To: [redacted]

From: [redacted]

Date: February 14, 2020

Subject: Study ERX-963-001 Tables, Listings, and Figures Delivery

This memo is to confirm that the tables, listings, and figures (TLFs) described in the text of the Statistical Analysis Plan (SAP) for Study ERX-963-001 will be produced and delivered as two separate deliveries.

The first delivery will include all TLFs, except for the ones specified below as belonging to the second delivery. Formats and additional specifications for the TLFs in the first delivery will be appended to the text of the SAP prior to study treatment unblinding. The TLFs in the first delivery will be produced and provided to Expansion Therapeutics after study treatment unblinding, according to a time schedule to be agreed between Innovative Analytics and Expansion Therapeutics. These TLFs will form the basis for the study clinical study report. Second delivery TLFs will be included in an addendum to the study clinical study report.

The second delivery includes TLFs that are not directly related to the primary or secondary study objectives. Formats and additional specifications for these TLFs will be created after study treatment unblinding. The schedule for the production of these formats and specifications, along with the schedule for the production of these TLFs shall be established by Innovative Analytics and Expansion Therapeutics after study treatment unblinding. Any additions or subtractions from the second delivery will also be determined at that time.

The TLFs to be included in the second delivery will be:

1. Summaries and listings of baseline Myotonic Dystrophy Health Index
2. TLFs related to electroencephalogram measurements
3. TLFs related to correlation of [redacted] concentrations with efficacy measurements
4. Listings of compartmental plasma pharmacokinetic parameters

EXPANSION THERAPEUTICS

To: [redacted]

Date: April 2, 2020

Subject: Study ERX-963-001 Tables, Listings, and Figures Delivery

This memo is to confirm the analyses and final tables, listings, and figures (TLFs) to be delivered for the Study ERX-963-001. This memo supersedes the memo issued on February 14, 2020 and will be attached to the Statistical Analysis Plan (SAP) Text, Version 1.0, December 6, 2019.

The Primary objective of the study is an assessment of the safety and tolerability of ERX-963 compared to placebo; accordingly, the TLFs of safety and tolerability will be produced and delivered. A subset of TLFs for the Secondary objective endpoints of the effect of ERX-963 compared to placebo will be produced and delivered. These TLFs will be the basis of the final Clinical Study Report (CSR). The pharmacokinetic analysis of Cohort 1 will be provided as separate report to be included as an appendix to the CSR.

The specific TLFs that are removed from the SAP Mockups, Version 1.0, February 7, 2020, are highlighted in yellow in Attachment A. The tables without highlighting will be included in the clinical study report.

In the memo issued on February 14, 2020, the following TLFs were specified to be delayed until a later analysis delivery or clinical study report addendum. These TLFs will no longer be created nor contained in any part of the Clinical Study Report:

1. Summaries and listings of baseline Myotonic Dystrophy Health Index
2. TLFs related to electroencephalogram measurements
3. TLFs related to correlation of [redacted] concentrations with efficacy measurements
4. Listings of compartmental plasma pharmacokinetic parameters

[redacted]

9880 Campus Point Dr, Ste 310
San Diego, CA 92121

Attachment A

2.2 Table of Contents for Mockups of Statistical Tables

The statistical tables will appear in Section 14 of the clinical study report. The statistical tables, therefore, have a prefix of "14."

2.3 Table of Contents for Mockups of Patient Listings

The Patient listings will appear in Appendix 16.2 of the clinical study report. The Patient listings, therefore, have a prefix of "16.2."

Innovative Analytics

STATISTICAL ANALYSIS PLAN (SAP)

Protocol Number:	ERX-963-001
Protocol Title:	Double-Blind, Placebo-Controlled, Dose-Range-Finding, Crossover Trial of Single Day Administration of ERX-963 in Adults with Myotonic Dystrophy Type 1
Protocol Date	October 31, 2019 (Amendment 2)
Product Name or Number:	ERX-963
Sponsor:	Expansion Therapeutics, Inc. 10996 Torreyana Road, Suite 280 San Diego, CA 92121 USA
SAP Prepared by:	[redacted] Innovative Analytics, Inc. 161 East Michigan Ave. Kalamazoo, MI 49007 USA
SAP Version Number (Date):	Version 1.0 (December 6, 2019)

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	Adverse event
Alpha	Distribution rate constant
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
AUC_{inf}	AUC from zero to infinity
AUC_t	AUC from time zero to the time of the last measurable concentration
$\%AUC_{extrap}$	Percent of AUC extrapolated to infinity
Beta	Elimination rate constant
BLQ	Below limit of quantitation
BMI	body mass index
BP	Blood pressure
CGI-I	Clinical Global Impression – Improvement Scale
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CL/F	Apparent oral clearance
CV	Coefficient of variation
DM1	Myotonic dystrophy type 1
ECG	Electrocardiogram
EEG	Electroencephalograph
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
GCP	Good clinical practice
K10	Elimination rate constant
K21	Intercompartmental distribution rate constant
MedDRA	Medical Dictionary for Regulatory Activities
n, N	number
PGI-I	Patient Global Impression – Improvement Scale
PK	pharmacokinetic(s)
PVT	Psychomotor Vigilance Task
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SSS	Stanford Sleepiness Scale

Abbreviation or Term	Definition
TEAE(s)	Treatment-emergent adverse events
$t_{½}$	Terminal elimination half-life
T_{max}	Time of maximum observed plasma concentration
V	Volume of distribution
V1	Volume of central compartment
λ_z	Terminal elimination rate constant

2 STUDY OVERVIEW

This is a multi-center, randomized, double-blind, placebo-controlled, two-treatment crossover study in participants with DM1.

In this study participants who have consented and meet all-eligibility criteria will receive two treatments, IV Placebo (Treatment A) and ERX-963 (Treatment B or C) in a crossover fashion with approximately 4 to 18 days washout between the treatments (Note: washout days are counted from the day of dosing in Period 1). The study will be conducted in two cohorts.

In cohort 1, approximately six (6) participants will be randomized to one of two sequences:

Sequence 1: Treatment A: IV Placebo in Period 1 →
4 to 18 days washout →
Treatment B: 1 mg ERX-963 in Period 2
Sequence 2: Treatment B: 1 mg ERX-963 in Period 1 →
4 to 18 days washout →
Treatment A: IV Placebo in Period 2

ERX-963 1 mg or placebo will be administered intravenously over 5 minutes.

In cohort 2, approximately six (6) participants will be randomized to one of two sequences:

Sequence 1: Treatment A: IV Placebo in Period 1 →
4 to 18 days washout →
Treatment C: Selected ERX-963 dose in Period 2
Sequence 2: Treatment C: Selected ERX-963 dose in Period 1 →
4 to 18 days washout →
Treatment A: IV Placebo in Period 2

The selected ERX-963 dose (0.5 mg, 1 mg or 2 mg) or placebo will be administered intravenously over 5 minutes (0.5 mg or 1 mg) or 15 minutes (2 mg).

ERX-963 dose for cohort 2 will be selected based on a *blinded review* of safety data from cohort 1. A decision to proceed to cohort 2 with the planned 2 mg dose, to lower the dose to 1 mg or 0.5 mg, or cease dosing altogether, will be made jointly by the medical monitor and the principal investigators and will be based on the clinical nature of adverse events, safety laboratory and vital signs abnormalities observed during cohort 1.

Blinding of placebo and investigational drug will be maintained during randomization, drug administration, and complete assessment periods for each cohort.

3 STUDY OBJECTIVES

Primary

The primary objectives of the study are to assess the safety and tolerability of a single dose of ERX-963 versus placebo in patients with Myotonic Dystrophy Type 1 (DM1).

Secondary

The secondary objectives for the study are to assess the effect of intravenously administered ERX-963 versus placebo on sleepiness, vigilance, and working memory in patients with DM1.

Exploratory

There are two exploratory objectives for this study:

- To correlate ERX-963 plasma concentrations to clinical efficacy endpoints in patients with DM1
- To assess the effect of intravenously administered ERX-963 versus placebo on brain activity in patients with DM1.

4 GENERAL METHODS

4.1 Analysis Populations

Screened Population: The screened population will be defined as all patients who sign the informed consent documents.

Safety Population: The safety population will be defined as all patients who sign the study-specific informed consent documents and receive at least 1 dose of study medication. Participants will be analyzed according to the intervention they received.

Evaluable Population: All treated patients who complete all the protocol specified assessments in both treatment periods.

Enrolled Population: All participants who receive at least one dose of study intervention.

PK Population: The PK Population will include all patients who receive the dose of ERX-963 study drug, have no major protocol deviation that may impact PK, and have enough postbaseline concentration data to obtain at least one reliable estimate of a key PK parameter.

4.2 Summarization of Data

Study results will be summarized by treatment group [for example., A, B, or C] or by treatment sequence [for example, A-B, B-A, A-C, C-A] unless otherwise specified.

No imputation of missing data will be performed. No windowing of visits will be performed unless otherwise specified.

4.3 Sample Size Justification

No formal sample size calculations were performed.

Approximately 20 participants will be screened and at least 6 evaluable participants per cohort are expected to complete the study.

Participants who do not complete the crossover portion of the study will be discontinued and replaced with a new participant.

4.4 Randomization

On the day of dosing in Period 1 participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the two treatment sequences of the study [Sequence 1: AB and Sequence 2: BA in Cohort 1; Sequence 1: AC and Sequence 2: CA in Cohort 2], according to the randomization schedule generated prior to the study. Each participant will be administered blinded study intervention, labeled with his/her unique randomization number, throughout the study.

4.5 Output Production and Validation

All analyses will be performed using SAS V 9.3 or higher (SAS Institute, Inc, Cary, North Carolina, USA). Validation and quality control of the tables and listings, which display the results of the statistical analysis of the data from this study, will follow the appropriate Innovative Analytics standard operating procedures (SOPs).

5 SUBJECT DISPOSITION

The number of patients who are screened, who receive at least one dose of study intervention, completed the study or who discontinue, and the reasons for discontinuation from the study will be summarized in tabular format for the safety population. All disposition data will be displayed for all patients in the safety population in a subject listing. An additional listing will be provided with information on patients who were screened but did not receive study treatment.

6 DEMOGRAPHIC CHARACTERISTICS

For quantitative variables (e.g., age, height, weight, and body mass index [BMI]), summary statistics (number [n], mean, standard deviation [SD], minimum, median, and maximum) will be presented for the safety population. For the qualitative variables (e.g., sex, race, and ethnicity), results will be summarized as counts and percentages for the safety population. Individual demographic information for the safety population will be displayed in subject listings.

7 MEDICAL HISTORY

The number and percent of patients with past and current medical disorders at Screening will be presented by SOC and preferred term. All findings will be displayed for the safety population in a subject listing.

8 DM1 DIAGNOSIS HISTORY

Variables collected in the DM1 Diagnosis History will be summarized as counts and percentages for the safety population. The only 2 exceptions will be the age of DM1 diagnosis, age of onset of symptoms and time since onset of excessive sleepiness or hypersomnia which will analyzed with summary statistics (number [n], mean, standard deviation [SD], minimum, median, and maximum). All history findings will be displayed for the safety population in a subject listing.

9 MDHI AND EPWORTH SLEEPINESS SCALE

Variables collected in the MDHI and Epworth Sleepiness Scale will be summarized as counts and percentages for the safety population. Both scales will be displayed for the safety population in subject listings.

10 PHYSICAL EXAM

A full physical exam is collected at Screening and brief physical exams are conducted once during Period 1, Period 2 and at the End of Study visit/Early Discontinuation. Any clinically significant findings are to be recorded on the Medical History Form or the Adverse Event forms. Abnormal findings which are not clinically significant are captured on the Physical Exam CRF. Therefore, there will be no summaries of physical exam findings or changes in physical exam findings. All Physical Exam data will be provided in patient listings.

11 PRIOR AND CONCOMITANT MEDICATIONS

The prior medications and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) Class and Preferred name using the World Health Organization Drug (WHODrug) Dictionary (Enhanced), March 2019 version.

Summaries will be done for concomitant medication and will present the number and percentage of patients who use each medication by cohort. Patients who report more than one medication within the same ATC class or within the same preferred name within the same category (e.g., concomitant medications) will be counted only once within each level. The summary table will include all medications from the time of the first dose of study drug until the End of Study visit.

Medications other than the study drug will be classified based on start date and end date relative to the date of the first dose of study drug. The categories of prior medications and concomitant medications are defined as the following:

- A ‘prior medication’ is any medication started and stopped prior to date of the first dose of study drug

- A 'concomitant medication' is any medication started on or after the date of first dose of study drug or any medication which started prior to the date of first dose of study drug and is ongoing at the time of dosing. In addition, only those medications which have started prior to the End of Study visit will be included.

The patient listing will include all medications.

12 SAFETY ANALYSES

12.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (using the MedDRA Version stated in Data Management Plan). An overall summary table will be presented by treatment group that summarizes all treatment-emergent adverse events (TEAEs), all serious TEAEs, all drug-related TEAEs, number of deaths, and all severe TEAEs for the safety population. In addition, frequency tables will be presented by treatment group for all TEAEs, for all drug related adverse events, and for all adverse events resulting in discontinuation from study, by system organ class and preferred term for the safety population. The frequency tables will be ordered by system organ class. Subject listings of all TEAEs, serious TEAEs, and drug related TEAE will also be provided.

In all displays, TEAEs will be displayed by MedDRA System Organ Class and Preferred Terms, with patients who have the same TEAE counted only once for that event and with patients who have more than one TEAE within a System Organ Class counted only once in that System Organ Class.

Pretreatment adverse events are defined as those events which occur between time of signing the informed consent and the first dose of study medication. Pretreatment AEs will be listed separately from the TEAEs.

Treatment-emergent AEs will include AEs which start between the date and time of study drug dosing and through Study Day 2, within each period.

All TEAEs will be listed by treatment sequence, subject, and timing of event. Treatment taken just prior to the event will be provided in the listing.

12.2 Laboratory Tests (Hematology, Serum Chemistry, and Urinalysis)

Hematology and serum chemistry laboratory tests are collected at Screening, one time at the end of each assessment period, and at the follow-up/early termination visit. Urinalysis is collected at Screening and at the follow-up/early termination visit.

For hematology and chemistry quantitative tests, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values at Screening, end of the experimental treatment period, and end of the placebo treatment period for the safety population by treatment group. Summary statistics will also be presented for the change from baseline to the end of the experimental treatment period, and to the end of the placebo treatment period. In these displays, baseline will be defined as the sample collected at Screening.

Hematology, chemistry and urinalysis results will be displayed in subject listings, with those values falling outside the laboratory reference range flagged. Laboratory reference ranges will be provided by the laboratory site(s) and will be included in an appendix of the clinical study report.

12.3 Vital Signs

Vital signs are collected at Screening and at the follow-up/early termination visit. They are also collected within each period at predose and at the completion of all assessments.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values for systolic and diastolic blood pressure, pulse and respiration rate at each time point by treatment group for the safety population. Summary statistics will also be presented for the change from baseline values to each post baseline time point. In these displays, baseline will be defined as the values that are obtained immediately predose to each treatment.

All vital signs results will be displayed in subject listings.

13 PHARMACOKINETIC ANALYSES

13.1 General Methods

All PK analyses will be performed using non-compartmental methods in Phoenix® WinNonlin® version 7.0 or higher (Certara Corporation, Mountain View, California, USA). Statistical analyses of PK parameters will be performed using SAS V 9.3 or higher.

Pharmacokinetic blood samples are collected at the end of 5-minute IV infusion and after conclusion of each set of outcome measure tests at approximately 30 minutes, 1 hour, 1 hour 30 minutes and at 2 hours after the start of IV infusion. Blood samples for Cohort 2 (if selected dose is 2 mg) will be at the end of 15-minute IV infusion and after conclusion of each set of outcome measure tests at approximately 40 minutes, 1 hour and 10 minutes, 1 hour 40 minutes, and at 2-hours and 10 minutes after the start of IV infusion.

Parameter Definitions

Cmax	observed maximum concentration
Tmax	time of observed maximum concentration
AUCt	area under the concentration–time curve from time zero to the last measurable concentration estimated by linear trapezoidal method
AUC∞	area under the concentration–time curve from time zero extrapolated to infinity, calculated as AUC∞ = AUCt + Ct/λz, where Ct is the last measurable drug concentration and λz is the elimination rate constant
$\%AUC_{extrap}$	area under the concentration–time curve extrapolated from the last measurable concentration to infinity as a percentage of AUC∞
λz	elimination rate constant estimated as the slope of log concentration vs time in the terminal phase of the concentration-time profile
t½	elimination half-life estimated as 0.693/ λz

The following methods will be utilized for analysis of PK data:

- The exact time of sample collection will be used for PK calculations and for individual subject graphs.
- The scheduled time of sample collection will be used in the summary statistics for concentration results and in mean graphs.
- Pre-dose sampling times will be set to a time value of zero.
- Concentration-dependent PK parameters will be reported in the same units as the assay results.
- Lambda z (λ_z) will be estimated if a given subject has >2 concentration values in the terminal portion of the curve and will be reported if r^2 (goodness of fit) >0.80.
- The values included in the regression analyses will be determined by WinNonlin and will be reviewed by the pharmacokineticist.
- No value for λ_z, AUC_{inf}, $\%AUC_{extrap}$, or $t_{½}$ will be reported for cases where a valid estimate of λ_z is not obtained.
- When $AUC_{inf, and}$ $\%AUC_{extrap}$ exceeds 20%, values will be flagged in the patient listing.
- All plasma concentrations below the limit of quantitation (BLQ) for the assay prior to the first quantifiable concentration following each dose will be treated as "0" in the PK analyses (and for summary statistics). All BLQ plasma concentrations after the first quantifiable concentration following each dose will be treated as "missing" in the PK analyses, however, for summary statistics, BLQ plasma concentrations will be set to zero.

The following methods will apply for graphical presentation and calculation of summary statistics for individual concentrations and/or PK parameters:

- For concentrations, individual subject data for the time point must be collected within ±10% of the scheduled protocol time (within 1 minute for the first time point). If more than half of the individual subject's collection time varies from this guideline, appropriate model predicted values may be used for the calculation of summary statistics for individual concentrations.
- For concentrations, at least half of the individual subject data for the time point must have quantifiable measurements. If fewer than half of the subjects have quantifiable measurements at a given time point, the summary statistics will be reported as not calculated.
- For a given PK parameter, at least half of subjects must have estimable values; otherwise descriptive statistics for the given parameter will be reported as not calculated.

13.2 Summary Statistics

Summary statistics (n, arithmetic mean, SD, percent coefficient of variation [%CV], minimum, median, and maximum) will be presented for ERX-963 concentrations through the end of the study for the PK population. In addition, summary statistics (n, arithmetic mean, SD, %CV, minimum, median, maximum, geometric mean [converting back to the original units], and %CV

for the geometric mean) will be presented for the PK parameters by ERX-963 dose. All PK data will be displayed in subject listings.

13.3 Figures

The following figures will be provided for the concentration data:

- Individual plasma concentration time figures (linear and semi-log)
- Mean plasma concentration time figures (linear and semi-log)
- Additional figures may be presented (e.g. bar chart for PK parameter AUC_{inf} by dose level)

14 EFFICACY ANALYSES

Efficacy Level	Endpoint
Primary	Not Applicable
Secondary	SSS, PGI-I, PVT, One-back test, CGI-I
Exploratory	EEG, Correlations of ERX-963 plasma concentrations to clinical efficacy endpoints (PVT, SSS, One-back test)

A priori, PGI-I and SSS are the efficacy variables expected to have the greatest sensitivity to treatment with [redacted].

14.1 Psychomotor Vigilance Task (PVT), Stanford Sleepiness Scale (SSS), One-back Task

The PVT, SSS and One-back Task assessments are collected at Screening, and within Periods 1 and 2 for Cohorts 1 and 2, at predose, 15 minutes, 45 minutes, 1 hour 15 minutes and 1-hour 45minutes after the start of study intervention. However, for Cohort 2, if the selected dose is 2 mg, the PVT, SSS and One-back Task assessments will be measured at 25 minutes, 55 minutes, 1 hour 25 minutes and 1 hour 55 minutes after the start of study intervention. Since the duration of administration of a 2 mg dose is ten minutes longer than the duration of administration for lower dose levels, the time points of these tests in the two cohorts are the same when measured from the end of administration – 10 minutes, 40 minutes, 1 hour 10 minutes and 1 hour 40 minutes.

Descriptive statistics will be computed for PVT, SSS, and One-back Task (n, mean, SD, minimum, median, and maximum) by treatment group.

For each PVT, SSS, and One-back Task efficacy variable, data will be reported for the predose baseline and each time point of the study period. Change from baseline will be summarized for each time point of the study period by treatment. In addition, the median response over time will be found for each subject and then an average will be computed by treatment.

Treatment effects will be declared to be statistically significant at the alpha level of 0.05 and sequence effects will be declared to be statistically significant at the alpha level of 0.10.

Nominal measurement time points will be used for all analyses.

For PVT and SSS, plots of change from baseline at each measurement timepoint for each treatment will also be provided along with plots of individual patient data.

14.2 Psychomotor Vigilance Task (PVT)

For PVT, three variables will be analyzed: the number of attentional lapses, the reciprocal of the longest 10% response time of each trial, and the median reaction time.

Cohort 1 and Cohort 2 data will be combined. Treatments will be analyzed such that there are 4 treatment groups: Placebo in Cohort 1, 1 mg ERX-963, Placebo in Cohort 2, and Selected ERX-963.

A mixed effects model will be used to compare efficacy effects following ERX-963 versus placebo. The change from baseline for each of the three PVT variables will be used in the model as the dependent variable. The model will include cohort, sequence, cohort-by-sequence interaction, treatment, treatment period, predose baseline, measurement time point, measurement time-by-baseline interaction, and measurement time-by-treatment interaction as fixed effects, with subject (within cohort and sequence) as random effect. The test statistic will be based on the treatment effects (experimental versus placebo, averaged across the post-dose measurements), using the equally weighted mean of the Cohort 1 and Cohort 2 treatment effects.

The SAS code will be as follows:

```
Proc mixed data = xxxx;
Class patnum cohort sequence period treatment timept;
Model cfb_effvariable = cohort sequence cohort*sequence treatment period
       baseline timept timept*baseline timept*treatment;
Random patnum(cohort sequence)/ subject = patnum(cohort sequence);
Estimate 'ERXvPBO' treatment 0.5 -0.5 0.5 -0.5;
Estimate 'ERXvPBOC1' treatment 1 -1 0 0;
Estimate 'ERXvPBOC2' treatment 0 0 1 -1;
Run;
```

14.3 Stanford Sleepiness Scale (SSS)

For SSS, the analysis variable will be the numerical rating of sleepiness. The change from baseline will be used in the model as the dependent variable.

Cohort 1 and Cohort 2 data will be combined. Treatments will be analyzed such that there are 4 treatment groups: Placebo in Cohort 1, 1 mg ERX-963, Placebo in Cohort 2, and Selected ERX-963.

A mixed effects model will be used to compare efficacy effects following ERX-963 versus placebo. The change from baseline will be used in the model as the dependent variable. The model will include cohort, sequence, cohort-by-sequence interaction, treatment, treatment period, predose baseline, measurement time point, measurement time-by-baseline interaction, and measurement time-by-treatment interaction as fixed effects, with subject (within cohort and sequence) as random effect. The test statistic will be based on the treatment effects

(experimental versus placebo, averaged across the post-dose measurements), using the equally weighted mean of the Cohort 1 and Cohort 2 treatment effects.

The SAS code will be as follows:

```
Proc mixed data = xxxx;
Class patnum cohort sequence period treatment timept;
Model cfb_effvariable = cohort sequence cohort*sequence treatment period
      baseline timept timept*baseline timept*treatment;
Random patnum(cohort sequence)/ subject = patnum(cohort sequence);
Estimate 'ERXvPBO' treatment 0.5 -0.5 0.5 -0.5;
Estimate 'ERXvPBOC1' treatment 1 -1 0 0;
Estimate 'ERXvPBOC2' treatment 0 0 1 -1;
Run;
```

14.4 One-back Task

For the One-back Task, the analysis variable will be the change from baseline for the proportion of correct responses. The analyses will be done on the arcsine transformation of the square root and the tables will contain the results transformed back to the original scale.

Cohort 1 and Cohort 2 data will not be combined as the difficulty level of the test is different in the two cohorts. There will be two treatment groups in each cohort: ERX-963 and Placebo.

For Cohort 1, only summary statistics (n, mean, SD, minimum, median, and maximum) for the observed data and change from baseline data will be presented.

For Cohort 2, a mixed effects model will be used to compare efficacy effects following ERX-963 versus placebo. The model will include sequence, treatment, treatment period, predose baseline, measurement time point, measurement time-by-baseline interaction, and measurement time-by-treatment interaction as fixed effects, with subject (within sequence) as random effect. The test statistic will be based on the treatment effects (experimental versus placebo, averaged across the post-dose measurements). The comparison in Cohort 2 will be considered the primary comparison for this variable.

The SAS code will be as follows:

```
Proc mixed data = xxxx;
Class patnum sequence period treatment timept;
Model cfb_effvariable = sequence treatment period baseline timept
      timept*baseline timept*treatment;
Random patnum(sequence)/ subject = patnum(sequence);
Estimate 'ERXvPBO' treatment 1 -1;
Run;
```

14.5 Clinical Global Impression – Improvement (CGI-I) and Patient Global Impression – Improvement Scale (PGI-I)

The CGI-I and PGI-I assessments are collected after the last outcome measure test in each study period.

Descriptive statistics will be computed for CGI-I and PGI-I (n, mean, SD, minimum, median, and maximum) by treatment.

Summary bar charts giving each treatment's distribution of responses will be provided for the GCI-I and PGI-I.

The difference between the experimental and placebo responses will be estimated using a model with terms for cohort, sequence, cohort-by-sequence interaction, treatment, and treatment period as fixed effects, and subject within cohort and sequence as a random effect. The dependent variable in the model will be the assessment. The test statistics will be based on the average of the treatment effects in Cohort 1 and Cohort 2.

The SAS code will be as follows:

```
Proc mixed data = xxxx;
Class patnum cohort sequence period treatment;
Model effvariable = cohort sequence cohort*sequence treatment period;
Random patnum(cohort sequence)/ subject = patnum(cohort sequence);
Estimate 'ERXvPBO' treatment 0.5 -0.5 0.5 -0.5;
Estimate 'ERXvPBOC1' treatment 1 -1 0 0;
Estimate 'ERXvPBOC2' treatment 0 0 1 -1;
Run;
```

15 EXPLORATORY ANALYSES

15.1 Electroencephalogram (EEG)

Brain activity will be continuously monitored by EEG during the predose and post-dose outcome measures testing in each period. The EEG parameters of interest are theta/alpha and theta/beta spectral ratios and theta, alpha and beta percentage power.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values for the EEG parameters at each time point by treatment group for the safety population. Summary statistics will also be presented for the change from baseline values to the post baseline time point. In these displays, baseline will be defined as the values that are obtained immediately predose to each treatment.

All EEG results will be displayed in subject listings.

15.2 Plasma [redacted] PK model

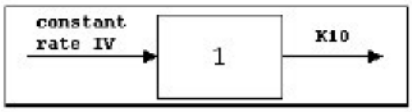
A one or a two-compartment IV infusion model as shown in Figure 1 and Figure 2 will be used to describe the [redacted] concentration-time profile for each subject. The model will be implemented in Phoenix® WinNonlin® version 7.0 or higher (Certara Corporation, Mountain View, California, USA). The individual subject model parameters will be used to estimate the concentrations at the time of the pharmacodynamic assessment (Cp (t_{ij})) to facilitate the correlation of plasma [redacted] with the clinical efficacy endpoints (see Section 15.3).

Figure 1: One-compartment model with constant IV input and first-order output.

The model parameters include:

V - volume of distribution;

K10 - elimination rate constant.



$$C(T) = \left(\frac{D}{TI}\right)\frac{1}{VK10}[\exp(-K10\,TSTAR) - \exp(-K10\,T)]$$

where:

TI = infusion length

$TSTAR = T - TI$ for $T > TI$

$TSTAR = 0$ for $T \le TI$

Figure 2: Two-compartment model with constant IV input and first-order output.

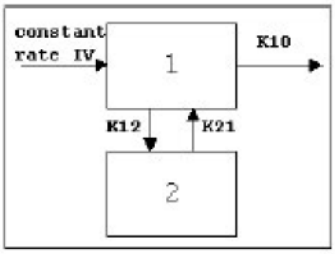
The model parameters include

V1 - volume of central compartment;

Alpha – distribution rate constant;

Beta - elimination rate constant;

K21 – intercompartmental distribution rate constant.



$$C(T) = \frac{A}{TI \cdot ALPHA}[\exp(-ALPHA \cdot TSTAR) - \exp(-ALPHA \cdot T)] + \frac{B}{TI \cdot BETA}[\exp(-BETA \cdot TSTAR) - \exp(-BETA \cdot T)]$$

where:

TI = infusion length

$TSTAR = T - TI$ for $T > TI$

$TSTAT = 0$ for $T \le TI$

$$A = \frac{D}{V1}\frac{(ALPHA - K21)}{(ALPHA - BETA)}$$

$$B = -\frac{D}{V1}\frac{(BETA - K21)}{(ALPHA - BETA)}$$

15.3 Correlations of ERX-963 Plasma Concentrations to Clinical Efficacy Endpoints

Correlations between [redacted] concentrations and responses on efficacy measures (PVT, SSS, and One-back Task) will be explored with a Frequentist 3-parameter Emax model.

The Emax model is defined as $E_{0i} + [(E_{maxi} * C_p(t_{ij}))/(Cp(t_{ij}) + EC_{50i}))] + e_{ij}$

where $C_p(t_{ij})$ is the predicted concentration.

The dependent variable will be the change from pre-dose measurement to the post-dose measurement. The plasma concentrations will be explanatory/independent variables in the

statistical model. Concentrations for the placebo periods will be set to zero. At the patient level, cohort, sequence, cohort * sequence interaction, and subject within cohort and sequence will be included. Within the patient level, baseline, period, and measurement time point (as a categorical variable) will be included. Both the model and the within patient error term will assume a normal distribution.

If problems are encountered fitting a three parameter Emax model, or if the Emax shape is a poor fit for the data, additional models may be tried.

```
proc nlmixed data=_____;
 parms E0=__   Emax=__   EC50=__
          s2b1=__   s2b2=__   s2b3=__   s2=__
          cb12=__   cb13=__   cb23=__
          c2=__   seq2=__   cseq22=__
          bl = __   per=__   t2=__   t3=__   t4=__;
 ** construct part of response not related to concentrations;
 fixed = c2 * Cohort2 + seq2 * Sequence2 + cseq22 * CohortSeq22 + bl * baseline +
        per * period
          + t2 * time2 + t3 * time3 + t4 * time4;
 ** construct individual patient Emax model parameters;
 E0i = E0 + b1;
 Emaxi = Emax + b2;
 EC50i = EC50 + b3;
 ** construct individual patient expected pharmacodynamic variables;
 If conc eq 0 then pd_mean = fixed + E0i;
 else pd_mean = fixed + E0i + Emaxi*conc / (conc + EC50i);
 model response ~ normal (pd_mean, s2);
 random b1 b2 b3 ~ normal ([0, 0, 0], [ s2b1,
                                        cb12, s2b2,
                                        cb13, cb23, s2b3]) subject=subject;
run;
```

For the one-back test, only data from Cohort 2 will be included in the analysis. Therefore, all terms related to cohort will be excluded from the modeling of one-back data.

16 SUBJECT LISTINGS

Data that are collected and entered into the study database but that are not displayed in the summary tables specified in the preceding sections will be presented in subject listings. These will include (but will not be limited to) data from the following modules:

Serum Pregnancy Test

Protocol Deviations

Inclusion and Exclusion Criteria

Pulmonary Function Test with Spirometry

Actigraph

Polysomnograph

12 Lead ECGs

17 INTERIM ANALYSES

A blinded interim analysis of safety will be performed after all participants from the first cohort have completed the study.

A sponsor-unblinded interim analysis of efficacy parameters will be performed for administrative purposes after all patients from the first cohort have completed the study and may include participants from the second cohort who have completed the crossover portion of the study by the time of the interim analysis. An additional sponsor-unblinded analysis of selected parameters may be performed with additional participant data if necessary, for administrative purposes. Details of the analyses will be provided in an interim analysis plan. Results of the interim efficacy analyses will not be shared with the clinical sites prior to the completion of the study.

18 FINAL SIGN-OFF FOR ERX-963-001 STATISTICAL ANALYSIS PLAN

[redacted] December 6, 2019
Date

Clinical Biostatistician
Innovative Analytics, Inc.
Kalamazoo, Michigan, 49007

[redacted] December 6, 2019
Date

Chief Medical Officer
Expansion Therapeutics, Inc.
San Diego, CA 92121

[redacted] December 6, 2019
Date

Director of Clinical Development and Project Management
Expansion Therapeutics, Inc.
San Diego, CA 92121

[redacted] December 6, 2019
Date

Biostatistician
Expansion Therapeutics, Inc.
San Diego, CA 92121

[redacted]

Dec 8, 2019.

Date

Clinical Pharmacologist
Expansion Therapeutics, Inc.
Bangalore, India

19 REVISIONS TO STATISTICAL ANALYSIS PLAN

Date	Revision	Statistician's Signature
•	•	•
•	•	•
•	•	•
•	•	•
•	•	•
•	•	•