16.1.9 Statistical Methodology

SAREPTA
THERAPEUTICS

Protocols 4658-us-201 & 4658-us-202

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability, and Pharmacokinetics Study of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, Administered Over 28 Weeks in the Treatment of Ambulant Subjects with Duchenne Muscular Dystrophy

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Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201

Week 20 (Study 4658-us-202) Interim Analysis Plan
FINAL
13 SEPTEMBER 2012

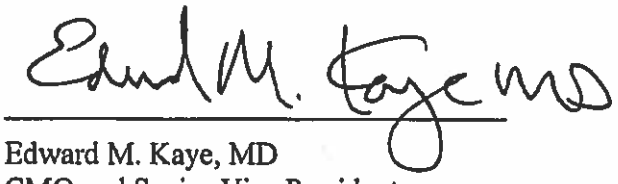
Sarepta Therapeutics, Inc.
3450 Monte Villa Parkway
Bothell, WA 98021 USA

SIGNATURE PAGE

Prepared by:

Jay B. Saoud, PhD
Senior Director, Statistics
Sarepta Therapeutics, Inc.

Approved by:



Edward M. Kaye, MD
CMO and Senior Vice President
Sarepta Therapeutics, Inc.

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1. STUDY AND ANALYSIS OBJECTIVE

Study 4658-us-201 was designed as a double-blind placebo-controlled study to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of eteplirsen in both 50.0 mg/kg and 30.0 mg/kg doses in subjects diagnosed with Duchenne muscular dystrophy (DMD).

Study 4658-us-202 is designed as an open label study to assess the ongoing efficacy, safety, and tolerability of an additional 80 weeks of treatment with 50.0 mg/kg and 30.0 mg/kg doses of eteplirsen in DMD subjects who had successfully completed study 4658-us-201.

This interim analysis plan summarizes the planned analysis and presentation of the efficacy and select safety data of study 4658-us-201 through Week 20 of the ongoing study 4658-us-202, henceforth referred to as "Week 48".

2. INTERIM ANALYSIS OVERVIEW

2.1. Analysis Variables

2.1.1 Subject Disposition

Study drug exposure. This will be characterized by calculating, for each subject, the total amount of eteplirsen taken during the study and the time in days between the first dose and the last dose on Week 48.

2.1.2 Demographics and Baseline Characteristics

Age, weight, height, body mass index (BMI), time since DMD diagnosis (in months) and associated parameters, and race.

For the purposes of the demographic summaries, weight will be the last available measurement taken before the first study drug administration.

BMI will be calculated as BMI = Weight (kg) / Height $(m)^2$. Any measurements in other units will be converted to kilograms and meters prior to the calculation. Weight (kg) = weight (lb)/2.2. Height (m) = height (inches)*0.0254.

All continuous baseline characteristics will be calculated from Screening Day or Visit 1 of study 4658-us-201, as appropriate, and from the beginning of Week 25 for the four placebo subjects who were switched to eteplirsen treatment.

2.1.3 Efficacy Variables

Primary Efficacy Endpoints:

1. Biological: Change from Baseline at Week 48 in percent of dystrophin positive fibers (type = anti-dystrophin antibody MANDYS106) as measured in the muscle biopsy tissue using immunohistochemistry (IHC).
2. Functional: Change from Baseline to Week 48 in 6-Minute Walk Test (6MWT).

Additional Exploratory and Supportive Efficacy Endpoints:

1. Changes from Baseline to Week 48 in the following functional assessments:
   - Timed 4 Step Test.

(b) (4) [redacted]

   - NSAA total score.

(b) (4) [redacted]

2. Change from Baseline at Week 48 in percent of dystrophin positive fibers (type = anti-dystrophin antibody Dys2 & Dys3) as measured in the muscle biopsy tissue using IHC. .

3. Changes from Baseline (b) (4) in CD3, CD4, and CD8 lymphocyte counts in muscle biopsy tissue.
4. Changes from Baseline at Week 48 in muscle biopsy levels of dystrophin intensity per fiber (determined by Bioquant), total dystrophin protein (DYS & MANDYS106 assessed by Western blot analysis), and exon skipping (assessed by reverse transcriptase-polymerase chain reaction [RT-PCR]), and MHC-I and MHC-II expression.
5. Pulmonary Function Tests (FVC, percent predicted FVC (FVC%), FEV1, FEV1%, FEV1/FVC ratio, MIP, and MEP)

2.1.4 Safety Variables

The safety and tolerability of eteplirsen will be assessed from the start of study 4658-us-201 through the review of:

- The frequency and severity of AEs, serious adverse events (SAEs), and discontinuations due to AEs. Adverse events are coded using MedDRA (version 14.1) and are reported by primary System Organ Class (SOC) and Preferred Term Name (PT).

  Adverse events (AEs) will be classified as treatment-emergent AE (TEAE) and non-emergent. TEAEs are those events that develop or worsen during the on-treatment period. Non-emergent events are those that develop during the pre-treatment period
- Safety laboratory tests including hematology, coagulation, serum chemistry (including serum cystatin C), and urinalysis (including urinary cystatin C and KIM-1).
- Vital signs.
- 12-lead electrocardiograms (ECGs).
- Echocardiogram (ECHO).

3. STATISTICAL METHODS

3.1. Analysis Populations

3.1.1 Safety Population

The safety population will include all subjects randomized into study 4658-us-201 who receive any amount of study drug. Analyses performed on the safety population will be according to the treatment actually received.

3.1.2 Intent-to-Treat Population (ITT)

The ITT will include all subjects randomized into study 4658-us-201. Analyses performed on the ITT will be according to the treatment actually received.

3.1.3 Modified Intent-to-Treat Population (mITT)

The mITT will be similar to the ITT but will exclude 2 subjects who showed rapid disease progression during the first few weeks of study 4658-us-201. Analyses performed on the mITT will be according to the treatment actually received.

3.2. Handling of Missing Data

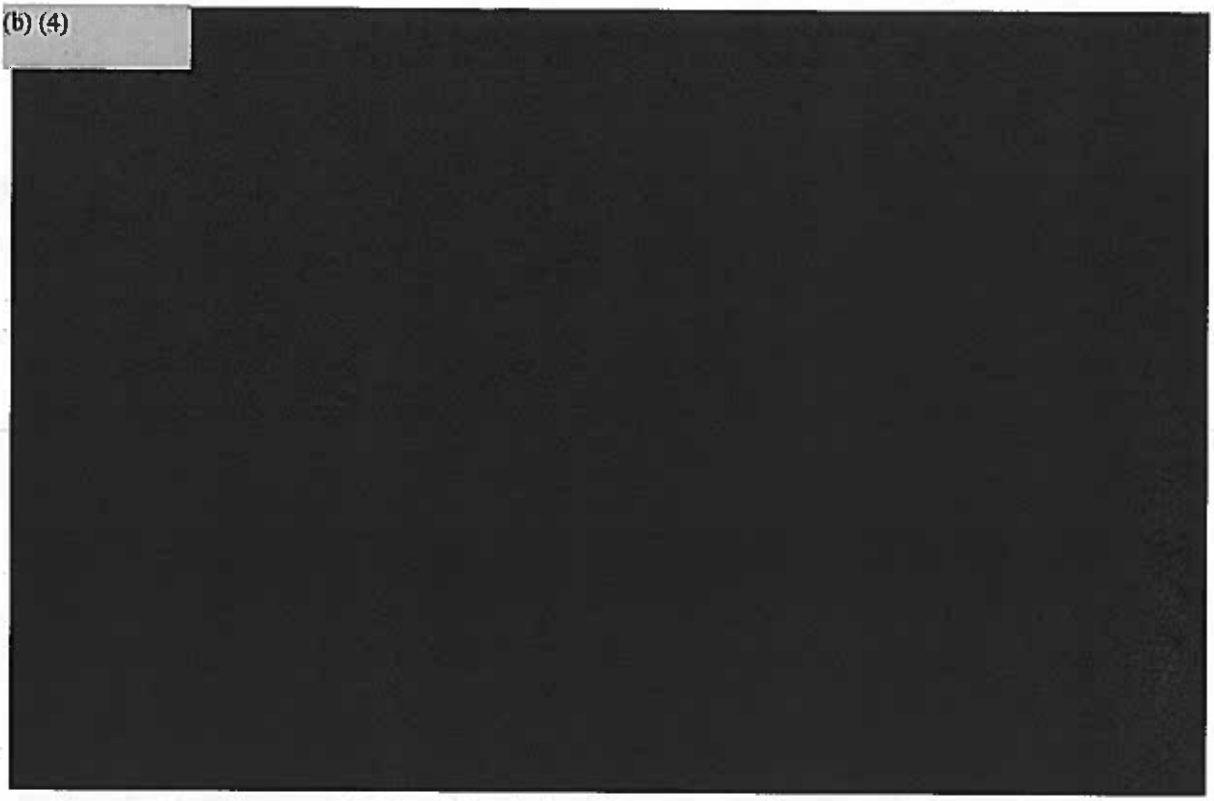
Imputation of missing data will not be performed unless otherwise specified. Descriptive statistics will be based upon reported data.

3.3. Conventions and Methods

(b) (4)

[redacted]

(b) (4)



- Adverse events (AEs) with missing relationship or severity will be presented as "Severe" or "Related", respectively; however, missing values will be presented in the data listings as missing.

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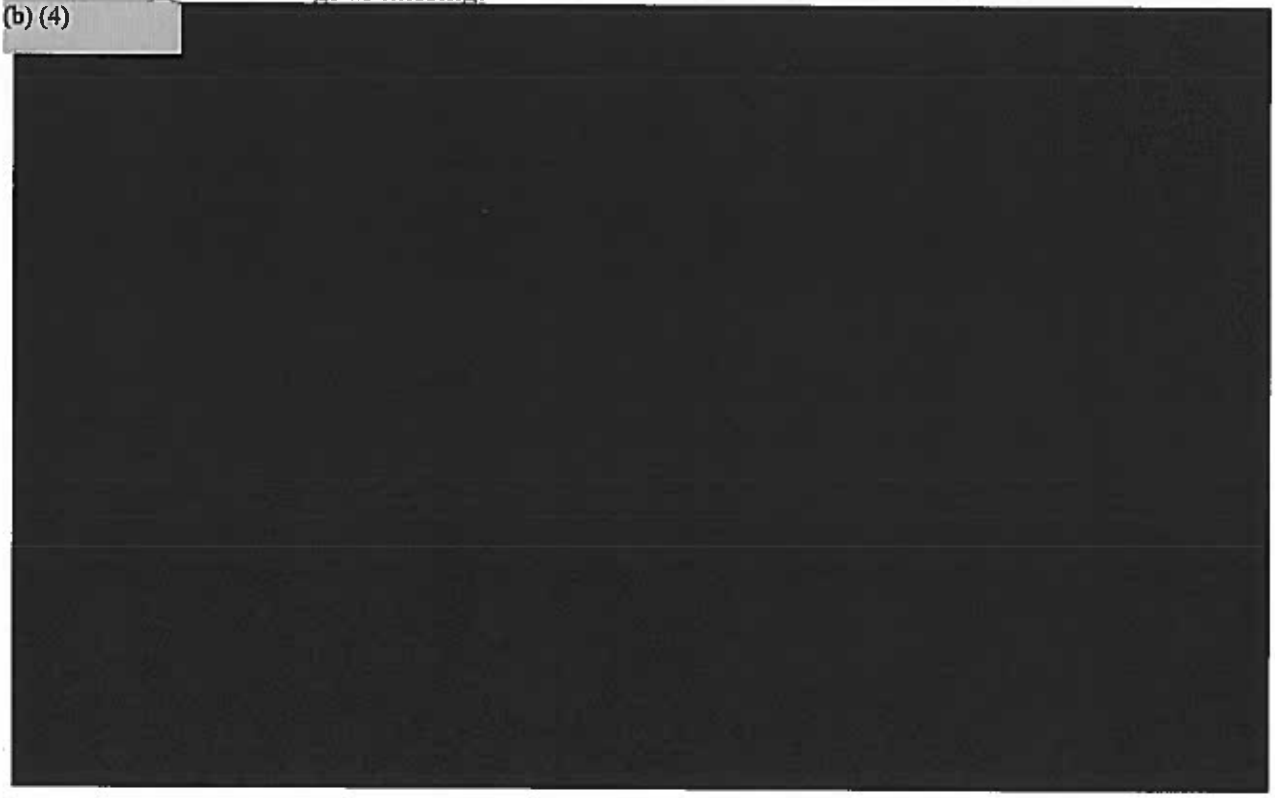

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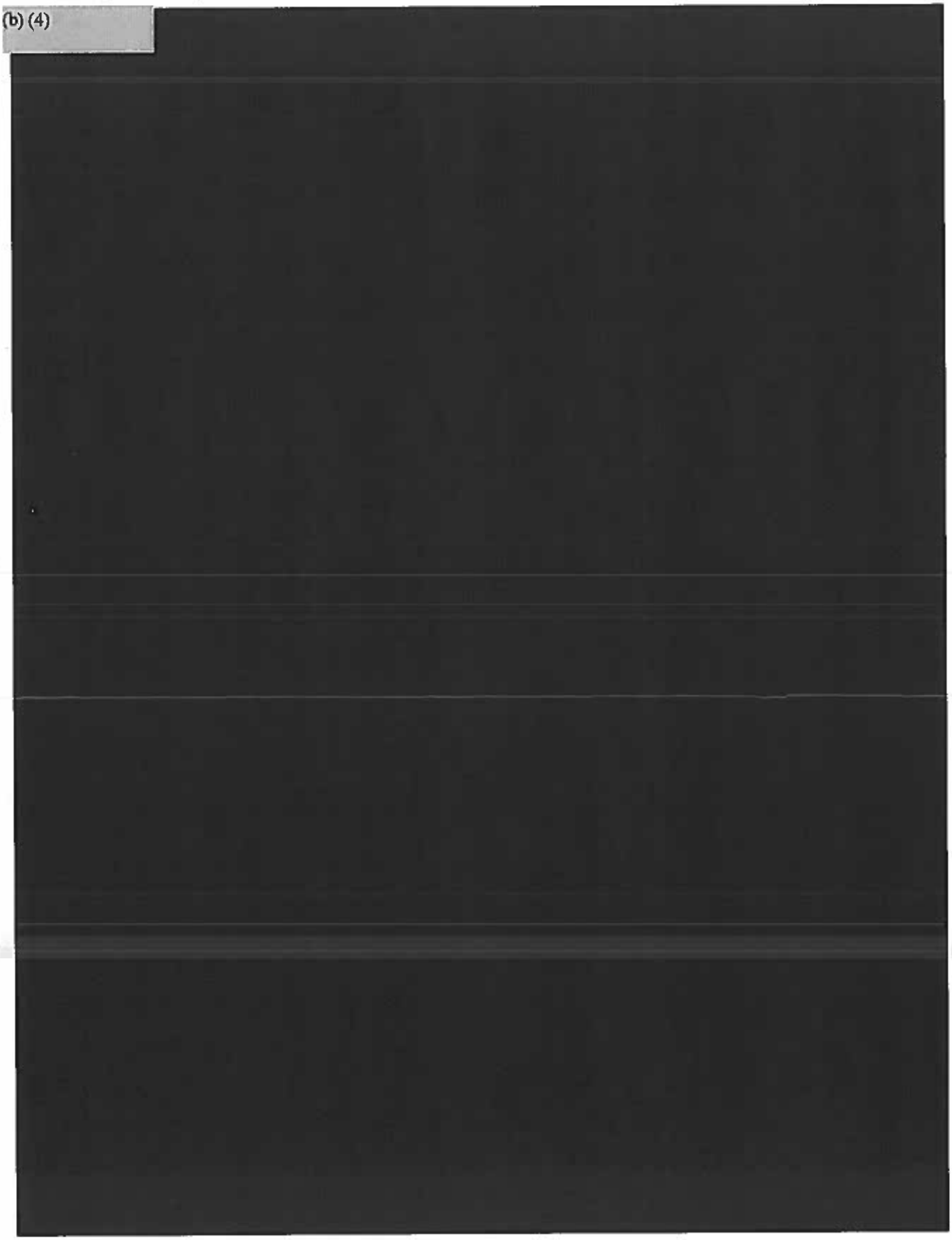

(b) (4) [redacted]

- P-values will be reported as two-sided p-values. If a p-values is less than 0.001 it will be reported as <0.001.
- SAS® Version 9.2 or higher will be the statistical software package used for all data analysis.

3.4. Statistical Analyses

3.4.1 Demographics and Baseline Characteristics

Demographic characteristics including age (years), race, ethnicity, and Baseline characteristics including genetic mutation, height (cm), weight (kg), and BMI (kg/m^2) will be summarized by treatment and overall. Demographic data and Baseline characteristics will be presented in the data listings.

3.4.2 Dosing

The cumulative exposure to eteplirsen (mg), total volume of drug administered (mL) and the total number of infusions received will be summarized by treatment group. Dosing information will be provided in a listing.

3.4.3 Efficacy

3.4.3.1. Primary Efficacy Endpoints

The analysis of the change from Baseline at Week 48 in percent of dystrophin positive fibers (type = anti-dystrophin antibody MANDYS106) as measured in the muscle biopsy tissue using IHC will be based on a restricted maximum likelihood (REML)-based mixed model with treatment (Placebo to 30 mg/kg for 24 weeks, Placebo to 50 mg/kg for 24 weeks, 30.0 mg/kg for 48 weeks, 50.0 mg/kg for 48 weeks) as fixed effect, subject nested within treatment as random effect, with the Baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix will be used. Pairwise treatment comparison using the least square difference will be made between each of the 4 treatment groups. The same mixed model will be repeated using Eteplirsen for 24 weeks and Eteplirsen for 48 weeks as the fixed treatment effect. Weeks 12 and 24 data will NOT be included in these analyses. However, the associated summary tables will include Weeks 12 and 24 data.

If there is strong evidence suggesting that the change from baseline in the MANDYS106 data deviate from normal distribution, then ANCOVA for ranked data as described by Stokes et al 2000 will be utilized.

Additionally, for each of the four treatment groups, for the "Eteplirsen for 48 weeks" (N=8), and for "Eteplirsen for 24 weeks" (N=4), a paired t-test will be used to compare the on treatment value of MANDYS106 with the Baseline value.

The analysis of changes from Baseline to Week 48 in the 6MWT will be based on a REML-based mixed model repeated measures (MMRM) with treatment (placebo to eteplirsen, 30.0 mg/kg, 50.0 mg/kg), time, and treatment-by-time interaction terms as fixed effect, subject nested within treatment as random effect, with the Baseline value

and time since DMD diagnosis as covariates. A spatial power SP(POW) covariance structured matrix will be used to adjust for the unequal intervals in the repeated measurements. The treatment comparison will be made between the treatment groups as described in Section 3.3 above at Week 48 and at each of the other post-Baseline visits.

This procedure does not imply to replace missing data, as the mixed model would use all available on-treatment assessments. In this analysis in which the MMRM is fitted to all post-Baseline data, subjects in the ITT & mITT populations who do not have complete data will still contribute to the estimates at Week 48, but will have less weight in the analysis than those subjects with complete data. Estimates for changes from Baseline at each time-point in each treatment group and for treatment difference will be provided with 95% confidence intervals and p-values using the least significant difference contrasts from the model.

If there is strong evidence suggesting that the 6MWT results deviate from normal distribution, then ANCOVA for ranked data (ranked at every visit for the subjects included in the analysis) as described by Stokes et al 2000 will be utilized.

Sub-Group analysis comparing "Placebo to eteplirsen" versus "Eteplirsen for 48 weeks" based on the mITT population will be performed based on age grouping (< 9.5 & ≥ 9.5 years old at Baseline), on Baseline 6MWT performance grouping (high & low), and for subjects with Genotype 49-50 deletion. Associated summary tables will be produced.

3.4.3.2. Additional Exploratory and Supportive Efficacy Endpoints

The analysis of changes from Baseline to Week 48 in the clinical assessment parameters (Timed 4 Step Test, NSAA Timed 10-meter run and Total Score, (b) (4) and (b) (4)) will be based on a REML-based MMRM with treatment (placebo, 30.0 mg/kg, 50.0 mg/kg), time, and treatment-by-time interaction terms as fixed effect, subject nested within treatment as random effect, with the Baseline value and time since DMD diagnosis as covariates. A SP(POW) covariance structured matrix will be used to adjust for the unequal intervals in the repeated measurements. The treatment comparison will be made between the treatment groups as described in Section 3.3 above at Week 48 and at each of the other post-Baseline visits.

If there is strong evidence suggesting that any of these endpoints data deviate from normal distribution, then ANCOVA for ranked data as described by Stokes et al 2000 will be utilized.

The changes from Baseline in percent of dystrophin positive fibers (type = anti-dystrophin antibody Dys2 & Dys3), and in CD3, CD4, and CD8 lymphocyte counts in muscle biopsy tissue at Week 48 will be analyzed similar to the MANDYS106 (dystrophin primary endpoint) analysis shown above.

The remaining continuous muscle biopsy parameters (levels of dystrophin intensity per fiber, total dystrophin protein, and MHC-I and MHC-II expression) will be summarized by time point (Baseline, on-treatment) and treatment group (as described in Section 3.3 above). These summaries will include descriptive statistics for the observed, on-treatment change from Baseline, and the percent of on-treatment change from Baseline values.

Exon skipping data will be summarized using the number and percent of subjects with no skip in each of the following categories of exon skipping.

- Skip (1)=Correct skip found and sequenced in a low percentage of experiments under improved conditions.
- Skip (2)=Correct skip found and confirmed by sequencing under improved conditions.
- Skip (3)=Correct skip found and confirmed by sequencing under standard conditions.

No inferential testing of these parameters will be performed.

Pulmonary Function Tests (FVC, FVC%, FEV1, FEV1%, FEV1/FVC ratio, MIP, and MEP) will be summarized using descriptive statistics by treatment group (as described in Section 3.3 above) and visit using the observed, on-treatment change from Baseline, and the percent of on-treatment change from Baseline. Furthermore, an MMRM analysis as described above will be utilized.

Additional analysis such as evaluating the relationship between change from baseline at Week 48 in 6MWT (dependent variable) and dystrophin positive fibers using regression analysis with treatment and DMD duration as covariates and with backward elimination model may be performed.

3.4.4 Safety

Safety analyses will be descriptive in nature.

3.4.4.1. Adverse Events

Only treatment emergent adverse events (TEAEs) will be summarized. Non-emergent events will be recorded in the data listings. For all AE tables, the number and percent of subjects reporting AEs, grouped by MedDRA body system and PT, will be summarized by treatment groups. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in the frequency tables. If a subject experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to study drug will be used to summarize AEs by relationship and severity. Repeat occurrence of TEAE after switching to eteplirsen in the 4 subjects who initially received placebo will be summarized as new events and will be presented under the eteplirsen dose they are receiving.

The following summary tables will be produced:

1. Treatment emergent adverse events
2. Treatment emergent adverse events by severity
3. Treatment related treatment emergent adverse events
4. Treatment related treatment emergent adverse events by severity
5. Serious adverse events

Additionally, all SAEs, regardless of their treatment-emergent status will be summarized by SOC and PT.

The following listings will be produced

1) Non-treatment emergent AEs
2) All TEAEs
3) AEs leading to discontinuation
4) SAEs

3.4.4.2. Laboratory Measurements

Descriptive statistics for continuous hematology, clinical chemistry, urinalysis and coagulation laboratory measurements will be generated. Laboratory data will be presented in the data listings showing all predefined change (PC) values, as appropriate.

Additionally, the following will be provided:

- A table of descriptive statistics of the laboratory analytes will be given for Baseline and Week 48, and for the change from Baseline at Week 48.
- Shift table will compare N (%) of low, normal, and high status of the lab values at Baseline to Week 48.
- A table of frequencies of predefined change abnormal (PCA) increases and PCA decreases by time point.

3.4.4.3. Vital Signs

Descriptive statistics for vital signs parameters will be generated. Vital signs data will be presented in the data listings showing all predefined change (PC) values, as appropriate.

Additionally, the following will be provided:

- A table of descriptive statistics of the vital sign parameters will be given for Baseline and Week 48, and for the change from Baseline at Week 48.
- A table of frequencies of PCA and last predefined change abnormal (LPCA) increases and decreases by time point.

3.4.4.4. 12-Lead ECGs

Descriptive statistics for ECG parameter will be generated. ECG data will be provided in a listing showing all predefined change (PC) values, as appropriate.

Additionally, the following will be provided:

- A table of descriptive statistics of the ECG parameters will be given for Baseline and Week 48, and for the change from Baseline at Week 48.
- A shift table will compare N (%) of ECG status at Baseline to Week 48.
- A table of frequencies of PCA and LPCA increases and decreases by time point.

3.4.4.5. Echocardiograms

The actual value and change from Baseline to each on-treatment time point will be summarized by treatment group for each ECHO for ejection fraction (EF) and shortening fraction (SF). All of the ECHO parameters will be listed by subject in a data listing.

4. REFERENCES

Stokes, ME, Davis, CS, and Koch, GG. Categorical data analysis using SAS® system, 2nd Edition. SAS Publishing. 2000.