NCT #: NCT02090959

PTC124-GD-020e DMD

A PHASE 3 EXTENSION STUDY OF ATALUREN (PTC124) IN PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

Statistical Analysis Plan

Version 2.0
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TABLE OF CONTENTS

TABLES

ABBREVIATIONS

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase
ATC	Anatomical-Therapeutic-Chemical classification
BUN	blood urea nitrogen
CI	confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CK	blood urea nitrogen
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
D/C	discontinuation
DBP	diastolic blood pressure
DMD	Duchenne muscular dystrophy
ECG	electrocardiogram
EK	Egen Klassifikation
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GGT	gamma glutamyl transferase
LOCF	last observation carried forward
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MMRM	mixed model repeated measures
nmDMD	nonsense mutation Duchenne muscular dystrophy
NSAA	North Star Ambulatory Assessment
PCF	peak cough flow
PEF	peak expiratory flow
SAP	statistical analysis plan
SOC	System Organ Class
SBP	systolic blood pressure
TEAE	treatment-emergent adverse event
TFT	Timed function test
TID	ter in die (3 times per day)
Tx	treatment
UE	upper extremity
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary
WNL	within normal limits

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-020e-DMD, also referred to as Study 020e. Preparation of this SAP incorporates statistical design elements present in the protocol amendment version 2.0 (dated 18 November 2015). Details are documented in sections 1-7.

In addition to the protocol defined analyses, a natural history control using the Cooperative International Neuromuscular Research Group (CINRG) will be utilized in order to help to better understand the long-term ataluren data. Although the planned analysis will not be included in the CSR it will be presented in Section 8 for completeness.

Where conflicts exist between this SAP and the study protocols, the information contained in this SAP supersedes the protocol.

2. STUDY DESIGN

All patients who successfully completed the Phase 3 double blind, placebo controlled study (PTC124-GD-020-DMD) were eligible for this Phase 3 open label, extension study (PTC124-GD-020e-DMD). This Phase 3 extension study will evaluate the long term safety of ataluren 10, 10, and 20 mg/kg.

The primary objective of this Phase 3 extension study will be to obtain long-term safety data to augment the overall safety database. The secondary objectives will be to augment the efficacy data collected in the double-blind study (PTC124-GD-020-DMD).

Screening and baseline procedures are structured to avoid a gap in treatment between the double-blind study (PTC124-GD-020-DMD) and this extension study. When possible, Screening/Baseline (Visit 1) for this extension study should occur on the same day as the End-of-Study visit for the double-blind study (PTC124-GD-020-DMD). During the treatment period, study assessments will be performed at clinic visits at Week 12 and thereafter every 12 weeks until the end of the study.

The proposed types and timing of data to be recorded are described in Table 1 for amendment 2.0 (dated 19 November 2015).

Table 1. Schedule of Events

Study Period	Screening/Baseline	Treatment Period											Post-Treatment	
Study Week (±7 days)	Day 1	12	24	36	48	60	72	84	96	108	120	132	144	6 Weeks Post-Tx
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Informed consent	X													
Vital signs	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[a]				X				X				X	
Hematology	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal ultrasound	X[a]				X				X				X	
12-lead ECG	X[a]				X				X				X	X
Study drug assignment	X													
Drug Dispensed	X	X	X	X	X	X	X	X	X	X	X	X		
Drug compliance		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6-minute walk test	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Timed function tests	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
North Star Ambulatory Assessment	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Activities of Daily Living/Disease Status Survey	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
PODCI Questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry	X		X		X		X		X		X		X	
PUL assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics		X	X	X	X	X	X	X	X	X	X	X	X	

a Study procedure need not be performed if Day 1 is within 14 days of the end-of-study evaluations at Week 48 (Visit 8) of the preceding Phase 3 double-blind study (PTC124-GD-020-DMD).

Abbreviations:; D/C = discontinuation; ECG = electrocardiogram; F/U = follow-up; PUL = Performance of Upper Limb, Tx = treatment

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety of ataluren in boys with nonsense mutation dystrophinopathy, as determined by adverse events and laboratory abnormalities.

3.2. Secondary Objectives

The secondary objectives, which evaluate the effects of ataluren on major clinical manifestations of DMD, are:

Physical

- To determine the effect of ataluren on ambulation in patients who are ambulatory.
- To evaluate the effect of ataluren on proximal muscle function in patients who are able to perform timed function tests.
- To evaluate the effect of ataluren on physical function in patients who are able to perform the North Star Ambulatory Assessment.
- To evaluate the effect of ataluren on upper limb function.

Pulmonary function

- To evaluate the effect of ataluren on pulmonary function.

Patient-reported outcomes

- To determine the effect of ataluren on health-related quality of life (HRQL) as reported by patients and parents/caregivers.
- To assess the effect of ataluren on activities of daily living.

Exposure

- To assess long-term ataluren plasma exposure.

3.3. Study Endpoints

Primary:

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

Secondary:

Physical

- Change in ambulation as measured by the 6MWT
- Change in proximal muscle function as assessed by timed function tests (time to rise from supine position, time to run 10 meters, and time to climb/descend 4 stairs)

- Change in physical function as assessed by the North Star Ambulatory Assessment
- Change in motor performance of the upper limb as measured by the Performance Upper Limb (PUL)

Pulmonary function

Change in pulmonary function as measured by spirometry (eg. FVC, FEV1)

Patient-Reported Outcomes

- Change in patient- and parent/caregiver-reported HRQL as measured by the PODCI Transfer/Basic Mobility and Sports/Physical Functioning scores
- Change in patient and parent/caregiver reported activities of daily living

Exposure

- Pre-dose ataluren plasma concentrations prior to morning ataluren administration at each clinic visit as assessed by a validated bioanalytical method

Safety

- Change from baseline in other safety parameters (eg, vital signs)

3.4. Sample Size

The sample size for this extension study is not based upon any formal statistical hypothesis, but its upper bound is determined by the requirement that patients must have participated in the previous Phase 3 study of PTC124 (PTC124-GD-020-DMD) in which ~ 220 patients are expected to be enrolled.

4. STUDY POPULATION

- As-Treated population: All subjects who receive at least 1 dose of ataluren treatment in the extension phase. This population will be evaluated in the analyses of safety and efficacy.
- PK population: All subjects who has at least one PK concentration data. This population will used for the PK concentration and parameter summary.

5. STATISTICAL ANALYSIS

5.1. General Statistical Considerations

Summary tables for continuous variables will contain the following statistics: n, mean, standard deviation, standard error, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include N, n, and percentages. In by-visit summaries, the analysis visits will be derived via visit mapping windows.

For descriptive summary tables, the all data will be analyzed and displayed by ambulatory status (ambulatory or non-ambulatory) at baseline, unless specified otherwise. Where applicable, the summary data (mean, standard error) will be presented in graphical form of against time of visit.

By-patient listings will be created for each CRF module. The data will be listed by center/subject ID and visit.

5.2. Subject Disposition

A summary of subjects who discontinued ataluren treatment prematurely or were removed from the study prematurely will be reported for overall subjects and a subgroup of ambulatory/non-ambulatory subjects at study entry. Reasons for treatment early discontinuations will be described.

Since the sponsor has decided to discontinue the Study 020e, subjects who discontinue the study due to this reason or complete the study per protocol will be considered as censored in the time to discontinuation analysis. The time to discontinuation (in weeks) is calculated as (discontinuation date - first dose date +1)/7 for subjects who discontinue from the study due to reasons other than sponsor's decision of termination the study or transitioning to commercial drug. For subjects who discontinue due to these reasons or complete the study, the censor time is (discontinuation date - first dose date +1)/7 and (study completion date - first dose date + 1)/7, respectively. Time to discontinuation will be assessed using Kaplan-Meier methods and the Kaplan-Meier curve will be displayed.

The protocol deviations will be summarized by type. A listing of protocol deviations will be provided.

5.3. Demographic and Baseline Characteristics

Subject demographic and disease characteristics (age, age group (6-11, 12-17, and ≥18 years), gender, race, ethnicity, height, weight, body mass index, six minute walk distance, six minute walk distance groups (<300 meters, ≥300-<400 meters, ≥400 meters), time to run/walk 10 meter, time to stand from supine, time to stand from supine (<5s, ≥5s), performance of Upper Limb Assessment (PUL), corticosteroid use (Yes/No), and ambulatory/non-ambulatory) at study entry will be summarized for overall subjects, a subgroup of subjects with corticosteroid use duration (<12 months, ≥12 months) at baseline, a subgroup of subjects with corticosteroid type (deflazacort vs prednisone/prednisolone) at baseline, and a subgroup of ambulatory/non-ambulatory subjects at study entry.

5.4. Clinical History

N/A.

5.5. Concomitant Medications and Procedures

Prior medications and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG) dictionary dated 2017DEC01 into Anatomical-Therapeutic-Chemical (ATC) classification codes. The prior medications are defined as any medications that subjects started before the first dose date. Concomitant medications are defined as any medications that subjects took after/on the first dose date. The prior and concomitant medications will be summarized by ATC level 3 and preferred terms. The concomitant cardiac medications will be summarized similarly.

Specific attention will be focused on corticosteroid use. The numbers of subjects receiving/not-receiving corticosteroids at baseline or during the study, switching in different types of corticosteroids during the study, and duration of corticosteroid use during the study and by type will be summarized.

The prior and concomitant non-drug therapies will be defined similar to the prior and concomitant medications. They will be coded by MedDRA version 20.1 and summarized by SOC and PT.

5.6. Study Drug Exposure and Compliance

Study drug compliance will be assessed in terms of the percentage of drug actually taken relative to the amount that should have been taken during the study. Treatment duration (weeks) will be calculated as (last dose date – first dose date +1)/7, if date of last study drug intake was not known: (last visit date – first dose date +1)/7. The summary of the overall compliance and treatment duration will be represented for overall subjects and a subgroup of ambulatory/non-ambulatory subjects at study entry.

5.7. Primary Variables

5.7.1. Adverse Events

Adverse events will be classified using MedDRA version 20.1 classification system. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 3.0 whenever possible. 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 6 weeks after the last dose of study drug in this study.

If a subject has multiple events under any given SOC and PT, the subject will be counted only once under that SOC and PT. If a subject has the same AE on multiple occasions, the highest severity (fetal, life-threatening, severe, moderate, and mild) recorded for the event will be presented and the highest drug relationship (1 = 'Unrelated', 2 = 'Unlikely', 3 = 'Possibly', 4 = 'Probably', 5 = 'Related'), reclassified into Related ('Possibly Related', 'Probably Related', 'Related') or Not Related ('Unrelated' and 'Unlikely'), will be presented on the respective tables.

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 overall group,
4) by PT in the descending order of the PT frequency in overall 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 events leading to special diagnostic evaluations TEAEs and possibly or probably treatment-related 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 hepatic and renal AEs leading to special diagnostic evaluations will be provided.

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 336. That is, a year is defined as 48 weeks.

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.

5.7.2. Laboratory Tests

Hematological, serum biochemistry, adrenal laboratories, and urine data and their changes (only for continuous laboratory parameters) from baseline will be summarized by visit.

Shift tables for hematology and biochemistry data 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]).

Summary of abnormalities in laboratory variables pre-defined for safety monitoring will be done per the following Table 2.

Table 2: Safety Monitoring Parameters and Actions to be Taken

Organ System and Laboratory Parameter	Stop Study Drug Immediately, Confirm Abnormal Value, and Then Start Work-Up	Stop Study Drug After Confirming[a] Abnormal Value, and Then Start Work-Up	Continue Study Drug, Confirm Abnormal Value, and then Start Work-Up[a]
Hepatic			
Serum total bilirubin	≥Grade 3 (≥3.0 x ULN)	Grade 2 (1.5 – 3.0 x ULN)	---
Serum GGT	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Serum ALT			↑ of >150 U/L with stable or ↓ CK
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 protein: urine osmolality (spot)	---	>0.30 mg/L:mOsm/kg	---
Urine blood (by dipstick)	4+ (Large)	3+ (Moderate)	2+ (Small)
Serum electrolytes	**Grade 3-4**	**Grade 2**	**Grade 1**
Serum Na+, high	>155 mmol/L	>150 – 155 mmol/L	---
Serum Na+, low	<130 mmol/L	---	---
Serum K+, high	>6.0 mmol/L	>5.5 – 6.0 mmol/L	---
Serum K+, low	<3.0 mmol/L	---	---
Serum Mg^{2+}, high	>1.23 mmol/L	---	---
Serum Mg^{2+}, low	<0.4 mmol/L	<0.5 – 0.4 mmol/L	---
Total serum Ca^{2+}, high	>3.1 mmol/L	>2.9 – 3.1 mmol/L	---
Total serum Ca^{2+}, low	<1.75 mmol/L	<2.0 – 1.75 mmol/L	---
Serum phosphorous	<0.6 mmol/L	<0.8 – 0.6 mmol/L	---
Serum HCO_3-	<11 mmol/L	<16 – 11 mmol/L	---

a Laboratory abnormalities may be confirmed immediately or at the next scheduled clinic visit based on investigator judgment.

Abbreviations: ALT = alanine aminotransferase, BUN = blood urea nitrogen, Ca^{2+} = calcium, CK = creatine kinase, GGT = gamma glutamyl transferase, HCO_3- = bicarbonate, K+ = potassium, Mg^{2+} = magnesium, Na+ = sodium, ULN = upper limit of normal

5.8. Other Variables

5.8.1. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, body weight, height, ulna length, arm span, and body temperature) will summarized by visit for overall subjects.

Number (%) of subjects with meeting hypertension criteria as the following will be summarized.

- If age <18 years old, the hypertension criteria are based on age, gender, and height-adjusted systolic blood pressure (SBP) and diastolic blood pressure (DBP) percentile results (Hypertensive: ≥ 95th percentile; Pre-hypertensive: 90 - < 95th percentile; Normal: < 90th percentile).
- If age ≥ 18 years old, hypertensive: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; pre-hypertensive: SBP 120 - 139 mmHg or DBP 80 - 89 mmHg; Normal: SBP 90 -119 mmHg and DBP 60 - 79 mmHg.

5.8.2. ECGs

Number (%) of subjects experiencing a normal/abnormal ECG assessment will be tabulated by visit for overall subjects.

5.8.3. 6-Minute Walk Test

The distance walked at each visit and the change from baseline at each post baseline visit, as obtained from the 6-minute walk test (6MWT), will be summarized descriptively for ambulatory subjects with non-missing baseline 6MWT assessments. The distance walked at each will also be summarized for each actual age.

5.8.4. Timed Function Tests

Timed function test data (ie, time to stand from supine, time to run/walk 10 meters, time to climb 4 stairs, and time to descend 4 stairs) and change from baseline to each post baseline visit will be summarized descriptively by visit for ambulatory subjects with non-missing baseline timed function tests assessments. Similarly the time to stand from supine, time to run/walk 10 meters, time to climb 4 stairs, and time to descend 4 stairs will also be summarized for each actual age.

Timed function test (TFT) data imputation rules as the following will be used in the summary.

- If time to run/walk 10 meters > 30 sec, then set to 30 sec.
- If time to stand from supine > 30 sec, then set to 30 sec.

The Kaplan-Meier method will be applied to the analysis of age at loss of ambulation. The median age at loss of ambulation will be reported by treatment group in studies 020/020e (ataluren/ataluren, placebo/ ataluren, and overall), corticosteroid use duration (<12 months, ≥12 months), and corticosteroid type (deflazacort vs prednisone/prednisolone) at baseline. The Kaplan-Meier curves will also be displayed. The age at loss of ambulation is defined as age of the disease progression reported as the adverse event. The subjects who are ambulatory at the end of study or discontinuation will be censored on the last valid visit date. Age on that date will be used in the analysis.

5.8.5. North Star Ambulatory Assessment

The NSAA consists of 17 activities, each scored as 0, 1, or 2. The sum of these 17 scores will be used to form a total score. If fewer than 13 of the 17 activities are performed, the total score will be considered missing. If from 13 to 16 activities are performed, the total score will be calculated by multiplying the sum of the scores in the x activities that were performed by 17/x. If an activity cannot be performed due to disease progression/loss of ambulation, a score of zero will be assigned. The linear score is a transformation of the NSAA score to a scale of 0 to 100 [Mayhew 2013].

Total scores and linear scores from the North Star Ambulatory Assessment will be summarized by visit and change from baseline to each post baseline visit will be summarized descriptively for ambulatory subjects with non-missing baseline NSAA assessments. Similarly the total and linear scores will also be summarized for each actual age.

The number and proportion of loss of function of each North Star Ambulatory Assessment item at week 48 will be tabulated. The function loss defined as a shift from non-zero at baseline to zero at week 48. The missing data will be handled by last observation carried forward (LOCF).

5.8.6. Pediatric Outcomes Data Collection Instrument (PODCI)

The two PODCI domains (transfers/mobility and sports participation) each provide a numerical score from 0-100. The PODCI domain scores and changes from baseline will be summarized by visit for ambulatory subjects.

5.8.7. Spirometry

Pulmonary function parameters of %-predicated FVC, %-predicted FEV1 (adjusted using ulna length and age), peak expiratory flow (PEF), and peak cough flow (PCF) and their absolute and relative changes from baseline will be summarized by visit. Similarly the observed values of the endpoints will also be summarized for each actual age.

5.8.8. Performance Upper Limb (PUL) Assessment

The PUL assessment includes 22 items (with an entry item to define starting functional level to avoid testing functional dimensions in which the subject lacks the lower limit of function, and 21 items subdivided into shoulder level (4 items), elbow level (9 items), and distal level (8 items) dimensions. Scoring varies across the scale from 0-1 to 0-6 according to performance. Each dimension will be scored separately with a maximum score of 16 for shoulder level, 34 for elbow level, and 24 for distal level. The total score will be calculated by adding the 3 level scores (maximum global score of 74). The total score and 3 dimension scores and their changes from baseline will be summarized by visit for non-ambulatory subjects. Similarly the PUL assessment will also be summarized for each actual age.

5.8.9. Activities of Daily Living/Disease Status Survey

For change in activities of daily living/disease status of prospective survey data, number (%) of subjects with changes from baseline to each visit will be summarized by each category for overall subjects. If there are multiple symptoms under a category, the highest score/worse case of all available symptoms was selected for the category in the summary.

5.8.10. Renal Ultra Sound

Shift tables for renal ultrasound results ("normal", "abnormal and not clinically significant", abnormal and clinically significant") will be presented at each visit.

5.8.11. Physical Examination

Since abnormal findings in physical examination need to be reported in AE and vital signs, a data listing of physical examination will be provided.

5.8.12. Ataluren Plasma Concentrations

Ataluren plasma concentrations (µg/mL) collected prior to the morning dose will be summarized by visit.

6. DATA HANDLING

6.1. Analysis Visits based on Visit Windows

Since some subjects had early terminations or unscheduled visits in during, the derived analysis visits will be generated by visit window defined as follows. For the 6 weeks post-treatment visit, assign AVISITN=14 and AVISIT=6-Weeks Post-Treatment.

Let Study day=assessment date –first dose date +1.

Study Day	AVISITN	AVISIT
Study Event='SCR' or . < study day ≤ 1	1	Baseline
1 < study day ≤ 126	2	Week 12
126 < study day ≤ 210	3	Week 24
210 < study day ≤ 294	4	Week 36
294 < study day ≤ 378	5	Week 48
378 < study day ≤ 462	6	Week 60
462 < study day ≤ 546	7	Week 72
546 < study day ≤ 630	8	Week 84
630 < study day ≤ 714	9	Week 96
714 < study day ≤ 798	10	Week 108
798 < study day ≤ 882	11	Week 120
882 < study day ≤ 966	12	Week 132
966 < study day	13	Week 144

If there are more than 1 valid assessment within one visit window, the last one will be chosen as the analysis value.

6.2. Baseline

In general, Baseline is defined as the last non-missing valid assessment prior to or on the date of the first dose of the study. For spirometry tests, Visit 1 measurements can be used as baseline even if they are after the first dose.

6.3. 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.

6.4. Missing Dates of AE and Prior and Concomitant Medications

6.4.1. 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.

6.4.2. 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.

6.4.2.1. *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.

6.4.2.2. *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.

7. ANALYSIS CHANGES FROM PROTOCOL

The supportive analyses on 6-minute walk test have been removed because they are not of the scientific interest any more after the early termination of the study. All paired t-tests have been removed.

8. CINRG DATA

8.1. Overview of CINRG Data

CINRG is a natural history registry database which collects DMD data using consortium of medical and scientific investigators from academic and research centers on neuromuscular disease. Demographics and baseline characteristics, corticosteroids medication use (and type), efficacy endpoints including 6MWT, time taken to stand from supine, time taken to run/walk 10 meters, NSAA, spirometry, and EK will be analyzed. Other endpoints collected by CINRG but not in Study 020e will not be included into this analysis plan. The CINRG natural history control (data transferred on November 18, 2016) will be compared to ataluren's efficacy data to assess the ataluren's long- term treatment benefit.

8.2. Matched Populations

To compare CINRG with Study 020e, the matched populations are defined in the following table for different endpoints and analyses.

Endpoint/Analysis	Age (Years) at Study Entry	Age (Years) at Assessment	Steroid Use	Ambulation status	Exclude EXON 51 and 45	Baseline value	Visit Year
Age at loss of ambulation	7-14	Not applicable	Cumulative Steroid use duration at each assessment ≥6 months	Ambulatory at study entry	Yes		Not applicable
Piece-wise regression based on FVC	Not applicable	≤ 19	Cumulative Steroid use duration at each assessment ≥24 months	Non-ambulatory at each assessment	Yes	Not applicable	≥2012
%-predicted FVC	7-15	Not applicable	Not applicable	Non-ambulatory at study entry	Yes		Not applicable
%-predicted FEV1	7-15	Not applicable	Not applicable	Non-ambulatory at study entry	Yes		Not applicable
PEF	7-15	Not applicable	Not applicable	Non-ambulatory at study entry	Yes		Not applicable
6MWT	7-15	Not applicable	Cumulative Steroid use duration at each assessment ≥6 months	Ambulatory at study entry	Yes		Not applicable
time taken to run/walk 10 meters	7-15	Not applicable	Cumulative Steroid use duration at each assessment ≥6 months	Ambulatory at study entry	Yes		Not applicable
time taken to stand from supine	7-15	Not applicable	Cumulative Steroid use duration at each assessment ≥6 months	Ambulatory at study entry	Yes		Not applicable
NSAA	7-15	Not applicable	Cumulative Steroid use duration at each assessment ≥6 months	Ambulatory at study entry	Yes		Not applicable

8.3. Analyses Based on Matched Populations of CINRG and Study 020e

Demographics and baseline characteristics (age, race, ambulation status, corticosteroid use (yes or no), duration of corticosteroid use, corticosteroid type, baseline 6MWD, baseline time to run/walk 10 meters, baseline time to stand from supine, baseline %-predicted FEV1, %-predicted FVC, PEF, NSAA total score) will be summarized descriptively for CINRG and Study 020e

based on each matched population. The summary will be displayed by corticosteroid use (yes vs no) and cumulative steroid use (≥12 months vs <12 months) for baseline ambulatory and non-ambulatory subjects separately. The baseline is defined as the first visit in CINRG data.
The comparison to the natural history data (ie, CINRG data) based on matched subjects will be performed in FVC using piece-wise regression models and age to loss of ambulation using Kaplan-Meier method.
Piece-wise regression models will be applied to log FVC in CINRG and study 020e data, separately, using different ages as the changepoint. The most possible changepoint in terms of age will be chosen at the best model fit (ie, AICC value is the maximal). Scatter plots of log FVC and the most fitted piece-wise regression line will be generated for CINRG and study 020e, separately. Comparison between the observed and predicted FVC in study 020e will be performed using repeated measures analysis of variance to account for within-subject correlation, where the predicted values are based on the regression equation estimated by the best fit regression model based on CINRG data. `
In study 020e, the loss of ambulation is defined as the disease progression reported as the adverse event or the time to run/walk 10 meters >30 seconds, whichever occurs earlier. The event age is the one on the AE start date. The subjects who are ambulatory at the end of study will be censored on the last valid timed function tests assessment date. Age on that date will be used in the analysis. In the CINRG data, the age at the earliest report of the non-ambulation or the time to run/walk 10 meters >30 seconds, whichever earlier, will be picked as the event age. If subjects in CINRG data do not report non-ambulation, the age at the last report of ambulation will be chosen as the censor age. A sensitivity analysis will be performing based on the loss of ambulation defined only by disease progression AE.

For CINRG data only, the observed values will be summarized descriptively for each actual age on 6MWT, time to run/walk 10 meters, time to stand from supine, NSAA total and linear scores, %-predicted FVC, %-predicted FEV1, and PEF by corticosteroid use at baseline (yes or no) and overall based on the matched populations.

NSAA score derivation algorithms in Study 020e will be applied to CINRG data.

9. BIBLIOGRAPHY

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10. DOCUMENT HISTORY

Version Number	Author	Description
Version 1	[redacted]	Initial version – Sept. 18, 2018
Version 2	[redacted]	Jan. 23, 2019 Removed the comments that accidently left in the document Corrected document date in the header.