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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number:	201820
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Indication(s):	Management of Cystic fibrosis
Applicant:	Chiesi Pharmaceuticals, Inc
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1. EXECUTIVE SUMMARY

In this submission, Chiesi Pharmaceuticals, hereafter referred to as Applicant, addresses the deficiencies identified in the Complete Response Letter (CRL), sent on 25 August, 2011, through a Class 2 resubmission of New Drug Application 201820 which also provides updated data regarding drug product stability and safety of Tobramycin 300 mg/4mL inhalation Solution.

This review focuses on the clinical deficiency identified in the letter, particularly, that *"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 CT-02 trial individuals at all sites that were affected by inaccurate recording of/loss of source input data including height and age."* The Applicant provided the requested recalculations along with their associated methodologies and formulae in the Type A meeting package for the 16 December 2011 meeting with the FDA. During the Type A meeting it was agreed that the Applicant's method of recalculation of the various pulmonary function variables appeared appropriate and that the Applicant should provide FDA with the full datasets and details of the recalculation and the source data errors at each site. The details of the recalculation and the verified database for CT-02's Baseline and Visit 8 were submitted on 13 April, 2012. Findings from this data together with the primary efficacy results in the original NDA statistical evaluation will only be presented in this review.

The Applicant conducted source data verification for the CT02 clinical sites that used the same version of spirometer software as in Site 26. The input data located on the printed spirometer output were verified against the corresponding values in the clinical database. The source data verification was then extended to all clinical sites that participated in study CT02. Nearly all identified discrepancies were related to height, albeit most of the differences were very small (≤ 1 cm). Focusing on Visit 2 (baseline) and Visit 8 (endpoint visit), height differences between the spirometry source input and clinical database were detected on 14.7% (72) of total measurements. The potential impact of this inaccurate recording of/loss of source input were evaluated through three sensitivity analysis for the change from baseline to endpoint visit (i.e., Visit 8-after completion of the 3rd "ON" cycle.

The findings for Forced Expiratory Volume in one minute (FEV1) % predicted, the primary efficacy endpoint, in the sensitivity analyses are numerically consistent, statistically significant and corroborate the conclusion based on the original NDA. Based on the original statistical review using the ITT population, the mean change from baseline in FEV1 % predicted (using multiple imputation for missing values) was higher in the CHF 1538 group (6.88%) than in the placebo group (0.64%) with a difference of 6.24% [95% CI: 2.71, 9.77; p.value: <0.001] at Visit 8, Week 20 (at the end of the third "ON" cycle of randomized treatment. Hence, the absolute mean change from baseline curves are clearly delineated (See Section 3.1.4, Figure 1). Similar trend can be seen on the relative change as well, albeit it is not the primary endpoint.When Baseline observation is carried forward to the missing Visit 8 values, the mean change from baseline to Visit 8 in FEV1 % predicted normal in the CHF 1538 group ranges from 5.84 to 6.36 compared to the Placebo group which ranges from -0.62 to 0.33. The Difference in mean change from baseline ranges from 5.95 to 6.47 and all are statistically significant [95% CI ranges: 2.20-2.38, 9.65-10.55; p-value ranges: 0.0018-0.0022). When the last observation is carried forward is

applied in the sensitivity analysis, the mean change from baseline to Visit 8 in FEV1 % predicted normal in the CHF 1538 group ranges from 5.94 to 6.55 compared to the Placebo group which ranges from -0.64 to 0.21. The Difference in mean change from baseline ranges from 6.21 to 6.56 and all are also statistically significant [95% CI ranges: 2.35-2.40, 10.02-10.78; p-value ranges: 0.0015-0.0024). Therefore, the results of the sensitivity analyses using two types of imputation method corroborate the findings presented in the original statistical review stated above.

Sensitivity analysis for the other secondary pulmonary functions, e.g. FEV% predicted and $FEF_{25-75\%}$ % predicted were also conducted. Their results provide similar findings that corroborate the analyses submitted in the original NDA and the original statistical review.

Results of Study CT01 show that, using multiple imputations for missing observations, the FEV1 % predicted normal had increased by 13.3% at Week 2 and 15.9% at Week 4 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV1 % predicted normal were 0.5% in Week 2 and 4.9% in Week 4 in the Placebo group. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups were 12.8% [95% CI: 4.3, 21.2; p.value: 0.002] in Week 2 and 11.0% [95% CI: 3.0, 18.9; p-value: 0.003] in Week 4 and the effect is slightly below placebo at week 8, the off-therapy phase with -1.2% [95% CI; -10.2, 7.7; p-value: 0.700. These findings indicate that CHF 1538 significantly improves FEV1 % predicted at the end of the "ON" cycle (Week 4) of randomized treatment. Note that this study was not designed to evaluate similar effect that was seen in Study CT02 for multiple ON-OFF cycles. Hence, the sustained effect in CT01 cannot be replicated nor compared to what was observed in CT02.

2. INTRODUCTION

2.1 Overview

Cystic fibrosis (CF) is an autosomal recessive genetic disease resulting from a defect in the CF transmembrane regulator gene resulting in an accumulation of mucus in many endocrine and exocrine-associated organs [1]. In these patients, the most significant morbidity is the progressive respiratory failure resulting from endobronchial infections [2, 3], commonly associated with infectious agents such as *Staphylococcus aureus* (*S. aureus)*, *Haemophilus influenzae* (*H. influenzae*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) [3]. Of these, *P. aeruginosa* is the primary pathogen associated with pulmonary exacerbation in CF contributing to significant morbidity and mortality [3]. In fact, respiratory failure is the major cause of death in over 90% of these patients [4, 5].

Currently, therapy for CF includes interventions that slow or prevent progressive airway deterioration and destruction. One such intervention is the use of an inhaled microbial agent because it is believed to offer improved efficacy by delivering sufficient antibiotic directly to the site of infection and decreased toxicity by reducing systemic absorption [6, 7, 8]. In 1997, an inhaled antibiotic TOBI® (PathoGenesis) was approved in the United States for the treatment of CF patients with *P. aeruginosa* on the basis of data from duplicate large, multicenter trials demonstrating sustained clinical improvement in pulmonary and clinical function in CF patients after inhalation of 300 mg tobramycin twice daily (BID) for intermittent 4-week periods [7]. Long-term improvements in weight gain and decreased frequency of hospitalizations and use of intravenous antipseudomonal antibiotics were also evident in adolescent CF patients who were administered intermittent TOBI [9].

In 2006, Chiesi developed a new formulation of tobramycin nebulizer solution (Tobramycin 300 mg/4 mL Inhalation Solution, hereafter referred to as CHF 1538) that was first approved for marketing outside the US as Bramitob® to be used for the management of chronic pulmonary infections resulting from *P. aeruginosa* in patients with CF aged six years or older. CHF 1538 is currently marketed in 15 countries. It has been demonstrated that the systemic bioavailability of CHF 1538 is similar to TOBI; however, in sputum samples the peak tobramycin concentration was greater after CHF 1538 than TOBI [10]. Efficacy and safety of CHF 1538 is evaluated in three randomized clinical studies (as listed in Table 1) in patients with CF and *P. aeruginosa.*

Study CT01 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter (Moldova, Italy, France, Spain) study. Its primary objective was to evaluate the efficacy of CHF 1538 compared to placebo in the 4-week treatment of patients with CF and *P. aeruginosa* infection. This study included 29 patients randomized to the CHF 1538 arm versus 30 patients randomized to placebo and was powered to evaluate change from baseline in FEV_1 % of predicted after four weeks of treatment as the primary endpoint. Participating patients were required to have moderate pulmonary function impairment with an FEV_1 % predicted normal $\geq$ 40% and $\leq$ 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, this difference

being not statistically significant (CI, p-value). All patients were individually provided with a PARI TurboBOY compressor and a PARI LC Plus® nebulizer for use during the trial.

Results of Study CT01 show that, using multiple imputations for missing observations, the FEV1 % predicted normal had increased by 13.3% at Week 2 and 15.9% at Week 4 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV1 % predicted normal were 0.5% in Week 2 and 4.9% in Week 4 in the Placebo group. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups were 12.8% in Week 2 and 11.0% in Week 4 and the effect is slightly below placebo at week 8, the off-therapy phase.

Table 1: List of clinical studies included in the Original NDA Submission

Study	Phase and Design	Study and Control drugs Dose, Route and Regimen	Duration	# of Subjects per Arm (randomized/patients completed the run-out period)	Study Population
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 washout	CHF 1538: 29/28 Placebo: 30/23	Cystic Fibrosis with P. aeruginosa infection 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

Study CT02 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter (Hungary, Poland, Russia) study with the primary objective of demonstrating the efficacy 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. Each of the three "ON"cycles was followed by an "OFF" cycle. Patients were required to have *P. aeruginosa* present at Visit 1, but in this study,

susceptibility to tobramycin at Visit 1 was not a requirement for enrollment. All patients were individually provided with a PARI TurboBOY compressor and a PARI LC Plus nebulizer for use during the trial. A total of 247 patients were randomized 2:1 into the study. Of these, 161 were randomized to CHF 1538 and 86 to placebo. No significant differences were observed between groups with respect to any of the baseline demographic data. The two groups were different, however, with respect to colonization with *P. aeruginosa*. Patients assigned to CHF 1538 were more likely to have 'chronic' colonization with *P.aeruginosa* (90.1%) than the Placebo group (81.0%) (95% CI: 0.17%, 19.48%, p=0.045). 'First' or 'intermittent' colonization was found in 9.9% of the CHF 1538 group and 19.0% of the Placebo group. Prior to first dose (Visit 2), the group randomized to CHF 1538 had a mean FEV1 % predicted normal of 60.7 compared to 63.6 for the group randomized to placebo, with ranges of 31.4-95.1 and 34.1-104.1, respectively. As in Study CT01, the baseline FEV1% predicted was included as a covariate in the primary efficacy analysis to adjust for differences.

Results for Study CT02 show that, FEV1 % predicted normal had increased by 8.02% at Week 2 and 7.82 % at Week 4, 7.28% at Week 12 and 6.88% at Week 20 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV1 % predicted normal were 1.91% in Week 2, 0.51% in Week 4, 2.26% in Week 12, and 0.64% in Week 20 in the Placebo group. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups were significant in all the "ON" periods.

Study CT03 is an open-label, multinational, multicenter, randomized, reference product controlled, parallel group study designed to compare the efficacy and tolerability of aerosolized CHF 1538 and TOBI, both administered via a nebulizer (PARI LC Plus with the PARI Boy N compressor, Pari, Germany), over a 4-week treatment in a twice-daily regimen in patients with CF and *P. aeruginosa* chronic infection and with $FEV_1 \geq 40\%$ and $\leq 80\%$ of the predicted normal value. Subjects were recruited from hospitalized patients or patients attending outpatient clinics in Russia, Ukraine, Poland, Hungary, Germany, Czech Republic, Spain and France.

Results of Study CT03 cannot be meaningfully interpreted since it is an open label trial with the potential for biases. Furthermore, the Applicant provided no justification for the non-inferiority margin of 4.5% using the primary endpoint of FEV_1 % predicted normal difference in mean changes from baseline.

In all three clinical trials, CHF 1538 was evaluated using PARI LC Plus® nebulizer accompanied by either PARI TurboBOY compressor (Studies CT01 and CT02) or PARI Boy N compressor (Study CT03). However, the intended to-be-marketed combination product is the proposed tobramycin solution, along with the either the Pari LC Plus Nebulizer or the (b) (4) Nebulizer. The proposed compressor for both nebulizers is the Vios Compressor.

Reviewer comments: In the previous NDA submission, the Regulatory Device Consult concluded that it is not clear whether in vitro bridging data between the to-be-marketed combination product and the product tested in clinical study will be sufficient to justify not providing additional clinical data for the to-be-marketed version. Hence, we concluded that it is uncertain whether these new devices will provide similar or better results than the one used in the clinical

trials. We defer to the Regulatory Device Consult for their findings on the bridging study conducted.

There were several concerns about data integrity and reliability, particularly in Study CT02. One site in Poland (Site #26, Dr. Maria Trawinska Barnicka, n=29) had some discrepancies in the calculation of FEV1% predicted values. In the preliminary report provided by the DSI, it appears that change in predicted FEV_1, FVC, and FEF did not occur despite changes in age and/or height. Similarly, in some cases changes in predicted FEV_1, FVC, and FEF were observed without a change in age and/or height. The other site (Site #32, Dr Nikolai Kapranov, n=24) had issues (based on preliminary report) with drug accountability. The Inspection found difficulty deciphering which patients received what medication.

These issues were echoed in the Complete Response Letter that the Agency sent on 25 August 2011. In the letter there were two main deficiencies that the Agency noted and they are the following:

1. You propose labeling the product to be used with either the PARI LC Plus or (b) (4) nebulizer with the PARI Vios compressor, and this drug device combination is not the same as that evaluated in clinical trials. You have not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination. In addition, we note that the osmolality of the test drug used in trials CT-01 and CT-02 was higher than the osmolality of the to-be-marketed product. You should provide comprehensive drug device combination bridging data as recommended in the CLINICAL/DELIVERY DEVICES section below. The data submitted should allow the Agency to make a proper evaluation of the comparability of the various drug-device combinations used in clinical trials and proposed for marketing. If the device data provided are not adequate to bridge the clinical trial and to-be-marketed drug device configurations, then additional clinical trial data will be required. We recommend that you consider conducting a placebo-controlled trial similar in design to trial CT-01 using the to-be-marketed drug device combination. We recommend that you meet with the review division to discuss your plans for providing a complete response.

   Reviewer Comments: (i) We defer to the Regulatory Device Consult to ascertain whether sufficient data has been provided to evaluate the change in compressor or the new nebulizer compressor combination. (ii) Change in osmolality between test drugs used in CT-01 and CT-02 with the to-be-marketed product is reasonable per Medical Officer's evaluation. For more details see Medical Officer's review.

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.

This review focuses on the second deficiency. We defer to the device and the medical reviewer to assess whether the Applicant has satisfactorily addressed the first deficiency.

2.2 Data Sources

The response to the CRL were provided in an electronic submission located in **CDSESUB1\EVSPROD\NDA201820**. Datasets for the sensitivity analysis of primary and secondary endpoints are provided in the electronic submission as well. Overall, the data sets (including the analysis sets) were adequately documented.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

The study CT02 in consideration is a double blind, multinational, multicenter, randomized, placebo-controlled clinical trial in patients with CF and *P. aeruginosa* infection. The study compared the efficacy and tolerability of inhaled aerosolized CHF 1538 300 mg to placebo given over a 24-week study period (three 4-week "ON" cycles, each followed by a 4-week "OFF" cycle) in a BID regimen.

The study plan included a screening visit (Visit 1, study entry), a run-in period (minimum one, maximum eight days), and three 4-week treatment periods ("ON" cycle) with the assigned drug treatment, each followed by a 4-week run-out period ("OFF" cycle) without any treatment. Procedures at Visit 1 and Visit 2 are similar to Study CT01. After baseline measures were collected, the patients received their first dose of treatment at the clinic and patients were instructed on administering study drug and using the Pari LC Plus nebulizer and the Pari TurboBOY® compressor. Thereafter, patients received either tobramycin or placebo in alternating 28-day "ON" and 28-day "OFF" cycles for a total of three complete "ON"/"OFF" cycles. Visits took place at the clinics before and after the run-in period (baseline), and after 2, 4, 8, 12, 16, 20 and 24 weeks, with an acceptable window of a maximum of three days between scheduled visits.

Table 2 Study Design for CT02

	Run-in Period (1-8 days)	"ON" Cycle		"OFF" Cycle	"ON" Cycle	"OFF" Cycle	"ON" Cycle	"OFF" Cycle
Weeks	-1 (Approx.) to 0	0 to 2	2 to 4	4 to 8	8 to 12	12 to 16	16 to 20	20 to 24
Visit	1	2 to 3	3 to 4	4 to 5	5 to 6	6 to 7	7 to 8	8 to 9

3.1.2 Endpoints

The primary efficacy variable in the original NDA submission was the change from baseline in Forced Expiratory Volume in one second (FEV_1) expressed as percentage of predicted normal at the end of the third "ON" cycle (Visit 8, Week 20) or to the last "ON" cycle visit for patients who terminated prematurely. In the current submission, change from baseline in Forced Expiratory Volume in one second (FEV_1) is expressed as percentage of predicted normal at the end of the third "ON" cycle (Visit 8, Week 20) or the Forced Expiratory Volume in one second (FEV_1) from the Baseline visit when the Visit 8 value is missing.

Reviewer remarks: (i) The new analysis will be more conservative because a missing value at Visit 8 usually implies that the patient had pulmonary exacerbation which happens more often in the placebo group. Prior to this visit, FEV_1 values are lower than they are at baseline. Hence the placebo group mean change is overestimated. (ii) In this resubmission, the analysis will only focus on the resubmitted data that only includes the Baseline Visit and the Visit 8.

Secondary efficacy variables are changes from baseline to Visit 8 or to the last "ON" cycle visit in the following measurements: FEV_1 expressed as absolute value (Liters); Forced vital capacity (FVC) (in liters and % of predicted normal), FEF25-75% (L/sec and % of predicted normal), respiratory volume (RV) in liters, total lung capacity (TLC) in liters and respiratory rate (RR) in breaths/minute; Microbiological tests [bacterial load of *P. aeruginosa* in sputum; Tobramycin susceptibility (MIC, MIC50 and MIC90 values); categorical results (eradication, morphotype analysis, which was not pre-specified in the protocol or statistical analysis plan (SAP); Clinical symptoms (wheezing, cough); Pulmonary exacerbations; Hospitalizations due to the disease; Loss of school or/and working days due to the disease; Use of parenteral antipseudomonal drug (and parenteral tobramycin); and Body measurements (body weight, height, body mass index [BMI]).

Note that in this submission, only data from (FEV_1) expressed as percentage of predicted normal, FVC % of predicted normal, and FEF25-75% (L/sec and % of predicted normal) at Baseline (Visit 2) and the end of the third "ON" cycle (Visit 8, Week 20) were provided.

3.1.3 Source Data Verification

Following identification of inaccurate recording of/loss of source input data during the FDA inspection of Site 26, the Applicant conducted source data verification for the CT02 clinical sites that used the same version of spirometer software as Site 26. The input data located on the printed spirometer output were verified against the corresponding values in the clinical database. The source data verification was then extended to all clinical sites that participated in study CT02.

Nearly all identified discrepancies were related to height measurements and can be partially explained by the fact that height was measured twice during study visits: 1) during the physical examination and 2) by the spirometry technician at the time of pulmonary function testing. These two independent measurements did not match in all instances. Focusing on Visit 2 (baseline) and Visit 8 (endpoint visit), height differences between the spirometry source input and clinical database were detected on 14.7% of total measurements, albeit most of the differences were very small (≤ 1 cm).

Table 3 Discrepancies Between Spirometer Source Printouts and Clinical Database

Variable	Total No. of Measurements in Database	Available No. of Measurements from Printouts	Frequency of Discrepancies	Percentage of Discrepancies	Height Discrepancy details
Age	245	239	1	0.4	
Sex	245	216	0	0.0	
Height	490	435	49	11.2	Discrepancy less than or equal 10 1cm
			16	3.7	Discrepancy equal to 2cm
			7	1.6	Discrepancy more than 2cm
FEV1	481	479	7	1.5	
FVC	481	479	6	1.3	
FEF 25-75%	479	475	9	1.9	

Table 3 shows the percentage of discrepancies identified across all CT02 clinical sites for each input variable used in the determination of predicted values of pulmonary function tests at baseline and Visit 8 (endpoint visit). Percentages are based on the number of measurements in the clinical database by variable. In instances where data were not available at Visit 8 because the patient discontinued from the study, the comparison was done on the carried forward value by means of the LOCF imputation method.

Source input data obtained from the spirometer printouts is used to calculate the following for the pulmonary function parameters:

- FEV_1% predicted (the primary endpoint for Study CT02);
- FVC % predicted; and
- $FEF_{25-75\%}$ % predicted.

The same formulae were used for all patients at all sites in a consistent fashion to determine the predicted normal values. The formulae are summarized in Table 3.3 below.

Table 4 Formulae to Determine the Predicted Normal Values for Pulmonary Function parameter in the Re-analysis 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]	

Sponsor's Table

Reviewer remark: A small sample of the data was queried for accuracy. The reviewer finds that the calculations were accurate.

3.1.4 Efficacy Results from Study CT02

Because inaccurate recording of/loss of source input data has potential impact on study results, sensitivity analysis were done for the change from baseline to endpoint visit (i.e., Visit 8-after completion of the 3rd "ON" cycle). These sensitivity analyses are

- Sensitivity A: data from the clinical database submitted to FDA in the original NDA (SN 0000) have been used to re-calculate predicted normal values and % predicted values, representing 100% of the patients, but applying the same formulae for the determination of percent predicted values across all clinical sites;

- Sensitivity B: Input data from the spirometer printouts have been used for the calculation of the predicted normal values and percent predicted values, representing approximately 87 to 89% of the total patient database. As with Sensitivity Analysis A, the same formulae for the determination of percent predicted values have been applied across all clinical sites;

- Sensitivity C: Input data from the clinical database have been used to re-calculate predicted normal values and percent predicted values, but in the same subset of patients used in Sensitivity Analysis B; therefore, this analysis has been done on approximately 87 to 89% of the patients of the total patient database. As with Sensitivity Analyses A and B, the same formulae have been applied across all clinical sites for the calculation of the predicted value.

In all instances the sensitivity analyses of the pulmonary function tests are based on recalculated percent predicted values using height, age, gender and absolute pulmonary function result in liters. Note that no updated data was provided for Visits 3 to 7.

Table 5 FEV1 % Predicted 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	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	8.02	1.91	< 0.001
		Difference (95% CI)	6.11 (3.08, 9.15)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	7.82	0.51	< 0.001
		Difference (95% CI)	7.32 (4.24, 10.40)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	4.84	1.85	
		Difference	3.00 (-0.09, 6.09)		0.057
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	7.28	2.26	
		Difference (95% CI)	5.02 (1.70, 8.33)		0.003
		N imputed	3	4	
7	16 "OFF" Drug	Mean Change from Baseline1,2	6.14	0.74	
		Difference (95% CI)	5.40 (1.95, 8.85)		0.002
		N imputed	4	5	
8	20 "ON" Drug (1° endpoint)	Mean Change from Baseline1,2	6.88	0.64	
		Difference (95% CI)	6.24 (2.71, 9.77)		0.001
		N imputed	7	6	
9	24 "OFF" Drug	Mean Change from Baseline1,2	6.94	0.67	0.001
		Difference (95% CI)	6.27 (2.74, 9.81)		

Note: The shaded row indicates the primary endpoint

In the original NDA statistical review, the change in FEV1 % predicted from baseline, with multiple imputation for missing Visit 8 values, is significantly greater in the CHF 1538 group than in the Placebo group at Visit 8 (see Table 5). The mean change from baseline to endpoint in

FEV1 % predicted was higher in the CHF 1538 group (6.88%) than in the Placebo group (0.64%) ($p < 0.001$). A similar conclusion can also be arrived at based on the three sensitivity analyses either using the baseline observation (Table 6) or last observation carried forward (Table 7) for the missing Visit 8 values. The slight deviations in the mean change from baseline to endpoint in FEV1 % predicted from the three sensitivity analysis, ranging from 5.95 to 6.56, implies that this reported change is robust despite inaccurate recording of/loss of source input data. Therefore, the findings for FEV_1 % predicted are numerically consistent, statistically significant and corroborate the analyses found in the original NDA.

Table 6 Study CT02 – Efficacy Analysis of FEV1 % Predicted – Visit 8 (Week 20) – ITT Population – Baseline Observation Carried Forward - Sensitivity Analyses (A, B, and C)

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	N	161	84	
	"ON" Drug	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	N	142	73	
	"ON" Drug	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	N	142	73	
	"ON" Drug	Mean Change from Baseline	5.84	-0.62	
		Difference (95% CI)	6.47 (2.38, 10.55)		0.0021

Table 7 Study CT02 – Efficacy Analysis of FEV1 % Predicted – Visit 8 (Week 20) – ITT Population – Last Observation Carried Forward - Sensitivity Analyses (A, B, and C)

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	N	161	84	
	"ON" Drug	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	N	142	72	
	"ON" Drug	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	
	20	N	142	72	
8	"ON" Drug	Mean Change from Baseline	5.93	-0.64	
		Difference (95% CI)	6.56 (2.35, 10.78)		0.0024

Reviewer remark: For absolute Visit 2 and Visit 8 FEV1, if no value in the spirometer printouts matched the value in the clinical database, the highest absolute value from the printouts was selected from amongst multiple efforts which were produced during Visit 2 or Visit 8. Otherwise, the spirometer printout value matching the one from the original database was used.

FVC % predicted normal mean baseline (Visit 2) and mean change from baseline for the ITT population are presented in Table 8. The mean change from baseline to the primary endpoint for FVC % predicted normal was greater in the CHF 1538 group (5.85%) than in the Placebo group (1.52%) in the original NDA review. The efficacy of CHF 1538 on FVC % predicted normal was found to be significantly greater than placebo. The findings from the three sensitivity analysis also corroborate the analyses submitted in the original NDA which found that in the intent-to-treat population, the change in FVC % predicted normal from baseline was significantly greater in the CHF 1538 group than in the Placebo group at Visit 8. The mean change from baseline to Visit 8, Week 20 for FVC % of predicted normal in the CHF 1538 group, from the sensitivity analyses, ranges from 4.70% to 5.22%, while it ranges from -0.90% to 0.38% in the Placebo group.

Table 8 Study CT02 - Efficacy Analysis of FVC% Predicted – Visit 8 (Week 20) - ITT Population - Original and Sensitivity Analyses (A, B, and C)

Visit	Week		CHF 1538	Placebo	P-Value
Original results from previous review with MI					
2	Baseline	N	161	84	
		Mean	70.77	73.58	
8	20	N	161	84	
	"ON" Drug	Mean Change from Baseline	5.78	1.49	0.026
		Difference (95% CI)	4.29 (0.51, 8.07)		
Sensitivity A: Re-calculated % predicted values using data from clinical database with LOCF					
2	Baseline	N	161	84	
		Mean	71.91	68.70	
8	20	N	161	84	
	"ON" Drug	Mean Change from Baseline	5.22	0.38	
		Difference	4.84 (1.10, 8.57)		0.011
Sensitivity B: Re-calculated % predicted values using data from Spirometry printouts with LOCF					
2	Baseline	N	142	73	
		Mean	68.30	72.75	
	20	N	142	72	
8	"ON" Drug	Mean Change from Baseline	4.84	0.19	
		Difference (95% CI)	4.64 (0.91, 8.38)		0.015
Sensitivity C: Re-calculated % predicted values using data from clinical database, in the same subset of patients used in analysis B with LOCF					
2	Baseline	N	142	73	
		Mean	68.31	73.12	
	20	N	142	72	
8	"ON" Drug	Mean Change from Baseline	4.70	-0.90	
		Difference (95% CI)	5.60 (1.61, 9.55)		0.006

Reviewer remark: For Visit 2 and Visit 8 absolute FVC; if no value in the spirometer printouts matched the value in the clinical database, the absolute value from the printouts corresponding to

the effort associated with the highest absolute FEV_1 for Visit 2 and Visit 8 was used. Otherwise, the spirometer printout value matching the one from the original database was used.

$FEF_{25-75\%}$ % predicted normal mean baseline (Visit 2) and mean change from baseline for the ITT population are presented in Table 9. The mean change in FEF25-75% % predicted normal from baseline to the primary endpoint in the original NDA review was greater in the CHF 1538 group (8.75%) than in the Placebo group (0.69%). CHF 1538 efficacy on $FEF_{25-75\%}$ % of predicted normal was significantly greater than that of placebo at all visits. Likewise, the reanalysis of $FEF_{25-75\%}$ corroborates the analyses in the original NDA review which found that in the intent-to-treat population, the change in $FEF_{25-75\%}$ % predicted normal from baseline was significantly greater in the CHF 1538 group than in the Placebo group at Visit 8, Week 20. The mean change from baseline to Visit 8 in $FEF_{25-75\%}$ % predicted normal in the CHF 1538 group, from the sensitivity analyses, ranges from 8.37% to 8.77% while it ranges from 1.02% to 1.68% in the Placebo group (0.69%).

Table 9 Study CT02 - Efficacy Analysis of FEF25-75%% Predicted – Visit 8 (Week 20)-ITT Population - Original and Sensitivity Analyses (A, B, and C)

Visit	Week		CHF 1538	Placebo	P-Value
Original results from previous review with MI					
2	Baseline	N	158	80	
		Mean	41.76	43.92	0.531
8	20	N	3	5	
	"ON" Drug	Mean Change from Baseline	8.42	0.70	0.002
		Difference (95% CI)	7.72 (2.91, 12.53)		
Sensitivity A: Re-calculated % predicted values using data from clinical database with LOCF					
2	Baseline	N	160	84	
		Mean	43.32	45.76	
8	20	N	160	84	
	"ON" Drug	Mean Change from Baseline	8.72	1.02	
		Difference	7.70 (2.78, 12.62)		**0.002**
Sensitivity B: Re-calculated % predicted values using data from Spirometry printouts with LOCF					
2	Baseline	N	139	73	
		Mean	42.54	46.16	
8	20	N	139	72	
	"ON" Drug	Mean Change from Baseline	8.77	1.68	
		Difference (95% CI)	7.09 (1.65, 12.52)		0.011
Sensitivity C: Re-calculated % predicted values using data from clinical database, in the same subset of patients used in analysis B with LOCF					
2	Baseline	N	139	73	
		Mean	42.30	46.41	
8	20	N	139	72	
	"ON" Drug	Mean Change from Baseline	8.37	1.28	
		Difference (95% CI)	7.09 (1.82, 12.35)		0.009

Reviewer remark: Visit 2 and 8 absolute $FEF_{25-75\%}$; if no value in the spirometer printouts matched the value in the clinical database, the absolute value from the printouts corresponding to the effort associated with the highest absolute FEV_1 for Visit 2 and Visit 8 were used. Otherwise, the spirometer printout value matching the one from the original database was used.

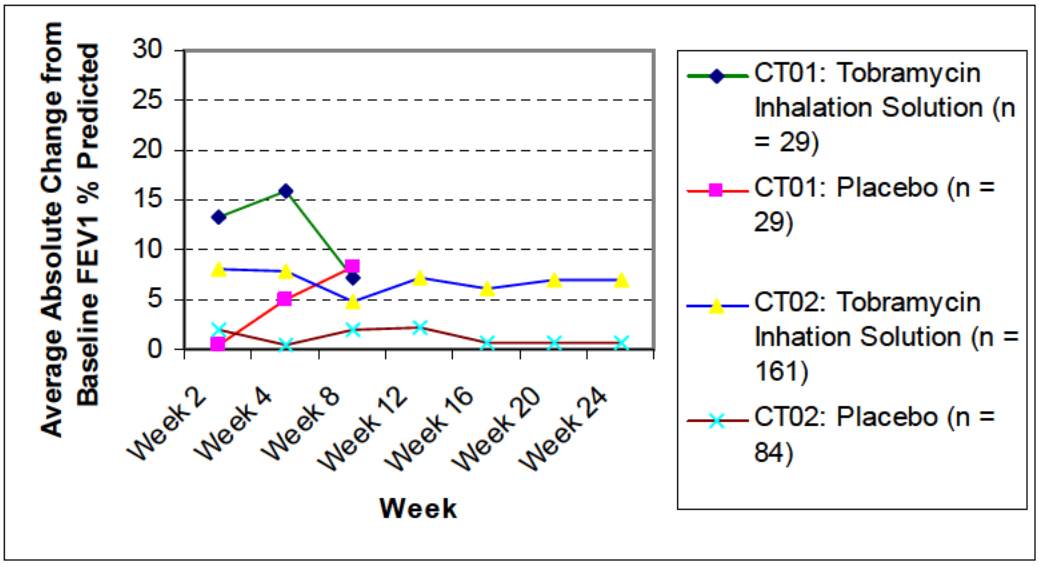

Figure 1 Absolute Change from Baseline FEV1 % Predicted

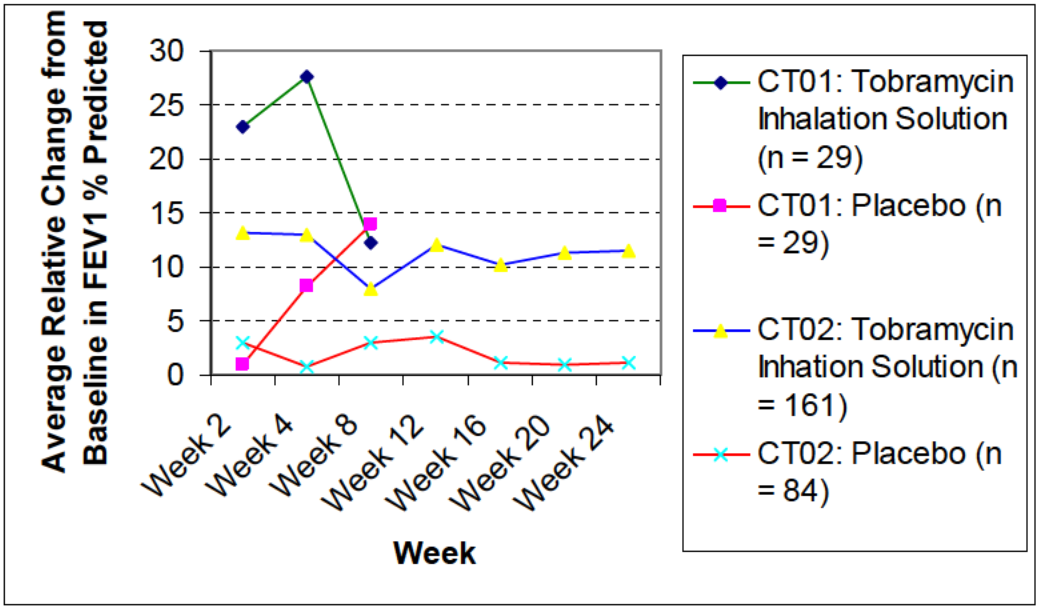

Figure 2 Relative Change from Baseline in FEV1 % Predicted

Figure 1 above shows the absolute change from baseline FEV1% Predicted over the course of the randomized treatment and Figure 2 shows the corresponding relative change. In these figures, results from CT-01 are also shown. Since the mean change from baseline FEV1% Predicted is significantly greater in CHF-1538 than in Placebo and both groups have comparable baselines, the relative change from baseline FEV1% Predicted for CHF-1538 will, obviously, be above that of placebo. The graph shown in Figure 2, however, amplifies the difference between the effects and interpretation of the curves must be carried out judiciously.

As pointed out in the previous NDA statistical review, how these improvement in pulmonary function translate to clinically meaningful effect remains suspect and needs to be investigated more carefully in the future.

In the previous review, a comparison of the number and percentage of patients with pulmonary exacerbation in each treatment group at all visits was made and is presented in Table 3.18. A pulmonary exacerbation was defined as the presence of at least three of 11 pre-defined symptoms. However, in the following table pulmonary exacerbation is defined as what the investigators diagnosis at the time of presentation regardless of whether at least three of 11 pre-defined symptoms are satisfied. In this table, CHF 1538 patients had lower percentage of exacerbations compared to placebo although only Visit 4 is significant.

Table 10 Pulmonary Exacerbations

Visit	Week	CHF 1538 n (%) 161	Placebo n(%) 84	P-Value2
2	Baseline	11(6.8%)	5(6.0%)	1.00
3	2 “ON” Drug	22 (13.7%)	15 (17.9%)	0.45
4	4 “ON” Drug	13 (8.1%)	17 (20.2%)	0.01
5	8 “OFF” Drug	36 (22.4%)	25 (29.8%)	0.21
6	12 “ON” Drug	33 (20.5%)	19 (22.6%)	0.74
7	16 “OFF” Drug	19 (11.8%)	18 (21.4%)	0.06
8	20 “ON” Drug	18 (11.2%)	15 (17.9%)	0.17
9	24 “OFF” Drug	20 (12.4%)	17 (20.2%)	0.13

Figure 3 shows the time to first exacerbation by treatment arm. Again, although there is a clear delineation between the two survival curves, the test of equality over the two strata is not significant (Wilcoxon test : 0.0622). When sites 26 and 32 are excluded from the analysis the test of equality over the two strata is still not significant (Wilcoxon test : 0.1742). Its survival curve hardly differs from Figure 3 and so will not be shown.

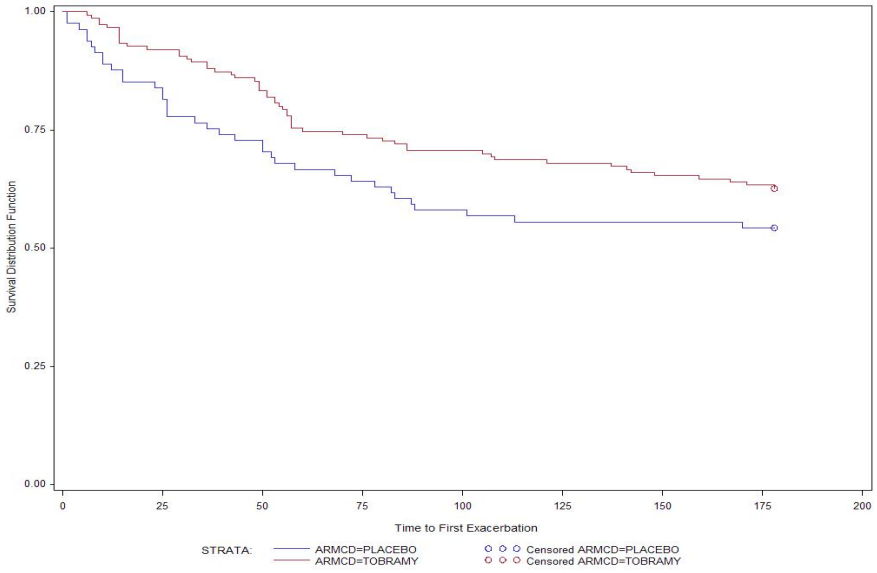

Figure 3 Time to First Exacerbation: ITT Population

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The Applicant only provided source input data obtained from the spirometer printouts used to calculate pulmonary function parameters at two visits, Baseline and Visit 8. The search could have been extended to all visits so that multiple imputations of the missing Visit 8 data can be performed more appropriately. As noted in the previous review, missing data is generally related to an exacerbation and therefore the immediate previous visit is essential to the imputation of the missing Visit 8 data. Although, the reviewer thinks that sensitivity analysis using multiple imputation would probably not affect the results significantly as to alter conclusion that the drug is superior to placebo.

There are no further statistical issues identified in this re-submission.

4.2 Conclusions and Recommendations

The findings in the sensitivity analyses for FEV1 % predicted based on either source data verified clinical database or input data from spirometer printouts show that the results of the CT02 trial as submitted and reviewed originally are robust. In particular, it was concluded in the original statistical review that the change in FEV1 % predicted normal from baseline was significantly greater in the CHF 1538 group than in the Placebo group at Visit 8, Week 20 (at the end of the third "ON" cycle of randomized treatment). In fact, findings show that in the ITT population, the mean change from baseline to endpoint in FEV1 % predicted, using multiple imputation for missing values, was higher in the CHF 1538 group (6.88%) than in the placebo group (0.64%) with a difference of 6.24% [95% CI: 2.71, 9.77; p.value: <0.001] at Visit 8, Week 20 (at the end of the third "ON" cycle of randomized treatment. When Baseline observation is carried forward to the missing Visit 8 values, the mean change from baseline to Visit 8 in FEV1 % predicted normal in the CHF 1538 group ranges from 5.84 to 6.36 compared to the Placebo group which ranges from -0.62 to 0.33. The Difference in mean change from baseline ranges from 5.95 to 6.47 and all are statistically significant [95% CI ranges: 2.20-2.38, 9.65-10.55; p-value ranges: 0.0018-0.0022). When the last observation is carried forward is applied in the sensitivity analysis, the mean change from baseline to Visit 8 in FEV1 % predicted normal in the CHF 1538 group ranges from 5.94 to 6.55 compared to the Placebo group which ranges from -0.64 to 0.21. The Difference in mean change from baseline ranges from 6.21 to 6.56 and all are also statistically significant [95% CI ranges: 2.35-2.40, 10.02-10.78; p-value ranges: 0.0015-0.0024). The findings in the sensitivity analyses corroborate the result presented in the original statistical review.

Sensitivity analysis for the other secondary pulmonary functions, e.g. FEV% predicted and $FEF_{25-75\%}$ % predicted were also conducted. Their results provide similar findings that corroborate the analyses submitted in the original NDA and the original statistical review.

Results of Study CT01, which were presented in the earlier review, also show that, using multiple imputations for missing observations, the FEV1 % predicted normal had increased by 13.3% at Week 2 and 15.9% at Week 4 above baseline values for CHF 1538-treated patients. In

contrast, changes in FEV1 % predicted normal were 0.5% in Week 2 and 4.9% in Week 4 in the Placebo group. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups were 12.8% [95% CI: 4.3, 21.2; p.value: 0.002] in Week 2 and 11.0% [95% CI: 3.0, 18.9; p-value: 0.003] in Week 4 and the effect is slightly below placebo at week 8, the off-therapy phase with -1.2% [95% CI; -10.2, 7.7; p-value: 0.700]. These findings indicate that CHF 1538 significantly improves FEV1 % predicted at the end of the "ON" cycle (Week 4) of randomized treatment.

However, the question still remains how these results translate to a clinically meaningful effect is still not clear. As was illustrated in the original review, although there is a clear delineation between the two survival curves of time to first exacerbation, the test of equality over the two strata is not significant (Wilcoxon test: 0.0622). Time to exacerbation could be a more meaningful clinical endpoint if it is defined objectively. CHF 1538 has not shown to have an improvement than placebo for time to first exacerbation as designed in the current trial.

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10/01/2012

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10/02/2012