NCT #NCT02647359

STATISTICAL ANALYSIS PLAN

STAR: A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, PLACEBO CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF ATALUREN (PTC124) FOR THE TREATMENT OF NONSENSE MUTATION ANIRIDIA

PTC124-GD-028-ANI

05 FEBRUARY 2020

VERSION 4.0

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best corrected visual acuity
β-HCG	Beta-human chorionic gonadotropin
CI	Confidence interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
EOS/EOT	End of study/end of treatment
[redacted]	[redacted]
ITT	Intent to treat
Lea	LEA Symbols Visual Acuity Test System
LOCF	Last observation carried forward
MCMC	Markov Chain Monte Carlo
MNREAD	Minnesota Low Vision Reading Test (MNREAD) Acuity Charts
MRS	MNREAD Maximum Reading Speed
OCT	Optical coherence tomography
OD	Right eye
OS	Left eye
OU	Both eyes
PAX6	Paired box 6
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Software from SAS Institute
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) outlines the proposed statistical methods to be implemented in the analysis of data collected within the scope of PTC Therapeutics, Inc. Protocol PTC124-GD-028-ANI, "STAR: A Phase 2, Multicenter, Randomized, Double-Masked, Placebo Controlled Study of the Safety and Efficacy of Ataluren (PTC124) for the Treatment of Nonsense Mutation Aniridia," protocol, Version 7, dated 17 December, 2019.

It is not intended that each and every table, listing, or graph will be included in the clinical study report (CSR). It is also possible that additional analyses will be conducted after review of the data. Any analyses or summaries not specified in the SAP, but performed after review of the data, will be identified in the CSR as post hoc.

2 OBJECTIVES

2.1 Primary

The primary objective of this study is to evaluate the effect of ataluren on Maximum Reading Speed as measured using the Minnesota Low Vision Reading Test (MNREAD) Acuity Charts in subjects with nonsense mutation aniridia.

2.2 Secondary

The secondary objectives of this study are to:

- Evaluate the effect of ataluren on the following:
  - Reading Accessibility Index
  - Best-corrected visual acuity (BCVA)
  - Critical Print Size
  - Reading Acuity
  - Severity of corneal keratopathy
  - Iris area
- Characterize the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia.

2.3 [redacted]

2.4 Study Design

This is a Phase 2, multicenter, stratified, randomized, double-masked, placebo-controlled study with a 4-week screening period, a 144-week treatment period, an optional 96-week open label sub-study, and a 4-week post-treatment follow-up period (either study completion or early termination). A minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age are planned for enrollment into this study at investigator sites in US and Canada.

During the 4-week screening period, subjects will be assessed for eligibility.

Eligible subjects will enter the 144-week treatment period consisting of two stages:

- Stage 1 (Weeks 1 to 48) during which subjects will receive either ataluren or placebo in a masked fashion;
- Stage 2 (Weeks 49 to 144) during which subjects will receive open-label ataluren.

Eligible subjects will be randomized in a masked 2:1 fashion to either ataluren or placebo. Randomization will be stratified by age: ≤10 years versus >10 years. Masked study drug will be dosed three times a day: 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 48 weeks. Subjects (or parent/legal guardian) will record each dose on a diary card provided by PTC Therapeutics.

After completion of the Stage 1 (Week 48), subjects will be eligible for an additional 96 weeks of open-label ataluren treatment. Subjects who received ataluren during Stage 1 will continue to receive ataluren; subjects who had been randomized to placebo will receive ataluren during Stage 2

There will be an optional sub-study at the end of the Stage 2 Open-Label Extension. Subjects will be able to consent to receive an additional 96 weeks of ataluren treatment, returning to the clinic every 24 weeks. The assessments to be conducted are outlined in the schedule of events. Subjects who choose not to participate in the sub-study will be required to complete the Post-treatment follow-up visit at the end of the Stage 2 Open-Label Extension.

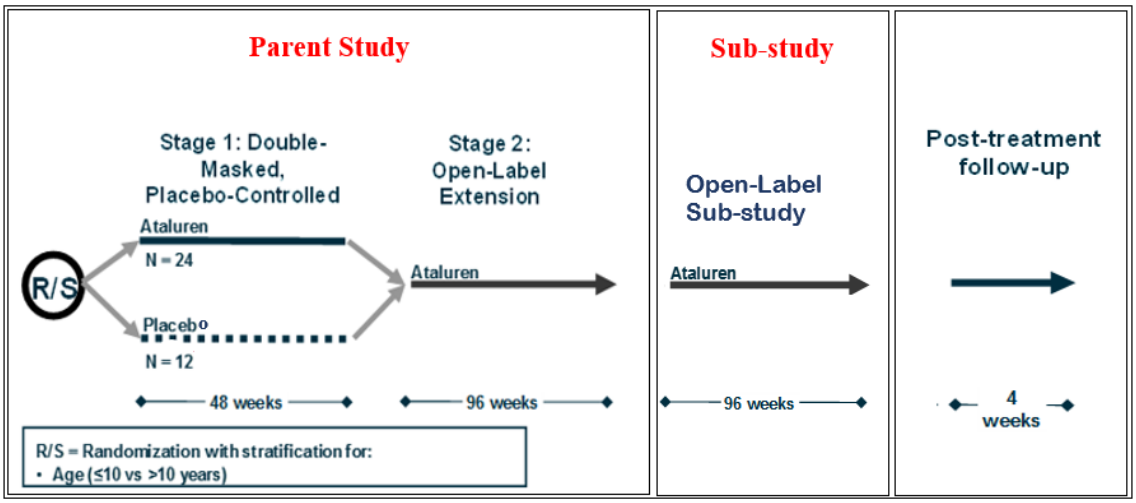
The start of the sub-study will require prior approval of a protocol amendment from applicable Institutional Review Boards and will continue for 96 week or until commercial availability of ataluren for this indication, whichever is first, or until a positive risk-benefit assessment in this indication is not demonstrated.

After the subject's last dose of ataluren, there will be a 4-week post-treatment follow-up period. A primary analyses of the double-masked phase will be conducted after the last subject has completed Week 96.

Subjects who complete the parent study will be eligible to participate in the sub-study. The principal investigator or sub-investigator will discuss the possibility of participation directly with study subjects and/or parent/legal guardian in the clinic.

A schematic of the study design is provided in Figure 1.

Figure 1. STAR Aniridia Study Schematic



2.5 Sample Size

The study was planned to enroll a minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age. This number of subjects has been reduced to 24 and should provide adequate information for an initial evaluation the efficacy safety of ataluren in this population.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is the percent change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts.

3.2 Secondary Endpoints

The key secondary efficacy endpoints of this study are:

- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OU
- Change from baseline (Visit 2/Day 1) to Week 48 in BCVA

Other secondary efficacy endpoints of this study are as follows:

- Percent change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Critical Print Size of OU, OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Acuity of OU, OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in severity of corneal keratopathy
- Change from baseline (Visit 2/Day 1) to Week 48 in iris area
- Change from baseline (Visit 2/Day 1, Stage 1) to Week 240 (Sub-study End of Treatment Visit) in BCVA. Note: This endpoint will be assessed only for the cohort of subjects who enroll into the sub-study.

The secondary safety endpoint of this study is the overall systemic and ocular safety profile of ataluren as determined by:

- Incidences of treatment-emergent adverse events (TEAEs)
- Abnormal findings on laboratory assessments
- Vital signs
- Physical examinations
- Ophthalmoscopy
- Slit-lamp examination
- Visual field testing

3.3 [redacted]

[redacted]

4 HYPOTHESES

1) Percent change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed (MRS) of OU as measured using the MNREAD Acuity Charts:

   Null Hypothesis: $\mu A = \mu P$
   Alternate Hypothesis: $\mu A \neq \mu P$

   Where μA = mean percent change in MRS in ataluren arm; μP = mean percent change in MRS in placebo arm.

5 DEFINITIONS

Adverse Event

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug (investigational medicinal product) in humans, whether or not it is considered related to the drug. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a study subject who is administered study drug in this study. A specific list of occurrences that should be reported as AEs is provided in section 9.1.1 of the study protocol. Subjects must be followed for adverse events for at least 28 days after the last dose of ataluren administration, or until any drug-related adverse events and/or ongoing serious adverse events (SAEs) have resolved or become stable, whichever is later. Any event that starts within 35 days (to account for visit window) after last dose of ataluren will be summarized.

Adverse events will be graded for severity using Common Terminology Criteria for Adverse Events (CTCAE) Version 4 grading, where 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, and 5=Fatal.

Relationship to study treatment will be coded using the following categories: Unrelated, Unlikely related, Possibly related, and Probably related. In summaries where relatedness is dichotomized to related or not, Unrelated and Unlikely related will be classified as not related and Possibly related and Probably related will be classified as related.

Serious Adverse Event:

A serious adverse event is defined as an adverse event that

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Treatment-Emergent AE:

A TEAE is any AE that begins or increases in severity after the initial dose of study drug and within 5 weeks of the last dose of study drug.

Age

Subject's age is defined as from date of birth to randomization date. The formula used is (randomization date – date of birth+1) / 365.25.

Ataluren Exposure

The duration of exposure to ataluren treatment is defined as the last dose date minus the first dose date + 1 day.

Baseline

For any variable, unless otherwise defined, baseline is the last assessment taken prior to the first study drug administration.

Change from Baseline

The arithmetic difference between a post-baseline value and the baseline value:

Change from Baseline = (Post-baseline Value – Baseline Value)

Percentage Change from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

End of Double-masked study period

End of double-masked study period is at Week 48 (day 337 ± 28 days), unless terminated early.

End of Study

End of study is at Week 144 (day 1008 ± 7 days), unless terminated early.

Early termination from study

Early termination would be assigned to the visit whose visit window included the termination date. In the event that an early termination visit does not fall within a nominal visit window, then the termination visit will be assigned to the visit closest to that date. If duplicate data result from the assignment of a termination visit, then the values measured last will be selected for analysis.

Enrollment date
Enrollment date will be assigned after confirmation of eligibility has been received from PTC Therapeutics, but not after the first day of study drug administration.

Study drug
Study drug in this study is ataluren (PTC124) or placebo.

Randomization date
Randomization date is the day the subject is assigned a randomization number on study Day 1.

Study Day 1

Day 1 is defined as the first day that study drug is administered to the subject.

Study Day

Day on study = Starting from Day 1

6 ANALYSIS POPULATIONS

6.1 Safety Analysis Population

The safety population will include all randomized subjects who receive at least 1 dose of study drug. Subjects will be analyzed as treated.

6.2 Intent-to-Treat Analysis Population

The intent-to-treat (ITT) population will include all randomized subjects who receive at least 1 dose of study drug. Subjects will be analyzed as randomized. The ITT population will be the primary efficacy population.

6.3 Efficacy Analysis Populations

The efficacy analysis population will include subjects for the ITT analysis population who have a baseline value and at least 1 post-baseline value. Subjects will be analyzed as treated. Analyses based on the efficacy analysis population will be supportive of those performed on the ITT population.

7 STATISTICAL METHODS OF ANALYSIS

All statistical analyses will be programmed using Statistical Software from SAS Institute (SAS®) software version 9.4 or later. Standard macros will be used in programming when possible. Testing and validation plans for all programs will be developed in accordance with Promedica International Inc. guidelines and will include independent programming of tables and analyses.

7.1 Sample Size

The study is planned to enroll a minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age. This number of subjects should provide adequate information to evaluate the safety of ataluren in this population. For a statistical hypothesis test for any efficacy endpoint, the study will have 60% power to detect an effect size (i.e., standardized mean difference) of 0.85, or 80% power to detect an effect size of 1.06, at the 0.05 significance level (2-sided).

7.2 General Principles

By-subject listings will be created for each eCRF module. Summary tables for continuous variables will contain the following statistics: N, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence interval (CI) as appropriate. Summary tables for categorical variables will include N, percentage, and 95% CIs on the percentage, as appropriate. Confidence intervals for proportions, when provided, will be calculated using the Clopper-Pearson exact method (Clopper 1934). Graphical techniques will be used when such methods are appropriate and informative. For safety summaries, CIs will not be presented, unless specified otherwise. Tables will separate data by treatment arm.

Transformations of the data may be explored if warranted by the distribution of the data. Analyses resulting from transformations applied after the data are unmasked will be considered to be exploratory.

The primary efficacy analyses are based on percent changes in the MNREAD Maximum Reading Speed endpoint at Week 48, the period where the double-masked randomized phase of the study will end. Hypotheses are stated to test for differences in this clinical outcome relative to baseline between ataluren-treated and placebo-treated subjects at this time. At Week 48, subjects will proceed to the open-open label Stage 2 of the study until week 96, where subjects originally on placebo will receive ataluren. Subsequent to Week 96, subjects will have the option of continuing study drug (ataluren) through Week 144. Descriptive statistics will be provided for all visits till Week 144 for all efficacy endpoints by placebo and ataluren treatment groups. In addition, all descriptive statistics for combined ataluren treatment will also be provided till Week 144. For the latter analysis the baseline for placebo group will be Week 48 value.

Differences in non-visit specific safety data, for example, AE and concomitant medication, will be compared directly between ataluren-treated and placebo-treated subjects during the first stage of the study, through Week 48. Ataluren experience during the whole study will also be displayed. For visit specific data, for example, lab data, similar analysis will be performed as for efficacy data except no hypothesis testing will be performed.

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

All analyses will be performed using SAS® Software (Version 9.4, or later) (SAS Institute Inc. 1990).

7.3 Study Population

7.3.1 Subject Disposition

The number of subjects who are screened, randomized, receive study drug, and complete each study stage will be summarized. The number of subjects included in the safety/ITT, and efficacy analysis populations will be included in the table. Attendance at each visit, including missed visits, discontinuations, lost to follow-up, and percentage accountability will be summarized. Accountability is determined by dividing the number of subjects attending a visit by the sum of those who attended the visit, who missed the visit, or who were lost to follow-up at the visit). Subjects discontinued or who have not yet reached the visit of interest, are not counted in the denominator. The formula would read:

% Accountability = 100* (number attending visit /

(number attending visit + number missing visit + number lost to follow-up)

A list of subjects who withdraw early will be provided. This listing will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be provided. In addition, significant known protocol deviations will be noted for individual subjects; a summary table may also be provided for these deviations.

7.3.2 Demographic and Baseline Characteristics

Age, race, ethnicity, sex, height, weight, body mass index, and medical history will be summarized by treatment arm for ITT subjects receiving study drug, using descriptive statistics.

7.3.3 Medical History and Prior Medication

Medical history and prior medication information will be summarized.

7.4 Extent of Exposure

7.4.1 Defining Rules

The extent of exposure to ataluren treatment is defined as the last dose date minus the first dose date + 1 day. The frequency will be presented according to the duration ranges as follows:

The extent of exposure to ataluren treatment is defined as the last dose date minus the first dose date + 1 day. The frequency will be presented according to the duration ranges in each Stage (i.e., Stage 1 [double-masked dosing] or Stage 2 [open-label dosing]): <24 weeks, >24 to <48 weeks, >48 to <72 weeks, >72 to <96 weeks, >96 to <120 weeks, >120 to <144 weeks, and ≥144 to <168 weeks, ≥168 to <192 weeks, ≥192 to <216 weeks, and ≥216 to ≥240 weeks. Descriptive statistics (mean, standard deviation, median, min, max) will be presented for Stage 1, Stage 2, Week 144 – end of the study, and the whole study.

7.4.2 Study Drug Compliance

Study drug compliance will be assessed by analysis of unused study drug reported. Compliance will be summarized by treatment arm in terms of the percentage of drug actually taken, as reported by the subject, relative to the amount that should have been taken during the study, per the protocol.

Based on the mg total from number of color-coded sachets prescribed (125 mg in yellow, 250 mg in pink, and 1000 mg in blue), the protocol-specified dose will be calculated for each subject at each administration. The amount in mg reported taken by the subject will be recorded. The sum of the reported mg taken, divided by the mg prescribed, will be the basis upon which percentage compliance is calculated.

The numerator and denominator are based on these calculations

The amount taken (numerator) is the sum of

(Number of tablets distributed – number of tablets remained in 125 mg sachets)*125,
(Number of tablets distributed – number of tablets remained in 250 mg sachets)*250, and
(Number of tablets distributed – number of tablets remained in 1000 mg sachets)*1000.

Protocol specified sum to be taken (denominator) is calculated using the rules below.

The amount supposed to be taken between Visit i and Visit i+1 is

m_i = (weight at Visit i)*40*(number of days between Visit i and Visit i+1)

The amount supposed to be taken in a period (for example, stage 1) is the sum of m_i for the visits in the period.

Compliance will be assessed in Stage 1, Stage 2 and the entire study.

7.5 Safety Analyses

The safety profile will be based on adverse events, concomitant medications, vital signs, physical examinations, and clinical laboratory measurements. All treated subjects will be included in the safety analyses.

Adverse event and SAE summaries will also be presented for the following periods:

- Through Week 48 (double-masked phase)
- Through End of Treatment (entire study, including the sub-study)

7.5.1 Adverse Events

Adverse events will be grouped by system organ class and by preferred term within system organ class according to the latest version of the Medical Dictionary for Regulatory Activities coding dictionary. The number of subjects reporting at least 1 adverse event will be summarized by treatment group. Tables and/or narratives of any on-study death, serious or significant adverse events, including early withdrawals because of adverse events, will be provided should they occur.

Summary information (the number and percent of subjects by treatment) will be tabulated for:

- Treatment-emergent adverse events, including clinical and laboratory adverse events
- Treatment-related adverse events
- Treatment-emergent adverse events by severity
- Treatment-related adverse events by severity
- SAEs
- Adverse events leading to discontinuation
- Ocular adverse events

Adverse events will be summarized separately through Week 48 (Study Phase 1), from Week 48 through Week 148, through Week 148, and through end of treatment, including sub-study. Adverse events will be assigned to a study phase based on the start date of the adverse event. In study Stage 1 and entire study, AEs will be summarized by treatment. In addition, AEs while subjects are on ataluren will be presented for the entire study.

7.5.2 Concomitant Medications

The number and percentage of patients receiving concomitant medications or treatments prior to and during each study stage and over both study stages will be tabulated and presented overall and by treatment group for the Safety analysis population. Concomitant medications and treatments will be summarized using descriptive statistics and will be presented by type of drug (WHO DRUG classification preferred term and Anatomical Therapeutic Chemical Classification [ATC] level 1) by treatment group.

7.5.3 Clinical Laboratory Tests

Summary of observed values and changes from baseline (last measurement prior to entering the study) will be summarized at each visit. In addition, for laboratory adverse events, severity will be graded by CTCAE, when such grading is available. The frequency of subjects with values below, within, and above the normal reference range will be also be summarized in shift tables at each visit. Worst CTCAE grade will be presented for Stage 1, Stage 2, Week 144 – end of the study, and over the entire study. A subject having the same abnormality more than once within a time interval will be counted only once based on the worst severity grade observed.

7.5.4 Vital Signs

Vital signs will be listed for each subject. These will include temperature, respiration, pulse, and blood pressure. Summaries over time and changes from baseline will be provided at each visit.

7.5.5 Physical Examinations and Other Parameters

Height, weight, physical examination, ophthalmoscopy, slit-lamp examination, and visual fields will be summarized by visit using descriptive statistics over the course of the study. Medications taken prior to entering the study and started while on study (i.e., concomitant) will be summarized to Week 48, from Week 48 to Week 148, and through end of treatment, including sub-study.

7.6 [redacted]

7.7 Efficacy Analysis

All efficacy analyses will be conducted in both ITT population as the primary analysis. Visual acuity, corneal keratopathy, and iris area will also be analyzed using the efficacy analysis population as a supportive analysis.

The primary efficacy analysis will be by analysis of covariance (ANCOVA) where baseline Maximum Reading Speed (OU) and age will be included as covariates, with treatment as a fixed effect. LS means for the two treatment arms will be provided along with 95% confidence intervals.

To assess treatment effect on the change from baseline in secondary endpoints, general linear models/ANCOVA models, with baseline adjustment and treatment as factors will be used. For the analysis of MNREAD endpoints, age will be included as a continuous covariate; all other secondary endpoints will include age stratum as a factor in the model.

To adjust for other potential effects, some other appropriate statistical models, e.g., ANCOVA models, and/or mixed effect models, may be explored. The p-value of testing treatment difference will be provided. The trend of assessments overtime may be assessed. A summary of the efficacy endpoints listed above will also be provided by visit to assess the trend. Tests of trend, if performed, would include repeated measures over visits with an appropriate covariance structure fitted (first order autoregressive). The effect of linear time would be fit along with its product with treatment to test for differences in trend over time between the two treatment arms. If missing Week 48 assessments for the primary efficacy endpoint exist, sensitivity analyses will be conducted. The reasons of missing will be reported. Analysis results for data with and without imputations (using methods defined in Section 10.1) will be compared.

7.8 Multiplicity Adjustment

The key secondary endpoints will be tested sequentially in the order of Reading Accessibility Index and then BCVA at the two-sided significance level 0.05. For example, if the hypothesis for the primary endpoint, Maximum Reading Speed, is rejected at 0.05 level, then Reading Accessibility Index will be tested at 0.05 level. Further, if the hypothesis for Reading Accessibility Index is rejected at 0.05 level, then BCVA will be tested at 0.05 level. If the hypothesis for the primary endpoint is not rejected at 0.05 level, then no hypothesis testing will be performed for the key secondary endpoints.

All other analyses are exploratory and will not be corrected for multiplicity.

7.9 [redacted]

[redacted]

7.10 Subgroup Analyses

Data may be summarized within subject subgroups of interest based on potentially relevant demographic, and clinical factors, such as age, nonsense mutation stop codon type (UGA, UAG, UAA), and/or baseline efficacy parameters, baseline VA, baseline iris area, and corneal keratopathy.

7.11 Post Hoc/Exploratory Analyses

Correlations between subject characteristics and outcome measures, and correlations among outcomes measures may be explored using regression models or other appropriate techniques.

8 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Modifications to the planned statistical analyses should be minimized. Nonetheless, the data obtained from the study may indicate that the planned analyses are inappropriate or that additional analyses need to be performed. The study report will document any deviations from the planned analyses.

9 LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

Tables are categorized and numbered in accordance with ICH E3 guidelines. Each table, figure and listing are presented by treatment arm. Efficacy tables will be provided both for ITT and Efficacy Evaluable populations. Accountability tables will also include an overall column. Listings will be sorted by treatment, subject identification, and by visit, if multiple visits exist.

10 MISSING DATA HANDLING

10.1 Handling Missing Efficacy Data

Missing data for the primary efficacy endpoint will be imputed through Week 48 using last observation carried forward (LOCF) as the primary method of imputation for the efficacy and ITT analysis populations.

As a sensitivity analysis to the use of LOCF, multiple imputation (using SAS PROC MI and SAS PROC MIANALYZE) will also be used to impute missing endpoint data. Missing data at week 48 will be imputed for the primary endpoint for the ITT population only. Missing data predictors will be baseline MRS, MNREAD baseline parameters of reading acuity index, critical print size, reading acuity, and subject age. Twenty iterations will be generated with a prespecified seed number of 20191015 using the Markov Chain Monte Carlo (MCMC) method.

A second sensitivity analysis will be performed using a tipping point approach. The best and worst MRS change will be selected over the entire sample. These values will be rounded to one decimal places. All ataluren-treated subjects with missing endpoint data will be imputed with the worst value and all placebo treated subjects with missing endpoint data will be imputed with the best value and a p-value derived. Next, all ataluren-treated missing values will be replaced by the next worst value all placebo-treated missing data will be replaced by the next best value and a p-value derived. This process will be continued until all ataluren-treated missing data are replaced with the best value and all placebo-treated missing data are replaced by the worst value. The point at which the p-value “tips” from non-significance to significance will be noted relative to its order and number of analyses performed. In the event that all permutations are statistically significant, then it can be concluded that imputation does not result in a false positive.

Efficacy data will not be imputed for the open-label study period.

If any needed/permitted surgical treatment is performed during the study, and as a consequence, any assessment outcomes are affected significantly due to the surgical procedure, these assessment outcomes on and after the surgery will be set as missing and the last assessment prior to the surgery will be used for later assessment time points.

10.2 Handling Partial Dates or Missing Dates

10.2.1 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date is incomplete (i.e., partially missing).

Missing day and month

- If the year is same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose of double-blind study drug will be assigned to the missing fields.
- If the year is prior to the year of the date of the first dose double-blind study drug, then December 31 will be assigned to the missing fields.
- If the year is after the year of the date of the first dose double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

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

Missing day only

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

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

10.2.2 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete

(i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

10.2.2.1 Incomplete Start Date

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

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose of double-blind study drug will be assigned to the missing fields.
- If the year of the incomplete start date is prior to the year of the date of the first dose of double-blind study drug, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

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

Missing day only

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

10.2.2.2 Incomplete Stop Date

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

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of double-blind study drug, then the day and month of the date of the last dose of double-blind study drug will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the date of the last dose of double-blind study drug, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

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

Missing day only

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

11 REFERENCES

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Appendix A Schedule of Events

The types and timing of data to be recorded are summarized in Table 1 (Stage 1, double-masked period), Table 2 (Stage 2, open-label period), and Table 3 (open-label sub-study).

Table 1. Schedule of Events (Stage 1)

Protocol Activities	**Screening**		**Double-Masked Treatment**					
Day±Window **Week**	**-28**	**-4**	**1[a]**	**1**	**169±28**	**24**	**337±28**	**48/ End of Stage 1[b]**
Visit	**1**		**2**		**3**			**4**
Informed consent	X							
Medical and ophthalmic history[c]	X							
Serum viral screen	X							
Physical exam	X		X					X
Height and weight	X		X		X			X
Vital signs	X		X		X			X
Ophthalmoscopy	X		X		X			X
Hematology, biochemistry, urinalysis	X				X			X
Serum β-HCG[d]	X		X		X			X
Study drug and diary dispensing			X		X			X
Study drug administration			X		X			X
Study drug compliance and return					X			X
Collect diary					X			X
Adverse events			X		X			X
Concomitant meds	X		X		X			X
MNREAD			X					X
[redacted]			X		X			X
Slit-lamp examination[e]			X		X			X
Slit-lamp photography			X		X			X
OCT			X		X			X
Fundus photography			X		X			X
Humphrey visual fields			X					X
BCVA (visual acuity and refraction)[f]	X		X		X			X
[redacted]			X		X			X
[redacted]			X		X			X
[redacted]			X		X			X
[redacted] blood sample for plasma PK[g]			If feasible (i.e., during surgery for glaucoma, cataracts, etc.)					

Abbreviations: β-HCG, beta-human chorionic gonadotropin; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; [redacted]; LEA, LEA Symbols Visual Acuity Test System; MNREAD, Minnesota Low Vision Reading (MNREAD) Acuity Charts; OCT, optical coherence tomography; PK, pharmacokinetic(s)

[a] All study and laboratory assessments on the first day of treatment must be done prior to in-clinic administration of the first dose.

[b] Open-label study drug administration will start at the end of Stage 1 (Visit 4/Week 48).

[c] Should include capture of available historical values for ocular assessments included in this study, such as visual acuity, [redacted], etc.

[d] Sample taken only for female subjects of childbearing potential.

[e] Slit-lamp examination should precede [redacted] measurement.

[f] Visual acuity and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) or an age-appropriate alternative (e.g., LEA).

Table 2. Schedule of Events (Stage 2)

Protocol Activities		**Open-Label Treatment**						**End of Study)/ Early Termination[a]**		**Follow-Up[b]**	
Day±Window	**Week**	**505±28**	**72**	**673±28**	**96**	**841±28**	**120**	**1009±28**	**144**	**28 Days Post EOS/ET±7**	**148**
Visit		**5**		**6**		**7**		**8**		**9**	
Physical exam				X				X		X	
Height and weight		X		X		X		X		X	
Vital signs		X		X		X		X		X	
Ophthalmoscopy		X		X		X		X		X	
Hematology, biochemistry, urinalysis		X		X		X		X		X	
β-HCG[c]		X		X		X		X			
Study drug and diary dispensing		X		X		X					
Study drug administration		X		X		X					
Study drug compliance and return		X		X		X		X			
Collect diary		X		X		X		X			
Adverse events		X		X		X		X		X	
Concomitant meds		X		X		X		X		X	
[redacted]		X		X		X		X			
MNREAD				X				X			
Slit-lamp examination[d]		X		X		X		X			
Slit-lamp photography		X		X		X		X			
OCT		X		X		X		X			
Fundus photography		X		X		X		X			
Humphrey visual field				X				X			
BCVA (visual acuity and refraction)[e]		X		X		X		X			
[redacted]		X		X		X		X			
[redacted]		X		X		X		X			
[redacted]		X		X		X		X			
[redacted]		blood sample for plasma PK[f]				If feasible (e.g., during surgery for glaucoma, cataracts, etc.)					

Abbreviations: β-HCG, beta-human chorionic gonadotropin; BCVA, best corrected visual acuity; EOS/EOT, end of study/end of treatment; ETDRS, Early Treatment Diabetic Retinopathy Study; [redacted]; LEA, LEA Symbols Visual Acuity Test System; MNREAD, Minnesota Low Vision Reading (MNREAD) Acuity Charts; OCT, optical coherence tomography; PK, pharmacokinetic(s)

[a] Refer to Table 3 for the schedule of events for subjects participating in the sub-study for Visits 8-13.

[b] This visit is only required for subjects not participating in the sub-study.

[c] Sample taken only for female subjects of childbearing potential.

[d] Slit-lamp examination should precede [redacted] measurement.

[e] Visual acuity and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) or an age-appropriate alternative (e.g., LEA).

[f] [redacted]

Table 3. Schedule of Events (Open-label Sub-study)

Protocol Activities	**Open-Label Treatment**			**End of Study)/ Early Termination**		**Follow-Up**
Week	**144 ±28 days**	**168±28 days**	**192±28 days**	**216±28 days**	**240 ±28 days**	**28 Days (4 weeks) Post EOS/ET (Week 244±7days)**
Visit	**8**	**9**	**10**	**11**	**12**	**13**
Informed consent	X					
Physical exam	X					X
Height and weight	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Ophthalmoscopy	X	X	X	X	X	X
Hematology, biochemistry, urinalysis	X	X	X	X	X	X
β-HCG[a]	X	X	X	X	X	
Study drug and diary dispensing	X	X	X	X		
Study drug administration	X	X	X	X		
Study drug compliance and return	X	X	X	X	X	
Collect diary	X	X	X	X	X	
Adverse events	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X
[redacted]	X					
MNREAD	X	X	X	X	X	
Slit-lamp examination[b]	X					
Slit-lamp photography	X					
OCT	X					
Fundus photography	X					
Humphrey visual field	X				X	
BCVA (visual acuity and Refraction)[c]	X	X	X	X	X	
[redacted]	X					
[redacted]	X	X	X	X	X	
[redacted]	X					
Schedule next visit	X	X	X	X	X	

Abbreviations: β-HCG, beta-human chorionic gonadotropin; BCVA, best corrected visual acuity; EOS/EOT, end of study/end of treatment; ETDRS, Early Treatment Diabetic Retinopathy Study; [redacted]; LEA, LEA Symbols Visual Acuity Test System; MNREAD; Minnesota Low Vision Reading (MNREAD) Acuity Charts; OCT, optical coherence tomography

[a] Sample taken only for female subjects of childbearing potential.

[b] Slit-lamp examination should precede [redacted] measurement.

[c] Visual acuity and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) or an age-appropriate alternative (e.g., LEA).