STATISTICAL ANALYSIS PLAN

Version 1.0

14 July 2017

Protocol PTC124-GD-023-CF

An Open-Label Safety and Efficacy Study for Patients with Nonsense Mutation Cystic Fibrosis Previously Treated with Ataluren (PTC124®)

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ABBREVIATIONS

Abbreviation	Definition
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
ß-HCG	beta human chorionic gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CF	Cystic fibrosis
CI	Confidence interval
CK	Creatine kinase
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data monitoring committee
ECG	Electrocardiogram
FEF_{25-75}	Forced expiratory flow between 25% and 75% of expiration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
ITT	Intent-to–treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PT	Preferred Term
QT	Ventricular depolarization-repolarization (interval on ECG)
QT_c	QT interval corrected for heart rate
REF	Respiratory Event Form
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
ULN	Upper limit of normal
WHODRUG	World Health Organization Drug (dictionary)

1. OVERVIEW

This statistical analysis plan (SAP) details the statistical methods to be used in the analyses and presentation of the data collected in Study PTC124-GD-023-CF (Study 023). Preparation of this SAP incorporates statistical design elements present in the study protocol version 3.0 (dated 03 February 2016). Where conflicts exist between this SAP and the study protocol, the information contained in this SAP supersedes the protocol. Any refinements to the SAP will be incorporated by amendment before the databases are locked.

2. STUDY OVERVIEW

2.1. Study Design

Study 023 is a Phase 3, international, multicenter, long-term safety study of ataluren in patients with nmCF that have completed participation in the double-blind study PTC124-GD-009-CF (Study 009).

It is planned that approximately 70 patients that completed participation in Study 009 will be enrolled into the study. All participating sites must therefore have had at least 1 patient that completed participation in Study 009. It is anticipated that most eligible patients would have also been enrolled in PTC124-GD-009e-CF (Study 009e), the 96-week open-label study that immediately proceeded Study 009. Eligible subjects will receive oral ataluren administered 3 times per day (TID) at respective morning, midday, and evening doses of 10-, 10-, and 20-mg/kg for ~192 weeks. The detailed schedule of assessments are displayed in Table 1.

Planned interim safety analyses will be conducted by an independent data monitoring committee (DMC). The first safety review will occur when ~35 patients have completed ≥32 weeks of treatment. The second safety review will occur when ~35 patients have completed ≥64 weeks of treatment.

The study will be terminated prematurely according to company's strategic decision on March 2, 2017. All subject who are on-going by then will be discontinued.

Table 1. Schedule of Events

Study Period	Screening	Ataluren Treatment							
Study Week	**Week -4 to -1**	**Week 1**	**Week 8 (Phone Call)**	**Week 16**	**Week 24 (Phone Call)**	**Week 32**	**Week 40 (Phone Call)**	**Week 48**	**Week 56 (Phone Call)**
Study Day	**-28 to -1**	**1 (+7 days)**	**56 (±7 days)**	**112 (±7 days)**	**168 (±7 days)**	**224 (±7 days)**	**280 (±7 days)**	**336 (±7 days)**	**392 (±7 days)**
Visit / Call	**1**	**2**	**2a**	**3**	**3a**	**4**	**4a**	**5**	**5a**
Informed Consent	X								
IVR/IWR System Screening	X								
Clinical and Medication History	X								
Vital Signs (including pulse oximetry)	X	X		X		X		X	
Height	X	X		X		X		X	
Weight	X	X		X		X		X	
Physical Examination	X	**As clinically indicated**						X	**As clinically indicated**
Serum Viral Screen	X								
β-HCG[a]	X	X		X		X		X	
Cortisol, Renin, and Aldosterone	X	**As clinically indicated**							
Biochemistry[b]	X	X		X		X		X	
Hematology	X	X		X		X		X	
Urinalysis	X	X		X		X		X	
Ataluren PK (trough)				X		X		X	
Renal Ultrasound	X	**As clinically indicated**							
12-Lead ECG	X			X		X		X	
Ataluren Administration in Clinic		X[c]							
Ataluren Dispensation		X		X		X		X	
Review Ataluren Compliance				X		X		X	
Adverse Events	X[d]	X		X		X		X	
Concomitant Medication / Non-Drug Therapy	X	X		X		X		X	
Spirometry	X	X		X		X		X	
Respiratory Event Evaluation[e]	X	X	X	X	X	X	X	X	X
Presence of *P. aeruginosa* in Sputum	X	X		X		X		X	

Table 1. Schedule of Events - Continued

Study Period	Ataluren Treatment									
Study Week	**Week 64**	**Week 72 (Phone Call)**	**Week 80**	**Week 88 (Phone Call)**	**Week 96**	**Week 104 (Phone Call)**	**Week 112**	**Week 120 (Phone Call)**	**Week 128**	**Week 136 (Phone Call)**
Study Day	**448 (+7 days)**	**504 (±7 days)**	**560 (±7 days)**	**616 (±7 days)**	**672 (±7 days)**	**728 (±7 days)**	**784 (±7 days)**	**840 (±7 days)**	**896 (±7 days)**	**952 (±7 days)**
Visit / Call	**6**	**6a**	**7**	**7a**	**8**	**8a**	**9**	**9a**	**10**	**10a**
Vital Signs (including pulse oximetry)	X		X		X		X		X	
Height	X		X		X		X		X	
Weight	X		X		X		X		X	
Physical Examination	**As clinically indicated**				X	**As clinically indicated**				
Serum Viral Screen										
β-HCG[a]	X		X		X		X		X	
Cortisol, Renin, and Aldosterone	**As clinically indicated**									
Biochemistry[b]	X		X		X		X		X	
Hematology	X		X		X		X		X	
Urinalysis	X		X		X		X		X	
Ataluren PK (trough)	X		X		X		X		X	
Renal Ultrasound	**As clinically indicated**									
12-Lead ECG	X		X		X		X		X	
Ataluren Administration in Clinic										
Ataluren Dispensation	X		X		X		X		X	
Review Ataluren Compliance	X		X		X		X		X	
Adverse Events	X		X		X		X		X	
Concomitant Medication /										

Non-Drug Therapy	X		X		X		X		X	
Spirometry	X		X		X		X		X	
Respiratory Event Evaluation[c]	X	X	X	X	X	X	X	X	X	X
Presence of *P. aeruginosa* in Sputum	X		X		X		X		X	

Table 1. Schedule of Events - Continued

Study Period	**Ataluren Treatment**							**4-Week Post-Treatment Follow-Up (End of Study)**
Study Week	**Week 144**	**Week 152 (Phone Call)**	**Week 160**	**Week 168 (Phone Call)**	**Week 176**	**Week 184 (Phone Call)**	**Week 192 EOT/ Early D/C[f]**	
Study Day	**1008 (±7 days)**	**1064 (±7 days)**	**1120 (±7 days)**	**1176 (±7 days)**	**1232 (±7 days)**	**1288 (±7 days)**	**1344 (±7 days)**	**1372 (±7 days)**
Visit / Call	**11**	**11a**	**12**	**12a**	**13**	**13a**	**14**	**15**
Vital Signs (including pulse oximetry)	X		X		X		X	X
Height	X		X		X		X	X
Weight	X		X		X		X	X
Physical Examination	X	**As clinically indicated**					X	X
Serum Viral Screen								
β-HCG[a]	X		X		X		X	X
Cortisol, Renin, and Aldosterone	**As clinically indicated**							
Biochemistry[b]	X		X		X		X	X
Hematology	X		X		X		X	X
Urinalysis	X		X		X		X	X
Ataluren PK (trough)	X		X		X		X	
Renal Ultrasound	**As clinically indicated**							
12-Lead ECG	X		X		X		X	X

Ataluren Administration in Clinic								
Ataluren Dispensation	X		X		X			
Review Ataluren Compliance	X		X		X		X	
Adverse Events	X		X		X		X	X
Concomitant Medication / Non-Drug Therapy	X		X		X		X	X
Spirometry	X		X		X		X	X
Respiratory Event Evaluation[e]	X	X	X	X	X	X	X	
Presence of *P. aeruginosa* in Sputum	X		X		X		X	

[a] Testing for female subjects only.
[b] Ideally, subjects should have fasted for at least 8 hours prior to blood collection.
[c] Clinic staff will administer the first dose of study drug at Study Day 1 (Visit 2).
[d] Adverse events (AEs) should be elicited from subjects at all study visits; however, any untoward medical occurrences collected at Screening will be used to assess study eligibility only and will not be reported as AEs in the CRF.
[e] Includes completion of the Respiratory Event Form (REF).
[f] Patients that do not complete ≥192 Weeks of treatment will be considered prematurely discontinued.

Abbreviations: β-HCG = human chorionic gonadotropin, D/C = discontinuation, ECG = electrocardiogram, EOT = end of treatment, IVR/IWR = Interactive Voice Response/Interactive Web Response, PK = pharmacokinetic

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to determine the long-term safety and tolerability of 10-, 10-, 20- mg/kg ataluren in patients with nmCF who completed participation in the double-blind study (PTC124-GD-009-CF) as assessed by adverse events and laboratory abnormalities.

2.2.2. Secondary Objectives

The secondary objectives are to determine the efficacy and safety of ataluren as assessed by spirometry (FEV_1), pulmonary exacerbation rate, and other safety parameters (eg, 12-lead ECG measurements, vital signs).

2.2.3. Tertiary Objectives

The tertiary objectives are to determine the efficacy of ataluren as assessed by other parameters of pulmonary function (FVC and FEF_{25-75}), and changes in body weight BMI.

2.3. Study Endpoints

2.3.1. Primary Endpoint

- Safety profile characterized by type, frequency, severity, timing, and relationship to ataluren of any adverse events, and laboratory abnormalities

2.3.2. Secondary Endpoints

- Change from baseline to end of treatment in spirometric performance as measured by FEV_1
- Rate of pulmonary exacerbations, as assessed by modified Fuchs (primary definition), Fuchs and expanded Fuchs criteria
- Change from baseline in other safety parameters (eg, 12-lead ECG measurements, vital signs)

2.3.3. Tertiary Endpoints

- Change from baseline to end of treatment in spirometric performance as measured by FVC and FEF_{25-75}
- Change from baseline to end of treatment in body weight and BMI

2.3.4. Other Endpoints

- Study drug extent of exposure and characterization of investigator-prescribed dosing modifications

- Study drug compliance as assessed by a subject daily diary and by quantification of used and unused study drug
- Incidence of concomitant therapies

2.4. Sample Size

Approximately 70 patients that completed participation in Study 009 will be enrolled into the study. The sample size is not determined by statistical power.

3. STUDY POPULATIONS

3.1. As-Treated Population

The As-Treated population consists of all subjects who received at least 1 dose of ataluren. This population will be evaluated in the analyses of safety and treatment administration.

3.2. Intention-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population consists of all subjects who have at least 1 post-baseline efficacy assessment. This population will be evaluated in the analysis of efficacy.

4. STATISTICAL AND ANALYTICAL PROCEDURES

4.1. General Statistical Considerations

By-subject listings will be created for each CRF module. Summary tables for continuous variables will contain the following statistics: n, mean, standard deviation, standard error, and 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include N, n, percentage, and 95% CIs on the percentage. Where applicable, the summary data (mean, standard error) will be presented in graphical form by time of visit.

The baseline value used in each analysis will be the last (most recent) non-missing pretreatment value, except as noted for spirometry data.

Unless otherwise specified, all applicable analyses will be 2-sided at the 0.05 level of significance.

All analyses and tabulations of data will be performed using SAS (Version 9.1 or higher).

4.2. Control of the Multiplicities

Since all analyses are descriptive in this study, there is no need to control the multiplicity.

4.3. Missing Data Handling

In general, the missing data in safety endpoints will not be imputed, unless specified otherwise. The imputation rules of missing start/stop dates in adverse events and prior/concomintant medications/therapies will be documented in Section 5.5.

4.4. Multiple Centers

Study centers from different countries will be pooled by geographic region (North America [US and Canada], Europe, and Other [ie, Australia, Israel, Argentina, and Brazil]). The number of subjects in each region will be reported.

4.5. Subject Disposition

4.5.1. Accounting for Subjects

Subject enrollment status will be summarized by country and site for the As-Treated population. The number and percentage of subjects will also be reported by all enrolled subjects, the ITT population, and the As-Treated population. The number of subjects at each scheduled visit will be tabulated for the As-Treated population. For the As-Treated population, the number of completers, subjects who discontinue prematurely from the study, and reasons of discontinuation will be tabulated. In addition, reasons of screening failures will be summarized and listed.

4.5.2. Protocol Deviations

All major protocol deviations will be summarized by type for the ITT population. A listing of major and minor protocol deviations will be provided.

4.6. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized for ITT and As-Treated populations.

The continuous baseline characteristics include age (years), baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2), %-predicted FEV_1 at screening and baseline. The categorical baseline characteristics include gender, race, region, age group (<18 vs ≥18 years), baseline %-predicted FEV_1 group (<65% vs ≥65%), presence of pancreatic insufficiency, chronically infected *Pseudomonas aeruginosa*, and diabetes in medical history.

4.7. Medical History

The medical history will be summarized by the system organ class and preferred term. The listing of medical history will be provided as well.

4.8. Prior and Concomitant Medications and Procedures

Prior medications will be defined as those medications that were used prior to the first dose of study treatment. Concomitant medications will be defined as those medications that were used during the study treatment period. If the start date of a medication is missing and the end date is

prior to study start, the medication will be deemed prior. If the end date is after study start or is also missing, the drug will be deemed concomitant. If the end date is missing or the medication is ongoing, the medication will be considered concomitant. If the medication start date is completely missing and end date is missing or ongoing, the medication will be considered both prior and concomitant. Prior and concomitant therapies will be defined similarly.

Prior and concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) into Anatomical-Therapeutic-Chemical classification (ATC) codes. Subject incidence of prior and concomitant medications will be tabulated by ATC level 2 and preferred term for the As-Treated population. Subjects will only count once for each ATC or preferred term in the event that they have multiple records of the same ATC or preferred term in the database.

Prior and concomitant non-drug therapies will be coded and analyzed similarly.

4.9. Study Treatment Administration and Compliance

The study treatment duration in weeks is defined as (last dose date – first dose date +1)/7 and will be summarized overall. This duration is irrespective of the dose interruptions.

The drug compliance of a specific time period is defined as 100*(number of sachets taken during the period/number of planned sachets during the period). It will be summarized for overall treatment duration. The percentages will take into account physician-prescribed reductions and interruptions.

The number and percentage of subjects having dose interruptions and dose changes will be summarized using descriptive statistics for overall treatment duration.

The above analyses will be performed for the As-Treated population.

4.10. Primary Analyses

All primary analyses will be performed for the As-Treated population.

4.10.1. Adverse Events

Adverse events will be classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA Version 17.0). In order to remain consistent in the adverse event data collected in previous trials, the severity of adverse events will be graded by the investigator according to the CTCAE, Version 3.0 whenever possible. The adverse event CTCAE/severity grades include Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-threatening), and Grade 5 (Fatal). The relationship of study drug to adverse event has 4 categories: probable, possible, unlikely and unrelated.

A treatment-emergent adverse event (TEAE) is defined as an adverse event that occurs or worsens in the period extending from the day of a subject's first dose of study drug to 4 weeks after the last dose of study drug in this study. In the following analyses, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst CTCAE/severity grade.

Total numbers of AEs, TEAEs and serious AEs (SAE) and the number and percentage of subjects experiencing ≥1 TEAE, ≥1 SAE, discontinuation due to AE, and death will be tabulated. The number and percentage of subjects with TEAEs and SAEs will be by Relationship to study drug and CTCAE/severity, respectively.

The number and percentage of subjects experiencing a specific TEAE will be tabulated

1) by SOC, and PT
2) by SOC, PT, and CTCAE/severity grade
3) by SOC in the descending order of the SOC frequency in ataluren group,
4) by PT in the descending order of the PT frequency in ataluren group.

The following TEAEs will be analyzed similarly:

1) by SOC, and PT and
2) by SOC, PT, and CTCAE/severity grade.
    - Possibly or probably treatment-related TEAEs
    - Serious TEAEs and possibly or probably treatment-related serious TEAEs
    - TEAEs leading to discontinuation from treatment
    - Adrenal, hepatic and renal TEAEs and possibly or probably treatment-related adrenal, hepatic and renal TEAEs leading to special diagnosis evaluation
    - TEAEs with CTCAE/severity grade ≥3 and possibly or probably treatment-related TEAEs with CTCAE/severity grade ≥3
    - Common TEAEs (subject frequency of ≥5%)

Listings of death, serious AEs, AEs leading to discontinuation from treatment, and adrenal, hepatic and renal AEs leading to special diagnostic evaluations will be provided. Renal AEs for subjects not using nephrotoxic concomitant medications, subjects using nephrotoxic concomitant medications, and subjects with postbaseline creatinine > 1.5*ULN will also be listed, separately.

The drug exposure adjusted TEAE incidence rate will be summarized by SOC and PT, where the incidence rate of the TEAE per 100 patient-year = (number of events/number of patient-years) *100. The number of patient-years is defined as the sum of the number of days on study drug of all patients divided by 365.25.

In addition, the number of subjects with clinical laboratory abnormalities, abnormal vital signs, and abnormal electrocardiogram reported as TEAE will be summarized.

Non-serious TEAE will be displayed by SOC and PT. The common non-serious TEAE (subject frequency of ≥5%) will also be displayed by SOC and PT.

Numbers of occurrence of serious TEAE and the numbers of occurrence of non-serious TEAE will be summarized by SOC and PT, separately.

4.10.2. Clinical Laboratory Evaluations

Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total red cell count with morphology, and platelet count. These parameters will be measured at all study visits.

Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, globulin, albumin:globulin ratio, bilirubin (total, direct and indirect), creatine kinase (CK), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and cystatin C. These parameters will be measured at all study visits. Ideally, subjects should have fasted for at least 8 hours prior to blood collection.

Urinalysis assessments will include pH, specific gravity, glucose, ketones, blood, protein, creatinine, urobilinogen, bilirubin, nitrite, and leukocyte esterase. These parameters will be measured at all study visits.

Hematology, serum biochemistry, and urinalysis data and their changes from baseline (only for continuous laboratory parameters) will be summarized by visit. Maximal and minimal change from baseline in each parameter will also be summarized.

Shift tables for hematology, serum biochemistry, and urinalysis will also be presented showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low, and high [or abnormal]) to each visit (normal, low, and high [or abnormal]).

Frequency tables will be presented for safety monitoring parameters to show the number and percentages of subjects by severity grade categories defined in Table 2. If a CTCAE grade does not exist, abnormal results will be summarized by protocol-defined thresholds as noted in Table 2. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during the time period of interest.

By-subject listings will be provided for viral screen (hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV)), Serum beta chorionic gonadotropin (β-HCG), and CFTR gene sequencing in addition to the above mentioned clinical laboratory tests.

As necessary, laboratory abnormalities will be described by duration of study drug exposure, by dose, by age group, by sex, by race, by weight, and for special populations (eg, antibiotic use).

Table 2. Safety Monitoring Parameters and Actions To Be Taken

Organ System and Laboratory Parameter	Stop Study Drug Immediately, Confirm[a] Abnormal Value, and Then Start Work-Up	Stop Study Drug After Confirming[a] Abnormal Value, and Then Start Work-Up	Continue Study Drug, Confirm[a] Abnormal Value, and then Start Work-Up
Hepatic			
Serum total bilirubin[b]	≥Grade 3 (≥3.0 x ULN)	Grade 2 (1.5 – 3.0 x ULN)	---
Serum ALT	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Serum AST	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Serum GGT	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Renal			
Serum cystatin C	>2.00 mg/L	>1.33 – 2.00 mg/L	---
Serum creatinine	≥ Grade 2 (≥1.5 x ULN for age)	Grade 1 (>ULN – 1.5 x ULN for age)	---
Serum BUN	≥3.0 x ULN	≥1.5 – 3.0 x ULN	---
Urine protein: urine creatinine (spot)	---	>0.40 mg:mg	---
Urine blood (by dipstick)	4+ (in absence of menstruation)	3+ (in absence of menstruation)	2+ (in absence of menstruation)

[a] Laboratory abnormalities may be confirmed immediately or based on investigator judgment.

[b] Patients with a diagnosis of Gilbert's syndrome need not confirm the laboratory parameter and/or stop study drug unless the total bilirubin value exceeds 3.0 x ULN

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, Ca2+ = calcium, GGT = gamma glutamyl transferase, HCO3- = bicarbonate, K+ = potassium, Mg2+ = magnesium, Na+ = sodium, ULN = upper limit of normal

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4.11. Secondary Analyses

4.11.1. Vital Signs

Vital sign parameters include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), pulse oximetry (%), and body temperature (°C). Vital sign assessments and the changes from baseline for each parameter will be summarized by visit for the As-Treated population. Maximal and minimal change from baseline in each parameter will also be summarized.

Weight gain and loss will be tabulated for the following categories: normal change from baseline, weight gain (5-<10%), weight gain (10-<20%) (Grade 2), weight gain (>=20%) (Grade 3), weight loss (5-<10%) (Grade 1), weight Loss (10-<20%) (Grade 2), and weight loss (>=20%) (Grade 3).

For adults (≥18 years of age), blood pressure parameters will be programmatically flagged for Stage 1 hypertension (systolic: ≥140 to <160 mmHg, diastolic: ≥90 to <100 mmHg), Stage 2 hypertension (systolic: ≥160 mmHg, diastolic: ≥100 mmHg), and hypotension (systolic: <90 mmHg, diastolic: <60 mmHg) [USDHHS 2003]. For children and adolescents (<18 years of age), blood pressure parameters will be programmatically evaluated based upon height- and age-specific nomograms, and categorized by percentile (<95%, ≥95% to <99%, and ≥99%) [USDHHS 2005]. A summary of the number and percent of subjects by systolic and diastolic blood pressure categories of <95%, ≥95% to <99%, and ≥99% as defined as follows.

<95%: for age <18 years old, SBP <95% and DBP <95%; for age ≥18 years old, SBP <140 mmHg and DBP <90 mmHg.

≥95% to <99%: for age <18 years old, SBP ≥95% to <99% or DBP ≥95% to <99%; for age ≥18 years old, SBP ≥140 to <160 mmHg or DBP ≥90 to <100 mmHg. In addition, none of SBP and DBP meets the following criteria of ≥99%.

≥99%: for age <18 years old, SBP ≥99% or DBP ≥99%; for age ≥18 years old, SBP ≥160 mmHg or DBP ≥100 mmHg.

Shift tables will be presented showing change in results from baseline using above <95%, ≥95% to <99%, and ≥99% categories.

As necessary, vital signs will be described by duration of study drug exposure, by dose, by age group, by sex, by race, by weight, and for special populations (eg, antibiotic use).

4.11.2. Electrocardiographic Analyses

The assessments and change from baseline in electrocardiographic (ECG) parameters (e.g., RR, PR, QRS, QT, heart rate, QTcB, and QTcF) will be summarized by visit for the As-Treated population. Maximal and minimal change from baseline in each parameter will also be summarized.

Standard ECG intervals will be determined. The QT interval will be corrected by both the Bazett's and Fridericia's method as follows:

Bazett's: $QTcB = QT / (RR)^{1/2}$

Fridericia: $QTcF = QT / (RR)^{1/3}$

The QTc data obtained by using the Bazett and Fridericia corrections will be categorized separately into the following classifications and summarized by visit:

- QTc interval >450 msec and ≤480 msec
- QTc interval >480 msec and ≤500 msec
- QTc interval >500 msec

The change of the QTc values obtained by using the Bazett and Fridericia corrections will also be categorized separately as follows and summarized by visit:

- QTc interval increases from baseline by >30 msec and ≤60 msec
- QTc interval increases from baseline by >60 msec

QTc data will be presented in shift tables from baseline to each visit based on the categories: <450 msec, 450-480 msec, >480 msec.

The number and percentages of subjects with abnormal ECG parameter assessments will be tabulated by visit. Below list the abnormal criteria for the parameters:

- Heart rate > 140 bpm or < 50 bpm for age > 17 (or <60 for age 13-17, or <75 for age 6-12 and/or increase/decrease by > 30 bpm for heart rate;
- PR > 250 and/or increase by > 50 ms for PR interval;
- QRS > 120ms and/or increase by > 20 ms for QRS duration;
- QT, QTcB or QTcF > 500 ms and/or increase by > 60 ms for QT interval and its corrections.

Shift tables for the interpretation of the 12-lead ECG results ("normal", "abnormal, clinically insignificant", "abnormal, potentially clinically significant") will be presented by treatment group to show the change in results from baseline ("normal", "abnormal, clinically insignificant", "abnormal, potentially clinically significant") to each visit ("normal", "abnormal, clinically insignificant", "abnormal, potentially clinically significant").

4.11.3. Change from Baseline in %-predicted FEV_1

The descriptive statistics of %-predicted FEV_1, absolute, and relative change in %-predicted FEV_1 will be summarized for each visit for the ITT population. The highest FEV_1 assessment at each visit will be included into the analyses.

4.11.4. Pulmonary Exacerbation Rates

The descriptive statistics of the 48-week pulmonary exacerbation rates based on different definitions in Section 5.6 will be reported for the ITT population. The number of subjects with 0, ≥1, ≥2, and ≥3 pulmonary exacerbations based on different definitions will also be tabulated as well.

4.12. Tertiary Analyses

4.12.1. FVC

The absolute change in FVC will be analyzed using descriptive statistics for each visit for the ITT population.

4.12.2. Body Weight, Height, and BMI

Descriptive statistics on change from baseline in the body weight (kg), height (cm), and BMI will be displayed at each visit for the As-Treated population.

The change in weight or height percentiles calculated by using Centers for Disease Control and Prevention (CDC) growth chart [CDC] will be analyzed similarly for subjects < 18 years old at baseline.

4.13. Pharmacokinetics Analyses

The ataluren plasma concentrations collected prior to the morning dose will be listed.

For ataluren plasma concentrations, those that are below the limit of quantification will be identified by "BQ" in listings. Those values that are missing will be left blank in listings.

4.14. Interim Analyses

Interim safety analyses are planned when ~35 subjects have completed ≥32 weeks of treatment and when ~35 subjects have completed ≥64 weeks of treatment. Additional interim safety analyses may be performed based on the discretion of the DMC and will be described in the DMC charter. Based on the results of its deliberations, the DMC can recommend continuation of the study unchanged, study interruption, study termination, modification of the study, or alteration in the DMC monitoring plan.

The planned interim analysis will be based on the DMC Charter focusing on the safety review.

5. DATA HANDLING

5.1. Baseline

In general, Baseline is defined as the last non-missing valid assessment prior to or on the date of the first dose. However, Baseline for FEV_1, %-predicted FEV_1 , FVC, or FEF_{25-75} is the average of the corresponding valid assessments at Screening and Week 1 visit if they met ATS criteria.

5.2. Analysis Visits

Analysis visits are the scheduled visits in the protocol, unless specified otherwise. They are not derived via visit window mapping. Baseline is derived as noted in Section 5.1. Final Visit is derived as the last non-missing on-treatment visit during the study for each subject and included into the by-visit summary analyses. Early termination visit should also be derived as the visit right after the non-missing scheduled visit. For example, if the subject discontinued after Week 8, the early termination visit should be derived as Week 16.

5.3. Repeated Measurements in Spirometry Data

If there are multiple valid assessments in spirometry data at a particular visit, the highest value will be chosen for analysis.

5.4. Absolute and Relative Change from Baseline

The absolute change from baseline at each post-baseline visit is calculated as (post-baseline value – Baseline), while the relative change (%) from baseline at each post-baseline visit is calculated as (post-baseline value – Baseline)/Baseline×100.

5.5. Missing Dates of AE and Prior and Concomitant Medications

5.5.1. Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date is incomplete (ie, partially missing) for adverse events.

Missing day and month

- If the year is same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose of double-blind study drug will be assigned to the missing fields.

- If the year is prior to the year of the date of the first dose double-blind study drug, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first dose double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year are same as the year and month of the date of the first dose double-blind study drug, then the date of the first dose double-blind study drug will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of double-blind study drug or if both years are the same but the month is before the month of the date of the first dose of double-blind study drug, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of double-blind study drug or if both years are the same but the month is after the month of the date of the first dose of double-blind study drug, then the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

5.5.2. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

5.5.2.1. Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose of double-blind study drug will be assigned to the missing fields.

- If the year of the incomplete start date is prior to the year of the date of the first dose of double-blind study drug, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of double-blind study drug, then the day of the date of the first dose of double-blind study drug will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of double-blind study drug or if both years are the same but the month is before the month of the date of the first dose of double-blind study drug, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of double-blind study drug or if both years are the same but the month is after the month of the date of the first dose of double-blind study drug, then the first day of the month will be assigned to the missing day.

5.5.2.2. Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of double-blind study drug is missing, replace it with the last visit date or data cut-off date if the subject is on-going. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of double-blind study drug, then the day and month of the date of the last dose of double-blind study drug will be assigned to the missing fields.

- If the year of the incomplete stop date is prior to the year of the date of the last dose of double-blind study drug, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of double-blind study drug, then the day of the date of the last dose of double-blind study drug will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of double-blind study drug or if both years are the same but the month is before the month of the date of the last dose of double-blind study drug, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the last dose of double-blind study drug or if both years are the same but the month is after the month of the date of the last dose of double-blind study drug, then the first day of the month will be assigned to the missing day.

5.6. Pulmonary Exacerbation Definitions

A respiratory event evaluation form has been developed to collect CF pulmonary exacerbation information from the physician perspective. This form is designed to systematically characterize health-care provider observations related to exacerbations, and to allow categorization and scoring consistent with Fuch's or Rosenfeld CF exacerbation definitions. The data generated from these forms will provide the basis for recording incidence and rate of pulmonary exacerbations.

The following 12 Fuchs' signs and symptoms will be assessed in the definitions of Fuch's, modified Fuch's, and expanded Fuch's exacerbation.

1. Increased cough
2. Change in sputum volume, color, or consistency
3. New or increased hemoptysis
4. Increased dyspnea during moderate exertion, during mild exertion, or at rest
5. Sinus pain or tenderness
6. Change in sinus discharge
7. Malaise, fatigue, or lethargy
8. Anorexia or weight loss
9. Temperature above 38°C
10. Change in findings on chest examination
11. Relative 10% decrease in %-predicted FEV_1
12. Chest radiography results consistent with pulmonary infection

The modified Fuchs exacerbation is defined as the presence of at least 4 of 12 Fuchs' signs and symptoms without the requirement for treatment with antibiotics [Rowe 2012].

The expanded Fuchs exacerbation is defined as the presence of at least 4 of 12 Fuchs' signs and symptoms requiring treatment with any form of antibiotic treatment [inhaled, oral, or intravenous]. This antibiotic treatment is defined either as the addition of new antibiotics or an increase in the dose of an existing antibiotics within 14 days of the pulmonary exacerbation start/stop date.

The classic Fuchs exacerbation is defined as the presence of at least 4 of 12 Fuchs' signs and symptoms requiring treatment with parenteral antibiotics. This antibiotic treatment is defined either as the addition of new antibiotics or an increase in the dose of an existing antibiotics within 14 days of the pulmonary exacerbation start/stop date.

Pulmonary exacerbation based on investigator's assessments is recorded in the conclusion of respiratory event evaluation form.

6. ANALYSIS CHANGES FROM PROTOCOL

Due to the premature termination of the study, the time of withdrawal from the study analysis has been removed compared to current protocol version 3.0. The paired t-test on FEV_1 and the summary of FEF25-75 have also been removed. On the other hand, the drug exposure adjusted incidence rate of TEAEs has been added. Summary of occurrence of TEAE has been added as well.

7. BIBLIOGRAPHY

Centers for Disease Control and Prevention. CDC Growth Charts. Available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm.

Rowe SM, Sermet-Gaudelus I, Konstan M, Kerem E, Wilschanski M, DeBoeck K et al. Results of the Phase 3 Study of Ataluren in Nonsense Mutation Cystic Fibrosis (nmCF). Pediatric Pulmonology 2012 Sep; 47(S35): 290 (abst #193)

U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 03-5233. Bethesda, MD: National Heart, Lung, and Blood Institute. Revised December 2003.

U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. NIH Publication No. 05-5268. Bethesda, MD: National Heart, Lung, and Blood Institute. Revised May 2005.