STATISTICAL ANALYSIS PLAN

AN OPEN-LABEL STUDY EVALUTATING THE SAFETY AND PHARMACOKINETICS OF ATALUREN IN CHILDREN FROM ≥6 MONTHS TO <2 YEARS WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY

PTC124-GD-048-DMD

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VERSION 1.0

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse event
BMI	Body mass index
BP	Blood pressure
CK	Creatine kinase
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DMD	Duchenne muscular dystrophy
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TID	Three times a day
WHODRUG	World Health Organization Drug Dictionary

1. OVERVIEW

This statistical analysis plan (SAP) details the statistical methods to be used in the analyses and presentation of the data collected in Study PTC124-GD-048-DMD, also referred to as Study 048.

This document is prepared on the basis of the final study protocol version 4.0 (dated 06May2022). The reader is referred to the study protocol, the electronic case report form (eCRF), general eCRF completion guidelines, and various data collection instruments employed in the study for details of study design, conduct and data collection.

This SAP is to be reviewed and approved prior to the study database lock.

2. STUDY OVERVIEW

2.1. Study Design

Study 048 is a Phase 2, open-label study to evaluate safety, tolerability, and PK of ataluren in male children with nmDMD aged ≥6 months to <2 years of age treated three times a day (TID) for 24 weeks with orally administered ataluren 10, 10, 20 mg/kg (morning, mid-day, and evening dose, respectively).

This study will include five on-site visits, each at screening (Visit 1), Week 0 (Visit 2), Week 4 (Visit 3), Week 12 (Visit 4), and Week 24 (Visit 5) and one follow-up phone call at Week 28 (Visit 6). A minimum of 6 subjects (up to 10 subjects) will be selected according to the study inclusion and exclusion criteria. Visits 2, 3, and 5 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.

Ataluren administration will begin at baseline (Visit 2) and continue for up to 24 weeks. Three ataluren doses should be taken per day; the first dose in the morning, the second dose during the middle of the day (mid-day), and the third dose in the evening. Ideally each dose should be taken within ~30 minutes after a meal (eg, ~7:00 AM after breakfast, ~1:00 PM after lunch, and ~7:00 PM after dinner). Intervals for dosing should be ~6 hours (±1 hour) between morning and mid-day doses, ~6 hours (±1 hour) between mid-day and evening doses, and ~12 hours (±1 hour) between evening doses and the morning dose on the next day.

The study will include 3 PK profile assessments (baseline, Week 4, and end of treatment (EOT) at Week 24). At these visits, PK parameters will be investigated based on blood sampling at pre-dose, and 1-, 2-, 3-, and 4-hours post-dose following both the morning and mid-day ataluren doses, and immediately pre-dose, and 1, 2, 3, 4 and 12 (before the next day morning dose) hours post-dose following the evening dose. The PK parameters, including $AUC_{0\text{-}24}$ (following the morning dose), $AUC_{0\text{-}tau}$ (AUC0-6 following the morning and mid-day dose and AUC0-12 following the evening dose), and T_{max}, C_{max}, C_{trough} after each dose. If feasible, apparent clearance (CL/F), and $T_{1/2}$ will also be assessed after each dose. Additional samples will be taken at 2.5 hours and 4.5 hours post morning dose to be processed to plasma.

Data from clinical labs, vital signs, ECGs, and physical examinations will be collected at each on-site visit (note: ECG data are not collected at Week 12/Visit 12). The detailed schedule of assessments is attached in Appendix 1.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to assess the safety and tolerability of ataluren in male children with nmDMD aged ≥6 months to <2 years old.

2.2.2. Secondary Objectives

The secondary objective of this study is to assess the PK of ataluren in male children with nmDMD aged ≥6 months to <2 years old.

2.2.3. Exploratory Objectives

The exploratory objective of this study is to assess changes from baseline in creatine kinase (CK) levels.

2.3. Study Endpoints

2.3.1. Primary Endpoint

The primary endpoint of this study is the overall safety profile of ataluren in terms of type, frequency, severity, seriousness, timing, and relationship to study therapy of any TEAE during the 24 weeks of treatment.

2.3.2. Secondary Endpoints

The secondary endpoint of this study is the evaluation of PK parameters after 24 weeks of treatment as follows:

- AUC_{0-24} and AUC_{0-6}
- T_{max}
- C_{max}
- C_{trough}

2.3.3. Exploratory Endpoints

Changes from baseline in CK levels after 24 weeks of treatment

2.4. Sample Size

Sample size is not based on any formal statistical hypothesis for this study. It is anticipated that up to 10 subjects (minimum of 6 subjects) will be enrolled.

2.5. Randomization

Not applicable for this study.

2.6. Blinding

Not applicable for this study.

2.7. Study Assessments

2.7.1. Physical Examination

A full physical examination (including evaluation of cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, and extremities) will be conducted at Screening (Visit 1), Week 0 (Baseline/Visit 2), Week 4 (Visit 3), Week 12 (Visit 4), and Week 24 (Visit 5-EOT/Early Termination).

2.7.2. Laboratory Assessment

Hematology, biochemistry, and urinalysis laboratory assessment will be analyzed by the local laboratory at the investigative site. These parameters will be collected at Screening (Visit 1), Week 0 (Visit 2/Baseline), Week 4 (Visit 3), Week 12 (Visit 4), and Week 24 (Visit 5 - EOT/Early Termination).

2.7.3. Confirmation Gene Sequencing

A blood sample for dystrophin gene sequencing to confirm the presence of a nonsense mutation will be drawn at screening (Visit 1).

2.7.4. Pharmacokinetic Assessment

The PK parameters will be evaluated based on frequent blood sampling During PK assessments at baseline (Visit 2) Week 4 (Visit 3), and EOT at Week 24 (Visit 5), subjects will remain in the clinic until all blood draws are complete. At each assessment period, blood sampling will occur immediately pre-dose, and at 1-, 2-, 3-, and 4-hours post-dose following the morning and midday doses and immediately pre-dose and at 1, 2, 3, 4 and 12 (before the next day morning dose) hours post-dose following the evening ataluren dose. The PK parameters, including AUC0-24 (following the morning ataluren dose), AUC0-tau (AUC0-6 following the morning and mid-day ataluren doses and AUC0-12 following the evening ataluren doses), Tmax, Cmax, and Ctrough after each dose will be assessed.

The blood/plasma partition sampling will occur at 2.5 hour and 4.5 hour post morning dose at baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5).

2.7.5. Height, Weight, and Body Mass Index

Height (in cm), weight (in kg) and body mass index (BMI) (kg/m^2) will be measured at all study visits.

2.7.6. Vital Signs

Vital signs (heart rate and systolic and diastolic blood pressure [BP]) will be monitored at all protocol -required study visits. Heart rate and BP determinations will be performed with the subject in a supine position after a 5-minute rest.

2.7.7. Electrocardiogram

A 12-lead ECG will be obtained at screening (Visit 1), baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24(Visit 5). The ECGs will be read locally at investigational sites and interpreted for clinical significance. The findings will be captured in source documents and within the eCRF.

2.7.8. Adverse Events

An Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered related to the drug.

All AEs (both serious and nonserious) that occur in subjects during the AE reporting period must be recorded. All AEs are to be recorded in the source documents and on the eCRF using concise

medical terminology; whenever possible terms contained in Medical Dictionary for Regulatory Activities (MedDRA) should be employed.

2.7.9. Concomitant Medications

Concomitant medication information will be collected and documented at each scheduled clinic visit, from screening (Visit 1) through EOT at Week 24 (Visit 5) and at the post-treatment follow-up visit (if applicable).

3. STUDY POPULATIONS

3.1. Safety Population

The safety population will include all subjects who receive at least one dose of ataluren and will be used for all safety analyses.

3.2. PK Population

The PK population will include all subjects who receive at least one dose of ataluren and have one PK concentration datum. The PK population will be used for all PK analyses.

4. GENERAL CONSIDERATIONS

4.1. Tables, Figures, and Listings

Summary statistics for continuous variables will include n (number of subjects), mean, median, minimum, and maximum. For PK analysis, n, mean, SD, coefficient of variation (CV), geometric mean, and geometric mean CV will also be provided for PK population only. Summary statistics for categorical variables will include N (number of subjects in population), n (number of subjects in category), % (percent of subjects in category). Where applicable, the summary data will also be provided in graphical presentation.

By-subject data listings will be created for each eCRF domain sorted by treatment, subject, and associated dates, where applicable.

4.2. Baseline and Endpoint Definitions

The study baseline, defined as the last assessment prior to the first dose of ataluren, will be used for analyzing and summarizing safety endpoints.

4.3. Interim Analyses

There is no interim analysis planned for this study.

4.4. Missing Data Handling

No missing value imputation will be applied to this study.

4.5. Analysis Visits

All data analyses for this study will be performed based on nominal visits collected on the eCRF.

5. SUBJECT DATA

All subject data described in this section will be summarized based on safety population. Additional summaries will be provided based on PK population if PK population is different from the safety population in demographic tables.

5.1. Subject Disposition and Study Populations

The number of subjects in each analysis population will be summarized using frequency count. The number of subjects who completed or discontinued from the study and the reasons of discontinuation will be summarized based the safety population. Reasons for screening failures and early discontinuations, and time of withdrawal from study will also be summarized.

5.2. Duration of Treatment with Study Drug

Duration of treatment with study drug during study will be calculated as:

$$Duration\ (days) = Date\ of\ last\ dose\ of\ study\ drug\ -\ Date\ of\ first\ dose\ of\ study\ drug + 1$$

Duration of treatment with study drug in days will be presented in by-subject listing only on safety population.

5.3. Treatment Administration and Drug Compliance

Study drug administration information including study drug start and end dates, dose interruptions start and stop dates, and reasons for dose interruption or dose deviations will be presented in a by-subject listing based on safety population.

5.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics including age (in month), gender, race, ethnicity, height, weight, and BMI will be summarized for safety population.

5.5. Disease Characteristics

Disease characteristics including prior dystrophin gene sequencing, location of nonsense point mutation, and stop codon type will be provided in the by-subject listings only. Age at diagnosis of dystrophinopathy, signs/symptoms/laboratory results used to support diagnosis will be listed as well.

5.6. Medical History

Medical history will be presented in the by-subject listing for safety population.

5.7. Concomitant Medications and Non-Drug Treatments

Concomitant medications and non-drug treatments will be coded using the World Health Organization Drug Dictionary (WHODD), version March 2023 or higher.

Prior medications and non-drug treatments are defined as those taken any time prior to the first dose of ataluren (Week 0). Concomitant medications and non-drug treatments are defined as those taken any time during the study treatment period (the first dose date of Ataluren through the last follow-up date within study).

The use of concomitant medications and non-drug treatments will be listed.

6. EFFICACY EVALUATION

No functional assessments will be captured for this study. The change from baseline in the CK levels will be considered as an exploratory efficacy endpoint for this study.

6.1. Primary Analysis

Not applicable to this study.

6.2. Exploratory Endpoints

Summary tables on change from baseline in CK levels by visits will be provided.

7. ATALUREN CONCENTRATIONS AND PHARMACOKINETIC PARAMETERS

7.1. Descriptive Analysis

Descriptive statistics (n, mean, SD, CV%, Geo mean, Geo CV%, median, min, and max) will be used to summarize the blood and plasma ataluren concentrations at each timepoint and PK parameters by cycle, day, and dose interval at 2.5 hour and 4.5 hour post morning ataluren dose at each visit.

7.2. Blood and Plasma Concentrations

Blood and plasma concentration values below the quantitation limit (BQL) of the bioanalytical assays were treated as zero for the descriptive statistics. Individual values that were BQL were presented as BQL in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject had a concentration value BQL for the given timepoint, then the minimum value was displayed as BQL. If over 50% of the subjects at a given timepoint have values BQL then the descriptive statistics will not be presented and will instead display as '<LLOQ' for the mean and missing for all other statistics. Concentration values that were BQL were considered missing for any ratio or natural log transformed statistical analyses.

7.3. Blood Pharmacokinetic Parameters

Blood PK parameters for ataluren will be estimated using non-compartmental methods with WinNonlin®. Any data points designated as anomalous values that would impact PK should be predefined before database lock if possible and identified in the report with a rationale for exclusion. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using the Linear-Log Trapezoidal method (equivalent to the linear up / log down option in WinNonlin). For the estimation of PK parameters, BQL concentration following first dose at pre-dose and up to the first measurable concentration will be set to zero, BQL concentration will be set to missing otherwise. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. Actual dose will be used to calculate dose-dependent parameters. Parameters will be summarized by dose (morning, mid-day, evening) and entire day, and visits (baseline, Week 4, and EOT at Week 24). AUC0-tau and AUC0-inf for a subject at any specific dose interval will be reported as NR (not reportable) if there is one sample missing during the dose interval, and consequently the AUC0-24 for the subject at the specified day will be reported as NR.

The following blood PK parameters will be determined using non-compartmental methods as appropriate, for each visit:

Parameter	Description	Dose
C_{max}	Maximum blood concentration; determined directly from the concentration time profile; if the maximum blood concentration occurs at more than one time point, C_{max} is defined as the first maximum value.	Morning, Mid-day, Evening
T_{max}	Time to C_{max}; if the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.	Morning, Mid-day, Evening
C_{trough}	Trough blood concentration; measured blood concentration at the end of the dosing interval, directly before next administration.	Morning,

Parameter	Description	Dose
AUC_{0-24}	Area under the blood concentration vs time curve (AUC) from time 0 to 24 hours post first morning dose.	Morning
$AUC_{0-\tau}$	AUC from time 0 to 6 hours post-dose following the morning and mid-day ataluren doses and AUC from time 0 to 12 hours post-dose following the evening ataluren doses. AUC from time 0 to 6 hours post-dose following the evening ataluren dose will also be calculated.	Morning, Mid-day, Evening
AUC_{0-t}	AUC from time 0 to the last quantifiable blood concentration (C_{last})	Morning, Mid-day, Evening
AUC_{0-inf}	AUC from time 0 to infinity; calculated as ($AUC_{0-\tau}$ + $C_{last}/\lambda z$)	Morning, Mid-day, Evening
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated, represented as (1 – AUC_{0-t}/AUC_{0-inf})*100.	Morning, Mid-day, Evening
λz	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the blood concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using points in the terminal log-linear phase.	Morning, Mid-day, Evening
$T_{1/2}$	Apparent first-order terminal half-life; calculated as ln(2)/λz	Morning, Mid-day, Evening
CL/F	Apparent total blood clearance after oral administration; calculated as Dose/AUC_{0-inf}	Morning, Mid-day, Evening
Vz/F	Apparent volume of distribution during terminal elimination phase after oral administration; calculated as Dose/[λz* AUC_{0-inf}]	Morning, Mid-day, Evening
AR_{Cmax}	Accumulation ratio calculated as C_{max} Visit 3 Dose / C_{max} Visit 2 Dose	Morning, Mid-day, Evening
AR_{Cmax}	Accumulation ratio calculated as C_{max} Visit 5 Dose / C_{max} Visit 2 Dose	Morning, Mid-day, Evening
AR_{AUC}	Accumulation ratio calculated as $AUC_{0-\tau}$ Visit 3 Dose / $AUC_{0-\tau}$ Visit 2 Dose	Morning, Mid-day, Evening
AR_{AUC}	Accumulation ratio calculated as $AUC_{0-\tau}$ Visit 5 Dose / $AUC_{0-\tau}$ Visit 2 Dose	Morning, Mid-day, Evening

Planned dose will be used for the derivation of dose-dependent PK Parameters, planned dose will be determined with use of the PTC124-GD-048-DMD Ataluren Dosing Table (10-, 10-, 20-mg/kg).

In order to estimate the apparent first-order terminal elimination constant, λz, linear regression of concentration in logarithmic scale versus time will be performed using at least three data points spanning 1.5 $T_{1/2}$. Uniform weighting will be selected to perform the regression analysis to estimate λz. The constant λz will not be assigned if one of the following occurs:

1. The terminal elimination phase is not linear (as it appears on a semi-logarithmic scale) as determined by R2adj <0.8.
2. The terminal elimination rate constant indicates a positive slope ($\lambda z > 0$).
3. T_{max} is one of the three last data points.

Subject experiences vomiting within 3 hours of dose administration will be flagged for the dose period and the day. The PK parameters of the flagged period and day will be excluded from descriptive analysis. Subjects experienced other deviations which may significantly impact PK analysis may be flagged and excluded from descriptive analysis for the specified dose period/day.

No PK parameters will be calculated for subjects with two or fewer detectable concentrations in their PK profile.

No value for λz, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL/F, Vz/F, or $T_{½}$ will be reported for cases that do not exhibit an acceptable terminal log-linear phase in the concentration-time profile.

8. SAFETY EVALUATION

8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 26.0 or higher) lower level term closest to the verbatim term. The linked MedDRA Preferred Terms (PT) and primary system organ class (SOC) are also captured in the database. The severity of AEs will be graded using the latest version of the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

A treatment-emergent adverse event (TEAE) during study is defined as an AE that occurs or worsens while on ataluren (on or after first dose of ataluren) up to 4 weeks after last dose of ataluren.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings. An overview table of TEAEs, including number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), deaths, TEAEs classified as CTCAE Grade 3 or higher, study drug related TEAEs, TEAEs leading to study drug withdrawal will be provided. A summary table on the incidence of TEAEs by SOC and PT will be produced.

In the summary tables subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity (5=fatal, 4=life-threatening, 3=severe, 2=moderate, 1=mild) recorded for the event will be presented and the highest drug relationship (1 = 'Unrelated', 2 = 'Unlikely to be Related', 3 = 'Possibly Related', 4 = 'Probably Related'), reclassified into Related ('Possibly Related', 'Probably Related') or Not Related ('Unrelated'), will be presented on the respective tables. Percentages are based on the number of subjects in the safety population.

8.2. Clinical Laboratory

Mean and mean change from baseline in clinical laboratory parameters listed in Table 1 will be summarized at each scheduled visit. Shift tables for laboratory parameters listed in Table 1 from baseline to each of the post-baseline visit will also be provided. Other laboratory parameters will be presented in the by-subject listings only.

Table 1:Clinical Laboratory Parameters

Type	Parameters
Biochemistry	creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, creatinine kinase, and cystatin C

8.3. Electrocardiogram

Overall interpretation of ECG data, including normal, abnormal and clinically significant, abnormal and not clinically significant will be presented in the by-subject listings only.

8.4. Physical Examination

Physical examination results will be presented in the by-subject listings only.

8.5. Vital Signs

Mean and mean change from baseline in height, weight, and vital signs data will be summarized by visit. The hypertension status will be classified as below based on age, gender, and height-adjusted systolic or diastolic BP percentile results [Flynn 2017]. The hypertension status will be summarized by visit.

- Normal BP: BP <90th percentile for age, sex, and height; or <120/<80 mm Hg for adolescents ≥13 years old;
- Elevated BP: BP reading ≥90th percentile and <95th percentile for age, sex, and height; or 120 to 129/<80 mm Hg for adolescents ≥13 years old;
- Hypertension: BP ≥95th percentile for age, sex, and height; or ≥130/80 mm Hg for adolescents ≥13 years old.

9. CHANGES FROM THE PROTOCOL

No changes are made to the planned analyses from the study protocol.

10. BIBLIOGRAPHY

Flynn, JT and Falkner, BE. New Clinical Practice Guideline for the Management of High Blood Pressure in Children and Adolescents. Hypertension 2017;70(4):683-686.

11. TABLE OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS

The tables, listings, and graphs shells for the study will be provided in a separate document.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period	**Screening**[a]	**Baseline/ Start of Treatment**[b]	**Treatment Phase**		**EOT/ET**[c]	**Post-Treatment Follow-Up/ EOS**[d]
Visit	**Visit 1**	**Visit 2**[e]	**Visit 3**[e]	**Visit 4**	**Visit 5**[e]	**Visit 6**
Week	**-**	**Week 0**	**Week 4**	**Week 12**	**Week 24**	**Week 28**
Visit Window (days)	**(-28 to -1)**	**0**	**±7**	**±7**	**±7**	**±7**
Eligibility						
Informed Consent[f]	X					
Inclusion/Exclusion	X	X				
Medical/Surgical History	X	X				
Demographics	X					
Safety Assessments						
Physical Examination[g]	X	X	X	X	X	
Clinical Labs[h]	X	X	X	X	X	
Blood Sample for Gene Sequencing[i]	X					
Height/Weight[j]/BMI	X	X	X	X	X	
Vitals (HR and BP)[k]	X	X	X	X	X	
ECG[l]	X	X	X		X	
AE/SAE Monitoring	X	X	X	X	X	X
Concomitant Medications[m]	X	X	X	X	X	X
PK Blood Sampling (VAMS)[n]		X	X		X	
Blood/Plasma Partition Sampling[o]		X	X		X	
Study Drug Administration						
Dispense Drug		X		X		
Unused Drug Return/Compliance			X	X[p]	X	

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; CL/F, apparent clearance; C_{trough}, trough concentration (plasma concentration pre morning dose); ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, early termination; HR, heart rate; PK, pharmacokinetic; SAE, serious adverse event; VAMS, volumetric absorptive microsampling

[a] Screening procedures must take place within 28 days of baseline (Visit 2).

[b] Any screening procedure completed within and including 14 days of baseline (Visit 2) can serve as baseline assessment and does not need to be repeated at Visit 2.

[c] Subjects who terminate the study early are to complete all assessments required for EOT/ET (Visit 5) prior to leaving the study and will be contacted by phone 4 weeks from the final dose of study medication for the post-treatment follow-up/EOS (Visit 6).

[d] Post-treatment follow-up will be conducted by phone 4 weeks ± 7 days from last day of study treatment for review of adverse events and concomitant medications. Post-treatment follow-up is not required if subjects are transitioning to another ataluren clinical trial.

[e] Visits 2, 3, and 5 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.

[f] A signed and dated informed consent must be obtained before conducting any study procedures. Remote informed consent is permitted consistent with local policies and procedures.

[g] A full physical examination will include evaluation of the cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, and extremities.

[h] Blood and urine collection will be obtained locally and submitted to the local or central laboratory for analysis. Use of standard of care labs is permitted when samples were obtained within the visit window. Clinical labs will include hematology, biochemistry, and urinalysis parameters as follows: Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count. 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), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, creatinine kinase, lactate dehydrogenase, alkaline phosphatase, total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides, and cystatin C. Urinalysis assessments will include analysis for pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, urine protein: urine creatinine ratio (spot), and leukocyte esterase.
[i] This is to ensure a blood sample has been drawn for sequencing of the dystrophin gene. The sample will be sent to a central laboratory for analysis.
[j] Weight-based dose adjustment will be assessed at Week 12.
[k] Heart rate and BP determinations will be performed with the subject in a supine position after a 5-minute rest.
[l] ECGs will be read locally at investigational sites and interpreted for clinical significance.
[m] Concomitant medication information will need to be collected starting 28 days prior to the first dose of study drug (Screening, Visit 1).
[n] PK samples (VAMS method) will be drawn at baseline (Visit 2), Week 4 (Visit 3), and Week 24 (EOT/ET) for evaluation. Samples will be drawn immediately pre-dose, and at 1-, 2-, 3-, and 4-hours post-dose following both the morning and mid-day doses and immediately pre-dose and at 1-, 2-, 3-, 4-, and 12- (before the next day morning dose) hours post-dose following the evening dose.
[o] Blood sampling via venous draw will be conducted at Visits 2, 3, and 5. These additional samples will be taken at 2.5 -hours and 4.5 -hours post morning dose (1.5 ml each timepoint). Out of the 1.5 mL blood sample collected, at the 2.5 hour and 4.5 hour timepoints, 1 mL blood sample will be processed to plasma and the remaining 0.5 mL blood will be processed to dried blood sample using a VAMS device.
[p] Parent(s)/caregiver(s) will record daily dose administration on a Study Drug Administration Record (dosing sheet) and Subjects are required to return any unused study drug.