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ReveraGen BioPharma, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy
Study Number:	VBP15-BMD-001
Phase:	Phase 2
Sponsor:	ReveraGen BioPharma, Inc. 155 Gibbs St. Suite 433 Rockville, MD 20850
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SAP Date:	11-Jun-2025
Status:	Final V1.0

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SAP Version: Final V1.0
SAP Date: 11-Jun-2025

The statistical analysis plan has been reviewed and approved.

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2. VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
Final 1.0	TBD	Not Applicable	Original version

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
ADaM	Analysis Data Model
AE	Adverse event
ANCOVA	Analysis of covariance
AR(1)	Autoregressive-1
ATC	Anatomical Therapeutic Chemical
BMD	Becker muscular dystrophy
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CK	Creatine kinase
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMD	Duchenne muscular dystrophy
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
GGT	Gamma glutamyl transferase
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
LDL	Low-density lipoprotein
LS	Least squares
MDC	Macrophage derived chemokine

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Abbreviation/Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
NSAA	North Star Ambulatory Assessment
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred term
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOC	System organ class
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse events
TTRW	Time to Run/Walk
TTRWV	Time to Run/Walk velocity
TTSTAND	Time to Stand
TTSTANDV	Time to Stand velocity
WHO-DD	World Health Organization – Drug Dictionary

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4. INTRODUCTION

4.1. Preface

This document presents a statistical analysis plan (SAP) for ReveraGen BioPharma, Inc. Protocol VBP15-BMD-001 (*A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy*).

Reference materials for this statistical plan include the protocol VBP15-BMD-001 Amendment #5 (21 April 2025).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to database lock and study unblinding.

For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

All pharmacokinetic (PK) analyses will be detailed in a separate PK analysis plan.

All muscle biopsy analyses will be detailed in a separate ancillary SAP.

4.2. Purpose of Analyses

The purpose of this SAP is to describe the statistical analyses to be applied to data resulting from study protocol VBP15-BMD-001. Although the primary objective of the SAP is to detail the statistical procedures that will be used, various other details have been selectively included. These details convey aspects of the experimental design and study procedure considered to be important to a fully informed understanding of the context underlying the analyses, and therefore the aim and purpose of the analyses.

This SAP has been written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed to reveal study participant characteristics, safety and tolerability, pharmacodynamics (PD), and efficacy. Whereas the protocol presents a general discussion of statistical procedures, this SAP provides greater detail and further clarifies a particular application of a general procedure. Nevertheless, in the event of any discrepant directives between the protocol and this SAP, the SAP will supersede the protocol.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report but will be fully documented in the document containing the additional analyses.

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4.3. Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the Study protocol except for the following departures noted here.

Time to Stand velocity (TTSTANDV) is not included in the protocol as a standalone clinical efficacy motor endpoint; the SAP adds Week 12 and Week 24 change from baseline to the list of Exploratory Endpoints.

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5. TRIAL OBJECTIVES AND ENDPOINTS

Trial Objectives	**Trial Endpoints**
Primary Objective	**Endpoint**
To evaluate the safety and tolerability of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy	• Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC) and preferred term (PT): Overall by treatment, by treatment and relationship, and by treatment and intensity • Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points • Body weight: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points • Clinical laboratory values: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points in hematology and clinical chemistry; gamma glutamyl transferase (GGT); creatine kinase (CK); lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]); and urinalysis • 12-lead ECG: Change from baseline to Week 12 and Week 24 • Physical examination findings at each of the pretreatment, on-treatment, and post-treatment assessment time points • Premature discontinuation of study treatment due to adverse event
Secondary Objectives	**Endpoints**
To evaluate the pharmacokinetics of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy	• Detailed in a separate PK analysis plan.
To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily	• Adrenal suppression. First-in-morning salivary cortisol levels will be measured. Cortisol measures falling below 3.6 µg/dL (or 100 nM) will be considered to be indicative of the development of adrenal suppression: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points

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Trial Objectives	Trial Endpoints
administered orally vs. placebo in subjects with Becker dystrophy.	• Bone turnover. Measure of serum osteocalcin is reflective of bone turnover and will be assessed for all participants: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points • Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance, with serum elevations of both insulin and glucose. Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose, fasting insulin, and Hb1Ac will be measured as biomarkers of insulin resistance: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points • Exploratory biomarkers for treatment response including MDC and CD23 (Fiorillo et al., 2015; Conklin et al., 2018a; Conklin et al., 2018b): Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points
To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in patients with Becker dystrophy.	• For the clinical efficacy motor endpoints, TTRWV and NSAA score: Change from baseline to Week 24
Exploratory Objectives	**Exploratory Endpoints**
To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 12-week treatment period in subjects with Becker dystrophy.	• For the clinical efficacy motor endpoints TTRWV and NSAA score: Change from baseline to Week 12; TTSTANDV: Change from baseline to Week 12 and Week 24
To evaluate the effect on patient-reported outcomes of treatment response of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.	• Participants will be asked to complete the NeuroQOL scales for fatigue, mobility, and sleep: Change from baseline to Week 24

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6. STUDY METHODS

6.1. General Study Design and Plan

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

This Phase II pilot study is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg (250mg if <50kg body weight) compared to placebo administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory male participants with Becker muscular dystrophy (BMD).

A total of 39 participants ages 18 to <65 years will be dosed in the study. Participants will be randomized to one of two treatment groups in a 1:2 ratio (placebo: vamorolone 500mg/day [250mg if <50kg body weight]).

The study is comprised of a 1-day Prescreening visit (optional), an up to 35-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period.

Participants will be enrolled into the study at the Screening visit, at the time written main informed consent is obtained. All participants will begin study medication (vamorolone or placebo) treatment on Treatment Period Day 1 and will continue to receive study medication treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24).

The Schedule of Assessments for the study is provided in Table 1.

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Table 1: Schedule of Assessments

Study Day or Week/Visit	Pretreatment Period			Treatment Period				Dose-tapering Period
	Prescreening	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Prescreening Consent	X[a]							
Main Informed Consent		X						
Enrollment		X						
Inclusion/exclusion criteria		X	X					
Randomization[b]		X						
Medical History	X	X						
Medication History	X	X	X					
Physical Examination		X	X			X	X	X
Varicella immunity		X						
Height		X				X	X	
Weight		X	X			X	X	X
Vital Signs		X	X	X	X	X	X	X
Neuro-QOL questionnaires[c]			X				X	
TTRW		X	X			X	X	
NSAA		X	X			X	X	
Blood for Clinical Labs[d]		X		X	X	X	X	X
Urinalysis[d]		X		X	X	X	X	X
Blood for PK[e]				X				

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Study Day or Week/Visit	Pretreatment Period			Treatment Period				Dose-tapering Period
	Prescreening	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Blood for Safety PD Biomarker Panel[f]				X		X[g]	X	
Blood for Efficacy PD Biomarker Panel[h]				X		X	X	
Fasting blood for insulin and glucose [i]				X		X	X	
Saliva for cortisol[j]				X		X	X	
12-lead ECG			X			X	X	
Dispense Study Medication				X		X	X	
Return Study Medication/ Compliance Monitoring					X[k]	X	X	X[m]
Study Medication Dosing[l]				X →	→	X →	X →	
Study Medication dose tapering[m]								X
Dispense Subject Diaries				X		X	X[m]	
Return Subject Diaries					X	X	X	X[n]
AE/SAE Recording		X	→	→	→	→	→	→
Concomitant Medications				X	→	→	→	→
Follow up phone call								X[n]
Discharge from Study[o]							X	X

w = week; TTRW = time to run/walk 10 meters test; NSAA = North Star Ambulatory Assessment

a. After signing the optional Prescreening Visit informed consent, participants will provide HIPPA authorization to release medical records, including a genetic report confirming the diagnosis of BMD
b. Randomization occurs by Almac's-WebEZ™ System after participants are confirmed to have met all study entry criteria, prior to the Baseline Day -1 Visit.
c. NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep

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d. Clinical safety labs: chemistry, hematology, CK, GGT, lipids; urinalysis by dipstick and microscopic
e. Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose
f. Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin
g. Only hemoglobin A1c (HbA1c)
h. Serum efficacy pharmacodynamic biomarkers: MDC and CD23
i. Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic
j. Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening
k. On week 4, only empty bottles of study medication and the current bottle in use will be returned
l. The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home
m. Only for subjects participating in the Dose-tapering Period
n. At Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication
o. Discharge from the study will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication

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6.2. Randomization and Blinding

Randomization

Participants will be randomized to one of two treatment groups in a 1:2 ratio (placebo:vamorolone 500mg/day [250mg if <50kg body weight]). Note that participants who withdraw early from the study may be replaced.

Following main consent and review of study entry criteria to confirm subject eligibility for the study, the subject can be randomized to treatment. Randomization should be performed in advance of the baseline visit and will be achieved using Almac's-WebEZ™ system with username and password access. Randomization will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study, and to verify that the subject has not previously been randomized.

When the site investigator/designee completes the randomization procedures via Almac's-WebEZ™ system, an e-mail report will be generated and sent to the clinical trials supply company confirming randomization into the trial. The subject enrollment ID entered in the system will be the number Almac's-WebEZ™ will use for the subject.

The sites will be pre-seeded with individual, uniquely numbered bottles labeled with a write-in area to add the patient number after the bottles are assigned. Almac's-WebEZ™ will assign 6 bottles at a time. If the patient weighs greater than 50kg, the site will be required to access the WebEZ™ Patient Resupply module to assign an additional six bottles. 12 bottles will be sufficient supply for 12 weeks of dosing.

Blinding

To achieve double-blinding, the supplies company will manufacture identical liquid formulations for vamorolone and placebo. Each dose of study medication will consist of a liquid formulation (vamorolone or placebo).

To blind the liquid formulation, the supplies company will manufacture 4.0% wt/wt vamorolone suspension formulations, and placebo suspension formulation, identical in appearance. Participants who are randomized to receive vamorolone 500mg/day (250mg/day if <50kg body weight) will receive the 4.0% vamorolone suspension. Study medication will be shipped to the sites in 120 mL bottles labeled with a write-in area to add the patient number after the bottles are assigned.

Participants, site investigators and all other site study staff will not know to which treatment group the subject has been assigned and will remain blinded to the identity of the treatment assignment until the end of the study (last subject last visit) and the database has been locked.

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7. SAMPLE SIZE

The primary objective is to evaluate safety and tolerability in this Becker dystrophy population, for which this is the pilot study and no effect sizes are available. A sample of 26 Becker dystrophy patients on vamorolone will be large enough to have a confidence interval of no wider than 39% for the proportion of treatment-emergent adverse events (TEAEs) assessed or any other event outcome in the vamorolone group.

The power for motor efficacy comparisons (secondary objective) of vamorolone to placebo was assessed and these calculations needed to detect a similar effect as that observed for TTRWV in Duchenne muscular dystrophy (DMD) patients in Becker dystrophy. The calculation is presented here.

A sample size calculation was conducted based on observed TTRW values from the VBP15-003 DMD vamorolone trial (11 subjects for 24 weeks on 6.0 mg/kg/day) and VBP15-004 (25 participants for 24 weeks on 6.0 mg/kg/day). Using observed baseline and 24-week measurements for TTRW velocities, it is estimated that 39 participants (randomized 1:2 placebo:vamorolone) will ensure that a two-sided t-test with alpha=0.05 has 83% power to detect a pooled mean difference of 0.275 m/s (standard deviation [SD]=0.2715) in Becker dystrophy subjects on vamorolone vs. no mean change in participants on placebo (SD=0.2715). Assuming dropout of 5%, the study has 80% power. Note that participants who withdraw early from the study may be replaced.

Given the sample size calculations and that the study aims to recruit 39 subjects, there should be enough power to detect a difference in TTRW velocities (primary efficacy endpoint within overall secondary endpoint/objective). Thus, the chosen sample size balances the need for precision in safety estimates and adequate power for secondary efficacy assessments.

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8. DETAILS OF EFFICACY AND PATIENT REPORTED OUTCOME MEASURES

8.1. Clinical Efficacy Measures

8.1.1. Time to Run/Walk 10m Velocity (TTRWV)

TTRWV is calculated as (10 ÷ TTRW) and is expressed in meters/second (m/s). If the participant is unable to perform the TTRW test due to disease progression at Week 12 or Week 24, as captured on the eCRF or with assessment attempt graded as "Unable to walk even with aids (sticks, walker)", then TTRWV will be set to 0 m/s for analysis. If TTRW response is missing for any other reason, then velocity will not be calculated and will remain missing in the analysis. Note that a participant will not have velocity imputed as 0 at Week 12 if he is able to perform the test at Week 24. Also note, as per Study Inclusion Criteria, participants must be able to perform the TTRW test at Screening. If, in the unlikely event the participant is unable to perform the test at Baseline, then the Screening assessment will be used as the baseline response (see Section 9.3.6 for definition of baseline).

8.1.2. North Star Ambulatory Assessment (NSAA)

The NSAA is a clinical assessment scale designed to measure functional ability in ambulant boys and men with BMD. The NSAA consists of 17 scored items including 2 timed tests, namely the TTRW test and the TTSTAND. The NSAA will be completed for participants at the Screening, Baseline, Week 12 and Week 24 visits.

The NSAA total score ranges from 0 to 34 and is calculated in the eCRF.

8.1.3. Time to Stand from Supine Velocity (TTSTANDV)

TTSTANDV is calculated as (1 ÷ TTSTAND) and is expressed as rises/second. If the participant is unable to perform the TTSTAND test due to disease progression at Week 12 or Week 24, as captured on the eCRF or with assessment attempt graded as "Unable to stand from supine, even with use of chair" or "Assisted Gowers", then TTSTANDV will be set to 0 rises/second for analysis. If TTSTAND response is missing for any other reason, then velocity will not be calculated and will remain missing in the analysis. Note that a participant will not have velocity imputed as 0 at Week 12 if he is able to perform the test at Week 24. Also, if a participant does not have a response at both Screening and Baseline (i.e, participant does not have a pre-dosing assessment), then this imputation will not be carried out at Week 12 and 24.

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8.2. Patient Reported Outcome Measures

8.2.1. NeuroQOL Patient-Reported Outcome

Physical functioning will be assessed by completion of the NeuroQOL Patient-Reported Outcome scales for fatigue, upper and lower extremity function, and sleep. The subject will be asked to complete this instrument at Day -1 and Week 24 Visits.

The completed Instrument is considered the source documentation for this assessment. Results will be recorded in the eCRF.

The four NeuroQOL scales consist of 8 questions each with a total score ranging from 8 to 40. The total score for each scale is generated by summing the responses to each individual question when no responses are missing. In case of missing responses, within each domain, when calculating the total score, if 4 or more questions are missing responses, then the total score will not be calculated. If 1, 2, or 3 questions are missing responses, then the total score will be calculated using the following formula:

- total domain score = ceiling[(sum of responses from non-missing questions)/(# of questions with non-missing responses)] x 8.

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9. GENERAL CONSIDERATIONS

9.1. Analysis Populations

There will be four (4) analysis populations defined for this study.

9.1.1. Modified Intent-to-Treat (mITT) Population

All participants who receive at least one dose of study medication and have at least one post-baseline efficacy assessment will be included in the mITT Population. The mITT Population is the primary analysis population for clinical efficacy. Participants who receive at least one dose of study medication but never have post-baseline assessments will be excluded. Results will be presented "as randomized" unless otherwise noted.

9.1.2. Per-Protocol (PP) Population

The PP Population will be those participants in the mITT Population who had no important protocol deviations and will be the secondary analysis population for analysis of the efficacy data. Results will be presented "as randomized" unless otherwise noted.

9.1.3. Safety Population

All participants who receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety and PD assessments. Results will be presented "as treated" unless otherwise noted.

9.1.4. Pharmacokinetic (PK) Population

The PK Population will consist of all participants who received a dose of vamorolone on Day 1 and had sufficient quantifiable plasma concentration data for PK analysis.

9.2. Covariates and Subgroups

9.2.1. Planned Covariates

Baseline age in years, calculated to 1 decimal place as (date of Baseline visit – birthdate)/365.25, and baseline outcome collected for the various endpoints will be utilized as covariates in the various analyses. Weight and site will also be included in various sensitivity analyses as baseline covariates.

9.2.2. Planned Subgroups

Due to the small sample size, subgroups will not be evaluated.

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9.3. Management of Analysis Data

9.3.1. Data Handling

For the summaries of continuous values and shift tables of laboratory data and ECG data, unscheduled tests will be included with the time of the nearest regularly scheduled test. If there is a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results or a test with abnormal results) will be used, unless on review, the medical monitor determines that the most conservative test result was spurious. Repeated tests will be included only if they reflect abnormal (low or high) results and the corresponding original results are normal.

9.3.2. Missing Data

9.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates
   1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
   2) If the month is unknown, then:
      i) If the year matches the first dose date year, then impute the month and day of the first dose date.
      ii) Otherwise, assign ‘January.’
   3) If the day is unknown, then:
      i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
      ii) Otherwise, assign the first day of the month.

B. Stop Dates
   1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
   2) If the month is unknown, then assign ‘December.’
   3) If the day is unknown, then assign the last day of the month.

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9.3.2.2. Imputation Methods

Unless otherwise specified, observed cases, without imputation, will be used for the analyses.

Adverse Events

Missing adverse event (AE) severity or relationship to study drug will not be imputed and will be summarized as missing in any tabulations.

TTRWV and TTSTANDV

See Section 8.1.2 for details on imputing velocity when a TTRW or TTSTAND response is not collected because the participant is unable to perform the test due to disease progression.

9.3.3. Study Day

Study day will be calculated as the number of days from the first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

The day when the study drug is first administered is designated as Day 1.

9.3.4. Handling of Early Termination Visit Information

If a participant is terminated early from this study the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

9.3.5. Pooling of Study Centers

This clinical trial will be conducted at two sites, one in the United States and one in Italy. Due to the limited sample size, in general, data over the 2 sites will be pooled for analysis, noting exceptions for some sensitivity analyses that include site as a model effect, as detailed elsewhere in this document.

9.3.6. Definition of Baseline

Baseline will be defined as the last available, valid, non-missing assessment prior to the first dose of study drug.

9.3.7. Definition of Change from Baseline

Change from baseline scores will be calculated as the post-baseline measurement minus the baseline value.

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9.3.8. Coding Conventions for Events and Medications

All adverse events and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA® Version 25.0) system for reporting (preferred term and body system).

Prior and concomitant medications will be coded using World Health Organization - Drug Dictionary (WHO-DD) (Version 4.03).

9.3.9. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS® (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

9.3.10. Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.

9.4. Planned Study Analyses

9.4.1. Statistical Summaries: Descriptive and Inferential

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n), mean, SD, median and 1st and 3rd quartiles, and minimum and maximum will be tabulated by treatment. For categorical variables, the counts and proportions of each value will be tabulated by treatment. 95% confidence intervals (CIs) may be provided, where appropriate.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, and 1st and 3rd quartiles, will be displayed to one level of precision greater than the data collected. The SD/standard error will be displayed to two levels of precision greater than the data collected.

All statistical tests will be two-sided at the 0.05 level. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or figures but will be included in the data listings.

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9.4.2. Interim Analyses and Data Monitoring

No formal interim statistical analyses are planned, apart from the interim data views and presentations to be created for the Data Safety Monitoring Board (DSMB).

9.5. Multiple Testing Procedures

Where presented, statistical testing will be carried out at the 0.05 level using two-sided tests without multiplicity adjustments, and nominal p-values will be provided.

9.6. Analysis Windows

For the purposes of data analysis, though the Study Schedule of Assessments indicates assessment windows of +/- 1 week around the scheduled visits at Week 4, Week 12, and Week 24, the SAP will utilize an analysis window of +/- 2 weeks. In other words, data collected within 2 weeks of the scheduled visits at Week 4, 12, and 24, will be included in summaries and analyses described in the SAP.

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10. SUMMARY OF STUDY DATA

10.1. Participant Disposition

The number of participants screened, randomized, and the number and percentage of participants included in each analysis population (mITT, PP, Safety, PK) will be summarized by treatment group and overall. End of trial information will also be summarized, including the number and percentage of participants completing the study and prematurely discontinuing the study with reasons for withdrawal. All percentages will be based on the number of participants that received at least 1 dose of study medication.

Disposition and analysis population data will be provided in by-participant data listings.

10.2. Protocol Deviations

Important protocol deviations, as determined by a Sponsor blinded review of the data prior to database lock and unblinding of the study, may result in the removal of a participant's data from the PP population. The Sponsor or designee will be responsible for producing the final deviation file; this file will include a description of the protocol deviation and clearly identify whether or not each deviation warrants exclusion from the PP population.

All protocol deviations will be presented in a by-participant data listing, with a flag to indicate if a deviation was considered important and resulted in the exclusion of the participant from the PP population. A summary table will be generated for important deviations by protocol deviation category, treatment group, and overall using the mITT population.

10.3. Demographics and Baseline Characteristics

Subject demographic data (age, race, ethnicity) and baseline characteristics (height, ulnar length of the non-dominant arm, weight, body mass index [BMI]) will be tabulated and summarized descriptively by treatment group and overall for the Safety population.

Individual subject demographics and baseline characteristics will be provided in by-participant data listings.

10.4. Medical History

Medical history will be tabulated and summarized descriptively by MedDRA SOC and PT by treatment group and overall using the Safety population.

If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

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BMD history (age when symptoms of BMD were first identified, initial signs or symptoms, time [years] since BMD diagnosis) will be summarized for the Safety population. Time (years) since BMD diagnosis will be calculated as (date of randomization – date of BMD diagnosis +1) ÷ 365.25. Partial dates of BMD first diagnosis date will be handled as follows:

- If only month and year are known: (month/year of randomization – month/year of diagnosis +1) ÷ 12.
- If only year is known: (year of randomization – year of diagnosis +1).

By-participant listings of medical history and BMD history will be generated separately.

10.5. Prior and Concomitant Medications

All medications taken within 3 months prior to the Screening Visit and through Baseline Day -1 (until just prior to the administration of the first dose of study medication) will be considered as prior medications. All medications taken on or after administration of the first dose of study medication will be considered as concomitant medications. Medication that has a start date prior to administration of first dose of study medication and is ongoing after administration of first dose of study medication will be considered both prior and concomitant medication.

The number and percentage of all concomitant medications will be summarized by WHODD Anatomical Therapeutic Chemical (ATC) level 4 and PT. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins) then the drug name will be summarized as the preferred name. The number and percentage of participants with at least 1 concomitant medication will be summarized. Participants may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if they report one or more medications. All summaries will be performed by treatment group and overall using the Safety population.

The number and percentage of prior medications will be summarized similarly to concomitant medications in a separate table.

A by-participant listing of prior and concomitant medications will be generated.

10.6. Treatment Compliance and Exposure

Treatment compliance and exposure will be summarized by treatment group for the Safety population. Descriptive statistics for treatment compliance percentage will be summarized. The summary table will also include number and percentage of participants with overall (Weeks 1-24) treatment compliance 80-120% by treatment group. Treatment compliance is calculated as described in the equations below and following examples:

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Total scheduled dose volume (in mL) is calculated as daily dose volume x days in the dosing interval for each dosing interval (Day 1 through Week 12 and Week 12 through Week 24), using the following conventions:

Daily dose volume calculation for a subject receiving 500 mg/day with a body weight ≥ 50kg:

- Dose level (500.0 mg) ÷ 40 mg/mL = 12.5 mL/day

Daily dose volume calculation for a subject receiving 250 mg/day with a body weight < 50kg:

- Dose level (250.0 mg) ÷ 40 mg/mL = 6.25 mL/day

Note, as in previous vamorolone clinical trials, 1 ml of suspension will be assumed to be equivalent to 1 g of suspension). For each subject, the total suspension administered will be estimated from the total weight of the suspension bottles dispensed and returned (amount dispensed g – amount returned g).

The actual visit dates for Day 1, Week 12, and Week 24 visits will be used to calculate the number of days a subject should have been on a scheduled dose. The dispensed and returned bottle dates will NOT be used as there may be instances where they do not match the visit dates of interest.

As an example, assume a subject weighed < 50 kg at the start of the study and ≥ 50 kg at 12 weeks. This subject was to receive 6.25 mL (6.25 g) every day for the first dosing interval and 12.5 mL (12.5 g) every day for the second dosing interval (the first dosing interval is the actual number of days between the Day 1 visit and the Week 12 visit, inclusive, and the second dosing interval is the actual number of days between the day after the Week 12 visit and the Week 24 visit, inclusive). Assume for this subject the actual number of days in the first dosing interval is 80 and in the second dosing interval is 82. For the Day 1 to Week 12 interval, total scheduled g in the dosing interval = (6.25 mL/day x 80 days) = 500 mL (500g), and for the Week 12 to Week 24 interval, total scheduled g in the dosing interval = (12.5 mL/day x 82 days) = 1025 mL (1025g). The total scheduled g overall is 1525 g.

For illustrative purposes, assume the subject was dispensed 20 bottles (each bottle is filled with 107 mL) which gives the dispensed volume of 2140 mL (2140 g), and returned 500 g. The actual total dose taken = 1640 g (note that treatment compliance will not be calculated if any bottle is not returned or amount returned is not recorded for any bottle).

% Compliance is calculated as actual total dose taken in g ÷ total scheduled g (Day 1 to Week 12 scheduled g + Week 12 to Week 24 scheduled g).

In this example, % compliance is 1640 g ÷ 1525 g = 107.5% (overall compliance).

Descriptive statistics (n, mean, median, 1st and 3rd quartiles, min and max) for total study drug exposure (mg) (Weeks 1 to 24) will be summarized. Total exposure (mg) is calculated as a subject's assigned daily actual total dose taken in mL x 40 mg/mL.

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Dosing compliance data, including a flag to indicate a percentage between 80% and 120%, and total exposure (mg) will also be presented in by-subject listings.

11. EFFICACY ANALYSES

11.1. Secondary

11.1.1. Secondary Endpoints

11.1.1.1. Clinical Efficacy Endpoints

- Change from Baseline to Week 24 in TTRWV
- Change from Baseline to Week 24 in NSAA total score

11.1.2. Secondary Endpoint Analyses

11.1.2.1. Clinical Efficacy Endpoints

11.1.2.1.1. TTRWV

The primary efficacy endpoint (within the overall secondary endpoint/objective for the trial) is change in TTRWV from baseline at week 24 compared between the vamorolone and placebo groups. The key primary hypothesis being tested here is that vamorolone vs. placebo groups will show a statistically significant difference in TTRWV at week 24 at a two-sided alpha of 0.05.

TTRWV at each time point (Baseline, Week 12, Week 24) will be summarized for observed and change from baseline using descriptive statistics by treatment group.

The change from baseline to each time point in TTRWV will be compared between the vamorolone dose group and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). The model will include fixed effects for treatment (vamorolone, placebo), week, treatment-by-week interaction, baseline TTRWV, and baseline age. Study week will be included in the model as a categorical variable (Week 12, 24) along with the treatment-by-week interaction. Within the model, the comparison (using least squares [LS] mean contrasts with associated two-sided 95% confidence intervals and p-values) will be made to compare TTRWV at week 24 for the vamorolone group with placebo. An unstructured covariance matrix will be used, and underlying modelling assumptions will be checked. If this analysis fails to converge, Akaike's information criterion will be used to select the best covariance structure from compound symmetry and autoregressive-1 (AR(1)). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If differences between baseline characteristics exist between the treatment groups, it will be investigated if adjustment for these characteristics is clinically relevant or necessary. This analysis will be carried out using imputed data as described in Section 8.1.2.

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This analysis will also be repeated with baseline weight included as a baseline covariate, as an exploratory investigation of the effect of weight on the dose effect on efficacy.

This analysis may also be repeated with site in the model as a baseline covariate.

This analysis may also be repeated where baseline response is calculated as the arithmetic mean of the screening and baseline assessments (in the situation where a measurement is available at a rescreening visit, the baseline response will be calculated as the arithmetic mean of the rescreening and baseline assessments).

The primary analysis will be based on the mITT population. A supportive analysis will be based on the PP population.

Plots of TTRWV mean +/- standard error by treatment group over time will be presented for observed and change from baseline response using the mITT population and PP population. Additional plots may be generated if deemed useful.

A by-participant listing of TTRWV will be generated.

11.1.2.1.2. NSAA

The secondary efficacy endpoint (within the overall secondary endpoint/objective for the trial) is change in NSAA from baseline at week 24 compared between the vamorolone and placebo groups. The hypothesis being tested here is that vamorolone vs. placebo groups will show a statistically significant difference in NSAA at week 24 at a two-sided alpha of 0.05.

NSAA total score at each time point (Baseline, Week 12, Week 24) will be summarized for observed and change from baseline using descriptive statistics by treatment group.

The change from baseline to each time point in NSAA total score will be compared between the vamorolone dose group and the placebo group using the same modeling approach as is described in the Section 11.1.2.1.1 for TTRWV. The model will include fixed effects for treatment (vamorolone, placebo), week, treatment-by-week interaction, baseline NSAA total score, and baseline age.

This analysis will also be repeated with baseline weight included as a baseline covariate, as an exploratory investigation of the effect of weight on the dose effect on efficacy.

This analysis may also be repeated with site in the model as a baseline covariate.

This analysis may also be repeated where baseline response is calculated as the arithmetic mean of the screening and baseline assessments.

The primary analysis will be based on the mITT population. A supportive analysis will be based on the PP population.

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Plots of NSAA total score mean +/- standard error by treatment group over time will be presented for observed and change from baseline response using the mITT population and PP population. Additional plots may be generated if deemed useful.

A by-participant listing of NSAA data will be generated.

11.2. Exploratory

11.2.1. Exploratory Endpoints

11.2.1.1. Clinical Efficacy Endpoints

- Change from Baseline to Week 12 in TTRWV
- Change from Baseline to Week 12 and Week 24 in TTSTANDV
- Change from Baseline to Week 12 in NSAA total score

11.2.1.2. Patient Reported Outcome Endpoints

- Change from Baseline to Week 24 in NeuroQOL scales for fatigue, mobility (lower extremity function, upper extremity function), and sleep

11.2.2. Exploratory Endpoint Analyses

11.2.2.1. Clinical Efficacy Endpoints

The Week 12 change from baseline in TTRWV and NSAA total score statistical analyses will be derived from the modeling described above in Section 11.1.2 as Week 12 is included in the MMRM modeling.

The Week 12 and Week 24 change from baseline in TTSTANDV will be modeled in the same manner as described for TTRWV and NSAA total score.

11.2.2.2. Patient Reported Outcome Endpoints

Each NeuroQOL scale (fatigue, upper extremity function, lower extremity function, sleep) at each time point (Baseline, Week 24) will be summarized for observed and change from baseline using descriptive statistics for the mITT population by treatment group.

Change from baseline to Week 24 for each of the 4 NeuroQOL scales will be compared between the vamorolone dose group and the placebo group using an ANCOVA model. The model will include fixed effects for treatment (vamorolone, placebo), baseline response, and baseline age. Change from baseline for the vamorolone treatment group will be compared to the placebo treatment group using the LS mean with associated two-sided 95% confidence interval and p-value.

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This analysis will be carried out using total domain scores calculated as described in Section 8.2.1.

This analysis will also be repeated with baseline weight included as a baseline covariate, as an exploratory investigation of the effect of weight on the dose effect on efficacy.

This analysis may also be repeated with site in the model as a baseline covariate.

This analysis may also be repeated where baseline response is calculated as the arithmetic mean of the screening and baseline assessments.

Plots of each NeuroQOL scale mean +/- standard error by treatment group over time will be presented for observed and change from baseline response using the mITT population. Additional plots may be generated if deemed useful.

A by-participant listing of NeuroQOL scale data will be generated.

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12. SAFETY ANALYSES

All safety analyses will be conducted using the Safety population.

12.1. Adverse Events

Tabular summaries of AEs will be provided for those events that are considered treatment emergent (TE), where TE is defined as any AE with onset or worsening on or after the first dose of study drug through the subject's last study visit (study completion or early termination). In general, if a missing/incomplete start date is not clearly prior to initiation of treatment, then the AE will be considered TE. If the AE end date is prior to the initiation of treatment, the AE will not be considered TE.

The number and percentage of participants with any TEAEs will be displayed by SOC and PT. Within each SOC and PT, participants will be counted only once if they had more than one event reported. The number of events will also be reported.

TEAEs will also be summarized by greatest reported severity (severity captured using Common Terminology Criteria for Adverse Events [CTCAE]) for each event PT. Counts indicate participants reporting one or more TEAEs that map to the severity grade classification for each PT. At each level of summarization (SOC or PT) participants are only counted once and the worst severity case of repeated instances of the same TEAE will be used in tabulations. TEAEs will also be summarized by strongest investigator assessment of relationship to study drug in a similar manner.

All TEAEs will be listed individually by subject. In addition, a separate listing will be produced for AEs that are not TE.

An overall summary will display the total number of AEs and the total number of TEAEs, as well as the number and percentage of participants who experience one or more events in each of the following categories:

- Any TEAE
- Any TEAE by CTCAE severity grade
- Any TEAE by relationship to study drug
- Any TE serious adverse event (TESAE)
- Any TEAE with fatal outcome
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to discontinuation of study

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The following summary tables will be presented for TEAE data:

- TEAEs by SOC and PT
- TEAEs by descending incidence of PT
- TEAEs by maximum severity, SOC, and PT
- TEAEs by maximum relationship to study drug, SOC, and PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to discontinuation of study by SOC and PT

Summaries will be presented by treatment group and overall.

12.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

12.2.1. Deaths

All deaths, regardless of causality, will be provided in by-participant listings and written clinical narratives.

12.2.2. Serious Adverse Events

The number and percentage of participants with TESAEs will be displayed by SOC and PT by treatment group and overall. Within each PT, participants will be counted only once if they had more than one TESAE event reported. Similar summaries will also be produced for TESAEs by maximum severity and TESAEs by maximum relationship to study drug.

A by-participant listing will be provided that includes all participants who had a reported TESAE.

12.3. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized descriptively by treatment group and overall for the observed values as well as for the change from baseline values. In addition, laboratory shift summary tables from baseline to each post-baseline visit will be provided for all laboratory parameters where clinical significance (low/normal/high or abnormal/normal) can be ascertained. The following lab parameters will be assessed:

- Hematology, clinical chemistry, urinalysis
- GGT
- CK
- Lipid profile (triglycerides, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL)

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Plots of GGT and CK mean +/- standard error by treatment group over time will be presented for observed and change from baseline response. Additional plots may be generated if deemed useful.

A by-participant listing of all clinical laboratory data will be provided, as well as a separate listing of all abnormal laboratory values.

12.4. Vital Signs

Vital sign results (sitting blood pressure, heart rate, respiration rate, and body temperature) will be summarized descriptively for each treatment group and overall by time point for the observed values as well as for the change from baseline values. Anthropometric data height, ulnar length of the non-dominant arm, weight, and BMI will be summarized in a similar manner.

Plots of BMI mean +/- standard error by treatment group over time will be presented for observed and change from baseline response. Additional plots may be generated if deemed useful.

By-participant listings of all vital sign data and anthropometric data will be provided.

12.5. Physical Examinations

All physical examination results will be included in a by-participant data listing.

12.6. 12-Lead Electrocardiogram (ECG)

ECG results (QRS duration, PR [PQ] interval, RR interval [interbeat interval], QT interval, QTc, and heart rate) will be summarized descriptively for each treatment group and overall by time point for the observed values as well as for the change from baseline values. ECG interpretation will also be summarized by time point.

A by-participant listing of all ECG data will be provided.

12.7. Other Safety Measures

No other safety analyses have been prospectively defined. If, however, after study results are reviewed, or Sponsor recommend additional safety parameters or analyses be completed, they will be fully described and documented in the final clinical study report. The SAP does not need to be amended to complete any other safety measures identified as post-hoc.

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13. PHARMACOKINETIC (PK) ANALYSES

All PK analyses will be detailed in a separate PK analysis plan.

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14. PHARMACODYNAMIC (PD) ANALYSES

Blood will be collected to evaluate the effects of vamorolone on biomarkers of safety associated with insulin resistance (fasting glucose and insulin, hemoglobin A1c) and bone turnover (osteocalcin), and additional exploratory biomarkers. Blood will also be collected to evaluate the effects of vamorolone on biomarkers of efficacy (CD23 and MDC). Saliva samples will be collected to evaluate the effects of vamorolone on biomarkers associated with adrenal suppression (morning cortisol). All evaluations of PD biomarkers will be performed using the Safety Population. All analyses will be performed using the treatment actually received.

All PD biomarkers will be summarized descriptively for each treatment group and overall by time point for the observed values as well as for the change from baseline values.

Plots of PD biomarker mean +/- standard error by treatment group over time will be presented for observed and change from baseline response. Additional plots may be generated if deemed useful.

For the safety PD biomarkers associated with insulin resistance (fasting glucose and insulin, hemoglobin A1c), paired t-tests with associated two-sided 95% confidence intervals and p-values will be used to statistically test if the change from baseline is not equal to 0 at each post-baseline time point, within each treatment group. Additionally, if this data appears log normal, it may be log transformed and the geometric means evaluated.

For the safety PD biomarkers osteocalcin and morning cortisol, the change from baseline at each time point will be compared across the vamorolone dose group and the placebo group using the same modeling approach as is described for the clinical efficacy endpoints (see Section 11.1.2.1.1). This model will include fixed effects for treatment (vamorolone, placebo), week, treatment-by-week interaction, baseline value, and baseline age.

For the efficacy PD biomarkers, CD23 and MDC data will be transformed to a log scale and summarized descriptively for each treatment group and overall by time point for the log observed values as well as for the log change from baseline, calculated as log(post-baseline) – log(baseline). The log change from baseline at each time point will be compared between the vamorolone dose group and the placebo group using the same modeling approach as is described for the clinical efficacy endpoints (see Section 11.1.2.1.1). This model will include fixed effects for treatment (vamorolone, placebo), week, treatment-by-week interaction, baseline value, and baseline age.

A by-participant listing of all PD data will be provided. Additionally, in the listing, biomarker blood samples collected after dosing during the visit will be flagged.

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15. MUSCLE BIOPSY DATA

All muscle biopsy analyses will be detailed in a separate ancillary SAP.

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Certificate Of Completion

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Eric Hoffman, PhD ericphoffman@gmail.com CEO Security Level: Email, Account Authentication (Required)	Signed by: Eric Hoffman, PhD Signer Name: Eric Hoffman, PhD Signing Reason: I approve this document Signing Time: 16-Jun-2025 | 3:55:27 AM PDT 2D4B2107E8EF4D4EBC2CA800BEA57CEF Signature Adoption: Pre-selected Style Signature ID: 2D4B2107-E8EF-4D4E-BC2C-A800BEA57CEF Using IP Address: 24.142.44.128 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 11 June 2025 | 13:17 Viewed: 16 June 2025 | 04:55 Signed: 16 June 2025 | 04:55
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Utkarsh Dang, PhD UtkarshDang@cunet.carleton.ca Security Level: Email, Account Authentication (Required)	Utkarsh Dang, PhD Signature Adoption: Pre-selected Style Signature ID: CAF6D9D1-2316-4EBB-B048-A9C26D5B617B Using IP Address: 174.95.10.169 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 11 June 2025 | 13:17 Viewed: 16 June 2025 | 05:08 Signed: 16 June 2025 | 05:09
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Signer Events	Signature	Timestamp
Philip Shale, PhD pshale@summitanalytical.com Director, Biostatistics Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 011B3204-338E-4B32-8A86-D28A99BF3322 Using IP Address: 76.93.152.184 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I am the author of this document	Sent: 16 June 2025 I 05:10 Viewed: 16 June 2025 I 09:46 Signed: 16 June 2025 I 09:48
Electronic Record and Signature Disclosure: Accepted: 16 June 2025 I 09:46 ID: 7cac9b85-23eb-443d-96ff-a5ebfd727f91		
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