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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number:	201820
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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.

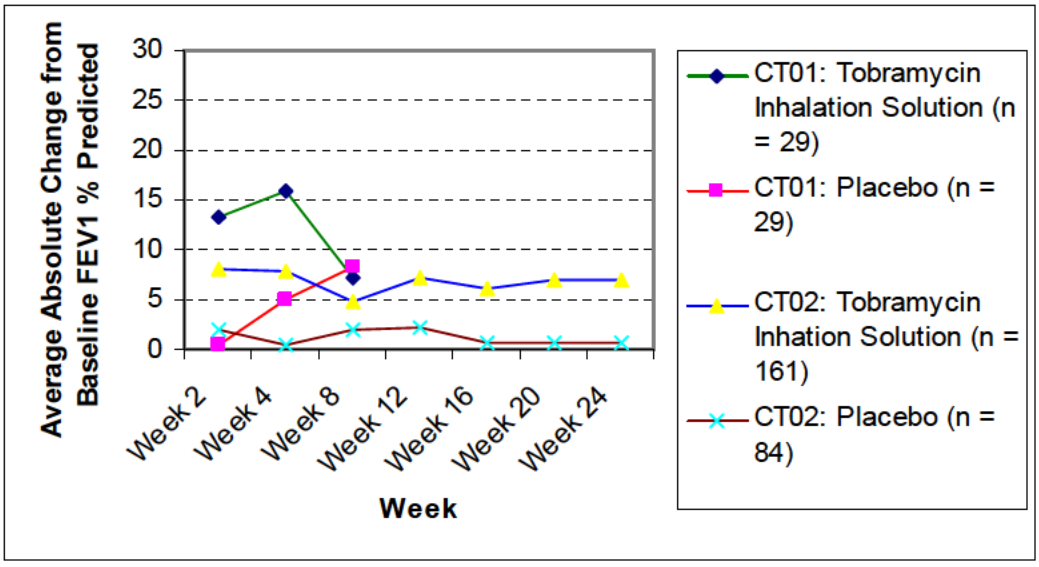

Figure 1 Absolute Change from Baseline FEV1 % Predicted

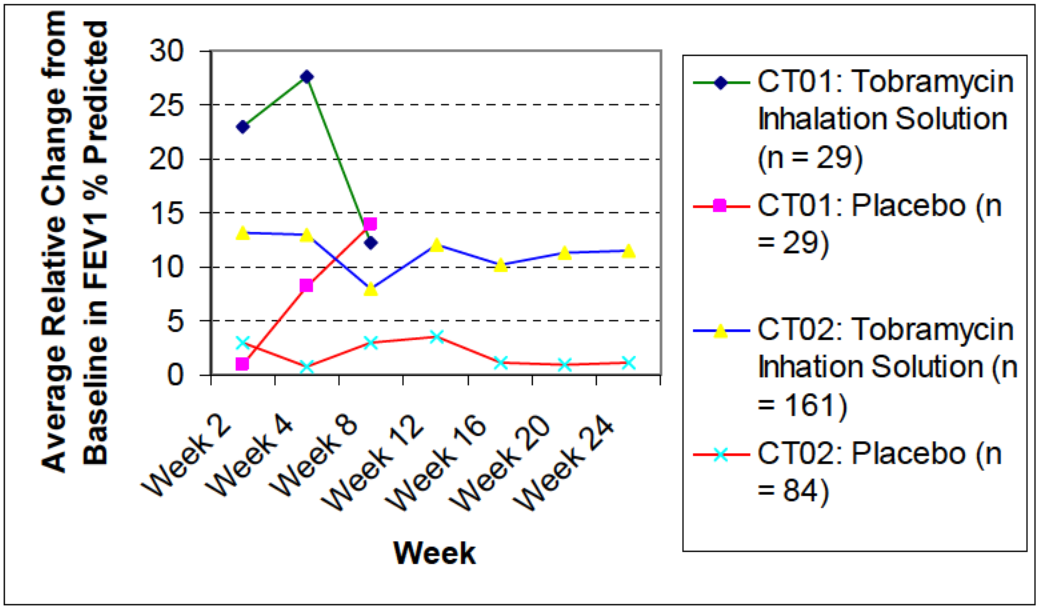

Figure 2 Relative Change from Baseline in FEV1 % Predicted

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.

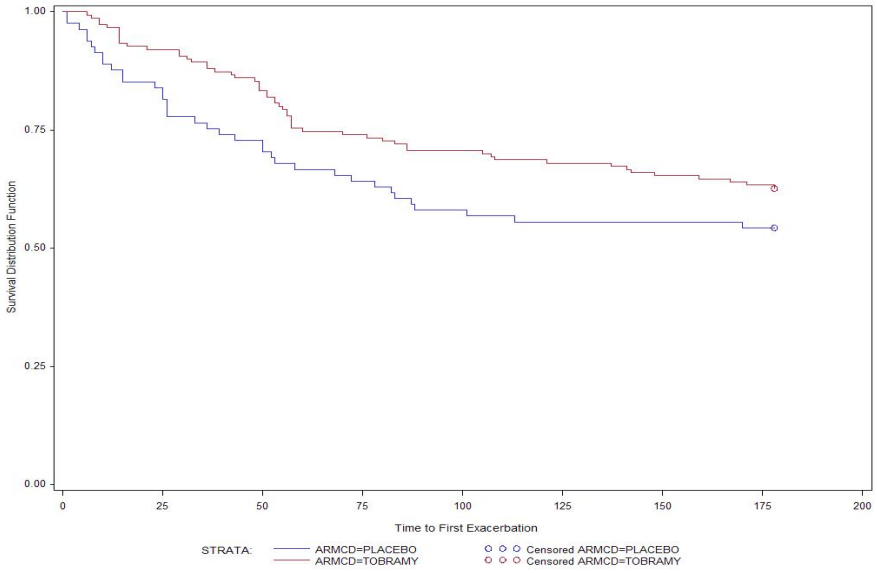

Figure 3 Time to First Exacerbation: ITT Population

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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REFERENCES

1. Wine J. Cystic fibrosis: How do CFTR mutations cause cystic fibrosis? Curr Biol. 1995 Dec 1;5(12):1357-9.

2. Kerem E, Corey M, Gold R, Levison H. Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonization with *Pseudomonas aeruginosa*. J Pediatr. 1990 May;116(5):714-9.

3. Hoiby N. Microbiology of lung infections in cystic fibrosis patients. Acta Paediatr Scand. 1982;301:33-54.

4. Wood R, Boat T, Doershuk C. Cystic fibrosis. Am Rev Respir Dis. 1976;113:833-78.

5. Boat T, Welsh M, Beaudet A, Tsui L. Cystic Fibrosis. In: Schriver C, Beaudet A, Sly W, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease: 7th Edition. New York: McGraw-Hill;1995. p. 3799-3876.

6. Touw D, Brimicombe R, Hodson M, Heijerman H, Bakker W. Inhalation of antibiotics in cystic fibrosis. Eur Respir J. 1995;8(9):1594-604.

7. Ramsey B, Pepe M, Quan J, Otto K, Montgomery A, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med. 1999;340(1):23-30.

8. Toso C, Williams C, Noone P. Inhaled antibiotics in cystic fibrosis: a review. Ann Pharmacother. 1996 Jul-Aug;30(7-8):840-50.

9. Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest. 2002 Jan;121(1):55-63.

10. Poli G, Acerbi D, Pennini R, Soliani RA, Corrado M, Eichler H, et al. Clinical pharmacology study of Bramitob, a tobramycin solution for nebulization, in comparison with Tobi. Paediatr Drugs. 2007;9 Suppl(1):3-9.

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/s/

MARK A GAMALO
10/01/2012

THAMBAN I VALAPPIL
10/02/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number:	201820
Drug Name:	CHF 1538 (Tobramycin 300 mg/4mL Inhalation Solution)
Indication(s):	Management of Cystic fibrosis
Applicant:	Chiesi Pharmaceuticals, Inc
Date(s):	
Review Priority:	Standard
Biometrics Division:	IV
Statistical Reviewer:	Mark A. Gamalo, PhD
Concurring Reviewers:	Thamban Valappil, PhD
Medical Division:	Anti-infective and Ophthalmology Products
Clinical Team:	Shrimant Mishra, MD
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Project Manager:	Carmen DeBellas, PharmD

Keywords: Non-inferiority, Superiority, Multiple Imputation, ANCOVA

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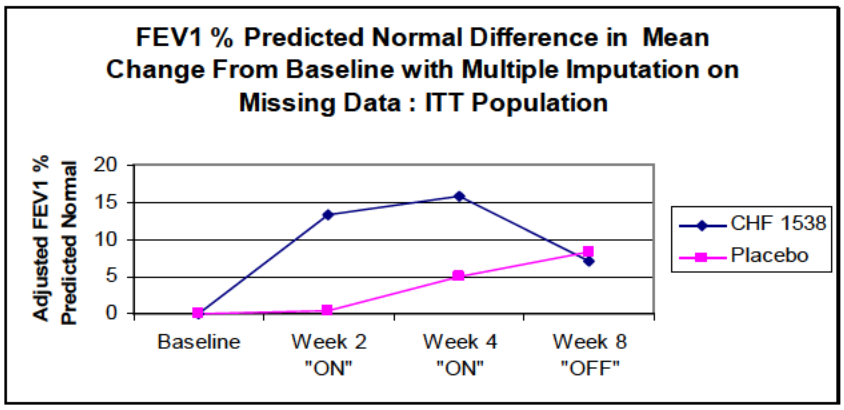
1. EXECUTIVE SUMMARY

Chiesi Pharmaceuticals, Inc, hereafter referred to as Applicant, submitted this NDA to request FDA approval of a tobramycin sterile, preservative-free, aqueous solution for nebulization containing 300 milligrams tobramycin in a four milliliter unit-dose ampule, or Tobramycin 300 mg/4 mL Inhalation Solution (hereafter referred to as CHF 1538) for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. As designed, the Applicant states that their development program provides a series of new clinical investigations of CHF 1538 that when combined with the data from the reference-listed product, TOBI, will provide support of the 505(b)(2) application. The series of clinical investigations include studies CT01 and CT02 which were designed to demonstrate superior efficacy and safety of CHF 1538 compared to placebo in the treatment of CF patients with *P. aeruginosa* infection. Both studies CT01 and CT02 were randomized, double-blind, placebo-controlled clinical studies with aerosolized CHF 1538 or placebo delivered via the PARI LC Plus nebulizer and the PARI TurboBOY compressor. (b) (4)

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).

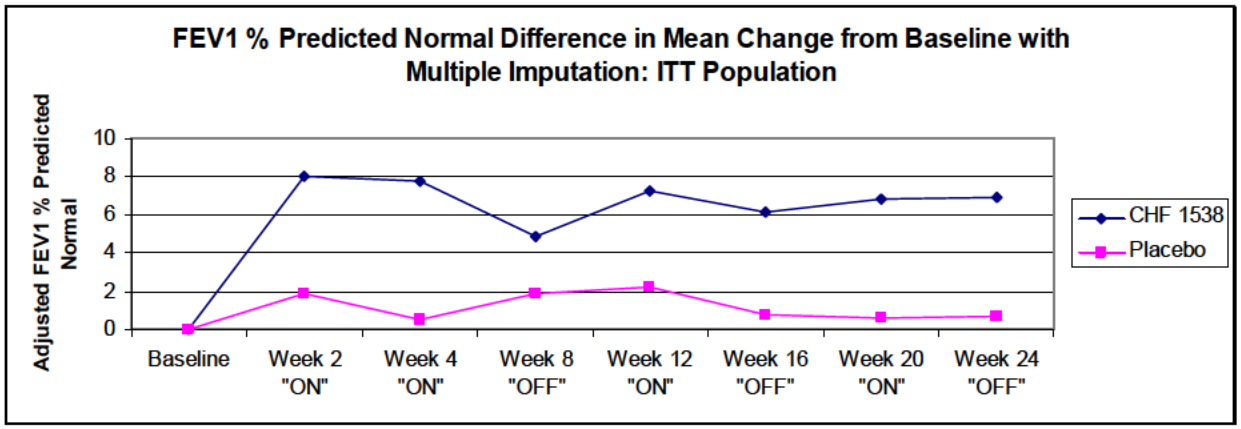
Figure 1.1 Study CT01



Results of Study CT01 show that, using multiple imputations for missing observations, the FEV_1 % 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 FEV_1 % 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 (see Figure 1.1). On the other hand, for Study CT02, FEV_1 % 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 FEV_1 % predicted normal

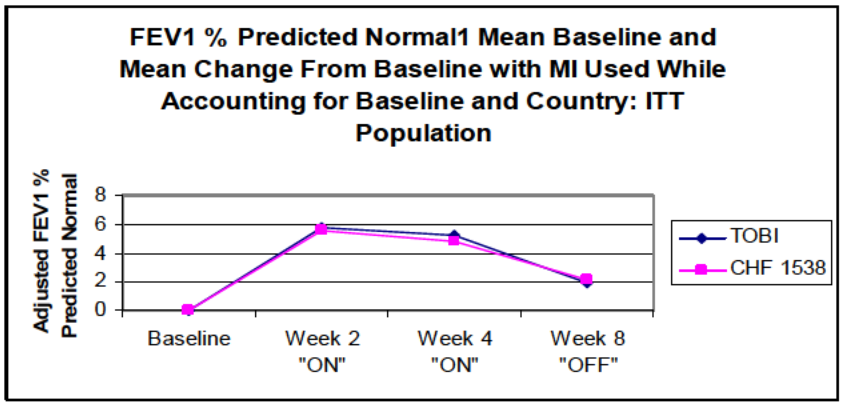
were 1.91% in Week 2, 0.51% in Week 4, 2.26% in Week 12, and 0.64% in Week 20 in the Placebo group. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups were significant in all the "ON" periods (see Figure 1.2).

Figure 1.2 Study CT02



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. Nevertheless, the results are shown in Figure 1.3.

Figure1.3 Study CT03



Note that in the 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). From the information provided for review, it appears that the intended to-be-marketed combination product is the proposed tobramycin solution, along with the either the Pari LC Plus Nebulizer or the [redacted] (b) (4) Nebulizer. The proposed compressor for both nebulizers is the Vios Compressor. Yet, the clinical studies for the combination product were done using the new Pari LC Plus Nebulizer and the TurboBoy N and S compressors. The Regulatory Device Consult 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, it is uncertain

whether these new devices will provide similar or better results than the one used in the clinical trials.

There were several concerns about data integrity and reliability. One site in Poland (Study CTO2 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 (Study CTO2 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. Furthermore, Audiometric Test data at Site 17 (CT01) have a particular threshold repeated for every subject while many of the other sites have their own patterns of results. For example, one site may have lots of results between the 0-10dB range, whereas others will have thresholds within the 10-20dB range.

It is also interesting to note that there is stark difference between the results of Study CT01 and CT02 despite having been adjusted for their baseline values. In Study CT01 FEV_1 % 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 FEV_1 % predicted normal were 0.5% in Week 2 and 4.9% in Week 4 in the Placebo group. As a result, the comparison of the difference in mean changes from baseline between the CHF 1538 and placebo groups were 12.8% in Week 2 and 11.0% in Week 4. In Study CT02, FEV_1 % predicted normal had increased by 8.0% at Week 2 and 7.8% at Week 4 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV_1 % predicted normal were 1.9% in Week 2 and 0.5% in Week 4 in the Placebo group. As a result, the comparison of the difference in the mean changes from baseline between the CHF 1538 and placebo groups were 6.1% in Week 2 and 7.3% in Week 4 which are about half of what was observed in CT01, i.e., 12.8% in Week 2 and 11.0% in Week 4. It is not clear whether these differences are due to varying strategies to manage care across centers, data collection, enrolled patient severity and other potential confounders.

Lastly, it is unclear how small changes in FEV_1 % predicted normal would translate into clinically meaningful benefit the patients get from taking the drug. In CT01, after treatment with 28 days of CHF 1538, the improvement in FEV1 % predicted normal above baseline levels was nearly 11% greater than the response in placebo patients. In CT02, improvement at a similar time point is 6.9% and the improvement at Week 20 is 5.5%. However, investigations on how the drug delays exacerbation show that the CH1538 and the placebo group are no different, despite delineated survival curves. Potentially, an effect may be present but this study has not been designed to detect such difference.

In summary, the results of Studies CT01 and CT02 show that intermittent (28-day "ON"/28-day "OFF"), twice daily administration of CHF 1538 300 mg is significantly superior to placebo in improving pulmonary function in CF patients with *P. aeruginosa* infection. However, any final conclusion on this submission is contingent on the data being deemed reliable after all Division of Scientific Investigation (DSI) inspections have been completed and on whether the in vitro bridging data based on the product tested in clinical trial is sufficient to justify the efficacy and safety of the to-be-marketed product, for which no clinical studies have been performed. We

recommend that at least one adequate and well controlled clinical trial be conducted to assess the efficacy and safety of CHF 1538 using the to-be marketed combination product.

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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 below) in patients with CF and *P. aeruginosa.*

Table 2.1 List of all studies included in 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. TOB	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 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 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 normal 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 ≥ 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, this difference being not statistically significant. All patients were individually provided with a PARI TurboBOY compressor and a PARI LC Plus® nebulizer for use during the trial.

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%) (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.

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.

2.2 Data Sources

The clinical study reports were provided in an electronic submission located in **CDSESUB1\EVSPROD\NDA201820**. Datasets and SAS codes for 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

3.1.1.1 Design for Study CT01

This is a double-blind, multinational, multicenter, randomized, placebo-controlled study designed to assess the efficacy and safety of a CHF 1538 BID compared with nebulized placebo BID for a 4-week treatment period in CF patients with *P. aeruginosa* infection. Subjects were recruited from hospitalized patients or patients attending outpatient clinics. A maximum of 140 patients were targeted for enrollment to potentially obtain 74 completed patients (randomized population only include 59 patients). This outpatient study included five clinic visits that occurred over an approximate 8- to 9-week period.

At Visit 1 (screening or start of the 1- to 8-day, run-in period), eligibility for the study was assessed along with a medical and medication history, physical exam, microbial tests, laboratory tests, audiometric tests, vital signs and measures of pulmonary function. For eligible patients, all non-permitted medications were then withdrawn at Visit 1.

At Visit 2 (end of the run-in period and beginning of 4-week treatment period), eligible patients were randomized. During this visit, baseline safety and efficacy measures were collected. 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.

Patients returned to the clinic at Week 2 (Visit 3) and Week 4 (Visit 4) during the 4-week treatment period. On these visits, patients brought unused study drug and the nebulizer with them. Patients were also instructed to abstain from taking their morning dose of treatment on the days of these visits. Treatment was administered at the clinic during these visits.

At Visit 4, all treatment was terminated and all unused drug was returned to the site staff. After four weeks of treatment, the patients could be excluded from the study or assigned an alternative therapy if pulmonary function or clinical condition had deteriorated or if persistence or superinfection occurred requiring a treatment that was contraindicated by the protocol. Otherwise, patients returned to the clinic (Visit 5) after four weeks without treatment. Safety and efficacy measures were collected. In the case of an adverse event (AE) ongoing at Visit 5, a supplementary visit was arranged to assess the outcome of the event and complete the appropriate sections of the case report form (CRF).

3.1.1.2 Design for Study CT02

This 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 3.1 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

3.1.1.3 Design for Study CT03

This 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. Subjects were recruited from hospitalized patients or patients attending outpatient clinics. A maximum of 320 patients were targeted for enrollment to obtain 286 evaluable patients.

This outpatient study included five clinic visits that occurred over an approximate 8- to 10-week period.

At Visit 1 (screening or start of the 1-to-10-day run-in phase), eligibility for the study was assessed along with a medical and medication history, physical exam, microbial tests, laboratory tests, audiometric tests, vital signs and measures of pulmonary function. For eligible patients, all nonpermitted medications were then withdrawn at Visit 1.

At Visit 2 (end of the run-in phase and beginning of 4-week treatment phase), eligible patients were randomized. During this visit, baseline safety and efficacy measures were collected. 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 Boy N compressor.

Patients returned to the clinic at Visit 3 (after two weeks of test treatment) and Visit 4 (after four weeks of test treatment). On these visits, patients were instructed to bring their nebulizers and compressors with them and to abstain from taking their morning dose of treatment on the days of these visits. Treatment was administered at the clinic during these visits after all scheduled assessments were completed.

At Visit 4, all unused drug was returned to the site staff. After 4 weeks of treatment, the patients started a 4-week period without treatment (follow-up phase) and returned to the clinic at Visit 5. Efficacy and safety measures and assessments were performed and collected.

Reviewer comments:
1. Concomitant medications were allowed in all the studies. This includes mucolytics, steroidal and nonsteroidal anti-inflammatory drugs, bronchodilators and therapies for the treatment of a concomitant disease or non-pulmonary feature of CF if it did not interfere with evaluation of the study endpoints
2. In Study CT02, anti-PA drugs were allowed, except aminoglycosides and nebulized antibiotic and non anti pseudomonal antibiotics in the events of a positive culture for other pathogens than P. aeruginosa, which required a specific treatment (e.g., Staphylococcus aureus, Hemophilus influenzae).
3. In CT03, non anti pseudomonal antibiotics were allowed in the events of a positive culture for other pathogens than P. aeruginosa, which required a specific treatment (e.g., Staphylococcus aureus, Hemophilus influenzae).

3.1.2 Endpoints

3.1.2.1 Endpoints for Study CT01

The primary efficacy variable was defined as the final value of Forced Expiratory Volume in one second, FEV_1 % predicted normal at the end of treatment (Visit 4).

Secondary pulmonary efficacy variables included the following: 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; RV (L); Total lung capacity (TLC, L); and RV/TLC ratio (RV/TLC, %); and Body measurements (body weight, height, body mass index [BMI]).

3.1.2.2 Endpoints for Study CT02

The primary efficacy variable 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.

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]).

3.1.2.3 Endpoints for Study CT03

The primary efficacy variable was defined as the change from baseline of FEV_1, expressed as % of predicted normal at the end of the treatment phase (Visit 4).

Secondary pulmonary efficacy variables included the following: FEV_1 % predicted normal measured at Visits 3 and 5; FEV_1, expressed as liters measured at Visits 3, 4 and 5; FVC, expressed as liters and % predicted normal measured at Visits 3, 4 and 5; and FEF25-75%, expressed as liters/second and % predicted normal measured at Visits 3, 4 and 5.

Reviewer comments: Notes on the difference between the endpoint measurements in the studies.

1. *In all three studies, patients rested in a seated position for at least ten minutes before all pulmonary function tests. One measure was recorded for each of the static parameters. For dynamic parameters of pulmonary function, three measurements were collected and the greatest FEV_1 value was recorded in the CRF.*
2. *In CT01, if inhaled short- or long-acting β_2-agonists were administered, a minimum period of six hours and 12 hours, respectively, were required to elapse before measuring pulmonary function.*
3. *In all three studies, it was suggested that the spirometer used to measure pulmonary function at each center was not changed during the course of the trial.*
4. *In CT03, if a patient could not perform three acceptable spirometry attempts and could not respect repeatability criteria, the best spirometric curve was accepted.*

3.1.3 Analysis Populations

The *Total* population includes all patients who entered the study (all screened patients). The *Randomized* population includes all patients who were randomized to study medication. The *Safety* population includes all patients who received at least one dose of study medication. The *Intent To Treat (ITT)* population includes all randomized patients who received at least one dose of study medication, and, who has a post baseline data (for Study CT01), who have an evaluation of FEV, (% of predicted normal) at baseline (V2), and, who have an evaluation of FEV1 (% of predicted normal) at V4 for Study CT02, who has available baseline FEV1 value and with at least one available post-baseline FEV1 value during treatment period (For Study CT03). The ITT population is the primary analysis population. The As Treated (AT) population includes all patients in the ITT population according to the treatment actually received (for Study CT03

only). The *Per Protocol (PP)* population will include all ITT patients: who meet all inclusion/exclusion criteria, and, who do not have any major protocol deviation.

Reviewer comments: Notes on the differences of populations considered and population definitions.

1. *Study CT01 only considers the Safety, ITT and PP populations. Study CT02 considers the Total, Randomized, Safety, ITT and PP populations. Study CT03 considers the Safety, ITT, AT, and PP populations.*
2. *The three studies differ in the definition of the ITT population. Although all three defines this population to primarily include all randomized patients who received at least one dose of study medication, they differ in their criteria for availability of baseline and post-baseline measurements.*
3. *The exclusion criteria in the ITT population, i.e., must receive at least one dose of study medication is a post-randomization exclusion and can potentially bias results. However, the impact is probably minimal*.

3.1.4 Patient Disposition and Protocol Deviations

3.1.4.1 Study CT01:

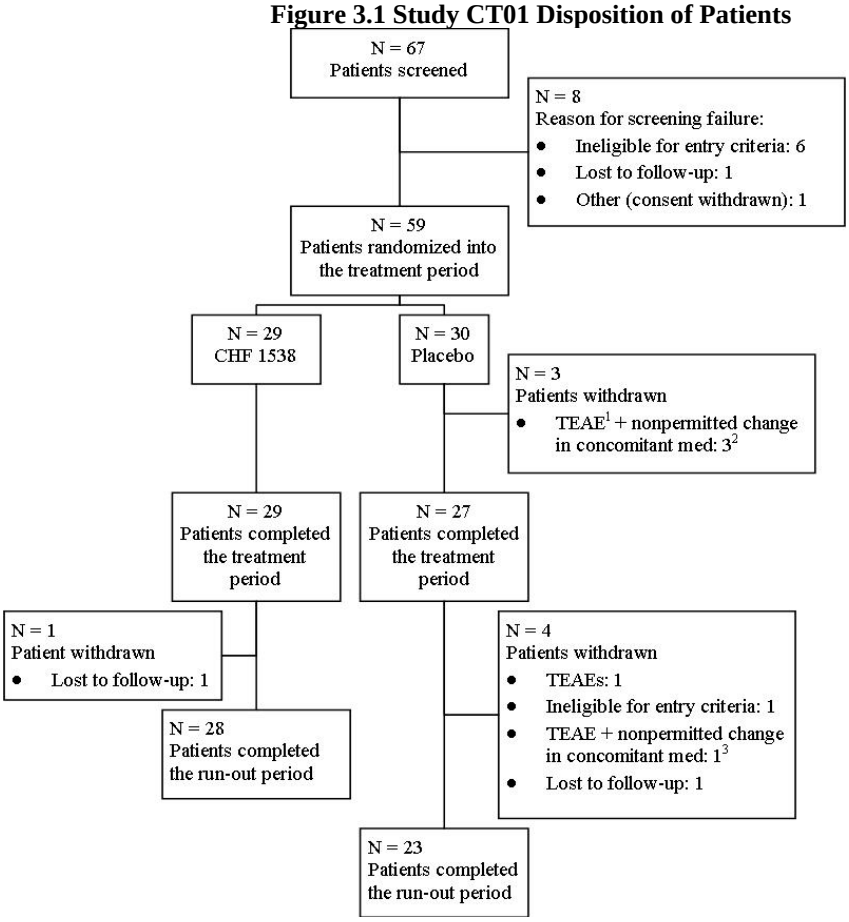
Of the 74 patients planned for enrollment into this study, only 59 patients were randomized. Of the 29 patients randomized to CHF 1538, only one (3.4%) withdrew from the study as opposed to seven of 30 (23.3%) patients in the Placebo group (see Figure 3.1).

Four major protocol violations were observed in three patients from the ITT population: one patient (3.4%) in the CHF 1538 group and two patients (6.7%) in the Placebo group. These three patients having major protocol violations were excluded from the PP population. Major deviations are described as follows:

- One patient in the CHF 1538 group had a treatment compliance below the required 75% limit;
- One placebo-treated patient did not have a positive *P. aeruginosa* culture at study entry and had a treatment compliance below the required 75% limit; and
- One placebo-treated patient was administered a non-permitted concomitant medication.

Minor deviations were observed in 28 patients: 11 of 29 patients (37.9%) in the CHF 1538 group and 17 of 30 patients (56.7%) in the Placebo group. The majority of these deviations were scheduled visits that fell outside the allowed 3-day window. Some patients had more than one minor protocol deviation. Patients having minor deviations were included in the PP population.

Figure 3.1 Study CT01 Disposition of Patients



1 treatment-emergent adverse event(s)
2 Patients could be withdrawn for more than one reason.
3 Patient 17-002 dropped out at Visit 5 because of a TEAE and intake of nonpermitted change in concomitant medications. The drop-out was anticipated, so regular assessments for this visit were performed.
Source: Applicant's Figure 1, verified

Reviewer comment: TEAE + nonpermited change in concomitant medication is actually due to CF exacerbation.

The final composition of the analysis populations are given in the following table.

Table 3.2 Study CT01 Composition of Analysis Populations

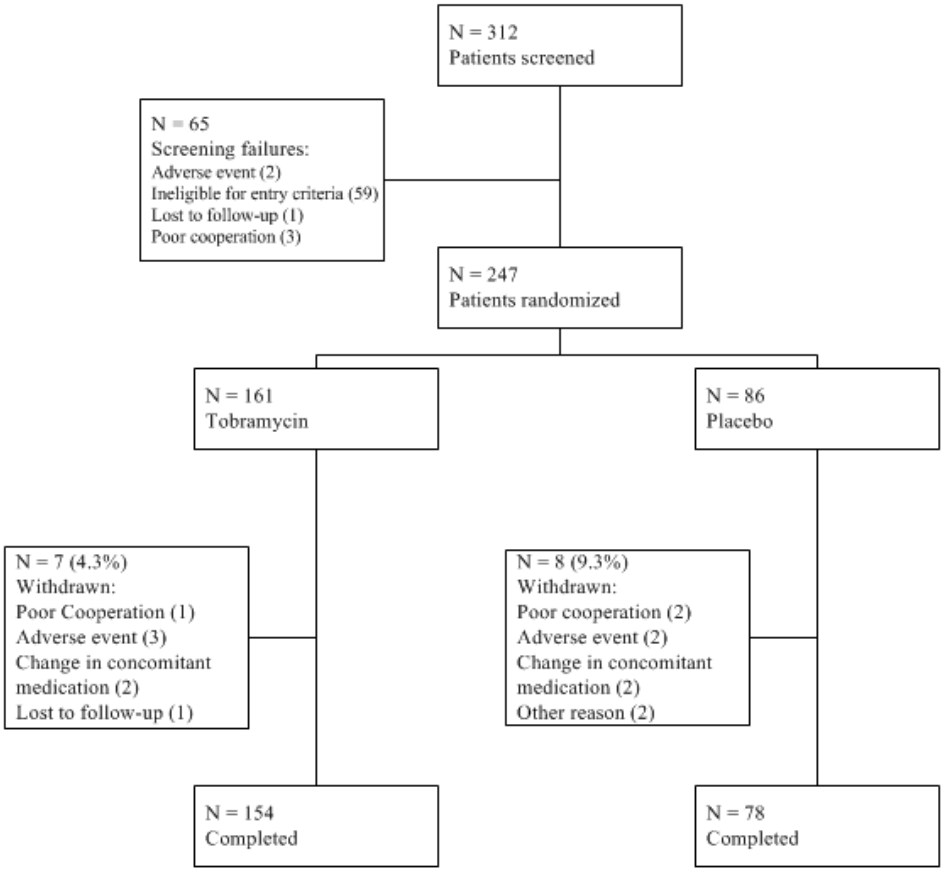
Population	CHF 1538	Placebo
Safety	29	30
Intent-to-Treat	29	30*
Per Protocol	28	28

*Patient 11-001 was excluded from all pulmonary function test analysis as a result of missing baseline data; therefore, the primary analysis was done on N = 58 patients rather than N = 59.

3.1.4.2 Study CT02:

A total of 312 patients were screened for the study in three countries (Hungary, Poland and Russia). Among them, 65 patients (20.8%) were screening failures due to failed enrollment criteria (59 patients), AE (two patients), lost to follow-up (one patient) and poor cooperation (three patients). A total of 247 patients were randomized in 21 centers: eight centers in Hungary, nine centers in Poland and four centers in Russia. A total of 57 patients were randomized in Hungary, 126 in Poland and 64 in Russia. A total of 15 patients (6.1%) were prematurely withdrawn from the study after randomization: seven patients (4.3%) in the CHF 1538 group and eight patients (9.3%) in the Placebo group. The reasons of these withdrawals were AEs (three patients in the CHF 1538 group and two patients in the Placebo group), change in concomitant medication (two patients in each group), poor cooperation (one patient in the CHF 1538 group and two patients in the Placebo group), lost to follow-up (one patient in the CHF 1538 group) and other reasons (two patients in the Placebo group).

Figure 3.2 Study CT02 Disposition of Patients



Source: Applicant's Figure 1, verified

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. The most frequent reason for a major

protocol deviation was inappropriate timing or use of permitted concomitant medications (8.7% of patients in the CHF 1538 group and 9.3% in the Placebo group). The other reasons were use of non-permitted concomitant medications (1.9% of patients in the CHF 1538 group and 4.7% in the Placebo group) and lack of adequate compliance (2.3% in the Placebo group).

Table 3.3 Major Deviations From Protocol

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	**0 (0.0%)**	**2 (2.3%)**	**2 (0.8%)**
Bad compliance (< 70%)	0 (0.0%)	2 (2.3%)	2 (0.8%)

Source: Applicant's Table 6

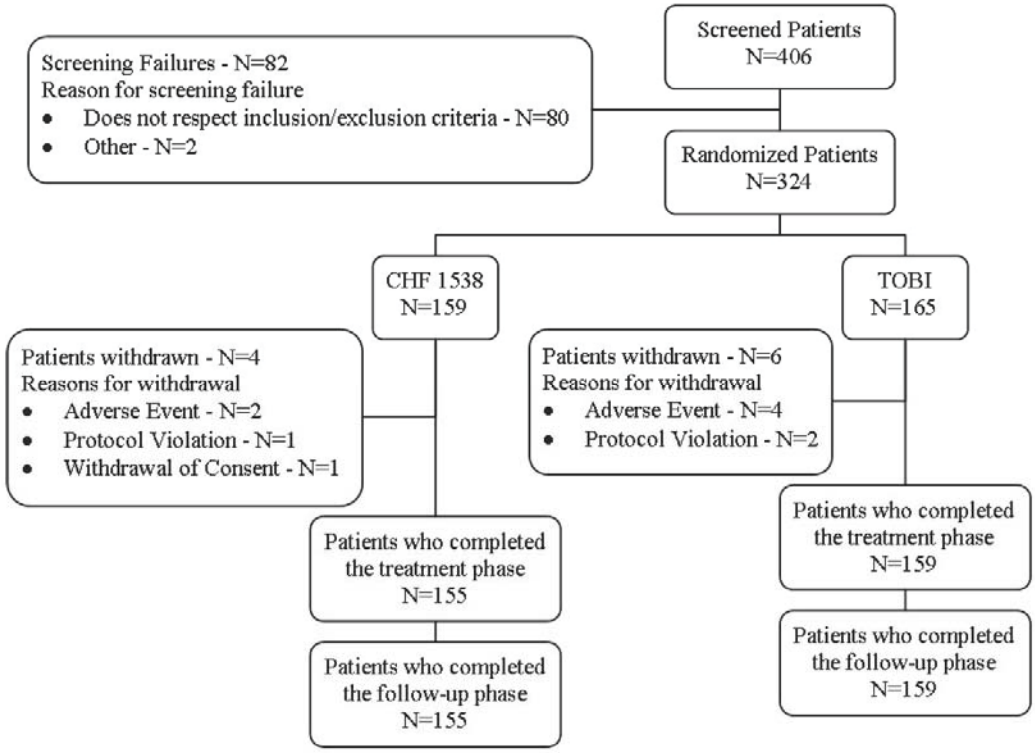
The final composition of the analysis populations are given in the following table.

Table 3.4 Study CT02 Composition of Analysis Populations

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

Reviewer comment: Two randomized patients in the Placebo group were not included in the ITT population. Patient 11008 was randomized at Visit 2 on 30 May 2003, and withdrew consent the same day without taking any trial medication. Patient 32016 was withdrawn at Visit 3 for a TEAE-related to study treatment. These two patients were excluded from all efficacy analyses and only Patient 11008 was also excluded from the safety population. The safety population was composed of a total of 246 patients: 161 patients (100%) in the CHF 1538 group and 85 patients (98.8%) in the Placebo group.

Figure 3.3 Study CT03 Disposition of Patients



Source: Applicant's Figure 1, verified

3.1.4.3 Study CT03

A total of 406 patients were screened for the study of whom 82 (20.2%) failed screening and 324 patients were randomized; 159 to the CHF 1538 group and 165 to the TOBI group. Patients were randomized from eight countries; Czech Republic eight patients, France 10, Germany 4, Spain 5, Hungary 17, Poland 131, Russia 69 and the Ukraine 80. Of the 159 patients randomized to CHF 1538, four patients withdrew; two (1.3%) due to an adverse event, one (0.6%) due to a protocol violation and one (0.6%) withdrew consent leaving a total of 155 patients who completed the treatment phase (Visit 4). Of the 165 patients randomized to TOBI, six withdrew; four (2.4%) due to an adverse event and two (1.2%) due to a protocol violation and a total of 159 completed the treatment phase (Visit 4). In both treatment groups, all the patients who completed the treatment phase (Visit 4) also completed the treatment-free follow up phase (Visit 5).

Table 3.5 Study CT03 Disposition of Patients

	CHF 1538	TOBI	TOTAL (N=324)
Randomized Population	159	165	324 (100%)
Safety Population1			
Reason for exclusion			
Not treated	0	0	0
Number of patients excluded from the Safety population	0	0	0
Number of patients included in the Safety	156	168	324 (100%)

population			
ITT Population2			
Reason for exclusion			
Excluded from the Safety population	0	0	0
No baseline or no post-baseline FEV1 value	1	2	3 (0.9%)
Number of patients excluded from the ITT population	1	2	3 (0.9%)
Number of patients included in the ITT population	158	163	321 (99.1%)
As Treated Population3	155	166	321 (99.1%)

3.1.5 Demographics and Baseline Characteristics

Demographic data for the ITT population are presented in Table 3.6.

Table 3.6 Demographic Data for ITT Population in 3 Studies

	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)	11.0 (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)			17.56 (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%)		

In Study CT01, among 59 ITT patients CHF 1538 and Placebo groups included a relatively equal percentage of male and female patients. However, patients in the Placebo group are generally older, hence heavier and taller. The majority of patients in both CHF 1538 and Placebo groups had chronic colonization with *P. aeruginosa* (defined as continuous presence of *P. aeruginosa* in the lung for more than six months). Additionally, the time since first diagnosed with CF was similar among patients in the CHF 1538 and Placebo groups at approximately 9.6 years.

In Study CT02, among the 245 patients included in the ITT population, 55.1% were male and 44.9% were female. The mean patients' age was 14.8 ± 6.0 years. At baseline (Visit 1), the overwhelming majority of patients had chronic colonization with *P. aeruginosa*. First or intermittent colonization was significantly more frequent in the Placebo group (p=0.045). The

mean time from diagnosis of cystic fibrosis was similar in both treatment groups: 12.1 ± 5.6 years in the CHF 1538 group and 11.8 ± 5.8 years in the Placebo group.

In Study CT03, the ITT population included a relatively equal percentage of male and female patients (48.6% males). The mean age was 15.73 years and ranged from 6 to 46 years; 214 of the 321 (66.7%) were aged 17 years or under. All patients were white. Mean height was 153.15 cm (range 104 to 195 cm), mean weight 43.08 kg (range 15 to 97 kg) and mean BMI was 17.63 kg/m2 (range 11.5 to 28.4 kg/m2). The CHF 1538 and TOBI groups were well balanced with respect to these characteristics. There was a slightly higher proportion of patients age 17 years and under in the TOBI group (69.4%) as compared with the CHF 1538 group (63.9%). The mean time from first CF diagnosis was 11.99 years (range 1.10 to 32.80 years) and was similar among patients in the CHF 1538 and TOBI groups. The median time from diagnosis of chronic colonization with *P. aeruginosa* was 0.33 years. In over 90% of cases in both groups the tobramycin MIC value was < 16 µg/mL for all morphotypes. The FEV_1 % predicted normal was ≥ 50 in 76.9% of patients and 70.4% of patients used rhDNase. The CHF 1538 and TOBI groups were well balanced with respect to these characteristics.

Reviewer comments:

1. *Results from the statistical analysis demonstrated a significant difference between CHF 1538 and Placebo groups with respect to age (p = 0.024), weight (p = 0.003), and height (p = 0.001). Specifically, patients in the Placebo group were aged approximately three years older than patients in the CHF 1538 group, and therefore, patients in the Placebo group were, on average, heavier and taller than those in the CHF 1538 group. Because of these baseline differences, age was included as a covariate in the analysis of the primary efficacy variable to assess its effect on the response to treatment.*
2. *In Study CT02, CHF has more patients with chronic colonization of P. aeruginosa as indicated by the Chi-square test. A sensitivity analysis will be performed to assess its effect on the treatment response.*

3.1.6 Statistical Methodologies

Statistical analysis plans from the three studies vary. However the case study reports were submitted according to the following general principles:

1. Efficacy analyses will be performed on the ITT population but primary efficacy variable analysis will be repeated on the PP population as supportive analysis.

2. Efficacy analyses will be conducted according to the treatment assigned instead of the treatment actually received.

3. Pulmonary function tests and clinical symptoms will be analyzed on patients having at least the assessment at baseline (V2) and the first scheduled post-baseline visit (V4 for CT02).

   Reviewer comment: This was not specified in the SAP for Study CT01.

4. By visit descriptive analysis on FEV1 (% predicted value) will be performed including mean changes from baseline (V2) and their 95% confidence interval.

5. Primary efficacy analysis: FEV1 (% predicted value) between treatment groups will be compared using an ANCOVA with treatment group as main effect and baseline value (V2) as covariate. The estimated difference between groups and its 95% CI will be provided, as well as the corresponding unilateral p-value.

   Reviewer comments:
   i. *In CT01's SAP, formal comparisons will use baseline value as covariate and with centers and treatment as factors. Values at the end of the run-out period will be compared to those measured after 4 weeks of treatment by means of paired t-test.*
   ii. *In CT02's SAP, if the size of patients is not too unbalanced (not less than 25% in one class) between the 2 classes of differential diagnosis (chronic or first/intermittent colonization of P. aeruginosa, a preliminary test for the differential diagnosis by treatment interaction will be performed at 0.10 significance level. In case of significance level 2! 0.10, the differential diagnosis by treatment interaction will be removed from the model.*

6. Secondary efficacy analysis: All pulmonary function tests, CFUs and MIC_{90} variables will be analyzed as for the primary efficacy variable. Categorical results will be summarized (standard descriptive statistics) and compared between treatment groups (Chi-square or Fisher's exact test) at each visit. Pulmonary exacerbation variables will be summarized using standard descriptive statistics. In addition, comparison between treatment groups will be made using the appropriate statistical tests (Chi-square or Fisher's exact test for the frequency of subjects with at least one exacerbation, Student t test for the total number of exacerbations by subject). Wheezing and cough scores will be analyzed as for the primary efficacy variable. Each body measurement variable will be analyzed as for the primary safety variable. Hospitalization variables will be analyzed as for the pulmonary exacerbation variables). Loss of school/work days variables will be analyzed as for the pulmonary exacerbation variables. Use of parenteral tobramycin variables will be analyzed as for the pulmonary exacerbation variables.

   Reviewer comment: In CT01 SAP, it was stated that the formal comparisons will use baseline, centers and treatment group as co-variates.

7. Handling of missing data: For analyses that require complete patient data, missing values during the treatment period are replaced, for all primary and secondary variables, with the LOCF technique (Last Observation Carried Forward). If a subject has only basal primary or secondary variable value, no replacement will be done and the subject will be excluded from the LOCF analysis for that particular primary or secondary efficacy variable. The LOCF technique will be applied only on variables collected during the treatment period. Missing data at follow-up visit will not be replaced.

   Reviewer comments:
   i. *In CT01, the SAP calls for no specific technique to handle missing data.*

ii. *In CT03, to assess for robustness of the primary analysis results, the effect of imputing missing values using LOCF approach for patients who discontinued before Visit 4 (end of treatment phase) will be examined using a sensitivity analysis. A mixed effects model for repeated measures (MMRM) based on all observed post baseline FEV1 % predicted values over time will be used to compare treatment effects. The MMRM will include treatment group, country, visit and treatment group-by-visit interaction as fixed effects and baseline and baseline-by-visit interaction as covariates. An unstructured covariance will be used to model the correlation over time in change from baseline in FEV1 % predicted.*

3.1.7 Analysis Results

3.1.7.1 Primary Efficacy Result from Study CT01

Administration of CHF 1538 increased FEV_1 % predicted normal. FEV_1 % predicted normal had increased by 13.5% at Week 2 and 16.0% at Week 4 above baseline values for CHF 1538-treated patients (see Table 3.7). In contrast, minimal changes in FEV_1 % predicted normal were observed in the Placebo group. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups was significant at both Week 2 and 4.

After four weeks of CHF 1538 withdrawal, mean FEV_1 % predicted normal in the CHF 1538 group decreased to near baseline values such that there was no statistical difference between the response of the placebo and CHF 1538 groups at Visit 5 or Week 8 (Table 3.7). Therefore, by the end of the run-out period, mean FEV_1 % predicted normal values were relatively equivalent among patients in the placebo and CHF 1538 groups.

Table 3.7 FEV1 % Predicted Normal1 Mean Baseline and Mean Change From Baseline with LOCF Used for "ON" Drug Visits: ITT Population

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

Note: The shaded row indicates the primary endpoint

In the table above, missing pulmonary function data were replaced by using the LOCF method that was applied to data measured at Visit 3 and carried forward to Visit 4. For example, for a patient who discontinued after the assessment at Visit 3, the patient's Visit 3 value (for parameters measured at this visit) was used in the LOCF analysis. If a patient had only a baseline primary or secondary variable value, no replacement was made and the patient was excluded from the LOCF analysis for that particular primary or secondary efficacy variable. Taking into

account that study drug was discontinued at Visit 4 (end of treatment period), the LOCF method was not applied in patients who discontinued the study after that visit, thus having no values carried forward to Visit 5 (end of run-out period). If patients discontinued after Visit 4 (end of the treatment period), the LOCF method was not applied to carry forward data to Visit 5 (end of runout period).

To assess the affect of missing observation on the results, two additional sensitivity analyses were performed. The first sensitivity analysis uses Multiple Imputation procedure in SAS. Five observations were generated using change from baseline in Visit 3 and 4 to impute missing data in these visits. In a similar manner, five observations were generated using change in from Visit 4 and 5 to impute missing data in Visit 5. Then a mixed model is fitted with treatment group as main effect and baseline value (V2) as covariate for each imputation; hence, generating five sets of estimates for the parameters. Then these parameters are aggregated through the MIANALYZE procedure in SAS to get the treatment effect at each visit which is given in Table 3.8.

Table 3.8 Sensitivity Analysis FEV1 % Predicted Normal1 Mean Baseline and Mean Change From Baseline with Multiple Imputation on Missing Data : ITT Population

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

Note: The shaded row indicates the primary endpoint

In this table (Table 3.8), FEV_1 % 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 FEV_1 % predicted normal were 0.5% in Week 2 and 4.9% in Week 4 in the Placebo group. As a result, the difference in mean changes from baseline between the CHF 1538 and placebo groups were 12.8% in Week 2 and 11.0% in Week 4. These mean changes, although lower than what is observed in Table 3.7, Visit 3 and 4, are still significant at both weeks.

Table 3.9 Sensitivity Analysis FEV1 % Predicted Normal1 Mean Baseline and Mean Change From Baseline with Worst Outcome Imputation on Missing Data : ITT Population

Visit	Week		CHF 1538 (%)	Placebo (%)	P-Value
2	Baseline	N	29	29	
		Mean	57.7	59.8	0.580
3	2	N imputed	0	2	
	"ON" Drug	Mean Change from Baseline	13.3	-2.7	0.001
		Difference (95% CI)	16.0 (7.1, 24.9)		
4	4	N imputed	0	3	
	"ON" Drug	Mean change from Baseline	16.0	2.7	0.003
	(1° endpoint)	Difference (95% CI)	13.3 (4.7, 21.8)		
5	8	N imputed	2	7	

	"OFF" Drug	Mean Change from Baseline	3.0	-3.9	0.258
		Difference	6.8 (-5.2, 18.8)		

Note: The shaded row indicates the primary endpoint

The other sensitivity analysis uses the worst change from baseline observed from Visits 3, 4, and 5. The rationale for using worst observation is based on the fact that missing data happen because patients experienced CF exacerbations and are either withdrawn or given additional prohibited concomitant antibiotics. In most cases, it was observed that a decrease in pulmonary function preceeds the missing observations. Had these patients remain on the same course of treatment and/or are not withdrawn, it can be expected that the FEV1 % predicted value at any of these missing Visits will be lower and can be conservatively estimated by the worst change from baseline observed from the group.

Using imputation by worst observation, FEV_1 % predicted normal had increased by 13.3% at Week 2 and remained 16.0% at Week 4 above baseline values for CHF 1538-treated patients (See Table 3.9). In contrast, changes in FEV_1 % predicted normal decreased by 2.7%% in Week 2 and increased by 2.7% 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 16.0% in Week 2 and 13.3% in Week 4. These mean changes are still significant at both weeks.

The stark contrast in these results is due to the fact that most missing observations happen in the placebo group. Replacing the missing by the worst observation attenuates the difference in the treatment effect of CHF 1538 over placebo. On the other hand, by using multiple imputation which uses the covariance between two observations Visit 3 and Visit 4, the imputed value shrinks to the average tendency in these Visits, i.e., increase in pulmonary function. Hence, the approach yields a more conservative estimate of the difference in the treatment effect of CHF 1538 over placebo.

Table 3.10 FEV1 % Predicted Normal Mean Baseline and Mean Change From Baseline Adjusted by AGE with LOCF Used for "ON" Drug Visits: ITT Population

Visit	Week		CHF 1538 (%)	Placebo (%)	P-Value
2	Baseline	N	29	29	
		Mean	57.7	59.8	0.580
3	2	N			
	"ON" Drug	Mean Change from Baseline	12.4	1.1	0.01
		Difference (95% CI)	11.3 (2.7, 19.9)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline	15.3	3.4	0.01
	(1° endpoint)	Difference (95% CI)	11.9 (3.0, 20.8)		
5	8	N			
	"OFF" Drug	Mean Change from Baseline	4.9	8.8	0.454
		Difference	-3.8 (-14.0, 6.4)		

Note: The shaded row indicates the primary endpoint

A third sensitivity analysis, not related to treatment of missing data, is conducted because of a baseline imbalance with respect to age. The results of this analysis showed that the imbalance has no statistically significant effect FEV1% predicted normal results on Visit 3, 4, and 5. Nevertheless, FEV_1 % predicted normal had increased by 12.4% at Week 2 and marginally

increased at 15.3% at Week 4 above baseline values for CHF 1538-treated patients (see Table 3.10). In contrast, changes in FEV_1 % predicted normal increased by 1.1% in Week 2 and increased by 3.4% 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 11.3% in Week 2 and 11.9% in Week 4. Table 3.11 gives a similar result using multiple imputations for missing observations.

Table 3.11 FEV1 % Predicted Normal Mean Baseline and Mean Change From Baseline Adjusted by AGE with Multiple Imputation on Missing Data: ITT Population

Visit	Week		CHF 1538 (%)	Placebo (%)	P-Value
2	Baseline	N	29	29	
		Mean	57.7	59.8	0.580
3	2	N			
	"ON" Drug	Mean Change from Baseline	12.4	1.4	0.01
		Difference (95% CI)	11.0 (2.2, 19.7)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline	15.2	5.7	0.02
	(1° endpoint)	Difference (95% CI)	9.5 (1.2,17.8)		
5	8	N			
	"OFF" Drug	Mean Change from Baseline	6.1	9.5	0.463
		Difference	-3.5 (-12.7, 5.8)		

Note: The shaded row indicates the primary endpoint

For analysis results of secondary pulmonary functions please see Appendix.

3.1.7.2 Primary Efficacy Result and Time to First Exacerbation from Study CT02

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 (see Table 3.12). The mean change from baseline to endpoint in FEV1 % of predicted normal was 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).

Table 3.12 FEV1 % Predicted Normal1 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	N			
	"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			
	"ON" Drug	Mean change from Baseline	7.82	0.51	< 0.001
		Difference (95% CI)	7.32 (4.24, 10.40)		
5	8	N	159	83	
	"OFF" Drug	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)		

In the table above, missing pulmonary function data were replaced by using the LOCF method that was applied to data measured at Visit 3 and carried forward to Visit 4, 6, and 8. For example, for a patient who discontinued after the assessment at Visit 3, the patient's Visit 3 value (for parameters measured at this visit) was used for Visit 4, 6, and 8 in the LOCF analysis. For a patient who discontinued after the assessment at Visit 4, the patient's Visit 4 value (for parameters measured at this visit) was used for Visit 6, and 8 in the LOCF analysis. If a patient had only a baseline primary or secondary variable value, no replacement was made and the patient was excluded from the LOCF analysis for that particular primary or secondary efficacy variable. Taking into account that study drug was discontinued at Visit 4 (end of treatment period), the LOCF method was not applied in patients who discontinued the study after that visit, thus having no values carried forward to Visit 5 (end of run-out period). If patients discontinued after Visit 4 (end of the treatment period), the LOCF method was not applied to carry forward data to Visit 5 (end of runout period).

To assess the affect of missing observation on the results, two sensitivity analyses were performed. The first sensitivity analysis uses Multiple Imputation procedure in SAS. Five observations were generated using change from baseline in Visit 4 and 5 to impute missing data in these visits. In a similar manner, five observations were generated using change in from Visit 4, 5 and 6 to impute missing data in Visit 6, five observations were generated using change in from Visit 5, 6 and 7 to impute missing data in Visit 7, five observations were generated using change in from Visit 5, 7 and 8 to impute missing data in Visit 8, and five observations were generated using change in from Visit 7, 8 and 9 to impute missing data in Visit 9. Then a mixed model is fitted with treatment group as main effect and baseline value (V2) as covariate for each imputation; hence, generating five sets of estimates for the parameters. Then these parameters are aggregated through the MIANALYZE procedure in SAS to get the treatment effect at each visit which is given in Table 3.13.

Table 3.13 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	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 “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)		

Note: The shaded row indicates the primary endpoint

Table 3.14 FEV1 % Predicted Normal Mean Baseline and Mean Change From Baseline with Worst Observation 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 (24, 10.40)		
5	8 “OFF” Drug	N imputed	2	1	
		Mean Change from Baseline	4.03	1.38	0.1249
		Difference	2.66 (-0.74, 6.05)		
6	12 “ON” Drug	N imputed	3	3	
		Mean Change from Baseline1,2	6.26	0.48	0.004
		Difference (95% CI)	5.78 (1.85, 9.70)		
7	16 “OFF” Drug	N imputed	3	4	
		Mean Change from Baseline1,2	5.26	-1.53	0.001
		Difference (95% CI)	6.79 (2.77, 10.82)		
8	20 “ON” Drug (1° endpoint)	N imputed	4	5	
		Mean Change from Baseline1,2	5.78	-1.99	<0.001
		Difference (95% CI)	7.78 (3.62, 11.93)		
9	24 “OFF” Drug	N imputed	7	6	
		Mean Change from Baseline1,2	3.56	-4.24	<0.001
		Difference (95% CI)	7.80 (3.42, 12.18)		

Note: The shaded row indicates the primary endpoint

Using multiple imputation, FEV_1 % 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 (See Table 3.13). In contrast, changes in FEV_1 % 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. These mean changes, however, are generally lower than what is observed in Table 3.12 that was obtained using LOCF.

The other sensitivity analysis uses the worst change from baseline observed from Visits 3 to 8. However, if this change is more than the baseline value in a particular patient then the latter is used to impute for the missing values in that patient. The results of this analysis are shown in Table 3.14. In this stable, FEV_1 % predicted normal had increased by 8.02% at Week 2 and 7.82 % at Week 4, 6.26% at Week 12 and 5.78% at Week 20 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV_1 % predicted normal were 1.91% in Week 2, 0.51% in Week 4, 0.48% in Week 12, and -1.99% 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 still significant in all the "ON" periods.

Table 3.15 Exclusion of Sites 26 and 32: 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	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)		
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	6.81	2.91	0.045
		Difference (95% CI)	3.90 (0.09, 7.72)		
		N imputed	3	4	
7	16 "OFF" Drug	Mean Change from Baseline1,2	5.96	0.94	0.017
		Difference (95% CI)	5.01 (0.87, 9.16)		
		N imputed	3	4	
8	20 "ON" Drug (1° endpoint)	Mean Change from Baseline1,2	6.71	1.27	0.009
		Difference (95% CI)	5.45 (1.34, 9.56)		
		N imputed	6	5	
9	24 "OFF" Drug	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

During inspection conducted by the DSI, two sites were identified to be problematic. One site in Poland (Site #26, Dr. Maria Trawinska Barnicka, n=29) has discrepancies in the calculation of FEV1% predicted values. The other site (Site #32, Dr Nikolai Kapranov, n=24) has with drug accountability issues based on preliminary report. A sensitivity analysis excluding these sites is conducted and the results are shown in Table 3.15. 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. As a result, the comparison of mean changes from baseline between the CHF 1538 and placebo groups were still significant in all the "ON" periods.

Table 3.16 FEV1 % Predicted Normal Mean Baseline and Mean Change From Baseline Accounting for Colonization of P. aeruginosa 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	9.05	2.74	<0.001
		Difference (95% CI)	6.31 (3.26, 9.36)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	7.41	0.17	<0.001
		Difference (95% CI)	7.23 (4.13, 10.34)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	5.20	2.13	0.0536
		Difference	3.07 (-0.05, 6.18)		
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	9.03	3.68	0.002
		Difference (95% CI)	5.35 (2.02, 8.68)		
		N imputed	3	4	
7	16 "OFF" Drug	Mean Change from Baseline1,2	8.29	2.47	<0.001
		Difference (95% CI)	5.82 (2.38, 9.27)		
	20 "ON" Drug	N imputed	4	5	
8	(1° endpoint)	Mean Change from Baseline1,2	8.80	2.18	<0.001
		Difference (95% CI)	6.62 (3.09, 10.16)		
		N imputed	7	6	
9	24 "OFF" Drug	Mean Change from Baseline1,2	7.41	0.06	<0.001
		Difference (95% CI)	7.34 (3.79, 10.90)		

Note: The shaded row indicates the primary endpoint

As noted earlier, CHF treatment group has more patients with chronic colonization of *P. aeruginosa*. To assess its effect on the treatment response difference, a sensitivity analysis is performed. The results are shown in Table 3.16. Using multiple imputations for missing observations, FEV_1 % predicted normal had increased by 9.05% at Week 2 and 7.41% at Week 4, 9.03% at Week 12 and 8.80% at Week 20 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV_1 % predicted normal were 2.74% in Week 2, 0.17% in Week 4, 3.68% in Week 12, and 2.18% in Week 20 in the Placebo group. The comparison of mean changes from baseline between the CHF 1538 and placebo groups were still significant in all the "ON" periods.

Table 3.17 Exclusion of Sites 26 and 32: FEV1 % Predicted Normal Mean Baseline and Mean Change From Baseline Accounting for Colonization of P. aeruginosa with Multiple- ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	126	67	
		Mean	60.28	62.75	0.281
3	2	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	9.39	3.12	<0.001
		Difference (95% CI)	6.27 (2.61, 9.92)		
4	4	N imputed	0	0	

	"ON" Drug	Mean change from Baseline	7.45	0.61	<0.001
		Difference (95% CI)	6.84 (3.12, 10.55)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	6.06	2.36	0.050
		Difference	3.69 (-0.00, 7.39)		
		N imputed	2	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	8.97	4.50	0.023
		Difference (95% CI)	4.47 (0.61, 8.34)		
		N imputed	2	4	
7	16 "OFF" Drug	Mean Change from Baseline1,2	9.02	3.17	0.006
		Difference (95% CI)	5.84 (1.67, 10.02)		
		N imputed	4	4	
8	20 "ON" Drug (1° endpoint)	Mean Change from Baseline1,2	10.14	3.74	0.002
		Difference (95% CI)	6.40 (2.28, 10.51)		
		N imputed	4	4	
9	24 "OFF" Drug	Mean Change from Baseline1,2	9.41	1.71	<0.001
		Difference (95% CI)	7.70 (3.53, 11.87)		

Note: The shaded row indicates the primary endpoint

For analysis results of secondary pulmonary functions please see Appendix.

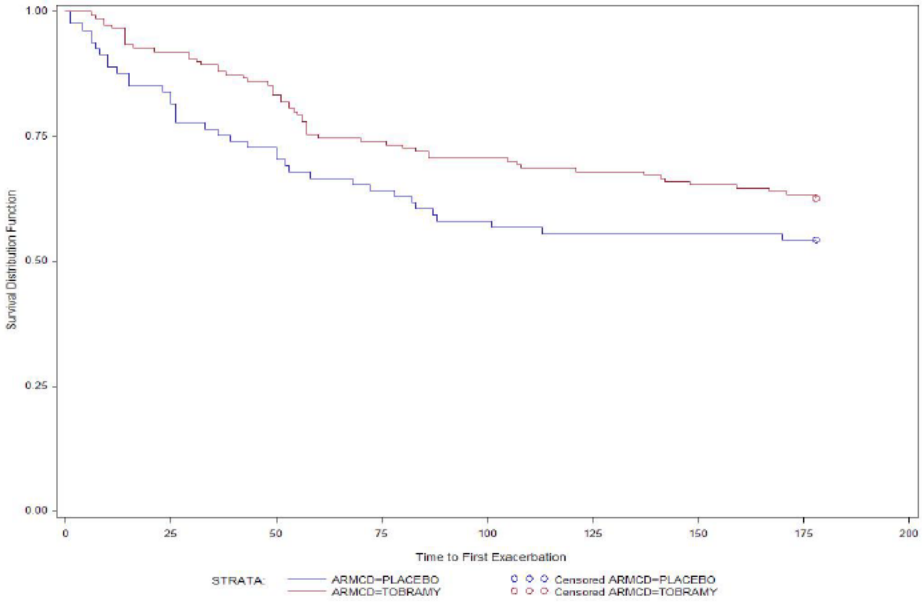
A comparison of the number and percentage of patients with pulmonary exacerbation in each treatment group at all visits is presented in Table 3.18. A pulmonary exacerbation was defined as the presence of at least three of 11 pre-defined symptoms. However, in the following table pulmonary exacerbation 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 3.18 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 3.4 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 3.4 and so will not be shown.

Figure 3.4 Time to First Exacerbation: ITT Population



3.1.7.3 Primary Efficacy Result from Study CT03

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 3.19). 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). CHF 1538 is not inferior to TOBI because the lower limit of the 95% CI is within the pre-specified non inferiority margin of -4.5%.

Table 3.19 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

The ANCOVA model used in the Applicant's analysis adjusts for baseline and country. In the original statistical analysis, however, the predefined model only adjusts for baseline. The results of this pre-specified analysis are shown below. Using the ANCOVA model the least squares (LS) means of the change from baseline in FEV_1 % predicted normal were 7.01% in the CHF

1538 group and 7.50% in the TOBI group with a difference of -0.49 (95% CI: -2.58 to 1.61). From the results, the effect of country is quite substantial.

Table 3.20 FEV1 % Predicted Normal1 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

The Applicant investigated the difference in response among the countries in a post hoc analysis by country. They stated that the majority of patients were randomized in Poland, Russia and Ukraine where the changes from baseline in FEV_1 % predicted normal to Weeks 2 and 4 were positive and relatively similar in both treatment groups. In Poland, the mean change in FEV_1% predicted normal at Visit 4 was 6.93% and 8.26% in the CHF 1538 and TOBI group, respectively; in Russia, it was 6.52% in the CHF 1538 group and 6.95% in the TOBI group, while in Ukraine it was 9.24% and 8.71%. Smaller changes from baseline were observed in the Czech Republic, France, Germany, Hungary and Spain where 17 patients or fewer were randomized per country. The reviewer, however, could not identify potential reasons for such variation in results.

Table 3.21 FEV1 % Predicted Normal1 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

Another sensitivity analysis is performed this time using multiple imputations for the missing observations in Visit 4 and Visit 5. In this analysis, the least squares (LS) means of the change from baseline in FEV_1 % predicted normal were 4.75% in the CHF 1538 group and 5.27% in the TOBI group with a difference of -0.51 (95% CI: -2.60 to 1.57) (see Table 3.21). The amount of

missing observations hardly changes the analysis results in Table 3.19. As a result, imputation by worst observation will not be performed as it is redundant.

For analysis results of secondary pulmonary functions please see Appendix.

3.2 Evaluation of Safety

3.2.1 Extent of exposure

Overall, mean extent of exposure is similar across treatment groups in all three studies.

In CT01, the mean extent of exposure to CHF 1538 BID in the safety population was 29.9 ± 2.3 days (range: 26 to 37 days) in the CHF 1538 group. The mean extent of exposure to nebulized placebo was 29.2 ± 6.9 days (range: 14 to 48 days) in the Placebo group.

In Study CT02, extent of exposure data are presented in Table 3.22. The mean extent of exposure to study drug for the Safety Population was 87.5 ± 8.3 days (range 26 to 104 days) in the CHF 1538 group and 85.8 ± 14.5 days (range 4 to 102 days) in the Placebo group.

Table 3.22 Duration of Exposure by Treatment Group: Safety Population

Duration (days)	CHF 1538 (N=161)	PLACEBO (N=85)
Mean	87.5	85.8
Median	88	88
Standard Deviation	8.3	14.5
Range	26-104	4-102

Source: Applicant's Table 31

In Study CT03, the mean extent of exposure in the safety population was 29.08 ± 2.91 days (range: 4 to 34 days) in the CHF 1538 group and 28.67 ± 4.33 days (range: 1 to 35 days) in the TOBI group.

3.2.2 Overview of TEAE Profile

In general, a lower percentage of patients randomized to CHF 1538 reported TEAEs than patients randomized to placebo while similar percentages of patients in CH1538 and TOBI reported TEAEs and treatment related TEAEs (ADRs)

In Study CT01, no patient treated with CHF 1538 was withdrawn from the study because of a TEAE as opposed to five patients (16.7%) in the Placebo group. A greater percentage of Placebo patients had treatment-emergent SAEs; one patient in the Placebo group died during the study. The majority of these serious and significant TEAEs resulted from the worsening of the patients' underlying condition.

Table 3.23 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%)
Total number of treatment-emergent SAEs[3, 4]	20	27
Number of patients with treatment-emergent SAE(s)	17 (10.6%)	22 (25.9%)
Number of patients who died	1 (0.6%)	2 (2.4%)
Number of patients withdrawn from study	7 (4.3%)	8 (9.4%)
Due to TEAE	3 (1.9%)	2 (2.4%)
Not due to TEAE	4 (2.5%)	6 (7.1%)

1 Treatment-emergent adverse events 2 Adverse drug reactions (TEAEs classified as possibly, probably/likely, or certainly/definitely related to treatment) 3 Serious adverse events
4 Patient 26009, a 24 year-old female, was not eligible for the study but experienced a severe SAE (coded to pneumonia) two days after her screen failure and withdrawal from the study. The patient recovered. This patient's information is not used in any safety analysis.
Source: Applicant's Table 33

In Study CT02, a total of 1344 TEAEs were reported by 216 patients. The frequency of patients reporting TEAEs was lower in the CHF 1538 group (84.5%) than in the Placebo group (94.1%). The percentage of patients reporting ADRs was essentially equivalent in both treatment groups (15.5% CHF 1538 patients vs. 15.3% Placebo patients). A lower percentage of CHF 1538 patients (10.6%) reported treatment emergent SAEs than in the Placebo patients (25.9%). Three patients died due to TEAEs; one patient (0.6%) in the CHF 1538 group and two patients (2.4%) in the Placebo group. Five patients withdrew from this study due to a TEAE, with approximately equivalent percentages of patients in either treatment group (1.9% in the CHF 1538 group vs. 2.4% in the Placebo group).

In Study CT03, similar percentages of patients in both groups reported TEAEs and treatment related TEAEs (ADRs). In the CHF 1538 group 49 (31.4%) patients reported 102 events and in the TOBI group 47 (28.0%) patients reported 80 events. Adverse drug reactions were reported by 10 (6.4%) patients in the CHF 1538 group and 10 (6.0%) patients in the TOBI group. One patient (0.6%) treated with CHF 1538 was withdrawn from the study because of a TEAE as opposed to five patients (3.0%) in the TOBI group. A greater percentage of CHF 1538-treated patients had serious TEAEs (six patients, 3.8%) compared with the TOBI group (two patients, 1.2%). None of the SAEs was assessed as related to study drug. No patients died during the study.

3.2.3 Analysis of Adverse Events

In Study CT01, exacerbation of patients' underlying disease was the most frequently reported TEAE for both groups occurring at a similar frequency (10.3 vs. 13.3%, respectively for CHF 1538 vs. placebo).

In Study CT02 in general, respiratory, thoracic and mediastinal disorders were the most commonly reported TEAEs in both groups (67.7% patients in the CHF 1538 group and 78.8% patients in the Placebo group). Overall, a higher percentage of Placebo patients reported TEAEs than did the CHF 1538 patients.

In study CT03, similar percentages of patients in both groups reported TEAEs. The Applicant reported that in the CHF 1538 group 49 (31.4%) patients reported 102 TEAEs and in the TOBI group 47 (28.0%) patients reported 80 TEAEs. The most frequently reported TEAEs (reported with similar frequency in both groups) were in the SOC Infections and Infestations (16.7% and 14.9% of patients for CHF 1538 and TOBI, respectively) followed by the SOC Respiratory, Thoracic and Mediastinal Disorders (10.3% and 11.9% of patients for CHF 1538 and TOBI, respectively).

Please refer to Medical Officer's review for a detailed analysis of safety and adverse events in the three studies.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender and Age

In Study CT01, majority of the patients are 13 years and older. In this age category, the difference in the mean change from baseline of FEV1 % predicted normal is significant on Visit 3 and 4 which corresponds to the ON drug visit. The difference in the mean change from baseline of FEV1 % predicted normal is numerically higher for the CHF 1538 group than the Placebo group in age category 6-12 years.

Table 4.1FEV1 % Predicted Norma1 Mean Baseline and Mean Change From Baseline with LOCF on Missing "ON" Visits: By Age Group

Visit	Week		CHF 1538	Placebo	P-Value
AGE 6-12					
2	Baseline	N	7	3	
		Mean	55.31	56.90	0.8994
3	2	N	7	3	
	"ON" Drug	Mean Change from Baseline	14.92	5.03	0.1423
		Difference (95% CI)	9.89 (-4.26, 24.02)		
4	4	N	3	7	
	"ON" Drug (1° endpoint)	Mean change from Baseline	12.89	6.05	0.451
		Difference (95% CI)	6.84 (-13.41, 27.09)		
5	8	N	7	2	
	"OFF" Drug	Mean Change from Baseline	8.72	9.47	0.944
		Difference	-0.75 (-25.80, 24.29)		
AGE 13 and older					
2	Baseline	N	22	26	
		Mean	58.41	60.09	0.694
3	2	N	22	24	
	"ON" Drug	Mean Change from Baseline	12.84	-0.58	0.008
		Difference (95% CI)	13.41 (3.68, 23.14)		
4	4	N	22	26	
	"ON" Drug (1° endpoint)	Mean change from Baseline	16.98	2.26	0.005
		Difference (95% CI)	14.72 (4.80, 24.64)		
5	8	N	20	20	
	"OFF" Drug	Mean Change from Baseline	5.39	6.89	0.789
		Difference	-1.50 (-12.80, 9.79)		

Analysis of the primary efficacy variable by gender reveals similar trends with the whole ITT population. Caution has to be exercised in interpreting significance in these results due to multiplicity problem.

Table 4.2 FEV1 % Predicted Norma1 Mean Baseline and Mean Change From Baseline with LOCF on Missing "ON" Visits: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
Males					
2	Baseline	N	15	17	
		Mean	54.15	55.31	0.8248
3	2	N	15	16	
	"ON" Drug	Mean Change from Baseline	14.68	2.98	0.060

		Difference (95% CI)	11.70 (-0.54, 23.95)		
4	4	N	15	17	
	"ON" Drug	Mean change from Baseline	14.17	3.36	0.089
	(1° endpoint)	Difference (95% CI)	10.81 (-1.75, 23.36)		
5	8	N	15	13	
	"OFF" Drug	Mean Change from Baseline	2.92	11.03	0.171
		Difference	-8.11 (-19.96, 3.75)		
	FEMALES				
2	Baseline	N	14	12	
		Mean	61.43	66.07	0.344
3	2	N	14	11	
	"ON" Drug	Mean Change from Baseline	11.59	-3.82	0.017
		Difference (95% CI)	15.41 (3.07, 27.75)		
4	4	N	14	12	
	"ON" Drug	Mean change from Baseline	18.14	1.42	0.011
	(1° endpoint)	Difference (95% CI)	16.71 (4.25, 29.18)		
5	8	N	12	9	
	"OFF" Drug	Mean Change from Baseline	9.41	2.83	0.431
		Difference	6.59 (-10.61, 23.79)		

In Study CT02, majority of the patients are again13 years and older. In this age category, the difference in the mean change from baseline of FEV1 % predicted normal is significant on all visits except Visit 5 which corresponds to the end of the OFF cycle. For age category 6-12 no meaningful inference can be made due to small sample size.

Table 4.3 FEV % Predicted Norma1 Mean Baseline and Mean Change From Baseline with LOCF Used for Missing "ON" Drug Visits: Age 6-12 ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	15	8	
		Mean	69.69	66.04	0.721
3	2	N	15	8	
	"ON" Drug	Mean Change from Baseline	10.27	1.54	0.020
		Difference (95% CI)	8.72 (1.56, 15.90)		
4	4	N	15	8	
	"ON" Drug	Mean change from Baseline	8.93	2.11	0.151
		Difference (95% CI)	6.82 (2.71, 16.34)		
5	8	N	14	8	
	"OFF" Drug	Mean Change from Baseline	5.98	4.98	0.859
		Difference	0.99 (-10.50, 12.48)		
		N	15	8	
6	12 "ON" Drug	Mean Change from Baseline	10.28	5.37	0.351
		Difference (95% CI)	4.90 (-5.80, 15.61)		
		N	14	8	
7	16 "OFF" Drug	Mean Change from Baseline	7.46	8.39	0.881
		Difference (95% CI)	-0.94 (-13.84, 11.92)		
		N	15	8	
8	20 "ON" Drug	Mean Change from Baseline	10.30	6.23	0.475
		Difference (95% CI)	4.07 (7.60, 15.75)		
		N	14	8	
9	24 "OFF" Drug	Mean Change from Baseline	6.93	5.51	0.815
		Difference (95% CI)	1.42 (-11.09, 13.93)		

Table 4.4 FEV % Predicted Norma1 Mean Baseline and Mean Change From Baseline with LOCF Used for Missing "ON" Drug Visits: Age 13 and older ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	146	76	
		Mean	60.36	63.34	0.1627
3	2	N imputed	146	76	
	"ON" Drug	Mean Change from Baseline	7.79	1.95	<0.001
		Difference (95% CI)	5.84 (2.57, 9.11)		
4	4	N	146	76	
	"ON" Drug	Mean change from Baseline	7.71	0.34	<0.001
		Difference (95% CI)	7.37 (4.09, 10.64)		
5	8	N	145	75	
	"OFF" Drug	Mean Change from Baseline	4.57	1.57	0.068
		Difference	3.00 (-0.23, 6.23)		
		N	146	76	
6	12 "ON" Drug	Mean Change from Baseline	7.02	1.95	0.005
		Difference (95% CI)	5.07 (1.54, 8.60)		
		N	146	75	
7	16 "OFF" Drug	Mean Change from Baseline	6.03	-0.13	<0.001
		Difference (95% CI)	6.17 (2.58, 9.75)		
		N	146	76	
8	20 "ON" Drug	Mean Change from Baseline	6.62	0.01	<0.001
		Difference (95% CI)	6.61 (2.96, 10.26)		
		N	146	75	
9	24 "OFF" Drug	Mean Change from Baseline	5.82	-1.91	<0.001
		Difference (95% CI)	7.73 (4.05, 11.41)		

As for the treatment effect by gender, it is hard to make conclusions that CHF 1538 is more effective in males. However, both groups tend to behave similarly as the ITT population.

Table 4.5 FEV % Predicted Norma1 Mean Baseline and Mean Change From Baseline with LOCF Used for Missing "ON" Drug Visits: Males ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	89	46	
		Mean	62.03	64.85	0.272
3	2	N	89	46	
	"ON" Drug	Mean Change from Baseline	8.42	2.62	0.009
		Difference (95% CI)	5.80 (1.49, 10.11)		
4	4	N	89	46	
	"ON" Drug	Mean change from Baseline	8.85	0.54	<0.001
		Difference (95% CI)	8.31 (4.15, 12.48)		
5	8	N	88	46	
	"OFF" Drug	Mean Change from Baseline	5.98	1.41	0.034
		Difference	4.56 (0.34, 8.78)		
		N	89	46	
6	12 "ON" Drug	Mean Change from Baseline	9.35	3.06	0.006
		Difference (95% CI)	6.29 (1.82, 10.77)		
		N	88	46	
7	16 "OFF" Drug	Mean Change from Baseline	7.23	0.83	0.003
		Difference (95% CI)	6.40 (2.17, 10.64)		
8	20 "ON" Drug	N	89	46	

		Mean Change from Baseline	8.17	0.31	0.001
		Difference (95% CI)	7.87 (3.15, 12.58)		
		N	88	46	
9	24 “OFF” Drug	Mean Change from Baseline	6.30	-1.81	<0.001
		Difference (95% CI)	8.11 (3.39, 12.83)		

Table 4.6 FEV % Predicted Norma1 Mean Baseline and Mean Change From Baseline with LOCF Used for Missing “ON” Drug Visits: Females ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	72	38	
		Mean	59.00	62.08	0.338
3	2	N	72	38	
	“ON” Drug	Mean Change from Baseline	7.51	1.07	0.004
		Difference (95% CI)	6.45 (2.16, 10.73)		
4	4	N	72	38	
	“ON” Drug	Mean change from Baseline	6.54	0.50	0.011
		Difference (95% CI)	6.04 (1.39, 10.68)		
5	8	N	71	37	
	“OFF” Drug	Mean Change from Baseline	3.09	2.54	0.815
		Difference	0.54 (-4.03, 5.13)		
		N	72	38	
6	12 “ON” Drug	Mean Change from Baseline	4.81	1.36	0.174
		Difference (95% CI)	3.45 (-1.55, 8.44)		
		N	72	37	
7	16 “OFF” Drug	Mean Change from Baseline	4.84	0.50	0.137
		Difference (95% CI)	4.34 (1.40, 10.08)		
		N	72	38	
8	20 “ON” Drug	Mean Change from Baseline	5.47	0.96	0.088
		Difference (95% CI)	4.51 (-0.68, 9.71)		
		N	72	37	
9	24 “OFF” Drug	Mean Change from Baseline	5.45	-0.42	0.033
		Difference (95% CI)	5.87 (0.47, 11.26)		

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Device used in trial is not the recommended to be marketed device

CHF 1538 was evaluated in three clinical trials using PARI LC Plus® nebulizer accompanied by either PARI TurboBOY compressor (Studies CT01 and CT02) or PARI Boy N compressor (Study CT03). However, the PARI TurboBOY compressor used in the clinical studies is not available for the U.S. commercial market. In addition, PARI may soon phase out older nebulizer technologies, e.g., the PARI LC Plus nebulizer. The Applicant conducted a series of *in vitro* studies (IMR-J-BB-01, SP-096-002-01, SP-096-002-02, SP-096-002-04, and SP-096-002-05) to bridge the PARI TurboBOY, the (b) (4) and the Vios compressors. Results of statistical analyses on the test data comparing compressors (TurboBOY/LC Plus versus Vios/LC Plus) showed the *in vitro* measurements for delivered dose and gravimetric output post-sputter were significantly different. On the other hand, results and show that the fine particle dose (FPD) and the FPF of the dose from the LC Plus and (b) (4) nebulizers are comparable. There were no clinical trials conducted to bridge efficacy of the recommended devices to the one that were used in the three clinical studies. Hence, it is uncertain whether these new devices will provide similar or better results. For more information, please refer to the Regulatory Device Consult.

FEV result in CT01 is not consistent with result in CT02 and CT03

In Study CT01 FEV_1 % 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 FEV_1 % 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. In Study CT02, FEV_1 % predicted normal had increased by 8.0% at Week 2 and 7.8% at Week 4 above baseline values for CHF 1538-treated patients. In contrast, changes in FEV_1 % predicted normal were 1.9% in Week 2 and 0.5% 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 6.1% in Week 2 and 7.3% in Week 4 which are about half of what was observed in CT01. These results are already adjusted for their baseline values. The result of CT03 with respect to CHF 1538 is similar to the result obtained in CT02. Here, FEV_1 % predicted normal had increased by 5.81% at Week 2 and 5.53% at Week 4 above baseline values for CHF 1538-treated patients. This result, however, is adjusted by country and baseline. If adjustment by country is removed, the values match with what is observed in CT02.

It is also interesting to note that CT02 and CT03 allowed anti-PA, except aminoglycosides and nebulized antibiotic, and non anti pseudomonal antibiotics on top of other concomitant medications. Hence the expected change from baseline in both groups should have been comparable or higher than the ones observed in CT01.

Inspection Issues in CT02

One site in Poland (Study CTO2 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. Hence, reliability of the information coming from this site is suspect.

The other site (Study CTO2 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.

Data integrity

The medical officer, upon reviewing the Audiometric Test data, noticed that Site 17 (CT01) have a particular threshold repeated for every subject while many of the other sites have their own patterns of results. For example, one site may have lots of results between the 0-10dB range, whereas others will have thresholds within the 10-20dB range. The observation raises suspicion that this site might have fabricated data and could possibly be related to the issue why the FEV_1 result obtained in CT01 is much higher than the results obtained from CT02 and CT03.

An inspection has been requested for this site.

FEV_1 vs Time to first exacerbation

In CT01, after treatment with 28 days of CHF 1538, the improvement in FEV1 % predicted normal above baseline levels was nearly 11% greater than the response in placebo patients. In CT02, improvement at a similar time point is 6.9% and the improvement at Week 20 is 5.5%. The concern is how these values translate to clinically meaningful benefit that the patients get from taking the drug. Investigations of how the drug delays exacerbation show that the CH1538 and the placebo group are no different, despite delineated survival curves. Potentially, an effect may be present but this study has not been designed to detect such difference.

Non-inferiority trial

Study CT03 is an open-label non-inferiority trial. However, the non-inferiority margin has not been clearly established. In CT01, the lower bound of the 95% CI for the difference between FEV1% predicted mean change from baseline for CHF 1538 compared to placebo is 4.7%. This trial results will only be used for supportive information.

5.2 Conclusions and Recommendations

The results of Studies CT01 and CT02 show that intermittent (28-day "ON"/28-day "OFF"), twice daily administration of CHF 1538 300 mg is significantly superior to placebo in improving

pulmonary function in CF patients with *P. aeruginosa* infection. In Study CT01, after treatment with 28 days of CHF 1538, the improvement in FEV1 % predicted normal above baseline levels was nearly 11% greater than the response in placebo patients (p-value=. In Study CT02, the mean percent increase from baseline to the last on-treatment visit (Week 20) for the primary endpoint was 6.7% for the CHF 1538 group and 1.3% for the placebo group (p = 0.009).

How these results translate to clinically meaningful effect is suspect. For example, although there is a clear delineation between the two survival curves of time to first exacerbation (see Figure 3.4), 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). Other scores for cough and wheezing are unreliable because they have not been validated.

The results presented above are also contingent on data reliability. FEV_1 results are inconsistent across studies CT01 and CT02. The effects also vary by country, particularly in CT03, when measurement by spirometry is relatively objective. Furthermore, in some sites, change in predicted FEV, FVC, and FEF did not occur despite changes in age and/or height. Similarly, in some cases changes in predicted FEV, FVC, and FEF were observed without a change in age and/or height. All these information raises the issue about the reliability of the data in all the studies and its ensuing results.

We recommend that an adequate and well controlled clinical study be done to assess efficacy and safety of CHF 1538 using the to be marketed combination product.

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APPENDIX

A.1 Secondary Pulmonary Efficacy Variables for Study CT01

Secondary pulmonary efficacy variables were also investigated. In the subsequent discussion, analysis results for 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, RV (L), Total lung capacity (TLC, L); and RV/TLC ratio (RV/TLC, %) are discussed.

Baseline FEV_1 was significantly greater in the Placebo group compared with the CHF 1538 group. Although absolute FEV_1 increased in the CHF 1538 group but remained relatively stable in the Placebo group, the comparison between the changes from baseline for the CHF 1538 and Placebo groups failed to reach statistical significance (p=0.146) as shown in Table A.1 below. After the CHF 1538 run-out period, mean FEV_1 values at Week 8 decreased toward baseline values in the CHF 1538 group and increased slightly in the Placebo group such that the difference between the two groups with respect to change from baseline was -0.135 (95% CI: -0.331, 0.061)

Table A.1 FEV1 (L) Mean Baseline and Mean Change From Baseline with Multiple Imputation Used for Missing Data: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	29	29	
		Mean	1.029	1.641	0.002
3	2	N	29	27	
	"ON" Drug	Mean Change from Baseline	0.182	0.001	0.076
		Difference (95% CI)	0.181 (-0.019, 0.381)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline	0.230	0.090	0.146
	(1° endpoint)	Difference (95% CI)	0.140 (-0.049, 0.330)		
5	8	N			
	"OFF" Drug	Mean Change from Baseline	0.069	0.204	0.1760
		Difference	-0.135 (-0.331, 0.061)		

The mean baseline value for FVC % of predicted normal was relatively equivalent between CHF 1538 and Placebo groups. Treatment with CHF 1538 increased FVC % of predicted normal such that the change from baseline response between CHF 1538 and Placebo groups was significant by Week 4 of the treatment period. After the 4-week run-out period, FVC % predicted normal decreased in the CHF 1538 group while the Placebo group increased (see Table A.2).

Table A.2 FVC % of predicted normal Mean Baseline and Mean Change From Baseline with Multiple Imputation Used for Missing Data: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	29	29	
		Mean	59.3	62.1	0.513
3	2	N			
	"ON" Drug	Mean Change from Baseline	12.0	3.2	0.056
		Difference (95% CI)	8.8 (-0.2, 17.9)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline	13.5	4.9	0.031
	(1° endpoint)	Difference (95% CI)	8.7 (0.8, 16.6)		
5	8	N			
	"OFF" Drug	Mean Change from Baseline	4.0	6.9	0.458
		Difference	-2.9 (-10.5, 4.7)		

Mean FVC was significantly different between the CHF 1538 and Placebo groups at baseline. After both two and four weeks of treatment with CHF 1538, FVC increased; little change was observed among placebo patients during the treatment period. At Week 2 and Week 4 of the treatment period, the treatment group comparison with respect to FVC change from baseline was not statistically significant. At Week 8, after four weeks of CHF 1538 withdrawal, FVC decreased towards baseline values in the CHF 1538 group (see Table A.3).

Table A.3 FVC (L) Mean Baseline and Mean Change From Baseline with Multiple Imputation Used for Missing Data: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	29	29	
		Mean	1.284	1.999	0.005
3	2	N			
	"ON" Drug	Mean Change from Baseline	0.218	0.098	0.393
		Difference (95% CI)	0.119 (-0.155, 0.393)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline	0.251	0.149	0.359
	(1° endpoint)	Difference (95% CI)	0.102 (-0.116, 0.319)		
5	8	N			
	"OFF" Drug	Mean Change from Baseline	0.019	0.204	0.0767
		Difference	-0.185 (0.390, 0.020)		

Although the mean baseline value for $FEF_{25-75\%}$ % of predicted normal was less in CHF 1538 group compared with Placebo group, the difference between CHF 1538 and Placebo groups was not significantly different. At both Weeks 2 and 4 of the treatment period, $FEF_{25-75\%}$ (% of predicted normal) had increased significantly in the CHF 1538-treated patients compared with little to no change in placebo-treated patients (see Table A.4). After the 4-week tobramycin run-out period, $FEF_{25-75\%}$ (% of predicted normal) decreased to near baseline values so that the difference between CHF 1538 and Placebo groups was no longer significant at Visit 5 (Week 8).

Table A.4 FEF25-75% % of predicted normal Mean Baseline and Mean Change From Baseline with Multiple Imputation Used for Missing Data: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N			
		Mean	42.3	50.2	0.178
3	2	N			
	"ON" Drug	Mean Change from Baseline			0.001
		Difference (95% CI)	16.0 (6.8, 25.1)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline			0.005
	(1° endpoint)	Difference (95% CI)	14.7 (4.4, 25.0)		
5	8	N			
	"OFF" Drug	Mean Change from Baseline			0.789
		Difference	1.4 (-9.0, 11.8)		

The mean baseline $FEF_{25-75\%}$ (L/sec) for CHF 1538-treated patients was significantly less than that measured for the Placebo group. CHF 1538 administration increased absolute $FEF_{25-75\%}$ (L/sec) values from baseline to Weeks 2 and 4 during the treatment period (see Table A.5). The response of the CHF 1538 group was significantly different than that observed for the placebo patients in which mean absolute $FEF_{25-75\%}$ (L/sec) values decreased slightly. At Visit 5 (end of the run-out period), mean $FEF_{25-75\%}$ (L/sec) was slightly greater than baseline values among patients in both treatment groups such that no significant treatment group difference was detected

Table A.5 FEF25-75% (L/sec) Mean Baseline and Mean Change From Baseline with Multiple Imputation Used for Missing Data: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N			
		Mean	1.027	1.682	0.004
3	2	N			
	"ON" Drug	Mean Change from Baseline	0.164	-0.070	0.078
		Difference (95% CI)	0.233 (-0.027, 0.494)		
4	4	N imputed			
	"ON" Drug	Mean change from Baseline	0.323	0.018	0.0247
	(1° endpoint)	Difference (95% CI)	0.305 (0.039, 0.570		
5	8	N			
	"OFF" Drug	Mean Change from Baseline	0.100	0.160	0.687
		Difference	-0.060 (-0.352, 0.232)		

A.2 Secondary Pulmonary Efficacy Variables for Study CT02

Mean baseline absolute FEV1 (Visit 2) and mean change from baseline with LOCF are presented in Table A.6. The changes from baseline in FEV1 were significantly greater for the CHF 1538 group than for the Placebo group at all visits except Visit 5 (the end of the first "OFF" cycle). Similarly, the mean change from baseline to the primary endpoint for FEV1 was significantly greater in the CHF 1538 group (0.188 L) than in the Placebo group (0.037 L). CHF 1538 efficacy on FEV1 was significantly superior to placebo at all individual visits except Visit 5, which was the end of the first "OFF" cycle.

Table A.6 FEV1 (L) Mean Baseline and Mean Change From Baseline with MI Used for "ON" Drug Visits: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	161	84	
		Mean	1.598	1.646	0.614
3	2	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	0.206	0.037	<0.001
		Difference (95% CI)	0.169 (0.083, 0.255)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	0.206	0.016	<0.001
		Difference (95% CI)	0.190 (0.105, 0.276)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	0.133	0.054	0.071
		Difference	0.080 (-0.006, 0.166)		
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline	0.207	0.072	0.004
		Difference (95% CI)	0.135 (0.044, 0.226)		
		N imputed	3	4	
7	16 "OFF" Drug	Mean Change from Baseline	0.176	0.043	0.005
		Difference (95% CI)	0.133 (0.041, 0.225)		
		N imputed	4	5	
8	20 "ON" Drug	Mean Change from Baseline	0.184	0.038	0.008
		Difference (95% CI)	0.146 (0.0389, 0.253)		
		N imputed	7	6	
9	24 "OFF" Drug	Mean Change from Baseline	0.190	0.018	<0.001
		Difference (95% CI)	0.172 (0.070, 0.274)		

FVC % predicted normal mean baseline (Visit 2) and mean change from baseline with MI for the ITT population are presented in Table A.7. 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%). The efficacy of CHF 1538 on FVC % predicted normal was significantly greater than placebo at all visits except Visits 5 through 7, which marked the end of the first "OFF" cycle through the end of the second "OFF" cycle.

Table A.7 FVC % Mean Baseline and Mean Change From Baseline with MI Used for "ON" Drug Visits: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	161	84	
		Mean	70.77	73.58	0.113
3	2	N imputed	161	84	
	"ON" Drug	Mean Change from Baseline	5.96	2.15	0.0193
		Difference (95% CI)	3.81 (0.62, 7.00)		
4	4	N imputed	161	84	
	"ON" Drug	Mean change from Baseline	5.79	1.67	0.010
		Difference (95% CI)	4.12 (1.01, 7.23)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	3.89	2.50	0.398
		Difference	1.39 (-1.83, 4.62)		
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline	5.61	3.54	0.261
		Difference (95% CI)	2.07 (-1.54, 5.68)		
7	16 "OFF" Drug	N imputed	3	4	

		Mean Change from Baseline	4.97	2.89	0.153
		Difference (95% CI)	2.67 (-0.99, 6.37)		
		N imputed	4	5	
8	20 “ON” Drug	Mean Change from Baseline	5.78	1.49	0.026
		Difference (95% CI)	4.29 (0.51, 8.07)		
		N imputed	7	6	
9	24 “OFF” Drug	Mean Change from Baseline	6.18	0.46	0.006
		Difference (95% CI)	5.73 (1.61, 9.84)		

Absolute FVC mean baseline (Visit 2) and mean change from baseline with LOCF are presented in Table A.8. The mean change in FVC from baseline to the primary endpoint was greater in the CHF 1538 group (0.226 L) than in the Placebo group (0.059 L). The efficacy of CHF 1538 on FVC was significantly greater compared to that of the placebo at all visits except Visits 5 through 7, which marked the end of the first “OFF” cycle through the end of the second “OFF” cycle.

Table A.8 FVCL Mean Baseline and Mean Change From Baseline with MI Used for “ON” Drug Visits: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	161	84	
		Mean	2.217	2.289	0.585
3	2	N	0	0	
	“ON” Drug	Mean Change from Baseline	0.196	0.040	0.007
		Difference (95% CI)	0.156 (0.042, 0.270)		
4	4	N imputed	0	0	
	“ON” Drug	Mean change from Baseline	0.192	0.045	0.006
		Difference (95% CI)	0.147 (0.043, 0.252)		
5	8	N	2	1	
	“OFF” Drug	Mean Change from Baseline	0.142	0.082	0.276
		Difference	0.061 (-0.049, 0.170)		
		N	3	3	
6	12 “ON” Drug	Mean Change from Baseline	0.200	0.120	0.165
		Difference (95% CI)	0.081 (-0.033, 0.195)		
		N	3	4	
7	16 “OFF” Drug	Mean Change from Baseline	0.193	0.091	0.084
		Difference (95% CI)	0.103 (-0.014, 0.219)		
		N	4	5	
8	20 “ON” Drug	Mean Change from Baseline	0.225	0.056	0.007
		Difference (95% CI)	0.169 (0.047, 0.291)		
		N	7	6	
9	24 “OFF” Drug	Mean Change from Baseline1,2	0.258	0.068	0.005
		Difference (95% CI)	0.190 (0.058, 0.322)		

FEF25-75% % predicted normal mean baseline (Visit 2) and mean change from baseline with MI for the ITT population are presented in Table A.9. The mean change in FEF25-75% % predicted normal from baseline to the primary endpoint was greater in the CHF 1538 group (8.75%) than in the Placebo group (0.69%). CHF 1538 efficacy on FEF25-75% % of predicted normal was significantly greater than that of placebo at all visits.

Table A.9 FEF % Predicted Normal Mean Baseline and Mean Change From Baseline with MI: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	158	80	
		Mean	41.76	43.92	0.531
3	2	N imputed	0	1	
	"ON" Drug	Mean Change from Baseline	11.72	3.07	0.001
		Difference (95% CI)	8.65 (3.61, 13.68)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	11.62	-1.16	<.001
		Difference (95% CI)	12.73 (7.39, 18.97)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	9.63	1.94	0.017
		Difference	7.69 (1.39, 13.98)		
		N	3	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	10.60	2.59	0.007
		Difference (95% CI)	8.00 (2.22, 13.78)		
		N	4	4	
7	16 "OFF" Drug	Mean Change from Baseline1,2	7.93	0.68	0.004
		Difference (95% CI)	7.24 (2.39, 12.11)		
		N	3	5	
8	20 "ON" Drug	Mean Change from Baseline1,2	8.42	0.70	0.002
		Difference (95% CI)	7.72 (2.91, 12.53)		
		N	6	6	
9	24 "OFF" Drug	Mean Change from Baseline1,2	6.23	-1.76	0.004
		Difference (95% CI)	7.98 (2.57, 13.40)		

Absolute FEF25-75% mean baseline (Visit 2) and mean change from baseline with MI are presented in Table A.10 . The mean change in FEF25-75% from baseline to the primary endpoint was greater in the CHF 1538 group (0.288 L/sec) than in the Placebo group (0.073 L/sec). The efficacy of CHF 1538 on FEF25-75% was significantly greater than the placebo in all visits except Visit 5, which marked the end of the first "OFF" cycle.

Table A.10 FEF (L) Mean Baseline and Mean Change From Baseline with MI: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	160	84	
		Mean	1.34	1.37	0.806
3	2	N imputed	0	1	
	"ON" Drug	Mean Change from Baseline	0.325	0.120	0.008
		Difference (95% CI)	0.206 (0.057, 0.354)		
4	4	N imputed	0	0	
	"ON" Drug	Mean change from Baseline	0.335	0.001	<.001
		Difference (95% CI)	0.335 (0.172, 0.498)		
5	8	N imputed	2	1	
	"OFF" Drug	Mean Change from Baseline	0.260	0.103	0.054
		Difference	0.156 (-0.002, 0.315)		
		N imputed	3	3	
6	12 "ON" Drug	Mean Change from Baseline1,2	0.345	0.104	0.007
		Difference (95% CI)	0.240 (0.065, 0.415)		
7	16 "OFF" Drug	N imputed	4	4	
		Mean Change from Baseline1,2	0.243	0.056	0.011

		Difference (95% CI)	0.188 (0.044, 0.332)		
		N imputed	3	5	
8	20 “ON” Drug	Mean Change from Baseline1,2	0.276	0.068	0.007
		Difference (95% CI)	0.209 (0.056, 0.361)		
		N imputed	6	6	
9	24 “OFF” Drug	Mean Change from Baseline1,2	0.207	0.004	0.015
		Difference (95% CI)	0.204 (0.039, 0.368)		

Respiratory Rate (breaths/minute)

Respiratory rate mean baseline (Visit 2) and adjusted mean change from baseline with MI for the ITT population are presented in Table A.11. The mean change in respiratory rate from baseline to the primary endpoint was lower in the CHF 1538 group (-0.62 breaths/minute) than in the Placebo group (1.65 breaths/minute). CHF 1538 resulted in a significantly lower respiratory rate compared to that of the placebo except for Visit 3 (in the middle of the first “ON” cycle), and Visits 5 and 9 which marked the end of the first and third “OFF” cycles, respectively.

Table A.11 Respiratory Rate (breaths/min) Mean Baseline and Adjusted Mean Change From Baseline with MI Used: ITT Population

Visit	Week		CHF 1538	Placebo	P-Value
2	Baseline	N	161	84	
		Mean	23.32	22.86	0.460
3	2	N imputed	0	0	
	“ON” Drug	Mean Change from Baseline	-0.2	0.48	0.473
		Difference (95% CI)	-0.51 (-1.48, 0.47)		
4	4	N imputed	0	0	
	“ON” Drug	Mean change from Baseline	11.60	-1.13	<0.001
		Difference (95% CI)	12.73 (7.39, 18.07)		
5	8	N imputed	1	1	
	“OFF” Drug	Mean Change from Baseline	-0.22	0.69	0.059
		Difference	-0.91 (-1.85, 0.03)		
		N imputed	3	3	
6	12 “ON” Drug	Mean Change from Baseline	-0.75	0.74	0.001
		Difference (95% CI)	-1.48 (-2.39, -0.58)		
		N imputed	3	3	
7	16 “OFF” Drug	Mean Change from Baseline	-0.58	1.06	0.006
		Difference (95% CI)	-1.64 (-2.81, 0.47)		
		N imputed	4	5	
8	20 “ON” Drug	Mean Change from Baseline	-0.62	1.65	0.001
		Difference (95% CI)	2.27 (-3.55, -0.98)		
		N imputed	7	6	
9	24 “OFF” Drug	Mean Change from Baseline	-0.66	0.14	0.157
		Difference (95% CI)	-0.80 (-1.92, 0.31)		

A.2 Secondary Pulmonary Efficacy Variables for Study CT03

The baseline FEV_1 in liters (Visit 2) and the changes from the baseline values to Visits 3 and 4 (Week 2 and Week 4 on treatment) and Visit 5 (“OFF” treatment) observed values are summarized for the ITT population in Table A.12. In the CHF 1538 group the mean FEV_1 (L) had increased above baseline values by 0.179 L at Week 2 and 0.131 L at Week 4. Similarly the increases in the TOBI group were 0.19 L at Week 2 and 0.147 L at Week 4. The change from baseline in mean FEV_1 (L) after four weeks off treatment (Visit 5) was 0.048 L in the CHF 1538

group and 0.046 L in the TOBI group showing a decreasing response following treatment withdrawal at Week 4.

Table A.12 FEV1 (L) 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	1.73	1.76	0.666
3	2	N imputed	0	0	
	"ON" Drug	Mean Change from Baseline	0.192	0.179	0.660
		Difference (95% CI)	-0.013 (-0.073, 0.046)		
4	4	N imputed	2	3	
	"ON" Drug	Mean change from Baseline	0.147	0.131	0.618
	(1° endpoint)	Difference (95% CI)	-0.015 (-0.076, 0.045)		
5	8	N imputed	4	3	
	"OFF" Drug	Mean Change from Baseline	0.046	0.048	0.964
		Difference	0.002 (-0.069, 0.073)		

The baseline FVC % predicted normal (Visit 2) and the changes from the baseline values to Visits 3 and 4 (Week 2 and Week 4 on treatment) and Visit 5 ("OFF" treatment) observed values are summarized for the ITT population in Table A.13.In the CHF 1538 group the mean FVC % predicted normal had increased above baseline values by 3.03% at Week 2 and 2.06% at Week 4. Similarly the increases in the TOBI group were 4.06 % at Week 2 and 2.41% at Week 4. The change from baseline in mean FVC % predicted normal after four weeks off treatment (Visit 5) was -0.47% in the CHF 1538 group and 1.05% in the TOBI group showing a decreasing response following treatment withdrawal at Week 4.

Table A.13 FVC % 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	164	156	
		Mean	74.41	75.19	0.638
3	2	N imputed	1	2	
	"ON" Drug	Mean Change from Baseline	4.06	3.03	0.388
		Difference (95% CI)	-1.03 (-3.36, 1.31)		
4	4	N imputed	1	1	
	"ON" Drug	Mean change from Baseline	2.41	2.06	0.768
	(1° endpoint)	Difference (95% CI)	-0.36 (-2.72, 2.01)		
5	8	N imputed	4	3	
	"OFF" Drug	Mean Change from Baseline	1.05	-0.47	0.274
		Difference	-1.52 (-4.23, 1.20)		

The baseline FVC (L) (Visit 2) and the changes from the baseline values to Visits 3 and 4 (Week 2 and Week 4 on treatment) and Visit 5 ("OFF" treatment) observed values are summarized for the ITT population in Table A.14. In the CHF 1538 group the mean FVC (L) had increased above baseline values by 0.102 L at Week 2 and 0.061 L at Week 4. Similarly the increases in the TOBI group were 0.131 L at Week 2 and 0.077 L at Week 4. The change from baseline in mean FVC (L) after four weeks off treatment (Visit 5) was -0.017 L in the CHF 1538 group and 0.048 L in the TOBI group showing a decreasing response following treatment withdrawal at Week 4.

Table A.14 FVC (L) 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	164	156	
		Mean	2.412	2.483	0.528
3	2	N imputed	1	2	
	"ON" Drug	Mean Change from Baseline	0.131	0.102	0.446
		Difference (95% CI)	-0.029 (-0.103, 0.045)		
4	4	N imputed	1	1	
	"ON" Drug	Mean change from Baseline	0.077	0.061	0.685
	(1° endpoint)	Difference (95% CI)	-0.016 (-0.091, 0.060)		
5	8	N imputed	4	3	
	"OFF" Drug	Mean Change from Baseline	0.048	-0.017	0.140
		Difference	-0.064 (-0.150, 0.021)		

The baseline $FEV_{25-75\%}$ % predicted normal (Visit 2) and the changes from the baseline values to Visits 3 and 4 (Week 2 and Week 4 on treatment) and Visit 5 ("OFF" treatment) observed values are summarized for the ITT population in Table A.15. In the CHF 1538 group the mean $FEF_{25-75\%}$ % predicted normal had increased above baseline values by 6.02% at Week 2 and 7.21% at Week 4. Similarly the increases in the TOBI group were 5.32% at Week 2 and 7.00% at Week 4. The change from baseline in mean $FEF_{25-75\%}$ % predicted normal after four weeks off treatment (Visit 5) was 4.21% in the CHF 1538 group and 1.80% in the TOBI group showing a decreasing response following treatment withdrawal at Week 4.

Table A.15 FEF25-75% % 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	156	
		Mean	45.05	42.91	0.397
3	2	N imputed	1	3	
	"ON" Drug	Mean Change from Baseline	5.32	6.02	0.734
		Difference (95% CI)	0.69 (-3.28, 4.67)		
4	4	N imputed	2	1	
	"ON" Drug	Mean change from Baseline	7.00	7.21	0.912
	(1° endpoint)	Difference (95% CI)	0.21 (-3.27, 3.88)		
5	8	N imputed	4	3	
	"OFF" Drug	Mean Change from Baseline	2.40	4.21	0.425
		Difference	1.80 (-2.64, 6.25)		

The baseline $FEV_{25-75\%}$ in liters/second (Visit 2) and the changes from the baseline values to Visits 3 and 4 (Week 2 and Week 4 on treatment) and Visit 5 ("OFF" treatment) observed values are summarized for the ITT population in Table A.16. In the CHF 1538 group the mean $FEF_{25-75\%}$ (L/sec) had increased above baseline values by 0.232 L/sec at Week 2 and 0.259 L/sec at Week 4. Similarly the increases in the TOBI group were 0.190 L/sec at Week 2and 0.220 L/sec at Week 4. The change from baseline in mean $FEF_{25-75\%}$ (L/sec) after four weeks off treatment

(Visit 5) was 0.147 L/sec in the CHF 1538 group and 0.063 L/sec in the TOBI group showing a decreasing response following treatment withdrawal at Week 4.

Table A.16 FEF25-75% (L) 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	157	
		Mean	1.493	1.412	0.391
3	2	N imputed	1	3	
	"ON" Drug	Mean Change from Baseline	0.190	0.232	0.482
		Difference (95% CI)	0.042 (-0.076, 0.160)		
4	4	N imputed	2	1	
	"ON" Drug	Mean change from Baseline	0.220	0.259	0.500
	(1° endpoint)	Difference (95% CI)	0.039 (-0.075, 0.154)		
5	8	N imputed	4	3	
	"OFF" Drug	Mean Change from Baseline	0.063	0.147	0.235
		Difference	0.084 (-0.055, 0.223)		

REFERENCES

1. Wine J. Cystic fibrosis: How do CFTR mutations cause cystic fibrosis? Curr Biol. 1995 Dec 1;5(12):1357-9.

2. Kerem E, Corey M, Gold R, Levison H. Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonization with *Pseudomonas aeruginosa*. J Pediatr. 1990 May;116(5):714-9.

3. Hoiby N. Microbiology of lung infections in cystic fibrosis patients. Acta Paediatr Scand. 1982;301:33-54.

4. Wood R, Boat T, Doershuk C. Cystic fibrosis. Am Rev Respir Dis. 1976;113:833-78.

5. Boat T, Welsh M, Beaudet A, Tsui L. Cystic Fibrosis. In: Schriver C, Beaudet A, Sly W, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease: 7th Edition. New York: McGraw-Hill;1995. p. 3799-3876.

6. Touw D, Brimicombe R, Hodson M, Heijerman H, Bakker W. Inhalation of antibiotics in cystic fibrosis. Eur Respir J. 1995;8(9):1594-604.

7. Ramsey B, Pepe M, Quan J, Otto K, Montgomery A, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med. 1999;340(1):23-30.

8. Toso C, Williams C, Noone P. Inhaled antibiotics in cystic fibrosis: a review. Ann Pharmacother. 1996 Jul-Aug;30(7-8):840-50.

9. Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest. 2002 Jan;121(1):55-63.

10. Poli G, Acerbi D, Pennini R, Soliani RA, Corrado M, Eichler H, et al. Clinical pharmacology study of Bramitob, a tobramycin solution for nebulization, in comparison with Tobi. Paediatr Drugs. 2007;9 Suppl(1):3-9.

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