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**
Short Title:	Safety, Tolerability and Pharmacokinetics of ERX-963 in Adults with Myotonic Dystrophy Type 1
Protocol Number:	ERX-963-001
Version:	Amendment 2
Compound Number:	ERX-963
Study Phase:	Phase 1b
Sponsor Name:	Expansion Therapeutics, Inc.
Legal Registered Address:	10996 Torreyana Road, Suite 280, San Diego CA 92121
Approval Date:	October 31, 2019

SPONSOR SIGNATORY

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31 OCT 19

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Date

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Investigator Agreement Page is provided as a stand-alone document. The investigator should retain the original in the site study files and return a copy to the sponsor for archiving.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
ERX-963-001 Amendment 2	October 31, 2019
ERX-963-001 Amendment 1	March 7, 2019
ERX-963-001 Original (v1.1)	December 19, 2018
ERX-963-001 Original (v1)	November 15, 2018

Amendment 2 (31-October-2019)

Summary of Amendment 2 Changes:

This amendment modifies two exclusion criteria and one inclusion criterion. The endpoint of EEG is removed from the list of secondary endpoints. Additionally, the total number of completed participants is provided as an estimate rather than a maximum number, the interim analysis plan is clarified, the washouts between Periods 1-2 and Period 2-EOS visit are extended, and additional specifics around data collection for screen failures are provided.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria #1	Significant respiratory compromise as indicated by pulmonary function tests routinely conducted in the clinic including FVC <70% predicted. **Changed to** Significant respiratory compromise as indicated by **clinical assessment (e.g. dyspnea) and by** pulmonary function tests routinely conducted in the clinic.	Pulmonary function tests in the DM1 population may show a pseudo-restrictive pattern due to muscle weakness with parallel decrease in FEV-1 and FVC. The decline in respiratory function is typically gradual and patients may be able to compensate without significant respiratory distress. The change in the exclusion criteria removes the specific numerical FVC % predicted threshold and enables the investigator to make an overall assessment of respiratory function including both clinical and pulmonary function test assessments.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria #3	Diagnosis of symptomatic Restless Leg Syndrome or significant nocturnal hypoxias by nocturnal polysomnography performed within the last three years. Patients with obstructive or central sleep apnea who do not demonstrate compliance with non-invasive ventilation (NIV) strategy. Compliance will be determined by review of NIV device records from within the past 6 months and is defined as use of NIV for approximately 4 hours/night for 15 days out of a 1 month period. (Note: Patients with mild sleep apnea are eligible). **Changed to** 3a. Diagnosis of symptomatic Restless Leg Syndrome **OR** 3b. Diagnosis of significant nocturnal hypoxias **(moderate or severe obstructive or central sleep apnea)** by nocturnal polysomnography performed within the last three years. Note: Patients with mild sleep apnea are eligible. **Patients with a history of moderate to severe sleep apnea who are treated by and comply with non-invasive ventilation (NIV) are eligible to participate in the study and do not require repeat PSG prior to study entry. Patients with a history of moderate to severe sleep apnea who are not compliant with NIV treatment are not eligible.** Compliance will be determined by review of NIV device records within the past 6 months and is defined as use of NIV for approximately ≥ 4 hours/night for 15 days out of a 1 month period.	1. Clarify that Restless Leg Syndrome diagnosis does not require a polysomnography. 2. The intent of the exclusion criteria requiring a polysomnography within three years is to exclude patients who have sleep apnea treatable with non-invasive ventilation. This change clarifies that if a patient is compliant with non-invasive ventilation, then the patient is eligible to participate in the study without a prior polysomnography
3 Objectives and Endpoints	**Removed** brain activity as a secondary objective and EEG as a secondary endpoint **Added text** under Exploratory Objective **To assess the effect of intravenously-administered ERX-963 vs. placebo on brain activity in patients with DM1**	The original intent was for EEG to be an exploratory objective; therefore the protocol has been corrected.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria #1	Participant must be at least 18 to 60 years of age, at the time of signing the informed consent. **Changed to** Participant must be at least 18 to **65** years of age, at the time of signing the informed consent.	To allow inclusion of participants between age 60 and 65, as there is no rationale to support their exclusion.
9.5 Interim Analysis	An interim analysis of efficacy parameters will be performed for administrative purposes after all patients from the first cohort have completed the study. **Changed to** 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.**	Clarify that the interim analysis of efficacy requires unblinding of the sponsor. Clarify that the efficacy interim analysis may not be limited to results from the first cohort. Added the option for an additional administrative analysis if necessary.
1.1 Synopsis	A total of up to 14 participants completing **Changed to** An **estimated** total of 14 participants completing	Removed the limit on the total number of completing participants, due to potential overlapping enrollment in a multi-center study
1.2 Schema	Approximately 4 to 8 days washout **Changed to** Approximately 4 to **18** days washout	Extension of the washout between periods 1-2 and the time between Period 2 and the End of Study visit will provide more flexibility for the participant. Extending by ten days should not impact the reliability of the study procedures.
4.1 Overall Design	Approximately 4 to 8 days washout **Changed to** Approximately 4 to **18** days washout	
8 Study Assessments	Approximately 4 to 8 days after Period 1 **Changed to** Approximately 4 to **18** days after Period 1	

Section # and Name	Description of Change	Brief Rationale
8 Study Assessments	Approximately 4 to 8 days after Period 2 **Changed to** Approximately 4 to **18** days after Period 2	
5.4 Screen Failures	**Added text** **If additional study procedures were performed during screening, information from these procedures should be recorded in the CRF.**	To provide additional guidance for data entry expectations
1.2 Schema	Polysomnography within 3 years **Added text** **If required** Washout 4-8 days **Changed to** Washout 4-**18** days	For alignment with revised Exclusion Criterion 5.3 and extended washout period
1.2 Schema	4-8 days after Period 2 **Changed to** 4-**18** days after Period 2	For alignment with extended time between Period 2 and End of Study visit
1.3 Schedule of Activities (SoA)	Pulmonary function test of FVC with spirometry **Changed to** Pulmonary function test with spirometry	For alignment with revised Exclusion Criterion 5.2
8 Study Assessments and Procedures, Screening Visit 1	Pulmonary function test (Spirometry to obtain FVC value) **Changed to** Pulmonary function test (**including** Spirometry)	For alignment with revised Exclusion Criterion 5.2
1.3 Schedule of Activities (SoA), footnote e	**Added text** **If the participant has not had the test performed within 3 years and is treated by and compliant with NIV, then this test is not required for eligibility.**	For alignment with revised Exclusion Criterion 5.3
8 Study Assessments and Procedures, Screening Visit 1	Nocturnal Polysomnography (schedule a visit day for participants who have not taken the test within the last 3 years) **Added text** **or who are not being treated by NIV**	For alignment with revised Exclusion Criterion 5.3

Section # and Name	Description of Change	Brief Rationale
9.4 Statistical Analyses	The statistical analysis plan will be developed and finalized before database lock for the first cohort **Deleted text** **for the first cohort**	The database will not be locked for the first cohort, therefore the text was removed.
9.4 Statistical Analyses	**Moved text from section 9.4.1 to 9.4.3:** For the EEG, the analysis variables are the theta/alpha and theta/beta spectral ratios, along with the theta, alpha, and beta percentages. Additional exploratory parameters may be included in the analysis.	For alignment with the deletion of EEG from Secondary Endpoints
9.4.1 Efficacy Assessments	A mixed effect model will be used to compare efficacy effects (PVT, SSS, One-back, and EEG test **Deleted text** and EEG test	For alignment with the deletion of EEG from Secondary Endpoints

TABLE OF CONTENTS

ABBREVIATIONS

TERMS	DEFINITIONS
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CGI-I	Clinical Global Impression – Improvement scale
CFR	Code of federal regulations
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DM1	Myotonic dystrophy type 1
ECG	Electrocardiogram
EEG	Electroencephalograph
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FVC	Force vital capacity
$GABA_A$	Endogenous type A gamma-amino-butyric-acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

TERMS	DEFINITIONS
IH	Idiopathic hypersomnia
IRB	Institutional Review Board
IUD	Intrauterine device
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDHI	Myotonic dystrophy health index
NIV	Non-invasive ventilation
PGI-I	Patient Global Impression – Improvement scale
PK	Pharmacokinetic
PR	PR interval
PVT	Psychomotor Vigilance Task
QRS	QRS interval
QT	QT interval
RBC	Red blood cell count
RT	Response time
SAE	Serious adverse event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of Assessments
SOC	System organ classification
SSS	Stanford Sleepiness Scale
TSH	Thyroid stimulating hormone
WBC	White blood cell count
WOBCP	Woman of child bearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: Safety, Tolerability and Pharmacokinetics of ERX-963 in Adults with Myotonic Dystrophy Type 1

Rationale:

Myotonic dystrophy type 1 (DM1) is a multisystem disorder that includes central nervous system (CNS) involvement (Thornton-2014). The symptoms of CNS involvement include excessive daytime sleepiness (EDS) and cognitive dysfunction; these symptoms are recognized to have significant impact on quality of life (Heatwole-2012, Laberge-2013).

Dysregulation of the endogenous type A gamma-amino-butyric-acid ($GABA_A$) neurotransmitter system is hypothesized to be a primary cause of EDS and cognitive dysfunction in patients with DM1. There are two potential factors that underlie $GABA_A$ dysregulation in DM1.

Firstly, patients with DM1 have an increased prevalence of the short form of the γ2 subunit of the $GABA_A$ receptor which may alter the sensitivity and activity of the receptor (Goodwin-2015). In the normal adult brain, the long isoform of the γ2 subunit predominates whereas in DM1, the fetal, or short, isoform predominates. The increase in the prevalence of the short isoform of the $GABA_A$ receptor γ2 subunit is a consequence of a broader mRNA splicing defect which is a well-characterized feature of DM1. The short isoform has been shown to have higher affinity to GABA compared to the long isoform (A. Jenkins, Personal communication). Mice expressing only the short isoform exhibit increased sensitivity to benzodiazepines (Quinlan-2000). Secondly, DM1 may be associated with the presence of a somnogen (an endogenous substance with GABAergic like effects) in the cerebrospinal fluid (CSF) which has been observed in patients with idiopathic hypersomnia (IH) (Rye-2012). For an individual patient with DM1, either or both of these factors could contribute to the clinical presentation of EDS and cognitive dysfunction.

Because of the role of $GABA_A$ receptor dysfunction in DM1, it is hypothesized that [redacted] may reverse the sedative effect of the somnogen or normalize the activity of the $GABA_A$ γ2 short isoform. [redacted] is a selective benzodiazepine antagonist, administered intravenously, that is approved by the FDA and widely used to treat benzodiazepine overdose and reverse benzodiazepine effects in the context of conscious sedation or surgical anesthesia. Rye et al. (Rye-2012) and Trotti et al. (Trotti-2016) have reported that treatment with [redacted] can yield significant improvements in sleepiness and related symptoms in selected patients with IH. One of the IH patients who showed benefit with intravenous (IV) [redacted] (Rye-2012) was later diagnosed with DM1 (D. Rye, Personal communication).

The safety and efficacy of ERX-963 (IV [redacted] to treat EDS/hypersomnia have not been formally evaluated in patients with DM1 in a placebo-controlled fashion. The purpose of this study therefore is primarily to investigate the safety and tolerability of ERX-963, and secondarily to evaluate its potential to reduce EDS/hypersomnia and improve cognitive function in patients diagnosed with DM1.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
• To assess the safety and tolerability of a single dose of ERX-963 vs. placebo in patients with DM1	• The proportion of participants with adverse events, serious adverse events (SAEs), and drug related adverse events
Secondary	
• To assess the effect of intravenously-administered ERX-963 vs. placebo on sleepiness, vigilance, and working memory in patients with DM1	Repeated measurements of the following: • Stanford Sleepiness Scale (SSS) score • Psychomotor Vigilance Task (PVT) – No. of lapses and 1/Longest 10% Response time (1/RT) and median reaction time • One-back task – proportion of correct response • Clinical Global Impression – Improvement scale (CGI-I) • Patient Global Impression – Improvement scale (PGI-I)
Exploratory	
• To correlate ERX-963 plasma concentrations to clinical efficacy endpoints in patients with DM1 • To assess the effect of intravenously-administered ERX-963 vs. placebo on brain activity in patients with DM1	Repeated measurements of the following: • Plasma ERX-963 concentration • Stanford Sleepiness Scale (SSS) score • Psychomotor Vigilance Task (PVT) – No. of lapses and 1/Longest 10% Response time (1/RT) and median reaction time • One-back task – proportion of correct response • EEG – theta/alpha and theta/beta spectral ratios, and theta, alpha, and beta percentages

Overall Design:

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

Participants who have consented and meet eligibility criteria will receive two treatments, IV Placebo (Treatment A) and ERX-963 (Treatment B or C) in a randomized 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, 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 IV 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, 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).

This study is evaluating single administration of two doses levels (1 mg and 0.5 or 2 mg) of ERX-963 to explore the relationship between dose, exposure and safety, tolerability and clinical benefit. Both dose levels to be evaluated in this study are within the FDA approved dose range of IV [redacted] and have been used with favorable safety and tolerability for over 25 years in clinical practice in the treatment of patients following benzodiazepine anesthesia and benzodiazepine overdose.

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 (Section 6.6).

Disclosure Statement: This is a crossover treatment study with two cohorts that are blinded to the participant and investigator. Blinding of placebo and investigational drug is during randomization, drug administration, and assessment periods for each cohort.

Number of Participants:

Approximately 20 potential participants will be screened to dose at least 6 participants in each cohort (for an estimated total of 14 participants completing the study). Participants who do not complete the crossover portion of the study will be discontinued and replaced with a new participant.

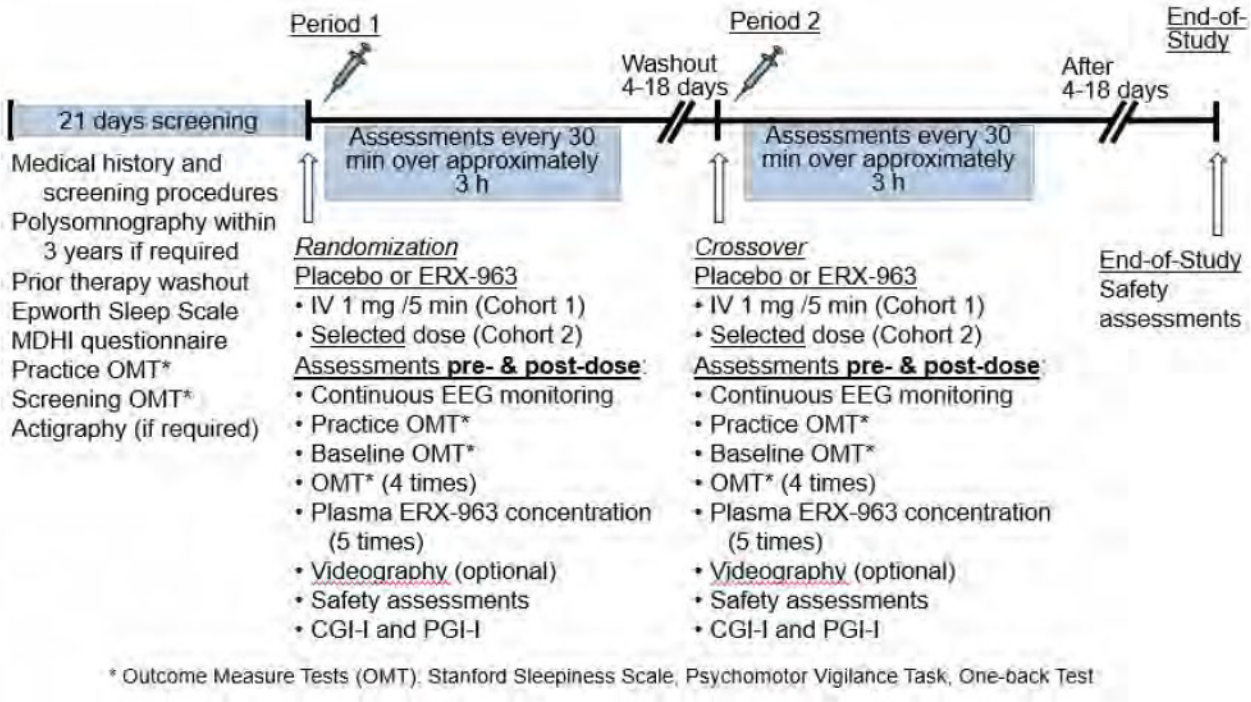
Intervention Groups and Duration:

The total duration of the study for an individual participant is approximately 57 days.
The screening period is ≤ 21 days; the intervention and assessment in the two dosing periods will be conducted over 1 day with approximately 4 to 18 days washout period between the two periods. The follow up period is approximately 4 to 18 days.

The study will be conducted in two cohorts. Participants will receive two treatments in each cohort: IV Placebo (Treatment A) and ERX-963 (Treatment B or C) in a randomized crossover fashion.

Data Monitoring Committee: No

1.2. Schema


Period 1
Period 2
End-of-Study
Washout 4-18 days
After 4-18 days
21 days screening
Assessments every 30 min over approximately 3 h
Assessments every 30 min over approximately 3 h
Medical history and screening procedures
Polysomnography within 3 years if required
Prior therapy washout
Epworth Sleep Scale
MDHI questionnaire
Practice OMT*
Screening OMT*
Actigraphy (if required)
Randomization
Placebo or ERX-963
• IV 1 mg /5 min (Cohort 1)
• Selected dose (Cohort 2)
Assessments pre- & post-dose:
• Continuous EEG monitoring
• Practice OMT*
• Baseline OMT*
• OMT* (4 times)
• Plasma ERX-963 concentration (5 times)
• Videography (optional)
• Safety assessments
• CGI-I and PGI-I
Crossover
Placebo or ERX-963
• IV 1 mg /5 min (Cohort 1)
• Selected dose (Cohort 2)
Assessments pre- & post-dose:
• Continuous EEG monitoring
• Practice OMT*
• Baseline OMT*
• OMT* (4 times)
• Plasma ERX-963 concentration (5 times)
• Videography (optional)
• Safety assessments
• CGI-I and PGI-I
End-of-Study
Safety assessments
* Outcome Measure Tests (OMT): Stanford Sleepiness Scale, Psychomotor Vigilance Task, One-back Test

1.3. Schedule of Activities (SoA)

Procedure	Screening Visit (up to 21 days before Period 1)	Intervention Period			End of Study (4-18 days after Period 2) or Early Discontinuation
		Period 1	Washout Period: 4-18 days	Period 2	
Informed consent	X				
Inclusion and exclusion criteria	X				
Medical history (including myotonic dystrophy diagnosis history)	X				
Medication history[a]	X				
Full physical examination and Demography including height and weight	X				
Brief physical exam		X[b]		X[b]	X
Vital signs (BP, Respiration Rate and Pulse Rate)	X	X[c]		X[c]	X
Laboratory assessments (hematology, clinical chemistries)[l]	X	X[b]		X[b]	X
Hepatitis C antibody test	X				
Plasma biomarker exploration (subjects who consented to provide the sample only)	X				
Serum pregnancy test (WOCBP only)	X				X
Urinalysis	X				X
12-lead ECG	X				
Pulmonary function test with spirometry	X				
MDHI, Epworth sleepiness scale (ESS)	X				
Actigraph[d]	X				
Polysomnograph[e]	X				
Outcome Measure Tests (Stanford sleepiness scale [SSS], Psychomotor vigilance task [PVT] and One-back test)	X[f]	X[g]		X[g]	
Randomization		X			
Video (subjects who consented only)		X[h]		X[h]	
EEG		X[h]		X[h]	
Study intervention (IV Infusion)[k]		X		X	
PK sampling		X[i]		X[i]	
CGI-I and PGI-I		X[j]		X[j]	

Procedure	Screening Visit (up to 21 days before Period 1)	Intervention Period			End of Study (4-18 days after Period 2) or Early Discontinuation
		Period 1	Washout Period: 4-18 days	Period 2	
AE review	X	X	←==========	==========	==========→
Concomitant medication review		X	←==========	==========	==========→

[a] Prescription and non-prescription (over the counter, OTC) medications, herbal medications, vitamins, minerals and medications over the past 30 days. Lifetime history of medication taken for DM1 or sleep.

[b] After completion of all assessments (after PGI-I is completed).

[c] Pre-dose vital signs within 60 minutes prior to start of study intervention; post-dose vital signs after completion of all assessments (after PGI-I is completed).

[d] To qualify participants per inclusion criteria #3.

[e] To be performed during screening period if participant has not had this test performed within 3 years. If the participant has not had the test performed within 3 years and is treated by and compliant with NIV, then this test is not required for eligibility.

[f] Practice outcome measure tests and screening visit outcome measure tests with 20 minute rest in between.

[g] Practice outcome measure tests and pre-dose baseline outcome measure tests with 20 minute rest in between prior to start of study intervention; Cohort 1 (1mg) and Cohort 2 (if selected dose is 0.5 or 1 mg): post-dose outcome measure tests at 15 minutes, 45 minutes, 1 hour 15 minutes and 1 hour 45 minutes after the start of study intervention. Cohort 2 (if selected dose is 2 mg): post-dose outcome measure tests at 25 minutes, 55 minutes, 1 hour 25 minutes and 1 hour 55 minutes after the start of study intervention.

[h] Start video and EEG recording prior to practice outcome measures test until all the post-dose tests (last blood sample) has been completed.

[i] Blood samples for Cohort 1 (1 mg) and Cohort 2 (if selected dose is 0.5 or 1 mg): 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): 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

[j] After the video and EEG recordings are completed.

[k] Cohort 1: ERX-963 1 mg or placebo will be administered intravenously over 5 minutes; Cohort 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).

[l] Fasting not required.

2. INTRODUCTION

ERX-963 is an intravenous (IV) preparation of [redacted] a benzodiazepine receptor antagonist. IV [redacted] (ERX-963) is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anaesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose ([redacted] USPI-2018). The goals of this study are as follows: 1) Evaluate the safety and tolerability of ERX-963 and 2) Determine the effect of ERX-963 on excessive daytime sleepiness (EDS)/ hypersomnia and other cognitive features in patients with myotonic dystrophy type 1 (DM1) disorder.

2.1. Study Rationale

DM1 is a multisystem disorder that includes central nervous system (CNS) involvement (Thornton-2014). The symptoms of CNS involvement include EDS and cognitive dysfunction; these symptoms are recognized to have significant impact on quality of life (Heatwole-2012, Laberge-2013).

Dysregulation of the endogenous type A gamma-amino-butyric-acid ($GABA_A$) neurotransmitter system is hypothesized to be a primary cause of EDS and cognitive dysfunction in patients with DM1. There are two potential factors that underlie $GABA_A$ dysregulation in DM1.

Firstly, patients with DM1 have an increased prevalence of the short form of the γ2 subunit of the $GABA_A$ receptor which may alter the sensitivity and activity of the receptor (Goodwin-2015). In the normal adult brain, the long isoform of the γ2 subunit predominates whereas in DM1, the fetal, or short, isoform predominates. The increase in the prevalence of the short isoform of the $GABA_A$ receptor γ2 subunit is a consequence of a broader mRNA splicing defect which is a well-characterized feature of DM1. The short isoform has been shown to have higher affinity to GABA compared to the long isoform (A. Jenkins, Personal communication). Mice expressing only the short isoform exhibit increased sensitivity to benzodiazepines (Quinlan-2000). Secondly, DM1 may be associated with the presence of a somnogen (an endogenous substance with GABAergic like effects) in the cerebrospinal fluid (CSF) which has been observed in patients with idiopathic hypersomnia (IH) (Rye-2012). For an individual patient with DM1, either or both of these factors could contribute to the clinical presentation of EDS and cognitive dysfunction.

Because of the role of $GABA_A$ receptor dysfunction in DM1, it is hypothesized that [redacted] may reverse the sedative effect of the somnogen or normalize the activity of the $GABA_A$ γ2 short isoform. [redacted] is a selective benzodiazepine antagonist, administered intravenously, that is approved by the FDA and widely used to treat benzodiazepine overdose and reverse benzodiazepine effects in the context of conscious sedation or surgical anesthesia. Rye et al (Rye-2012) and Trotti et al. (Trotti-2016) have reported that treatment with [redacted] can yield significant improvements in sleepiness and related symptoms in selected patients with IH. One of the IH patients who showed benefit with IV [redacted] (Rye-2012) was later diagnosed with DM1 (D. Rye, Personal communication).

The safety and efficacy of ERX-963 (IV [redacted] to treat EDS/hypersomnia have not been formally evaluated in patients with DM1 in a placebo-controlled fashion. The purpose of this study therefore is primarily to investigate the safety and tolerability of ERX-963, and secondarily to evaluate its potential to reduce EDS/hypersomnia and improve cognitive function in patients diagnosed with DM1.

2.2. Background

Myotonic dystrophy is the most common adult muscular dystrophy with a prevalence of over one in 8000 persons. The disorder is genetically heterogeneous; currently mutations in two different genes (DMPK and CNBP) have been shown to cause the disease, labeled as myotonic dystrophy type 1 (DM1) and type 2 (DM2), respectively. Both disorders are inherited in an autosomal dominant mode. Both DM1 and DM2 are truly multi-system disorders. While progressive muscle weakness due to increasing muscle fiber atrophy and myotonia (a delayed relaxation of skeletal muscles after voluntary contraction) often are key features of the disease, both types of DM exhibit many other symptoms and signs such as early cataracts, central nervous system dysfunction (cognitive-affective disorders), cardiac disease (usually conduction system anomalies), gastrointestinal dysfunction and endocrine abnormalities including diabetes and gonadal dysfunction in a variable manner (Thornton-2014).

As described in Section 2.1, both the presence of a somnogen (an endogenous compound with GABAergic effects) and increased prevalence of the short isoform of the γ2 subunit of the $GABA_A$ receptor could play a role in the cognitive features and sleepiness seen in DM1 patients.

[redacted] a selective benzodiazepine binding site antagonist has been reported to be effective for the therapy of primary hypersomnia when given as a topical cream in conjunction with lozenges at doses of 24 to 48 mg per day (Trotti-2016). Open label treatment of refractory hypersomnolence patients using [redacted] as administered by these routes of delivery showed sustained clinical benefit in 39% of participants refractory to all other treatment paradigms. Adverse events when [redacted] has been given chronically in this fashion included dizziness, anxiety, paresthesia, insomnia and cognitive dysfunction. One of the patients enrolled in the study by Rye et. al. (Rye-2012) was later diagnosed to have DM1 and their EDS/hypersomnia was subsequently attributed to the disease (D. Rye, Personal communication). Three additional DM1 patients have been evaluated at the Emory sleep center and received oral and topical [redacted] and had significant improvement in their sleepiness, fatigue and daily function (D. Rye, Personal communication).

[redacted] is currently indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anaesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose ([redacted] USPI-2018). [redacted] IV dose is 0.2 mg repeated at intervals to a maximum of 5 mg and not to exceed 3 mg per hour.

Frequent adverse events considered to be related to [redacted] administration in individuals who received [redacted] alone or for the reversal of benzodiazepine effects were vomiting, dizziness, injection site pain, and agitation ([redacted] USPI-2018). More rarely, confusion and cognitive changes, cardiac rhythm disturbances, seizures, anxiety and panic attacks have been noted. However, these adverse events have been reported in acutely ill individuals who have overdosed on benzodiazepines (Penninga-2016). A detailed description of the chemistry, pharmacology, efficacy, and safety of IV [redacted] is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

No drugs are currently approved for the treatment of (EDS)/hypersomnia in DM1 patients. These symptoms significantly impact the quality of life for DM1 patients.

Rye et al (Rye-2012) reported significant improvement in vigilance with 1.5-2.0 mg IV [redacted] in hypersomnolent patients. Open label treatment of IH patients using [redacted] administered as topical cream in conjunction with lozenges at doses of 24 to 48 mg per day showed sustained clinical benefit in 39% of participants refractory to all other treatment paradigms (Goodwin-2015). Adverse events when [redacted] has been given chronically in this fashion included dizziness, anxiety, paresthesia, insomnia and cognitive dysfunction.

In this study a single dose of 1.0 and 2.0 or 0.5 mg IV [redacted] is planned for IV administration. The results of this study would give increased confidence to the potential therapeutic effects of [redacted] It is one component of an overall program to develop a novel re-formulation of [redacted] for the management of EDS/hypersomnia and cognitive symptoms in DM1 patients.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of IV [redacted] given alone may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of a single dose of ERX-963 vs. placebo in patients with DM1	• The proportion of participants with adverse events, serious adverse events (SAEs), and drug related adverse events
Secondary	
• To assess the effect of intravenously-administered ERX-963 vs. placebo on sleepiness, vigilance, and working memory in patients with DM1	Repeated measurements of the following: • Stanford Sleepiness Scale (SSS) score • Psychomotor Vigilance Task (PVT) – No. of lapses and 1/Longest 10% Response time (1/RT) and median reaction time • One-back task – proportion of correct response • Clinical Global Impression – Improvement scale (CGI-I) • Patient Global Impression – Improvement scale (PGI-I)
Exploratory	
• To correlate ERX-963 plasma concentrations to clinical efficacy endpoints in patients with DM1 • To assess the effect of intravenously-administered ERX-963 vs. placebo on brain activity in patients with DM1	Repeated measurements of the following: • Plasma ERX-963 concentration • Stanford Sleepiness Scale (SSS) score • Psychomotor Vigilance Task (PVT) – No. of lapses and 1/Longest 10% Response time (1/RT) and median reaction time • One-back task – proportion of correct response • EEG – theta/alpha and theta/beta spectral ratios, and theta, alpha, and beta percentages

4. STUDY DESIGN

4.1. Overall Design

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, 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 EX-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, 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 (See Section 6.6).

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

4.2. Scientific Rationale for Study Design

This Phase 1b study is designed to be a randomized, double-blind, placebo-controlled, two-treatment crossover trial comparing the safety, tolerability, and the exploratory endpoints evaluating the effectiveness of a single dose of ERX-963 (IV [redacted] versus IV placebo.

Since this is an exploratory study, it is designed as a two cohort study to allow for safety evaluation after completion of cohort 1 and prior to initiation of cohort 2.

This study is designed as a crossover trial in which participants will receive both ERX-963 and IV placebo with approximately 4 to 18 days washout in between the two treatments. A crossover design was chosen to allow participants to serve as their own controls, thus increasing the ability to detect clinical effects with a minimum number of participants. In each cohort, 6 participants will be randomized in a 1:1 ratio to receive two treatments in one of 2 treatment sequences (ERX-963 followed by placebo or placebo followed by ERX-963; 3 subjects/sequence) to balance for potential first-order carryover effects.

[redacted] half-life is reported to be 40-80 minutes ([redacted] USPI-2018). The exploratory end points and PK samples will be collected at half-hour intervals over a 2 hour period after dosing. The duration of assessment is based on prior experience suggesting that [redacted] effect lasts for about 2 hours (Rye-2012) which is consistent with its short half-life.

The PK sampling times have been selected to correlate serum [redacted] concentration to potential clinical improvement as measured by the efficacy endpoints.

Given the short half-life, the planned washout period of approximately 4 to 18 days would be more than sufficient to ensure both the drug and the drug's effects are completely cleared prior to dosing in the second period.

4.3. Justification for Dose

Rye et al (Rye-2012) investigated the effects of placebo (0.9% saline) followed by [redacted] 0.375 to 0.5 mg and then by [redacted] 1.5 to 2.0 mg, each dose administered IV over 5 minutes. Wakefulness and vigilance were assessed using Stanford sleepiness scale (SSS) and psychomotor vigilance test (PVT) after 10, 30, 60, 90, 120, and 150 min of each infusion. Reduction in attentional lapses was seen over 2 hours after both low and high [redacted] doses. Reemergence of lapses at 2.5 hours post-dose approaches baseline (saline) performance levels. The initial number of lapses under high [redacted] dose was significantly lower than that under

saline conditions [4.58 (± 1.7, SEM) versus 15.1 (± 5.3, SEM), Wilcoxon Z = 70.0, two-tailed P=0.049]. In these case reports, no new adverse events were reported.

Based on these data, a single dose of 1 mg (administered over 5 minutes) and 2 mg (administered over 15 minutes) of ERX-963 (IV [redacted] was selected for cohort 1 and cohort 2, respectively.

This study is evaluating two doses levels (1 mg and 2 mg) of ERX-963 (IV [redacted] to explore the relationship between dose, exposure and safety, tolerability and clinical benefit. Both dose levels to be evaluated in this study are within the FDA approved dose range for IV [redacted] and have been used with favorable safety and tolerability for over 25 years in clinical practice in the treatment of patients following benzodiazepine anesthesia and benzodiazepine overdose. As such, it is expected that the 1 and 2 mg doses will have acceptable safety and tolerability in this study. Nonetheless, a blinded review of adverse events will be performed by sponsor and reviewed with the principal investigators following the initial cohort of 6 participants has completed the two treatments. Initiation of the second cohort of 6 participants will take place following the review of safety (See Section 6.6).

[redacted] IV dose for reversal of benzodiazepine effects is 0.2 mg repeated at intervals to a maximum of 5 mg and not to exceed 3 mg per hour ([redacted] USPI-2018). However, IV [redacted] alone (i.e. not after a benzodiazepine) has been administered safely in doses up to 100 mg over 5 minutes in healthy volunteers ([redacted] USPI-2018).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed both treatment periods of the study.

The end of the study is defined as the date of last scheduled procedure shown in the Schedule of Activities (Section 1.3) for the last participant in the trial globally.

5. STUDY POPULATION

Participants in this study will be adults with DM1.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, must be discussed with the Expansion medical monitor before randomization.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 to 65 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants must have DM1 defined genetic testing or clinically-confirmed (including symptomatic subjects for whom diagnosis is based on DNA analysis of affected family members).
3. Participants who have an Epworth Sleepiness Scale (ESS) of > 11 or participants who have long sleep periods of an average of > 10 hours a day, including naps, as measured by actigraphy monitoring for seven consecutive days.
4. Age of onset of DM1 greater than 16 years.

Weight

5. Body mass index (BMI) less than 35 kg/m^2.

Sex

6. Males and females are eligible to be included if the following apply:

    a. Male participants must be surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, must be willing to use a highly effective method of contraception throughout their study participation.

    b. Female participants must not be pregnant or lactating. Women of child-bearing potential must use a highly effective method of contraception throughout their study participation.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1, Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
8. Be able to read, speak, understand English and effectively communicate with the investigator and other study personnel.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Significant respiratory compromise as indicated by **clinical assessment (e.g. dyspnea) and by** pulmonary function tests routinely conducted in the clinic.
2. Significant cardiac disease with documented low ejection fraction (< 40%), or heart rate < 60 beats per minute, or history of type 2 second-degree heart block or other indication for cardiac pacemaker that has not been treated with an implanted cardiac pacemaker, or presence of implantable cardioverter defibrillator (ICD) (**Note: subjects with a history of type 2 second-degree heart block treated with a pacemaker are eligible for the study**).
3. a. Diagnosis of symptomatic Restless Leg Syndrome OR
   b. Diagnosis of significant nocturnal hypoxias (moderate or severe obstructive or central sleep apnea) by nocturnal polysomnography performed within the last three years. Note: Patients with mild sleep apnea are eligible. Patients with a history of moderate to severe sleep apnea who are treated by and comply with non-invasive ventilation (NIV) are eligible to participate in the study and do not require repeat PSG prior to study entry. Patients with a history of moderate to severe sleep apnea who are not compliant with NIV treatment are not eligible. Compliance will be determined by review of NIV device records within the past 6 months and is defined as use of NIV for approximately ≥ 4 hours/night for 15 days out of a 1 month period.
4. Significant moderate to severe hepatic insufficiency as defined by Child-Pugh B or C score.
5. Clinically active depression, anxiety, or other medical condition that, in the investigator's opinion, would interfere with the safety and efficacy assessments.
6. History of seizures.
7. History of panic disorder.
8. History of current or recent alcohol or illicit drug abuse.
9. Significant abnormalities on screening safety laboratory tests.

Prior/Concomitant Therapy

10. Use of benzodiazepines within 14 days of administration of intervention.
11. Currently taking a medication that can, in the judgement of the PI, influence sleep and fatigue including (but not limited to) sleep inducing drugs such as antihistamines or tricyclic antidepressants, stimulant drugs such as modafinil or armodafinil, clarithromycin, or dextroamphetamine. Participants may be included in the study if these medications are discontinued for more than 7 days and are not expected to resume during the entire study duration.
12. Prior use of [redacted] for treatment of EDS/hypersomnia.

Prior/Concurrent Clinical Study Experience

13. Interventional experimental trial participation in the last 30 days.

Diagnostic assessments

14. Inability to complete efficacy measures.

Other Exclusions

15. History of hypersensitivity or allergic reaction to [redacted] or benzodiazepines.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

1. Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 6 hours prior to and during screening session and 6 hours prior to and during both IV treatment periods.
2. Participants will abstain from alcohol for 6 hours prior to and during screening session and 6 hours prior to and during both IV treatment periods.
3. Participants who use tobacco products will be instructed not to use nicotine-containing products (including nicotine patches) 6 hours prior to and during screening session and 6 hours prior to and during both IV treatment periods.
4. Participants will abstain from eating from the beginning of each visit until the final PK blood sample collection is completed. Consumption of water is permitted.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). If additional study procedures were performed during screening, information from these procedures should be recorded in the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at a later time after discussion with the Expansion medical monitor and resolution of the issue that led to the initial screen failure.

6. STUDY INTERVENTION

In this study participants who have consented and meet all-eligibility criteria will receive two treatments, IV Placebo (Treatment A) and ERX-963 (IV [redacted] Treatment B or C) in a crossover fashion with approximately 4 to 18 days washout between the treatments.

6.1. Study Intervention(s) Administered

Treatment Name	ERX-963	Placebo
Intervention Name	[redacted]	Normal saline (0.9% Sodium Chloride)
Type	Drug	Placebo
Dose Formulation	Intravenous	Intravenous
Unit Dose Strength(s)	0.1 mg/ml [redacted]	Not Applicable
Dosage Level(s) **Cohort 1** **Cohort 2**	 Single IV Administration 1 mg over 5 minutes Single IV Administration 0.5 mg or 1 mg over 5 minutes or 2 mg over 15 minutes	 Single IV Administration over 5 minutes Single IV Administration over 5 minutes or 15 minutes
Route of Administration	IV infusion	IV infusion
Investigational Medical Product (IMP) and Non-IMP	[redacted] (IMP)	Normal Saline (NIMP)
Sourcing	Each site will source the drug product, IV [redacted] through their pharmacy.	Each site will source the placebo, normal saline, through their pharmacy.
Packaging and Labeling	Not Applicable	Not Applicable

6.1.1. Medical Devices

Medical devices provided for collecting data in this study are:

- EEG
- Actigraph

6.2. Preparation/Handling/Storage/Accountability

ERX-963 (IV [redacted] will be procured by the pharmacy at the clinical sites. IV [redacted] is available as 5 mL or 10 mL vial, containing 0.1 mg/mL of drug. Appropriate volumes for each dose level as summarized in the Table below will be administered over the duration specified.

Dose	Total Volume	Dosing Plan
0.5 mg	5 mL	ERX-963 0.5 mg or placebo will be administered intravenously over 5 minutes.
1.0 mg	10 mL	ERX-963 1 mg or placebo will be administered intravenously over 5 minutes.
2.0 mg	20 mL	ERX-963 2 mg or placebo will be administered intravenously over 15 minutes.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

   IV [redacted] vial should be stored at 25 ° C (77 ° F); excursions permitted to 15 ° to 30 ° C (59 to 86° F).

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using Pre-Coded Randomization provided to site	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.
Blinded study with unblinded site pharmacist who is dispensing drug	Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4. Study Intervention Compliance

In this study a single dose of the study drug (ERX-963 or placebo) will be administered as a short (5 minute or 15 minute) IV infusion during each of the two treatment periods. The study intervention will be administered by the clinic staff. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant was receiving within the last 30 days or is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Lifetime history of medication taken for the treatment of myotonic dystrophy type 1 or sleep will be recorded with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs as outlined in Exclusion Criteria under Prior/Concomitant Medications (Criteria # 10, 11, 12).

6.5.1. Rescue Medicine

Not applicable for this protocol.

6.6. Dose Modification

This is a single dose study and hence dose modification in cohort 1 is not applicable.

Intravenous [redacted] has been used for over two decades for reversal of benzodiazepine induced anesthetic sedation and management of benzodiazepine overdose with an acceptable safety profile. The 1 and 2 mg infusions of ERX-963 (IV [redacted] specified in this protocol are lower than the 5 mg maximal dose specified in the FDA approved [redacted] product label. Although it is anticipated that the safety profile of single doses of [redacted] in participants with DM1 will be similar to the established safety profile of [redacted] blinded review of safety (adverse events, safety laboratories and vital signs) will be performed following completion of cohort 1 and prior to initiation of cohort 2. 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 adverse events and/or safety laboratory abnormalities observed during cohort 1, their potential for relatedness to active study medication, and the degree of unexpectedness as compared to the existing known [redacted] safety profile.

6.7. Intervention at the End of Study

There will be no study intervention after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In this study single dose of the drug or placebo is administered on two occasions (Study Period 1 and 2). If a decision is made to discontinue the study intervention after Period 1, the participant will not participate further in the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

Not applicable

7.1.2. Rechallenge

Not applicable

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Reasons that a participant may be withdrawn include the following:

- the need to take medication that may interfere with study measurements;
- intolerable or unacceptable AEs;
- clinically significant safety laboratory and other test results;
- positive pregnancy test;
- major deviation of study protocol procedures;
- non-compliance of subject with the protocol;
- subject unwilling to proceed and/or consent is withdrawn;
- withdrawal from the study is, in the Investigator's judgment, in the subject's best interest;
- sponsor decision, after discussion with the Investigator;
- study is stopped for any reason.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1, Appendix 1.

7.4 Replacement of Subjects

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions must be discussed with the Expansion medical monitor.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

The estimated amount of planned blood collected from each participant over the duration of the study is described below. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Blood Sample Reason	No. of Samples	Volume per Sample (mL)	Total Volume (mL)
Total PK samples in study	10	6	60
Serum pregnancy test	2	5	10
Clinical laboratory tests (hematology and clinical chemistry)	4	20	80
Hepatitis C Antibody	1	10	10
Biomarker test	1	10	10
Total Estimated Blood Volume During Entire Study (mL)			**170**

Screening

During screening, potential participants for the study will be fully informed about the nature of the study and possible AEs. Participants must read and understand the ICF and sign the document after the investigator has answered all questions to the candidate's satisfaction. Further procedures can begin only after the ICF has been signed. Screening will occur within 21days before the first dose of study drug. Potential study participants will be evaluated for entry into the study according to the stated inclusion and exclusion criteria.

Individuals who are identified during this screening as not eligible for study enrolment should complete the requirements described in Section 5.4.

The following procedures will be obtained or performed to evaluate each participant's general health and qualifications for enrolment into the study:

Screening Visit 1

- Signed, written informed consent;
- Medical history, including myotonic dystrophy diagnosis history;
- Medication history over the past 30 days, including prescription and non-prescription (over the counter, OTC) medications, herbal medications, vitamins, and minerals. Lifetime history of medication taken for DM1 or sleep;
- MDHI questionnaire to establish baseline disease condition;
- ESS
- Complete physical examination and recording of demographic data including height and weight;
- Vital signs (systolic and diastolic blood pressure [BP], respiration rate and pulse rate);
- Administer the practice outcome measure tests (in the order specified below):
    1. Stanford sleepiness scale [SSS]
    2. Psychomotor vigilance task [PVT]
    3. One-back test
    4. 20 minute rest
- Administer the screening visit outcome measure tests (in the order specified below):
    1. Stanford sleepiness scale [SSS]
    2. Psychomotor vigilance task [PVT]
    3. One-back test
- Other tests to be conducted to verify inclusion and exclusion criteria:
    1. 12-lead ECG and a Pulmonary function test (including Spirometry)
    2. Collection of blood for hematology, clinical chemistry, Hepatitis C antibody and in female subjects of child bearing potential, a serum pregnancy test;
       An additional plasma sample will be taken from patients who have given consent for future exploration of disease markers;
    3. Urinalysis;
    4. Actigraph will be given for collection of data over 7 consecutive days if ESS is <=11.
    5. Nocturnal Polysomnography (Schedule a visit day for participants who have not taken the test within the last 3 years. If the participant has not had the test performed within 3 years and is treated by and compliant with NIV, then this test is not required for eligibility.)
- Review inclusion and exclusion criteria and restrictions;
- Review of AEs and medication history;

- Instructions and paperwork will be given on when and how to return the actigraph and schedule the visit to conduct polysomnography and/or Period 1.

Period 1 and Period 2 Evaluation Day

- Allot randomization number (Period 1 only);
- Pre-dose Vital Signs (systolic and diastolic BP, respiration rate and pulse rate within 60 minutes prior to dosing) and brief clinical review;
- Hook up EEG and start recording;
- Place two IV lines on two separate limbs (identify one line for drug administration and the second one for blood sampling);
- Start recording video (if patient consented);
- Administer practice outcome measure tests (order of tests: SSS-PVT-One back; approximate duration of 15 minutes);
- Administer pre-dose baseline outcome measure tests (order of tests: SSS-PVT-One back; approximate duration of 15 minutes) 20 minutes after completion of practice outcome measure test;
- Administration of study intervention (at approximately the same time of day [±1h] in both Period 1 and 2);
  - **Cohort 1 (1 mg)** and **Cohort 2 (if selected dose is 0.5 mg or 1 mg)**: administer as a 5 minute infusion.
  - **Cohort 2 (if selected dose is 2 mg):** administer as a 15 minute infusion
- Administer outcome measure tests (approximate duration of 15 minutes each) starting at:
  - **Cohort 1 (1 mg) and Cohort 2 (if selected dose is 0.5 mg or 1 mg):** 15 minutes, 45 minutes, 1 hour 15 minutes and 1 hour 45 minutes after the start of IV infusion;
  - **Cohort 2 (if selected dose is 2 mg):** 25 minutes, 55 minutes, 1 hour 25 minutes and 1 hour 55 minutes after the start of IV infusion;
- Obtain blood samples (PK sampling) after conclusion of each set of outcome measure tests to measure plasma [redacted] concentrations:
  - **Cohort 1 (1 mg):** at the end of drug administration (5 minutes after the start of dosing) and at approximately 30 minutes, 1 hour, 1 hour 30 minutes and at 2 hours after the start of IV infusion;
  - **Cohort 2 (if selected dose is 0.5 mg or 1 mg):** at the end of drug administration (5 minutes after the start of dosing) and at approximately 30 minutes, 1 hour, 1 hour 30 minutes and at 2 hours after the start of IV infusion;
  - **Cohort 2 (if selected dose is 2 mg):** at the end of drug administration (15 minutes after the start of dosing) and 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.
  - The exact time when the blood samples were taken will be recorded.

- End video recording;
- General clinician- and patient-reported questionnaire (CGI-I and PGI-I);
- Vital Signs (systolic and diastolic BP, respiration rate and pulse rate) after completion of all assessments;
- Brief physical examination;
- Obtain blood samples for clinical laboratory tests (hematology and clinical chemistry) at the end of the assessment period;
- Review of AEs and concomitant medications (throughout the day, continuing until the end of the study).

Subjects will be given instructions on when to return to the clinic for Period 2 (approximately 4 to 18 days after Period 1), and for End-of-Study visit (after approximately 4 to 18 days after Period 2).

End of Study or Early Termination

The following evaluations will be conducted at the End-of-Study (or early termination) visit, which will be conducted approximately 4 to 18 days after Period 2:

- Physical examination;
- Review of AEs and concomitant medications;
- Vital signs (systolic and diastolic BP, respiration rate and pulse rate);
- Clinical laboratory tests (hematology, urinalysis and clinical chemistry);
- Serum pregnancy test (female subjects of child-bearing potential only).

If a subject discontinues from the study prematurely, every attempt will be made to conduct all these evaluations at the time of discontinuation.

8.1. Efficacy Assessments

8.1.1. Vigilance and Sleepiness

The following battery of outcome measure tests will be administered at times specified in the SoA (Section 1.3), in the order specified below:

1. **Stanford Sleepiness Scale (SSS) [1 minute]**

   Stanford Sleepiness Scale (SSS) consists of a seven-point scale of equal intervals varying from 1 ("Feeling active and vital; alert; wide awake") to 7 Sleep, ("almost in reverie; sleep onset soon, lost in struggle to remain awake")

2. **Psychomotor Vigilance Task (PVT) [5 minutes]**

   Psychomotor vigilance task (PVT) is a sustained-attention, reaction-timed task that measures the speed with which subjects respond to a visual stimulus.

3. **One-back Task [~4 minutes]**

   The One-back task is a memory test in which the participants are presented with a sequence of stimuli, and the task consists of indicating when the current stimulus matches the item presented one step earlier in the sequence.

In addition, after the last outcome measure test, the Clinical Global Impression – Improvement scale (CGI-I) and Patient Global Impression – Improvement Scale (PGI-I) will be recorded in each study period (Guy-1976).

8.1.2. Electroencephalogram (EEG)

Brain activity will be continuously monitored by electroencephalogram (EEG) during the pre-dose and post-dose outcome measures testing. The EEG parameters of interest are theta/alpha and theta/beta spectral ratios, and theta, alpha, and beta percentage power. Additional exploratory parameters may be included in the analysis.

EEG data from the time periods when patients are taking the psychomotor vigilance task will be used to determine the theta/alpha and theta/beta spectral ratios, along with the theta, alpha, and beta percentages. If the PVT test duration does not provide sufficient data to estimate spectral ratios, a longer time period will be used.

8.2. Safety Assessments

Safety will be evaluated based on the occurrence of AEs, clinical laboratory testing (clinical chemistry, urinalysis and hematology), vital signs assessments (systolic and diastolic BP, respiration rate and pulse rate) and physical examinations.

During the study, the Investigator or study site personnel will be responsible for querying and recording AEs and SAEs, as detailed in this section of the protocol. In this study, AEs (including qualifying SAEs) will be reported from the time of signing of the informed consent until the End-of-Study evaluation (approximately 4 to 18 days after Period 2) or early discontinuation. Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, respiration rate and pulse rate.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. Fasting is not required for the clinical laboratory tests.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.
The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Laboratory tests with values considered clinically significantly abnormal during participation in the study from the first dose (Period 1) to End of Study visit (or early discontinuation) should be repeated until the values return to normal or to pre-dose levels or are no longer considered clinically significant by the investigator or medical monitor.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3, Appendix 3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF) until the End-of-Study visit or early discontinuations at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the End-of-Study visit or early discontinuations at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3, Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3, Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3, Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until the End-of-Study visit. If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Section 10.4, Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, the protocol specified dose is a short (5 minute) IV infusion which will be prepared and administered by the clinic staff and as such an overdose is not expected.

In the event of an overdose due to improper preparation or administration of the study medication, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Document the quantity of the excess dose in the CRF.

8.5. Pharmacokinetics

Plasma samples of approximately 6 mL will be collected for measurement of plasma concentrations of [redacted] (or its metabolites) as specified in the SoA (Section 1.3).

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of [redacted] Each plasma sample will be divided into 2 aliquots (primary sample and a back-up]. Samples collected for analyses of [redacted] plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6. Pharmacodynamics

Pharmacodynamic parameters are described under Efficacy Assessments (Section 8.1).

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

At the screening visit, a single blood sample will be collected from all participants who provide consent for the purpose of exploring disease determinants at a future date.

8.9. Health Economics

Health economics is not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is a safety and tolerability study and is not powered for any of the secondary or exploratory efficacy endpoints.

9.2. Sample Size Determination

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.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Enrolled	All participants who receive at least 1 dose of study intervention.
Randomly Assigned to Study Intervention	All participants assigned a randomization number according to the procedure described in Section 6.3.
Evaluable	All participants who complete all the protocol specified assessments in both treatment periods.
Safety	All participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock, will describe the participant populations to be included in the analyses, and will describe the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	N/A
Secondary	PVT, SSS, One-back test, CGI-I, PGI-I
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

Descriptive statistics will be computed for PVT, SSS, One-back test, EEG, CGI-I and PGI-I parameters.

For PVT, three variables will be analyzed: the number of attentional lapses, the reciprocal of the longest 10% response time (1/RT) of each trial, and the median reaction time.

For SSS, the analysis variable will be the numerical rating of sleepiness.

For the One-back test, the analysis variable will be the proportion of correct responses (the arcsine transformation of the square root will be used for analysis).

For each PVT, SSS, and One-back test efficacy variable, data will be reported for the pre-dose baseline and each time point of the study period. Differences from pre-dose baseline will be calculated for each time point as well as the median change over the two-hour study period for each participant. Changes from baseline for each patient on [redacted] will be compared to their placebo experience.

Cohort 1 and Cohort 2 data will be combined to assess the secondary efficacy parameters.

- A mixed effect model will be used to compare efficacy effects (PVT, SSS, and One-back test) following ERX-963 (IV [redacted] vs placebo. The model will include cohort, sequence, cohort-by-sequence interaction, treatment, treatment period, pre-dose 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 a random effect. The test statistic will be based on the treatment effects (experimental vs. placebo, averaged across the post-dose measurements), using the equally weighted mean of the Cohort 1 and Cohort 2 treatment effects.
- For CGI-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 with subject within cohort and sequence as a random effect. The test statistic will be based on the average of the treatment effects in Cohort 1 and Cohort 2.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Proportion of patients experiencing AEs, SAEs, drug-related AEs, adverse events resulting in discontinuation, by treatment and cohort
Exploratory	Will be described in the statistical analysis plan finalized before database lock

Safety and tolerability are assessed by tabulation of the frequency per participant of adverse events, drug-related adverse event, adverse events that cause discontinuation, and serious adverse events. Tabulation will be by primary term and system organ classification (SOC), cohort and treatment.

9.4.3. Other Analyses

Blood samples will be analyzed for plasma [redacted] concentration. [redacted] PK will be evaluated. The statistical analysis of the association of [redacted] concentration to response on efficacy measures will be described prospectively in the Statistical Analysis Plan.

For the exploratory EEG objective, the analysis variables are the theta/alpha and theta/beta spectral ratios, along with the theta, alpha, and beta percentages. Additional exploratory parameters may be included in the analysis.

9.5. 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.

9.5.1. Data Monitoring Committee

Not Applicable

10. APPENDICES

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

1. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. Applicable ICH Good Clinical Practice (GCP) Guidelines
3. Applicable laws and regulations
4. The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
5. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

1. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
2. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
3. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

A cohort review committee consisting of medical monitor and investigators will collectively review all safety data in a blinded fashion, ERX-963 dose for cohort 2 will be selected based on the *blinded review of* safety data from cohort 1.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of 2 years following the FDA or other regulatory approval date of the drug or until 2 years after the drug investigational program is discontinued unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Study Manual.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table A1 will be performed by the local laboratory. Fasting is not required for the clinical laboratory tests.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table A1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry ([redacted] USPI-2018)	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Gamma-glutamyl transferase (GGT)
Routine Urinalysis	• pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Serology -Hepatitis C virus antibody. • Prothrombin time, serum albumin, serum magnesium and Thyroid Stimulating Hormone [TSH]. The results of each test must be entered into the CRF or recorded electronically.			

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor/designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor/designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor/designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship (Related or Unrelated) between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor/designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** sponsor/designee**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor/designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide medical monitor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to sponsor/designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to sponsor/designee will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Medical Monitor can be contacted at: mobile telephone +1 617 308 8979. Other contacts for SAE reporting can be found in the study manual.

SAE Reporting to sponsor/designee via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone or email is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Medical Monitor can be contacted at: mobile telephone +1 617 308 8979. Other contacts for SAE reporting can be found in the study manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Utilize an effective method of contraception from screening through to at least 4 weeks after the last dose of study drug, using one of the following: barrier methods (diaphragm or partner using condoms plus use of spermicidal jelly or foam, preferably double-barrier methods); oral or implanted hormonal contraceptive; intrauterine device (IUD); or vasectomized male partner

Collection of Pregnancy Information:

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (07-March-2019)

Overall Rationale for the Amendment:

This amendment incorporates comments provided by the FDA Study May Proceed letter (dated February 26, 2019), provides additional clarity, and addresses inconsistencies across the protocol.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria #4	Significant moderate to severe hepatic insufficiency **Changed to** Significant moderate to severe hepatic insufficiency ***as defined by Child-Pugh B or C score***	To define significant moderate or severe hepatic insufficiency according to the Child-Pugh scoring system described in the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (2003)
10.2 Appendix 2: Clinical Laboratory Tests	**Added prothrombin time, serum albumin** to the list of blood tests to be conducted at screening	To determine Child-Pugh score
	Added serum magnesium and thyroid stimulating hormone (TSH) to the list of blood tests to be conducted at screening	To screen for increased risk of arrhythmia
5.3.1. Meals and Dietary Restriction	Participants will be provided a standard snack **Changed to** Participants will abstain from eating from the beginning of each visit until the final PK blood sample collection is completed. Consumption of water is permitted.	To minimize the potential variable of the presence or absence of a snack between subjects
8. Study Assessments and Procedures; Period 1 and Period 2 Evaluation Day	**Deleted** Offer a standard snack (Ensure or equivalent…)	To minimize the potential variable of the presence or absence of a snack between subjects

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) – Footnote 6.5 Concomitant Therapy 8. Study Assessments and Procedures	**Added** Lifetime history of medication taken for DM1 or sleep [will be recorded]	To reflect the intended collection of the medication history information
8. Study Assessments and Procedures	**Increased** blood volume collection values	To account for the lab tests added in this amendment
8. Study Assessments and Procedures; End of Study or Early Termination	**Deleted** The end of study or early termination evaluations may be conducted through a home health service and phone call with site staff	Removed due to lack of operational feasibility
1.2 Schema	**Added** to the procedures and assessments listed in the schema	Clarification
1.3. Schedule of Activities (SoA)	**Added** check mark for Urinalysis to End of Study	Correct inconsistency versus Section 8
	Added Spirometry to obtain FVC value to pulmonary function test	Clarification of the test to be administered
1.3. Schedule of Activities (SoA) - Footnote	**Added** Fasting is not required	Clarification
8. Study Assessments and Procedures	**Added** text throughout to specify order of outcomes measure tests	Clarification
8. Study Assessments and Procedures; Screening Visit 1	**Added** Spirometry to obtain FVC value to pulmonary function test	Clarification of the test to be administered
8.2.4 Clinical Safety Laboratory Assessments	**Added** Fasting is not required for the clinical laboratory tests	Clarification
10.2 Appendix 2: Clinical Laboratory Tests	**Added** Fasting is not required for the clinical laboratory tests	Clarification
10.3.3. Assessment of Causality - First Bullet	**Added** (Related or Unrelated)	Clarification
Throughout Protocol	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

SUMMARY OF CHANGES FOR VERSION 1.1, ORIGINAL

Section	Revisions
Title page	Revised Study Phase from "2" to "1b".
Summary of Changes for Version 1.1	Added.
1.1 Synopsis, Overall Design	Revised "1 week washout" to "4 to 8 days washout".
1.1 Synopsis, Number of Participants	Revised number of participants from "a total of up to 12" to "a total of up to 14".
1.1 Synopsis, Intervention Groups and Duration	Revised text as follows: - "1 week washout" to "4 to 8 days washout". - "The follow up period is 7 days" to "The follow up period is approximately 4 to 8 days".
1.2 Schema, Column Titles	Changed "Day" to "Period" and added "Washout 4-8 days".
1.3 Schedule of Activities (SoA), Table Column Titles	Changed "Day" to "Period" and revised Washout Period from "Days 2-7" to "4-8 days".
4.1 Overall Design	Revised "1 week washout" to "4 to 8 days washout".
4.2 Scientific Rationale for Study Design, Last Paragraph	- Revised from "one week" to "approximately 4 to 8 days". - Revised Study Phase from "2" to "1b".
5.3.1 Meals and Dietary Restrictions	Revised "provided" to "offered".
6. Study Intervention	Revised "a one-week" to "approximately 4 to 8 days".
8. Study Assessments and Procedures, Period 1 and Period 2 Evaluation Day	- Deleted "(Day 1 and 8)". - Revised "Allot randomization number (Day 1 only)" to "Allot randomization number (Period 1 only)". - Revised "Subjects will be … (approximately 7 [±1] days after Period 1), and for End-of-Study visit (after approximately 7 [±1] days after Period 2)." to "Subjects will … (approximately 4 to 8 days after Period 1), and for End-of-Study visit (after approximately 4 to 8 days after Period 2)."
8. Study Assessments and Procedures, End of Study or Early Termination	- Revised "which will be conducted on Day 7 (+1 day) after Period 2" to "which will be conducted approximately 4 to 8 days after Period 2". - Added "The end of study or early termination evaluations may be conducted through a home health service and phone call with site staff."

SUMMARY OF CHANGES FOR VERSION 1.1, ORIGINAL

Section	Revisions
8.2 Safety Assessments, second paragraph	Revised from "End-of-Study evaluation (Day 7±1 day after Period 2)" to "End-of-Study evaluation (approximately 4 to 8 days after Period 2)".
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Deleted "Medical occurrences that…not the AE section."
10. Supporting Documentation and Operational	Revised section title from "10. SUPPORTING DOCUMENTATION AND OPERATIONAL" to "10. APPENDICES".
10.3.1 Definition of AE, Events Meeting the AE Definition	Deleted '"Lack of efficacy"…definition of an AE or SAE.' and "The signs, symptoms,…constitutes an AE or SAE.".

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