STATISTICAL ANALYSIS PLAN

PRODUCT UNDER INVESTIGATION:

PTC124

NCT #: NCT02819557

TITLE:

A PHASE 2 STUDY OF THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ATALUREN (PTC124®) IN SUBJECTS AGED ≥2 TO <5 YEARS OLD WITH NONSENSE MUTATION DYSTROPHINOPATHY

PROTOCOL NUMBER
PTC124-GD-030-DMD

STUDY SPONSOR
PTC Therapeutics, Inc.
100 Corporate Court
South Plainfield, NJ 07080 USA

PREPARED BY
WCCT Global
5630 Cerritos Ave.
Cypress CA 90630

DATE AND VERSION
March 19, 2018
(Based on Protocol Version 2 dated January 28, 2016)

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STUDY PHASE
Phase II

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SIGNATURE PAGE – PTC THERAPEUTICS, INC.

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

[redacted]
PTC Therapeutics, Inc.

Date (dd mmm yyyy)

[redacted]
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SIGNATURE PAGE - WCCT

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1. LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
6MWT	6-minute walk test
AE	Adverse event(s)
ALT	Alanine aminotransferase
AR	Accumulation Ratio
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC_{0-t}	Area under the plasma concentration time curve from time zero to the time of last quantifiable concentration
AUC_{0-10}	Area under the plasma concentration time curve from time zero up to 10 hours after the morning dosing
AUC_{0-24}	Area under the concentration curve versus time curve from time zero to 24 hours
BMI	Body mass index
BCRP	Breast Cancer Resistant Protein
BUN	Blood urea nitrogen
Bayley-III	Bayley-III Scales of Infant and Toddler Development
CD-ROM	Compact disc read-only memory
CF	Cystic fibrosis
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CK	Creatine kinase
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CL/F	Apparent clearance
CLd/F	Apparent distribution clearance
C_{max}	Maximum observed plasma concentration
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough@6h}$	Concentration at the end of the first (morning) dosage interval
CV%	Coefficient of variation
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase

HPLC-MS/MS	High performance liquid chromatography-mass spectrometry
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
ka	Rate constant of absorption
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmelonic acidemia
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCA	Non-compartmental analysis
nmDMD	Nonsense mutation Duchenne muscular dystrophy
nmCF	Nonsense mutation cystic fibrosis
NSAA	North Star Ambulatory Assessment
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B3	Organic anion transporting polypeptide 1B3
PD	Pharmacodynamic(s)
PIP	Pediatric Investigation
PK	Pharmacokinetic(s)
popPK	Population PK
PTC124	Ataluren
SAS	Statistical Analysis System
SAE	Serious adverse event
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TFT	Timed function tests
TID	3 times per day
tmax	Time of maximum observed plasma concentration
UGT	Uridine diphosphate glucuronosyltransferase
UGT1A9	Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A9
US	United States
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
WHODRUG	World Health Organization Drug Dictionary

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to prospectively (a priori) outline the types of analyses and presentations of the safety, efficacy, and PK data.

This document contains information to support the generation of a Clinical Study Report (CSR) for Clinical Protocol PTC124-GD-030-DMD, including detailed descriptions of the statistical methodologies to be applied, as well as the post-text tables, figures, analysis summary tables, and subject data listings intended to present the analysis results.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The primary objective of this study is to evaluate the safety of ataluren as measured by type, frequency, severity, timing, and relationship to study drug of treatment emergent adverse events (TEAEs), laboratory abnormalities and electrocardiograms (ECGs).

There are 5 secondary objectives of the study, presented in the order from section 3.2 of the protocol:

- Evaluate the plasma pharmacokinetics (PK) of ataluren in subjects aged ≥2 to <5 years old with nmDMD
- Assess proximal muscle function using timed function tests (TFTs)
- Assess change in physical function using the North Star Ambulatory Assessment (NSAA)
- Determine the effect of ataluren on weight, height, and body mass index (BMI)
- Assess the palatability of ataluren

3.2. Study Design

Protocol PTC124-GD-030-DMD is a Phase 2, multiple-dose, open-label study evaluating the safety, and pharmacokinetics (PK) of ataluren in subjects aged ≥2 to <5 years old with Nonsense Mutation Dystrophinopathy (nmDMD). In nmDMD, early start of treatment is important and, therefore, it is relevant to understand the correct and tolerable dose in this age group, particularly since ataluren is dosed by weight. This study is composed of 4 periods: a 4-week screening period, a 4-week study period, and a 48-week extension period for subjects who complete the 4- week study period (52 weeks total treatment), and a 4-week post-treatment follow-up period. The objective of the 48-week extension period is to assess the long-term safety of chronic administration of ataluren in this subject population.

3.3. Schedule of Assessments

The Schedule of Assessments is presented in Table 2 of the protocol. The planned assessment times are Day -28 (Screening); Day 1 for Baseline assessment for the Ataluren Treatment Period; Day 28, 112, 196, 280, 364 (Ataluren Treatment Period), and Day 392 (Follow-up Period).

3.4. Endpoints

3.4.1. Primary Endpoints

There are 4 primary endpoints defined in the protocol for the study.

- Overall safety profile in terms of the type, frequency, severity, timing, and relationship to study therapy of any adverse events or abnormalities of physical findings, laboratory tests, or ECGs

- Occurrence of any dose-limiting toxicities (DLTs)
- Drug discontinuations due to adverse events
- Serious adverse events (SAEs)

Adverse events will be monitored throughout the course of the study and TEAEs will be reported from the time of study drug administration during the 4-week PK study period through the extension period (study day 392 / week 56). Subjects must be followed for adverse events and serious adverse events for at least 28 days after the last dose of ataluren. A subject withdrawn from the study because of an AE or SAE must be followed by the Investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized.

The physical examinations will include the following body system or organ assessments. The results will be classified as normal or abnormal.

- Cardiovascular system
- Chest and lungs
- Thyroid
- Abdomen
- Nervous System
- Skin and mucosae
- Musculoskeletal
- Eyes, Ears, Nose, Mouth, Throat
- Spine
- Lymph Nodes
- Extremities
- Other

Abnormal laboratory tests will be reported as adverse events under the system organ class of Investigations. Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count. These parameters will be measured at every protocol-specified study visit. Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, bilirubin (total, direct, and indirect), AST, ALT, GGT, CK, lactate dehydrogenase, alkaline phosphatase, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and cystatin C. These parameters will be measured at every protocol-specified study visit. Urinalysis will include analysis for pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, and leukocyte esterase. These parameters will be measured at every protocol- specified study visit.

A 12-lead ECG will be obtained at screening, Week 4 (Visit 3), Week 52 (Visit 7/End of Treatment), and 4-week Follow-up (Visit 8). ECGs will be interpreted for clinical significance and classified as Normal, Abnormal, Not Clinically Significant, or Abnormal, Clinically Significant.

3.4.2. Secondary Endpoints

There are 5 secondary endpoints that cover PK, performance measurements, physical examination and palatability (ref. Section 3.4 from the protocol):

Ataluren concentrations in plasma will be analyzed to derive the pharmacokinetics using standard, non-compartmental methods. On each of the sampling days (Study Days 1 and 28), blood samples for ataluren concentration assessments will be collected immediately pre-dose and at specified time points following the morning, midday, and evening doses. The parameters to be derived are as follow:

- Area under the plasma concentration time curve from time zero to the time of last quantifiable concentration (AUC_{0-t})
- Area under the plasma concentration time curve from time zero up to 10 hours after the morning dosing (AUC_{0-10})
- Maximum observed plasma concentration (C_{max})
- Concentration at the end of the first (morning) dosage interval ($C_{trough@6h}$)
- Time of maximum observed plasma concentration (t_{max})
- The accumulation ratio for the AUC from day 1 and 28:
  AR(AUC) = (AUC0-t) on Day 28 / (AUC0-t) on Day 1
- The accumulation ratio for the C_{max} from day 1 and 28: AR(C_{max}) = (C_{max}) on Day28 / (C_{max}) on Day 1

TFTs assessed prior to ataluren dosing on the first day of treatment (Visit 2), Week 28 (Visit 5), and Week 52 (Visit 7/ET). TFTs include:

- Time taken to run/walk 10 meters,
- Time to climb 4 stairs,
- Time to descend 4 stairs, and
- Time to stand up from a supine position.

NSAA will be performed prior to ataluren dosing on the first day of treatment (Visit 2), Week 28 (Visit 5), and Week 52 (Visit 7/ET). For each of the evaluations, the subject will be scored with a 0 (Unable to achieve independently), 1 (Modified method but achieves goal independent of physical assistance from another) or a 2 (Normal – no obvious modification of activity). The full scale is presented below.

- Stand (0, 1 or 2)
- Walk (0, 1 or 2)
- Stand up from chair (0, 1 or 2)
- Stand on one leg – right (0, 1 or 2)
- Stand on one leg – left (0, 1 or 2)
- Climb box step – right (0, 1 or 2)
- Climb box step – left (0, 1 or 2)
- Descend box step – right (0, 1 or 2)
- Descend box step – left (0, 1 or 2)

- Gets to sitting (0, 1 or 2)
- Rise from floor (0, 1 or 2)
- Lifts head (0, 1 or 2)
- Stands on heel (0, 1 or 2)
- Jump (0, 1 or 2)
- Hop right leg (0, 1 or 2)
- Hop left leg (0, 1 or 2)
- Run (10m) (0, 1 or 2)

The total of the previous 17 items will be summed on an intra-subject basis to obtain the total score. The best total score is 34 and the worst is 0.

Recent updates to the NSAA have removed 'Lifts Head' from the total score. Although the results from all 17 items have been collected, a summary will be presented based on the 16 items without the result from 'Lifts Head'. The results of these 16 items will be summed on an intra- subject basis to obtain the total score. The best total score is 32 and the worst is 0.

Two additional subset summaries will be generated from the 17 items in the NSAA. The first is an 8-item NSAA subscale. This 8-item subscale will include the following 8 items from the full NSAA.

- Stand (0, 1 or 2)
- Walk (0, 1 or 2)
- Stand up from chair (0, 1 or 2)
- Climb box step – right (0, 1 or 2)
- Climb box step – left (0, 1 or 2)
- Gets to sitting (0, 1 or 2)
- Jump (0, 1 or 2)
- Run (10m) (0, 1 or 2)

The total of these 8 items will be summed on an intra-subject basis to obtain the total score for the 8-item subscale. The best total score is 16 and the worst is 0.

The second is a 3-item NSAA subscale. This 3-item subscale will include the following 3 items from the full NSAA.

- Stand (0, 1 or 2)
- Walk (0, 1 or 2)
- Stand up from chair (0, 1 or 2)

The total of these 3 items will be summed on an intra-subject basis to obtain the total score for the 3-item subscale. The best total score is 6 and the worst is 0.

Two additional measures will also be recorded and summarized.

- Rise from Floor Time (seconds)
- Run (10m) Time (seconds)

Ataluren palatability characteristics will be based on the parent/caregiver questionnaire. The first question below will be asked of the subject and the response from the subjects will be recorded as *bad, not sure*, or *good*. The second and third questions will be asked of the caregiver and the response from the caregiver will be recorded as *strongly disagree, disagree, neither agree nor disagree, agree,* or *strongly agree.* The specific questions are presented below.

- *How did the medicine taste?*
- *On the basis of reaction/facial expression of your child, do you think that the medication is pleasant?*
- *You sometimes have problems in giving the medication to your child because he/she refuses to take it or throws it up.*

3.5. Sample Size Justification

The planned sample size of 12 subjects for this study should provide adequate precision for the prediction of PK parameters (apparent clearance and volume of distribution).

3.6. Study Treatments and Dose Administration

Dosing of ataluren is based on milligrams of drug per kilogram of subject body weight; body weight is re-assessed every 12 weeks. All subjects will receive approximately 10, 10, 20 mg/kg ataluren 3 times daily (TID) for 4 weeks during the PK portion and for 48 weeks during the extension period. Three doses will be administered each day; the first dose will be in the morning, the second dose will be administered in the middle of the day (midday), and the third dose will be administered in the evening.

3.7. Estimated Duration of Subject Participation and Follow-up

Subjects who do not terminate early from the study will be followed for 56 weeks; a total of 52 weeks after the initial administration of the study drug. If a subject completes the study with an ongoing AE, the site will continue to follow up with the subject until resolution if ≤28 days from the last dose of study drug. If, after 28 days the AE is still continuing but not assessed as serious, the outcome will be recorded as ongoing and no further follow up will be necessary. If a subject completes the study with an ongoing SAE, the subject will be followed until resolution or stabilization or until no further information can be obtained.

3.8. Interim Analyses

An interim safety analysis is planned and will be conducted by an independent Data Monitoring Committee (DMC). The analysis will be based on a safety review when all subjects have completed at least 12 weeks of treatment. The safety analysis plan will be prepared separately.

3.9. CINRG Natural History Population

The largest prospective multicenter study of the natural history of DMD, performed by the Cooperative International Neuromuscular Research Group (CINRG), enrolled more than 400

ambulant and non-ambulant male patients with DMD and collected a comprehensive set of clinical measures over a 10-year period. In order to illustrate the clinical benefit of ataluren in subjects ≥2 and ≤5 years of age in Protocol PTC124-GD-030-DMD, subjects from the CINRG database will be selected based on ≥2 and ≤5 of age-match at study entry. Additional selection criteria (i.e. baseline TFTs, NSAA scores, etc.) maybe selected if significant differences in baseline demographics are observed between the CINRG cohort and the Study 030 population. The data extracted from the CINRG database will include demographics at study entry, and available Timed Function Test and North Star Ambulatory Assessment by the same time points: study entry, Weeks 28 and 52. The selected CINRG data will be summarized similarly to Study 030.

The data extracted from the CINRG database will not be included in study databases with the data collected in PTC124-GD-030-DMD. That is, the CINRG data will not be included in the SDTM and ADaM databases which support the tables, listings, and figures for the study CSR and will not be included in the study submission package.

Instead, the data from the CINRG database will exist as standalone SAS datasets. Separate ADaM datasets, tables, and listings will be generated to present results from the natural history CINRG database alongside results from PTC124-GD-030-DMD. These summaries will be kept separate from the study CSR.

4. ANALYSIS POPULATIONS

All subjects who receive at least 1 dose of ataluren will be included in the analyses of safety. The results from this study will be presented using 4 populations:

Enrolled Subjects: All subjects who were successfully screened and enrolled into the study.

Safety Population: All subjects who receive at least 1 dose of ataluren. The safety population will be used for the safety summary.

PK Population: All subjects who receive at least 1 dose of ataluren and have at least 1 PK concentration data. The PK population will be used for PK analyses.

Evaluable Population: All subjects who receive at least 1 dose of ataluren and have baseline and at least 1 post-baseline measurement for TFTs, NSAA, or response to the *palatability of ataluren* questions. The evaluable population will be used for the efficacy analyses.

5. ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the footer of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS® program name, including the path that generates the output;
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all subjects combined. Row entries in tables are made only if data exist for at least 1 subject (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of subjects (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables will clearly indicate the number of subjects to which the data apply and data points that are "unknown" or "not performed" will be distinguished from missing data.

Individual Subject Data Listings will be sorted and presented by subject number and visit date, if applicable. Listings will also include the number of days relative to the exposure to the study drug (active or placebo), if applicable.

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data are flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. The imputed data will be retained in the derived / analysis datasets.

The total duration for a subject *on study* will be calculated as the difference between the date of initial exposure to the study drug and the last day of observation plus one day. All calculations for defining the duration on study will follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE –DRUG DOSE DATE + 1].

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will comprise the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. SD values will be formatted to 2 more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%).

- Although the primary interest will be descriptive for summarizing the results from this study, there may be interest in calculating probability values for certain parameters for informational purposes. If presented, probability values will be rounded to 4 decimal places. All probability values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999'. Probability values <0.05 will be considered statistically significant.

- All summary tables will include the analysis population sample size (i.e., number of subjects).

- Study Day 1 is defined as the day the subject is exposed to the study drug. All *study days* are determined relative to the day of exposure to the study drug (active or placebo).

- Baseline values will be defined as those values recorded closest to, but prior to, the first study treatment on Day 1.

- Change from baseline will be calculated as follows:

  Change = Post-baseline value – baseline value

- Missing data may have an impact upon the interpretation of the trial data. However, as this study is of short duration, it is anticipated that missing data will be minimal. Missing data will not be imputed; however, a methodology is defined for missing and partial dates (see Section 9.1.3). In the event of a missing laboratory test result, the result will be treated as missing for the laboratory abnormality summary.

- Date variables will be formatted as DDMMMYYYY for presentation.

- Tables, figures, and listings will be presented in landscape orientation.

- SAS® Version 9.3 or higher will be the statistical software package used for all data analyses.

- The subject number will be included in all data listings. All listings will be sorted by subject number and visit date, as applicable.

6. STUDY DISPOSITION

A complete accounting of subject participation in the study will be presented in Table 14.1.1 entitled *Subject Disposition* (All Screened Subjects). The purpose of this table is to provide an accounting of subjects from their entrance into the study through the final visit and to account for subject evaluation in major analyses of safety and tolerability, including reasons for early study termination. The table will display the number and percentage of subjects that:

- were enrolled,
- are included in the Safety population,
- are included in the PK population,
- are included in the evaluable population
- completed or discontinued the study.

In addition, the reason for early study termination will be summarized separately using the number and percentage of subjects for each reason.

Listing 16.2.1 entitled *Subject Disposition* supports Table 14.1.1. This listing will be sorted by subject number.

Listing 16.2.3.1 entitled *Inclusion and Exclusion Criteria* displays the data from the Inclusion Criteria and Exclusion Criteria case report forms (CRF). The data will be displayed for each subject and for each inclusion criterion not met or each exclusion criterion met. The listing will be sorted by subject number and inclusion/exclusion criterion number.

Listing 16.2.3.2 entitled *Eligibility Criteria* displays the data from the Study Eligibility CRF. This form confirms that the appropriate informed consent has been obtained for study participation. The listing will be sorted by subject number.

7. PROTOCOL DEVIATIONS

In accordance with ICH E3, Sponsor-defined eligibility and important post-dosing protocol deviations will be identified and listed separately by subject. Deviation type/code provided by the Sponsor will be used to classify the events as:

- Subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who entered the study even though they did not satisfy the entry criteria
- Subjects who received an excluded concomitant treatment
- Subjects who received the wrong treatment or incorrect dose
- Other

Deviations are then categorized into:

- Major
- Minor

Table 14.1.2 entitled *Summary of Protocol Deviations* (All Screened Subjects) will provide a tabular summary of the protocol deviations by category and type of deviation. Listing 16.2.2 entitled *Protocol Deviations* supports Table 14.1.2. The listing will be sorted by subject number and date of the protocol violation.

8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1. Baseline Demographic Factors and Medical History

All subjects in the Safety Population will be included in summary of demographic information in Table 14.1.3 entitled *Demographics and Baseline Characteristics* (Safety Population). This table summarizes the subject population with respect to gender, age (years) at screening, race and ethnicity. Age will be reported in months and years and summarized with descriptive statistics: n, arithmetic mean, SD, median, range (*i.e.*, minimum and maximum values). The number and percent of each gender, race, and ethnicity category will be presented using counts and percentages. Race will be presented using the following categories:

- Caucasian or White
- Black or African American
- Asian
- American Indian or Alaska Native
- Native Hawaiian or other Pacific Islander
- Other

The supportive data for Table 14.1.3 are presented in Listing 16.2.4.1 entitled *Demographics and Subject Characteristics* (Safety Population). This listing will be sorted by subject number.

8.2. Medical History

Medical history data will be mapped with the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and categorized by system organ class (SOC) and preferred term (PT). The medical history will be summarized using counts and percentages by SOC and PT for the Safety Population in Table 14.1.4 entitled *Summary of Medical History*.

Medical history will be presented in Listing 16.2.4.2 entitled *Medical History (Safety Population).* This listing will be sorted by subject number and start date of the medical history.

8.3. Prior and Concomitant Medications

A prior medication is a medication that was started and ended prior to the first dose of study medication. Concomitant medications are medications that the subject starts after the first dose of study medication or medications that began prior to the first dose of study medication and continue afterwards.

All prior and concomitant medications will be coded using the Anatomical-Therapeutic- Chemical (ATC) classification text from the WHO Drug Dictionary. Medications will be presented by ATC Class 1, ATC Class 3, and Preferred Term. The data will be presented for subjects in the Safety Population. Subjects will only be counted one time in each unique ATC Class 1, ATC Class 3, and Preferred Term. For the summary tables, the count and percentage of subjects under each anatomical therapeutic chemical (ATC) class and PT will be summarized.

Prior medications will be summarized in Table 14.1.5.1 entitled *Summary of Prior Medications* (Safety Population). Concomitant medications, prescribed and over the counter, that the subject takes or continues to take after the first dose of study medication will be summarized in Table 14.1.5.2 entitled *Summary of Concomitant Medications* (Safety Population). Concomitant non-drug treatments will be summarized in Table 14.1.5.3 entitled *Summary of Concomitant Non- drug Treatments* (Safety Population).

Corticosteroids that the subject takes or continues to take after the first dose of study medication will be summarized in Table 14.1.5.4 entitled *Summary of Corticosteroids* (Safety Population).

Nephrotoxic medications that the subject takes or continues to take after the first dose of study medication will be summarized in Table 14.1.5.5 entitled *Summary of Nephrotoxic Medications* (Safety Population).

A listing of prior and concomitant medications will be provided for all enrolled subjects. A flag will be included in the listing to distinguish concomitant versus prior medications. Listing 16.2.8.7 entitled *Prior and Concomitant Medications and Non-drug Treatments* supports the analysis presented in Tables 14.1.5.1 through 14.1.5.5. This listing will be sorted by subject number and medication start date. A flag will be added to the listings to identify corticosteroids and nephrotoxic medications summarized in the tables.

9. STUDY DRUG ACCOUNTABILITY

A summary of study drug administration will be presented in Table 14.1.6 entitled *Summary of Administration of Study Drug* (Safety Population). The total duration of treatment in days will be summarized with descriptive statistics: n, arithmetic mean, SD, median, range (*i.e.*, minimum and maximum values). Total Duration will be calculated as the last date of treatment minus the first date of treatment + 1 day. Treatment duration will also be presented using a series of non-overlapping categories. The number and percent of each treatment duration category will be presented using counts and percentages. The treatment duration categories will be presented using the following categories:

- 1 to 28 Days
- 29 to 112 Days
- 113 to 196 Days
- 197 to 280 Days
- 281 to 364 Days
- > 364 Days

Listing 16.2.5.1 entitled *Administration of Study Drug* will support the analysis presented in Table 14.1.6. This listing will be sorted by subject number and relative day.

Listing 16.2.5.2 entitled *Study Drug Accountability* presents the accountability of the study drug including the number of sachets dispensed, the number of used sachets returned, and the number of unused sachets returned. This listing will be sorted by subject number and date dispensed.

10. EFFICACY

Observed values and changes from baseline in timed function tests and NSAA total score will be summarized using descriptive statistics for the evaluable population.

10.1. Timed Function Test

The timed function tests will be performed on the first day of treatment (Visit 2 - Study Day 1), Week 28 (Visit 5 - Study Day 196), and Week 52 (Visit 7/ET - Study Day 365). Results summarizing the baseline values (Study Day 1), post-baseline values, and the change from baseline values will be presented separately for each of the 4 tests:

- Time taken to run/walk 10 meters,
- Time taken to climb four standard sized stairs,
- Time taken to descend four standard sized stairs, and
- Time to stand up from a supine position

If the time taken to perform a test exceeds 30 seconds or if a subject cannot perform the test due to disease progression, a value of 30 seconds will be set for the summary analysis. A sensitivity analysis will also be performed using a maximum time threshold of 45 seconds instead of 30 seconds.

The time values in seconds will be summarized using descriptive statistics: n, mean, SD, median, range, and 95% confidence intervals. Only paired quantitative data will be summarized in the tables; all data will be presented in the listings. Results will be summarized and presented in Table 14.2.1 entitled *Summary of Timed Function Tests by Visit* (Evaluable Population). The supportive listing will be Listing 16.2.6.1 entitled *Timed Function Tests*. This listing will be sorted by subject number and relative day.

10.2. North Star Ambulatory Assessment (NSAA)

NSAA will be performed prior to ataluren dosing on the first day of treatment (Visit 2), Week 28 (Visit 5), and Week 52 (Visit 7/ET). The NSAA consists of 17 activities. For each of the evaluations, the subject will be scored with a 0 (Unable to achieve independently), 1 (Modified method but achieves goal independent of physical assistance from another) or a 2 (Normal – no obvious modification of activity). The maximum score is 34; the sum of the responses to the 17 individual questions will be the 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.

Recent updates to the NSAA have removed ‘Lifts Head’ from the total score. Although the results from all 17 items have been collected, a summary will be presented based on the 16 items without the result from ‘Lifts Head’. The results of these 16 items will be summed on an intra- subject basis to obtain the total score. The best total score is 32 and the worst is 0.

In addition, the logit score will be performed per a linear transformation of the NSAA score to a scale of 0 to 100 [Mayhew 2013] based on the following table. This table illustrates the transformation of the raw score to the linearized measurement on a scale of 0 to 100 via a logit transformation. For example, a male who scored 12 out of 32 on the NSAA (excluding his score on item12 – lifts head) can be calculated to have a linearized measurement of 42 out of 100.

Results from the 16-item NSAA subscale will be presented in Table 14.2.2.1 entitled *Summary of 16-item North Star Ambulatory Assessment Total Score by Visit* (Evaluable Population) and Table 14.2.2.2 entitled *Summary of 16-item North Star Ambulatory Assessment Logit Score by Visit* (Evaluable Population).

The results of the entire 17-item NSAA scale will be presented in Table 14.2.2.1.1 entitled *Summary of the North Star Ambulatory Assessment Total Score by Visit* (Evaluable Population).

The results of the 8-item NSAA subscale will be presented in Table 14.2.2.1.2 entitled *Summary of the 8-item North Star Ambulatory Assessment Subscale by Visit* (Evaluable Population). The maximum score on the 8-item subscale is 16. If any of the 8 items are not performed, the total score will be considered missing.

The results of the 3-item NSAA subscale will be presented in Table 14.2.2.1.3 entitled *Summary of the 3-item North Star Ambulatory Assessment Subscale by Visit* (Evaluable Population). The maximum score on the 3-item subscale is 6. If any of the 3 items are not performed, the total score will be considered missing.

The supportive listing will be Listing 16.2.6.2 entitled *North Star Ambulatory Assessment*. This listing will be sorted by subject number and relative day.

Raw score	Logit	Logit (transformed 0–10
0	−5.11	0[a]
1	−4.25	11
2	−3.63	17
3	−3.19	21
4	−2.83	24
5	−2.52	27
6	−2.24	30
7	−1.99	32
8	−1.74	34
9	−1.51	36
10	−1.29	38
11	−1.07	40
12	−0.85	42
13	−0.64	44
14	−0.44	46
15	−0.23	48
16	−0.03	50
17	0.17	52
18	0.37	53
19	0.57	55
20	0.77	57
21	0.98	59
22	1.19	61
23	1.42	63
24	1.65	65
25	1.91	67
26	2.19	70
27	2.50	73
28	2.87	76
29	3.29	80
30	3.82	85
31	4.54	91
32	5.50	100

10.3. Palatability Characteristics

The responses to the Ataluren Palatability Questionnaire will be summarized in Table 14.2.3 entitled *Summary of the Palatability Characteristics at Visit 3* for all subjects in the Evaluable Population. The Ataluren Palatability Questionnaire has three questions, one for the child and two for the parent/caregiver. The questions, along with the response choices are:

1. Child: How did the medicine taste?

   Responses: Bad, Not Sure, Good

2. Parent / Caregiver: On the basis of reaction/facial expression of your child, do you think that the medication is pleasant?

   Responses: Strongly Disagree, Disagree, Neither Agree nor Disagree, Agree, Strongly Agree

3. Parent / Caregiver: You sometimes have problems in giving the medication to your child because he/she refuses to take it or throws it up.

   Responses: Strongly Disagree, Disagree, Neither Agree nor Disagree, Agree, Strongly Agree

The counts and percentages for each question and response will be summarized at Visit 3. The supportive listing will be Listing 16.2.6.3 entitled *Palatability Characteristics*. This listing will be sorted by subject number and question.

11. PHARMACOKINETICS

11.1. Plasma Concentration

Collection of blood for ataluren plasma concentration analysis is critical for evaluating the exposure / safety relationships and profile in this study. Sampling pre-dose and then at 1, 2, 4, 6, 8, and 10 hours post-dose on Days 1 (Visit 2) and 28 (Visit 3) will provide information about single-dose and steady-state after 28-days of administration of ataluren. Plasma concentrations that are below the lower limit of detection will be set to zero for the tabular summary of the plasma concentrations by time point. Missing plasma concentrations will be excluded from the summary of the plasma concentrations by time point. The plasma concentration results will be summarized using descriptive statistics and presented in Table 14.2.4 entitled *Summary of the Plasma Concentrations of Ataluren by Visit* (PK Population). Listing 16.2.6.4 entitled *Plasma Concentrations of Ataluren* will contain the individual subject-level data sorted by subject number and date of the venipuncture sample used in the determination. Plasma concentrations will be summarized by scheduled time point in the tabular summary and all figures. However, the actual sampling times and the planned time points will be displayed in the plasma concentration listing.

Observed values of plasma concentrations for ataluren will be summarized at each visit and time point by dose level in the PK population. The descriptive statistics (n, mean, SD, CV%, median, minimum, and maximum) will be provided. In addition, geometric mean, its 95% CI, and CV% will be presented.

Figure 14.2.1 entitled *Mean (±SD) Ataluren Plasma Concentration by Visit over Time – Linear Scale* (PK Population) will plot the mean ataluren plasma concentrations over time for each visit in a linear scale. Figure 14.2.1.1 entitled *Mean (±SD) Ataluren Plasma Concentration by Visit over Time – Semi-Logarithmic Scale* (PK Population) will plot the mean ataluren plasma concentrations over time for each visit using a semi-logarithmic scale.

Plots of the plasma concentrations by subject will be presented in both linear and semi- logarithmic scale in Figure 14.2.2 entitled *Ataluren Plasma Concentration by Subject and Visit over Time – Linear Scale* (PK Population) and Figure 14.2.2.1 entitled *Ataluren Plasma Concentration by Subject and Visit over Time – Semi-Logarithmic Scale* (PK Population).

11.2. Pharmacokinetic Analysis

PK parameters (AUC_{0-t}, AUC_{0-10}, C_{max}, $C_{trough@6h}$, t_{max}, AR(AUC), AR(C_{max})) will be derived using actual sampling and dosing times. Concentrations below the limit of quantitation (LOQ) will be set to zero for the calculation of NCA parameters.

Parameters	Definition
AUC_{0-10}	Area under the plasma concentration time curve from time zero to the time of last quantifiable concentration (C_{trough}) prior to the midday dose 6 hours after the morning dose using the linear trapezoidal rule during the ascending portion of the

Parameters	Definition
	curve. For the purpose of calculating AUC, when two consecutive BLQ plasma concentrations are encountered after t_{max}, these and all subsequent values will be excluded from the analysis. If missing values occur between two quantifiable concentrations, they will be excluded from the analysis.
AUC_{0-10}	Area under the plasma concentration time curve from time zero up to 10 hours after the morning dosing using the linear trapezoidal rule during the ascending portion of the curve and the log-trapezoidal rule during the descending portion of the curve. For the purpose of calculating AUC, when two consecutive BLQ plasma concentrations are encountered after t_{max}, these and all subsequent values will be excluded from the analysis. If missing values occur between two quantifiable concentrations, they will be excluded from the analysis.
C_{max}	Maximum observed plasma concentration prior to the midday dose 6 hours after the morning dose. If multiple maxima occurred at equal concentrations, the first temporal value will be taken.
$C_{trough@6h}$	Concentration at the end of the first (morning) dosage interval (prior to the midday dose 6 hours after the morning dose)
t_{max}	Time of maximum observed plasma concentration prior to the midday dose 6 hours after the morning dose. If multiple maxima occurred at equal concentrations, the first temporal value will be taken.

The accumulation ratio on Day 28 will be calculated as follows:

Parameter	Description
AR(AUC)	AR(AUC) = (AUC_{0-t}) on Day28 / (AUC_{0-t}) on Day 1
AR(C_{max})	AR(C_{max}) = (C_{max}) on Day28 / (C_{max}) on Day 1

Note that Section 11.6 of the protocol also calls for the following PK parameters to be calculated:

λ_z The terminal rate constant

$t_{1/2}$ The terminal half-life, calculated as $\ln(2) / \lambda_z$

However, the dosing intervals, as planned by the protocol, will not allow for the calculation of these parameters.

PK parameters will be summarized with descriptive statistics on Day 1 and 28 (e.g., n, arithmetic mean, standard deviation, arithmetic CV %, median, minimum, and maximum, geometric mean, and geometric CV%). The analysis will be performed with a fully validated version of Phoenix WinNonlin V6.3. The individual pharmacokinetic parameters will be summarized using descriptive statistics and presented in the PK population in Table 14.2.5 entitled *Summary of the Ataluren Pharmacokinetics by Visit* (PK Population). Listing 16.2.6.5 entitled *Ataluren Pharmacokinetic Results* will contain the individual subject-level data sorted by subject number and date of the venipuncture sample used in the determination.

12. SAFETY

The following sections describe how the safety endpoints will be summarized.

12.1. Adverse Events

12.1.1. Definition of an Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a subject or clinical investigation administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the product as stipulated in the protocol or labeling, as well as from accidental use or intentional misuse. Any worsening of a pre-existing condition or illness is considered an AE. Changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be an AE. An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a preexisting condition and the surgery/procedure has been pre-planned prior to study entry. However, if the preexisting condition deteriorates unexpectedly during the study (e.g. surgery performed earlier than planned), the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. A treatment-emergent adverse event (TEAE) will be defined as any AE that first occurs after the first dose of study medication or any AE recorded prior to the first dose of study medication that worsens (increase in event severity) after the first dose of study medication.

12.1.2. Definition of Serious Adverse Event

An SAE is any AE occurring at any dose that meets one or more of the following definitions or outcomes:

- death
- life-threatening AE; the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe
- in subject hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a medically important event that the Investigator or the sponsor judges to be serious

12.1.3. Summaries of Adverse Events

All summaries of adverse events will be based on treatment-emergent adverse events. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 19.0. The number and percentage of subjects experiencing adverse events will be summarized by system organ class (SOC) and preferred term (PT). Summaries by maximum severity and relationship to study treatment will also be provided. Serious adverse events and adverse events leading to discontinuation from the study will be presented by SOC and PT.

12.1.3.1 Overall Summary of Treatment-Emergent Adverse Events

Table 14.3.1.1 entitled *Overall Summary of Treatment-Emergent Adverse Events* (Safety Population) provides an overview of the treatment-emergent adverse event (TEAE) data. This table will include the total number of TEAE, and the number and percentage of:

- Subjects with any TEAE
- Subjects with TEAE related to study drug
- Subjects with any TEAE leading to discontinuation of the study drug
- Subjects with any serious TEAE
- Subjects with any TEAE by maximum CTCAE grade

12.1.3.2 Summary of adverse events by System Organ Class and Preferred Term

Table 14.3.1.2.1 entitled *Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term* (Safety Population) contains the primary presentation of the AE data. This table is prepared without regard to causality or relationship to the study drug. Subjects will be counted only once at the SOC level and will be counted once for each applicable PT; multiple occurrences of the same PT for a subject will be counted only once. The number and percentage of subjects experiencing each SOC and PT will be displayed. SOCs, and PTs within SOC, will be displayed alphabetically. The overall incidence of AEs will be summarized using counts and percentages by phase of study.

Table 14.3.1.2.2 entitled *Summary of Adverse Events that Occurred in the 4-Week Follow-up Phase by System Organ Class and Preferred Term* (Safety Population) contains a summary of only those adverse events which occurred within 4 weeks after the last dose of study medication. The number and percentage of subjects experiencing adverse events for each body system and preferred term will be displayed by phase of study.

12.1.3.3 Assessment of Severity

All adverse events, both serious and non-serious, will be assessed for severity or intensity. The investigator or designee will use the following classification to rate the severity of each AE. Section 9.5 of the protocol contains the description of each of these severity grades.

- CTCAE Grade 1 Mild
- CTCAE Grade 2 Moderate
- CTCAE Grade 3 Severe
- CTCAE Grade 4 Life-threatening
- CTCAE Grade 5 Fatal

Table 14.3.1.3 entitled *Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity* (Safety Population) provides the presentation of adverse events with respect to the severity or intensity of the event using the scale presented above. Subjects with multiple occurrences of the same system organ class or preferred term will be summarized at the maximum severity reported for that AE. The number and percentage of subjects experiencing adverse events for each body system and preferred term will be displayed by phase of study.

12.1.3.4 Summary of Adverse Events by Descending Incidence of Preferred Term

Table 14.3.1.4 entitled *Summary of Treatment-Emergent Adverse Events by Descending Incidence of Preferred Term* (Safety Population) displays the AE data by descending incidence of preferred term in the PK phase. Subjects will be counted only once for each applicable PT. The number and percentage of subjects experiencing each PT will be displayed by phase of study.

12.1.3.5 Assessment of Relationship to Study Medication

The principal investigator must review each AE and make the determination of relationship to study drug using the following classification:

- Probable
- Possible
- Unlikely
- Unrelated

Table 14.3.1.5 entitled *Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to the Study Medication* (Safety Population) provides the presentation of adverse events by the relationship to the study drug. Subjects with multiple occurrences of the same system organ class or preferred term will be summarized using the event with the strongest relationship to study medication. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed by phase of study. *Probable* and *Possible* will be group together into the *Related* category. *Unlikely* and *Unrelated* will be grouped together into the *Not Related* category.

Listing 16.2.7.1 entitled *Adverse Events* provides supportive data for Tables 14.3.1.1 through 14.3.1.5 and will be sorted by subject number and relative day of the onset of the event.

12.1.3.6 Summary of Adverse Events Leading to Discontinuation of the Study Drug

Table 14.3.1.6 entitled *Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of the Study Drug by System Organ Class and Preferred Term* (Safety Population) displays all treatment-emergent adverse events resulting in an action taken of 'Discontinued'. This table will have the same structure as that of Table 14.3.1.1, however, only those treatment-emergent adverse events that led to discontinuation of study medication will be displayed. Subjects will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. The number and percentage of subjects experiencing each body system and preferred term leading to discontinuation of study drug will be displayed by phase of study. These summarized results will be supported by Listing 14.3.2.2 entitled *Treatment-Emergent Adverse Events Leading to Discontinuation of the Study Drug*; this listing will be sorted by subject number and relative day of the onset of the event.

12.1.3.7 Summary of Adverse Events Associated with Specific Toxicities

This table constitutes a subset of the events reported in Table 14.3.1.1 specific to potential hepatic and renal toxicities. Subjects with hepatic or renal events will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. The number and percentage of

subjects experiencing each system organ class and preferred term will be presented. All adverse events that meet this definition will be summarized in Table 14.3.1.7 entitled *Summary of Treatment-Emergent Adverse Events Associated with Specific Toxicities by System Organ Class and Preferred Term* (Safety Population) by phase of study. These summarized results will be supported by Listing 14.3.2.3 entitled *Treatment-Emergent Adverse Events Associated with Specific Toxicities*; this listing will be sorted by subject number and relative day of the onset of the event.

12.1.3.8 Summary of Serious Adverse Events

All serious adverse events will be summarized in Table 14.3.1.8 entitled *Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term*. This table constitutes a subset of the events reported in Table 14.3.1.1. Subjects with multiple serious adverse events will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed by phase of study. These summarized results will be supported by Listing 14.3.2.1 entitled *Serious Treatment-Emergent Adverse Events*; this listing will be sorted by subject number and relative day of the onset of the event. This listing constitutes a subset of the data provided in Listing 16.2.7.1 and will contain all serious adverse events.

12.2. Clinical Laboratory Assessments

Laboratory assessments performed during each study visit and will include hematology, biochemistry and urinalysis. The presentation of laboratory results focuses on the descriptive summaries at Baseline, each scheduled follow-up evaluation, and the change from baseline. All subjects in the Safety Population who have a baseline and at least one follow-up laboratory assessment will be included in the presentation of the laboratory data. In order for a subject to be included in the analysis for a particular laboratory test, the subject must have a baseline value and a follow-up laboratory assessment for the laboratory test. Unscheduled laboratory evaluations will be presented in the listings. The summarized results will be presented for the 4 week primary PK period of the study and for the extension study data.

For each quantitative laboratory parameter, the baseline results will be summarized using descriptive statistics: n, mean, SD, median, and range. Only paired quantitative data will be summarized in the tables; all data will be presented in the listings. Results will be summarized and presented in Tables 14.3.6.1 entitled *Summary of Hematology Results by Visit* (Safety Population), 14.3.6.2 entitled *Summary of Biochemistry Results by Visit* (Safety Population), and 14.3.6.3 entitled *Summary of Urinalysis Results by Visit* (Safety Population).

Laboratory shift tables will be prepared and presented based on the normal reference ranges and presented by parameter and the scheduled observation time. Shift tables will be prepared and presented for each quantitative hematology parameter in Table 14.3.6.4 entitled *Hematology Shift Table Results by Visit* (Safety Population). Shift tables will be prepared and presented for each quantitative biochemistry parameter in Table 14.3.6.5 entitled *Biochemistry Shift Table Results by Visit* (Safety Population). Shift tables will be prepared and presented for each

quantitative urinalysis parameter in Table 14.3.6.6 entitled *Urinalysis Shift Table Results by Visit* (Safety Population).

The supportive data for Tables 14.3.6.1 through 14.3.6.6 are presented in Listing 16.2.8.4 entitled *Hematology Results*, Listing 16.2.8.5 entitled *Biochemistry Results*, and Listing 16.2.8.6 entitled *Urinalysis Results.* These listings will be sorted by subject number, parameter, and relative day.

A summary of abnormalities in laboratory variables pre-defined for safety monitoring will be summarized in Table 14.3.6.7 entitled *Summary of Abnormal Laboratory Results by Visit* (Safety Population). The supportive data for this table can be found in Listing 14.3.7.1 entitled *Abnormal Hematology Values*, Listing 14.3.7.2 entitled *Abnormal Biochemistry Values*, and Listing 14.3.7.3 entitled *Abnormal Urinalysis Values*. These listings will be sorted by subject number, parameter, and relative day.

Table 3. 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
Adrenal			
Plasma ACTH	---	>ULN (and plasma cortisol <LLN)	>ULN (and cortisol WNL)
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: ACTH = adrenocorticotropic hormone, 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, WNL = within normal limits

12.3. Vital Signs

All vital signs will be taken each visit and include the following parameters:

- Pulse Rate (beats per minute)
- Temperature (^{0}C)
- Respiratory Rate (breaths/min)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)

Vital signs will be summarized for each clinical assessment using the summary statistics of n, mean, SD, median, and range. These summaries will be presented for the subjects who have data at baseline and the specific follow-up visit. The summarized results will be presented for the 4 week primary PK period of the study and for the extension study data. The organization of the

results is commensurate with the organization of the laboratory data. All subjects in the Safety Population who have a baseline and at least one follow-up vital sign assessment will be included in the presentation of the data. In order for a subject to be included in the analysis for a particular evaluation, the subject must have a baseline value and a follow-up assessment. Unscheduled laboratory evaluations will be presented in the listings. The summarized results will be presented for the 4 week primary PK period of the study and for the extension study data. The results will be presented in Table 14.3.3 entitled *Summary of Vital Sign Results by Visit* (Safety Population). The supportive data listing is Listing 16.2.8.1 entitled *Vital Signs.* This listing will be sorted by subject number, parameter, and relative day.

12.4. Electrocardiogram Results

ECGs will be taken at Screening, Day 28, Day 364, and at the 4 week follow-up visit (Visit 7 - Study Day 392) and include the classification of the findings *Normal, Abnormal*, *Clinically Significant*, and *Abnormal*, *Not Clinically Significant*. The results at each time point will be summarized using counts and percentages.

Shift tables for each digital ECG parameter will be prepared and presented by time point using the matched pairs for the qualitative interpretation of the ECG measurements. Results will be presented in Table 14.3.4entitled *Electrocardiogram Shift Table Results by Visit* (Safety Population). The number and percentage of subjects will be presented.

The supportive data for the ECG tables are presented in Listing 16.2.8.2 entitled *Electrocardiogram Results*. This listing will be sorted by subject.

12.5. Physical Examination Results

A physical examination will be performed for all subjects at Screening, at the 4 week follow-up visit (Visit 7 / Study Day 365), and whenever it is clinically indicated. Any findings or absence of findings relative to each subject's physical examination will be documented in the subject's eCRF. All subjects in the Safety population will be included in Table 14.3.5 entitled *Summary of Physical Examination Results* (Safety Population). This table will summarize the subject population with respect to 12 specific physical characteristics:

- Cardiovascular system
- Chest and lungs
- Thyroid
- Abdomen
- Nervous System
- Skin and mucosae
- Musculoskeletal
- Eyes, Ears, Nose, Mouth, Throat
- Spine
- Lymph Nodes
- Extremities
- Genitourinary

For each characteristic, the number and percentage of subjects found to be abnormal will be presented. The supportive data for Table 14.3.5 will be presented in Listing 16.2.8.3 entitled *Physical Examination Results*. This listing will be sorted by subject number and relative day; unscheduled physical examinations will be presented in the listings.

13. REFERENCES

1. SAS Institute Inc., SAS® Version 9.3 software, Cary, NC.

14. TABLES, LISTINGS, AND FIGURES

1. Demographic Data Summary Tables

- Table 14.1.1 Subject Disposition (All Screened Subjects)
- Table 14.1.2 Summary of Protocol Deviations (All Screened Subjects)
- Table 14.1.3 Demographics and Baseline Characteristics (Safety Population)
- Table 14.1.4 Summary of Medical History (Safety Population)
- Table 14.1.5.1 Summary of Prior Medications (Safety Population)
- Table 14.1.5.2 Summary of Concomitant Medications (Safety Population)
- Table 14.1.5.3 Summary of Concomitant Non-drug Treatments (Safety Population)
- Table 14.1.5.4 Summary of Corticosteroids (Safety Population)
- Table 14.1.5.5 Summary of Nephrotoxic Medications (Safety Population)
- Table 14.1.6 Summary of Administration of Study Drug (Safety Population)

2. Efficacy and Pharmacokinetic Data Summary Tables and Figures

- Table 14.2.1 Summary of Timed Function Tests by Visit (Evaluable Population)
- Table 14.2.2.1 Summary of the 16-item North Star Ambulatory Assessment Total Score by Visit (Evaluable Population)
- Table 14.2.2.1.1 Summary of the North Star Ambulatory Assessment Total Score by Visit (Evaluable Population)
- Table 14.2.2.1.2 Summary of the 8-item North Star Ambulatory Assessment Subscale by Visit (Evaluable Population)
- Table 14.2.2.1.3 Summary of the 3-item North Star Ambulatory Assessment Subscale by Visit (Evaluable Population)
- Table 14.2.2.2 Summary of 16-item North Star Ambulatory Assessment Logit Score by Visit (Evaluable Population)
- Table 14.2.3 Summary of the Palatability Characteristics at Visit 3 (Evaluable Population)
- Table 14.2.4 Summary of the Plasma Concentrations of Ataluren by Visit (PK Population)
- Table 14.2.5 Summary of the Ataluren Pharmacokinetics by Visit (PK Population)
- Figure 14.2.1 Mean (±SD) Ataluren Plasma Concentration by Visit over Time – Linear Scale (PK Population)
- Figure 14.2.1.1 Mean (±SD) Ataluren Plasma Concentration by Visit over Time – Semi-Logarithmic Scale (PK Population)
- Figure 14.2.2 Ataluren Plasma Concentration by Subject and Visit over Time – Linear Scale (PK Population)
- Figure 14.2.2.1 Ataluren Plasma Concentration by Subject and Visit over Time – Semi-Logarithmic Scale (PK Population)

3. Safety Data Summary Tables

- Table 14.3.1.1 Overall Summary of Treatment-Emergent Adverse Events (Safety Population)
- Table 14.3.1.2.1 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
- Table 14.3.1.2.2 Summary of Adverse Events that Occurred in the 4-Week Follow-up Phase by System Organ Class and Preferred Term (Safety Population)
- Table 14.3.1.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Safety Population)
- Table 14.3.1.4 Summary of Treatment-Emergent Adverse Events by Descending Incidence of Preferred Term (Safety Population)
- Table 14.3.1.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to the Study Medication (Safety Population)
- Table 14.3.1.6 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of the Study Drug by System Organ Class and Preferred Term (Safety Population)
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15. MISSING AND PARTIAL ADVERSE EVENT DATES

If the concomitant medication start date is completely missing then the medication will be considered concomitant unless it can be determined that the medication end date occurred prior to the start of the study. If the medication start date is partially missing and the partial date is not sufficient to determine if the medication was taken after the start of the study, then the medication will be considered concomitant for the study unless it can be ruled out by the partial date and/or medication end date.

The start dates for adverse events are important for defining the treatment emergent algorithm, and the designation of unique AE occurrences. Completely missing or partially missing AE onset dates will be imputed as follows after due diligence to obtain accurate AE information has failed.

If the AE start date is completely missing then the AE will be considered treatment emergent unless it can be determined that the AE end date occurred prior to the start of the study. If this is the case, the AE will not be considered treatment emergent.

If the AE start date is partially missing and the partial date is not sufficient to determine if the event occurred after the start of the study, then the AE will be considered treatment emergent unless it can be determined that the AE end date occurred prior to the start of the study.

Handling of Missing AE Start-dates (missing AE stop-dates are not filled)

Rules for assuming a full date for adverse events with incomplete or missing start-dates are addressed below. In the unusual case that the month portion of an AE start-date is missing but the day portion is not missing, the day portion of the AE will be assumed to be missing. Likewise in the case where the year portion of an AE start-date is missing but the month and/or day portion is not missing, the month and/or day portion of the AE will be assumed to be missing. All missing portion(s) of the AE start-dates will be handled using the same rules.

- In the event that the day portion (and only the day portion) of the AE onset date is missing:
    - If the AE started in the same month and year as the study procedure, the AE onset date will be assumed to be the date of the study procedure (*i.e.*, Study Day 1);
    - Otherwise, the AE onset date will be assumed to be the 15th day of the given month and year, *e.g.*, XX–DEC-2013 → 15-DEC-2013 where XX represents an unknown value.
- In the event that the day and month portion (and only the day and month portion) of the AE onset date are missing:
    - If the AE started in the same year as the study procedure, the AE onset date will be assumed the study procedure (*i.e.*, Study Day 1);

- Otherwise, the AE onset date will be treated as June 15th of the given year, *e.g.*, XX-XXX-2013 → 15-JUN-2013.

- In the event that the day, month, and year portion of the AE onset date are missing, the start-date of the AE will be assumed to be the study procedure (*i.e.*, Study Day 1).

Special Cases on Missing AE Start-dates

- If the assumed AE onset date using the above rules for handling of missing AE dates
  - is earlier than the screening date, the assumed AE onset date will be reset and assumed to be the screening date.
  - is later than the reported AE stop-date, the assumed AE onset date will be reset and assumed to be the AE stop-date.
  - is later than the date of study completion and the AE stop-date missing, the AE will be assumed to be treatment-emergent.

16. SCHEDULE OF EVENTS

	Screening	Ataluren Treatment						4-Week Follow-Up
Day (±2)	**-28**	**1[a]**	**28**	**112**	**196**	**280**	**364**	**392**
Weeks	**-4**	**0**	**4**	**16**	**28**	**40**	**52/ET[b]**	**56**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
Clinical and medication history	X							
Vital signs	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Physical examination	X	As clinically indicated						X
Hematology	X	X	X	X	X	X	X	X
Blood sample for gene sequencing [c]	X							
Biochemistry[d]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
12-lead ECG	X		X				X	X
Palatability questionnaire			X					
Blood for ataluren PK[e]		X	X					
Drug administration		X ----------					X	
Adverse events		X ----------						X
Concomitant medications	X ----------							X
Non-DMD-related adverse events								X

[A] All study and laboratory assessments on the first day of treatment must be done prior to ataluren dosing.

[b] Patients who terminate the study early should complete all assessments required for Week 52/ET (Visit 7) and will be required to return 4 weeks from the final dose of study medication for the 4-Week Follow-up Visit.

[c] Verification that a blood sample has been drawn for sequencing of the dystrophin gene. A patient who has written documentation of a nonsense mutation as the cause of DMD need not wait for confirmatory results to start study drug as long as the confirmatory blood sample for gene sequencing has been drawn.

[d] Biochemistry laboratory assessments will include hepatic transaminases and additional parameters as specified in Section 8.2.7.2.

[e] On Days 1 and 28, blood samples for PK assessment will be drawn pre-dose and 1 (±15 min), 2 (±15 min), 4 (±30 min), 6 (±30 min), 8 (±30 min), and 10 (±30 min) hours post-dose.

Abbreviations: ECG = electrocardiogram, ET = early termination, PK = pharmacokinetics