0.49 (-2.58, 1.62);

the results met the applicant's predefined non-inferiority margin of 4%; however, there was no justification provided for the non-inferiority margin in the clinical trial.

8. Safety

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

The safety database included 346 patients treated with CHF 1538 in phase 3 clinical trials, though only 161 patients received treatment for more than one 28-day course. There was 1 death in a CHF 1538 patient in the clinical trials, and this was attributed to cardiomyopathy of unclear etiology and considered unlikely related to drug treatment. Most serious adverse reactions seemed related to pulmonary exacerbations. Common adverse reactions included dysphonia, pharyngitis, epistaxis and headache. There was no evidence of ototoxicity or nephrotoxicity in the clinical trials. The Clinical reviewer noted that full audiometric results for all trials and complete laboratory data for trial CT03 were not provided. These data will be requested as a non-deficiency item in the CR letter.

9. Advisory Committee Meeting

There was no advisory committee meeting held for this product.

10. Pediatrics

The applicant has submitted a waiver request for pediatric patients 0-6 years of age. The waiver proposal will need to be discussed with PeRC during the next review cycle.

11. Other Relevant Regulatory Issues

In Trial CT02, inspection found that the FEV_1 % predicted measurements were not corrected for changes in height and weight over the course of the trial at one of the inspection sites. Based on the corrections to the pulmonary function test measurements from this site, the changes are highly unlikely to alter the conclusions regarding the primary endpoint. However, the applicant will be asked to provide corrected results for the PFT measurements at any other sites where a similar problem with stored height and weight data occurred as a Deficiency in the CR letter. Other than this deficiency, the DSI memorandum recommended that the primary efficacy and safety data from the three clinical sites inspected appears adequately reliable to support a regulatory decision.

There are no other unresolved relevant regulatory issues.

12. Labeling

The formal labeling review was deferred until additional data is submitted to support the proposed indication.

An acceptable proprietary name has not been submitted.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
The appropriate regulatory action is a complete response.

While trials CT01 and CT02 demonstrate efficacy of CHF1538 for the indication proposed and the safety profile of the CHF1538 is similar to TOBI®, the applicant proposes labeling the product to be used with either the PARI LC Plus or (b) (4) nebulizer with the PARI Vios compressor, and this drug device combination is not the same as that evaluated in clinical trials. The applicant has not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination.

As described above, there is a difference in osmolality between the to-be-marketed product and the product tested in trials CT01 and CT02. The higher osmolality product tested in trials CT01 and CT02 did not raise safety concerns. The osmolality of the product tested in trials CT03 was quite similar to the to-be-marketed product. There was an improvement in FEV_1 % predicted in the CHF1538 arm of trial CT03 which was similar to the improvement observed in trials CT01 and CT02. Whether the data from trial CT03 and additional *in vitro* data to be obtained by the applicant would be an adequate "bridge" in terms of efficacy will be a review issue in the next cycle.

Site inspections suggest that the primary and secondary endpoint results (pulmonary function tests) for the CT02 trial are not correct as submitted for some sites.

Recommendations to Address Deficiencies:
The applicant should provide comprehensive drug device combination bridging data based on the *in vitro* studies recommended by the CDRH reviewer. In addition, the particle characterization data obtained should include data for TOBI® (tobramycin 300 mg/5 mL solution for inhalation) concurrently with the testing for CHF 1538 with the Pari LC Plus Nebulizer and the DeVilbiss PulmoAide Compressor and the TurboBoy N Compressor. Comparative particle characterization data should be obtained for CHF 1538 with an osmolality of (b) (4) mOsmoles/kg and (b) (4) mOsmoles/kg.

If the device data provided are not adequate to bridge the clinical trial and to-be-marketed drug device configurations, then additional clinical trial data will be required. The applicant should consider conducting a placebo-controlled trial similar in design to trial CT01 using the to-be-marketed drug device combination.

Pulmonary function test results should be revised for all trial CT02 individuals at all sites that were affected by inaccurate recording of/loss of source input data including height and age. The primary and secondary outcomes (such as other pulmonary function variables and weight/BMI/height changes over time) that may have been affected by the above issues should also be recalculated and submitted. The methodology and formula for the above recalculations should be submitted. In addition, the applicant should provide an explanation of exactly what documentation/calculation errors occurred at various sites and how such errors were remedied, as well as a reassessment of trial CT02's results given the new data.

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

Recommendation for Postmarketing Requirements and Commitments:
Defer discussion to the next cycle.

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/s/

JOHN J FARLEY
08/25/2011

Cross-Discipline Team Leader Review

Date	(See Electronic Stamp)
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 201,820
Applicant	Chiesi Pharmaceuticals, Inc.
Date of Submission	October 22, 2010 (received October 25, 2010)
PDUFA Goal Date	August 25, 2011
Proprietary Name / Established (USAN) names	No Proprietary Name Accepted/ Tobramycin Inhalation Solution
Dosage forms / Strength	300 mg/4 mL Inhalation Solution
Proposed Indication(s)	1. Management of Cystic Fibrosis Patients with *Pseudomonas aeruginosa*
Recommended:	*Complete Response*

1. Introduction

Chiesi Pharmaceuticals Inc. has submitted NDA 201820 to obtain marketing approval for a 300 mg/4 mL inhalation solution of tobramycin (also known by code number, CHF 1538) for management of cystic fibrosis patients. This is a 505 (b)(2) application that relies, in part, on previous findings of safety and effectiveness for TOBI®, a 300 mg/5 mL tobramycin inhalation solution, approved for the proposed indication.

2. Background

Tobramycin is an aminoglycoside antibacterial approved in a parenteral formulation for treatment of bacterial infections since 1975. A 300 mg/5 mL inhalation solution of tobramycin (TOBI®) was approved for management of cystic fibrosis patients with *Pseudomonas aeruginosa* in 1997.

Chiesi Pharmaceuticals, Inc. submitted a pre-IND (72068) application in August 2005 to discuss their proposal for NDA submission of a 300 mg/4 mL formulation of tobramycin for inhalation. The applicant proposed submission of a 505(b)(2) application, relying in part of the Agency's findings of safety and effectiveness for TOBI. The pre-IND included several meetings, particularly for discussion of CMC and NDA content/format issues. It should be noted that no clinical studies were conducted under this pre-IND; the applicant had conducted or was in the process of completing clinical studies for marketing in the European Union. The applicant proposed to use these same studies for the US marketing application. During the pre-IND discussions, there was discussion of the nebulizer and compressor used in the EU clinical trials and the expectation that the nebulizer compressor combination identified in US labeling would be essentially the same as that used in clinical trials for the product.

3. CMC/Device

The chemistry and manufacturing controls (CMC) review was conducted by Dr. Shrikant Pagay. The product quality microbiology (PQM) review was conducted by Dr. Robert Mello. The reader is referred to their reviews for detailed information. Both the reviewers recommended approval of the NDA based on their reviews, though the CMC reviewer noted that labeling and device information were still to be addressed. The device issues are discussed further below.

- General product quality considerations

The drug substance tobramycin is [redacted] (b) (4). (b) (4) is the drug substance manufacturer. Per the CMC review, the drug substance is well characterized for related substances and degradation products. The drug substance is non-sterile, though the endotoxin level is controlled.

The drug product is a sterile aqueous solution of tobramycin in low density polyethylene single-dose ampoules. Four ampoules are packaged in a pre-printed secondary overpouch. The drug product solution includes sterile water (b) (4), sulfuric acid to (b) (4) pH adjustment, sodium hydroxide is also a pH adjuster, and sodium chloride is used to adjust (b) (4). (b) (4) processing was used throughout the product manufacturing. The tobramycin solution was prepared under a (b) (4). The solution underwent (b) (4) [redacted]. No deficiencies were noted in the product quality microbiology review.

- Facilities review/inspection

Catalent Pharma Solutions in Woodstock, IL is responsible for drug product manufacturing, in process controls, packaging and storage. (b) (4) is responsible for drug substance release testing, QC of finished product, and drug product release and stability testing. (b) (4) conducts drug product testing and leachables. Per the CMC review, all facilities received an acceptable status from the Office of Compliance.

- Other notable issues (resolved or outstanding)

As noted above, there were deficiencies in the NDA application regarding the nebulizer and compressor combinations used with the proposed product. A consult review of the device aspects of the NDA application was conducted by Sugato De, a biomedical engineer in CDRH. The applicant has proposed labeling to instruct patients to use either the PARI LC PLUS® or [redacted] (b) (4) nebulizers with the PARI Vios® Compressor for drug treatment. However, the clinical trials were conducted using the PARI LC PLUS® nebulizer in combination with either the PARI TurboBoy N or S compressor. The CDRH consult notes the limitations of relying on aerosol characteristics for drawing conclusions of the comparability

of drug delivery to patients, since many factors may affect individual breathing patterns in patients. Regardless, the CDRH review states that the in vitro data provided for aerosol characterization is not sufficient. The deficiencies outlined as CDRH clinical hold issues identify the additional information needed by the CDRH reviewer to assess the substantial equivalence of the drug delivery systems (nebulizer and compressor) for delivery of CHF1538.

(CDTL Comment: I agree with the deficiencies cited by the CDRH reviewer regarding the information needed to assess the comparability of the nebulizer and compressor combinations for aerosolization of CHF 1538. This information is needed to compare the aerosol characteristics of CHF 1538 with the nebulizer and compressor combinations used in clinical trials and those intended for use once marketed. It is important to know that the aerosol characteristics are sufficiently comparable to conclude that patients following label instructions would receive similar drug exposure to the patients receiving CHF1538 in clinical trials. In addition, I recommend that the same testing should be conducted with the reference drug, TOBI, delivered using the PARI LC PLUS nebulizer® and De Vilbiss® Pulmo-Aide® compressor. When comparing the aerosol characteristics of CHF1538 in the different nebulizer compressor combinations, the aerosol characteristics of TOBI may provide a useful reference mark for the proposed comparisons.)

4. Nonclinical Pharmacology/Toxicology

The pharmacology toxicology (PT) review was conducted by Dr. Amy Ellis. The reader is referred to her review for detailed information. The PT reviewer had no objections to approval of the NDA. The review noted differences in tobramycin concentration, sodium chloride concentration, and pH between the proposed product and TOBI®. The applicant conducted 7-day and 28-day repeat dose toxicity studies of their product to "bridge" to the reference product. No significant differences were noted in the toxicity profile of their product. Labeling information on carcinogenicity and reproductive toxicology for the proposed product would be based on FDA findings for the reference product. There were no outstanding PT issues identified in the review.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Dr. Yongheng Zhang. The reader is referred to his review for detailed information. The reviewer considered the clinical pharmacology information provided by the applicant to be acceptable. No deficiencies were identified in the review, and no additional information was requested. The information provided came from two studies: a single-dose, randomized, crossover trial (CP-01) comparing sputum and plasma pharmacokinetics of CHF 1538 with TOBI; and a PK sub-population of an efficacy trial (CT-01) that evaluated peak sputum concentrations of tobramycin (10 minutes after product inhalation) on days 1 and 28 and a sputum sample on day 56 (after a 4-week washout period). The CP-01 trial showed comparable plasma concentration-time profiles for the proposed and the reference product; demonstrating the low systemic exposure after inhalation of either formulation. The C_{max} for tobramycin was 0.549 mcg/mL after inhalation

of one dose of CHF 1538. The trial also demonstrated the high variability of sputum concentrations of tobramycin, after inhalation of both products. The results for the PK sub-population of CT-01 also demonstrated similar mean sputum concentrations of tobramycin on days 1 and 28, suggesting no accumulation of trial drug.

(CDTL Comment: The similar, low systemic exposure after inhalation of CHF1538 or TOBI provides reassurance that the change in formulation would not alter the low risk of tobramycin systemic toxicity identified in studies of TOBI. The similar sputum PK suggests that similar efficacy may be expected, but the high variability of sputum concentrations do not allow for conclusions of "bioequivalence" between the inhaled products. Since tobramycin in the inhaled product is acting locally within the lung, evidence of efficacy is needed to demonstrate that the change in formulation does not alter the effectiveness of the product.)

6. Clinical Microbiology

The clinical microbiology review was conducted by Dr. Frederic Marsik. The reader is referred to his review for detailed information. New information described in the review consisted mainly of evaluation of microbiological testing results from the applicant's clinical trials and recent in vitro susceptibility data for *Pseudomonas aeruginosa* isolates. The in vitro susceptibility data for isolates of *Pseudomonas aeruginosa* from the United States in 2007-2009 showed that tobramycin resistance (as defined by the breakpoint for systemic tobramycin treatment of ≥16 mcg/mL) was seen in 17-20% of isolates. However, the reviewer noted that no interpretive criteria have been established for inhaled tobramycin, since it is acting locally within the lung and achieves higher local lung concentrations than those seen with systemic treatment. The reviewer did note that in vitro susceptibility was comparable between the US isolates described above and the baseline isolates from the clinical trials performed by the applicant. The reviewer deferred to the clinical and statistical reviewers for conclusions about the primary endpoints for the clinical trials, but evaluated the microbiological endpoints measured in the clinical trials. The reviewer concluded that "there is no evidence in the data from the treatment trial groups (CHF1538 and TOBI) that suggest that CHF 1538 is inferior to TOBI for the treatment of Pseudomonas aeruginosa infection in the lungs of cystic fibrosis patients." There were no outstanding issues identified by the reviewer.

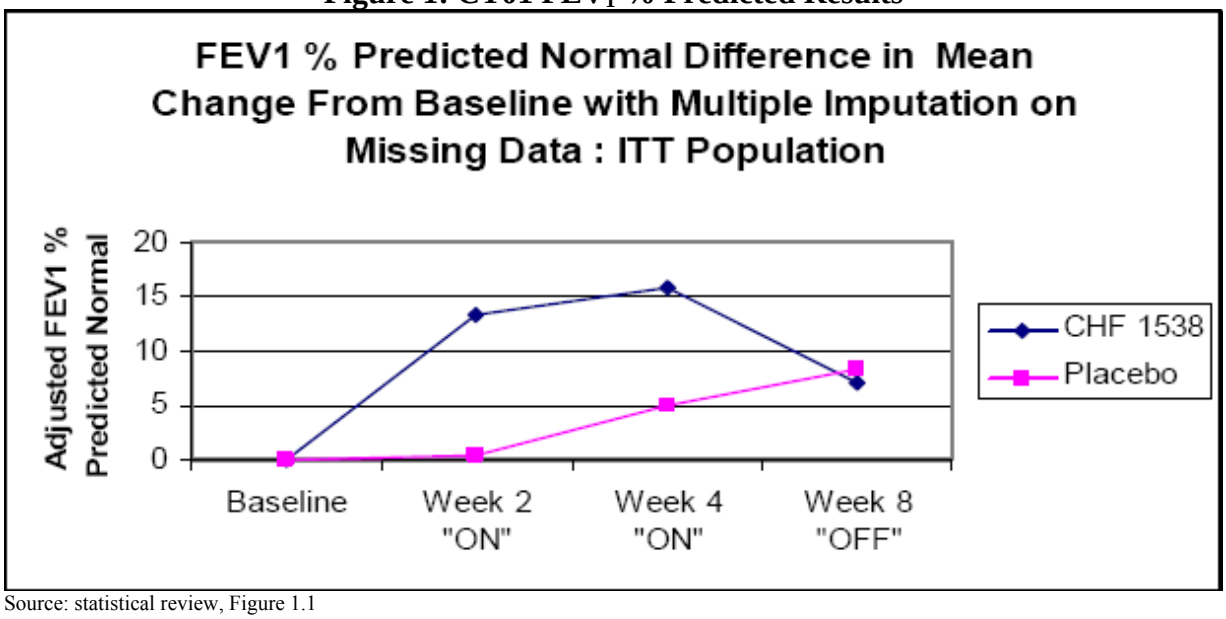
7. Clinical/Statistical- Efficacy

The efficacy findings for CHF1538 were described in the clinical review by Dr. Shrimant Mishra, and the Statistical review by Dr. Mark Gamalo. The reader is referred to their reviews for detailed information. The reviews describe the results of three clinical trials of CHF1538. CT01 was a randomized, double-blind, placebo-controlled trial of 28 days of CHF 1538 or placebo with a 28-day follow-up period. CT02 was a randomized, double-blind, placebo-controlled trial of three cycles (28 days on-/28 days off-treatment) of CHF1538 or placebo. CT03 was a randomized, open-label, comparative trial of CHF1538 or TOBI given for 28 days

with a 28-day follow-up period. The primary endpoint in all three clinical trials was change from baseline in FEV_1 % predicted, though the timing of the endpoint differed.

CT01 was a smaller trial, including only 29 patients in the CHF1538 arm and 30 placebo patients. Trial drug was administered using the PARI LC plus nebulizer and the PARI TurboBOY compressor (an early version of the Turbo BOY S compressor). At the end of 4 weeks of treatment, the change from baseline in FEV_1 % predicted was 15.9% for the CHF1538 arm and 4.9% for the placebo arm. The treatment difference was 11% with a 95% confidence interval of (3.0, 18.9). At the follow-up visit, 4 weeks after end of trial medication treatment, there was no significant difference between treatment arms; the change from baseline FEV1 % predicted was 7.1% for the CHF1538 arm and 8.3% for the placebo arm. These results from the statistical review are based on a multiple imputation method to account for missing values, though the conclusions about treatment effect on FEV_1 % predicted are not different from the applicant's results using a last observation carried forward (LOCF) analysis. The figure below shows the change in FEV_1 % predicted by treatment arm over the course of the clinical trial. Secondary outcomes for other pulmonary function tests showed changes consistent with the treatment effect on FEV_1 % predicted.

Figure 1: CT01 FEV_1 % Predicted Results

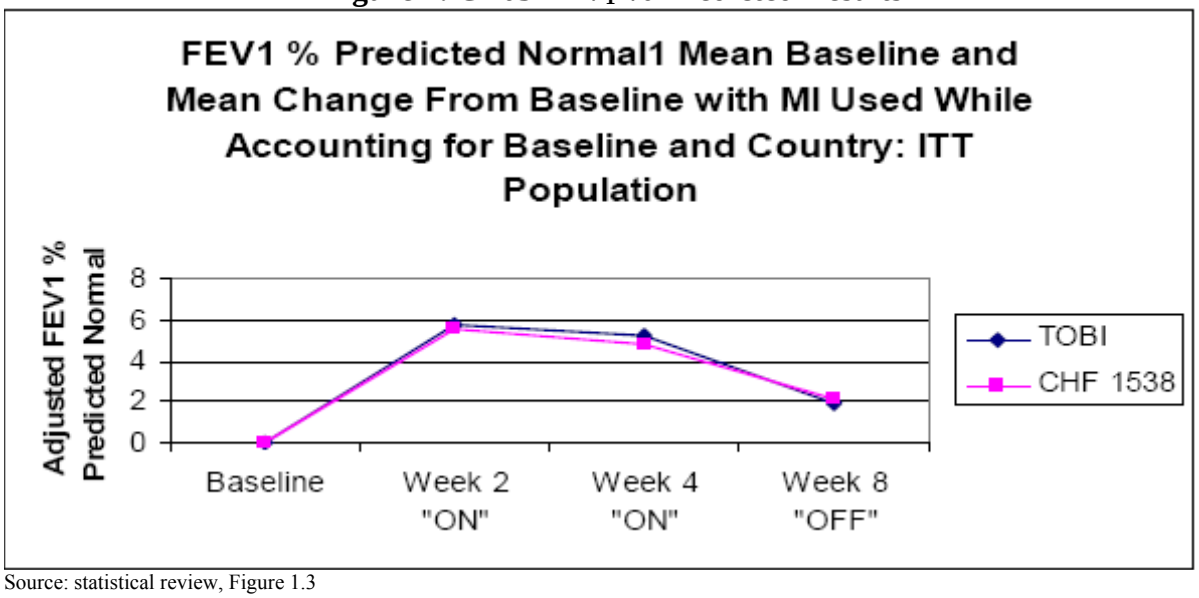


Source: statistical review, Figure 1.1

CT03 was an open-label trial comparing CHF 1538 and TOBI given over 4 weeks with a 4-week follow-up period. The ITT population consisted of 158 patients in the CHF 1538 group and 163 patients in the TOBI group. However, some patients in each group received the other medication, so 155 patients received CHF 1538 and 166 patients received TOBI. Further, the PARI LC plus nebulizer and PARI TurboBOY N compressor was used for drug delivery in both treatment arms; so TOBI was delivered using the labeled nebulizer, but not the labeled compressor (DeVilbiss Pulmo-Aide). At week 4, the change from baseline in FEV_1 % predicted was 7.01% in the CHF 1538 group and 7.50% in the TOBI group. The difference

and 95% CI were -0.49 (-2.58, 1.62); the results met the applicant's predefined non-inferiority margin of 4%; however, there was no justification provided for the non-inferiority margin in the clinical trial. The figure below shows the change in FEV_1 % predicted by treatment arm over the course of the clinical trial. While it is encouraging that the results for the two treatment arms are basically superimposed on one another, there are limitations to the analysis. It is unclear whether different results would have been obtained if the labeled compressor for TOBI had been used in the trial. Further, it is not clear that the proposed NI margin could be supported on the basis of the original TOBI clinical trials. The results of the trial do suggest that the change in concentration of the drug product does not significantly alter the treatment effect on pulmonary function tests.

Figure 2: CT03 FEV_1 % Predicted Results

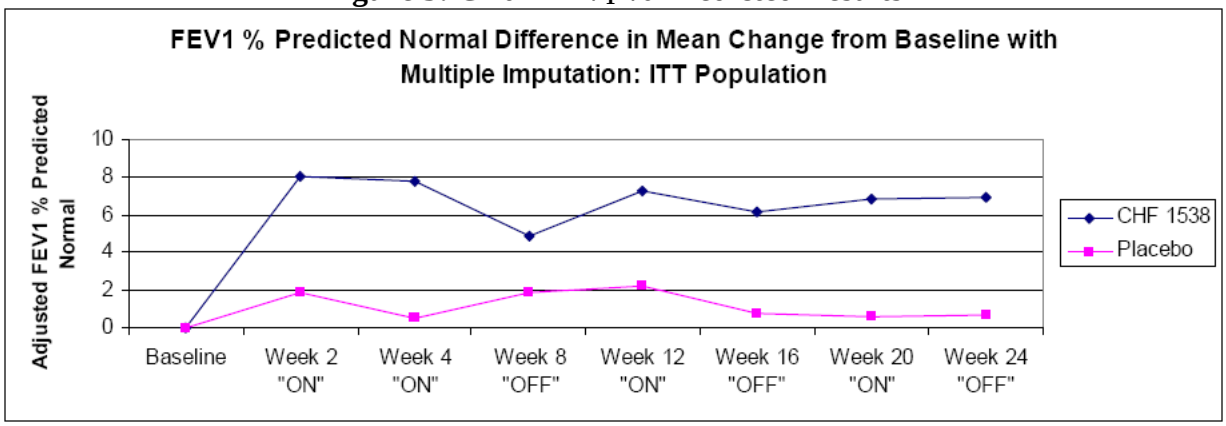


Source: statistical review, Figure 1.3

CT02 was a double-blind, randomized placebo-controlled trial of CHF 1538 over a 24-week period. Patients received either CHF 1538 (n=161) or placebo (n=85) over 3 cycles of treatment; one cycle consisted of 4 weeks of BID treatment with trial medication, followed by 4 weeks off-treatment. This was intended as the pivotal trial for the European marketing application. In this trial, the primary efficacy outcome was change in FEV_1 % predicted from baseline at 20 weeks. The results show that the change from baseline to week 20 in FEV_1 % predicted was 6.88% for the CHF 1538 arm and 0.64% for the placebo arm. At week 4, the same time point as the primary outcome for the CT01 and CT03 trials, the change from baseline in FEV_1 % predicted was 7.82% for the CHF 1538 arm and 0.51% for the placebo arm. One limitation of the results shown in the figure is related to findings from the clinical site investigations conducted by the Division of Scientific Investigations. The investigators noted that the FEV_1 % predicted measurements were not corrected for changes in height and weight over the course of the trial at one of the inspection sites. Based on the corrections to the pulmonary function test measurements from this one site, the changes are highly unlikely to alter the conclusions regarding the primary endpoint. However, the applicant should be asked to provide corrected results for the PFT measurements at any other sites where a similar

problem with stored height and weight data occurred. From the information already provided by the applicant, this did not appear to affect many clinical sites. The figure below shows the changes from baseline in FEV_1 % predicted over the course of the clinical trial. It should be noted that the differences between treatment arms were considered statistically significant at all time points, except for the week 8 visit.

Figure 3: CT02 FEV_1 % Predicted Results



Source: statistical review, Figure 1.2

This trial is also notable for collection of several clinically meaningful secondary endpoints. The clinical secondary outcomes included the frequency of pulmonary exacerbations, hospitalizations, and use of parenteral anti-pseudomonal antibacterials. For the analysis of time to pulmonary exacerbation, there was a numerical difference favoring CHF 1538 over placebo, but the difference was not statistically significant (Wilcoxon test: 0.0622). Exacerbations were reported in 66/161 (41%) patients in the CHF 1538 arm and 43/84 (51.2%) patients in the placebo arm.

The applicant reported on the rate of disease-related unplanned hospitalizations in the trial. There were 16/161 (9.9%) patients in the CHF1538 arm and 21/85 (24.7%) patients in the placebo arm with this type of unplanned hospitalization. The hazard ratio and 95% CI for unplanned hospitalization were 0.359 (0.187-0.688). However, in addition to these patients, there were 17 CHF 1538 patients and 9 placebo patients who had "planned" hospitalizations that could include treatment with antipseudomonal antibacterials. Counting both planned and unplanned events, the hospitalization rate was 33/161 (20.5%) in the CHF arm and 30/85 (35.3%) in the placebo arm. It appears that hospitalizations were reduced in the treatment group.

At least one dose of parenteral anti-pseudomonal antibacterials were given to 37/161 (23%) of CHF1538 patients and 30/85 (35.3%). The difference is statistically significant, favoring CHF 1538 treatment. The hazard ratio and 95% CI were 0.576 (0.356-0.933). However, the above included patients who were receiving antipseudomonal treatment on day 1. Excluding such patients, the proportions (21.7% for CHF 1538 and 32.9% for placebo) still favor CHF1538 treatment.

(CDTL Comment: As noted previously, this NDA application for a 300 mg/4 mL tobramycin solution is a 505 (b)(2) application, relying in part on FDA's previous findings of safety and effectiveness for TOBI, a 300 mg/5 mL inhalation solution. In my opinion, the main question for this NDA is whether the more concentrated solution shows a similar treatment effect to the approved product, so pulmonary function testing (particularly FEV_1 % predicted) seems to be a reasonable tool for making such comparisons. The efficacy findings for CHF 1538 show results on pulmonary function tests, and sputum microbiology that are consistent with efficacy findings for TOBI. In addition, the secondary outcomes from the CT02 trial support a similar treatment effect on clinically meaningful endpoints. From my perspective, the data are sufficient to demonstrate that a more concentrated tobramycin formulation shows a similar treatment effect to the reference product. While the clinical and statistical reviewers noted some variation in the amount of change in FEV_1 % predicted across the clinical trials, similar variability was seen between the two clinical trials conducted for TOBI.

However, the applicant has proposed labeling the product to be used with either the PARI LC Plus or (b) (4) with the PARI Vios compressor. The applicant has indicated that the (b) (4) nebulizer was proposed because (b) (4) The applicant has not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination. While new clinical trials using the proposed nebulizer/compressor would support the labeling, I believe that a comparison of aerosol characteristics of the different nebulizer compressor platforms could provide sufficient information to determine whether comparable clinical results would be expected.

The applicant should also be asked to provide corrected results for the analyses of pulmonary function test changes for trial CT02; accounting for corrections to height and weight measurements.)

8. Safety

The safety findings for CHF 1538 are described in the clinical review by Dr. Shrimant Mishra. The reader is referred to his review for detailed information.

The safety database included 346 patients treated with CHF 1538 in phase 3 clinical trials, though only 161 patients received treatment for more than one 28-day course. This is a reasonable size population, since there is a prior history with TOBI and the treatment is intended for a rare condition.

Deaths occurred in 1/190 CHF 1538 patients and 3/115 (2.6%) placebo patients in the placebo-controlled trials. There were no deaths in the active-control trial, CT03. The death in the CHF 1538 patient involved cardiomyopathy of unclear etiology, though it was considered unlikely related to drug treatment. Evaluation of other adverse reactions was difficult, because of the need to sort between adverse effects related to underlying CF and possible reactions to drug treatment. Most serious adverse reactions seemed related to pulmonary exacerbations. There

was one patient noted with bronchospasm as an adverse reaction. Common adverse reactions included dysphonia, pharyngitis, epistaxis and headache.

While systemic aminoglycoside treatment is associated with ototoxicity, nephrotoxicity, and rare events of neuromuscular blockade, there was no evidence of such adverse reactions related to inhalational treatment. The clinical reviewer did note concerns regarding documentation of the audiometry findings in the clinical trials, though complete information on the audiometry results is not likely to change the conclusions about effects on hearing. Similarly, need for additional documentation of laboratory data for the active comparator trial, CT03, was discussed in the clinical review. Again, such documentation is unlikely to change conclusions about the safety findings.

Overall, the reported adverse reactions for CHF 1538 are consistent with FDA's previous findings for safety of TOBI. The change in tobramycin concentration in the proposed product did not appear to result in different adverse reactions or a change in the frequency of such events.

9. Advisory Committee Meeting

There was no advisory committee meeting for this product.

10. Pediatrics

The applicant has submitted a waiver request for pediatric patients 0-6 years of age. This waiver request is based on the extremely small number of CF patients with *Pseudomonas aeruginosa* colonization in this age range and the feasibility of conducting studies in this age group. The reference drug, TOBI, already includes pediatric use labeling for children 6 years of age and older. The clinical studies conducted by the applicant include a number of pediatric patients as well. The results from the applicant studies show greater improvement in FEV_1 % predicted in pediatric patients compared to adults. No age-related increases in adverse reactions have been noted with CHF 1538 or the reference drug, TOBI. The submitted information for CHF1538 in conjunction with FDA's findings of safety and effectiveness for the reference drug, TOBI, should provide sufficient basis for pediatric use labeling. This is provided that the device-related deficiencies can be addressed.

(CDTL Comment: I agree with the proposal to waive studies for pediatric patients <6 years of age. The waiver proposal will need to be discussed with PeRC when the applicant provides their complete response.)

11. Other Relevant Regulatory Issues

The applicant submitted FDA form 3454 and certified that there were no significant financial arrangements with the listed clinical investigators.

The division of scientific investigations (DSI) conducted clinical site inspections of several foreign sites where the clinical studies were conducted. The reader is referred to the clinical inspection summary (CIS), by Dr. Kassa Ayalew, for detailed information about the inspection findings. There were two sites in Poland and one site in Russia selected for clinical inspections. The site inspection of the applicant was pending at the time the clinical inspection summary was completed. The preliminary findings for one site in Poland did not identify any regulatory violations, though the reviewer stated that a CIS addendum would be filed when the inspection reports for this site and the applicant's site were available.

The inspection of the Russian site found some regulatory violations, and the site was classified as VAI (voluntary action indicated). Of note, initial findings at this site raised questions about the documentation of the drug distribution to patients. However, the investigator was able to provide other documentation of the trial drug given to patients. The CIS review stated that the observations at this site do not appear to significantly impact data integrity or subject protection.

The inspection of the second site in Poland identified problems with the recordkeeping for FEV_1 % predicted measurements. Clinical inspection revealed that FEV_1 % predicted was recorded incorrectly at least once during the course of the trial for 21 of 29 subjects. This occurred because age and height measurements were not changed during the course of the trial. The applicant provided recalculated FEV_1 % predicted measurements for the subjects at this site, and showed that recalculated values did not change the conclusions about the pulmonary function test results. The preliminary classification for this site was also considered to be VAI.

(CDTL Comment: It should be noted that the statistical review evaluated the removal of the two VAI sites, though after further work by DSI the exclusion of these sites was not considered necessary. At the time this memo was written, I contacted DSI and was told that the preliminary classification for the applicant site was VAI. There were no new findings that would affect data integrity. The classification for the first Polish site is unchanged after receipt of the inspection report. The CIS addendum is still pending, but no new findings were identified that would affect the proposed complete response.)

12. Labeling

Labeling was not addressed during this review cycle by the review team, because of the proposed complete response. A labeling review was conducted by Dr. Yelena Maslov. The reader is referred to her review for detailed information. The applicant provided proposed proprietary names, [redacted] (b) (4), both of which were reviewed by the Division of

Medication Error Prevention and Analysis (DMEPA). Both names were considered vulnerable to medication error, and the applicant was notified. The applicant provided another proposed proprietary name, (b) (4), but subsequently withdrew this provisional name on July 13, 2011 because of (b) (4). No other provisional names have been submitted.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend a complete response action on this application.

- Risk Benefit Assessment

Overall, the clinical trials have demonstrated a favorable benefit/risk profile for the product as used in clinical trials; however, the applicant has not provided sufficient information to determine whether the nebulizer/compressor combinations recommended in labeling will provide comparable antibacterial delivery to the lung. In my view, the aerosol characteristics of the proposed product delivered by the nebulizer/compressor combinations as recommended by the CDRH reviewer, along with the aerosol characteristics of TOBI delivered using the approved nebulizer compressor combination, may provide sufficient information to conclude whether the product can be approved with the proposed nebulizer/compressor combinations in labeling. Alternatively, additional clinical trials of the drug product given using the nebulizer and compressor proposed for labeling may be needed if the comparability of tobramycin drug delivery can not established on the basis of the aerosol characteristics.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not Applicable – Approval is not recommended at this time.

- Recommendation for other Postmarketing Requirements and Commitments

Not Applicable – Approval is not recommended at this time.

- Recommended Comments to Applicant

A complete response letter should be sent to the applicant. The complete response letter should include the requests from the CDRH reviewer for information to evaluate the comparability of nebulizer/compressor combinations for the delivery of CHF 1538. In addition, I recommend the aerosol characteristics of TOBI, delivered using the labeled nebulizer compressor (PARI LC plus nebulizer/DeVilbiss Pulmo-Aide compressor) should also be evaluated in the in vitro testing. The applicant should also be notified of the deficiencies cited in the clinical review, and be asked to provide revised analyses of pulmonary function tests for clinical trial CT02, accounting for changes in patient height and weight over time. The applicant should also be asked to provide additional documentation of audiometry testing, and laboratory test results for the CT03 trial.

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/s/

JOHN J ALEXANDER
08/24/2011

CLINICAL REVIEW

Application Type	**NDA**
Application Number(s)	**201820**
Priority or Standard	**Standard**
Submit Date(s)	**10/22/2010**
Received Date(s)	**10/25/2010**
PDUFA Goal Date	**08/25/2010**
Division / Office	**DAIP**
Reviewer Name(s)	**Shrimant Mishra**
Review Completion Date	
Established Name	**Tobramycin 300 mg/4 mL /CHF 1538**
(Proposed) Trade Name	**(b) (4) ™**
Therapeutic Class	**Aminoglycoside**
Applicant	**Chiesi Pharmaceuticals Inc.**
Formulation	**Inhalation Solution**
Dosing Regimen	**300 mg/4 ml Inhaled BID**
Indication	**Management of Cystic Fibrosis patients with *Pseudomonas aeruginosa***
Intended Population	**Cystic Fibrosis patients colonized with *Pseudomonas aeruginosa*; age ≥ 6yo; FEV_1 % 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

From this reviewer's perspective, the recommendation for NDA 201820 is for a complete response letter to be issued. The ultimate reasoning behind this is a lack of clinical information regarding use of CHF 1538 with the to-be-marketed compressor/nebulizer combination. Moreover, besides differences between the trial and to be marketed device combinations, slightly different compressors were used for each of the two placebo controlled trials, and the implication of this is not known. This is in a setting where bridging information is already being relied upon due to changes in the study drug's osmolality from what was used in the placebo-controlled trials to what is to be marketed. However, if in vitro device data is submitted and ultimately found to be supportive of comparability between the device combination used in clinical trials and the to be marketed device combination, then at that point a case for approval could be made. The reason for this is that the data currently submitted is derived from adequate and well-controlled trials and seems to show some pulmonary function benefit of CHF 1538 in CF patients colonized with *Pa*. However, in the absence of any assurance that bridging the device data is appropriate, and given that other inhaled therapies for this indication are currently available to this population, a recommendation for approval must be withheld or now.

The main recommendations for a clinical response letter from this reviewer's perspective are as follows

1. Provide comprehensive device combination bridging data as recommended by CMC and CDRH. The data submitted should be such as to allow the Agency to make a proper evaluation as to how comparable the various device combinations used in clinical trials and for marketing are. This reviewer will defer the specifics of what data should be submitted to the expertise of CMC, CDRH, and the applicant.

2. A comprehensive recalculation of the primary efficacy variable for all trial CT02 individuals at all sites who were affected by inaccurate recording of/loss of source input data including height and age. Secondary variables (such as secondary pulmonary function variables or weight/BMI/height changes over time) that may have been affected by the above issues should also be recalculated and submitted. Resubmitted primary/secondary endpoints for the CT02 trial as a whole should be provided, and the method and formula used for recalculation should also be submitted. A document explaining exactly what documentation/calculation errors occurred at various sites and how such errors were remedied should be provided as well as a reassessment of CT02's results given the new data. This can be done in consultation with the DSI, statistical, and clinical reviewers.

1.2 Risk Benefit Assessment

As noted above, no true assessment can be made without a decision on the ability to bridge the device data. Thus, the comments made below are made with the assumption that the device data from the clinical trials is in fact comparable to what is to be marketed. If this is found not to be the case, then the following assessments would not apply and at that point a decision would have to be made as to what future studies were indicated.

Overall efficacy is being judged in the setting of a 505(b)(2) application. The applicant used a trial design and primary efficacy endpoint, namely FEV_1 % predicted, that was used in the registrational trials for TOBI. From this perspective, both placebo-controlled trials did show an effect of study drug on FEV_1 % predicted by the end of treatment. In the CT01 trial, the change in FEV_1% predicted from the beginning of treatment to the end of treatment (28 days) was 12-13% greater than that of placebo. In the CT02 trial, the change in FEV_1% predicted from the beginning of treatment to the end of treatment (140 days) was roughly 6% greater than that of placebo. Thus, clearly an effect is present though the magnitude of that effect is uncertain. The CT03 trial, which was primarily used for bridging data, showed a similar result to CT02 after 28 days of treatment, roughly a 7% change from baseline in FEV_1% predicted. The possible reasons for this disparity in effect size are discussed in other sections of this review.

Even though FEV_1% predicted was the primary efficacy variable, it should be noted that within the Agency the general consensus has been to try and move away from this endpoint because, among other things, it is difficult to know how various changes in FEV_1% predicted are to be interpreted clinically. Indeed, when an effect size of only 5-6% is seen, the clinical implications of this become more unclear. Thus, more clinically-oriented endpoints are now being recommended as primary endpoints in similar registration trials. In this particular NDA, the only relevant clinical endpoints were in the CT02 trial. In this trial, endpoints such as proportion of subjects with a predefined pulmonary exacerbation, time to pulmonary exacerbation, proportion of subjects hospitalized, and time to hospitalization were analyzed. Though these results should be viewed with a certain amount of caution because this trial was not specifically designed to track these endpoints, overall there did seem to be some benefit in these more clinically relevant measures. For example, there was an absolute reduction of 10% in the proportion of CHF 1538 subjects with a pulmonary exacerbation (though the effect might be less using a broader definition of exacerbations). Moreover, there was a trend toward prolonged time to pulmonary exacerbation in the CHF 1538 arm, though the median difference between the two arms was nonsignificant. Similarly, the absolute difference in hospitalization was 15% in favor of CHF 1538. The combination of these modest improvements in both pulmonary function and clinical endpoints provides more assurance that the study drug is indeed efficacious for this indication.

From a safety perspective, study drug CHF 1538 does not pose an unreasonable safety risk to subjects. No increase in nephrotoxicity or ototoxicity relative to control was noted, and bronchospasm occurred rarely. The most common adverse events were likely more reflective of underlying disease than of true drug-related effects. Adverse events that appeared to be more common in the study drug arm such as pharyngitis, dysphonia, and epistaxis would not be unexpected with inhaled therapies but could also still be reflective of underlying disease. There are concerns about the degree to which treatment increases *Pa* resistance to tobramycin and whether this has any actual clinical implications but this can be dealt with more thoroughly if and when approval is actually given in the future.

Though not necessarily required as part of a complete response, further data would better help fully understand the safety of this drug. Such data include:

1. Providing full audiometric results if available. This would include decibel thresholds recorded at every frequency at every visit for every patient in every trial. This will help to better understand what changes in hearing threshold were occurring during the course of treatment. If such data is unavailable, then any future assessments of otoxicity (including in labeling) will be based on what has been provided in this NDA.

2. Complete statistical tables describing more fully laboratory data in trial CT03. Tables describing mean and median changes in values over the course of the study should be provided, as well as a reference guide to help understand the shift tables provided in the current NDA submission (e.g., what values fall under the parameters of clinically significant, normal, and nonclinically significant for hemoglobin?).

All the above data will be used as supportive data should new clinical trials be indicated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not Applicable – Approval is not recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Not Applicable – Approval is not recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: CHF 1538 (Tobramycin 300 mg/4 mL inhalation solution)

Proposed name: (b) (4)®

Drug Class: Aminoglycoside

Indication: management of cystic fibrosis patients with *Pseudomonas aeruginosa (Pa)*. More specifically, management of cystic fibrosis patients ≥ 6yo with sputum colonization by *Pa*. Not indicated for patients who are colonized with *Burkholderia cepacia* or patients with FEV_1 % predicted < 40% or > 80%. This is an inhalational drug to be nebulized twice a day for alternating 28 day on-treatment /28 day off-treatment cycles

Brief description: Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It has *in vitro* activity against a wide range of Gram-negative organisms including *Pseudomonas aeruginosa*. Tobramycin has poor oral absorption and is normally administered parenterally. However, in cystic fibrosis patients, tobramycin (in the reference drug TOBI formulation) has been administered in inhalational form in the dosing regimen described above.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently 2 other drugs have similar indications

a) TOBI

TOBI® is indicated for the management of cystic fibrosis patients with *P. aeruginosa*. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*

b) Cayston

CAYSTON® is indicated to improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*. Safety and effectiveness have not been established in

pediatric patients below the age of 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 well known, extensively used parenteral antibacterial whose safety profile has been extensively studied.

2.4 Important Safety Issues With Consideration to Related Drugs

With the aminoglycoside class in general there is a well known adverse event profile that includes nephrotoxicity, oto- and vestibular toxicity, and neuromuscular blockade. Typically nephrotoxicity and ototoxicity reactions are dose and duration dependent, and while nephrotoxicity is generally reversible with treatment withdrawal, ototoxicity is usually permanent. Neuromuscular blockade is generally seen with overdose. These reactions are usually noted in association with systemic administration of aminoglycosides where plasma levels of drug are much higher than what is seen with inhalational administration of tobramycin. With inhaled tobramycin, other adverse events such as bronchospasm and, possibly, hemoptysis, are also monitored closely.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant had initially conducted trials in Europe with the purpose of gaining approval there. In 2005, a pre-IND discussion was held with the review division at which time the applicant discussed its plans to submit a 505(b)(2) application for CHF 1538. At that time, the applicant stated that it had used a compressor during clinical trials that was not available in the US. The Agency recommended finding a comparable compressor in the US and submitting specification information that could be evaluated. The Agency also recommended submitting plans for bridging studies. In 2007, the applicant noted that it had found a comparable compressor, the (b) (4), and submitted information that was evaluated by CMC. The CMC decision at that time was that the TurboBoy and (b) (4) were essentially equivalent and that a bridging study was not necessary. In 2009, discussions were held as to the need for a bridging study due to a change in osmolality of the to-be-marketed product. The Agency felt a bridging study might be necessary, and the applicant proposed CT03 be used as a bridging study. The applicant also notified the Agency of its plans to submit an NDA in the second quarter of 2010. Apart from these discussions, no filings in DARRTS document the applicant's current change to the Vios compressor and (b) (4) nebulizer as the to-be-marketed device combinations.

2.6 Other Relevant Background Information

As of April 30, 2010 CHF 1538 has received approval for marketing in the following 23 countries for the management of pulmonary infections caused by *Pseudomonas aeruginosa* in CF patients six years of age and older. The product has been launched in all but six of these countries (Argentina, Bosnia, Croatia, Ireland, Macedonia and Serbia). Please note the applicant table below.

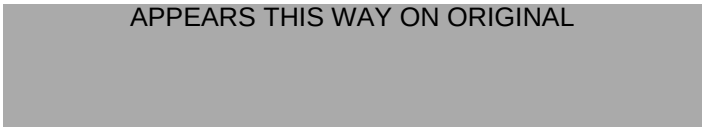


Table 2.6: CHF Marketing Approval in Foreign Countries

Country	Approval Date
Albania	Jul-09
Argentina	Oct-09
Austria	Dec-06
Bosnia	Feb-09
Brazil	Jan-09
Colombia	Mar-08
Croatia	Nov-08
Czech Republic	Apr-07
Germany	Dec-06
Greece	Nov-07
Hungary	Apr-07
Ireland	Jun-07
Italy	Mar-06
Macedonia	Nov-08
Netherlands	Jan-07
Poland	Apr-07
Portugal	Jul-07
Russia	May-08
Serbia	Aug-07
Slovakia	Dec-06
Spain	Mar-07
Switzerland	May-09
United Kingdom	Nov-08

- EDR SDN #0, 1.13.10 Foreign Marketing History; Table 1

CHF 1538 has not been withdrawn from marketing in any country for reasons related to safety or effectiveness.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the eCTD submission quality was adequate. Information requests were sent to the applicant but this had more to do with issues of trial design rather than how the data was submitted.

3.2 Compliance with Good Clinical Practices

The full DSI report has yet to be submitted, however there were several areas of concern in relation to trial conduct. During the course of its audit of some of the highest enrolling sites in CT02, DSI found issues related to proper accounting of drug administration and calculation fo the primary efficacy variable. Initially, there did not appear to be proper documentation of which drugs were administered to whom at site 32; however, drug administration was eventually verified at the site. The DSI audit also identified problems with correct calculation of FEV_1 % predicted values at one inspection site. At site 26, the inspector could not verify whether recorded FEV_1 % predicted values were accurate, primarily because height measurements were not available for verification. The inspector attempted to look at heights recorded at the time of spirometry to see if the FEV_1 predicted values (and thus FEV_1 % predicted values) were accurate, but he could not verify heights because the spirometry printouts did not have height recorded. Normally such data could have been retrieved from the spirometer itself, but the spirometer had a software change and thus all measurements were lost. Given this, the applicant attempted to recalculate FEV_1 % predicted based on heights taken at the corresponding study visit (rather than the height taken with spirometry). The recalculated values for change from baseline in FEV_1 % predicted are very similar to the original results for all visits. The recalculated values have not been used in this review because we are still awaiting further information regarding validation of the method used to recalculate such data. DSI is currently also awaiting the applicant's assessment of how widespread such issues were among other study sites as well as recalculations from other affected sites (this issue is ongoing and should be fully evaluated and addressed as part of the Complete Response).

From this reviewer's perspective, there were also several other areas in which conduct of the trial was marginal. First, physical exams in many sites were simply rudimentary and essentially consisted of just recording the subject's medical history where an actual exam should have been. Secondly, audiometric tests at some sites seemed to have been improperly/inadequately performed or recorded. In one site, all audiometric tests done on every subject had the same result. Protocol violations were in general recorded adequately though it appeared as if some criteria were adhered to less strictly than others (for example audiometric thresholds for inclusion/exclusion were observed less closely). Also, protocol violations for concomitant medications were more strictly enforced for some medications but not others (though major concomitant medications were monitored). Finally, in CT03 15 subjects (net of 3 given TOBI)

received the study drug opposite of what had been assigned making the interpretation of analyses with the ITT population in this study (which based analyses on planned analyses rather than what was actually given) more difficult.

3.3 Financial Disclosures

The applicant did not cite any financial conflicts of interest

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No significant issues were found with regard to the identity, strength, purity, and quality/sterility of the test product. Please see the CMC reviews performed by Dr. Shrikant Pagay and Dr. Robert Mello.

4.2 Clinical Microbiology

From this reviewer's perspective there was a moderate increase in *Pa* tobramycin MICs/resistant isolates on treatment that showed only modest improvement off treatment, particularly in CT02 and less so in CT03. How best to approach this issue can be decided if and when approval of the study drug occurs.

For further discussion of microbiology outcomes and a comprehensive review of application-related microbiology issues please see the efficacy sections of this review as well as the formal microbiology review performed by Dr. Fred Marsik.

4.3 Preclinical Pharmacology/Toxicology

Per the primary Pharmacology Toxicology reviewer, Dr. Amy Ellis, the nonclinical inhalation toxicity studies showed comparable toxicity profiles of the study drug, CHF 1538 and TOBI. Please see her review for further details.

4.4 Clinical Pharmacology

The results of the CP01 study appear to show that PK parameters derived from either plasma or sputum concentration-time profiles are comparable between CHF 1538

and TOBI following single administration. The PK substudy done as part of CT01 appears to suggest that tobramycin in sputum does not accumulate following repeated dosing for a 28-day treatment period. Please see the formal Clinical Pharmacology review performed by Dr. Yongheng Zhang for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Please see section 6.1.1 for a comprehensive table describing all relevant clinical trials

5.2 Review Strategy

Reviews were performed according to expertise (Clinical Pharmacology handled the major pharmacology review, etc.). This Clinical reviewer reviewed both safety and efficacy of the drug. Initially, this reviewer looked at CRF's to identify potential issues that could affect efficacy and safety calculations. The 21st century review template was then used to perform a more extensive NDA evaluation. For the most part, these reviews were not blinded.

5.3 Discussion of Individual Studies/Clinical Trials

This clinical review follows this general format:

a) Discussion of CT01
b) Discussion of CT02
c) Discussion of CT03
d) Discussion of pooled CT01 and CT02 results, when applicable

This format has been followed in sections 6 (Efficacy) and 7 (Safety) and will not be discussed further here. CT01 and CT02 are considered the pivotal (placebo- controlled) efficacy trials and all 3 trials (CT01, CT02, and CT03), in addition to a very small extent CP01, are considered informative for safety purposes.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The stated indication for the study drug CHF1538 is "for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*." The general intent of study drug is for management of cystic fibrosis patients chronically colonized with *Pseudomonas aeruginosa*, specifically by maintaining or improving pulmonary function. The indication would parallel the language used by the reference drug for this 505(b)(2) application - TOBI®.

6.1.1 Methods

The following table outlines salient details of the three major phase 3 trials and the 2 smaller PK studies.

Table 6.1: Overview of Submitted Clinical Trials

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. FEV_1 % 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 FEV_1 % 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 antibiotics 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 N compressor	Inclusion Criteria 1.Age ≥ 6yo 2. FEV_1 % 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 FEV_1 % 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
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. FEV_1 % 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 FEV_1 % 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 antibiotics 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 Substudy	Same as CT01				CHF 1538 concentration in sputum		Sputum obtained 10 minutes after 1st and last dose and on Day 565

1- Nine patients were assigned to CHF 1538 and received TOBI instead; Six patients were assigned to TOBI and received CHF 1538 instead; this is already reflected in the safety population ; however this is not reflected in the applicant's ITT population

This review will look at the efficacy variables for each of the trials individually. The applicant did perform integrated analyses of the pooled CT01 and CT02 studies for the primary variable and multiple secondary pulmonary function and microbiological indices. These will be examined, but it should be noted that these studies were not completely identical. CT01 did not allow the use of antipseudomonal medications (other than study drug) in the four weeks prior to and during the study, while CT02 had no such exception. This allowed for the enrollment of patients in CT02 who were having a pulmonary exacerbation and potentially receiving treatment at baseline or requiring it during study in CT02. Moreover, CT01 required subjects to be colonized with *Pa* susceptible to tobramycin, while CT02 did not have this restriction.

6.1.2 Demographics

CT01

Important demographic parameters in study CT01 are displayed in the applicant table below.

Table 6.1.2: CT01 Demographic Characteristics

	CHF 1538 (N[1]=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%)
First or Intermittent	7 (24.1%)	5 (16.7%)
p value	0.476	
Time from first CF[3] diagnosis (days)		
mean	3343	3565
Range	103.0-10126.0	96.0-9240.0
p value	0.704	

1 number of patients
2 body mass index
3 cystic fibrosis
-EDR SDN#0, section 5.3.5.1.3, CT01 Study Report Body, table 6

It is notable that placebo patients were older, and thus presumably, weighed more and were taller than their CHF 1538 counterparts. Placebo subjects were also more likely to be chronically colonized with *Pa* though this was not found to be significantly different from the treatment arm. More patients in the placebo arm (86.7%) had at least one

medical condition at baseline as compared to the CHF 1538 arm (72.4%). The number of patients with the use of at least one concomitant medication at baseline was roughly equivalent (89.7% vs. 93.3% for CHF 1538 and placebo, respectively), but there was some disparity in regards to the use of mucolytics (17.2% vs. 43.3% for CHF 1538 and placebo, respectively) and a slight imbalance in regards to the use of inhaled or oral steroids (more usage in the placebo group). The baseline FEV_1 % predicted (the primary efficacy variable) was essentially equivalent between CHF 1538 and placebo (please note the applicant table below). It should be noted that there was some difference between the 2 arms in terms of baseline $FEF_{25-75\%}$ (L/sec) with roughly an 8% difference in favor of the placebo arm.

Table 6.1.2.1: CT01 Baseline FEV_1 %Predicted; ITT Population

	CHF 1538	PLACEBO
Visit 1		
N[3]	29	30
Mean	58.2	62.3
SD[4]	14.13	12.35
Range	40.2-80.0	40.6-80.9
Visit 2		
N	29	29
Mean	57.7	59.8
SD	14.13	14.58
Range	40.0-82.0	23.5-83.3

-EDR SDN#0, 5.3.5.1.3, CT01 Study Report Body, table 48

CT02

Core demographic data for CT02 is displayed in the table below.

Table 6.1.2.2: CT02 Demographic Characteristics

Demographic Data	CHF 1538: (N=161)	Placebo: (N=84)	Total: (N=245)
Gender			
Male	89 (55.3%)	46 (54.8%)	135 (55.1%)
Female	72 (44.7%)	38 (45.2%)	110 (44.9%)
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%)
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

-EDR SDN#0, 5.3.5.1.3, CT02 Study Report Body, Tables 7,8, and 49).

The 2 arms were quite well matched in general. However, of significant note, a lower proportion of individuals in the placebo arm were chronically colonized with *Pa*. Also, there was a predominance of individuals in the CHF 1538 arm who took selective B-2 adrenoceptor agonists concomitantly (62% of subjects in CHF 1538 arm and 50% of

subjects in placebo). Despite this, the 2 arms were quite similar in terms of baseline pulmonary function measurements at Visit 2. Note the applicant table below.

Table 6.1.2.3- CT02 Demographic Characteristics- Pulmonary Function Variables

	CHF 1538	PLACEBO
RESPIRATORY RATE (breaths/min)		
N	161	84
Mean (SD)	23.3 (4.90)	22.9 (4.45)
Median	24.0	22.0
Range	12.0-42.0	16.0-36.0
FEV_1 (L)		
N	161	84
Mean (SD)	1.6 (0.68)	1.6 (0.70)
Median	1.5	1.5
Range	0.4-3.7	0.4-3.5
% FEV_1 PREDICTED NORMAL		
N	161	84
Mean (SD)	60.7 (14.78)	63.6 (15.04)
Median	62.0	65.0
Range	31.4-95.1	34.1-104.1

-EDR SDN#0, 5.3.5.1.3, CT02 Study Report Body, Table 9

The applicant states that the number of individuals undergoing a pulmonary exacerbation at baseline was similar. The parameter used for this analysis was individuals with 3 or more positive findings of 11 prespecified pulmonary exacerbation criteria (see Safety Review for more information on this checklist). Using these criteria, roughly 6-7% of individuals in both arms had a pulmonary exacerbation at Visit 2. See the applicant table below.

Table 6.1.2.4- CT02 Pulmonary Exacerbations at Visit 2 (Baseline)- ITT

Visit	Week	CHF 1538 n/N (%)	Placebo n/N (%)	P-Value
2	Baseline	11/161 (6.8%)	5/84 (6.0%)	1.0

-EDR SDN#0, 5.3.5.1.3, CT02 Study Report Body, Table 10

At the Agency's request, the applicant provided a measurement of the number of individuals with a pulmonary exacerbation at visit 2 who were taking antipseudomonals

or other antimicrobials. This was slightly increased in the CHF 1538 arm. Note the applicant table below.

Table 6.1.2.5- Number (%) of Patients in the CT02 Study Having a Pulmonary Exacerbation at Baseline and Were Taking Antimicrobials and Anti-Pseudomonal Antibiotics Within +/-7 days of Visit 2- Safety Population

Study	Antimicrobials[1]	Anti-Pseudomonal Antibiotics
CT02		
CHF 1538 (N=161)	11 (6.8%)	11 (6.8%)
Placebo (N=85)	3 (3.5%)	3 (3.5%)

1 There were 3 patients taking antimicrobials not classified as anti-pseudomonal antibiotics; however, these patients took these antimicrobials in combination with other concomitant anti-pseudomonal antibiotics.

-EDR SDN# 18, 1.11.2 Safety Information Amendment, Table 2

This reviewer attempted to look at the number of individuals in the ITT population of both arms who were taking antipseudomonal medications within +/- 7 days of visit 2 regardless of whether prespecified criteria for pulmonary exacerbation was met. Please note the table below.

Table 6.1.2.6- Number (%) of Patients in the CT02 Study Taking Anti-Pseudomonal Antibiotics Within +/-7 days of Visit 2 – ITT

Study	Individuals Taking Anti-Pseudomonal Antibiotics at Baseline
CT02	
CHF 1538 (N=161)	25 (15.5%)
Placebo (N=85)	12 (14.3%)

Looking at the information as a whole, the percentages of individuals in the CHF 1538 and placebo arms with a possible pulmonary exacerbation at baseline were similar.

CT03

The baseline demographic features of the TOBI and CHF 1538 arms are displayed in the applicant table below.

Table 6.1.2.7: CT03 Demographic Characteristics – ITT

	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%)

Note: Age, height, weight and BMI value, age of diagnosis of chronic colonization of *P. aeruginosa*, time from first CF diagnosis and tobramycin MIC value in classes are presented at V1; FEV_1 (% predicted) and use of rhDNase are presented at V2.
1 Age in years calculated as integer ((date of V1-date of birth)/365.25)
2 Body Mass Index (BMI) in kg/m2 calculated as (Weight in kg/(Height in m)2), rounded to one decimal place
3 Time from diagnosis of chronic colonization of *P. aeruginosa* in years calculated as ((date of V1 - date of diagnosis of colonization)/365.25), rounded to two decimal places
4 Time from first CF diagnosis in years calculated as ((date of V1 - date of first CF diagnosis)/365.25), rounded to one decimal place. If time from first CF diagnosis is greater than patient age then time from first CF diagnosis in years is equal to derived age.
5 Baseline use of rhDNase is set to 'Yes' if a patient has used rhDNase on the same date or within the 10 days prior to start of study drug administration. If the timing of rhDNase use cannot be identified because of missing date, then the use of rhDNase at baseline is considered as 'Yes'.
- EDR SDN#: 0, 5.3.5.1.3, CT03 Study Report Body, Table 11

Overall, the two arms were quite similar in the above demographic characteristics though the CHF 1538 arm was slightly more female and slightly older.

The following applicant table shows the baseline FEV_1 % predicted at Visits 1 and 2. The two arms were similar.

Table 6.1.2.8: CT03 Demographics- FEV_1% Predicted

	CHF 1538 (N=158)	TOBI (N=163)
Visit 1		
N	158	163
Mean (SD)	61.67 (12.12)	61.80 (12.33)
95% CI	[59.77 ; 63.58]	[59.89 ; 63.70]
Median	62.95	65.30
Min / Max	40.00 / 84.80	38.20 / 80.40
Missing	0	0
Visit 2		
N	158	163
Mean (SD)	61.32 (12.29)	61.68 (12.20)
95% CI	[59.39 ; 63.25]	[59.79 ; 63.57]
Median	62.35	64.70
Min / Max	38.90 / 82.00	39.80 / 80.00
Missing	0	0

-EDR SDN # 0, 5.3.5.1.3, CT03 Study Report Body, Table 73

The proportion of subjects in each arm with a concomitant disease other than CF in the SOC's Infections and Infestations and Respiratory, Thoracic, and Mediastinal disorders was similar between the two arms. The arms were also similar in terms of prior medication.

6.1.3 Subject Disposition

The following table displays the general disposition of subjects in each of the arms of the three phase 3 trials.

Table 6.1.3: Subject Disposition in CT01, CT02, and CT03

Trial	Randomized	Safety Population	Discontinuations	Lost to Follow Up	Analyzed For Efficacy (ITT)/AT[1]	Excluded from analysis
CT01	59	59	8	2	58	1
CHF1538	29	29	1	1	29	0
Placebo	30	30	7	1	29	1
CT02	247	246	15	1	245	2
CHF 1538	161	161	7	1	161	0
Placebo	86	85	8	0	84	2
CT03	324	324	10	0	321	3
CHF 1538	159	156	4	0	158/155	1
TOBI	165	168	6	0	163/166	2

1- In CT03, there were 15 individuals who were assigned a drug but received the opposite drug; nine individuals received TOBI rather than CHF and 6 individuals received CHF rather than TOBI; thus the ITT analysis reflects the original planned treatments and the actual treatment (AT) analysis reflects actual treatment given

The loss to follow-up was minimal in all three phase 3 studies and not expected to have a significant effect on outcomes. There was a discrepancy in discontinuations in CT01 only (more in the placebo arm). However, all of these discontinued subjects are included in the ITT analysis. It should be noted that in CT03, there were 15 individuals who were assigned one drug but received the opposite drug; nine individuals received TOBI rather than CHF and 6 individuals received CHF 1538 rather than TOBI; thus the ITT analysis reflects the original planned treatments and the AT analysis reflects actual treatment given.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable chosen for all three phase 3 trials was FEV_1 % predicted. Improvement in (or lack of deterioration of) FEV_1 % predicted has been shown to be correlated with improved mortality in CF patients. This was also the primary efficacy variable chosen for the registrational trials of the reference drug, TOBI. Given that this is a 505(b)(2) application, the chosen primary efficacy variable is adequate. FEV_1 % predicted provides an objective measure of pulmonary function that allows comparison of CHF 1538 (a more concentrated formulation of tobramycin) with the treatment effect of the reference product. However, it should be noted that currently there is

considerable debate about appropriate primary endpoints for trials of inhaled antimicrobials in CF. There are concerns about how to interpret clinically small changes in FEV_1 % predicted, and there is a focus on finding more clinically relevant endpoints, such as time to first pulmonary exacerbation. For the purposes of this review, changes in FEV_1 % predicted as well as other supportive clinical endpoints were used to make the case for approval/nonapproval.

CT01

CT01 was a randomized, placebo-controlled, double-blind, multicenter study that compared one cycle of 28 days of study drug treatment followed by 28 days off-treatment with either placebo or CHF1538. The primary endpoint was change in FEV_1 % predicted from baseline (Visit 2 - start of drug treatment) to Visit 4 (end of drug treatment). It was similar to the reference registration trial for TOBI in that it had only subjects who were ≥ 6 years of age and were not colonized by *Burkholderia cepacia*. However, the reference registrational trials allowed subjects with an FEV_1 % predicted between 25 and 75% (as opposed to 40 and 80% for this trial), were three cycles long (as opposed to one cycle for this trial), and were conducted only in the US (this trial was conducted completely in Europe). Some of the changes between the registrational trial and this trial had to do with protecting the safety of participating subjects; it was felt that if a placebo arm was necessary, then better functioning CF patients should be enrolled. As noted earlier, placebo patients were slightly older, weighed more, were taller, and slightly more likely to be chronically colonized than the CHF 1538 arm. The placebo arm also had increased usage of mucolytics. It should be noted for the purposes of this review, more significance is to be given to analyses in the ITT population rather than the per protocol (PP) population due to the fact that the ITT population does not suffer as much from lack of randomization. The ITT population has been defined as all patients who were randomized and received at least one dose of study drug and have at least one post-baseline assessment.

The applicant table below shows the change in FEV_1 % predicted from baseline to each subsequent visit.

Table 6.1.3.1: CT01 FEV_1 % Predicted Normal[1] Mean Baseline and Mean Change From Baseline with LOCF[2] Used for "ON" Drug Visits: ITT[3] Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N[4]	29	29	
		Mean	57.7	59.8	0.580
3	2 "ON" Drug	N	29	27	
		Mean Change from Baseline[5]	13.3	0.1	0.003
		Difference (95% CI[6])	13.2 (4.9, 21.5)		
4	4 "ON" Drug (1° endpoint)	N	29	29	
		N Imputed[7]	0	3	
		Mean Change from Baseline[5]	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]	5.8	7.7	0.709
		Difference (95% CI)	-1.8 (-11.6, 7.9)		

[1] forced expiratory volume in one second as a percent of predicted normal
[2] last observation carried forward
[3] Intent-to-Treat
[4] number of patients
[5] adjusted for baseline value
[6] confidence interval
[7] number patients with LOCF from Visit 3
Source: Table 50, Table 51, Table 52, Table 53, Table 54

-EDR SDN # 0, 5.3.5.1.3, CT01 Study Report Body, Table 7

There is a substantial and significant difference in change from baseline between the two arms at both visits 3 and 4 (the on-treatment visits). The overall trend is one of improvement of FEV_1 % predicted while on CHF1538 treatment and then a drop in this value toward baseline while off of treatment. The placebo arm stays relatively flat and then improves somewhat during the off-treatment period. Because there was a discrepancy in age, the applicant attempted to adjust for age (although using the predicted values should do this already) and found a similar result at visit 4. Please note the applicant table below.

Table 6.1.3.2: CT01 FEV_1 % of Predicted Normal[1] Mean Baseline and Mean Change From Baseline with LOCF[2] Used for On Drug Visits Adjusted for Age: ITT[3] Population

Visit	Week		CHF 1538	Placebo	P-Value
4	4 "ON" Drug (1° endpoint)	N[4]	29	29	
		Mean Change from Baseline[5]	15.3	3.4	0.010
		Difference (95% CI[6])	11.9 (3.0, 20.8)		

[1] forced expiratory volume in 1 second as a percent of predicted normal
[2] last observation carried forward
[3] Intent-to-Treat
[4] number of patients
[5] adjusted for baseline value
[6] confidence interval
-EDR SDN # 0, 5.3.5.1.3, CT01 Study Report Body, Table 8

Similar values were seen for the PP population (data not shown). The statistical reviewer attempted to account for missing data using methods other than LOCF (notably the multiple imputations and worst observation methods). Using these analyses, there still remained a significant difference in change in the primary efficacy variable between placebo and CHF 1538 at visit 4 (there was a slightly decreased change using the multiple imputation methods but the change was still significant (see the statistical review section 3.1.7.1 for further information). Though not emphasized by the applicant, there was the modest improvement seen in both arms, particularly the placebo arm, during the off-treatment period (though the placebo arm had more missing data at this time point).

CT02

CT02 was a randomized, placebo-controlled, double-blind, multicenter study that compared three cycles of 28 days on-treatment/28 days off-treatment with either placebo or CHF1538. The primary endpoint was change in FEV_1 % predicted from baseline (Visit 2 - start of drug treatment) to Visit 8 (end of 3rd on-treatment period). This trial was similar to the reference registrational trial for TOBI in that it had only subjects who were ≥ 6 years of age and were not colonized by *Burkholderia cepacia*. However, the reference registrational trials allowed subjects with an FEV_1 % predicted between 25 and 75% (as opposed to 40 and 80% for this trial) and were conducted only in the US (this trial was conducted completely in Europe). As noted earlier, the two arms were quite comparable, although in contrast to CT01, the CHF 1538 arm had more individuals who were chronically colonized.

The applicant table for the analysis for the primary endpoint is displayed below.

Table 6.1.3.3: CT02 FEV_1 % of Predicted Normal Mean Baseline and Mean Change From Baseline: 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	161	84	
		Mean Change from Baseline[1,2]	8.02	1.91	< 0.001
		Difference (95% CI)	6.11 (3.08, 9.15)		
4	4 "ON" Drug	N	161	84	
		Mean Change from Baseline[1,2]	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[1,2]	4.69	1.90	0.077
		Difference (95% CI)	2.79 (-0.30, 5.88)		
6	12 "ON" Drug	N	161	84	
		Mean Change from Baseline[1,2]	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 Baseline[1,2]	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 Baseline[1,2]	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 Baseline[1,2]	5.92	-1.19	< 0.001
		Difference (95% CI)	7.11 (3.59, 10.62)		

[1] LOCF used for "ON" Drug Visits and for "OFF" Drug Visits separately
[2] Adjusted for baseline value
- EDR SDN # 0, 5.3.5.1.3, CT02 Study Report Body, Table 12

As in CT01, there is a significantly greater change in FEV_1 % predicted from baseline to the end of on cycle visits (visits 4, 6, 8) in the CHF 1538 arm. However, as compared to CT01, the FEV_1 change seen in this study is smaller in magnitude in the CHF 1538 arm. The difference between CHF 1538 and placebo increases throughout the first On cycle, drops toward baseline during the first Off cycle, and then steadily increases again during the second On, second Off, third On, and third Off cycles primarily due to a

stabilization of improvement over the second and third On/Off cycles in the CHF 1538 arm and a steady decrease in improvement from baseline over the second and third On/Off cycles in the placebo arm. Only at Visit 5 was the difference between the two arms nonsignificant. The applicant performed various subgroup analyses on the primary endpoint variable and there did appear to be trends toward efficacy in various groups though they were not significant (see subgroups section below).

The statistical reviewer performed the same analyses using the multiple imputation and worst observation methods to account for missing data. The results were generally the same although there was a slight trend toward an increased difference in mean change from baseline between the two arms noted in the later visits using the worst observation method (see section 3.1.7.2 of the statistical review).

As noted earlier, there were concerns about the data integrity of two sites in CT02, site 26 and site 32. Because of this, a sensitivity analysis for FEV_1 % predicted was performed excluding these two sites. The following table created by the statistical reviewer Dr. Mark Gamalo displays those findings.

Table 6.1.3.4: CT02 Exclusion of Sites 26 and 32: FEV_1 % Predicted Normal Mean Baseline and Mean Change From Baseline with Multiple Imputation- ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	126	67	
		Mean	60.27	62.75	0.281
3	2	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	7.88	2.02	0.002
		Difference (95% CI)	5.87 (2.26, 9.48)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	7.65	0.76	<0.001
		Difference (95% CI)	6.89 (3.24, 10.54)		
5	8	N imputed	2	1	
	"OFF" Drug	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)		

Note: The shaded row indicates the primary endpoint
- Statistical Review, Table 3.15

Though the difference in mean change from baseline is significant for all visits except Visit 5, in general the differences are slightly lower than what was noted in the original analysis.

Sensitivity analyses were also performed adjusting for chronic colonization status at baseline with *Pa.* Again, no real difference in results was noted.

Though improvement is seen in the primary efficacy variable in the CHF 1538 arm as compared to placebo, it is unclear why the degree of improvement in the CHF 1538 arm was less than what was seen in CT01. Depending on which analysis is chosen, the difference in change from baseline in the primary efficacy variable between the CHF 1538 arm and placebo arm was between 11-13% in CT01 and around 7% (at visit 4) in CT02. It is possible the presence of subjects having an exacerbation at baseline and during the study in CT02 could have attenuated the degree of improvement seen in the CHF 1538 arm, although presumably the effect of this would have been spread out equally over both arms and thus the difference in change between the two arms would have been similar to CT01. There are differences in chronic colonization status with *Pa* at baseline but a sensitivity analysis accounting for this produced very little difference in results in the CT02 trial (though it should be noted that no sensitivity analysis accounting for this was done for the CT01 trial). It is possible that since each study was conducted in different regions of Europe that treatment patterns differed between regions. However, CF care is usually done by experienced personnel and it's unclear to what degree this would have had an effect on results. CT01 subjects in the CHF 1538 arm were younger than those in the CHF 1538 arm in CT02, and even though FEV_1% predicted was similar in both trials for both arms this difference in age representation may have partially explained the differential trial response. There seemed to be a trend toward increased use of mucolytics and steroids in the placebo arm of CT01 and increased use of B-selective adrenoceptor B-2 agonists in the CHF 1538 arm in CT02. The significance of this finding is unclear. (Does it represent sicker patients in these arms? Does it represent improved lung function in these arms?) CT01 had a requirement that subjects be colonized with *Pa* susceptible to tobramycin; this was not the case for CT02. However, using systemic interpretive breakpoints for tobramycin, in CT01 65% of subjects in the CHF 1538 arm had breakpoints in the susceptible range, while in CT02 85% of subjects in the CHF 1538 arm were in the susceptible range (it should be noted that in CT01, the definition of susceptible for inclusion criteria was zone diameter ≥16 mm with 10 mcg tobramycin disk); thus, this is unlikely to have played a role in the differing primary efficacy response. CT01 and CT02 used different compressors but the type used in CT02 appeared to have higher flow rates and operating pressure so it is doubtful that this played a role in the results. Overall, the etiology of this difference in response is unclear. What is also unclear is whether the difference in response between the two trials is clinically meaningful or simply falls within natural variation for the primary efficacy variable.

CT03

CT03 was an open label, randomized, active controlled, multicenter, noninferiority trial that compared the effects of CHF 1538 vs. TOBI on FEV_1 % predicted over one cycle of 28 day on/28 day off treatment. Entry criteria were essentially identical to those in CT01. This trial was conducted primarily "to address concerns by the French Health Products Agency regarding the lack in Chiesi's European clinical dossier of evidence derived from a head-to-head comparison of CHF 1538 versus TOBI, the gold standard, commercially available comparator product for the claimed indication." For the purposes of this NDA, however, CT03's primary purpose was to serve as a bridging study given the changed osmolality of the study drug substance; the osmolality of CHF 1538 in CT03 ([(b) (4)] mOsmol/kg) was closer to the to-be-marketed substance's osmolality than were the substances used in the placebo controlled trials [(b) (4)] mOsmol/kg). Thus, this reviewer will briefly examine results in CT03 primarily for comparison to the placebo-controlled trials rather than as a comparison to TOBI.

The following applicant table shows the change in FEV_1 % predicted from Visit 2 (beginning of on treatment) to Visit 4 (end of on treatment) using an ANCOVA model. Please note that these analyses were done on the ITT population of which a net of three subjects in the CHF 1538 arm actually received treatment with TOBI (as treated population is really 155 for CHF 1538 and 163 for TOBI).

Table 6.1.3.5: CT03 Lung Function Tests: FEV_1 (% Predicted) – Change from Baseline (V2) to V4 – LOCF[1] Values – ANCOVA[2]: ITT Population

	CHF 1538 (N=158)		TOBI (N=163)
DESCRIPTIVE STATISTICS			
Change from baseline (V2) to V4 in FEV_1 (% predicted)			
N	158		163
Mean (SD)	6.99 (9.52)		7.51 (9.63)
95% CI	[5.50; 8.49]		[6.02; 9.00]
Median	5.25		6.00
Min/Max	-11.00/36.20		-22.70/41.10
ANCOVA			
LSMEANS(SEM)	4.66 (1.18)		5.16 (1.16)
Fixed effects/Covariate: p-value[3]			
Treatment		0.640	
Country		0.087	
Baseline FEV_1 (% predicted) value		0.107	
CHF 1538 minus TOBI			
LSMEANS (SEM)		-0.50 (1.06)	
95% CI		[-2.58; 1.59]	

Source data: Appendix 16.2.6.1
[1] LOCF: last observation carried forward
[2] ANCOVA model: Change from baseline (V2) to V4 in FEV_1 (% predicted) value = treatment and country as fixed effects and baseline FEV_1 (% predicted) value as covariate
[3] All p-values are two-sided.
The non-inferiority is shown if the lower limit of the two-sided 95% CI is above the non-inferiority margin set at -4.5%.

- EDR SDN# 0, 5.3.5.1.3, CT03 Study Report Body, Table 14

This result is similar to what was seen in the As Treated population. Using the multiple imputation method to account for missing values, the findings were similar (see the table below created by the statistical reviewer).

Table 6.1.3.6: CT03 FEV_1 % Predicted Normal Mean Baseline and Mean Change From Baseline with MI Used 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)		

Note: The shaded row indicates the primary endpoint
-Statistical Review, table 3.21

The statistical reviewer looked at similar ANCOVA analyses controlling for baseline FEV_1 % predicted only (not country) and found improved results, suggesting a substantial effect of country on the results.

Table: 6.1.3.7: CT03 FEV_1 % Predicted Normal Mean Baseline and Mean Change From Baseline with LOCF Used for "ON" Drug Visits while accounting for baseline: 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	6.93	6.70	0.837
		Difference (95% CI)	-0.22 (-2.36, 1.91)		
4	4	N imputed	2	3	
	"ON" Drug	Mean change from Baseline	7.50	7.01	0.647
	(1° endpoint)	Difference (95% CI)	-0.49 (-2.58, 1.61)		
5	8	N	159	155	
	"OFF" Drug	Mean Change from Baseline	5.35	5.49	0.912
		Difference	0.14 (-2.41, 2.69)		

Note: The shaded row indicates the primary endpoint
-Statistical Review, table 3.20

Of note is that while the difference between the CHF 1538 and TOBI arms is minimal no matter what analysis is used, the degree of improvement seen in FEV_1 % predicted from Visit 2 to Visit 4 in the CHF 1538 arm is still considerably less than what was seen in CT01 (16.0%) and similar to what was seen in CT02 (7.82%). Compared to CT01, the CHF 1538 arm in CT03 was older and had a longer time since CF diagnosis. However, baseline FEV_1 % predicted did not significantly differ between the two. Also, more isolates in the CT03 CHF 1538 arm were susceptible to tobramycin (85%) using systemic breakpoints than in CT01 (65%), which would seem to be in contrast with the results. Of course, as noted before, the osmolality of CHF 1538 differed between the

two studies and were conducted in different European sites (though both studies shared Ukranian sites).

6.1.5 Analysis of Secondary Endpoints(s)

CT01

Other Pulmonary Function Parameters

When looking at changes in FVC % of predicted normal and $FEF_{25-75\%}$ % of predicted normal, the difference in mean change from baseline (Visit 2) to end of treatment (Visit 4) between the CHF 1538 and placebo arms for both parameters was both statistically significant:

FVC%: difference of 10.65% between CHF 1538 and placebo; with p value =.018; $FEF_{25-75\%}$: difference of 15.8% with p value of .004.

In terms of changes in absolute values for FVC and $FEF_{25-75\%}$, the difference in mean change from visit 2 to visit 4 between both arms was significant for $FEF_{25-75\%}$ in L/sec but not for FVC in L. For the latter comparison, differences between the two arms in height, age, and weight at baseline likely played a part.

Changes in Quantitative Sputum Microbiology

There was a significant change in quantitative bacterial counts in sputum Pa [measured as Log_{10} colony forming units (CFU)/g of sputum *Pa*] from visit 1 to visit 4 in the CHF 1538 arm as compared to the placebo arm. There was a decrease of 2.16 logs of CFU/g in the CHF 1538 arm as opposed to a decrease of 0.89 logs CFU/g in the placebo arm. Though this reached statistical significance, whether this is indicative of any real clinical significance is unclear. Please note the applicant table below.

Table: 6.1.5: CT01 Log_{10} Mean Bacterial Load[1] (CFU^2/g) at Baseline and Mean Change in Bacterial Load from Baseline: ITT[3] Population

Visit	Week		CHF 1538	Placebo	P-Value
1	Baseline	N[4]	27	26	
		Mean	5.79	5.84	0.907
4	4 "ON" Drug (1° endpoint)	N	27	26	
		Mean Change from Baseline[5]	-2.16	-0.89	
		Difference (95% CI[6])	-1.26 (-2.18, -0.34)		0.008
5	8 "OFF" Drug	N	25	23	
		Mean Change from Baseline	-0.55	-0.72	
		Difference (95% CI)	0.17 (-0.85, 1.20)		0.738

Note: Ns were lower for this analysis compared with other microbiological analyses because of missing data.
[1] A value of 20 was used for all instances where the *P. aeruginosa* pathogen was eradicated.
[2] colony forming units
[3] Intent-to-Treat
[4] total number of patients
[5] adjusted for baseline value
[6] 95% Confidence Interval

-EDR SDN# 0, 5.3.5.1.3, CT01 Study Report Body, Table 18

When looking at categorization of sputum samples as eradicated, persistent, or superinfected at visit 4, in the CHF 1538 arm there was a higher rate of eradication, lower rate of persistence, and higher rate of superinfection for the CHF 1538 arm as compared to placebo. By visit 5, there was much lower and similar rate of eradication in both arms, but the rate of superinfection remained higher in the CHF 1538 arm. Please note the table below.

Table 6.1.5.1: Microbiological Outcome at Visit 4 in CT01.

Visit 4	Eradication n/N (%)	Persistence n/N (%)	Superinfection n/N (%)
CHF 1538	10/29 (34.5%)	11/29 (37.9%)	8/29 (27.6%)
Placebo	5/24 (20.8%)	18/24 (75%)	1/24 (4.2%)

Please consult the microbiology review for more comprehensive information regarding microbiology results.

Other Endpoints

There was no significant difference in change from baseline between treatment groups with regards to changes in BMI, weight, or height during the course of the study.

CT02

Other Pulmonary Function Parameters

Similar to what was seen for FEV_1 % predicted, there was a significantly greater change in FEV_1 (L) from baseline to all visits, except visit 5 (1st off treatment) for the CHF 1538 arm compared to placebo in terms of FEV_1 (L). At visit 8 (end of 3rd on treatment) the change from baseline was an increase of 188 mL for CHF 1538 and 37 mL for placebo.

For both FVC (L) and FVC % predicted, there was a significantly greater change from baseline for all visits except visits 5 through 7 (end of 1st off cycle to end of 2nd on cycle). At visit 8, the change from baseline for FVC % predicted was 5.85% for the CHF 1538 arm and 1.52% for the placebo arm.

For $FEF_{25-75\%}$ in L/sec and $FEF_{25-75\%}$ % Predicted, there was a significantly greater change from baseline for all visits (in the case of percent predicted) except visit 5 (in the case of the absolute value). At visit 8, the change from baseline was 8.75% in the CHF 1538 group and 0.69% in the placebo group.

Similar to what was noted for FEV_1 % predicted, the change from baseline to visit 4 (end of 1st On Cycle) in the CHF 1538 arm was less in CT02 for these pulmonary function parameters than was seen in CT01. From visit 2 to visit 4, the change in FVC% predicted in CT01 was 13.6%, in CT02 was 5.79%. For $FEF_{25-75\%}$ % predicted, the change was 15.8% in CT01 and 11.6% in CT02.

Microbiological parameters

There was a significantly greater decrease in *Pa* Log_{10} CFU/g of sputum at the end of the 1st and 3rd on-treatment periods in the CHF 1538 arm as compared to the placebo arm. However, as noted earlier for CT01, it is unclear how clinically relevant this difference is. Of note, the decrease seen in 1st On Cycle for CHF 1538 was slightly less than what was seen in CT01 for the CHF 1538 arm (-2.16 log_{10} CFU/g decrease CT01 vs. -1.67 log_{10} CFU/g decrease CT02) albeit the sample size was much smaller. Please note the applicant table below.

Table 6.1.5.2: CT02 Log_{10} Bacterial Load[1] (CFU/gram) Mean Baseline and Mean Change from Baseline: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value[2]
1	Baseline	N	160	84	
		Mean	5.71	5.72	0.954
4	4 "ON" Drug	N	159	84	
		Mean Change from Baseline[3]	-1.67	-0.57	
		Difference (95% CI)	-1.10 (-1.59, -0.61)		< 0.001
5	8 "OFF" Drug	N	155	82	
		Mean Change from Baseline[3]	-0.97	-0.48	
		Difference (95% CI)	-0.50 (-0.97, -0.02)		0.040
8	20 "ON" Drug (1° endpoint)	N	155	78	
		Mean Change from Baseline[3]	-1.73	-0.62	
		Difference (95% CI)	-1.10 (-1.65, -0.56)		< 0.001
9	24 "OFF" Drug	N	150	77	
		Mean Change from Baseline[3]	-1.03	-0.72	
		Difference (95% CI)	-0.32 (-0.88, 0.25)		0.272

[1] a value of 20 was used for all instances where the *P. aeruginosa* pathogen was eradicated
[2] the significance level = 0.05
[3] Adjusted for baseline value
-EDR SDN# 0, 5.3.5.1.3 CT02 Study Report Body, Table 13

The applicant looked at microbiological outcomes for both treatment arms. The definitions for the various visits were as follows:

Figure 6.1.5- Definitions of Microbiological Outcomes in CT02

Visit 4

Eradication (elimination of the pseudomonas aeruginosae pathogens detected at Visit 1)

Persistence (presence of any pseudomonas aeruginosae pathogen detected at Visit 1)

Superinfection (appearance of any pathogen not detected at Visit 1)

Visit 5

Persistance of eradication (absence of pseudomonas aeruginosae pathogen detected at Visit 1 and eradicated at Visit 4 and still not detected at this visit)

Persistence (presence of a pseudomonas aeruginosae pathogen detected at Visit 1 and still present at V4 and at this visit)

Superinfection (appearance of any pathogen not detected at Visit 1 and Visit 4)

Reinfection (appearance at this visit of a pseudomonas aeruginosae pathogen detected at Visit 1 and eradicated at Visit 4)

Visit 8

Eradication (absence of the pseudomonas aeruginosae pathogen detected at Visit 5)

Persistence (presence of the pseudomonas aeruginosae pathogen detected at Visit 5)

Superinfection (appearance of a pathogen not detected at Visit 5)

Re-infection (appearance of pseudomonas aeruginosae pathogen eradicated at Visit 5)

Visit 9

Persistency of eradication (absence of the pseudomonas aeruginosae pathogen detected at Visit 5 but eradicated at Visit 8 and still not detected at this visit)

Persistence (presence of a any pseudomonas aeruginosae pathogens detected at Visit 5, Visit 8 and at this visit)

Superinfection (appearance of a pathogen not previously detected)

Re-infection (appearance of a pseudomonas aeruginosae pathogen eradicated at Visit 8)

-EDR SDN # 0, 5.3.5.1.5 Sample Case Report Form, pages 20, 27, 43, 50

Essentially Visits 1, 4, and 5 were treated as one cycle and Visits 5, 8, and 9 were treated as another cycle from a microbiological outcome standpoint. Using the above definition, it was found that at every visit there was little to no eradication seen in the CHF 1538 arm. Moreover, at Visits 4 and 8 (end of On-Treatment Cycle), the rate of persistence was equivalent to that seen for placebo. However, as in CT01, it appears that these microbiological outcome designations were treated as mutually exclusive though a subject might meet criteria for more than one category at a particular visit, and it is unclear in these situations how a particular designation was chosen. Thus, the value of these tables in unclear. Please note these findings in the following table.

Table 6.1.5.3: Microbiological Outcomes in CT02

Visit	Microbiological Outcome	CHF 1538 (N=161) n/N (%)	Placebo (N=84) n/N (%)
4	Eradication	0/134 (0%)	0/90 (0%)
	Persistence	108/134 (81%)	70/90 (78%)
	Superinfection	26/134 (19%)	20/90 (22%)
	Reinfection	0/134 (0%)	0/90 (0%)
5	Eradication	0/164 (0%)	0/92 (0%)
	Persistence	104/164 (63.4%)	67/92 (72.8%)
	Superinfection	30/164 (18.3%)	18/92 (19.6%)
	Reinfection	30/164(18.3%)	7/92 (7.6%)
8	Eradication	1/132 (0.8%)	0/85 (0%)
	Persistence	96/132 (72.7%)	62/85 (72.9%)
	Superinfection	27/132 (20.5%)	19/85 (22.4%)
	Reinfection	8/132 (6.1%)	4/85 (4.7%)
9	Eradication	1/138 (0.7%)	0/74 (0%)
	Persistence	93/138 (67.4%)	59/74 (79.7%)
	Superinfection	20/138 (14.5%)	12/74 (16.2%)
	Reinfection	24/138 (17.4%)	3/74 (4.1%)

-EDR SDN# 0, 5.3.5.1.3, Table 177

Please note that for the microbiological outcome data, sample sizes for the treatment arms at various visits was not stable.

Pulmonary Exacerbation

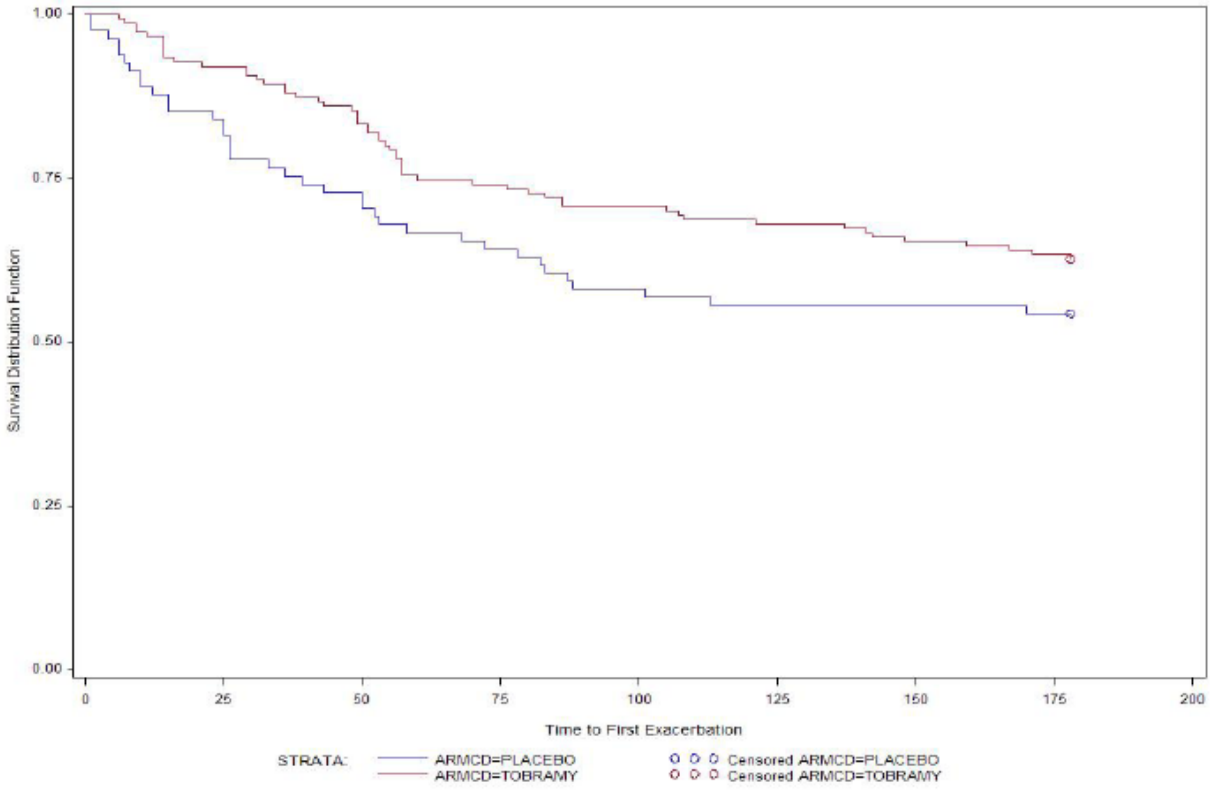
The applicant calculated the percentage of pulmonary exacerbations occurring at each visit for both arms. This data was disregarded primarily due to confusion over how this data was collected. For example a subject may have met the criteria for a pulmonary exacerbation at visit 4 and if this exacerbation was prolonged would be counted again at visit 5. From this reviewer's perspective, it would be important to know how many subjects in each arm had an exacerbation over the course of the study as well as the time to first prespecified exacerbation. The proportion of subjects in each arm with a pulmonary exacerbation over the course of the study is displayed in the table below. It should be noted that this table only takes into account patients who met the prespecified criteria for exacerbation and does not take into account those patients who did not meet criteria but were still treated as an exacerbation. The applicant provided a list of such patients and when those subjects are factored in, the proportions change to 53.6% for Placebo and 47.8% for CHF 1538.

Table 6.1.5.4 CT02 Proportion of Subjects with a Pre Specified Pulmonary Exacerbation

Placebo	43/84= 51.2%
CHF 1538	66/161= 41%

The statistical reviewer also looked at time to first pulmonary exacerbation in the ITT population. Though not significant, there was a trend towards a difference favoring CHF 1538. Please note the statistical reviewer figure below.

Figure 6.1.5.1: Time to First Exacerbation in CT02- ITT



-Statistical Review, Figure 3.4

Clinical Symptoms Score

The applicant presented data about changes in wheezing and cough scores throughout the course of the study. Because it is not clear how this score table was created, what differences in score actually mean, etc. these results are not discussed further.

Hospitalizations

The proportion of subjects in the CHF 1538 arm with an unplanned disease-related hospitalization was lower than in the placebo group as noted in the table below. The mean hospital stay for such patients was also lower. Please note the applicant table below.

Table 6.1.5.5: CT02 Analysis of 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 hospitalized		
Mean	1.61	4.35
Range	0-27	0-42

-EDR SDN#18, 1.11.2- Safety Information Amendment, Table 10- this is actually a corrected table submitted by the applicant at a later date because of incorrect durations recorded for 2 placebo and 1 CHF1538 subject

Besides these unplanned hospitalizations, there were 31 (20 CHF 1538 arm, 11 Placebo arm) subjects in the safety population who had "planned hospitalizations" where they might receive "preventive" courses of antipseudomonal antimicrobials. However, it was unclear from a review of the CRF's whether in some of these cases, a pulmonary exacerbation was actually occurring in a mild form. For example, one subject (26-016) had a drop in her FEV_1 % predicted from 83% to 70% and then was enrolled for "planned therapy" with tazobactam, cefoperazone, and ciprofloxacin. If these patients are added in (17 CHF 1538 patients added and 9 Placebo patients added due to some patients who had both planned and unplanned hospitalizations), the proportions change to 20.5% for CHF 1538 and 35.3% for placebo. The applicant states that the time to first disease-related, unplanned hospitalization was significantly increased for CHF 1538, but no clear table presented this information and the figure provided was incomplete. Per the statistical reviewer, there was no significant difference in time to hospitalization, though there was a clear trend favoring the CHF 1538 arm.

Days Lost From School and Work

There were significantly fewer days lost from school and work for the CHF 1538 arm at visits 4 and 5 than for placebo with a nonsignificant trend towards the same in visit 6 and 7. In general the improvement was by about 1-2 days.

Use of Antipseudomonal medications

The CHF 1538 arm had a lower proportion of subjects using antipseudomonal medications after Visit 2, had a longer time to first anti-pseudomonal use and a shorter duration of use. Please note the applicant table below.

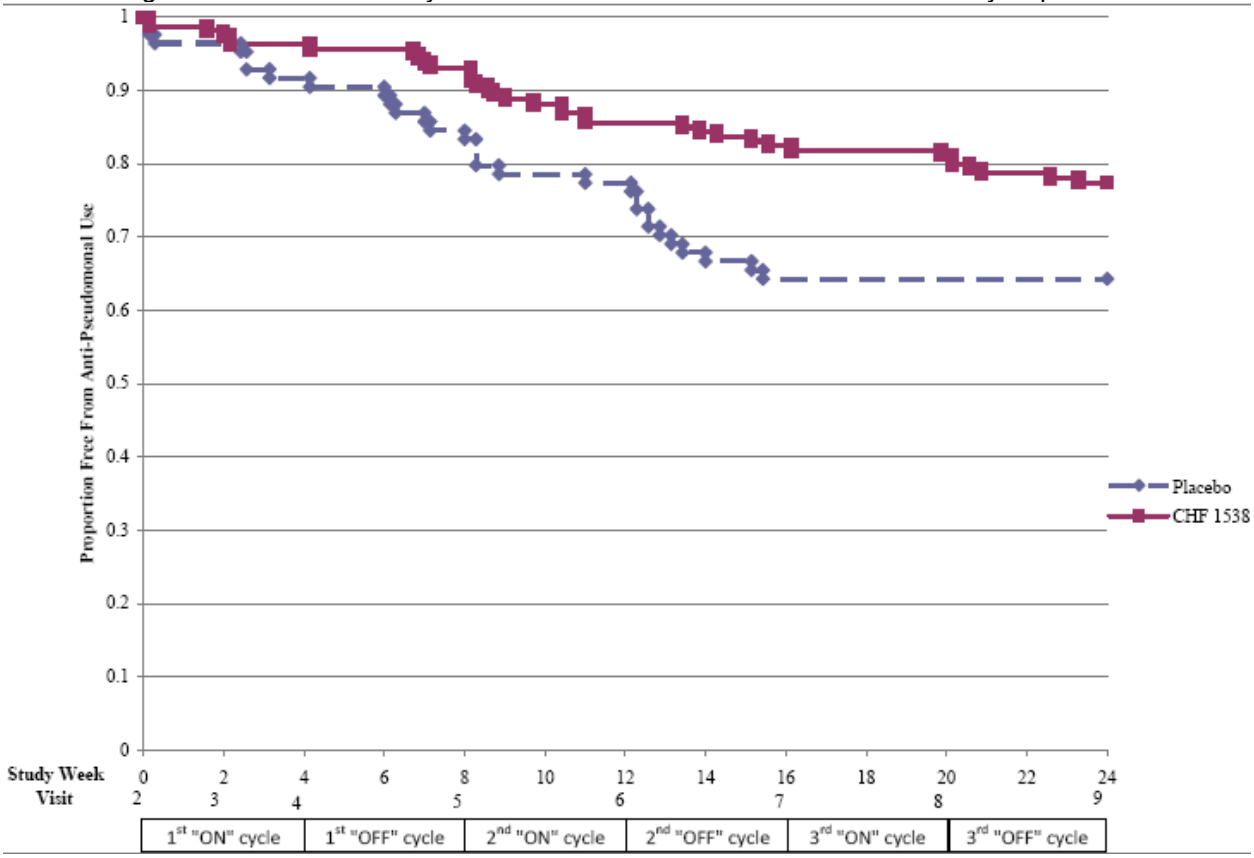
Table 6.1.5.6: CT02 Analysis of IM or IV Anti-PA Use and the Number of Days Using IM or IV Anti- PA: Safety Population

	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.
-EDR SDN# 0, 5.3.5.1.3, CT02 Study Report Body, Table 23.

Taking out individuals who started antipseudomonals on study day 1, the proportions are 21.7% for CHF 1538 and 32.9% for Placebo (mean duration and time to first use not recalculated; two placebo individuals started antipseudomonals on day 1 for duration of 41 and 85 days, respectively and 2 CHF 1538 subjects started antipseudomonals on Day 1 and both had durations of 14 days). The applicant figure below shows the time to first antipseudomonal use for both arms.

Figure 6.1.5.2: CT02 Analysis of Time to First IM or IV Anti-PA Use: Safety Population



-EDR SDN# 0, 5.3.5.1.3, CT02 Study Report Body, Figure 19

Height, Weight, BMI

There were no significant differences for change in height from baseline for the two arms but there was a significant difference for change in weight in BMI at all visits for the two arms. However, though the CHF 1538 arm had the greater increase for weight and BMI, the actual changes appear small and it is unclear how clinically relevant this is. See the applicant weight table below

Table 6.1.5.7: CT02 Weight (kg) Mean Baseline and Mean Change From Baseline: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
1	Baseline	N	161	84	
		Mean	40.7	39.9	0.690
4	4 "ON" Drug	N	161	84	
		Mean Change from Baseline[1]	0.76	0.28	0.003
		Difference (95% CI)	0.48 (0.16, 0.79)		
5	8 "OFF" Drug	N	160	83	
		Mean Change from Baseline[1]	0.87	0.38	0.011
		Difference (95% CI)	0.49 (0.12, 0.87)		
6	12 "ON" Drug	N	158	81	
		Mean Change from Baseline[1]	1.33	0.70	0.007
		Difference (95% CI)	0.63 (0.18, 1.09)		
7	16 "OFF" Drug	N	158	81	
		Mean Change from Baseline[1]	1.43	0.83	0.019
		Difference (95% CI)	0.60 (0.10, 1.11)		
8	20 "ON" Drug	N	157	79	
		Mean Change from Baseline[1]	1.65	0.84	0.003
		Difference (95% CI)	0.80 (0.27, 1.34)		
9	24 "OFF" Drug	N	154	78	
		Mean Change from Baseline[1]	1.79	0.99	0.006
		Difference (95% CI)	0.81 (0.24, 1.37)		

[1] Adjusted for baseline value, gender, and age (ages > 18 truncated to 18 years).

-EDR SDN# 0, 5.3.5.1.3, CT02 Study Report Body, Table 25

CT03

Please note that many of these calculations are done with the ITT population – in this group there were 15 individuals who received the nonassigned treatment (6 patients assigned to TOBI and received CHF 1538, and 9 patients assigned to CHF 1538 and received TOBI). No analyses were done by the applicant on the as treated population for secondary endpoints.

Other Pulmonary Function Parameters

This review will focus on the change from visit 2 to Visit 4 (on treatment cycle) for these parameters.

FEV_1 (L)

The change from baseline in mean FEV_1 (L) to Visit 4 for CHF 1538 was 200 mL and for TOBI it was 220 mL.

FVC (% Predicted)

The change from baseline in mean FVC % predicted to Visit 4 was 4.83% for CHF 1538 and 5.58% for TOBI. At Visit 5 (end of off-treatment), the change was 2.7% for CHF 1538 and 5.0% for TOBI.

FVC (L)

The change from baseline in mean FVC (L) to Visit 4 was 160 mL for CHF 1538 and 180 mL for TOBI.

$FEF_{25-75\%}$

The change from baseline in mean $FEF_{25-75\%}$ % Predicted to Visit 4 was 10.44% for CHF 1538 and 9.32% for TOBI.

The change from baseline in mean $FEF_{25-75\%}$ L/sec to Visit 4 was 340 mL/sec for CHF 1538 and 290 mL/sec for TOBI.

As noted earlier for the primary endpoint, the degree of change seen from baseline to Visit 4 in the mean values of these parameters in CT03 was less than what was seen in CT01. For example for FVC % predicted the change in mean values was 13.9% in CT01 and 4.8% in CT03. Similarly, for $FEF_{25-75\%}$ % predicted the change in mean values was 16.3% in CT01 and 10.4% in CT03.

Microbiological Endpoints

There was a -2.14 $\log_{10}$ CFU/g decrease in *Pa* colony counts from visit 2 to visit 4 for CHF 1538 and -2.07 for TOBI. It's unclear how clinically relevant this decrease is. This decrease is similar to what was seen for CHF 1538 in CT01 over the on-treatment period and slightly improved from what was seen in CT02 over the 1st on-treatment period. Please note the applicant table below.

Table 6.1.5.8: CT03 Microbiological Tests: *P. aeruginosa* Log_{10} Bacterial Load (CFU^1/gram) Change from Baseline (Visit 1): ITT Population

	CHF 1538 (N=158)	TOBI (N=163)
Visit 4		
N	152	156
Mean (SD)	-2.14 (2.41)	-2.07 (2.20)
95% CI	[-2.52; -1.75]	[-2.42; -1.72]
Median	-2.09	-1.79
Min/Max	-7.48/4.00	-7.48/1.72
Missing	6	7
Visit 5		
N	147	147
Mean (SD)	-0.72 (2.17)	-0.87 (2.23)
95% CI	[-1.07; -0.36]	[-1.24; -0.51]
Median	-0.40	-0.48
Min/Max	-6.54/4.90	-7.48/6.08
Missing	11	16

Source data: Appendix 16.2.6.2 and 16.2.6.3
[1] colony forming units
If a patient has more than one *P. aeruginosa* morphotype at a given visit, and therefore more than one bacterial load value, then the bacterial load value corresponding to the highest tobramycin MIC value regardless of the *P. aeruginosa* morphotype was used.
If the tobramycin MIC value was the same for different *P. aeruginosa* morphotypes, then the bacterial load value corresponding to morphotype 1 (mucoid colony) was used. If morphotype 1 was not available, bacterial load value corresponding to morphotype 2 (dry colony) was used.
In instances of *P. aeruginosa* eradication (i.e., < 20 CFU/g, based upon the dilution factor in the plating and counting procedure), the numeric value of 20 CFU/g was used for bacterial load.
Where the bacterial load was recorded as '> 600000000 CFU/g', the numeric value used for calculation of bacterial load was 600000000.
Patient 707002 is missing at V1 because the sputum was received partially frozen and consequently excluded from the analysis.

-EDR SDN# 0, 5.3.5.1.3 CT03 Study Report Body, Table25.

The rate of eradication of *Pa* was similar and low in both arms at Visit 4. The rate of reinfection was higher for CHF 1538 at Visit 5. Please note the applicant table below.

Table 6.1.5.9: CT03 Microbiological Tests: Microbiological Outcomes (Eradication, Persistence, Superinfection, Re-infection); Summary by Visit: ITT Population

	CHF 1538 (N=158)	TOBI (N=163)	CMH Test[1]
Visit 1			
Presence of *P. aeruginosa*	158 (100%)	162 (100%)	
Absence of *P. aeruginosa*	0	0	
Missing	0	1	
Visit 4[2]			
Eradication	14 (9.2%)	11 (7.1%)	p = 0.692
Persistence	126 (82.9%)	133 (85.3%)	
Superinfection	12 (7.9%)	12 (7.7%)	
Missing	6	7	
Visit 5[3]			
Eradication	4 (2.7%)	5 (3.4%)	p = 0.128
Persistence	116 (78.9%)	122 (83.0%)	
Superinfection	14 (9.5%)	14 (9.5%)	
Re-infection	13 (8.8%)	6 (4.1%)	
Missing	11	16	

Source data: Appendix 16.2.6.2 and 16.2.6.3

[1] Cochran-Mantel-Haenszel test controlling for country

Microbiological outcomes are derived considering all *P. aeruginosa* morphotypes together.

[2] At Visit 4:

Eradication = elimination of *P. aeruginosa*

Persistence = persistence of *P. aeruginosa* detected at V1

Superinfection = appearance of a pathogen (other than *P. aeruginosa*) not detected at V1

[3] At Visit 5:

Eradication = elimination of *P. aeruginosa*

Persistence = persistence of *P. aeruginosa* detected at V4 (or at V1 if V4 missing)

Superinfection = appearance of a pathogen (other than *P. aeruginosa*) not detected at V4 or at V1

Re-infection = re-appearance of *P. aeruginosa* detected at V1 and eradicated at V4

Superinfection supersedes eradication. Persistence for *P. aeruginosa* supersedes superinfection. Re-infection for *P. aeruginosa* supersedes superinfection.

Patient 707002 is missing at V1 because the sputum was received partially frozen and consequently excluded from the analysis.

-EDR SDN# 0, 5.3.5.1.3 CT03 Study Report Body, Table 36

Interestingly, applicant data also showed that while persistence occurred with isolates with higher MICs, this also occurred with a substantial portion of isolates with low MICs. Reinfection appeared to occur primarily in isolates with lower MICs.

It is interesting to note, that the eradication and persistence rates for CHF 1538 seen in this trial correspond more closely to those of the CHF 1538 arm in CT02 rather than those of CT01. Please note the table below.

Table 6.1.5.10: Comparison of *Pa* Eradication and Persistence Rates in the CHF 1538 Arm for CT01, CT02, CT03

	Eradication Rates V4	Persistence Rates V4
CT01	10/29=34.5%	11/29= 37.9%
CT02	0/134= 0%	108/134= 80.6%
CT03	14/152=9.2%	126/152=82.9%

Weight and BMI

Mean changes in weight and BMI on treatment for the CHF 1538 arm were minimal and unlikely to be clinically relevant.

6.1.6 Other Endpoints

The main endpoints analyzed have been discussed above.

6.1.7 Subpopulations

CT01

Subgroup analyses were performed for the primary efficacy variable with gender, age, baseline FEV_1 % predicted, and baseline MIC. No significant interactions were detected for these subgroups. However, in some subgroups, sample sizes were small (such as the age > 17 years group, or MIC > 16 mcg/dL group) and since the study was not designed initially to perform these subgroup analyses, the power to detect such interactions is low. Notably, there appeared to be a nonsignificant trend towards less success for the oldest subgroup (>17 years) and patients with baseline FEV_1 % predicted <50% (treatment interaction by age and baseline FEV_1 % predicted status, respectively), but given the caveats listed above, these trends must be viewed with caution. Please note the applicant table below.

Table: 6.1.7: CT01 Mean Change From Baseline in FEV_1 % Predicted at Last On Drug Visit
Subgroup Analyses: ITT Population

	CHF 1538	Placebo
Gender		
Male		
Mean[3] (N[4])	13.58 (15)	2.62 (17)
Difference (95% CI[5])	10.96 (-0.68, 22.61)	
Female		
Mean[3] (N)	18.46 (14)	2.83 (12)
Difference (95% CI)	15.63 (2.62, 28.64)	
Interaction P-value	0.594	
Age Group		
6-12 years		
Mean[3] (N)	18.03 (19)	1.92 (12)
Difference (95% CI)	16.11 (3.98, 28.24)	
13-17 years		
Mean[3] (N)	15.77 (7)	1.38 (11)
Difference (95% CI)	14.39 (-1.53, 30.31)	
> 17 years		
Mean[3] (N)	2.80 (3)	6.82 (6)
Difference (95% CI)	-4.01 (-27.87, 19.84)	
Interaction P-value	0.318	

Baseline FEV_1 % Predicted Normal		
< 50%		
Mean[3] (N)	3.67 (13)	-6.55 (8)
Difference (95% CI)	10.22 (-4.02, 24.46)	
≥ 50%		
Mean[3] (N)	24.99 (16)	6.92 (21)
Difference (95% CI)	18.07 (7.61, 28.52)	
Interaction P-value	0.375	
Baseline MIC[6]		
< 16 µg/mL		
Mean[3] (N)	15.61 (22)	2.23 (23)
Difference (95% CI)	13.38 (3.52, 23.23)	
≥ 16 µg/mL		
Mean[3] (N)	17.19 (7)	-0.61 (4)
Difference (95% CI)	17.80 (-2.90, 38.50)	
Interaction P-value	0.700	

[1] forced expiratory volume in 1 second as percent predicted normal
[2] Intent-to-Treat
[3] adjusted for baseline value
[4] total number of patients.
[5] confidence interval
[6] minimum inhibitory concentration

EDR SDN# 0, 5.3.5.1.3, CT01 Study Report Body, Table 24

CT02

Subgroup analyses were performed for both the primary and secondary endpoints.

For the primary efficacy variable, subgroup analyses were performed by the sponsor for gender, age, baseline FEV_1 % predicted, baseline rhDNase use, baseline MIC, and by country treatment sites. No significant treatment interactions were noted. Please see the applicant tables below.

Table 6.1.7.1: CT02 Mean Change From Baseline in % Predicted FEV_1 at Last "ON" Drug Visit Subgroup Analyses: ITT Population

	CHF 1538	Placebo
Gender		
Male		
Mean[1] (N)	8.07 (89)	0.13 (46)
Difference (95% CI)	7.94 (3.27, 12.61)	
Female		
Mean[1] (N)	5.60 (72)	1.17 (38)
Difference (95% CI)	4.43 (-0.72, 9.58)	
Interaction P-value	0.320	
Age Group		
6-12 years		
Mean[1] (N)	9.98 (63)	2.55 (37)
Difference (95% CI)	7.43 (2.18, 12.68)	
13-17 years		
Mean[1] (N)	7.42 (47)	-1.96 (25)
Difference (95% CI)	9.38 (3.11, 15.64)	
> 17 years		
Mean[1] (N)	2.70 (51)	0.53 (22)
Difference (95% CI)	2.17 (-4.31, 8.64)	
Interaction P-value	0.264	

Baseline rhDNase Use		
Yes		
Mean[1] (N)	6.65 (142)	1.09 (74)
Difference (95% CI)	5.56 (1.88, 9.25)	
No		
Mean[1] (N)	9.42 (19)	-3.19 (10)
Difference (95% CI)	12.60 (2.53, 22.68)	
Interaction P-value	0.197	
Baseline % Predicted FEV_1		
< 50%		
Mean[1] (N)	2.98 (48)	-1.00 (18)
Difference (95% CI)	3.98 (-3.09, 11.04)	
≥ 50%		
Mean[1] (N)	8.52 (113)	1.28 (66)
Difference (95% CI)	7.24 (3.27, 11.20)	
Interaction P-value	0.429	
Baseline MIC		
< 16 µg/mL		
Mean[1] (N)	7.39 (140)	0.88 (66)
Difference (95% CI)	6.51 (2.65, 10.37)	
≥ 16 µg/mL		
Mean[1] (N)	4.33 (20)	-2.09 (14)
Difference (95% CI)	6.42 (-2.53, 15.36)	
Interaction P-value	0.985	

EDR SDN# 0, 5.3.5.1.3 CT02 Study Report Body, Table 27.

Table 6.1.7.2: CT02 Mean Change From Baseline in % Predicted FEV_1 at Last "ON" Drug Visit by Country: ITT Population

	CHF 1538	Placebo
Country		
Hungary		
Mean[1] (N)	10.17 (36)	9.34 (20)
Difference (95% CI)	0.83 (-6.15, 7.81)	
Poland		
Mean[1] (N)	5.68 (82)	-2.61 (44)
Difference (95% CI)	8.28 (3.60, 12.96)	
Russia		
Mean[1] (N)	6.77 (43)	-1.15 (20)
Difference (95% CI)	7.92 (1.12, 14.72)	
Interaction P-value	0.195	

[1] Adjusted for baseline value.

-EDR SDN# 0, 5.3.5.1.3 CT02 Study Report Body, Table 28

There does appear to be a nonsignificant trend toward a treatment interaction by country (particularly the Hungary site - less improvement vs. placebo in Hungarian subjects), age, and baseline rhDNase usage, however samples sizes in many of these subgroups were small or unevenly distributed. Also, the trials were not designed to look at these subgroup analyses, so the power to detect interactions is low. It is notable, that in both CT01 and CT02, a trend toward decreasing success with the oldest age group was noted.

The sponsor also performed subgroup analyses for two secondary endpoints: time to first disease related hospitalization and time to first IM or IV antipseudomonal use. The subgroups analyzed were gender, age, and baseline rhDNase use. Please note the applicant tables below.

Table 6.1.7.3: CT02 Analysis of Time to First Disease-Related, Unplanned Hospitalization Subgroup Analyses: Safety Population

	CHF 1538	Placebo
Gender		
Male		
n/N (%) with one or more hospitalizations	8/89 (9.0%)	7/46 (15.2%)
Hazard Ratio (95% CI)	0.561 (0.203 – 1.548)	
Female		
n/N (%) with one or more hospitalizations	8/72 (11.1%)	14/39 (35.9%)
Hazard Ratio (95% CI)	0.260 (0.109 – 0.619)	
Interaction P-value	0.257	
Age Group		
6-12 years		
n/N (%) with one or more hospitalizations	6/63 (9.5%)	9/38 (23.7%)
Hazard Ratio (95% CI)	0.350 (0.125 – 0.985)	
13-17 years		
n/N (%) with one or more hospitalizations	4/47 (8.5%)	9/25 (36.0%)
Hazard Ratio (95% CI)	0.206 (0.063 – 0.671)	
> 17 years		
n/N (%) with one or more hospitalizations	6/51 (11.8%)	3/22 (13.6%)
Hazard Ratio (95% CI)	0.840 (0.210 – 3.361)	
Interaction P-value	0.321	
Baseline rhDNase Use		
Yes		
n/N (%) with one or more hospitalizations	14/142 (9.9%)	20/75 (26.7%)
Hazard Ratio (95% CI)	0.323 (0.163 – 0.640)	
No		
n/N (%) with one or more hospitalizations	2/19 (10.5%)	1/10 (10.0%)
Hazard Ratio (95% CI)	1.054 (0.096 – 11.63)	
Interaction P-value	0.344	

- EDR SDN#0, 5.3.5.1.3, CT02 Study Report Body, Table 29

Table 6.1.7.4: CT02 Time to First IM or IV Anti-PA Use Subgroup Analyses: Safety Population

	CHF 1538	Placebo
Gender		
Male		
n/N (%) with at least one dose	17/89 (19.1%)	12/46 (26.1%)
Hazard Ratio (95% CI)	0.700 (0.334 – 1.466)	
Female		
n/N (%) with at least one dose	20/72 (27.8%)	18/39 (46.2%)
Hazard Ratio (95% CI)	0.478 (0.253 – 0.905)	
Interaction P-value	0.447	
Age Group		
6-12 years		
n/N (%) with at least one dose	9/63 (14.3%)	13/38 (34.2%)
Hazard Ratio (95% CI)	0.343 (0.147 – 0.804)	
13-17 years		
n/N (%) with at least one dose	13/47 (27.7%)	13/25 (52.0%)
Hazard Ratio (95% CI)	0.500 (0.232 – 1.079)	
> 17 years		
n/N (%) with at least one dose	15/51 (29.4%)	4/22 (18.2%)
Hazard Ratio (95% CI)	1.637 (0.543 – 4.933)	
Interaction P-value	0.087	
Baseline rhDNase Use		
Yes		
n/N (%) with at least one dose	33/142 (23.2%)	25/75 (33.3%)
Hazard Ratio (95% CI)	0.626 (0.372 – 1.054)	
No		
n/N (%) with at least one dose	4/19 (21.1%)	5/10 (50.0%)
Hazard Ratio (95% CI)	0.335 (0.089 – 1.259)	
Interaction P-value	0.335	

-EDR SDN#0, 5.3.5.1.3, CT02 Study Report Body, Table 30

For time to first disease-related unplanned hospitalization, there were no significant interactions but again there was a trend toward less improvement in this parameter for the oldest age group (treatment interaction by age). For the time to first IM or IV

antipseudomonal endpoint, again there were no significant interactions; however, there was a nonsignificant trend toward decreased effectiveness for the oldest age group (treatment interaction by age).

The consistent trend toward decreased effectiveness in the oldest age group raises the issue of the existence of a true treatment interaction by age. However, given the limited ability of this trial to detect such an interaction, no clear assessment can be made. This issue should continued to be explored either in new clinical trials (in the event of a complete response) or through post marketing monitoring (in the event of approval of the drug). It is possible that, unsurprisingly, older patients are likely to have poorer baseline lung function. However, even if this is the case, it would worthwhile to know which age groups might benefit less from a treatment so that patients can make informed choices about whether they wish to adopt a specific medication.

CT03

Subgroup analyses on the primary endpoint were done on sex, age, baseline FEV_1 % predicted status, and baseline rhDNase usage. No significant interaction was noted for treatment by sex. When looking at age alone there is a significant interaction (less response in oldest age group), but when looking at a treatment interaction by age, no significant interaction is noted. No treatment interaction by use of rhDNase at baseline was noted. While there does appear to be an interaction based on baseline FEV_1 % predicted alone (less effect in subjects with baseline FEV_1 % predicted < 50% for both treatment arms) there is no significant treatment interaction based on FEV_1 % predicted. It should be noted that in many of these subgroup analyses, and also in evaluations of other pulmonary function variables, an interaction by country for both treatment arms was either significant or close to significance; however this was not thoroughly addressed by the applicant.

CT01 and CT02 Pooled Analyses

For the pooled study, subgroup analyses on the primary efficacy variable were performed for gender, age, baseline FEV_1 % predicted status, and baseline MIC status. For gender (p=0.683), baseline FEV_1 % predicted (p=.371), and baseline MIC status (p=.406) no significant interaction with treatment was noted. In addition various subgroup analyses were performed for particular concomitant medications, including inhaled non-rhDNase mucolytics (interaction p-value=0.838), inhaled rhDNase (interaction p-value=0.129), inhaled steroids (interaction p-value=0.724), inhaled short-acting beta agonists (interaction p-value=0.124), inhaled short-acting muscarinic agonists (interaction p-value=0.418), inhaled long-acting beta agonists (interaction p-value=0.723), inhaled glucocorticoids (interaction p-value=0.644) and glucocorticoids or steroids (interaction p-value=0.660); no significant interactions with treatment were noted. However, as in the individual trials, a significant interaction by age with treatment

was observed; older patients received less benefit from CHF 1538. Please note the applicant table below.

Table 6.1.7.5: Pooled CT01 and CT02 Mean Change From Baseline in % Predicted FEV_1 at Last On-Drug Visit of First On-Drug Cycle Age and Gender Subgroup Analysis: Integrated ITT Population

	CHF 1538	Placebo
Gender		
Male		
Mean[1] (N)	11.55 (104)	2.43 (63)
Difference (95% CI)	9.11 (5.12, 13.10)	
Female		
Mean (N)	10.09 (86)	2.21 (50)
Difference (95% CI)	7.88 (3.44, 12.32)	
Interaction P-value	0.683	
Age Group		
6-12 years		
Mean[1] (N)	13.24 (82)	1.73 (49)
Difference (95% CI)	11.51 (7.09, 15.92)	
13-17 years		
Mean[1] (N)	11.23 (54)	1.04 (36)
Difference (95% CI)	10.19 (4.90, 15.48)	
> 17 years		
Mean[1] (N)	5.70 (54)	4.31 (28)
Difference (95% CI)	1.39 (-4.36, 7.15)	
Interaction P-value	0.018	

-EDR SDN#0, 5.3.5.3.1 ISE Tables and Figures, Table 19

There was concern, particularly with regards to the placebo-controlled studies, that there might be an asymmetrical distribution of patients initiating typical concomitant chronic CF medications (such as oral or inhaled steroids, inhaled beta-agonists, mucolytics, and azithromycin) just prior to starting study. It was unclear what such an asymmetrical distribution might have on the primary efficacy variable. Thus, the applicant was asked to provide data on how many patients had started beta-agonists two weeks prior to starting study drug and how many patients had started oral or inhaled steroids, mucolytics, and azithromycin within two months of starting study drug. These time periods were chosen based on informal discussions with the pulmonary

division about how quickly the effect of these drugs would plateau. The following applicant table displays those results (the statistical files provided with this table were cross checked with this reviewer's evaluation of CRF's; the applicant appeared to select appropriately the patients in question).

Table 6.1.7.6: Patients Who Started Chronic Inhaled or Oral Steroids, Mucolytics (Including Pulmozyme), and Chronic Azithromycin Within 2 Months of Visit 2, or β-agonist Within 2 Weeks of Visit 2

Study	Started within 2 weeks of Visit 2	Started within 2 months of Visit 2		
	β-agonist	Chronic Inhaled or Oral Steroids	Mucolytics (Including Pulmozyme)	Chronic Azithromycin
CT01				
CHF 1538 (N=29)	0 (0%)	0 (0%)	5 (17.24%)	0 (0%)
Placebo (N=30)	0 (0%)	1 (3.33%)	3 (10.00%)	0 (0%)
CT02				
CHF 1538 (N=161)	3 (1.86%)	6 (3.73%)	18 (11.18%)	4 (2.48%)
Placebo (N=85)	1 (1.18%)	0 (0%)	9 (10.59%)	5 (5.88%)
CT03				
CHF 1538 (N=156)	2 (1.28%)	2 (1.28%)	14 (8.97%)	4 (2.56%)
TOBI (N=168)	0 (0%)	3 (1.79%)	11 (6.55%)	3 (1.79%)

EDR SDN # 18, 1.11.2,Safety Information Amendment, Table 5

Looking at the proportion of subjects in each treatment arm who fell into any one of the categories, the proportions were fairly comparable though in CT01, there was slight disparity between the two arms.

Table: 6.1.7.7: Proportion of Subjects Starting Inhaled or Oral Steroids, Mucolytics and Chronic Azithromycin within 2 months of Visit 2, or Beta Agonists within 2 Weeks of Visit 2

Trial	CHF 1538	Placebo/TOBI
CT01	5/29=17.2%	4/30= 13.3%
CT02	26/161= 16.1%	15/85= 17.6%
CT03	17/156=10.9%	14/168= 8.3%

Overall, these proportions were fairly comparable.

There was also concern that baseline comorbid conditions that could affect pulmonary function could be asymmetrically distributed. The applicant was asked to provide a list of all patients who might have a baseline comorbid condition that could affect pulmonary function for all three trials. The applicant first had a physician decide what would constitute such comorbid conditions and created the following table:

Table 6.1.7.8: Significant Comorbid Conditions with the Potential to Affect Pulmonary Function from CT01, CT02 and CT03 Studies

CT01 (Description as coded)	CT02 (Description)	CT03 (Preferred Term)
Asthma, unspecified w/o mention status asthmaticus	Asthma BR Asthma Asthma Bronchiale Bronchial Asthma	Asthma
Bronchitis, not specified as acute or chronic Unspecified chronic bronchitis Other diseases of trachea and bronchus NEC	Bronchitis Bronchiolectasia Bronchiectases Syndrome of bronchoobstruction	Bronchitis chronic Bronchitis chronic Bronchitis bacterial Bronchiectasis Bronchitis chronic Bronchopulmonary aspergillosis allergic Bronchopulmonary aspergillosis Aspergillosis
Secondary cardiomyopathy, other and unspecified	Cardiomyopathy Cor Pulmonale Chronic Cor Pulmonale	Cardiomyopathy Cor pulmonale Cor pulmonale chronic
Lobectomy of lung Pulmonary collapse Other diseases of lung not elsewhere classified Other dyspnea and respiratory abnormalities	Hypertension in arteria pulmon Fibrosis lobi superior righ	Pulmonary hypertension Pulmonary fibrosis

EDR SDN # 18, 1.11.2,Safety Information Amendment, Table 6

The following applicant table shows how these conditions were distributed among the two arms of the three phase 3 trials.

Table: 6.1.7.9: Patients Who Had a Significant Comorbid Condition Having the Potential to Impact Pulmonary Function

Study	Presence of Comorbid Condition
CT01	
CHF 1538 (N=29)	4 (13.79%)
Placebo (N=30)	9 (30.00%)
CT02	
CHF 1538 (N=161)	22 (13.66%)
Placebo (N=85)	10 (11.76%)
CT03	
CHF 1538 (N=156)	56 (33.33%)
TOBI (N=168)	48 (30.77%)

EDR SDN # 18, 1.11.2,Safety Information Amendment, Table 8

From these data, it's clear that there was an asymmetrical distribution in CT01. Whether this partially accounted for the primary efficacy results seen in the trial (particularly why CHF 1538's effect on FEV_1 % predicted was so much greater than that of placebo's, something not seen in CT02) is unclear. However, it should be noted that though there were roughly equivalent percentages of comorbid conditions in the CHF 1538 arm of CT01 and CT02, the change in FEV_1 % predicted differed substantially between the two.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing used in the phase 3 trials mirrors that of the reference drug TOBI and thus will not be discussed further. Please see the clinical pharmacology review by Dr. Yongheng Zhang for further details, including a more detailed review of study CP01-*Comparative Bioavailability Study of Aerosolized Tobramycin in Cystic Fibrosis Patients After Administration of 300mg CHF 1538 Tobramycin 300mg/4ml Inhalation Solution or TOBI.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No adequate way to assess persistence of CHF 1538's effect on FEV_1 % predicted exists from the submitted data. Of the three phase 3 trials, only the CT02 trial involved a somewhat extended period of treatment (3 cycles of 28 day On/Off treatment). There did appear to be some retention of effect to the end of 3rd Cycle in this trial (though the effect was gradually decreasing), but a longer open label

extension/post marketing observation would be needed to better assess this issue. There appears to be an effect of treatment drug as early as 2 weeks after the start of treatment. However, as discussed earlier, the magnitude of effect differs somewhat between CT01 and CT02/CT03 so the level of effect is unclear.

6.1.10 Additional Efficacy Issues/Analyses

Microbiology

The microbiology review was performed by Dr. Fred Marsik. Please see his review for a detailed evaluation of susceptibility issues, etc. with study drug CHF 1538. Moreover, microbiology outcome data has been discussed already in prior sections. His conclusions were as follows:

The data from CT01 and CT02 individually do not suggest any nonstatistical significant microbiological adverse events from use of aerosolized tobramycin for treating CF patients. Combining the data suggests the same.

Treatment-Emergent Microorganisms

In the CHF 1538-treated patients the organism identified most frequently was the Gram positive bacterium Staphylococcus aureus with the yeast Candida species (including C. albicans) being the next t most prevalent. In the placebo-treated group the same two organisms were the most prevalent. There was a variety of Gram-negative bacteria identified in both treatment groups, though the incidence of any individual species was low.

MIC Changes During Therapy

Table 42 is an assessment of MIC shifts from individual isolates from the baseline tobramycin MIC to those values observed at end of therapy or at follow-up. MIC values were unchanged (+/- 2-fold) for 41.7% and 42.5% in the CHF 1538 group at the end of therapy and the follow-up visit, and for 33.2% and 28.5% in the placebo group respectively. However, at both the end of therapy and the follow-up visits, a greater percentage of isolates in the CHF 1538 group showed a >4-fold increase in MIC than isolates in the placebo group. MIC values decreased >4-fold in a small percent of isolates in both treatment groups. Please note the applicant table below:.

Table 6.1.10: Assessment of MIC Shifts from Observed Baseline Values and MIC Values Observed at End of First "On" Cycle and at End of the First "Off" Cycle, Integrated Results for CT01 and CT02, ITT Population

Evaluability Criteria	Baseline vs. End of ON' Cycle		Baseline vs. End of 'OFF' Cycle	
	CHF 1538	Placebo	CHF 1538	Placebo
MIC increased[1]	22/187 (11.8%)	4/187 (2.1%)	30/207 (14.5%)	9/207 (4.3%)
MIC unchanged[2]	78/187 (41.7%)	62/187 (33.2%)	88/207 (42.5%)	59/207 (28.5%)
MIC decreased[3]	10/187 (5.3%)	11/187 (5.9%)	14/207 (6.8%)	7/207 (3.4%)

[1] Patients whose paired PA isolate exhibited ≥ 4-fold increase in the MIC between baseline and end of therapy or follow-up visits.
[2] Patients whose paired PA isolate exhibited ±2-fold change in the MIC between baseline and end of therapy or follow-up visits.
[3] Patients whose paired PA isolate exhibited ≥ 4-fold decrease in the MIC between baseline and end of therapy or follow-up visits.
Source: Module 5.3.5.1, CT01 Appendix 16.2.6.4 and Module 5.3.5.1, CT02 Appendix 16.2.6.17

-EDR SDN#0, 2.7.3 Summary of Clinical Efficacy, Table 6

Note: In the above applicant table, the denominator was comprised of both placebo and CHF 1538 isolates. The following microbiology reviewer table looks at the percentage of MIC changes using individual denominators for each drug (CHF 1538 or placebo).

Table 6.1.10.1 Assessment of MIC Shifts from Observed Baseline Values and MIC Values Observed at End of First "On" Cycle and at End of the First "Off" Cycle, Integrated Results for CT01 and CT02, ITT Population; Denominator Changed

NDA 201-820	Baseline vs. Last treatment		Baseline vs. Follow-up	
Evaluability Criteria	CHF 1538 (124)	Placebo (78)	CHF 1538 (151)	Placebo (73)
MIC Increased	41 (33.1%)	9 (11.5%)	52 (34.4%)	5 (6.8%)
MIC Unchanged	74 (59.6)	60 (76.9)	89 (58.9)	60 (82.2)
MIC Decrease	9 (7.3)	9 (11.5)	10 (6.6)	8 (10.9)

Both treatments (CHF 1538 and TOBI) during the CT03 study were able to significantly reduce baseline bacterial load in the sputum samples obtained from patients. However, bacterial load increased once treatment of both groups stopped. There was no significant difference in the bacterial load between both treatment groups after cessation of treatment. In both treatment groups there were increases in the tobramycin MIC for a portion of the P. aeruginosa population. There were a low percentage of microbiological eradications in both treatment groups with rates of superinfection and re-infection being similar between the two treatment groups. The rates of positive and negative outcomes observed for CHF 1538 and TOBI were similar. From a clinical microbiology perspective there is no evidence in the data from the treatment study groups (CHF1538 and TOBI) that suggest that CHF 1538 is inferior to TOBI for the treatment of Pseudomonas aeruginosa infection in the lungs of cystic fibrosis patients.

Trial Design Issues

The greatest deficiency in regards to trial design was that both the pivotal placebo-controlled trials were conducted with a formulation that differed in osmolality from the to-be-marketed substance and compressor/nebulizer devices that were not the to-be-marketed devices. Though the CT03 study provided some bridging data in regards to the osmolality question, there remains considerable uncertainty as to the efficacy (and safety) of the to-be-marketed drug device combination. There were some differences between the two placebo controlled trials in terms of inclusion/exclusion criteria (such as use of antipseudomonals at baseline and requirement for *Pa* tobramycin susceptibility at baseline) sample size that may have produced somewhat disparate efficacy results, and only one trial provides any real clinical data beyond pulmonary function and microbiological outcomes (CT02). Subgroup analyses appeared to be unplanned and so can only provide hints of subgroup issues.

7 Review of Safety

Safety Summary

The safety exposure for this 505(b)(2) application was overall adequate. There were 346 patients evaluated in three phase 3 trials. This compares with the original phase 3 trials for the reference drug, TOBI, in which 258 patients were exposed to study drug. However, in the TOBI trials, each subject was exposed to 3 cycles of 28 day on/28 day off treatment, while in this NDA only 161 subjects were exposed to such duration; 185 subjects were exposed to only one cycle. Also of note is that while the original TOBI trials actually consisted of two identical 24 week trials, the three phase 3 trials in this NDA possess enough differences from a safety evaluation standpoint that pooling is not ideal. Generally speaking, the study drug CHF 1538 conforms to the safety of what is expected with use of an inhaled antimicrobial agent in cystic fibrosis patients. Safety conclusions are as follows:

- no serious concerns arise in terms of deaths or serious adverse events; notably only one PT of “bronchospasm” was noted to have occurred in the CHF 1538 arm, though bronchospasm was not specifically tracked using post inhalation pulmonary function measurements. No increased risk of ototoxicity, nephrotoxicity or neuromuscular blockade was noted. However, similar to the reference drug, labeling is likely to reflect a potential for increased risk of these adverse reactions.

- Adverse reactions (AR) that could be reasonably associated with drug include dysphonia, pharyngitis, epistaxis, and headache (HA). Such AR would not be particularly surprising given the nature of the study drug but could also simply reflect underlying disease.

-The most frequent TEAEs noted may be more related to underlying disease than an actual drug reaction.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There were three primary sources of safety data for this review:

a. Study 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.* Data evaluated include study reports, line listings, case report forms, as well as statistical files provided by the applicant.

b. Study 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.* Data evaluated include study reports, line listings, case report forms, as well as statistical files provided by the applicant.

c. Study CT03- A Multicentre, Multinational, Open-Label, Randomised, Parallel Group Clinical Trial of Tobrineb/Actitob/Bramitob (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. Data evaluated include study reports, line listings, case report forms, as well as statistical files provided by the applicant.

Secondary sources of data include postmarketing data provided by the applicant, responses to information requests, labeling for the study drug in foreign countries (the drug is approved in Europe), appropriate literature reports, and study CP01 (Comparative bioavailability study of aerosolized tobramycin in cystic fibrosis patients after administration of 300 mg CHF 1538 Tobramycin 300 mg/4 mL Inhalation Solution (Chiesi Farmaceutici S.p.A.) or TOBI® (PathoGenesis).

The following table displays basic elements of all three phase 3 trials and the pharmacokinetic study.

Table 7.1.1. NDA 201820 Trials Overview

Study	Design	Location	Dosing/Duration	Compressor/ Nebulizer	Safety Popuation[1]	Database Lock

				Used		
CT01	Double-Blind, Randomized, Placebo-Controlled, Parallel Groups	Foreign (Italy, France, Ukraine, and Moldavia)	Arm 1: 300 mg/4 mL CHF 1538 BID for 28 days followed by 28 days off drug Arm 2: Inhaled saline/4 mL BID for 28 days followed by 28 days off drug	Pari Turbo Boy/LC Plus	59 Total 29 patients - CHF 1538 30 patients – Placebo	June 23,2004; cutoff date Sept. 2010
CT02	Double-Blind, Randomized, Placebo-Controlled, Parallel Groups	Foreign (Hungary, Poland, Russia)	Arm 1: 300 mg/4mL CHF 1538 BID for Three cycles of 28 day on/28 day off study drug Arm 2: Inhaled saline/4 mL BID for Three cycles of 28 day on/28 day off study drug	Pari Turbo Boy N/LC Plus	246 patients 161 patients -CHF 1538 85 patients - Placebo	June 1, 2004; cutoff date Sept. 2010
CT03	Open-Label, Randomized, Active Controlled, Parallel Groups	Foreign (Russia, Ukraine, Poland, Hungary, Germany, Czech Republic, Spain, France)	Arm 1: 300 mg/4 mL CHF 1538 BID for 28 days followed by 28 days off drug Arm 2: 300 mg/5 mL TOBI for 28 days followed by 28 days off drug	Pari Turbo Boy N/LC Plus	324 Total[2] 156 patients – CHF 1538 168 patients - TOBI	July 23, 2010; cutoff date Sept. 2010
CP01	Single Center, Single Dose, Randomized, Double Blind, Two Way Crossover	Foreign (Austria)	Crossover Study: Single dose of CHF 1538 (300mg/4ml) or TOBI (300mg/5ml) followed by single dose of crossover medication; washout period was 3 to 7 days between doses	Pari Boy/LC Plus	19 Total 10 patients -CHF 1538 9 patients -TOBI	

1- Safety population includes all patients who were randomized and took at least one dose of study drug
2- Nine patients were assigned to CHF 1538 and received TOBI instead; Six patients were assigned to TOBI and received CHF 1538 instead; this is already reflected in the safety population

7.1.2 Categorization of Adverse Events

This section focuses on issues encountered in the coding of adverse events.

CT01

Coding in CT01 has several issues to consider. There is some degree of splitting as concerns the coding of cystic fibrosis-related pulmonary exacerbations. Though exacerbations were typically coded to the Preferred Term (PT) 'condition aggravated' much depended on the investigator term used. If something different from 'pulmonary exacerbation' was used to describe such an event, then different PT might result. For example, some events which could have represented pulmonary exacerbations were coded with various PT including "dyspnea," "obstructive airways disorder" and "worsening of respiratory failure," which themselves code to different system organ

classes. In one instance the investigator term 'febrile dyspnea' was split into the two PT 'pyrexia' and 'dyspnea.' There are also several instances of respiratory infections being coded to PT such as "bronchitis bacterial" or "respiratory tract infection" (though these may not represent the prototypical CF exacerbation as many of these patients were treated with non-antipseudomonal antibiotics such as amoxicillin).

Individual 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" (no temperature was recorded on the CRF for this event so it is unclear what was the actual temperature measured). Also, the investigator term "giddiness" is coded under the preferred term "dizziness" which may not be appropriate.

CT02

This trial illustrated the difficulty in coding CF-related pulmonary exacerbations. Some of the difficulties arose from the design of the trial itself, while others are likely 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 hemoglobin saturation (as measured by oximetry) from baseline value within past three months of ≥10%, and new findings on chest radiography. As a consequence of this checklist, there were many individual criteria from the checklist that were also labeled as adverse events (AEs). This made it difficult to sort out AE that may have been elicited/part of a pulmonary exacerbation from those occurring individually, reported spontaneously, and possibly a consequence of study drug. Moreover, a pulmonary exacerbation might be coded as multiple individual adverse events based on the checklist rather than just one pulmonary exacerbation. In fact, some patients were coded as both a pulmonary exacerbation and multiple individual symptoms based off the checklist. Finally, the criterion of "school absence due to…." allowed for duplication of an AE. As an example, if a school absence was due to increased cough, then increased cough would be coded twice as an adverse event—once as the individual adverse event "increased cough" and the second as "school absence due to increased cough" (in both cases both would be coded to the same preferred term of cough).

Beyond the challenges posed by the checklist, depending on the investigator term used, a pulmonary exacerbation might be coded under numerous PT including tracheobronchitis, pneumonia, bronchopneumonia, bronchitis, respiratory failure, and hemoptysis. Thus, estimating the incidence of pulmonary excarbations would necessarily rely on some degree of subjective grouping of PT.

Instances of confusion with adverse event coding also appears with investigator terms such as “symptoms of cholelithiasis” or “signs of hemolytic anemia” being coded to cholelithiasis or hemolytic anemia when it is unclear whether these diagnoses have been confirmed or only assumed. Also AE of abnormal lab values or abnormal vital signs seem somewhat arbitrary; they are reported for some but not for others with similar values (some values were not truly abnormal).

CT03

In this trial, a more recent MedDRA dictionary was used and as such pulmonary exacerbations were coded to the PT ‘cystic fibrosis lung.’ As with the other trials, numerous PT were used for what, on closer review of the CRF, may have actually been a pulmonary exacerbation, including ‘bronchitis,’ ‘laryngitis.’

Despite some instances of questionable coding (one subject had a head contusion as a result of syncopal event and was coded for both terms), in general the coding in this trial was adequate.

Similar to issues involved in the coding of pulmonary exacerbations, some degree of subjective lumping by this reviewer was necessary to assess potential inhaled aminoglycoside-associated adverse events, such as ototoxic events or bronchospasm.

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

The applicant chose for its integrated summary of effectiveness to pool studies CT01 and CT02 citing the similarity in study designs and populations. However, there are important differences worth noting. CT01 and CT02 differed in the compressors used by subjects. CT02 covered a much longer duration than CT01 (6 months vs. 2 months) and so had a much higher chance for recording typical and atypical CF and study drug-associated adverse events. Also, in CT02, a specific checklist was used to assess for pulmonary exacerbation while in CT01 no such checklist was used. This has implications for the incidence of pulmonary exacerbation- associated symptoms in the two studies. Finally, the inclusion and exclusion criteria did vary somewhat between the studies. For example, prior antipseudomonal antibiotics in the last 4 weeks was allowed in CT02 but not in CT01, and CT01 subjects were required to have *Pa* isolates susceptible to tobramycin while in CT02 this was not a requirement.

CT03 is different from both placebo-controlled studies, most notably because it is open label and uses a formulation of study drug with a changed osmolality lower than

that used in the other studies. The decision by the applicant for the pooled/integrated results to not include this study reflect such differences.

Because of the above factors, pooled analyses for safety were done intermittently and not as a primary analysis. Where pooled analyses were performed, the effect of the differences in study design should be kept in mind.

7.2 Adequacy of Safety Assessments

In determining the adequacy of the safety database for this NDA, several factors should be taken into account. This drug is indicated for an orphan indication and as such there may be a limited pool from which to recruit subjects. This is also a drug from a heavily explored class of drugs with a known safety profile and as such a focus can be placed on particular areas. Finally, this is a 505(b)(2) application that in part relies on the safety findings of the reference drug TOBI. Moreover, the trial design of this application was heavily based on what was done with the reference drug.

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

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

CT01

In CT01, the mean exposure for the 29 subjects in the CHF 1538 arm was 29.9 days. For the 30 subjects randomized into the placebo arm, the mean exposure was 29.2 days. As discussed earlier, this trial was a randomized, double-blind, placebo-controlled trial comprised of one 28-day period of study drug treatment followed by 28 days off study drug. The same 300 mg bid dose of tobramycin used by the reference drug was used in this trial. Besides asking investigators to elicit information about adverse events at study visit, basic laboratory parameters including CBC with differential, serum electrolytes, serum blood urea nitrogen/creatinine levels, serum transaminases, and serum protein electrophoresis were collected at screen (visit 1) as well as at visit 4 (end of on-treatment period) and visit 5 (end of study). Given the known risks of nephrotoxicity, ototoxicity, and neuromuscular blockade associated with parenteral aminoglycosides, besides the lab tests and adverse event assessments outlined above, audiometric tests were to be done bilaterally between 250 and 8000 Hz at visits 1, 4 and 5. Particular populations of interest were excluded from the study including ages < 6 years old, patients with sputum colonized by *Pseudomonas aeruginosa* not susceptible to tobramycin, patients with renal impairment at baseline (defined by a serum creatinine level of 1.5 mg/dL, patients with sputum containing *Burkholderia cepacia*, patients with end-stage lung disease or candidates for lung

transplant, patients with extremely poor or normal lung function as defined by FEV_1 percent predicted <40% or > 80%, patients with CF sequelae or treatment that would interfere with interpretation of the results of the study, pregnant or lactating females, and patients with signs of ototoxicity at baseline as defined by an auditory threshold > 20 dB in either ear at frequencies between 250 and 8000 Hz. Some of these restrictions were in part due to the trial design of the reference drug. Despite these restrictions, it is expected that the enrollment criteria allowed for entry of quite typical cystic fibrosis patients who would be expected to use this drug (i.e., cystic fibrosis patients colonized by *Pseudomonas aeruginosa* who had significant but not overwhelming respiratory and non-respiratory CF-related morbidity).

CT02

In CT02, the mean days of exposure to study drug for subjects randomized to the CHF 1538 arm was 87.5 days. The mean days of exposure to study drug for subjects randomized to placebo was 85.8 days. As discussed earlier, this was a randomized, multicenter, double-blind, placebo-controlled trial consisting of three 28 day "ON"/"OFF" cycles using the same 300 mg bid inhaled dose used by the reference drug. Besides asking investigators to elicit information about adverse events at study visits, basic laboratory parameters including CBC with differential, serum electrolytes, serum blood urea nitrogen/creatinine, serum transaminases, and serum protein electrophoresis were collected at visits 1 (screen), 4 (end of 1st on cycle), 5 (end of 1st off cycle), 8 (end of 3rd on cycle), 9 (end of 3rd off cycle). Given the known risks of nephrotoxicity, ototoxicity, and neuromuscular blockade associated with parenteral aminoglycosides, besides the lab tests and adverse event assessments outlined above, audiometric tests were to be done bilaterally between 250 and 8000 Hz at visits 1, 4 and 5 (if abnormalities were noticed at visit 4), visit 8, and visit 9 (if abnormalities were noticed at visit 8). Particular populations of interest were excluded from the study including ages <6 years, patients with renal impairment at baseline (defined by a serum creatinine level of ≥1.5 mg/dL), patients with sputum containing *Burkholderia cepacia*, patients with end-stage lung disease or candidates for lung transplant, patients with extremely poor or normal lung function as defined by FEV_1 % predicted <40% or >80%, patients with CF sequelae or treatment that would interfere with interpretation of the results of the study, pregnant or lactating females, and patients with signs of ototoxicity at baseline as defined by an auditory threshold >20 dB in either ear at frequencies between 250 and 8000 Hz. These restrictions were based in part on what was done during the original clinical trials of the reference drug. Despite these restrictions, it is expected that the enrollment criteria allowed for entry of quite typical cystic fibrosis patients who would be expected to use this inhaled drug, i.e., cystic fibrosis patients colonized by *Pseudomonas aeruginosa* who had significant but not overwhelming respiratory and non-respiratory CF-related morbidity.

The following applicant table shows the demographic and exposure breakdown of the safety population.

Table 7.2.1: Patients Exposed to CHF 1538 or Placebo by Intervals: Integrated Safety Population (Pooled 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

-EDR SDN#0, 2.7.4, Summary of Clinical Safety, Table 1

There was adequate participation of gender and different age groups, though there was moderate tendency toward males and the youngest age group. Roughly 18% of subjects received CHF 1538 beyond ninety days, likely all from the CT02 trial. Given the nature of CF, racial diversity was not expected.

The following applicant table shows the baseline demographics of the safety population for patients in study CT01 and CT02.

Table 7.2.1.1: Demographic Data and Baseline of Cystic Fibrosis Characteristics: Integrated Safety Population (Pooled CT01 and CT02)

	CHF 1538 N=190	PLACEBO N=115[1]	TOTAL N=305
Gender			
Male	104 (54.7%)	63 (54.8%)	167 (54.8%)
Female	86 (45.3%)	52 (45.2%)	138 (45.2%)
p-value	0.994		
Age (years)			
Mean	14.2	14.5	14.3
SD	5.8	6.3	6.0
Range	6.0-31.0	6.0-45.0	6.0-45.0
p-value	0.677		
Age in Classes			
6-12 years	82 (43.2%)	50 (43.5%)	132 (43.3%)
13-17 years	54 (28.4%)	36 (31.3%)	90 (29.5%)
> 17 years	54 (28.4%)	29 (25.2%)	83 (27.2%)
p-value	0.789		
Height (cm)			
Mean	148.7	150.8	149.5
SD	20.7	20.1	20.5
Range	102.0-188.0	113.0-191.0	102.0-191.0
p-value	0.387		
Weight (kg)			
Mean	38.6	39.9	39.1
SD	15.2	16.5	15.6
Range	15.0-84.0	15.5-99.0	15.0-99.0
p-value	0.475		
BMI (kg/m^2)			
Mean	16.6	16.7	16.7
SD	2.8	3.3	3.0
Range	10.9-24.3	11.5-31.6	10.9-31.6
p-value	0.812		

FEV_1 % Predicted (%)			
Mean	60.2	62.9	61.2
SD	14.7	15.1	14.9
Range	31.4-95.1	23.5-104.1	23.5-104.1
p-value	0.132		
Colonization with *Pseudomonas aeruginosa*			
Chronic	167 (87.9%)	93 (80.9%)	260 (85.2%)
First or intermittent	23 (12.1%)	22 (19.1%)	45 (14.8%)
p-value	0.094		
Time from Diagnosis (years)[2]			
Mean	11.8	11.4	11.7
SD	5.7	5.9	5.8
Range	1.0-29.0	1.0-27.0	1.0-29.0
p-value	0.522		

[1] N = 114 in the Placebo group for FEV1 % predicted. This value was missing for one patient at baseline.
[2] Time from diagnosis (years) = year (visit 1) - year (diagnosis) +1
-EDR SDN#0, 2.7.4, Summary of Clinical Safety, Table 2

In general, the CHF 1538 and placebo populations were quite well matched. However, a slightly greater percentage of subjects in the CHF 1538 group were chronically colonized.

CT03

In CT03, the mean days of exposure to study drug for subjects randomized to each of the two treatment arms was 29 days. As discussed earlier, this was a randomized, multicenter, open-label, active-controlled trial consisting of one 28 day "ON"/"OFF" cycle using the 300 mg bid inhaled dose in both study arms (either 300 mg of inhaled CHF 1538 or 300 mg of inhaled TOBI). Besides investigator collection of information about adverse events at study visits, basic laboratory parameters including CBC with differential, serum electrolytes, serum blood urea nitrogen/creatinine, and serum transaminases were collected at visits 1 (screen) and 4 (end of 1st on cycle). Given the known risks of nephrotoxicity, ototoxicity, and neuromuscular blockade associated with parenteral aminoglycosides, besides the lab tests and adverse event assessments outlined above, air and bone audiometric tests were to be done bilaterally between 250 and 8000 Hz at visits 1, 4 and 5. Particular populations of interest were excluded from the study including ages <6 years old, subjects whose sputum was

colonized by tobramycin-resistant *Pseudomonas aeruginosa*, patients with renal impairment at baseline (defined by a serum creatinine level of ≥1.5 mg/dL), patients with sputum containing *Burkholderia cepacia*, patients with end-stage lung disease or candidates for lung transplant, patients with extremely poor or normal lung function (defined by FEV_1 % predicted <40% or >80%), patients with CF sequelae or treatment that would interfere with interpretation of the results of the study, pregnant or lactating females, and patients with signs of ototoxicity at baseline as defined by an auditory threshold >20 dB in either ear at frequencies between 250 and 8000 Hz. These restrictions were based in part on what was done during the original clinical trials of the reference drug. Despite these restrictions, it is expected that the enrollment criteria allowed for entry of quite typical cystic fibrosis patients who would be expected to use this inhaled drug, i.e., cystic fibrosis patients colonized by *Pseudomonas aeruginosa* who had significant but not overwhelming respiratory and non-respiratory CF-related morbidity.

The following applicant table looks at exposure to study drug in CT03.

Table 7.2.1.2: Extent of Exposure – CT03 Safety Population

	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.
-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Table 176

Virtually all subjects in both arms received at least 3 weeks of study drug. It should be noted that the extent of exposure as described in this table does not give a complete picture of exposure history. For example, a subject may report for Visit 4 after 27 days (27 days of exposure) but have taken only 52 vials rather than the expected exposure of 54 vials. Compliance in this case would still fall in the 80-120% category because the patient took 52 of 54 expected vials and actual exposure was 26 days.

7.2.2 Explorations for Dose Response

No explorations of dose response were done. This is a 505(b)(2) application and thus followed the dosing regimen approved for the reference drug TOBI, namely 300 mg inhaled drug BID.

7.2.3 Special Animal and/or In Vitro Testing

The sponsor is relying in part on nonclinical studies done in support of TOBI as well as all postmarketing TOBI safety experience. However, 1 week and 4 week inhalation studies with rats and dogs were performed in support of this NDA. Please refer to the Pharmacology Toxicology review performed by Dr. Amy Ellis for further details. The active ingredient in the study drug is tobramycin, a drug whose safety profile is well documented and includes nephrotoxicity, ototoxicity, and neuromuscular blockade with significant systemic exposures. The primary concern with the current study drug is potential local adverse effects caused by inhalation, and exploration of this issue relies on both studies included in the current NDA as well as studies in support of the reference drug.

7.2.4 Routine Clinical Testing

Please note the description under section 7.2.1 of how safety information was obtained in the three pivotal trials. Of note, though several laboratory parameters were obtained in these studies, some prominent laboratory parameters that were missing included serum bicarbonate, magnesium, phosphate, albumin, and bilirubin.

7.2.5 Metabolic, Clearance, and Interaction Workup

For the most part, this NDA relies on prior studies that have investigated the drug-drug interaction, metabolism in renal/hepatic impairment, and clearance qualities of parenteral tobramycin. This NDA contains 2 further pharmacological studies that assess the bioavailability, sputum concentrations, and accumulation over time of inhaled CHF1538; studies CT01 and CP01. The study drug is likely to have little absorption into plasma and also is excreted unchanged almost exclusively in the urine, so drug-drug interaction evaluations are likely unnecessary, although the sponsor did look at drug interactions as regards concomitant CF meds. Moreover, because of this, hepatic impairment is expected to have little effect on plasma concentrations of the drug and does not need further evaluation.

In Study CP01, 11 subjects participated in a double-blind, randomized, crossover study in which each subject received a dose of TOBI/CHF1538, had plasma and sputum sampling just prior to and after this, went through a washout period of 3 to 7 days and then received a single dose of crossover medication with plasma and sputum sampling done just prior to and after the dose (only 9 completed the full crossover

study). The sampling was used to calculate typical pharmacokinetic values. The two drugs were not found to have significantly different pharmacokinetic parameters.

As part of CT01, a sub study was conducted with 25 subjects. 21 subjects were in the CHF1538 group (4 in placebo) and had their sputum concentration of CHF1538 measured 10 minutes after study drug administration on day 1. Seventeen of these of subjects had a similar measurement on Day 28 (end of 1 month drug treatment), and five of these subjects had a similar measurement on day 56 (end of 1 month washout). The study concluded that there was no significant difference between the concentrations of drug in sputum seen on day one and day 28, suggesting a lack of accumulation of the drug. Similarly, in the five patients who had a measurement taken on both day 28 and day 56, there was a marked reduction in sputum study drug concentration, again suggesting a lack of study drug accumulation in sputum. Please see the Clinical Pharmacology review performed by Dr. Yongheng Zhang for further details.

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

Based on present knowledge of the aminoglycoside drug class, there are adverse events of specific interest that should be monitored. These include a) nephrotoxicity, b) oto-/vestibular toxicity, and c) neuromuscular blockade. Given that this is an inhaled product, the other adverse effects that are of interest include bronchospasm.

Ototoxicity

The applicant performed audiometric tests at several visits 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

Nephrotoxicity was assessed primarily through serial laboratory measurements of creatinine and blood urea nitrogen during the course of each study. Urinalysis and serum electrolyte measurements such as magnesium and calcium levels that may have helped to identify nephrotoxicity in a subject were not obtained in the studies.

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. Assessment of bronchospasm relied primarily on patient/clinician reported adverse events such as "wheezing."

7.3 Major Safety Results

7.3.1 Deaths

A review of deaths in the phase 3 trials was performed using three primary sources provided in the NDA – Case Report Forms, narratives created by the applicant, and statistical files.

There were very few deaths in the phase 3 studies (there were no deaths at all in study CT03), and the majority of deaths occurred in the placebo arm. In general deaths appeared to be a result of succumbing to underlying disease (pulmonary exacerbation in CF). The table below looks at the crude mortality rate in the safety populations of the pooled CT01 and CT02 studies.

Table 7.3.1: Crude Mortality Rate Pooled CT01/CT02 Trials- Safety Population

Placebo	3/115= 2.6%
CHF 1538	1/190= 0.5%

A tabular listing of deaths follows:

Table 7.3.1.1: Deaths - CT01, CT02, CT03

Trial	Center	Subject	Age	Sex	Drug[1]	Cycles completed[2]	Baseline FEV_1 % Predicted	Description	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%	Pulmonary Exacerbation/ Cardiomyopathy	Unlikely

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

Death Narratives

CT01/21-002: This 11 year-old female with a history of sinusitis and cardiomyopathy received placebo, and had worsening respiratory failure/sinusitis over a period of two to three weeks from visit 2 that did not respond to antimicrobials, steroids, ipratropium, and supportive care in the ICU. She passed away 18 days after visit 2.

CT02/34-008: This was an 11 year-old female on placebo with a history of malabsorption, cirrhosis, GERD, hypoplasia of gallbladder, chronic gastroduodenitis, and CF. Her baseline FEV_1 % predicted was 45.3%, but it appears that not only had she experienced a pulmonary exacerbation just prior to and during the run-in portion of the study (she had received antimicrobial therapy for this), she also met criteria for a pulmonary exacerbation at visit 2 and started ofloxacin and cefepime when starting study drug. She appeared to have improvement in her symptoms and her FEV_1 % predicted increased to 63.2% over the course of her 1st On cycle but during 1st Off cycle, she developed signs of symptoms of another pulmonary exacerbation as well as had a decrease in her FEV_1 % predicted (49.1%). She received antimicrobials such as ofloxacin and TMP-SMX for a brief period, then was off antimicrobial therapy for 2 weeks, then restarted on ofloxacin before eventually being hospitalized. Once hospitalized, the patient received numerous antimicrobials including cefepime, meropenem, ceftriaxone, and amikacin (this is a protocol violation). In fact, the patient was taking an antimicrobial during the vast majority of her participation in the study. Forty days after being hospitalized, the patient passed away despite steroids, oxygen therapy, antimicrobials, and care in the ICU. She received study drug (placebo) for only two cycles. She appeared to succumb to CF exacerbation either as a protracted course which waxed and waned or as several multiple recurrent pulmonary exacerbations.

CT02/24-018: This is a 14 year-old female on placebo with a history of CF, pancreatic insufficiency, and a pulmonary exacerbation that ended 18 days before screen. The patient had a WBC of 28.7 at screen. Baseline FEV_1 % predicted was 40.6%. After two weeks on study drug treatment (placebo), the patient's FEV_1 % predicted dropped to 30.7% and she was deemed to have a pulmonary exacerbation by criteria and hospitalized for 2 weeks. She was given IV tobramycin, ceftazidime, and cotrimoxazole at this time. Her FEV_1 % predicted slightly improved with treatment but then deteriorated again during the study drug treatment 1st off cycle and the 2nd on-treatment period; it was 30% at the end of the second on-treatment period and she appeared on the verge of having another exacerbation. One day after this visit, she was started on oral steroids and was withdrawn from the study. After another 24 days, ceftazidime, amikacin, and IV steroids were started and the patient was hospitalized. She appears to have deteriorated further in just 2-3 days (acidosis, hypercapnea, hypoxia) and required pressors and inotropic support as well as short acting beta agonists and mechanical ventilation. She passed away five days after hospitalization. The etiology was regarded

as a classical CF exacerbation. The patient only received 2 courses of study drug treatment (placebo).

CT02/29-001 – This 22 year-old male with a history of CF (diagnosed at age 15), GERD, depression, hepatitis B, and "distal intestinal obstruction syndrome" was assigned to the CHF 1538 arm (as an aside, the patient should have been excluded from the study based on his audiometric tests). 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 an FEV_1 % predicted of 56% at baseline. Throughout the study period, the patient had a steady decline in his FEV_1 % predicted save for some improvement during the 2nd on-treatment period.

Baseline FEV_1 % predicted: 56%
After visit 4 (on-treatment): 46%
After visit 5 (off-treatment): 33%
After visit 6 (on-treatment): 52%
After visit 7 (off-treatment): 41%
After visit 8 (on-treatment): 35%

At the end of the 3rd on-treatment period, the subject met criteria for pulmonary exacerbation (increased sputum, cough, new findings on chest examination, sputum still with *Pseudomonas aeruginosa* and MRSA) and was started on a 3-week course of oral ciprofloxacin. However, at the end of this treatment, subject was hospitalized for "bronchitis" and treated with IV ciprofloxacin, imipenem, vancomycin, and fluconazole. Concomitantly, the subject also appeared to be experiencing cardiomyopathy and received treatment with diuretics (furosemide), inotropes (dobutamine), pressors (dopamine), beta blocker (carvedilol), colloid, amiodarone, and ace-inhibitor (cilazapril). The subject passed away 3 weeks after admission. After requesting further information from the applicant, the applicant stated that the investigator was not sure if any autopsy had ever been performed. Moreover the investigator stated that the subject displayed no signs of cardiomyopathy or circulatory insufficiency prior to the adverse event. The investigator felt the cardiomyopathy was unrelated 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 performed a review of AERS and found one report of cardiomyopathy after exposure to inhaled tobramycin. From this reviewer's investigation, cardiac dysfunction has been associated with cystic fibrosis, potentially as either cor pulmonale or as a myocardial fibrosis leading to asystole/circulatory failure in infants (Pediatr Pathol Mol Med. 2002 May-Jun;21(3):343-52; Pediatrics Vol. 70 No. 5 November 1, 1982 pp. 728 -741). A group of 18 CF patients with sudden unexpected cardiac arrest were evaluated and generally had signs of profound ECG changes, early onset pancreatic insufficiency, limited respiratory disease, and death in infancy (Clin Genet 2000: 57: 56–60). Also, many of these

patients showed some prior clinical sign of cardiac dysfunction. Such a scenario does not fit this subject. The subject also does not appear to have shown signs of chronic heart failure associated with cor pulmonale (no weight gain, no notation of abnormalities on physical exam, normal vital signs) although acute heart failure associated with the hypoxemia of pulmonary exacerbation is possible. It's unlikely the inhaled tobramycin had an effect on the eventual cardiomyopathy given the minor systemic absorption as well as the generally known side effect profile of inhaled tobramycin (of which cardiomyopathy is not a part). A quick screen of the AERS database highlighted two cases of cardiomyopathy in conjunction with inhaled tobramycin, neither of which showed convincing evidence of a relationship between the two. However the circumstances surrounding this case still leave many questions unanswered- namely the underlying etiology of the cardiomyopathy.

CT03

There were no deaths in the CT03 trial

Overall, there was no increase in death rates with CHF 1538 relative to placebo or active control. The lone death that occurred in the treatment arm was not clearly related to study drug and other plausible explanations including underlying disease/intercurrent illness were apparent.

7.3.2 Nonfatal Serious Adverse Events

In performing a review of Nonfatal Serious Adverse Events, three primary sources were reviewed all of which were submitted with the NDA – case report forms, narratives provided in the clinical study reports, and statistical files. Please see the tables below that summarize Nonfatal Serious Adverse Events (NSAE) within each individual trial. Only in cases where a potential relationship between CHF 1538 and NSAE might exist, is a narrative included.

CT01

In CT01, there were three NSAE in three patients; the applicant lists four events but one event was coded by the investigator as "febrile dyspnea" and was split into two preferred terms both of which were coded as an NSAE though they corresponded to the same event. NSAE occurring in the placebo arm appeared primarily related to pulmonary exacerbations (whether they were coded as such or not). The sole NSAE occurring in the treatment arm was due to intestinal obstruction, and in this reviewer's opinion, appeared unrelated to the investigational drug; intestinal obstruction is not uncommon in cystic fibrosis. NSAE were reported in 2/30 subjects in the placebo and 1/29 subjects in the CHF 1538 arm. The following table summarizes all NSAE in CT01.

Table 7.3.2: NSAE - CT01

Center	Subj	Age	Sex	FEV_1 % Predicted at baseline	Drug	SOC[1]	PT[2]	Investigator Term	NSAE Type	Study Withdrawal	Action Taken	Outcome	Causality[3]
17	17-003	11	F	61.8%	CHF 1538	Gastrointestinal Disorders	Intestinal Obstruction	Cystic Fibrosis, Mixed Form, Coprostasis	Hospitalized	No	Drug Treatment	Recovered	Likely Not Related
17	17-004	15	M	49.8%	Placebo	General Disorders	Condition Aggravated	Cystic Fibrosis, Exacerbation	Hospitalized	Yes	Drug Treatment	Recovered with Sequelae	Not Applicable[4]
10	10-003	17	M	49%	Placebo	Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea/ Pyrexia	Febrile Dyspnea	Hospitalized	Yes	Drug Treatment	Recovered	Not Applicable

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

CT02

In CT02, there were a total of 44 NSAE in 37 subjects. There were 19 events in the study drug (CHF 1538) arm, and 25 events occurred in the placebo arm. NSAE occurred in 16/161 (9.9%) patients in the CHF1538 arm and 21/85 (24.7%) in the placebo arm.

NSAEs occurred most frequently during the Off cycle (26 NSAE) and were most prevalent during the 1st On/Off cycle (18). Three sites accounted for more than a third (sites 24, 21, 29) of the affected individuals; two of these sites were some of the highest enrolling sites, however site 29 was a low enrolling site with only 7 patients randomized, yet 4 individuals had NSAE. There was a slight predominance toward females (22 females vs. 15 males) though males made up 55% of the safety population; the slant toward females was more prominent in the placebo rather than the treatment arm. More NSAE occurred in children (6-12 year-olds), followed by adolescents (13-17 year-olds) and then adults (> 17 year-olds) respectively. This was reflected more clearly in the placebo arm but not in the CHF 1538 arm. In the CHF 1538 arm children, adults and then adolescents had the highest number of NSAE. In terms of comparison, the safety population itself had more representation by children (41%), followed by similar percentages of adults (30%) and adolescents (29%). The table below shows the distribution of NSAE by age, sex, and baseline pulmonary function in the ITT population. Overall, the distribution of NSAE in the CHF 1538 arm adhered slightly more closely to the underlying demographics of the safety population as a whole than did the placebo arm. Perhaps surprisingly, more NSAE were seen in those subjects with a baseline FEV_1 % predicted ≥ 50%.

Table 7.3.2.1: Demographics of NSAE in the Study Drug and Placebo Arms of CT02- ITT

Demographic	CHF 1538		Placebo		Total (ITT)
Age	ITT	NSAE	ITT	NSAE	
6-12	63 (39.1%)	6 (37%)	37 (44%)	8 (38%)	100 (40.8%)
13-17	47 (29.2%)	4 (25%)	25 (29.8%)	9 (43%)	72 (29.4%)
>17	51 (31.7%)	6 (37%)	22 (26.2%)	4 (19%)	73 (29.8%)
Sex	ITT	NSAE	ITT	NSAE	
M	89 (55.3%)	8 (50%)	46 (54.8%)	7 (33%)	135 (55.1%)
F	72 (44.7%)	8 (50%)	38 (45.2%)	14 (67%)	110 (44.9%)
Baseline FEV_1 % Pred.	ITT	NSAE	ITT	NSAE	
≥50%	113 (70.2%)	9 (56%)	66 (78.5%)	14 (67%)	179 (73.1%)
<50%	48 (29.8%)	7 (44%)	18 (21.4%)	7 (33%)	66 (26.9%)

The vast majority of NSAE (79.5%) were represented by pulmonary exacerbation-like investigator terms. Several other events were coded with terms such as “hemoptysis” or “tachycardia” but upon further examination of the CRF, could have represented pulmonary exacerbations as well. The table below shows how these probable pulmonary exacerbations were distributed between the CHF 1538 and placebo arms.

Table 7.3.2.2: CT02 Distribution of Pulmonary Exacerbation-Related NSAE Between CHF1538 and Placebo Arm[1]

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%

1- subjective determination made by reviewer whether various PTs might represent pulmonary exacerbation

It is clear from the table that such events were much more frequent in the placebo arm. Of those that occurred in the CHF 1538 arm, in this investigator’s opinion, none of those were likely related to study drug. In fact, of all the NSAEs that occurred in the CHF 1538 arm, only one event (hemoptysis) was felt to have any possible connection to study drug; the narrative for that event is below. Other, non-respiratory related events that occurred in the CHF 1538 arm, including coded terms such as ‘Abdominal Pain,’ ‘Polypectomy,’ and ‘Acute Pancreatitis’ are more likely explained by underlying illness or other confounders rather than any true relationship with the study drug.

Table 7.3.2.3 - NSAE CT02

Center	Subj	Age	Sex	FEV_1 % Pred at baseline	PT[1]	Investigator Term	SAE Type	Study Withdrawal	Action Taken	Outcome	Causality [2]
12	12-015	9	M	63%	Polypectomy	Polypectomy with Hospitalization	Hospitalization	No	None	Recovered	Not related
13	13-010	10	F	45%	Pneumonia	Pneumonia	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
13	13-010	10	F	45%	Pneumonia	Pneumonia	Hospitalization	No	Drug Treatment	Recovered	Likely not related
13	13-010	10	F	45%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
15	15-002	19	F	62%	Hemoptysis	Hemoptae with Hospitalization	Hospitalization	No	Drug Treatment/ Drug Stopped for 24 hrs.	Recovered	Possibly Related
15	15-012	16	M	45%	Bronchopneumonia	Bronchopneumonia with hospitalization	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
21	21-002	7	F	62 9%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
21	21-002	7	F	62 9%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
21	21-016	22	M	51 2%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
22	22-003	18	F	31.4%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	Yes	Drug Treatment	Recovered	Likely Not Related
24	24-001	16	F	56 3%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
24	24-010	7	F	69%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	Yes	Drug Treatment	Recovered	Likely Not Related
26	26-023	20	F	45%	Pancreatitis Acute	Acute Pancreatitis	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related [3]
27	27-003	18	M	58%	Abdominal Pain	Abdominal Pain (fecal impaction/ constipation)	Hospitalization	No	Drug Treatment	Recovered	Likely not related
29	29-008	8	M	60%	Bronchitis	Bronchitis	Hospitalization	No	Drug Treatment	Recovered with Sequelae	Likely not related
31	31-004	19	F	51 3%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
32	32-003	14	M	44%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
32	32-021	14	M	41%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
34	34-002	7	M	40 2%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug Treatment	Recovered	Likely Not Related
12	12-021	8	F	84%	Polypectomy	Polypectomy	Hospitalization	No	Operation	Recovered	N/A[4]
15	15-004	9	F	63%	Tracheobronchitis	Tracheobronchitis	Hospitalization	No	Drug Treatment	Recovered	N/A
15	15-006	9	F	60%	Bronchopneumonia	Bronchopneumonia	Hospitalization	No	Drug treatment	Recovered	N/A
15	15-006	9	F	60%	Bronchopneumonia	Bronchopneumonia	Hospitalization	No	Drug treatment	Recovered	N/A
16	16-001	9	F	54%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
21	21-008	16	M	69 6%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
21	21-024	13	F	63 9%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
21	21-030	11	M	70.1%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
21	21-030	11	M	70.1%	Bronchopneumonia	Bronchopneumonia	Hospitalization	No	Drug treatment	Recovered	N/A
21	21-040	6	F	37 9%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
22	22-005	25	M	55 8%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	Yes	Drug treatment	Recovered	N/A
22	22-007	21	F	76 9%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
23	23-002	11	F	42%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
24	24-003	17	M	48 5%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
24	24-014	13	M	34.1%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
24	24-014	13	M	34.1%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
24	24-018	14	F	40 6%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	Yes	Drug treatment	Recovered	N/A
24	24-021	13	F	77%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered	N/A
24	24-024	12	F	77%	Laryngitis	Acute laryngitis	Hospitalization	No	Drug treatment	Recovered	N/A
27	27-006	11	F	75%	Condition Aggravated	Pulmonary exacerbation	Hospitalization	Yes	Drug treatment	Recovered	N/A
29	29-003	15	F	51%	Acute bronchitis	Acute Bronchitis	Hospitalization	No	Drug treatment	Recovered	N/A
29	29-005	23	M	43%	Hemoptysis (possibly Pulm Exac)	Hemoptysis	Hospitalization	No	Drug treatment	Recovered	N/A

29	29-005	23	M	43%	Hemoptysis (possibly Pulm Exac)	Hemoptysis	Hospitalization	No	Drug treatment	Recovered	N/A
29	29-011	16	M	79%	Tachycardia; Note: Could have had Bronchitis or Cough code as well	Tachycardia	Hospitalization	Yes	No Drug treatment	Recovered	N/A
32	32-019	17	F	36%	Condition Aggravated[5]	Pulmonary exacerbation	Hospitalization	No	Drug treatment	Recovered with Sequelae	N/A

1 Preferred Term
2- In the opinion of this reviewer
3- Subject 26-023; event occurred in early off cycle; pancreatitis can happen in CF though uncommon; other medications possibly implicated; not likely to have much absorption of CHF1538
4 N/A = not applicable; If occurred in placebo then relationship of event to study drug not assessed
5 Subject 32-019 Had prior hospitalization that was "planned" but could have had a respiratory event at this time as well

Narratives

Only narratives of NSAE that may have had a relationship with CHF1538 are described.

CT02/15-002: This was a female subject aged 19 years at study entry. She entered the study with a history of CF diagnosed from infancy, asthma (since 09 Mar 1995), cholelithiasis (on Sep 2002) and hemoptysis (on 08 Sep 2002). No abnormalities were found in the physical examination at study entry. The patient's FEV_1 % predicted at visit 2 was 62.0% and she had chronic colonization of *Pseudomonas aeruginosa*. At study entry concomitant treatment for CF included:

acetylcysteine (3 x 300 mg/day) since 01 May 1984;
pancreatin (4 x 10000 UI/day) since 09 May 1984;
vitamins since 01 May 1989;
salbutamol (3 x 200 µg/day) since 1995;
dornase alfa (2500 UI/day) since 1997;
ursodeoxycholic acid (2 x 250 mg/day) since Sep 2002; and
budesonide (2 x 200 µg/day) from 1995 to 28 Mar 2003.

The patient entered the study on 04 Mar 2003, and was randomized to receive CHF 1538. On (b) (6), during the 1st On cycle, the patient experienced hemoptysis (preferred term) with hospitalization. She was hospitalized from (b) (6). This event was considered to be moderate in intensity and required concomitant pharmacological treatment with etamsilate (3 x 250 mg/day) from (b) (6); and rutoside (3 x 20 mg/day) and ascorbic acid (3 x 50 mg/day) from (b) (6).

There were no clear signs that a pulmonary exacerbation was occurring. Patient had study drug stopped for a day on (b) (6) and then was reintroduced without problem the next day. Patient also had a hemoptysis event during her 3rd on cycle that did not require hospitalization. Though certainly hemoptysis could represent underlying disease especially given her past history of hemoptysis, its relationship to study drug cannot be excluded.

CT03

In Study CT03, there were nine NSAE occurring in eight individuals. Seven events in six individuals occurred in the CHF 1538 arm and two events in two individuals occurred in the active control (TOBI arm). NSAE occurred in 6/156 (3.8%) patients in the CHF 1538 group and 2/168 (1.2%) patients in the TOBI arm. These results should be viewed with caution because this was an open-label trial and certainly biases in reporting could exist.

Though the numbers of NSAE were small, NSAE in the CHF 1538 arm involved subjects with a baseline FEV_1 % predicted ≥ 50% while in the TOBI arm, all affected subjects had baseline FEV_1 % predicted < 50%. Slightly over half of the events involved a pulmonary exacerbation/pulmonary exacerbation-like manifestations (whether coded as such or not), which was split almost evenly between the two arms. Three events that occurred in the CHF 1538 arm were felt by this reviewer to have a possible relationship with study drug though unlikely. A fourth event was thought to have a possible relationship with CHF 1538. All four narratives are presented below.

Table 7.3.2.4: NSAE - CT03

Center	Subject	Age	Sex	FEV_1 % Pred at baseline	PT[1]	Inv. Term	SAE Type	Withdrawal/ Lack of Completion of Study	Action Taken	Outcome	Causality Assessment[2]
104	104009	14	M	50.4%	Lung Infection	Exacerbation of Lung Infection in CF	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Likely not Related
109	109005	19	F	69.4%	Bronchitis	Exacerbation of Chronic Bronchitis in CF	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Likely not Related
203	203004	10	F	75.1%	Cystic Fibrosis Lung	Exacerbation of CF	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Likely Not Related
209	209006	17	F	56.5%	Appendicitis	Acute Appendicitis	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Possible though unlikely
302	302001	14	F	62.6%	Syncope	Syncope	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Possible though unlikely
302	302001	14	F	62.6%	Head Injury	Contusion of the Head	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Possible though unlikely
305	305011	7	M	76.7%	Laryngitis	Acute laryngitis	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Possible
109	109003	11	M	49.0%	Bronchitis	Exacerbation of Chronic Bronchitis due to CF	Hospitalized	No	Drug, medical or surgical treatment required	Recovered/ resolved	Likely Not Related
301	301010	26	M	42.4%	CF Lung	CF Exacerbation	Hospitalized	Yes	Permanent Discontinuation of Study Drug	Recovered/ resolved	Likely Not Related

Note: 2 pretreatment adverse events occurred in patients 206011, 301013 and are not included in this table
1- Preferred Term
2- In the opinion of this reviewer

Narratives

Only narratives where a possible relationship to CHF 1538 might exist are displayed.

CT03/209006**:** This was a female subject aged 17 years at study entry. She entered the study with a history of CF diagnosed as an adolescent (13 years old), chronic sinusitis (since 2006) and acne (since 2008). At baseline her physical exam findings included moist rales due to CF, steatorrhea due to CF, acne vulgaris, musculis hypotonia, digital clubbing, and barrel chest. Baseline weight was 50 kg. The subject's FEV_1 % predicted at baseline was 56.5% and only *Pseudomonas aeruginosa* was isolated from her sputum. Baseline WBC was 13.6 X 10^9/L with 73% neutrophils. At study entry, concomitant treatment for CF included:

- tocopherol acetate (400 mg/day) since Nov 2006;
- azithromycin (500 mg/3 times a week) since Nov 2006;
- sodium chloride (5 mL/day) since Nov 2006;
- colecalciferol (3000 IU/day) since Nov 2006;
- ursodeoxycholic acid (750 mg/day) since Nov 2006; and
- pancreatin (25,000 FIP, 12 capsules/day) since Nov 2006;

The subject entered the study on 18 Jan 2010, and was randomized to receive CHF 1538 from 29 Jan 2010 to 01 Mar 2010 (treatment period). The subject received sodium chloride (0.9% solution, 3-4 puffs intranasally/day) from 26 Jan 2010 to 04 Feb2010 as treatment for maxillary sinusitis.
The patient was hospitalized for acute appendicitis that began on (b) (6). She required concomitant pharmacological treatment with cefazolin (3000 mg IM/day) from (b) (6). By March 1st, WBC was 9.8 X 10^9/L . Physical exam throughout study was essentially unchanged (although GI exam at visit 5 was "normal" whereas prior "steatorrhea due to CF" had been noted). Appendicits is somewhat uncommon in the CF population, so the possibility of a relationship between study drug and appendicitis cannot be excluded. According to one reference appendicitis has an incidence rate of 1% to 2% in CF, lower than the 7% in the general population; however, the diagnosis is usually delayed until perforation and abscess formation have occurred (cite - ref. Chaudry et al. 2006; Gooding & Westaby 2007). However, it should be noted that tobramycin can often be used to treat appendicitis. Moreover, in this particular study serum concentrations of tobramycin are unlikely to be high and thus less likely to contribute to this adverse event. An association between TOBI and appendicitis is not noted on current labeling. The event was moderate in intensity and was considered not to be related to study drug. The subject recovered on (b) (4) and completed the study on 29 Mar 2010.

CT03/305011: This was a male subject aged seven years at study entry. He entered the study with a history of CF diagnosed from infancy. His medical history included urethral operation in 2003, nasal polypectomy in 2006, nasal polyps (since 2006) and pancreatic insufficiency (since 2003). Evidence of CF associated cough, nasal polyps, and scars post urethral valve surgery were reported in the physical examination at study entry. The patient's FEV_1 % predicted at baseline was 76.7% (note: the patient's visit 1 FEV_1 % predicted was >80% so patient should not have been enrolled in study but was

enrolled nonetheless) and *Staphylococcus aureus* and *Pseudomonas aeruginosa* were isolated from his sputum. Baseline weight was 27 kg. Baseline WBC was 10.8×10^9/L. At study entry, concomitant treatment for CF included azithromycin daily, pancreatic enzymes, vitamins, mucolytics, dornase alfa, sodium chloride intranasally, and ursodeoxycholic acid. The patient entered the study on 18 Nov 2009, and was randomized to receive CHF 1538 from 02 Dec 2009 to 02 Jan 2010 (treatment period). The subject developed acute laryngitis (Investigator term) on (b) (6) and was hospitalized, requiring concomitant pharmacological treatment with:

- (b) (6)

During this time, concomitant treatment for CF included:

- (b) (6)

The event was moderate in intensity and was considered not to be related to study drug by the investigator. However, though this event could easily have represented a modest pulmonary exacerbation event, inhaled TOBI has been associated with pharyngitis and voice alteration and this could have represented a similar event with CHF 1538. The subject recovered on (b) (6) and completed the study on 27 Jan 2010.

CT03/302001**:** This was a female subject aged 14 years at study entry. She entered the study with a history of CF diagnosed as a child (2½ years old). The following were reported in her medical history: distal intestinal obstruction syndrome in 2006; gastroesophageal reflux disease in 2008; head and neck contusion in 2008; distal intestinal obstruction syndrome in 2008; appendicitis in 2009; atopic dermatitis since 2004; liver disorder since 2004; right forearm contusion since 2009; and glucose intolerance since 2008. A right forearm contusion and skin dryness probably due to atopic dermatitis were found in the physical examination at study entry. The subject's FEV_1 % predicted at baseline was 62.6% and *Staphylococcus aureus, Haemophilus parainfluenzae* and *Pseudomonas aeruginosa* were isolated from her sputum. Her baseline weight was 51 kg. At study entry, concomitant treatment for CF included:

- dornase alfa (2.5 mL/day) since 28 Apr 1998;
- betacarotene (1 tab/day) since 22 Mar 1999;
- Centrum Junior (1 tab/qoday) since 22 Mar 1999;

- ambroxol hydrochloride (45 mg/day) since 14 Mar 2000;
- salmeterol xinafoate (100 µg/day) since 16 Mar 2000;
- pancreatin (10-12 capsules/day) since 10 Apr 2002;
- retinol (2 drops/day) since 10 Apr 2002;
- salbutamol (200 µg/day + PRN) since 15 Nov 2002;
- phytomenadione (5 mg/qoday) since 30 Nov 2003;
- calcifediol (3 drops/day) since 15 Nov 2004;
- ambroxol hydrochloride (60 mg/day) since 16 Apr 2007;
- budesonide (400 µg/day) since 16 Apr 2007; and
- tocopherol (400 mg/day) since 20 Nov 2008.

At study entry, concomitant treatment for hepatopathy included:
- silybum marianum extract (70 mg/day) since 23 Jun 2006;
- ursodeoxycholic acid (1 g/day) since 18 Jun 2007; and
- Essentiale (2 capsules/day) since 20 Nov 2008.

The subject entered the study on 25 May 2009, and was randomized to receive CHF 1538 from 03 Jun 2009 to 01 July 2009 (treatment period). The patient experienced syncope, occurring on (b) (6), and a contusion of the head (Investigator term) beginning on (b) (6). The subject was hospitalized and required concomitant pharmacological treatment with:

- (b) (6)

The events were severe in intensity and were considered not to be related to study drug by the investigator. Though this occurred during the off-treatment period, a relationship cannot be completely excluded given the fact that the subject's vestibular system may have been affected by CHF 1538, and thus could have incurred what was viewed as a syncopal event. Still, the subject likely did not accumulate study drug to such systemic concentrations that auditory and vestibular function were damaged (though there have been cases of tinnitus with TOBI). Also, the symptoms and treatment appear more compatible with syncope rather than dizziness/vestibular dysfunction. It's unclear from a review of the CRF whether other risk factors may have played a role in the development of the subject's syncope. There is no documentation of arrhythmias or cardiovascular disorders on the subject's medical history, though the subject did have a history of previous contusions suggesting possible prior syncopal events. All of the subject's physical exams were unchanged from baseline, and the subject was not hypoglycemic on two separate laboratory measurements. Moreover, there was no decrease in weight suggesting normal oral intake, However, it should be noted that at

visit 4, seven days prior to the event, that the subject's systolic blood pressure was slightly decreased (SBP of 90 compared to a baseline of 100-110), though the subject was not tachycardic. This suggests an alternate etiology for the event. The syncope resolved on (b) (6). The subject recovered from the head injury on (b) (6) and completed the study on 31 Jul 2009.

7.3.3 Dropouts and/or Discontinuations

CT01
In CT01, eight randomized patients discontinued from the study (14% of all randomized patients), one subject from the CHF1538 arm and seven subjects from the placebo arm. More than half (5) of the discontinuation patients completed the 28-day treatment period (including the only CHF 1538 subject). Although 5 of the 8 patients discontinued due to an adverse event/change in concomitant medication, 3 patients discontinued due to loss to follow-up or ineligibility according to inclusion/exclusion criteria. Of note, CRF were not provided for such patients unless discontinuation was due to an adverse event, therefore there is uncertainty whether other factors may have played a role in discontinuations attributed to loss to follow up, etc. The table below highlights each of the patients who discontinued/withdrawn from study.

Table 7.3.3: Discontinuations - CT01

Center	Subject	Age	Sex	FEV_1 % Pred at baseline	Drug	Reason for Discontinuation	Last visit	Notes
17	17-013	7	F	62.2%	CHF 1538	Lost to follow up	Visit 4	Lung function appeared to be improving up through final visit; had URI and increased ESR (17 mm/h) on treatment, but was not treated
10	10-003	17	M	49%	Placebo	TEAE: Febrile Dyspnea	Visit 4	Withdrawn after had exacerbation/ started inhaled colistin, IV imipenem,, tobramycin
10	10-004	9	F	64%	Placebo	Ineligible according to entry criteria - No *pseudomonas* on culture at visit 1	Visit 4	No CRF provided; had improvement of 5% in FEV_1 % predicted over on treatment; no AE recorded
17	17-002	15	M	50.3%	Placebo	Change in concomitant medication due to TEAE: CF Exacerbation	Visit 5	Two episodes of hemoptysis during treatment but PFT and weight were stable; 7 days after 4^{th} visit had a PE, started on ceftriaxone, and was withdrawn for this reason
17	17-004	15	M	49.8%	Placebo	Change in concomitant medication due to TEAE: CF exacerbation	Visit 3	PE with severe drop in PFT at visit 3 and withdrawn from study due to start of amikacin and ceftazidime
17	17-007	14	M	52.1%	Placebo	Lost to follow-up	Visit 4	Slight decrease of FEV_1 % predicted on treatment; had hemoptysis on treatment; no CRF provided
17	17-010	12	M	36.2%	Placebo	Change in Concomitant medication: Ciprofloxacin TEAE: Exacerbation of CF	Visit 3	PE between 2^{nd} and 3^{rd} visit and at 3^{rd} visit was tachypneic with no improvement in PFT; started 3 days later on ciprofloxacin for 17 days
21	21-002	11	F	59.3%	Placebo	Change in concomitant medication: antipseudomonal antibiotics TEAE: Worsening of respiratory failure and death	Visit 3	worsening respiratory failure/ sinusitis over a period of two to three weeks from visit 2 that did not respond to antimicrobials, steroids, ipatropium, and supportive care in the ICU

Of note, many of the subjects who discontinued were from site 17; this site also was by far the site with the highest number of subjects randomized in CT01 (14 patients randomized). Discontinuations involved males and females, subjects with a FEV_1 % predicted above and below 50%, but did not involve anyone over the age of 17. The majority of subjects were discontinued due to pulmonary exacerbation-like manifestations that led to the use of an antipseudomonal medication (which was prohibited in the protocol). All such cases occurred in the placebo arm. It should be noted that there was one placebo subject (Subject 11-001) who took ceftazidime and imipenem for preferred term "airways obstruction" who was not discontinued from the study so it is somewhat unclear how this standard was applied; this subject received the drugs at very end of study period, however. The lone case of discontinuation that occurred in the treatment arm was due to a loss to follow up; no further information is available. There does not appear to be a clear bias to discontinue placebo subjects who were improving or subjects taking CHF 1538 who were not improving. It also appears that the lone discontinuation in the CHF 1538 arm is likely not related to study drug.

CT02

There were 15 patients who were withdrawn from the study after randomization. Seven subjects were in the CHF 1538 group and 8 subjects were in the placebo group. Discontinuation occurred in 8/85 placebo patients and 7/161 patients in the CHF 1538 arm.

In the CHF 1538 arm, the majority (5/7) of subjects were able to complete at least 2 cycles of treatment before withdrawal. In the placebo arm, half of the subjects (4/8) were able to complete at least 2 cycles of treatment for withdrawal. In the CHF treatment arm, the majority of subjects who discontinued were either < 13 years old (3/7) or greater than 17 years old (3/7) and had a baseline FEV_1 % predicted of > 50% (5/7). There was more discontinuations than expected in the adult (>17 year old) group of the CHF 1538 arm. Older subjects may be more likely to have poor pulmonary function and thus more susceptible to a pulmonary exacerbation and possible discontinuation of study medication. Two of the three adults who discontinued had baseline FEV_1 % predicted < 50% (although admittedly this breakpoint is somewhat arbitrary; indeed in the CHF 1538 population as a whole more discontinuations occurred in those individuals with FEV_1 % predicted > 50%). None of the events in adults in the CHF 1538 arm was a clear drug-related discontinuation event. Of course, there were only a small number of discontinuation events so these results must be interpreted with caution. The following table looks at the demographics of withdrawals among the treatment arms in the ITT population.

Table 7.3.3.1 CT02 Discontinuation Demographics - ITT Population

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

6-12	63 (39.1%)	3 (43%)	37 (44%)	3 (37%)	100 (40.8%)
13-17	47 (29.2%)	1 (14%)	25 (29.8%)	3 (37%)	72 (29.4%)
>17	51 (31.7%)	3 (43%)	22 (26.2%)	2 (25%)	73 (29.8%)
Sex	ITT	Disc.	ITT	Disc.	
M	89 (55.3%)	4 (57%)	46 (54.8%)	4 (50%)	135 (55.1%)
F	72 (44.7%)	3 (43%)	38 (45.2%)	4 (50%)	110 (44.9%)
Baseline FEV_1 % Pred	ITT	Disc.	ITT	Disc.*	
>50%	113 (70.2%)	5 (71%)	66 (78.5%)	5 (62%)	179 (73.1%)
≤ 50%	48 (29.8%)	2 (29%)	18 (21.4%)	2 (25%)	66 (26.9%)

*- No value recorded for one subject

At least 4 of the 7 (57%) withdrawals in the CHF 1538 arm were, in the opinion of this reviewer, possibly related to pulmonary exacerbation-like manifestations. In the placebo arm, 4 of 8 (50%) withdrawals had a possible relationship with pulmonary exacerbation-like manifestations. The table below looks at potential etiologies for discontinuation.

Table 7.3.3.2: Potential Etiologies of Discontinuation Events - CT02

Possible Etiology	CHF 1538	Placebo
Possible Pulmonary Exacerbation	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

The table below provides a description of all discontinuations in both the CHF 1538 and placebo arm.

Table 7.3.3.3: Discontinuations - CT02

Center	Subject	Sex	Age	FEV_1 %[1] Pred at baseline	Drug	Reason for Discontinuation	Last visit	Notes
11	11-004	F	20	44.7%	CHF1538	Change in concomitant medication: amikacin	Visit 6	Started amikacin for increased sputum production; had slight decrease in FEV_1 at time of discontinuation
12	12-007	M	6	73%	CHF1538	Poor cooperation: withdrew consent for blood taking	Visit 4	Had slight improvement in FEV_1 % predicted at time of withdrawal
18	18-004	M	9	95.1%	CHF 1538	Lost to follow-up	Visit 8	Same FEV_1 % at baseline and at loss to f/u; Did not meet entry criteria for baseline FEV_1% predicted
22	22-003	F	18	31.4%	CHF 1538	Change in concomitant medication: colistin	Visit 7	Had slight improvement in FEV_1 % at time of loss to f/u; hospitalized for PE, released but then had another PE (not hosp.) and started inhaled colistin
24	24-010	F	7	69%	CHF 1538	Adverse event: dry cough attacks after drug delivery; both dechallenge and rechallenge positive	Visit 8	Had significant improvement in FEV_1 % at time of withdrawal
29	29-001	M	22	56%	CHF 1538	Adverse event: asystole cardiomyopathy (death)	Visit 8	See Narrative in "Deaths" section
32	32-025	M	17	68%	CHF1538	Adverse event: increased cough; decreased exercise tolerance; increased sputum production; fever; increased respiratory rate;	Visit 5	Had PE at baseline, during 1st on treatment, and during 1st off treatment. With latter PE, was withdrawn and started on ciprofloxacin; no improvement in FEV_1 % at time of withdrawal
11	11-008	M	25	None recorded	Placebo	Poor cooperation: withdrew Consent	Visit 2	No CRF or values in JMP; never received placebo
22	22-005	M	25	55.8%	Placebo	Change in concomitant medication: Colistin by inhalation	Visit 5	Took inhaled colistin for PE and was withdrawn; no real change in FEV_1 % predicted at time of withdrawal
24	24-018	F	14	40.6%	Placebo	Other: use of oral steroids (prednisolone)	Visit 6	See narrative in "Deaths" section; had decrease in FEV_1 % at withdrawal
27	27-006	F	11	75%	Placebo	Change in concomitant medication: Hydrocortisonum, increased doses of inhaled budesonide and salbutamol, amikacin, increased doses of ambroxol	Visit 4	Slight decrease in FEV_1 % at time of withdrawal; had PE during first On/Off cycle that eventually required hospitalization; required changes to CF meds. as well as amikacin all of which are prohibited concomitant meds.
29	29-011	M	16	79%	Placebo	Other: Medicament was not given to patient on Visit 7	Visit 8	No real change in FEV_1 % at withdrawal; medication not given at visit 7 for 3rd cycle
32	32-004	M	13	62%	Placebo	Poor cooperation: Withdrew Consent	Visit 7	FEV_1 % with significant decrease at withdrawal; 2 PE during study treated with ciprofloxacin and azithromycin but then eventually withdrew consent;
32	32-016	F	7	92%	Placebo	Adverse Event: increase of dry cough; vomiting because of bitter taste five minutes after inhalation	Visit 3	Had increase in dry cough and vomiting/bitter taste thought to be related to inhalation; positive dechallenge and rechallenge for bitter taste/vomiting; was also taking ciprofloxacin at the time of these events
34	34-008	F	11	45.3%	Placebo	Adverse Event: pulmonary Exacerbation	Visit 7	See narrative in "Deaths" section

No clear attempt to discontinue improving placebo subjects or worsening CHF 1538 subjects was noted.

CT03

In CT03, there were a total of 10 discontinuations. Three of these subjects were in the CHF 1538 arm and seven of these subjects were in the TOBI arm. One of the subjects (709002) was assigned to CHF 1538 but actually received TOBI and thus is evaluated for safety purposes in this arm. The discontinuations in the CHF arm were primarily adult male subjects. The table below compares the demographics of discontinuations in the CHF 1538, TOBI, and ITT populations.

Table 7.3.3.4 Discontinuation Demographics - CT03 ITT population

Demographic	CHF 1538		TOBI		Total (ITT)
Age	ITT	Disc.	ITT	Disc.	
6-12	49 (31.4%)	0 (0%)	54 (32.1%)	1 (14.3%)	103 (31.8%)
13-17	50 (32.1%)	0 (0%)	62(36.9%)	2 (28.6%)	112 (34.6%)
>17	57 (36.5%)	3(100%)	52 (31.0%)	4 (57.1%)	109 (33.6%)
Sex	ITT	Disc.	ITT	Disc.	
M	72 (46.2%)	2 (66.7%)	85 (50.6%)	3 (42.9%)	157 (48.5%)
F	84 (53.8%)	1 (33.3%)	83 (49.4%)	4 (57.1%)	167 (51.5%)
Baseline FEV_1 % Predicted	ITT	Disc.	ITT	Disc.	
≥50%	119 (76.3%)	1 (33.3%)	130 (77.4%)	6 (85.7%)	249 (76.9%)
<50%	37 (23.7%)	2 (66.7%)	38 (22.6%)	1 (14.3%)	75 (23.1%)

As in CT02, there were more discontinuations than expected in both adult arms; although given the small numbers of events, any comparisons should be made with caution. Two of the 3 discontinuations in adults in the CHF 1538 arm occurred in subjects with a baseline FEV_1 % predicted < 50%.

One of the discontinuations in the CHF 1538 arm are likely to have been related to adverse events associated with study drug. This event involved hemoptysis and cough. It should be noted that since this was an open-label trial; there is a potential for bias in identifying adverse events and assigning a relationship to study drug. The following table lists etiologies/associations for the discontinuations in each of the treatment arms.

Table 7.3.3.5: Etiologies/Associations of Discontinuation Events[1] by Treatment Arm in CT03

Association	CHF 1538	TOBI
Pulmonary Exacerbation	0	1
Protocol Violation	1	2
Adverse Event		
Cough	0	3
Hemoptysis	1	1
Hoarseness	0	1
Bronchospasm	0	1
Withdrawal of Consent	1	0

1- an event can correspond to more than one item

All of the adverse event-associated discontinuations appear in the labeling of the reference drug TOBI (including hemoptysis) and more than likely would appear in any labeling associated with CHF 1538. The following table displays discontinuation events for CT03.

Table 7.3.3.6: Discontinuation Events- CT03

Center	Subject	Age	Sex	FEV_1 % Pred at baseline	Drug	Reason for Discontinuation	Last visit	Notes
202	202001	21	M	77.5 %	CHF 1538	Protocol violation	Visit 3; took 13 days of study drug	Had *B. cepacia* at baseline; no real change in FEV_1 % at withdrawal
304	304001	20	M	40.5%	CHF1538	Adverse event: hemoptysis	Took 3 days of study drug	Hemoptysis considered related to study drug and discontinued drug
801	801002	23	F	43%	CHF 1538	Withdrawal of consent	Visit 4	FEV_1 % pred unchanged at withdrawal; cough, hypotension, depression, increased sputum, decreased FEV_1 %, and thoracic pain at baseline; not clear why consent was withdrawn
709	709002	30	M	74%	CHF1538	Adverse event: cough and hemoptysis	Took 5 days of study drug; withdrew 14 days after starting study	Hemoptysis and cough at 4 days study drug was discontinued; cough thought to be drug-related (not hemoptysis?); randomized to CHF 1538 but received TOBI
102	102002	16	F	64.7%	TOBI	Protocol Violation	Visit 2	Had *B. cepacia* in sputum
106	106002	6	F	74%	TOBI	Adverse Event	Took study drug for 5 days; discontinued 22 days into study	Cough and hoarseness thought to be related to study drug, stopped 5 days after starting; withdrawn from study later for chicken pox and "rhinitis" (needed ciprofloxacin)
106	106007	15	F	59.0%	TOBI	Adverse Event	Took drug for 2 weeks	D/c treatment due to dry cough thought to be drug-related; withdrew from study 4 weeks later (was starting a PE at time of withdrawal)
301	301010	25	M	42.4%	TOBI	Adverse event	Took study drug for 16 days	Pyrexia and then PE; withdrew 15 days after starting study; FEV_1 % had decreased by 7% at withdrawal
707	707002	29	M	53%	TOBI	Protocol violation	Visit 4	Took ciprofloxacin during entire study duration, used his own nebulizer, had visit 4 13 days after study medication was finished
803	803008	47	M	52%	TOBI	Adverse Event	Visit 2	Bronchospasm thought to drug-related a week after starting; discontinued study after 8 days

Discontinuations appeared to occur for legitimate reasons in both arms.

Discontinuations- Overall Conclusions

CHF 1538 did not have a higher rate of discontinuation than either placebo or TOBI. The few discontinuations that occurred secondary to a likely drug-related adverse event were not unexpected and currently appear in the labeling for TOBI. There appeared to be more discontinuations than expected in the adult group, but given the relatively small number of events, this should be interpreted with caution. Overall, no alarming trends were identified.

7.3.4 Significant Adverse Events

The important elements of the safety review have been incorporated into the other safety sections; no further discussion is included in this section.

7.3.5 Submission Specific Primary Safety Concerns

Given that CHF1538 is an inhaled aminoglycoside (tobramycin), particular safety concerns include ototoxicity, nephrotoxicity, bronchospasm, and neuromuscular weakness.

Ototoxicity

In general, in the opinion of this reviewer, audiometric tests performed were inadequate and poorly documented so that any assessment of ototoxicity cannot be made with assurance. Though it's unlikely that the study compound will be systemically absorbed to a degree that it will affect acoustic and vestibular functioning, it should be noted that post marketing reports of hearing loss have occurred with TOBI (though of course the relationship between the two is unclear). A discussion of audiometric results and other parameters of vestibular and ototoxicity are discussed below for each of the individual studies.

CT01

Bone conduction audiometric tests were performed at visits 1, 4, and 5 over a frequency range of 250-8000 Hz. However, often times the results were reported simply as an individual decibel measurement with no corresponding information about the actual frequency or range of frequencies tested. This made it difficult to assess whether the same frequencies were tested at each visit. It also made it difficult to assess whether at a particular frequency in a particular ear, significant increases had occurred in hearing threshold regardless of whether it remained in the normal range. The applicant's measure of ototoxicity was simply whether any threshold >20 dB was reported after Visit 1 (20-25 dB generally being considered the threshold of normal hearing). Moreover, some sites had no numerical results listed and instead had only designations such as "normal." Also, some sites, such as site 17, listed the exact same threshold of 10 dB for every visit for every patient bringing the conduct of the tests at those sites into question. The following applicant tables list the mean baseline audiometric results for the ITT population at visit 1 and the mean change from baseline at Visit 4 for the ITT population.

Table 7.3.5: CT01 Audiometric Summary by Visit: ITT1 Population

	CHF 1538	PLACEBO
Visit 1		
Right Ear (dB)		
N[2]	25	26
Mean	9.60	8.62
SD[3]	2.16	2.50
Median	10.0	10.0
Range	5.0-15.0	5.0-15.0
Left Ear (dB)		
N	25	26
Mean	9.98	8.92
SD	3.29	3.62
Median	10.0	10.0
Range	5.0-20.0	4.0-19.0

[1] Intent-to-Treat
[2] total number of patients
[3] standard deviation

- EDR SDN #0, 5.3.5.1.3 CT01 Study Report Body, Tables 146

Table 7.3.5.1: CT01 Audiometric Summary Change from Baseline: ITT1 Population

	CHF 1538	PLACEBO
Visit 4		
Right Ear (dB)		
N[2]	25	23
Mean	-0.92	0.28
SD[3]	2.00	3.11
Median	0.0	0.0
Range	-5.5-1.5	-5.0-10.0
Left Ear (dB)		
N	25	23
Mean	-0.64	-0.18
SD	1.55	1.86
Median	0.0	0.0
Range	-5.0-0.0	-6.7-5.0

[1] Intent-to-Treat
[2] total number of patients
[3] standard deviation

-EDR SDN #0, 5.3.5.1.3 CT01 Study Report Body, Tables 147

Of the reported results, no subject in the CHF 1538 arm had a threshold >20 dB at any time and minimal changes in dB thresholds from visit 1 to visit 4 or 5 were seen. Of course, given the limitations listed above, the results must be viewed with caution.

In the CHF 1538 arm, there were two TEAE reported that could have indicated vestibular or ototoxicity. One incident was designated by the investigator term “vertigo”

(coded to PT vertigo), and the other incident was designated by the investigator term "giddiness" (coded to PT dizziness). The vertigo event occurred on study day 3, lasted 15 days, and was moderate in severity. The giddiness event occurred on day 1 of study, lasted 24 hours and was mild in severity. In the placebo arm, there was one investigator term for "secretory otitis" which was coded to PT "otitis media."

Overall, no clear signs of oto- or vestibular toxicity emerge from this trial, but interpretation of the data is limited.

CT02

In CT02, bone and air conduction tests were to be performed at visits 1, 4 (end of first on cycle), and 8 (end of third on cycle), and if abnormal results (defined as having an auditory threshold >20 dB at any frequency) were seen at either visit 4 or 8 then tests were also to be performed at visits 5 and 9, respectively. The range of frequencies to be tested was between 250-8000 Hz in both ears. Though improved from CT01 in terms of reporting of results, there is still much to be desired in the way results were reported. This affects the ability to make assured assessments about whether the study drug CHF 1538 has the potential for ototoxicity. Some of the issues noted include:

1. For some subjects at certain visits, bone conduction tests were not performed. Bone conduction tests are preferred in this setting given the ability of the aminoglycoside to cause sensorineural hearing loss. With air conduction tests only, it is difficult to know whether abnormal results are actually from conductive hearing loss rather than sensorineural hearing loss. However, normal results on air conduction tests alone are adequate.
2. There is no clear standardization as to what frequencies were to be tested by all the centers. Thus, some centers appeared to test the full range of frequencies while others did not. For other centers, only the dB result from one frequency was reported (ostensibly the highest threshold recorded of frequencies tested) so it is unclear what frequencies were actually tested at the visit. Moreover, it's not clear whether for particular subjects, the same frequencies were tested for both bone and air conduction, thus making abnormal air conduction results difficult to interpret
3. For some subjects, the same frequencies did not appear to be tested from visit to visit.
4. Full audiometric reports showing all frequencies tested/audiometric thresholds at each frequency for both ears were not submitted again making it difficult to both compare and interpret data, particularly if interested in looking at changes in hearing threshold over the study period at all frequencies in both ears.

This reviewer submitted queries as to the interpretation of the audiometric results and received this response:

"Please provide further information on how to interpret the audiometric results on the case report forms. It is difficult to conclude what is being reported."
Applicant Response: In all 3 studies, the protocols indicated that audiometric tests be performed over a range of frequencies from 250 to 8000 Hz. The CRFs in all 3 studies captured the hearing threshold in decibels, but CRFs were not designed to collect the frequencies that were tested. Only in Study CT02 were the frequencies documented following a letter of general clarification sent by the Contract Research Organization to the study monitors. Therefore, Chiesi's responses to questions 3a and 3b below are restricted to study CT02.

a. ***"Often different frequencies are reported at different visits for a particular subject- is this because only the frequency with the highest decibel threshold is being reported for a particular visit?"***

Applicant Response: The monitors were instructed to inform the sites that the highest threshold should be recorded along with its corresponding frequency. However, a comparison of the source documentation, CRFs and the corresponding data in the dataset from 3 sites (Sites 21, 26, and 32) found that the method of recording the audiometric test frequencies was not performed in a consistent fashion. Regardless of the inconsistent manner in which frequency data were captured, the hearing threshold data do not imply a concern for ototoxicity beyond what is already well-known and established for aminoglycosides.

*b. "***Was the same range of frequencies tested at each audiometric test?"***

Applicant Response: While according to the protocol the audiometric test was to be performed to determine the auditory threshold in both ears at frequencies between 250 and 8000 Hz, in actuality the audiometric tests were performed at frequencies within the range 0-8192 Hz. Data from 54 patients, or 22% of the randomized patient population were collected below 250 and above 8000 Hz. As above in our response to 3a, despite this inconsistency, there is no concern for ototoxicity beyond what is already well-known and established for aminoglycosides.

c. ***"Was only a hearing threshold > 20 dB considered significant or were changes in dB threshold over time (for example, an increase of 15 dB at a particular frequency from one visit to the next) considered significant?"***

Applicant Response: For the purposes of evaluation of the audiometric findings during the preparation of the final CSRs, only hearing thresholds > 20 dB were considered significant.

d. ***"Are the complete audiometric tests available (dB levels for all frequencies tested for both ears at all visits for a particular subject)?"***

Chiesi contacted 3 sites involved in study CT02 (Sites 21, 26, and 32) who were readily able to retrieve the source documents from their study files and were able to provide Chiesi with copies. It should be noted that these 3 sites are currently involved with other current Chiesi studies. If source documentation is requested from a site with which Chiesi does not have a current relationship, there may be prolonged retrieval times.

The following applicant table shows the number of patients who had a bone conduction test >20 dB by treatment arm and visit.

Table 7.3.5.2: CT02 Bone Conduction Audiometric Test – Patients Hearing Threshold > 20dB in At Least One Ear: Safety Population

Visit	CHF 1538 N[1]=161	PLACEBO N=85
Visit 1	0 (0.0%)	0 (0.0%)
Visit 4	2 (1.24%)	0 (0.0%)
Visit 8	2 (1.24%)	2 (2.35%)

[1] total number in group

-EDR SDN # 0, 5.3.5.1.3 CT02 Study Report Body, Table 295

The results are comparable, however given the limitations outlined above, little can be made of this result.

There was one report of vertigo, one report of dizziness, one report of acoustic stimulation test abnormal, and one report of audiogram abnormal in the CHF 1538 group. There was one report of dizziness and one report of audiogram abnormal in the placebo group. The table below further describes these events.

Table 7.3.5.3: Ototoxicity related Adverse Events - CT02

Patient	Investigator Term	PT	Start Date (Study Day)	Stop Date (Study Day)	Severity	Serious	Outcome	Notes
CHF1538 Patients								
21-007	Vertigo	Vertigo	2/24/2003 (1)	2/25/2003 (2)	Mild	No	Recovered	12 y/o female; had epistaxis a day after and a viral infection a week after event
33-004	Dizziness	Dizziness	1/18/2003 (3)	1/19/2003 (4)	Mild	No	Recovered	16 y/o Male
32-031	Decreased air conduction	Acoustic Stimulation test abnormal	10/16/2003 (29)	2/9/2004 (149)	Mild	No	Recovered	13 y/o male; bone conduction thresholds fairly unchanged so may have been air conduction problem; by end of third on cycle had normal thresholds similar to baseline; limitations to interpreting data - see discussion above
15-003	Increased threshold without any signs	Audiogram Abnormal	9/4/2003 (29)	7/5/2003 (57)	Mild	No	Recovered	Given limitations in interpreting data, by end of 3rd on cycle there was a return to normal thresholds (after 1st on cycle had thresholds of 30dB in rt. ear and 25 in lt. ear)
Placebo Patients								
33-003	Dizziness	Dizziness	2/9/2003 (25)	2/9/2003 (25)	Mild	No	Recovered	12 y/o male
16-002	Increased Threshold	Audiogram Abnormal	6/25/2003 (57)	9/17/2003 (141)	Mild	No	Recovered	7 y/o female; limitations interpreting data but elevated thresholds at end of 1st on cycle and beginning of 2nd On cycle but normal threshold by end of third cycle

Looking at the data above, there was no real difference in ototoxicity/vestibular toxicity TEAE between the 2 treatment arms. Moreover, in some of the CHF 1538 cases, a relationship between event and study drug would be unlikely (i.e., subject 21-007 had an event on study day 1; doubtful that study drug create such toxicity so quickly).

Overall, there is nothing in trial CT02 to suggest a possible ototoxicity signal. However, given the significant limitations in documentation, it is not possible to make any assured claims about such a signal.

CT03

Audiometric tests were to be done at study Visits 1, 4, and 5. Bone conduction was to be performed over the range frequencies 250-8000 Hz in both ears. Many of the same limitations in data presentation that are noted with study CT01 apply to this study as

well (see above discussion). Similar to prior trials, hearing thresholds >20 dB were considered abnormal.

In the CHF 1538 arm, two subjects were found to have thresholds >20 dB at visit 4 which had returned to normal by visit 5, one subject had an elevated threshold at visit 4 which remained elevated at visit 5, and another subject which only had an elevated threshold at visit 5. In the TOBI arm, one subject had an elevated threshold at visit 4 that remained elevated at visit 5, another subject had an elevated threshold at visit 4 and then returned to normal, and a third subject had an elevated threshold at visit 5. The following applicant table displays the above results.

Table 7.3.5.4: CT03 Audiometric Test: Hearing Threshold >20 dB in at least One Ear: Safety Population

	CHF 1538 (N=156)	TOBI (N=168)
At Visit 1	0	0
At Visit 4	3 (1.9%)	2 (1.2%)
At Visit 5	2 (1.3%)	2 (1.2%)

-EDR SDN # 0, 5.3.5.1.3 CT03 Study Report Body, Table 60

The following table lists TEAE that could have represented ototoxicity or vestibular toxicity.

Table 7.3.5.5: Ototoxicity Related AE - CT03

Subject/Drug	Investigator Term	PT	Start Date (Study Day)	Stop Date (Study Day)	Severity	Serious	Outcome	Notes
103002 CHF 1538	Deterioration of auditory investigation (audiometric test abnormality)	Audiogram Abnormal	12/14/2009 (29)	ongoing	Mild	No	Not Recovered	Visit 1 – 20 dB Visits 4 and 5 – 25 dB
106003 CHF 1538	Sensorineural hearing loss	Deafness neurosensory	2/24/2010 (30)	3/31/2010 (65)	Moderate	No	Recovered	Visit 1 20 dB, Visit 4 55 dB, Visit 5 20 dB
109008 CHF1538	Decreased auditory function of right ear	Hypoacusis	12/7/2009 (32)	12/21/2009 (46)	Mild	No	Recovered	Visit 1 10 dB, Visit 4 25 dB, Visit 5 10 dB
109009 TOBI	Decreased auditory function of right ear	Hypoacusis	12/7/2009 (32)	12/22/2009 (47)	Mild	No	Recovered	Visit 1 15 dB, Visit 4 25 dB, Visit 5 10 dB
203004 CHF 1538	Sensorineural hearing loss	Deafness neurosensory	8/5/2009 (-13)	ongoing	Mild	No	Not Recovered	Unclear; no data recorded for this date; subject's audiometric results are normal
301028 CHF 1538	Dizziness	Dizziness	9/22/2009 (28)	9/22/2009 (28)	Mild	No	Recovered	Occurred in the setting of fatigue
102005 TOBI	Decrease on Bone Conduction on Right Ear	Audiogram Abnormal	4/6/2010 (29)	ongoing	Mild	No	Recovered	Visit 1 20 dB, Visit 4 30 dB, Visit 5 30 dB

Most of the above cases had fluctuating audiometric measurements which makes it less plausible that ototoxicity from study drug was involved. In subject 103002, an increase of only 5 dB was seen though this remained elevated at Visit 5 (as noted earlier, because of the way the results were reported, changes in hearing thresholds for different frequencies cannot be assessed). Based on these limited data, no clear sign of ototoxicity emerges but no true assurances can be made.

Overall, though no clear signs of ototoxicity or vestibular toxicity emerge from these trials, given the limitations in the data noted as well the risk for such adverse events with the aminoglycoside class, any labeling would likely have to contain some wording documenting the potential risk of such events, similar to what is contained in the current TOBI labeling.

Bronchospasm

It's unclear whether bronchospasm was specifically tracked in any of the trials. From a review of the protocols, it's unclear whether PFT were done after test treatment was administered, and a review of statistical files appears to corroborate this.

CT01
No TEAE coded to PT "bronchospasm" was noted. Looking at investigator terms that may signify a bronchospasm event, there was one subject with increased cough, and one subject with cough and airways obstruction; both subjects were in the placebo arm. From these limited data, there did not appear to be a signal for bronchospasm with CHF 1538.

CT02

There was one instance of investigator term "bronchospasm" – this occurred in a 15 year-old male in the CHF 1538 arm and was thought not related to study drug. Other terms such as cough or wheezing are difficult to assess because the pulmonary exacerbation checklist in this trial asked specifically to assess for cough or new findings on chest examination so these terms may not be very specific for bronchospasm. From these limited data, no signal for bronchospasm can be seen, however no real assurance can be made without actual PFT data looking for this. A calculation was made from a modified table which attempted to better tease out symptoms independent of a pulmonary exacerbation, and in this crude calculation there was a slightly higher level of bronchospasm seen in the CHF 1538 arm (see Table 7.4.1.11).

CT03

There was one investigator term for "bronchospasm" in the TOBI arm and none in the CHF 1538 arm. Looking at drug-related adverse events in the CHF 1538 arm, one

subject had a complaint of dyspnea, another had a complaint of chest tightness. In the TOBI arm, there were five subjects with complaints of cough, one subject with dyspnea post inhalation, and one subject with bronchospasm. Of course, these data must be viewed with caution given the open label format of trial.

Overall, no clear signal of bronchospasm emerges for CHF 1538 that is worse than the reference drug TOBI, but the lack of data provides only limited assurance of this.

Nephrotoxicity

No relationship between inhaled tobramycin and worsened renal laboratory parameters was noted. Please refer to the laboratory parameters section of this safety review for further discussions regarding change in serum creatinine and BUN over the course of all 3 studies.

CT01
Looking at adverse event terms that might represent a renal failure event, there was one adverse event with the investigator term “increase of creatinine level” and this occurred in the placebo arm on Day 29.

CT02

There was one subject in the CHF 1538 arm with an investigative term “increase of serum creatinine level.” However, the baseline of 0.97 mg/dL decreased to 0.86 mg/dL at the end of the 1st On Cycle, increased to 1.03 mg/dL at the end of the first off cycle, decreased to 0.97 mg/dL at the end of the 2nd On Cycle and decreased even further to 0.85 mg/dL at the end of 3rd off cycle. Based on this, levels only slightly ever increased above baseline and increases were not clearly associated with treatment.

CT03

No AE terms clearly implied a nephrotoxic event in either treatment arm.

Based on the above findings, no clear relationship between inhaled CHF 1538 and nephrotoxicity can be discerned. However, similar to the TOBI label, any labeling would likely contain wording warning users of the potential for such events.

Neuromuscular weakness

CT01

There was one report each of the investigative term “weakness” in the placebo and CHF 1538 arm. The CHF 1538 event occurred in a 14 year-old male on Day 52 of study (off treatment period) so any relationship is unlikely.

CT02

There were 2 subjects with the preferred term “asthenia,” and both subjects were in the placebo arm.

CT03

There was one event coded as investigative term “general weakness” that occurred in the CHF 1538 arm. This event occurred on days 20-22 of study, was mild in severity, and felt to be related to study drug.

It should be noted that looking for terms that might represent neuromuscular weakness is inherently subjective and prone to error. For example, investigative terms such as hoarseness, dyspnea, fatigue, and increased work of breathing were not included due to their low specificity in the setting of CF.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

CT01
In CT01, the overall number of TEAE as well as the number of patients with a TEAE was increased in the placebo safety population as compared to the CHF 1538 treatment arm. This was true whether looking at the safety population by gender, age, or baseline MIC. However, when looking at patients with baseline FEV_1 % predicted < 50%, a higher proportion of patients in the CHF 1538 arm had a TEAE as compared to placebo. The following applicant tables illustrate each of these analyses. Given the small numbers in these analyses, all conclusions drawn must be viewed with caution.

Table 7.4.1: CT01 Overview of Treatment-Emergent Adverse Events

Category	CHF 1538 (N^1=29)	Placebo (N=30)
Total number of TEAEs[2]	20	34
Number (%) of patients with TEAE(s)	14 (48.3%)	21 (70.0%)

1-*Total number of patients*
2 – Treatment Emergent Adverse Events
-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 25

Table 7.4.1.1: CT01 Summary of Treatment-Emergent Adverse Events by Gender and Treatment Group: Safety Population

Treatment-Emergent Adverse Event (TEAE)	Gender			
	Male		Female	
	CHF 1538 (N[1]=15)	Placebo (N=17)	CHF 1538 (N=14)	Placebo (N=13)
Total number of TEAEs	8	17	12	17
Number of patients with any TEAE	7 (46.7%)	11 (64.7%)	7 (50.0%)	10 (76.9%)
Infections and Infestations	0 (0.0%)	1 (5.9%)	4 (28.6%)	6 (46.2%)

[1] total number of patients in group
-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 28

Table 7.4.1.2: CT01 Summary of Treatment-Emergent Adverse Events by Age Group: Safety Population

Treatment-Emergent Adverse Event (TEAE)	Age Groups					
	6-12 years		13-17 years		> 17 years	
	CHF 1538 (N[1] = 19)	Placebo (N = 12)	CHF 1538 (N = 7)	Placebo (N = 11)	CHF 1538 (N = 3)	Placebo (N = 7)
Total number of TEAEs	10	12	8	15	2	7
Number of patients with any TEAE	7 (36.8%)	7 (58.3%)	5 (71.4%)	9 (81.8%)	2 (66.7%)	5 (71.4%)

[1] total number of patients in group
-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 29

Table 7.4.1.3: CT01 Summary of Total Treatment-Emergent Adverse Events by Baseline MIC[1] Value (< 16 µg/mL vs. ≥ 16 µg/mL)

Treatment-Emergent Adverse Event (TEAE)	Baseline MIC Value[2]			
	Less Than 16 (µg/mL)		Greater Than or Equal to 16 (µg/mL)	
	CHF 1538 (N[3]=22)	PLACEBO (N=23)	CHF 1538 (N=7)	PLACEBO (N=4)
Total number of TEAEs	14	25	6	6
Number of patients with any TEAE	9 (40.9%)	15 (65.2%)	5 (71.4%)	4 (100.0%)

[1] minimum inhibitory concentration
[2] analysis population included all patients in the Safety population with a baseline MIC value.
[3] total number of patients in group
-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 30

Table 7.4.1.4: CT01 Summary of Treatment-Emergent Adverse Events by Baseline FEV_1 % Predicted Normal: Safety Population

Treatment-Emergent Adverse Event (TEAE)	Baseline FEV_1 % of Predicted Normal[2,3]			
	Less Than 50%		Greater Than or Equal to 50%	
	CHF 1538 (N[4]=13)	Placebo (N=8)	CHF 1538 (N=16)	Placebo (N=21)
Total number of TEAEs	9	4	11	28
Number of patients with any TEAE	7 (53.8%)	3 (37.5%)	7 (43.8%)	17 (81.0%)

[1] forced expiratory volume as percent predicted normal
[2] Patient 11-001 of the Placebo group was excluded from all pulmonary function test analyses as a result of missing baseline data.
[3] analysis population included all patients in the Safety Population with a baseline FEV_1 value.
[4] total number of patients in group
-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 31

The following applicant table displays TEAE that occurred in at least two subjects of the safety population. Only 'Condition Aggravated' and 'Respiratory Infection' occurred in more than one individual in the CHF 1538 arm, and only 'Respiratory Infection' occurred with a higher frequency in the CHF 1538 arm than the placebo arm.

Table 7.4.1.5: CT01 Summary of Treatment-Emergent Adverse Events (by PT[1]) Reported Overall by Two or More Patients: Safety Population

Treatment-Emergent Adverse Event (PT)	CHF 1538 (N[2]=29)	PLACEBO (N=30)
Total number of TEAEs[3]	20	34
Overall Number of Patients with a TEAE	14 (48.3%)	21 (70.0%)
Condition aggravated	3 (10.3%)	4 (13.3%)
Respiratory tract infection	3 (10.3%)	1 (3.3%)
Pyrexia	1 (3.4%)	2 (6.7%)
Transaminases increased	1 (3.4%)	2 (6.7%)
Anaemia	1 (3.4%)	1 (3.3%)
Asthenia	1 (3.4%)	1 (3.3%)
Cough	0 (0.0%)	2 (6.7%)
Haemoptysis	0 (0.0%)	2 (6.7%)
Tachycardia	0 (0.0%)	2 (6.7%)

[1] preferred term
[2] total number of patients in group
[3] treatment-emergent adverse event(s)
-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 26

The following table looks at all TEAE (by PT) that occurred with a higher incidence in the CHF 1538 arm as compared to the placebo arm.

Table 7.4.1.6: CT01 TEAE (By PT) Occurring With A Higher Incidence in the CHF 1538 Arm - Safety Population

TEAE	CHF 1538 29 Subjects	Placebo 30 Subjects
Respiratory Tract Infection	3	2 (included respiratory tract infection viral)
Throat Irritation	1	0
Vertigo	1	0
Dizziness	1	0
Hyperglycemia	1	0
Eosinophilia	1	0
Intestinal Obstruction	1	0
Red Blood Cell Sedimentation Rate Increased	1	0
Nausea	1	0
Pharyngitis	1	0
Tonsillitis	1	0

From this, it is clear that only 'Respiratory Tract Infection' occurred in more than one individual in the CHF 1538 arm and no PT was increased in the CHF 1538 arm by at least 2 individuals.

The PT provide somewhat less clarity in evaluating TEAE because of splitting of AE that might actually be quite similar. This reviewer looked at investigator terms that might represent common adverse events of interest such as voice alteration, cough, and shortness of breath (earlier sections looked at other adverse events of interest such as bronchospasm, ototoxicity, nephrotoxicity, and neuromuscular weakness).

Table 7.4.1.7: CT01 Common AE of Interest – Safety Population

AE of Interest	CHF 1538	Placebo
Cough[1]	0	4
Throat Irritation[2]	2	1
Shortness of Breath[3]	0	1
Hemoptysis[4]	0	2

1- investigator terms include 'cough', 'cough increase,' and 'hemoptysis'
1- investigator terms include 'light irritation at beginning of aerosol', 'acute nasopharyngitis,' and 'tonsillitis/pharyngitis'
2- investigator terms include 'airways obstruction'
3- investigator terms include 'hemoptysis'

Overall, no clear safety signal emerges for CT01 in terms of common adverse events. However, given the very small size of this study, no clear conclusions can be drawn.

CT02
The following applicant table provides an overview of TEAE in the CT02 safety population. Though more TEAE occurred in the CHF 1538 arm, a higher proportion of individuals in the placebo arm had a TEAE. The proportion of individuals with an Adverse Drug Reaction (those AEs deemed by the investigator to be at least possibly, or probably related to the test drug) was virtually identical.

Table 7.4.1.8: CT02 Overview of Treatment-Emergent Adverse Events: Safety Population

Category	CHF 1538 (N=161)	PLACEBO (N=85)
Total number of TEAEs[1]	771	573
Number of patients with TEAE(s)	136 (84.5%)	80 (94.1%)
Total number of ADRs[2]	34	25
Number of patients with ADR(s)	25 (15.5%)	13 (15.3%)

1 Treatment-emergent adverse events
2 Adverse drug reactions (TEAEs classified as possibly, probably/likely, or certainly/definitely related to treatment)
-EDR SDN#0, 5.3.5.1.3 CT02 Study Report Body, Table 33

The applicant looked at the breakdown of TEAE by various demographic parameters, including gender, age, baseline FEV_1 % predicted, baseline MIC, and baseline DNase usage. CHF 1538 had either equivalent or a decreased proportion of TEAE as compared to placebo in each of these scenarios.

Within the CHF 1538 arm, there was a fairly even breakdown of TEAE among the various demographic groups except between the MIC groups (82% vs. 100% in the MIC <16 mcg/ml and MIC ≥16 mcg/ml groups, respectively). Also within the three different age groups, in the CHF 1538 arm, the youngest age group (6-12 years) had the highest proportion of TEAE (89%) while the adolescent age group (13-17 years) had the lowest proportion of TEAE (79%). In CT01, TEAE in CHF 1538 arm occurred with the highest frequency in the 13-17 year-olds' group (71%).

The following applicant table shows the frequency of TEAE by PT for the two treatment arms (only events with an occurrence in at least 5 individuals in a treatment arm are shown).

Table 7.4.1.9: CT02 Summary of Treatment-Emergent Adverse Events by decreasing frequency,by PT: Safety Population

TEAEs[1] (by PT[2])	CHF 1538 (N=161)	PLACEBO (N=85)
Total number of TEAEs	771	573
Number of Patients with any TEAE	136 (84.5%)	80 (94.1%)
Cough	86 (53.4%)	60 (70.6%)
Productive cough	62 (38.5%)	40 (47.1%)
Forced expiratory volume decreased	59 (36.6%)	33 (38.8%)
Exercise tolerance decreased	33 (20.5%)	24 (28.2%)
Rales	36 (22.4%)	18 (21.2%)
Pyrexia	30 (18.6%)	21 (24.7%)
Condition aggravated	22 (13.7%)	21 (24.7%)
Respiratory rate increased	20 (12.4%)	15 (17.6%)
Weight decreased	19 (11.8%)	12 (14.1%)
Rhinitis	13 (8.1%)	15 (17.6%)
Red blood cell sedimentation rate increased	15 (9.3%)	6 (7.1%)
Crepitations	10 (6.2%)	11 (12.9%)
Viral infection	10 (6.2%)	5 (5.9%)
Pharyngitis	9 (5.6%)	6 (7.1%)
Nasopharyngitis	8 (5.0%)	7 (8.2%)
Wheezing	10 (6.2%)	4 (4.7%)
Dysphonia	11 (6.8%)	2 (2.4%)
Haemoptysis	9 (5.6%)	4 (4.7%)
Dyspnoea	6 (3.7%)	7 (8.2%)
Sputum abnormal	6 (3.7%)	4 (4.7%)
Influenza	5 (3.1%)	2 (2.4%)
Pharyngolaryngeal pain	5 (3.1%)	2 (2.4%)
Leukocytosis	4 (2.5%)	3 (3.5%)
Headache	2 (1.2%)	5 (5.9%)
Epistaxis	6 (3.7%)	0 (0.0%)
Bronchitis	5 (3.1%)	1 (1.2%)

-EDR SDN#0, 5.3.5.1.3, Table: 280

Clearly, some of the most frequent TEAEs may simply represent the underlying disease. The following table only looks at those TEAEs that occurred with a higher incidence in the CHF 1538 arm.

Table 7.4.1.10: CT02 TEAEs with Higher Incidence in CHF 1538 Arm - CT02

TEAE by PT	CHF 1538 (N=161)	Placebo (N=85)
Rales	36 (22.4%)	18 (21.2%)
Sedimentation Rate Increased	15 (9.3%)	6 (7.1%)
Viral Infection	10 (6.2%)	5 (5.9%)
Wheezing	10 (6.2%)	4 (4.7%)
Dysphonia	11 (6.8%)	2 (2.4%)
Hemoptysis	9 (5.6%)	4 (4.7%)
Influenza	5 (3.1%)	2 (2.4%)
Pharyngolaryngeal Pain	5 (3.1%)	2 (2.4%)
Epistaxis	6 (3.7%)	0 (0%)
Bronchitis	5 (3.1%)	1 (1.2%)
Diarrhea	3 (1.9%)	1 (1.2%)
Immunoglobulins Increased	3 (1.9%)	0 (0%)
Tonsillitis	3 (1.9%)	0 (0%)
Abdominal pain upper	2 (1.2%)	0 (0%)
Body Temperature Increased	2 (1.2%)	0 (0%)
Eosinophilia	2 (1.2%)	0 (0%)
Liver Function Test Abnormal	2 (1.2%)	0 (0%)
Varicella	2 (1.2%)	0 (0%)
Acoustic stimulation tests abnormal	1 (0.6%)	0 (0.0%)
Alanine aminotransferase increased	1 (0.6%)	0 (0.0%)
Arthralgia	1 (0.6%)	0 (0.0%)
Aspergillosis	1 (0.6%)	0 (0.0%)
Back pain	1 (0.6%)	0 (0.0%)
Blood albumin decreased	1 (0.6%)	0 (0.0%)
Blood creatinine increased	1 (0.6%)	0 (0.0%)
Bronchospasm	1 (0.6%)	0 (0.0%)
Burkholderia cepacia infection	1 (0.6%)	0 (0.0%)
Cardiomyopathy	1 (0.6%)	0 (0.0%)
Cheilosis	1 (0.6%)	0 (0.0%)
Conjunctivitis infective	1 (0.6%)	0 (0.0%)
Cor pulmonale chronic	1 (0.6%)	0 (0.0%)
Culture urine positive	1 (0.6%)	0 (0.0%)
Dermatitis allergic	1 (0.6%)	0 (0.0%)
Diabetes mellitus inadequate control	1 (0.6%)	0 (0.0%)
Dyspepsia	1 (0.6%)	0 (0.0%)
Dysphagia	1 (0.6%)	0 (0.0%)
Eczema	1 (0.6%)	0 (0.0%)
Enterovirus infection	1 (0.6%)	0 (0.0%)
Eosinophil count abnormal	1 (0.6%)	0 (0.0%)
Flatulence	1 (0.6%)	0 (0.0%)
Gastritis	1 (0.6%)	0 (0.0%)
Glossitis	1 (0.6%)	0 (0.0%)
Gynaecomastia	1 (0.6%)	0 (0.0%)
Haemolytic anaemia	1 (0.6%)	0 (0.0%)
Hand fracture	1 (0.6%)	0 (0.0%)
Hepatitis C	1 (0.6%)	0 (0.0%)
Hepatosplenomegaly	1 (0.6%)	0 (0.0%)
Leukopenia	1 (0.6%)	0 (0.0%)
Migraine	1 (0.6%)	0 (0.0%)
Nasal congestion	1 (0.6%)	0 (0.0%)
Oral candidiasis	1 (0.6%)	0 (0.0%)
Palpitations	1 (0.6%)	0 (0.0%)
Pancreatitis acute	1 (0.6%)	0 (0.0%)
Platelet count decreased	1 (0.6%)	0 (0.0%)

Pneumonia	1 (0.6%)	0 (0.0%)
Pneumonia mycoplasmal	1 (0.6%)	0 (0.0%)
Radius fracture	1 (0.6%)	0 (0.0%)
Rash	1 (0.6%)	0 (0.0%)
Red blood cell sedimentation rate abnormal	1 (0.6%)	0 (0.0%)
Red blood cell sedimentation rate decreased	1 (0.6%)	0 (0.0%)
Respiratory tract infection viral	1 (0.6%)	0 (0.0%)
Rhinitis allergic	1 (0.6%)	0 (0.0%)
Rhinorrhoea	1 (0.6%)	0 (0.0%)
Salivary hypersecretion	1 (0.6%)	0 (0.0%)
Seasonal allergy	1 (0.6%)	0 (0.0%)
Seborrhoeic dermatitis	1 (0.6%)	0 (0.0%)
Sputum discoloured	1 (0.6%)	0 (0.0%)
Transaminases increased	1 (0.6%)	0 (0.0%)
Urinary tract infection	1 (0.6%)	0 (0.0%)
Vertigo	1 (0.6%)	0 (0.0%)
Viral sinusitis	1 (0.6%)	0 (0.0%)

Using a threshold of a 2% difference between treatment arms, only the PT 'epistaxis,' 'dysphonia,' and 'red blood cell sedimentation rate increased' were increased in the CHF 1538 arm. 'Epistaxis' may represent a true adverse event, but could also be confounded by background disease. 'Dysphonia' is a known adverse effect seen with inhaled tobramycin. 'Red blood cell sedimentation rate increased' is of unknown significance and likely to be confounded by underlying disease. Though not quite meeting the 2% threshold, slightly more subjects in CHF 1538 arm had PT indicative of possible allergic reactions (3.7% vs. 2.4%, respectively, combining incidences for PT of eczema, dermatitis allergic, urticaria, rash, and drug hypersensitivity). It should be noted that in only 4 SOC classes (Ear and Labyrinth Disorders, Cardiac Disorders, Reproductive System and Breast Disorders, and Skin and Subcutaneous Tissue Disorders) was the proportion of patients with TEAE higher in the CHF 1538 arm. In none of these classes did the difference between the CHF 1538 and placebo arms exceed 2%.

As noted earlier, investigators in study CT02 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 value within the past 3 months, decrease in hemoglobin saturation (as measured by oximetry) from baseline value within past three months of ≥10%, and new findings on chest radiography. By the nature of these questions, there were many individual criteria from the checklist that were also labeled as adverse events. This made it difficult to sort out AE that may have been elicited as part of a pulmonary

exacerbation rather than occurring individually/possibly as a consequence of study drug. This difficulty was explained to the applicant and they performed secondary analyses based on the inquiry. The inquiry and the applicant response are displayed below.

***Inquiry**:*
"In many cases, a subject in CT02 was noted to have a pulmonary exacerbation by the CT02 definition, yet "condition aggravated" was not coded as an adverse event but rather each individual criterion (increased cough, increased sputum production, etc.) was coded by an investigator as an adverse event. Also, these symptoms may have been coded as a non-serious adverse event when they eventually led to a serious adverse event such as hospitalization. This creates difficulty in discerning which adverse events, such as increased cough, are independent of a larger symptom complex such as pulmonary exacerbation. If possible, please provide safety analyses where symptoms listed in the Pulmonary Exacerbation definition are analyzed either as part of the definition (when appropriate) or separately so that the incidence of these occurrences can be better understood."

Applicant Response:
In order to discern which TEAEs are independent of a larger symptom complex in the CT02 study, Chiesi identified clusters of TEAEs which constituted a pulmonary exacerbation (MedDRA 9.1, PT "condition aggravated") in a given patient based on the definition of a pulmonary exacerbation defined in the protocol. Table 3 represents a revised version of Module 5.3.5.1, CT02 CSR, Table 279 in which the number (%) of patients for whom the clusters of TEAEs comprising pulmonary exacerbations were replaced with a TEAE of "condition aggravated," in addition to the TEAEs previously coded to "condition aggravated." The percentage of patients reporting a TEAE of "condition aggravated" has increased from 13.7% to 42.2% in the CHF 1538 treatment group and from 24.7% to 51.8% in the Placebo treatment group. Compared with CT02 CSR Table 279, the percentage of patients reporting the following individual TEAEs has decreased in Table 3: crepitations; exercise tolerance decreased; pyrexia; viral infection; forced expiratory volume decreased; oxygen saturation decreased; respiratory rate increased; weight decreased; headache; cough; dyspnoea; productive cough; rales; wheezing and hospitalization.

Though this analysis is not ideal (such as in cases where a subject initially met two individual criteria that later developed into a pulmonary exacerbation, or a situation where a patient had pulmonary exacerbation based on the check list but then "improved" to only two individual symptoms on a checklist) given that these symptoms are elicited rather than volunteered by the patient, it still provides a more accurate picture of AE in the two treatment arms. The table below lists the AE that occurred with increased frequency in the CHF 1538 arm based on the modified analysis.

Table 7.4.1.11: CT02 TEAE Modified Analysis Using Clustering of Symptoms for Pulmonary Exacerbations/Increased in CHF 1538 Arm - CT02

TEAE by PT	CHF 1538	Placebo
Forced Expiratory Volume Decreased	29 (18.0%)	15 (17.6%)
Sedimentation Rate Increased	15 (9.3%)	6 (7.1%)
Rales	12 (7.5%)	6 (7.1%)
Weight Decreased	11 (6.8%)	5 (5.9%)
Dysphonia	11 (6.8%)	2 (2.4%)
Hemoptysis	9 (5.6%)	4 (4.7%)
Influenza	5 (3.1%)	2 (2.4%)
Pharyngolaryngeal Pain	5 (3.1%)	2 (2.4%)
Epistaxis	6 (3.7%)	0 (0%)
Bronchitis	5 (3.1%)	1 (1.2%)
Crepitations	4 (2.5%)	2 (2.4%)
Diarrhea	3 (1.9%)	1 (1.2%)
Immunoglobulins Increased	3 (1.9%)	0 (0%)
Tonsillitis	3 (1.9%)	0 (0%)
Abdominal pain upper	2 (1.2%)	0 (0%)
Body Temperature Increased	2 (1.2%)	0 (0%)
Eosinophilia	2 (1.2%)	0 (0%)
Liver Function Test Abnormal	2 (1.2%)	0 (0%)
Varicella	2 (1.2%)	0 (0%)
Wheezing	2 (1.2%)	0 (0%)

In this modified table, once again using a threshold of a 2 % difference between treatment arms, the same three PT - 'epistaxis,' 'dysphonia,' and 'red blood cell sedimentation rate increased '- were the only PT that were increased in the CHF 1538 arm. However, in this modified table, percentages of other findings such as cough and rales changed between the two arms (as noted in the applicant response above).

From the current TOBI label, the only adverse events to be significantly increased in the TOBI arm were 'voice alteration' and 'tinnitus.' Moreover, common adverse events to be expected from an inhaled drug include cough (including hemoptysis), voice alteration/pharyngitis, and bronchospasm with associated wheezing and dyspnea. Ideally, one would try to review through investigator terms to look for AEs that might fall under the above designations. However, given the limitations with the original dataset due to the checklist, this is not feasible for certain AE, particularly cough. The applicant did provide an expanded version of the modified table above, but the dataset used to create it was not provided. Therefore, this reviewer looked through the PT in the modified table to see which PT might fall under the AE of interest and compared frequencies between the CHF 1538 and placebo arms. This is at best a crude approximation given the limitations in the modified table (discussed above) and also because the same individual may be represented for more than one PT. Tinnitus (ototoxicity) was already discussed earlier so this review primarily focused on cough including hemoptysis and voice alteration/pharyngitis. The table below displays those findings.

Table 7.4.1.12: CT02 AEs of Interest – Safety Population of CHF 1538 and Placebo Arms[1]

	CHF 1538	Placebo
Cough[2]	88 (54.6%)	52 (61%)
Voice Alteration/Pharyngitis[3]	37 (23%)	21 (24.7%)
Bronchospasm[4]	5 (3.1%)	1 (1.2%)

[1]- Though numbers are meant to represent individuals, some individuals may in fact have more than one preferred term in a particular category and be counted more than once
[2]-Cough – terms include 'cough,' 'hemoptysis,' 'productive cough,'
[3]-Voice Alteration/Pharyngitis- terms include 'tonsillitis,' 'laryngitis,' 'nasopharyngitis,' 'pharyngitis,' 'acute tonsillitis,' 'dysgeusia,' 'pharyngolaryngeal pain,' 'dysphonia,' and 'throat irritation'
[4]-Bronchospasm- terms include 'bronchospasm,' 'chest pain,' and 'wheezing'

With this crude assessment, only bronchospasm appeared to have a slightly higher frequency in the CHF 1538 arm.

Overall, few adverse events stood out in terms of potential association with CHF 1538, however there were difficulties in interpreting the data. Epistaxis, dysphonia, and red blood cell sedimentation rate increased were PT that seemed to have a slight higher incidence in the CHF 1538 arm. Using another crude analysis to estimate common adverse events associated with inhaled therapies, only bronchospasm stood out in terms of a slightly higher incidence in the CHF 1538 arm.

CT03

CT03 was an open-label trial. As such, all estimations of adverse events must be viewed with the potential for biases in reporting safety events. However, of importance, CT03 also used a formulation of CHF 1538 with a slightly different osmolality from what was used in the CT01 and CT02 trial; this formulation was similar to the to-be-marketed material.

In CT03, a slightly higher percentage of patients in the CHF 1538 arm had a TEAE as compared to the TOBI arm. The following applicant table illustrates these results.

Table 7.4.1.13: CT03 Adverse Events: Summary of TEAEs – Safety Population

	CHF 1538 (N=156)		**TOBI (N=168)**	
	n (%)[1]	**No.[2]**	**n (%)**	**No.**
TEAEs[3]	49 (31.4%)	102	47 (28.0%)	80

1 number (percent) of patients with at least one event
2 number of events
3 Treatment-Emergent Adverse Events defined as adverse events occurred after the first intake of study treatment
-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Table 51

The following applicant table lists those TEAE by PT and SOC that occurred in the CHF 1538 and TOBI arms.

Table 7.4.1.14: CT03 Adverse Events - All TEAEs by SOC and by PT: Safety Population

	CHF 1538 (N=156)		TOBI (N=168)	
	n (%)[1]	Number[2]	n (%)	Number
Patients with at least one TEAE[3]	49 (31.4%)	102	47 (28.0%)	80
Infections and infestations[4]	26 (16.7%)	29	25 (14.9%)	28
Rhinitis	7 (4.5%)	7	5 (3.0%)	5
Pharyngitis	6 (3.8%)	6	2 (1.2%)	2
Bronchitis	4 (2.6%)	4	4 (2.4%)	4
Upper respiratory tract infection	2 (1.3%)	2	3 (1.8%)	3
Appendicitis	1 (0.6%)	1	0 (0.0%)	0
Gastrointestinal viral infection	1 (0.6%)	1	0 (0.0%)	0
Influenza	1 (0.6%)	1	0 (0.0%)	0
Laryngitis	1 (0.6%)	1	0 (0.0%)	0
Lung infection	1 (0.6%)	1	1 (0.6%)	1
Nasopharyngitis	1 (0.6%)	1	2 (1.2%)	2
Respiratory tract infection	1 (0.6%)	1	3 (1.8%)	4
Respiratory tract infection viral	1 (0.6%)	1	1 (0.6%)	1
Tracheobronchitis	1 (0.6%)	1	0 (0.0%)	0
Viral upper respiratory tract infection	1 (0.6%)	1	0 (0.0%)	0
Acute tonsillitis	0 (0.0%)	0	1 (0.6%)	1
Pneumonia	0 (0.0%)	0	1 (0.6%)	1

	CHF 1538 (N=156)		TOBI (N=168)	
	n (%)	Number	n (%)	Number
Sinusitis	0 (0.0%)	0	1 (0.6%)	1
Tracheitis	0 (0.0%)	0	1 (0.6%)	1
Varicella	0 (0.0%)	0	1 (0.6%)	1
Viral pharyngitis	0 (0.0%)	0	1 (0.6%)	1
Respiratory, thoracic and mediastinal disorders	16 (10.3%)	25	20 (11.9%)	23
Cough	10 (6.4%)	12	10 (6.0%)	11
Haemoptysis	3 (1.9%)	3	2 (1.2%)	2
Oropharyngeal pain	3 (1.9%)	3	1 (0.6%)	1
Dysphonia	2 (1.3%)	2	3 (1.8%)	3
Dyspnoea	1 (0.6%)	2	2 (1.2%)	2
Nasal congestion	1 (0.6%)	1	0 (0.0%)	0
Rales	1 (0.6%)	1	0 (0.0%)	0
Sputum increased	1 (0.6%)	1	0 (0.0%)	0
Bronchospasm	0 (0.0%)	0	1 (0.6%)	1
Obstructive airways disorder	0 (0.0%)	0	1 (0.6%)	1
Productive cough	0 (0.0%)	0	1 (0.6%)	1
Rhinorrhoea	0 (0.0%)	0	1 (0.6%)	1
General disorders and administration site conditions	9 (5.8%)	15	6 (3.6%)	7
Pyrexia	5 (3.2%)	5	5 (3.0%)	5
Fatigue	2 (1.3%)	6	0 (0.0%)	0
Asthenia	1 (0.6%)	1	0 (0.0%)	0
Chest discomfort	1 (0.6%)	1	0 (0.0%)	0
Chest pain	1 (0.6%)	1	0 (0.0%)	0
Mucosal dryness	1 (0.6%)	1	0 (0.0%)	0
Catheter site phlebitis	0 (0.0%)	0	1 (0.6%)	1
Face oedema	0 (0.0%)	0	1 (0.6%)	1
Congenital, familial and genetic disorders	6 (3.8%)	6	5 (3.0%)	5
Cystic fibrosis lung	6 (3.8%)	6	5 (3.0%)	5
Nervous system disorders	6 (3.8%)	8	1 (0.6%)	1
Headache	5 (3.2%)	6	0 (0.0%)	0
Dizziness	1 (0.6%)	1	0 (0.0%)	0
Syncope	1 (0.6%)	1	0 (0.0%)	0
Somnolence	0 (0.0%)	0	1 (0.6%)	1

	CHF 1538 (N=156)		TOBI (N=168)	
	n (%)	Number	n (%)	Number
Investigations	4 (2.6%)	5	8 (4.8%)	9
Forced expiratory volume decreased	2 (1.3%)	2	1 (0.6%)	1
Aspartate aminotransferase increased	1 (0.6%)	1	0 (0.0%)	0
Audiogram abnormal	1 (0.6%)	1	1 (0.6%)	1
Red blood cell sedimentation rate increased	1 (0.6%)	1	3 (1.8%)	3
Blood glucose increased	0 (0.0%)	0	1 (0.6%)	1
Neutrophil count increased	0 (0.0%)	0	1 (0.6%)	1
Pulmonary function test decreased	0 (0.0%)	0	2 (1.2%)	2
Gastrointestinal disorders	3 (1.9%)	3	1 (0.6%)	1
Abdominal pain upper	2 (1.3%)	2	0 (0.0%)	0
Abdominal pain	1 (0.6%)	1	0 (0.0%)	0
Diarrhoea	0 (0.0%)	0	1 (0.6%)	1
Musculoskeletal and connective tissue disorders	3 (1.9%)	3	0 (0.0%)	0
Arthralgia	1 (0.6%)	1	0 (0.0%)	0
Back pain	1 (0.6%)	1	0 (0.0%)	0
Musculoskeletal pain	1 (0.6%)	1	v	0
Blood and lymphatic system disorders	2 (1.3%)	3	0 (0.0%)	0
Eosinophilia	1 (0.6%)	1	0 (0.0%)	0
Leukopenia	1 (0.6%)	1	0 (0.0%)	0
Thrombocytopenia	1 (0.6%)	1	0 (0.0%)	0
Ear and labyrinth disorders	2 (1.3%)	2	2 (1.2%)	2
Deafness neurosensory	1 (0.6%)	1	0 (0.0%)	0
Hypoacusis	1 (0.6%)	1	1 (0.6%)	1
Otosalpingitis	0 (0.0%)	0	1 (0.6%)	1
Injury, poisoning and procedural complications	1 (0.6%)	1	1 (0.6%)	1
Head injury	1 (0.6%)	1	0 (0.0%)	0
Skin injury	0 (0.0%)	0	1 (0.6%)	1
Psychiatric disorders	1 (0.6%)	1	0 (0.0%)	0
Depression	1 (0.6%)	1	0 (0.0%)	0
Vascular disorders	1 (0.6%)	1	0 (0.0%)	0
Hypotension	1 (0.6%)	1	0 (0.0%)	0
Metabolism and nutrition disorders	0 (0.0%)	0	1 (0.6%)	2
Hypokalaemia	0 (0.0%)	0	1 (0.6%)	1
Hyponatraemia	0 (0.0%)	0	1 (0.6%)	1

	CHF 1538 (N=156)		TOBI (N=168)	
	n (%)	Number	n (%)	Number
Skin and subcutaneous tissue disorders	0 (0.0%)	0	1 (0.6%)	1
Urticaria	0 (0.0%)	0	1 (0.6%)	1

[1] Number (percent) of patients with at least one event; % of patients is based on the total number of patients in each treatment group in the Safety population. At each level (Preferred Term and System Organ Class) each patient is counted only once.
[2] Number of events; one patient can have more than one TEAE
[3] Treatment-Emergent Adverse Events defined as adverse events occurred after the first intake of study treatment (or the same day)
[4] Table sorted by decreasing frequency of System Organ Class (SOC) and then within each SOC by descending frequency of Preferred Term within CHF 1538 treatment group. AEs are coded using MedDRA V13.0.
-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Table 122

Only two PT had an incidence in the CHF 1538 arm >2% above that of the TOBI arm – pharyngitis (3.8% CHF 1538 vs. 1.2% TOBI) and headache (3.2% CHF 1538 vs. 0% TOBI). Given the nature of the study drug, both PT could indeed represent a difference in the adverse event profile of CHF 1538 vs. TOBI. Only 2 SOC had an incidence in the CHF 1538 arm > 2% that of the TOBI arm – General Disorders and Administration Site Conditions (5.8% CHF 1538 vs. 3.6% Placebo) and Nervous System Disorders (3.8% CHF 1538 vs. 0.6% Placebo).

The applicant looked at the distribution of adverse events among various demographic groups, including gender, age, baseline FEV_1 % predicted, and baseline DNase usage. The following applicant tables summarize those findings.

Table 7.4.1.15: CT03 Summary of Adverse Events - All TEAE by Age by SOC: Safety Population

	CHF 1538 (N=156)						TOBI (N=168)					
	6-12 years (N=49)		13-17 years (N=50)		> 17 years (N=57)		6-12 years (N=54)		13-17 years (N=62)		> 17 years (N=52)	
	n (%)[1]	No.[2]	n (%)	No.	n (%)	No.	n (%)	No.	n (%)	No.	n (%)	No.
Patients with at least one TEAE[3]	12 (24.5%)	15	15 (30.0%)	29	22 (38.6%)	58	16 (29.6%)	27	14 (22.6%)	21	17 (32.7%)	32

1 number (percent) of patients with at least one event
2 number of events
3 Treatment-Emergent Adverse Events defined as adverse events occurred after the first intake of study treatment (or the same day)
4- % of patients is based on the total number of patients in each age group within treatment group in the Safety population.
-One patient can have more than one TEAE.

-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Tables 54

Table 7.4.1.16: CT03 Summary of Adverse Events - All TEAE by Sex by SOC: Safety Population

	CHF 1538 (N=156)				TOBI (N=168)			
	Male (N=72)		Female (N=84)		Male (N=85)		Female (N=83)	
	n (%)[1]	No[2].	n (%)	No.	n (%)	No.	n (%)	No.
Patients with at least one TEAE[3]	22 (30.6%)	38	27 (32.1%)	64	22 (25.9%)	32	25 (30.1%)	48

1 number (percent) of patients with at least one event
2 number of events
3 Treatment-Emergent Adverse Events defined as adverse events occurred after the first intake of study treatment (or the same day)
-% of patients is based on the total number of patients in each gender group within treatment group in the Safety population.
-One patient can have more than one TEAE.
-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Table 55

Table 7.4.1.17: CT03 Adverse Events: Summary of Adverse Events - All TEAEs by Baseline FEV_1 (% Predicted) value by SOC: Safety Population

	CHF 1538 (N=156)				TOBI (N=168)			
	< 50% (N=37)		≥ 50% (N=119)		< 50% (N=38)		≥ 50% (N=130)	
	n (%)[1]	No.[2]	n (%)	No.	n (%)	No.	n (%)	No.
Patients with at least one TEAE3	11 (29.7%)	18	38 (31.9%)	84	11 (28.9%)	18	36 (27.7%)	62

1 number (percent) of patients with at least one event
2 number of events
3 Treatment-Emergent Adverse Events defined as adverse events occurred after the first intake of study treatment (or the same day)
-% of patients is based on the total number of patients in each pulmonary function group within treatment group in the Safety population.
-One patient can have more than one TEAE.
-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Tables 56

Table 7.4.1.18: CT03 Adverse Events: Summary of Adverse Events - All TEAEs by Use of rhDNase at Baseline by SOC: Safety Population

	CHF 1538 (N=156)				TOBI (N=168)			
	Use of rhDNase = Yes (N=110)		Use of rhDNase = No (N=46)		Use of rhDNase = Yes (N=119)		Use of rhDNase = No (N=49)	
	n (%)[1]	No.[2]	n (%)	No.	n (%)	No.	n (%)	No.
Patients with at least one TEAE[3]	36 (32.7%)	80	13 (28.3%)	22	37 (31.1%)	64	10 (20.4%)	16

1 number (percent) of patients with at least one event
2 number of events
3 Treatment-Emergent Adverse Events defined as adverse events occurred after the first intake of study treatment (or the same day)
-% of patients is based on the total number of patients in each DNase group within treatment group in the Safety population.
-One patient can have more than one TEAE.
-EDR SDN#0, 5.3.5.1.3 CT03 Study Report Body, Table 57

In terms of age, the CHF 1538 group had a higher proportion of TEAE in the adolescent and adult groups as compared to TOBI. The adult group had the highest proportion of TEAE within the CHF 1538 arm. Drawing conclusions from these demographic studies can be difficult. In terms of gender, the CHF 1538 group had a slightly higher proportion of TEAEs in both genders as compared to TOBI. Within the CHF1538 arm, TEAE occurred in each gender in roughly the same proportion. In terms of baseline FEV_1 % predicted, the ≥ 50% group had a slightly higher proportion of TEAE in the CHF 1538 arm as compared to the similar group in the TOBI arm. Within the CHF 1538 arm, TEAE occurred with roughly equal frequency in both groups, though the two groups did not have equal sample sizes. In terms of baseline rhDNase usage, the non-using group in the CHF 1538 arm had a higher TEAE frequency than the similar group in the TOBI arm. Within the CHF 1538 arm, the positive usage group had a slightly higher frequency of TEAE than the non-usage group. It is difficult to interpret these findings especially given lack of randomization as well differential sample sizes. For example, does the findings in the age subset represent a lack of tolerance for CHF 1538 in the older age groups, or is this a direct result of bias from an open label trial (older people may be more willing to report adverse events)?

As with CT01, this reviewer attempted to look through investigator terms for AE that might help estimate the incidence of common AE of interest such as cough including hemoptysis, voice alteration/pharyngitis, and bronchospasm. The table below illustrates those findings.

Table 7.4.1.19: CT03 Common AE of Interest - Safety Populations for CHF1538 and TOBI in CT03

AE of Interest	CHF1538/started within days 1-28/onset outside of days 1-28	TOBI/started within days 1-28/onset outside of days 1-28
Cough	12 (7.7%)/7 (4.5%)/5 (3.2%)	12 (7.1%)/8 (4.8%)/4 (2.4%)
Voice alteration	13 (8.3%)/7 (4.5%)/6(3.8%)	10 (6.0%)/5 (3.0%)/5 (3.0%)
Bronchospasm	2 (1.3%)/2 (1.3%)/0	3 (1.8%)/2 (1.2%)/1 (0.6%)

1Cough- Investigator terms include 'dry, bad frequent cough,' 'dry cough,' 'increased cough,' 'cough,' 'increase of productive cough' 'hemoptysis,' ' cough more intense' 'coughing,' 'cough increase,' 'increase of cough'
2Voice Alteration – Investigator terms include 'acute nasopharyngitis,' 'hoarse voice,' 'rhinopharyngitis, ''acute laryngotracheitis,' 'sore throat,' 'hoarseness,' 'pharyngitis,' 'acute laryngitis,' 'tonsillitis,' 'acute tonsillitis,' 'throat pain,'
3Bronchospasm- Investigator terms include 'dyspnea,' 'chest tightness,' 'dyspnea post-inhalation of drug,' 'bronchospasm,'

In terms of cough, there does not appear to be a clear difference between the two treatment arms. In terms of voice alteration, there does appear to be a slightly increased frequency of such events in the CHF 1538 arm, including during the on-treatment period. In terms of bronchospasm, there appears to be no clear difference between the two treatment arms.

Overall, there may be an increased signal for voice alterations/pharyngitis and headaches relative to TOBI.

Pooled Analysis CT01 and CT02

Given the differences in duration, differences in eliciting adverse events, as well as slight differences in inclusion criteria, these analyses were not pooled.

CP01

Three subjects taking CHF 1538 had their treatment interrupted due to cough; these were not counted as TEAE. No other symptoms were noted for this drug. TOBI had three TEAE – rhinitis, cough, and urticaria – all mild. TOBI treatment was also interrupted due to cough for two subjects.

7.4.2 Laboratory Findings

In all 3 trials, the laboratory parameters obtained were similar – mainly hematological parameters including Complete Blood Count (CBC) with differential, Erythrocyte Sedimentation Rate (ESR), Aspartate and Alanine Aminotransferase (AST and ALT), serum sodium, potassium, and chloride levels, serum Blood Urea Nitrogen (BUN) and creatinine levels, serum glucose levels, serum protein electrophoresis (in CT01 and

CT02 only), serum GGT (CT03 only), and serum total proteins (CT03 only). Labs were obtained at the following visits for each study:

CT01: Visits 1, 4(end of On Cycle), 5 (End of Off Cycle)
CT02: Visits 1, 4(end of On Cycle), 5 (End of Off Cycle), 8 (end of 3rd On Cycle), 9 (End of 3rd Off Cycle)
CT03: Visits 1, 4(end of On Cycle)

CT01

For all serum chemistry parameters, there was more missing data from the placebo arm for Visits 4 and 5.

Serum Creatinine and BUN

The CHF 1538 and placebo arms had similar serum creatinine measurements at baseline. The change from baseline to visit 4 in serum creatinine was clinically insignificant for both arms and similar between the two arms. However, within the placebo arm, there were several patients at visits 1, 4, and 5 that did not have serum values recorded. Please note the applicant table below.

Table 7.4.2: CT01 Serum Creatinine (mg/dL) Mean Baseline and Mean Change From Baseline: Safety Population

Visit	Week		CHF 1538	Placebo	P-Value
1	Baseline	N[1]	29	26	
		Mean	0.609	0.720	0.087
4	4 "ON" Drug (1° endpoint)	N	29	26	
		Mean Change from Baseline[2]	0.065	0.074	0.850
		Difference (95% CI[3])	-0.009 (-0.110, 0.091)		
5	8 "OFF" Drug	N	28	22	
		Mean Change from Baseline[2]	0.027	0.065	0.529
		Difference (95% CI)	-0.038 (-0.158, 0.083)		

[1] total number of patients.
[2] adjusted for baseline value
[3] confidence interval
-EDR SDN#0, 5.3.5.13 CT01 Study Report Body, Table 34

No patient in the CHF 1538 or placebo arms had an increase of at least 1 mg/dL in serum creatinine from visit 1 to visit 4; the on-treatment period is the time where any

drug-related nephrotoxic effect would be expected to occur. The highest recorded value in a CHF 1538 subject was 1.15 mg/dL (at visit 4 in subject 21-001).

For BUN, the mean change from baseline to visit 4 was 1 mg/dL and for visit 5 was 1.54 mg /dL. The highest change seen in the CHF 1538 arm for either Visit 4 or 5 was 13.7 mg/dL and was not dissimilar from the highest change of 11.5 mg/dL seen in the placebo arm. Only two subjects had an increase greater than 8 mg/dL in the CHF 1538 arm from visit 1 to visit 4; the same was seen in the placebo arm.

Aspartate and Alanine Aminotransferase

No clinically significant changes were noted in AST and ALT from baseline to visits 4 and 5. The largest change noted for a subject in the CHF 1538 arm for AST was 20 U/L and 37 U/L for ALT. It should be noted that several subjects initially had transaminase measurements in nonstandard units that were then converted to the typical SI unit U/L. However, the converted units appeared to have a considerably lower reference range (for example an individual with a converted AST of 8 U/L was considered to be elevated) raising concerns of how these values were converted and whether all the converted and noncoverted values should be treated equally (ie. does 8 U/L in a nonconverted measurement mean the same thing as 8 U/L in a converted measurement?). Queries to the applicant did not help resolve this issue. Thus, using the assumption that all converted and noncoverted U/L transaminase values were equivalent, no hepatotoxic signal was noted. This would be expected given the limited systemic absorption with an inhaled aminoglycoside and the primary renal clearance of aminoglycosides.

Serum Sodium, Potassium, Chloride, and Glucose

In the CHF arm, only two subjects had 10 mmol/L or greater changes in serum sodium from visit 1 to visit 4 (one increase and one decrease). There was one subject with a post baseline value ≥150 mmol/L and one subject with a post baseline value <130 mmol/L. In the placebo arm, 3 subjects had 10 mmol/L or greater changes in serum sodium from visit 1 to visit 4 (two increases and one decrease). Three subjects had post baseline values ≥150 mmol/L and one subject had a post baseline value <130 mmol/L.

In the CHF 1538 arm, there were five subjects with 1 mmol/L or greater changes in serum potassium levels from visit 1 to visit 4 (three decreases and two increases). Three subjects had post-baseline levels >5.5 mmol/L; none had <3.5 mmol/L. In the placebo arm there was one subject with a greater than 1 mmol/L change from visit 1 to visit 4 (an increase). Two subjects had post-baseline levels >5.5 mmol/L; none had <3.5 mmol/L.

In the CHF arm, there were three subjects with changes of 10 mmol/L or greater from visit 1 to visit 4 (two increases and one decrease) in serum chloride. Five subjects had values of ≥110 mmol/L and one subject had a value ≤90 mmol/L. In the placebo arm,

there were two subjects with a change of 10 mmol/L or greater from visit 1 to visit 4 (both decreases). Two subjects had values of ≥110 mmol/L and three subjects had values ≤90 mmol/L.

In the CHF 1538 arm, six subjects had changes of 20 mg/dL or more from visit 1 to visit 4 (3 increases and 3 decreases) in serum glucose. Two subjects had values >140 mg/dL and two subjects had values <60 mg/dL. In the placebo arm, seven subjects had a change of 20 mg/dL or more from visit 1 to visit 4 (five increases and two decreases). One subject had a post-baseline value greater than 140 mg/dL and two subjects had a post-baseline value <60 mg/dL. Also, given patients' concomitant use of inhaled or oral steroids as well as the fact that subjects may have underlying pancreatic insufficiency, it is difficult to sort out what effect the study drug has on this variable (although this should be mitigated by randomization).

The following applicant tables further illustrate comparisons between the two arms.

Table 7.4.2.1: CT01 Electrolytes/Serum Glucose– Change from Baseline: Safety Population

	Visit 4		Visit 5	
	CHF 1538	PLACEBO	CHF 1538	PLACEBO
Glucose (mg/dL)				
N	29	26	28	23
Mean	1.24	-2.69	4.67	1.98
SD	17.45	27.02	21.62	23.24
Median	1.80	-3.05	2.70	5.40
Range	-28.80-43.20	-109.80-29.00	-39.60-82.90	-43.20-54.00
Sodium (mmol/L)				
N	27	25	26	21
Mean	-0.60	2.15	0.25	0.56
SD	5.09	6.55	4.42	10.74
Median	-1.00	2.00	0.00	-1.00
Range	-13.00-11.00	-14.20-22.00	-9.10-10.00	-17.20-36.00
Chloride (mmol/L)				
N	27	25	23	20
Mean	0.13	-0.79	-1.75	-2.95
SD	6.72	5.37	8.80	7.64
Median	0.00	0.00	-1.00	-0.45
Range	-19.00-15.00	-18.00-8.00	-25.00-15.00	-30.00-4.00
Potassium (mmol/L)				
N	27	24	26	21
Mean	-0.03	0.02	0.13	-0.05
SD	0.75	0.48	0.61	0.62
Median	0.10	-0.06	-0.07	0.00
Range	-1.60-1.60	-0.91-1.40	-0.71-1.93	-1.38-1.40

-EDR SDN#0, 5.3.5.1.3 CT01 Study Report Body, Table 140

From the above data, there does not appear to be any clear relationship between study drug and alterations in serum sodium, potassium, chloride, or glucose.

Serum Protein Electrophoresis

These tests are of unclear value (many CF patients likely have a polyclonal gammopathy) and it is unclear how to interpret changes in these tests over time. Moreover, there has not been any noted effect of aminoglycosides with monoclonal gammopathy. Thus, these tests are not evaluated further.

Hematologic Parameters

As with serum chemistry, the sample size for placebo was slightly less than the sample size for CHF 1538.

White Blood Cells

The mean change from baseline to visit 4 in the CHF 1538 arm for white blood cells was -0.94 $x10^9$/L with a range of -7.20 to 7.60 ; for placebo the change was -0.71 $x10^9$/L with a range of -9.90 to 3.20 $x10^9$/L .

Hemoglobin

The mean change from baseline to Visit 4 for hemoglobin was -0.23 g/dL with a range of -3.60 to 1.50 for CHF 1538 and 0.38 with a range of -3.80 to 3.10 for placebo.

Neutrophil

The mean change in the percentage of neutrophils for CHF1538 patients from baseline to visit 4 was -3.76% with a range of -34% to 24%. For placebo, the mean change was 3.62% with a range of -37% to 30%. No neutropenia was observed in the CHF 1538 arm.

Eosinophils

The mean change in percentage of eosinophils from baseline to visit 4 in the CHF 1538 arm was 0.32% with a range of -7% to 5%. For placebo, the mean change was .98% with a range of -9% to 42%. Only one subject in the CHF 1538 arm had an absolute count >500 $10^3/mm^3$ at visit 4.

Platelets

The mean change in level of platelets from baseline to visit 4 was -12.27 $x10^3/mm^3$ with a range of -136 to 244. For placebo, the change was 6.0 $x10^3/mm^3$ with a range of -206 to 77. No levels <100 $x10^3/mm^3$ or >500 $x10^3/mm^3$ were seen in the CHF 1538 arm at visit 4.

ESR

ESR was measured but given the relative nonspecificity of this value, this was not assessed further.

Taken together, no significant effect of study drug on the studied laboratory parameters is seen, particularly with regards to nephrotoxicity.

There were six subjects who had laboratory measurements classified as TEAE for visit 4. Three subjects were in the CHF 1538 arm (ESR increased, anemia, and elevated transaminases) and 3 subjects (elevated creatinine levels, anemia, and transaminases increased) were in the placebo arm. None of these required discontinuation of drug/study withdrawal. At visit 5, there were three subjects with such TEAE, one (eosinophilia and hyperglycemia) in the CHF 1538 arm and two (ALT increased and elevated transminases) in the placebo arm. The CHF 1538 cases were reviewed and either showed no clear relationship to study drug, were not of clinical significance, or could not be interpreted (one case of elevated transminases due to issues of interpreting units used for the transaminases).

CT02

Overall, there were few subjects who did not have laboratory data for various parameters (around 5% missing subjects for CHF 1538 and 9% missing subjects for placebo)

Serum Creatinine and BUN

The mean values for serum creatinine rose slightly over the course of the study, from 0.68 mg/dL at baseline to 0.72 mg/dL at visit 8 for CHF 1538 and from 0.68 mg/dL to 0.73 mg/dL for placebo over the same time period. During the on treatment cycles, there were no clinically significant changes in the mean or median values for serum creatinine for CHF 1538. The following applicant table illustrates these findings.

Table 7.4.2.2: Actual Serum Creatinine Values During Study Period- CT02 Safety Population

	Visit 1 -1 to 8 days Screening		Visit 4 Week 4 End of 1st ON Cycle		Visit 5 Week 8 Start of 2nd ON Cycle		Visit 8 Week 20 End of 3rd ON Cycle		Visit 9 Week 24 End of 3rd OFF Cycle	
	CHF	Placebo	CHF	Placebo	CHF	Placebo	CHF	Placebo	CHF	Placebo
CREA (mg/100 mL)										
N	161	85	160	84	160	83	157	79	154	77
Mean	0.68	0.68	0.69	0.70	0.71	0.71	0.72	0.73	0.72	0.75
SD	0.20	0.20	0.20	0.19	0.19	0.18	0.19	0.20	0.21	0.22
Median	0.68	0.66	0.68	0.68	0.70	0.71	0.71	0.70	0.70	0.71
Range	0.20-1.23	0.15-1.23	0.29-1.28	0.21-1.28	0.28-1.40	0.33-1.19	0.28-1.23	0.33-1.30	0.27-1.50	0.24-1.42

-EDR SDN#0, 5.3.5.1.3 CT02 Study Report Body, Table 290

No subject in either arm had an increase of 1 mg/dL from visit 1 to visit 4 or from visit 1 to visit 8. The highest creatinine value noted at any visit was 1.46 mg/dL in a CHF 1538 subject at visit 9 (there was fairly good reporting for this parameter; by visit 9 only seven and eight subjects did not have reported values from CHF 1538 and placebo, respectively). Note, the applicant in many cases reported the data in SI units so this reviewer had to make crude calculations to convert the values into traditional units. So, to some degree, these assessments are estimations.

For BUN, a proper assessment cannot be made. It is unclear how the conversion was made from SI units to traditional units. When looking at the recordings for several subjects, it appears that the conversion from mmol/L to mg/dL was done not using the typical conversion factor of 2.8. Therefore, the sponsor's assessments of change in mean/median BUN in mg/dl cannot be assessed. This will need further explanation and likely recalculation by the applicant in its complete response.

ALT and AST

It does appear that some of the problems with interpreting the transaminase results in CT01 do not exist for CT02 because it appears that sites recorded values in traditional units; issues with conversion do not arise. For AST, seven subjects had values >100 U/L, 5 in the CHF 1538 group and 2 in the placebo group. No person had a value >150 U/L. Four of the five subjects in the CHF 1538 arm had these values recorded during the on-treatment period, while only 1 of 2 placebo subjects had these values recorded during the on-treatment period. The following table shows how such values were distributed through on- and off-treatment periods . The mean change in this parameter over the course of the study was clinically insignificant. The highest change recorded for either arm was 110 units in the CHF 1538 arm during the 1st on-treatment period.

Table 7.4.2.3: Proportion of Patients with AST > 100 U/L – CT02 Safety Population

	End of 1st On	End of 1st Off	End of 3rd On	End of 3rd Off
CHF 1538	2/158=1.3%	1/158=0.6%	2/149=1.3%	1/152=0.7%
Placebo	0/84=0%	1/83=1.2%	1/77=1.3%	1/76=1.3%

Most of the values >100 U/L were not clearly correlated to on treatment cycles; they could occur during off periods or may occur only during one on cycle treatment of a subject (for example during the first on cycle but not the third on cycle).

For ALT, there were nine subjects who had values >100 U/L over the course of the study. Seven of the subjects were in the CHF 1538 arm and two were in the placebo arm. Five subjects had values >150 U/L, all in the CHF 1538 arm. The following table shows how such values were distributed through on- and off-treatment periods. The mean changes in this parameter were clinically insignificant for CHF 1538. The highest change recorded for either arm was 182 I/U on the CHF 1538 arm during the third off-treatment period. The highest increases generally occurred in the CHF 1538 arm.

Table 7.4.2.4: Proportion of Patients with ALT > 100 U/L – CT02 Safety Population

	End of 1st On	End of 1st Off	End of 3rd On	End of 3rd Off
CHF 1538	4/158=2.5%	2/158=1.3%	1/156=0.6%	3/153=2.0%
Placebo	1/84=1.2%	1/83=1.2%	0/79=0%	0/77=0%

Most of the values >100 U/L were not clearly correlated to on treatment cycles; they could occur during off periods or may occur only during one on cycle treatment of a subject. One elevated value was at baseline.

Overall, though mean changes in transaminases over the course of the study were clinically insignificant, elevated values were more likely to be seen in the CHF 1538 arm. However, elevations > 100 U/L were not clearly correlated with on cycle treatment and no nonfatal serious adverse events or discontinuations were related to hepatotoxicity. Therefore, no effect of inhaled drug on hepatotoxicity is anticipated.

Serum Sodium, Potassium, Chloride and, Glucose

There were six subjects in CHF 1538 with changes of at least 10 mmol in their serum sodium from baseline to visit 4 or 8 (five decreases and one increase). There was only one such subject in placebo (a decrease). There were seven subjects with post baseline values ≥150 mmol/L, five in the CHF 1538 arm and two in the placebo arm. There was one subject in each arm where such changes occurred on treatment. There were five subjects who had serum sodium post baseline values less than 130; three in the placebo arm and two in the CHF 1538 arm; all instances occurred in the off-treatment period. The mean changes in serum sodium over time were clinically insignificant; however, the highest increases and decreases both occurred in the CHF 1538 arm. No clear signal for an effect of study drug on serum sodium emerges from this trial.

There were 12 individuals with 1 mmol/L or greater changes in serum potassium from visit 1 to visit 4 or 8. In the CHF 1538 arm, there were seven such individuals (four decreases and three increases). In the placebo arm there were five such individuals

(three increases and two decreases). Three subjects had a potassium level >5.5 mmol/L all in the CHF 1538 arm; for one subject this occurred on treatment. There were five subjects with potassium levels <3.5 mmol/L, four of which were in the CHF 1538 arm. This occurred on treatment for three CHF 1538 subjects and one placebo subject. The mean and median changes over the course of the study were clinically insignificant. The highest increases or decreases occurred generally in the CHF 1538 arm. Given the above data, no clear relationship exists between study drug and serum potassium.

Serum Chloride

The mean and median changes in serum chloride were clinically insignificant for CHF 1538 over the study period. In general the range of increases and decreases over the study period was similar to placebo except for the 1st off period where the CHF 1538 group's range of increase was markedly elevated (one individual in the CHF groups had a serum value of 157 in this off period but the rest of the values were between 104-106 mmol/L; another individual with a serum value of 130.4 did not have readings for all other visits except for one when the value was 109 mmol/L). Given this, there is unlikely to be a relationship between CHF1538 and serum chloride changes.

Serum Glucose

The mean and median changes in serum glucose over the course of the study were clinically insignificant. Moreover, the range of increases and decreases were both large during the on-treatment periods suggesting no real effect of study drug. Also, given patients concomitant use of inhaled or oral steroids as well as the fact that subjects may have underlying pancreatic insufficiency, it is difficult to sort out what effect the study drug has on this variable (although this should be mitigated by randomization).

Serum Protein Electrophoresis

These tests are of unclear value (many CF patients likely have a polyclonal gammopathy) and it is unclear how to interpret changes in these tests over time. Moreover, there has not been any noted effect of aminoglycosides with monoclonal gammopathy. Thus, these tests are not evaluated further. A cursory review did not reveal any significant findings.

Hematologic parameters

WBC

The mean and median changes in serum WBC were clinically insignificant over the course of the study. Changes involved both increases and decreases though the range was skewed somewhat toward decreases for CHF 1538. However, these decreases were spread across both on and off cycles; the lowest value of 2.20 $10^3/mm^3$ occurred

during the off cycle. It should be noted that other comorbidities/clinical scenarios as well as concomitant medications could affect WBC as well.

Hemoglobin

The mean and median change from baseline in serum hemoglobin levels was clinically insignificant over the course of the study in the CHF 1538 arm. No clear relationship between study drug and hemoglobin levels could be discerned.

Neutrophils

The mean and median changes in serum neutrophils as a percentage of the WBC were clinically insignificant over the course of the study. The range of increases and decreases during various cycles were generally larger than those of placebo, though the decreases were generally larger. However, these changes were spread throughout both on and off cycles.

Eosinophils

The mean and median changes in serum eosinophils as a percentage of the WBC were clinically insignificant over the course of the study. The highest percentages were generally found in the CHF 1538 group. However, the highest values for eosinophil percentage as well as eosinophil percentage increases from baseline for the CHF 1538 arm were not clearly correlated with on treatment cycles. No serious adverse events or discontinuations were related to eosinophilia or allergies.

Platelets

The mean and median change from baseline in serum platelet count showed a mild decrease in every cycle in the CHF 1538 arm. The lowest platelet values and largest decreases in platelets from baseline were generally also seen in the CHF 1538 arm. One CHF subject had a platelet value of 9 $x10^3/mm^3$ after the third on-treatment period. A relationship between study drug and thrombocytopenia cannot be excluded though unlikely given the low systemic exposure to the drug.

ESR

Given the lack of specificity of this value, this was not evaluated further.

Clinical Laboratory TEAE

The following table summarizes clinical laboratory TEAE in the safety population. The number of events is roughly equivalent across treatment arms. The majority of events

related to elevated transaminases were in the CHF 1538 arm. All cases of eosinophilia were in the CHF 1538 arm. One case of blood creatinine increased was in the CHF 1538 arm as was one case of hemolytic anemia. Such cases were reviewed and except for one case of eosinophilia which truly may have had an association with CHF 1538 (subject 32-012), no clear association with study drug or clinical significance could be ascribed. The majority of cases in the CHF 1538 arm were for ESR increases. Please note the applicant table below:

Table 7.4.2.5: CT02 Summary of Clinical Laboratory TEAEs: Safety Population

Treatment-Emergent Adverse Event (by PT[1])	CHF 1538 (N=161)	PLACEBO (N=85)
Number of Patients with Laboratory TEAE(s)[2]	29 (18.0%)	17 (20.0%)
Alanine aminotransferase increased	1 (0.6%)	0 (0.0%)
Aspartate aminotransferase increased	2 (1.2%)	1 (1.2%)
Blood albumin decreased	1 (0.6%)	0 (0.0%)
Blood creatinine increased	1 (0.6%)	0 (0.0%)
Blood glucose increased	1 (0.6%)	2 (2.4%)
Electrophoresis protein abnormal	1 (0.6%)	1 (1.2%)
Eosinophil count abnormal	1 (0.6%)	0 (0.0%)
Eosinophilia	2 (1.2%)	0 (0.0%)
Haemolytic anaemia	1 (0.6%)	0 (0.0%)
Hyperglycaemia	0 (0.0%)	2 (2.4%)
Hypochromic anaemia	0 (0.0%)	1 (1.2%)
Immunoglobulins increased	3 (1.9%)	0 (0.0%)
Leukocytosis	4 (2.5%)	3 (3.5%)
Leukopenia	1 (0.6%)	0 (0.0%)
Liver function tests abnormal	2 (1.2%)	0 (0.0%)
Neutrophil count increased	1 (0.6%)	2 (2.4%)
Platelet count decreased	1 (0.6%)	0 (0.0%)
Platelet count increased	0 (0.0%)	2 (2.4%)
Red blood cell sedimentation rate abnormal	1 (0.6%)	0 (0.0%)
Red blood cell sedimentation rate decreased	1 (0.6%)	0 (0.0%)
Red blood cell sedimentation rate increased	15 (9.3%)	6 (7.1%)
Thrombocytopenia	0 (0.0%)	1 (1.2%)
Transaminases increased	1 (0.6%)	0 (0.0%)
White blood cell count abnormal	0 (0.0%)	1 (1.2%)
White blood cell count increased	3 (1.9%)	2 (2.4%)

[1] preferred term
[2] treatment-emergent adverse event
-EDR SDN#0, 5.3.5.1.3 CT02 Study Report Body, Table 39

CT03

The sponsor did not provide summary tables detailing numerical mean and median changes from baseline or mean/median measurements at visits 1 and 4. Instead, tables detailing investigator assessment of whether a result was one of several gradations of clinically significant or insignificant were provided along with individual laboratory data (in tabular and statistical form). Reference tables to serve as a guide for what was considered significant/insignificant for each parameter was not provided. An example is provided below.

Table 152: Laboratory Parameters - Hematology - Erythro-Sedimentation Rate - Summary by Visit - Safety Population

	CHF 1538 (N=156)	TOBI (N=168)
Visit 1		
Low NCS[1]	3 (2.0%)	5 (3.1%)
Normal	66 (43.4%)	79 (48.5%)
High NCS	80 (52.6%)	78 (47.9%)
High CS[2]	3 (2.0%)	1 (0.6%)
Missing	4	5
Visit 4		
Low NCS	6 (3.9%)	6 (3.7%)
Normal	82 (52.9%)	100 (61.7%)
High NCS	64 (41.3%)	52 (32.1%)
High CS	3 (1.9%)	4 (2.5%)
Missing	1	6

Source data: Appendix 16.2.8.3
[1] Non Clinically Significant
[2] Clinically Significant

Table 153: Laboratory Parameters - Hematology - Erythro-Sedimentation Rate - Shift from Baseline (V1) - Safety Population

	CHF 1538 (N=156)	TOBI (N=168)
Visit 1 to Visit 4		
Low NCS[1] to Low NCS	3 (2.0%)	2 (1.3%)
Low NCS to Normal	0	2 (1.3%)
Low NCS to High NCS	0	1 (0.6%)
Normal to Low NCS	3 (2.0%)	4 (2.5%)
Normal to Normal	51 (33.8%)	67 (42.4%)
Normal to High NCS	11 (7.3%)	7 (4.4%)
Normal to High CS[2]	1 (0.7%)	0
High NCS to Normal	27 (17.9%)	29 (18.4%)
High NCS to High NCS	50 (33.1%)	42 (26.6%)
High NCS to High CS	2 (1.3%)	3 (1.9%)
High CS to High NCS	3 (2.0%)	0
High CS to High CS	0	1 (0.6%)
Missing	5	10

Source data: Appendix 16.2.8.3
[1] Non Clinically Significant

In the absence of such summary tables and a reference guide for the shift tables, this reviewer attempted crude measurements of serum BUN and creatinine based on values provided in statistical files. More thorough statistical reviews/explanatory material will need to be provided by the applicant in its complete response so that these laboratory parameters can be assessed in a more accessible manner.

Serum Creatinine

No increases >1 mg/dL in serum creatinine was seen in any subject. No subject had a value >1.5 mg/dL.

Serum BUN

Seven subjects had an increase of serum BUN of 8 mg/dL or greater from visit 1 to visit 4, five of which were in the TOBI arm. The highest value recorded at visit 4 was 40 mg/dL, in a TOBI subject.

Considering how the data was offered and the strong likelihood of no effect on the rest of the parameters, this reviewer will not perform further evaluations until the applicant has provided better statistical analyses.

CP01

Labs were done at screen and after final visit. These were not evaluated given the more robust laboratory data in the phase 3 trials.

7.4.3 Vital Signs

CT01

Vital Signs data was compiled for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR).

SBP

No significant effect of CHF 1538 was seen on SBP. The mean change in SBP at Visit 4 was -1.66 mmHg (Range: -20 to +10 mmHg). Similar miniscule decreases were seen at visits 3 and 5. No noteworthy effect on SBP is suggested by this.

DBP

At Visit 4, the mean change from baseline for CHF 1538 was -0.48 mmHg (Range: -15 to +10 mmHg). At Visit 3, the mean change was 0.1 mmHg and at visit 5 it was 0.36 mmHg. No noteworthy effect on DBP is suggested by this.

HR

The mean change from baseline at Visit 4 was -4.76 beats/min (Range: -28 beats/min to +28 beats/min). This was accompanied by mean decreases of 5.11 and 4.17 beats/min at Visits 3 and 5, respectively. This does not suggest any clear effect of treatment on HR.

No clear evidence of an effect on VS by CHF 1538 was noted in this trial.

CT02

Vital Signs data were compiled for SBP, DBP, and HR.

SBP

For CHF 1538, there were no to minimal increases from baseline in SBP at all visits with wide ranges; for placebo there was a mix of minimal increases and decreases from baseline. At Visit 8, the mean change from baseline was 2.0 mmHg (Range: -42 to +42 mmHg) for the CHF 1538 arm and 1.2 mmHg for placebo (Range: -30 mmHg to +30 mmHg). No effect was seen on this variable by study drug.

DBP

For CHF 1538, there were both minimal increases and decreases from baseline during on-treatment periods with wide ranges. At Visit 4, the mean change from baseline for DBP was -0.5 mmHg (Range: -20 to +48 mmHg) and was +2.2 mmHg (Range: -20 mmHg to +48 mmHg) at visit 6. No effect was seen on this variable by study drug.

HR

There was decrease (with wide ranges) from baseline at every visit for both arms though these decreases were minimal. The decreases were slightly larger during the on-treatment periods but the difference is clinically irrelevant. At Visit 8, the mean change from baseline in HR for CHF 1538 was -3.0 beats/min (Range: -35 to +35 beats/min). At visit 9, the mean change was -2.1 beats/min (Range: -37 to +38 beats/min). No effect was seen on this variable by study drug.

No clear evidence of an effect on VS by CHF 1538 was noted in this trial.

CT03

No clear evidence was seen of an effect on SBP, DBP, or HR by CHF 1538 in this trial.

CP01

VS such as SBP, DBP, and HR were taken pre and post dose up to 24 hours after administration of either TOBI or CHF 1538.

No real relationship was noted between CHF 1538 and post dose SBP, DBP, or HR.

7.4.4 Electrocardiograms (ECG)

In Study CP01, subjects had ECG done at screen, received either TOBI/CHF 1538, had a washout period of 3-7 days, received either TOBI/CHF 1538 (crossover), and then again had an ECG one day following drug administration. Given the timing of the ECG, the clinical significance of any ECG changes is unclear. However, no significant signals were noted with QRS interval or other abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not Applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose was tested in these trials: the dose (300 mg inhaled bid) that was identical to the reference drug. Moreover, per the Clinical Pharmacology review, the plasma and sputum levels associated with a dose of TOBI or CHF 1538 were roughly comparable. It is well known that certain aminoglycoside-specific adverse events are

associated with increased dose and duration, particularly nephrotoxicity and ototoxicity. The risk for such adverse events has already been discussed earlier in the review.

7.5.2 Time Dependency for Adverse Events

This issue is of interest given the chronic use of this drug. For example, it would be of interest to know how typical inhaled drug-associated TEAEs such as cough, pharyngitis/voice alteration, or bronchospasm vary in their incidence over time However, the trial designs of the 3 phase trials in this NDA are not particularly suited to answer this question, namely because of their short duration. Only study CT02 was more than one cycle long; this trial included three 28-day on/28-day off cycles for a total of roughly 168 days. However, the applicant did not look at this specific issue for any of the three trials.

This reviewer did attempt to undertake a crude evaluation of voice alteration/pharyngitis and bronchospasm incidence over time, essentially by looking at when relevant PT were reported. The following table shows those findings.

Table 7.5.2: AEs of Interest By Time Point in CT02- CHF 1538 arm

	1st On (Days 1-28)	1st Off (Days 29-56)	2nd On (Days 57 – 84)	2nd Off (Days 85-112)	3rd On (Days 113-140)	3rd Off (Days 141-168)	
Pharyngitis/ Voice Alteration[1]	17	7	5	5	1	5	
Bronchospasm[2]	3	2	4	2	1	2	

[1]-Voice Alteration/Pharyngitis- terms include 'tonsillitis,' 'laryngitis,' 'nasopharyngitis,' 'pharyngitis,' 'acute tonsillitis,' 'dysgeusia,' 'pharyngolaryngeal pain,' 'dysphonia,' and 'throat irritation'
[2]-Bronchospasm- terms include 'bronchospasm,' 'chest pain,' and 'wheezing'

From this, it appears complaints of pharyngitis/voice alteration occur early, particularly in the 1st On Cycle, and then decrease. Bronchospasm also appeared to occur a bit more in the earlier periods. Of course this evaluation is quite crude, both because of the broad terms used to account for pharyngitis/voice alteration but also because of uncertainty about reporting. For example, if a subject came to his/her end of 1st on cycle visit and reported a complaint of laryngitis, he/she may relate that this actually started during the on cycle and is continuing currently. However, the subject might not be sure when the AE started and it might be recorded as having started at the visit itself, in which case the AE might be recorded as having occurred in a different time period (possibly 1st off cycle). Also, the periods themselves are somewhat arbitrary: a subject might have his end of 1st on visit at Day 34 and recount an event that occurred at Day 32 while still on study drug. In this table, it would be counted as occurring in the 1st off cycle. Also, AEs recorded as starting on day one likely have nothing to do with study drug as the first dose was not given at the first visit (was taken later in the evening). Nevertheless, a general sense of the occurrence of this AE in the CHF 1538 arm can be ascertained.

7.5.3 Drug-Demographic Interactions

In the CT02 study, dysphonia, epistaxis, and red blood cell sedimentation increased were PT that had occurred in the CHF 1538 arm 2% more than placebo. The following table shows their demographic distribution

Table 7.5.3: Distribution of PT: Dysphonia and Epistaxis in CT01, CT02, CT03 – CHF 1538 arm

Category	Dysphonia				Epistaxis			
Gender	CT02	CT03	CT01	Total	CT02	CT03	CT01	Total
Male	6 (6.7%)	0	0	6	4 (4 5%)	0	0	4
Female	5 (6.9%)	2 (2.4%)	0	7	2 (2 8%)	0	0	2
Age								
6-12 years	6 (9.5%)	0	0	6	2 (3.2%)	0	0	2
13-17years	0	1 (2.0%)	0	1	1 (2.1%)	0	0	1
>17 years	5 (9.8%)	1 (1 8%)	0	6	3 (5 9%)	0	0	3
Baseline FEV_1 % predicted								
≥50% Predicted	4 (3.5%)	2 (1.7%)	0	6	2 (1.8%)	0	0	2
<50% predicted	7 (14.6%)	0	0	7	4 (8 3%)	0	0	4
Inhaled Drug Chronic Use								
Yes	11	not examined			5	0	0	5
No	0	not examined			1	0	0	1

Looking at the distribution of these PT in the CHF 1538 arm in CT02, for dysphonia less effect on adolescents was seen, but many patients were on chronic inhaled meds. There was also more effect on those with decreased baseline FEV_1 % predicted. For epistaxis, most effect occurred with subjects on chronic inhaled medications, baseline FEV_1 % predicted <50%, and adults. This analysis is extremely limited given the sample size.

In CT03, pharyngitis and HA occurred at a rate 2% more than TOBI. The following table looks at their demographic distribution in the 3 trials

Table 7.5.3.1: Distribution of PT: Headache and Pharyngitis in CT01, CT02, CT03- CHF 1538 arm

Category	Headache				Pharyngitis			
Gender	CT03	CT02	CT01	Total	CT03	CT02	CT01	Total
Male	3 (4 2%)	0	0	3	0	7 (7 9%)	0	7
Female	2 (2.4%)	2 (2.8%)	0	4	6 (7.1%)	3 (4.2%)	1 (7.1%)	10
Age								
6-12 yo	0	0	0	0	1 (2%)	5 (7.9%)	0	6
13-17yo	1 (2.0%)	0	0	1	3 (6%)	2 (4.3%)	1 (14.3%)	6
>17 yo	4 (7.0%)	2 (3 9%)	0	6	2 (3 5%)	3 (5 9%)	0	5
Baseline FEV_1 % predicted								
≥ 50% Predicted	4 (3.4%)	0	0	4	5 (4.2%)	9 (8 0%)	1 (6 2%)	15
< 50% predicted	1 (2.7%)	2 (4.2%)	0	3	1 (2.7%)	1 (2.1%)	0	2

Looking at the distribution of these PT in the CHF 1538 arm for CT02, for headache, more effect was seen in adults and those with baseline FEV_1 % predicted <50%. For pharyngitis, it occurred primarily in females and adolescents.

Given the very limited sample size, it would premature to make conclusions based on this data.

7.5.4 Drug-Disease Interactions

Part of the exclusion criteria of these trials was to exclude patients with renal impairment and no special studies have been done in those with renal impairment. As such, no further analyses will be performed here.

7.5.5 Drug-Drug Interactions

Very low concentrations of this drug are expected to be absorbed into the plasma. Moreover, this drug is primarily renally excreted. Thus interactions with CYP enzymes, interactions affecting oral absorption, and even interactions with renal transport/excretion do not apply.

Because this is a 505(b)(2) application, the applicant is in part relying on information from the reference drug TOBI. However, the applicant did perform analyses with the integrated CT01/CT02 safety population looking at TEAE in relation to specific use of combinations of drugs including:

CHF 1538/antipseudomonal antibiotic use vs. CHF 1538 alone
CHF 1538/rhDNase vs. CHF 1538 alone
CHF 1538/ short acting B-agonists vs. CHF 1538 alone
CHF 1538/long acting B-agonists vs. CHF 1538 alone
CHF 1538/non-rhDNase mucolytics vs. CHF 1538 alone
CHF 1538/inhaled steroids vs. CHF 1538 alone
CHF 1538/inhaled short acting muscarinic agonist/vs. CHF 1538 alone

Similar comparisons were also made with placebo. The applicant tables are noted below:

Table 7.5.5: Treatment-Emergent Adverse Event Drug-Drug Interactions - Anti-Pseudomonal Antibiotics: Integrated Safety Population (Pooled Ct01 and CT02

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=34	PLACEBO N=28	CHF 1538 N=156	PLACEBO N=87
Total number of TEAEs	199	203	592	404
Number of patients with at least one TEAE	31 (91.2%)	28 (100.0%)	119 (76.3%)	73 (83.9%)

EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 14

Table 7.5.5.1: Treatment-Emergent Adverse Event Drug-Drug Interactions - Inhaled Non-rhDNase Mucolytic: Integrated Safety Population (Pooled CT01 and CT02)

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=53	PLACEBO N=30	CHF 1538 N=137	PLACEBO N=85
Total number of TEAEs	337	255	454	352
Number of patients with at least one TEAE	49 (92.5%)	29 (96.7%)	101 (73.7%)	72 (84.7%)

-EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 15

Table 7.5.5.2: Treatment-Emergent Adverse Event Drug-Drug Interactions - Inhaled rhDNase: Integrated Safety Population (Pooled CT01 and CT02)

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=142	PLACEBO N=76	CHF 1538 N=48	PLACEBO N=39
Total number of TEAEs	667	484	124	123
Number of patients with at least one TEAE	119 (83.8%)	71 (93.4%)	31 (64.6%)	30 (76.9%)

EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 16

Table 7.5.5.3: Treatment-Emergent Adverse Event Drug-Drug Interactions - Inhaled Steroid: Integrated Safety Population (Pooled CT01 and CT02)

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=36	PLACEBO N=21	CHF 1538 N=154	PLACEBO N=94
Total number of TEAEs	195	188	596	419
Number of patients with at least one TEAE	35 (97.2%)	20 (95.2%)	115 (74.7%)	81 (86.2%)

-EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 17

Table 7.5.5.4: Treatment-Emergent Adverse Event Drug-Drug Interactions - Inhaled Short Acting Beta Agonist: Integrated Safety Population (Pooled CT01 and CT02)

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=87	PLACEBO N=38	CHF 1538 N=103	PLACEBO N=77
Total number of TEAEs	457	242	334	365
Number of patients with at least one TEAE	75 (86.2%)	37 (97.4%)	75 (72.8%)	64 (83.1%)

EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 18

Table 7.5.5.5: Treatment-Emergent Adverse Event Drug-Drug Interactions – Inhaled Short Acting Muscarinic Agonist: Integrated Safety Population (Pooled CT01 and CT02)

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=59	PLACEBO N=30	CHF 1538 N=131	PLACEBO N=85
Total number of TEAEs	300	199	491	408
Number of patients with at least one TEAE	51 (86.4%)	29 (96.7%)	99 (75.6%)	72 (84.7%)

EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 19

Table 7.5.5.6: Treatment-Emergent Adverse Event Drug-Drug Interactions - Inhaled Long Acting Beta Agonist: Integrated Safety Population (Pooled CT01 and CT02)

Treatment-Emergent Adverse Event (TEAE) (by SOC[1] and PT[2])	Used the Drug		Never Used the Drug	
	CHF 1538 N=37	PLACEBO N=27	CHF 1538 N=153	PLACEBO N=88
Total number of TEAEs	231	259	560	348
Number of patients with at least one TEAE	36 (97.3%)	27 (100.0%)	114 (74.5%)	74 (84.1%)

-EDR SDN#0, 5.3.5.3.1 ISS Tables and Figures, Table 20

In every scenario, there were more subjects with TEAE in the combination group than in the study drug alone group (whether placebo or CHF 1538). Similarly, there were also roughly equivalent numbers or more TEAE in the placebo combination group than the CHF 1538 combination group in every scenario.

It would be of interest to know whether CHF 1538 + combination inhaled drug predisposes to more upper airway TEAE like dysphonia, epistaxis, or bronchospasm than CHF 1538 alone. In the case of epistaxis, it occurred with higher frequency in the inhaled non-rhDNase mucolytic/CHF1538 combination (7.5% vs. 1.5% CHF 1538 alone), inhaled rhDNase/CHF1538 combination (3.5% vs. 2.1%), inhaled short acting B-agonist/CHF 1538 combination (4.6% vs. 1.9%), inhaled short acting muscarinic agonist/CHF 1538 combination (3.4% vs. 3.1%) and inhaled long acting beta agonist/CHF 1538 combination (10.8% vs. 1.3%). Since bronchospasm was reported only once, it could not be evaluated in this manner. For dysphonia, the TEAE occurred with higher frequency in non-rhDNAse mucolytic/CHF 1538 (9.4% vs. 4.4%), inhaled rhDNAse/CHF 1538 combination (7.7% vs. 0.0%); inhaled steroid/CHF 1538 combination (13.9% vs. 3.9%), inhaled short acting muscarinic agonist/CHF 1538 (6.8% vs. 5.3%); and inhaled long acting beta agonist/CHF 1538 combination (8.1 % vs. 5.2%). As always, it's unclear whether the combination itself reflects greater underlying medical morbidity rather than an actual interaction. Also, these comparisons are subject to non-random bias and unequal sample sizes. Also, these comparisons look at these combinations in isolation when many of these drugs are taken simultaneously.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Evaluation of carcinogenic potential from the phase 3 trials is unrealistic given the length of the trials. Please the see review done by the Pharmacology Toxicology reviewer (Dr. Amy Ellis) for further information about in vitro and nonhuman testing. It should be noted that in the CT02 trial (the longest of 3 trials, no PT corresponding to a malignancy was noted).

7.6.2 Human Reproduction and Pregnancy Data

The applicant had exclusionary criteria for pregnant and lactating women. Also, the ability to conceive in these patients may be reduced. Since this a 505(b)(2) application, the applicant is relying on findings from the reference drug TOBI. Please the see review done by the Pharmacology Toxicology reviewer (Dr. Amy Ellis) for further information about in vitro and nonhuman testing.

7.6.3 Pediatrics and Assessment of Effects on Growth

The phase 3 studies in this trial have limited potential to assess growth in the pediatric population due to their limited durations. No z-score information to help relate height and weight data to a reference population was provided by the applicant. Please see the efficacy portion of this review for a discussion of effects of study drug on subject height and weight.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant is essentially relying on information provided by the reference drug TOBI given that this is a 505(b)(2) application. In terms of overdose, no overdose was known to have occurred during the drug development program. It should be noted, that some subjects returned very few study drug vials during study visits, and whether this means that excess drug was taken or that excess drug was simply lost/not returned is unclear. Tobramycin is not known to have drug abuse potential and no information on drug abuse, withdrawal or rebound was obtained in this drug development program.

7.7 Additional Submissions / Safety Issues

The sponsor submitted data in response to an information request by the Agency, which has been incorporated into the above narratives. Much data, particularly device bridging data and Reponses to DSI inquiries remain to be submitted but these have more implications for trial conduct and efficacy than safety.

8 Postmarket Experience

A 120 day Safety Update was submitted on Feb. 21, 2011. The findings were as follows:

Postmarketing surveillance in Europe was done from April 2006 (date of approval of study drug in Europe) to Jan. 2011 to look for ADR associated with CHF 1538.

Eighteen ADR were found, eight of which were SAE. The eight SAE were for illusion, bronchospasm, cough, dyspnea, wheezing, rash, and facial edema. NSAE included loss of consciousness, pallor, cough, dyspnea, dermatitis, asthenia, and malaise. The above reports were obtained passively and cover an estimated 1.3 million patient-treatment-day exposures to CHF1538 in the period from 09 April 2006 to 31 January 2011 and according to the defined daily dose of 300 mg (UK labeling is for bid usage).

In the published literature, the applicant found one serious US case of renal failure necessitating dialysis and eventually resulting in death that occurred in a 62 year-old patient with diabetes mellitus, chronic renal failure, hypertension, and history of myocardial dysfunction taking an extended period of inhaled tobramycin (TOBI). This case has other risk factors for nephrotoxicity including concomitant use of vancomycin and previous/recent use of IV tobramycin. This case suggests the potential for increased risk of nephrotoxic harm when inhaled tobramycin is used in elderly patients due to differences in renal clearance. However, the contribution of inhaled tobramycin to renal failure is unclear given the prior use of IV tobramycin and IV vancomycin.

The applicant searched the AERS database for the period from 1997 (TOBI approval) to second quarter 2010 using the search words 'TOBI' and 'tobramycin' and rate of administration 'resp.' and identified "*patient reports of 1586 adverse events meeting the search criteria. Among events reported five or more times, almost all have previously been identified and are indicated as possible side effects in the package insert (PI) for TOBI or in the summary of product characteristics (SmPC) for Chiesi's CHF 1538 which is already marketed outside the US. The remaining adverse events meeting these criteria and not present in the PI for TOBI or in the SmPC for Chiesi's marketed product are presented in [the following table]*."

Table 8: AERS Adverse Events Reported Five or More Times (4th Quarter 1997-2nd Quarter 2010)

AE Term[1]	Number of Reports
Blood creatinine increased	16
Condition aggravated	16
Chronic Obstructive Pulmonary Disease	6
Disease progression	6
Death	33
Dehydration	7
Drug ineffective	9
Drug level increased	12
Dysphonia	38
Eosinophilia	5
Fatigue	14
Feeling abnormal	5
Heart rate increased	7
Hyponatraemia	5
Hypotension	6
Medication error	7
Oxygen saturation decreased	8
Pollakiuria	5
Pseudomonas infection	17
Renal failure	6
Renal failure acute	10
Renal impairment	5
Respiratory failure	11
Sputum culture positive	5
Staphylococcal infection	7
Tachycardia	9
Vestibular disorder	8
Wheezing	8

[1] The AE terms presented represent the MedDRA coding of the verbatim term.
-EDR SDN # 0, 5.3.6, Reports of Postmarketing Experience, Table 2

It's unclear whether any of these cases showcase a true relationship between TOBI and the adverse event; many may represent manifestations of underlying disease and others are discussed in current TOBI labeling (such as risks of nephrotoxicity and ototoxicity). No changes to the safety assessment will be made based on the above safety update.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

None

9.3 Advisory Committee Meeting

None

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/s/

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08/19/2011

JOHN J ALEXANDER
08/19/2011