ReveraGen BioPharma, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase II Open-label, Multicenter Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)
Protocol Number	VBP15-003
Phase:	Phase II
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SUMMITANALYTICAL	**Statistical Analysis Plan Approval Form**

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SAP Version:
SAP Date:

The statistical analysis plan has been reviewed and approved.

Sponsor: *ReveraGen BioPharma, Inc.*
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Signature _____ Date 31 July 2018

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1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. 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.

ACTH	adrenocorticotropic hormone
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BL	baseline
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C	celsius
CD23	cluster designation 23
CDC	Centers for Disease Control and Prevention
CINRG	Cooperative International Neuromuscular Research Group
CK	creatine kinase
cm	centimeter
CTCAE	Common Terminology Criteria for Adverse Events
CTX	carboxy-terminal telopeptide
DHEA	dehydroepiandrosterone
dL	deciliter
DMD	Duchenne muscular dystrophy
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
F	fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice

HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
hr	hour
ICF	informed consent form
ICH	International Conference on Harmonisation
IGFBP-2	insulin-like growth factor-binding protein 2
IGFBP-5	insulin-like growth factor-binding protein 5
IL-22BP	interleukin-22 binding protein
IND	Investigational New Drug
IRB	Institutional Review Board
L	liter
LLC	Limited Liability Company
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LS	least squares
m	meter
MAD	multiple ascending dose (study)
MD	medical doctor (physician)
MDC	macrophage-derived chemokine
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
MIST	Metabolites in Safety Testing
mL	milliliter
MMP-3	matrix metalloproteinase-3
MMP-12	matrix metalloproteinase-12
MMRM	mixed model for repeated measures
MTD	maximum tolerated dose
ng	nanogram
No., n	number
nmol	nanomole
NSAA	North Star Ambulatory Assessment
%CV	percentage coefficient of variation
PD	pharmacodynamic(s)

P1NP	serum aminoterminal propeptide of type I collagen
PK	pharmacokinetic(s)
PODCI	Pediatric Outcomes Data Collection Instrument
PR [PQ]	time from onset of P wave to start of the QRS complex
QMT	quantitative muscle testing
QRS	in electrocardiography, the complex consisting of Q, R, and S waves, corresponding to depolarization of ventricles [complex]
QT	in cardiology, the time between the start of the Q wave and end of the T wave
QT_c	corrected QT interval
QTcF	QT corrected for HR using Fridericia's method
6MWT	Six-minute Walk Test
REML	restricted maximum likelihood
RR	in electrocardiography, the interval between successive Rs (peaks of QRS complexes)
SAD	single ascending dose (study)
SAE	serious adverse event
SAP	statistical analysis plan
SCR	screening
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TTCLIMB	Time to Climb (Test)
TTSTAND	Time to Stand (Test)
TTRW	Time to Run/Walk (Test)
ULN	upper limit of normal
US	United States
vs.	versus
WBC	white blood cell
WHO	World Health Organization

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for ReveraGen BioPharma, Inc. Protocol VBP15-003, (*A Phase II Open-label, Multicenter Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)*). This SAP will provide the details and methods for analysis and reporting of the subject characteristics, safety, and efficacy information.

Reference materials for this statistical plan include the protocol VBP15-003 (Revision #2 Dated: 22 February 2017) and Case Report Forms (Version 1.0).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

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

3.2. Purpose of Analyses

The purposes of the planned analyses described in this SAP are to assess the long-term safety, tolerability, clinical efficacy, and pharmacodynamics (PD) of vamorolone at dose levels up to 6.0 mg/kg administered daily by liquid oral suspension over a Treatment Period of 24 weeks to boys ages 4-7 years with DMD. Results from the analyses completed will be included in the final clinical study report for VBP15-003, and may also be utilized for regulatory submissions, manuscripts, additional endpoint specific reports, or other clinical development activities. Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data and provide context for study results. 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, additional endpoint specific reports, 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.

3.3. 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 with the exceptions noted below.

Change of Baseline comparator:

In the VBP15-003 Protocol Synopsis, General Statistical Considerations, it is stated "Baseline measurement is defined as the last non-missing value prior to the first dose of study drug in the extension study." In this VBP15-003 SAP, we have changed the baseline comparator to the Baseline visit of the preceding study (VBP15-002), with the exception of the PODCI, which is not collected in the VBP15-002 trial and whose baseline comparator is therefore the Baseline visit of the VBP15-003 trial. The rationale for this is as follows. All subjects enrolled in this study (VBP15-003) were recruited from a previous study (VBP15-002). VBP15-002 was a multiple-ascending dose, 2-week treatment, 2-week washout study, and all subjects maintained on the same dose level in VBP15-003 as they received in VBP15-002. During the conduct of the VBP15-002 trial, nearly all subjects (46/48) had the last visit of VBP15-002 commensurate with the first visit of VBP15-003. As all subjects had received drug treatment for two weeks in VBP15-002, the short period of time between baseline in VBP15-002 and measures in VBP15-003 led the study staff to change the baseline comparator to the Baseline visit of the preceding trial, VBP15-002.

External Comparator Databases:

The Cooperative International Neuromuscular Research Group (CINRG) was established in 2000 to enable robust clinical studies and clinical trials in pediatric neuromuscular disease via an international academic network with central coordinating center (Escolar et al. 2002). The CINRG group has become the leading neuromuscular clinical trial network, establishing outcome measures and training programs for clinical evaluators, and has recruited over 1,400 subjects into studies over the last 15 years (Bello et al. 2015, 2016a, 2016b; McDonald et al. 2018). From 2000 - 2015 the CINRG Coordinating Center was housed at Children's National Medical Center. In 2016, the CINRG Coordinating Center spun off into a stake holder owned and led company, TRiNDS LLC (www.trinds.com).

The CINRG group carried out the vamorolone Phase 2 studies VBP15-002 and VBP15-003, using established outcome measures, and well-trained evaluators and recruitment sites.
In communications with the FDA and EMA, and in developing the design of the vamorolone clinical trials, two previous CINRG studies were used to carry out sample size calculations for different outcome measures. These were:

- CINRG Prednisone-treated comparator
    - Publication: Escolar DM, Hache LP, Clemens PR, Cnaan A, McDonald CM, Viswanathan V, Kornberg AJ, Bertorini TE, Nevo Y, Lotze T, Pestronk A, Ryan MM, Monasterio E, Day JW, Zimmerman A, Arrieta A, Henricson E, Mayhew J, Florence J, Hu F, Connolly AM. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology. 2011 Aug 2;77(5):444-52.

  - Design: 64 steroid naïve DMD boys, ages 4 to <10 years, randomized to either daily or high dose weekend prednisone, 12 month treatment period
  - **Subset used in vamorolone studies:** We limited analysis to the subset with the same inclusion/exclusion criteria as the vamorolone studies (ages 4 to <7 years) on daily prednisone (0.7 mg/kg/day), comparing the 12-week and 24-week time points to the corresponding vamorolone trial time points.
- CINRG Steroid-naïve natural history comparator (Duchenne Natural History Study; DNHS)
  - Publication: McDonald CM, Henricson EK, Abresch RT, Han JJ, Escolar DM, Florence JM, Duong T, Arrieta A, Clemens PR, Hoffman EP, Cnaan A; CINRG Investigators. The cooperative international neuromuscular research group Duchenne natural history study--a longitudinal investigation in the era of glucocorticoid therapy: design of protocol and the methods used. Muscle Nerve. 2013 Jul;48(1):32-54.
  - Design: This is a natural history study that recruited 440 DMD children and 100 healthy peers over a period of 10 years (**Figure 1**). The outcome measures collected depended on the subject's age.
  - **Subset used in vamorolone studies:**
    - **Time to Stand (TTSTAND), Time to Climb (TTCLIMB), Time to Run/Walk (TTRW), and Quantitative Muscle Testing (QMT) endpoints (muscle strength testing):** A data cut from 2015 that was the same used for sample size calculations for the design of the vamorolone study was used in this SAP. This same data cut was also used in regulatory documents for the FDA and EMA. Note that only subjects who remained steroid-free through 24 weeks of the study were included.
    - **6-minute Walk Test (6MWT) and North Star Ambulatory Assessment (NSAA):** The original CINRG DNHS protocol did not include 6MWT or NSAA as outcome measures. These outcomes were added later in the study (**Figure 1**) and were not used for sample size calculations or in FDA or EMA communications in the Phase 1 – 2 transition meeting. In 2012, the CINRG DNHS protocol was amended to begin collection of 6MWT and NSAA outcomes. As noted below, however, comparisons to vamorolone data on these two endpoints were not done.

Efficacy Analyses:

The primary comparisons for efficacy will be between each of the 4 vamorolone dose groups and the historical untreated controls (CINRG DNHS). Additional exploratory analyses have been added and will include pairwise comparisons between the 4 vamorolone dose groups

within the VBP15-003 trial (0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg) for TTSTAND velocity and raw, TTRW velocity and raw, TTCLIMB velocity and raw, 6MWT, NSAA total score, and QMT. These comparisons (pairwise contrasts) will be added to the mixed model for repeated measures (MMRM) analysis used for each variable. Vamorolone dose groups will not be combined for any analyses.

Also, the VBP15-003 protocol indicates that 6MWT and NSAA results will be compared to the historical untreated controls (CINRG DNHS). The CINRG DNHS protocol enrolled DMD subjects from 2005-2014. The original CINRG DNHS protocol did not include 6MWT or NSAA as outcome measures. In 2012, the CINRG DNHS protocol was amended to begin collection of 6MWT and NSAA outcomes. Thus, while CINRG DNHS carried out subject assessments for 9 years for other outcomes (TTSTAND, TTRW, TTCLIMB, and QMT), only two years included 6MWT and NSAA assessments. The number of subjects and assessments in this narrow time window were insufficient to use as a comparator for these two outcome measures, and thus comparisons to vamorolone data were not done.

The VBP15-003 protocol also indicates that the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. prednisone-treated historical controls, on serum pharmacodynamic (PD) biomarkers of safety (insulin resistance, adrenal axis suppression, and bone turnover) will be investigated, as will vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. untreated historical controls, on serum PD biomarkers of efficacy (inflammatory protein suppression). These comparisons will not be carried out in this SAP as PD biomarker data were not collected in either of the CINRG DNHS or CINRG prednisone-treated cohort comparator studies.

SomaScan data, if available, will be presented in an addendum report.

Proteomics profiling data will be collected for potential analysis in future studies. These data will not be included in any by subject listing or in the CSR for this study. Any analysis of the proteomics profiling information will be reported in separate reports.

Serum creatine kinase will be analyzed as an exploratory efficacy biomarker.

Safety Analyses:

The protocol states, “The primary safety variable will be BMI z-score and will be assessed using the same type of statistical models used for efficacy.” This SAP has been revised to make it clear that the BMI z-score comparator group will be the prednisone-treated subjects from the CINRG prednisone trial.

Analyses of additional secondary safety data are as described in the protocol but will use Baseline of VBP15-002 for all baseline comparisons. GLDH has been added as an exploratory clinical chemistry analyte for liver damage.

Height z-scores will not be analyzed, ANCOVA models will not be utilized for vital signs and ECG endpoints, linear modelling will not be utilized for any other safety variables, and AE rates will not be compared using exact tests.

Ancillary Study:

Ancillary MS Band Study was not performed and is not included in the study analyses.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety, tolerability, clinical efficacy, and PD. These protocol listed objectives and pre-specified endpoints are as follows:

4.1. Study Objectives

4.1.1. Primary Objective

- To evaluate the long-term safety and tolerability of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period, in boys ages 4-7 years with DMD;

- To compare the efficacy, as measured by the Time to Stand Test (TTSTAND), of vamorolone administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. untreated DMD historical controls in boys ages 4-7 years with DMD; and

- To compare the safety, as measured by body mass index (BMI) z-score, of vamorolone administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. prednisone-treated historical controls in boys ages 4-7 years with DMD.

4.1.2. Secondary Objectives

- To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. prednisone-treated historical controls, on serum pharmacodynamic (PD) biomarkers of safety (insulin resistance, adrenal axis suppression, and bone turnover);

- To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. untreated historical controls, on serum PD biomarkers of efficacy (inflammatory protein suppression); and

- To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period, on muscle strength, mobility and functional exercise capacity vs. historical controls as measured by Quantitative Muscle Testing (QMT), Time to Run/Walk Test (TTRW), and Time to Climb Test (TTCLIMB). in boys ages 4-7 years with DMD.

4.1.3. Exploratory Objectives

- To investigate the effects of vamorolone administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period on an extended panel of PD biomarkers using SomaScan aptamer arrays, and proteomic profiling.

4.2. Study Endpoints

4.2.1. Primary Endpoints

Primary endpoints from the protocol include the following:

- Safety: BMI z-score: Comparison with a prednisone-treated historical control group for change from baseline to Week 24.

- Clinical Efficacy: TTSTAND velocity (rise/second): Comparison with an historical natural history (untreated) control group for change from baseline to Week 24.

4.2.2. Secondary and Additional Endpoints

Secondary and additional endpoints from the protocol include the following:

- Safety
    - BMI z-score: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
    - Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC): Overall by treatment, by treatment and relationship, and by treatment and intensity.
    - Vital signs [blood pressure, heart rate, respiratory rate, 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 (hematology and biochemistry): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
    - Glutamate dehydrogenase (GLDH): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
    - Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
    - Urinalysis by dipstick and microscopic analysis: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.

  - 12-lead electrocardiogram (ECG): Clinical assessment and shift from baseline to each of the scheduled on-treatment and post-treatment assessment time points.

- Clinical Efficacy
  - TTSTAND velocity (rise/second) and seconds: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
  - TTRW seconds and velocity: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
  - TTCLIMB seconds and velocity: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
  - NSAA: Change in timed assessments and total score from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
  - QMT: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
  - Total distance traveled, in meters, in completing the 6MWT: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points.
- PD
  - Concentrations of serum PD biomarkers: osteocalcin, adrenocorticotropic hormone (ACTH), insulin, glucose, 17-hydroxyprogesterone, carboxy-terminal telopeptide (CTX), serum aminoterminal propeptide of type I collagen (P1NP), cortisol, testosterone, corticosterone, 11-deoxycortisol, and hemoglobin A1c (HbA1c)

4.2.3. Exploratory Endpoint

- Levels of an extended panel of exploratory PD biomarkers are out of scope of the SAP and may be reported as addendum reports.

4.2.4. Endpoints for Subject Reported Outcomes

- Assessment of acceptability of vamorolone by a 5-point hedonic scale.
- Pediatric Outcomes Data Collection Instrument (PODCI).

5. STUDY METHODS

5.1. 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 extension study is an open-label, multicenter study to evaluate the long-term safety, tolerability, clinical efficacy, and PD of vamorolone at dose levels up to 6.0 mg/kg administered daily by liquid oral suspension over a Treatment Period of 24 weeks to boys ages 4-7 years with DMD.

The study is comprised of a Pretreatment Baseline Period of up to 24 hours in duration, which begins at the signing of the VBP15-003 study-specific informed consent, a 24-week Treatment Period, and a 2- to 5-week Dose-tapering Period for subjects who elect to transition off vamorolone treatment at the end of the study. Only subjects who have completed study VBP15-002 Week 4 Follow-up Visit assessments will be eligible for participation in this open-label VBP15-003 extension study. Each subject will retain the study identification number assigned to him at the start of the VBP15-002 study.

Subjects will begin dosing in this study on Study Day 1 at the same vamorolone dose level they received in VBP15-002. Subjects will continue to receive vamorolone at the dose received in VBP15-002 for the duration of the 24-week Treatment Period, unless new safety data indicate the dose level should be de-escalated. The planned dose levels are 0.25 mg/kg (Dose Level Group 1), 0.75 mg/kg (Dose Level Group 2), 2.0 mg/kg (Dose Level Group 3), and 6.0 mg/kg (Dose Level Group 4) (Table 1). Approximately 12 subjects may be eligible for extension study dosing at each of the dose levels tolerated in the VBP15-002 study.

Table 1: Dose level group composition

Planned Dose Level Group	No. Subjects in Dose Level Group	Vamorolone Dose
1	12	0.25 mg/kg
2	12	0.75 mg/kg
3	12	2.0 mg/kg
4	12	6.0 mg/kg

Table 2 presents the schedule of study activities.

Table 2 **Schedule of Study Activities**

	Pretreatment Period	Treatment Period							Dose-tapering Period
	Baseline								
	Day	Week							
Study Day or Week/Visit	**-1[a]**	**1[b]**	**2 (±1d)**	**4 (±2d)**	**8 (±5d)**	**12 (±1w)**	**16 (±1w)**	**20 (±1w)**	**24[c] (±1w)**	**26-29[d] (±1w)**
Inclusion/Exclusion Criteria	X									
Informed Consent	X[e]									
Enrollment	X									
Interim Medical History	X[f]									
Medication History	X[g]									
Physical Examination	X[h]								X	
Height	X					X			X	
Weight	X			X	X	X	X	X	X	
Vital Signs[i]	X		X	X	X	X	X	X	X	X
Blood for Clinical Labs[j]	X[h]			X	X		X		X	X
Urinalysis[k]	X[h]			X	X		X		X	
Blood for Serum PD Biomarker Panel[l]	X[h]				X		X		X	X
Fasting blood for insulin, glucose[m]						X			X	
12-lead ECG[n]	X[h]					X			X	
Dispense Study Medication	X					X			X[o]	
Return Study Medication/ Compliance Monitoring				X	X	X	X	X	X	X
Study Medication Dosing[p]		X	→	→	→	→	→	→	X	
Vamorolone dose tapering[q]										X
Time to Stand Test (TTSTAND)	X[h]					X			X	
Time to Climb Test (TTCLIMB)	X[h]					X			X	
Time to Run/Walk Test (TTRW)	X[h]					X			X	
NSAA[r]	X[h]					X			X	

Quantitative Muscle Testing (QMT)	X[h]					X			X	
Six-minute Walk Test (6MWT)	X[h]					X			X	
Pediatric Outcomes Data Collection Instrument	X					X			X	
Study Medication Acceptability Assessment[s]						X			X	
Dispense Subject Diaries[t]	X			X	X	X	X	X	X[p]	
Return Subject Diaries			X	X	X	X	X	X	X	X
AE/SAE Recording[u]	X →	→	→	→	→	→	→	→	X	X
Concomitant Medications		X	→	→	→	→	→	→	X	X
Discharge from Study									X[v]	X[w]

d = day(s); w = week.

a. Baseline Day -1, within 24 hours prior to administration of the first dose of study drug. The Baseline Visit for Study VBP15-003 can coincide with the final Week 4 Follow-up Visit for Study VBP15-002 or occur up to 8 weeks after the date of the VBP15-002 Week 4 Visit.
b. Treatment Day 1 begins at the time of administration of the first dose of VBP15-003 study medication at home. No scheduled study visit will occur on Day 1.
c. Subjects who prematurely discontinue from the study prior to Week 24 should complete the Week 24 assessments at the time of early discontinuation.
d. All subjects EXCEPT those who elect to continue vamorolone therapy in a further extension study must continue in the Dose-tapering Period and have their vamorolone dose tapered at weekly intervals over a 1-4 week period prior to discharge from this study. Subjects participating in the Dose-tapering Period will have one study site visit during this period, at the end of dose tapering (Weeks 25-29).
e. Informed Consent for this extension study may be obtained at the Study VBP15-002 Week 4 Follow-up Visit, after completion of all final VBP15-002 study assessments and prior to any extension study-specific procedures.
f. Interim Medical History will be collected on Baseline Day -1 for all subjects, and will include any AEs that occurred during the VBP15-002 core study and are ongoing at the time of entry into VBP15-003.
g. Any changes in medication/therapy including administration of new medication(s), change of dose, or discontinuation of medication after completion of the VBP15-002 core study and prior to administration of the first dose of study medication in VBP15-003 will be captured as Prior Medications.
h. If the Baseline Day -1 Visit occurs ≤ 28 days after the date of the final VBP15-002 core study Week 4 Visit, these assessments do not need to be repeated for the VBP15-003 study. Clinical laboratory and urinalysis test results from the VBP15-002 Week 2 or Week 4 Visit (whichever is available and later) may be used and should be reviewed by the Site Investigator to determine eligibility for Baseline Day -1 enrollment into the extension study.
i. Supine blood pressure, oral temperature, respiratory rate, and heart rate.
j. Blood for hematology, chemistry, and lipids.
k. Urinalysis by dipstick and microscopic analysis.
l. Blood collected for cortisol, P1NP, osteocalcin, 17-hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, CTX, ACTH, HbA1c (not collected at Baseline), SomaScan, and proteomic testing.
m. Blood will be collected for insulin and glucose determination in the morning after subjects have fasted for ≥ 6 hours, prior to the daily dose of study medication.
n. ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.
o. Only for subjects who will participate in the Dose-tapering Period.

p. The dose of study medication on the days of the Week 12 and Week 24 Visits will be administered after 1) a fasting blood draw for insulin and glucose; and 2) breakfast provided by the study site. All other doses will be taken at home.
q. Subjects who elect to switch to standard of care glucocorticoids, or discontinue vamorolone and not begin glucocorticoid treatment for DMD at the end of the study will have their vamorolone dose tapered at weekly intervals to a dose of 0 mg/kg/day prior to final study assessments.
r. North Star Ambulatory Assessment; includes the Time to Stand Test (TTSTAND).
s. Study medication acceptability assessed immediately before (smell) and after (taste) dosing at the Week 12 and Week 24 Visits.
t. Subject diaries used to record any concomitant medications taken and any AEs experienced during the study.
u. All AEs and SAEs must be collected in the source documents and eCRF from the date of the subject's written informed consent until the Week 24 Visit or the subject's participation in the study is completed. Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator agrees follow-up is not necessary.
v. Subjects who elect to continue vamorolone therapy in a subsequent extension study may be discharged from the study following completion of all final Week 24 procedures.
w. Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments.

5.2. Inclusion – Exclusion Criteria and General Study Population

All subjects who complete the Week 4 Follow-up assessments in the VBP15-002 study will be eligible for enrollment in this VBP15-003 study, provided they meet all VBP15-003 study entry criteria (up to 48 subjects total). The inclusion and exclusion criteria defined in the protocol apply to all subjects and are not repeated here in the SAP.

5.3. Randomization and Blinding

This is an open-label study, and no randomization schedule or blinding of study medication is applicable. In the VBP15-002 study, subjects were assigned to dosing cohort sequentially on enrollment and screening.

5.4. Analysis Variables

Variables to be analyzed include demographics and baseline characteristics, safety variables, clinical efficacy variables, PD variables, etc. as described throughout this SAP. Derived variables from study endpoints are described with the sections presenting the analyses for these endpoints.

Unless otherwise noted, baseline is defined as the last measurement taken prior to first exposure to study drug (Baseline visit of VBP15-002).

6. SAMPLE SIZE

Eligible subjects are those who enrolled in the VBP15-002 study and have completed up to and including the VBP15-002 Follow-up Week 4 study assessments, up to approximately 48 subjects (n=12 per vamorolone dose group). The VBP15-003 trial is carried out with daily dosing. The comparator group for efficacy consisted of 31 subjects from the CINRG DNHS study who met all entry criteria of VBP15-003 and remained untreated through a 24-week period. The comparator group for safety consisted of 14 subjects who met the entry criteria of VBP15-003 and received daily prednisone therapy in the CINRG prednisone trial.

The primary pharmacological safety outcome proposed in the VBP15-003 trial is change in BMI z-score. Daily glucocorticoids show a relatively rapid increase in BMI z-score (6 month change in non-treated = -0.14; 6 month change in prednisone-treated = +0.54). Vamorolone is not anticipated to show an increase in BMI.

See Section 9.1 of the protocol for full details.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

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

7.1.1. Safety Population

All subjects who receive at least one dose of vamorolone study medication in the VBP15-003 study will be included in the Safety Population. The Safety Population is the primary analysis population for safety and PD assessments. This is also the modified Intention to Treat (mITT) population.

7.1.2. Full Analysis Set (FAS)

All subjects who receive at least one dose of vamorolone study medication in the VBP15-003 study and have at least one post-baseline assessment will be included in the FAS. The FAS is the primary analysis population for efficacy assessments. This is the mITT population, with the additional requirement to have at least one post-baseline assessment. Subjects who receive at least one dose of vamorolone but never have post-baseline assessments will be excluded.

7.1.3. Control Population DNHS Study

The control population from the DNHS study will include all study subjects who were observed as part of the study in ages ≥ 4 years and <7 years of age at a start of an interval of observation and observed for at least one year. Further, the subjects need to have had at least two visits in a time interval of no more than 15 months (e.g., Month 24 and Month 36 of observation for a subject who entered at age 2 or 3). The subject should have been able to walk independently without assistive devices at the start of the interval and should have been able to complete the TTSTAND. The subject should not have had any history of disease or impairment or medications that would have made him ineligible to receive the vamorolone intervention as defined by the VBP15-002 and VBP15-003 study exclusion criteria. The subject should have been glucocorticoid-naïve for the entire interval considered in the control population for this study and should not have begun any investigational treatment for the interval considered for the control comparison. Finally, the control intervals to be considered should have the study outcomes of TTSTAND, TTCLIMB, TTRW, and QMT measured. It is acceptable if the participant had progressive disease and could not perform a measurement at a later point in the interval; this will be imputed as a velocity zero for TTSTAND, TTCLIMB, and TTRW.

7.1.4. Control Population Prednisone Study

The control population from the prednisone study will include all subjects who were 4 to <7 years at entry and who were randomized to the daily prednisone arm at the low (daily) dose level.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Baseline response will be included in the MMRM statistical analyses of BMI.

Baseline age and response will be included in the MMRM statistical analyses of efficacy endpoints. For the vamorolone subjects, age is calculated as (date of informed consent – birthdate)/365.25. For the prednisone and DNHS subjects, age is calculated as (date of Baseline visit used in this study – birthdate)/365.25. Note that the Baseline visit for a DNHS subject is the first visit that the subject meets the comparison eligibility criteria and has a non-missing response for at least one endpoint of interest.

7.2.2. Planned Subgroups

None.

7.2.3. Post hoc Subgroups

No post-hoc subgroups are initially planned for this study. However, after all planned analyses are completed additional post-hoc subgroups may be defined to further explore study results. Any additional post-hoc subgroups will be fully detailed in the final CSR.

7.3. Management of Analysis Data

7.3.1. Data Handling

For the summary of continuous values and laboratory shift tables, 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) will be used. Repeated tests will be included only if they reflect abnormal (low or high) results and the corresponding original results are normal. All laboratory values, for all visits, will be provided in by-subject listings.

Scheduled visits will be utilized for all analyses for data collected in the VBP15-003 study. The historical control data will be handled as follows:

CINRG DNHS (historical untreated controls): TTSTAND, TTRW, TTCLIMB using scheduled visits (baseline, 3 months (used for Week 12), and 6 months (used for Week 24)).

CINRG Prednisone trial: BMI z-score using scheduled visits (baseline, 3 months (used for Week 12), and 6 months (used for Week 24)).

7.3.2. Missing Data

Every effort will be made to collect all data. However, despite best efforts, missing or incomplete data may be reported. All missing or partial data will be presented in the subject data listing, as they are recorded on the eCRF.

Subjects lost to follow-up or withdrawn will be included in statistical presentations up to the point of their last evaluation. Unless otherwise specified, in general no imputation of values for missing data will be performed.

7.3.2.1. Handling of Missing Date Values

Partial or Missing Dates/Times

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.

For AEs, partial or missing times will be imputed in the following manner:

A. Start Times
   1) Day 1:
      i) If hour is missing on the CRF, hour will be imputed as hour of the first dose.
      ii) If minute is missing on the CRF, minute will be imputed as minute of the first dose.
      iii) If hour is missing for both start of the AE and for the time of the first dose on the CRF, hour will be imputed as 23.
      iv) If minute is missing for both start of the AE and for the time of the first dose on the CRF, minute will be imputed as 59.

   2) Study days other than Day 1:
      i) If hour is missing on the CRF, hour will be imputed as 00.
      ii) If minute is missing on the CRF, minute will be imputed as 00.

B. Stop Times
   1) If hour is missing on the CRF, hour will be imputed as 23.
   2) If minute is missing on the CRF, minute will be imputed as 59.

7.3.2.2. Imputation Methods

Velocity scores for TTSTAND, TTRW, and TTCLIMB will be imputed as 0 only at the first response missing due to disease progression and left missing for the remaining study visits.

Local lab responses that are missing a normal flag may have it imputed for by-subject listings.

All other data will be observed cases only, without imputation.

7.3.3. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study, the early termination (ET) 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. In instances where the next scheduled visit is too far in the future, from a clinical perspective, analyses may be presented

twice, once with the ET observation assigned to the next available visit, and once with the ET observation omitted.

7.3.4. Pooling of Investigational Sites

The data from all study centers will be pooled together for analyses.

7.3.5. Coding Conventions for Events and Medications

All adverse events, and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA version 19.0) system for reporting (preferred term and system organ class).

Prior and Concomitant medications will be coded using World Health Organization (WHO) Drug classification (Version June 1st, 2017).

7.3.6. Baseline Visits

Baseline for endpoints is defined as VBP15-002 Baseline or Screening Assessment, whichever is closer to the first dose of study medication in VBP15-003: physical exam (VBP15-002 Screening); vital signs (VBP15-002 Baseline); height (VBP15-002 Screening), weight and BMI (VBP15-002 Baseline); blood for chemistry, hematology, lipids (VBP15-002 Screening); urinalysis by dipstick and microscopic analysis (VBP15-002 Screening); 12-lead ECG (VBP15-002 Screening); PD biomarkers (VBP15-002 Baseline); and timed function tests (QMT, TTRW, TTSTAND, TTCLIMB, NSAA, and 6MWT) (VBP15-002 Baseline). Pediatric Outcomes Data Collection Instrument will use the baseline from the VBP15-003 study as these data were not collected in VBP15-002.

7.3.7. Analysis Software

Data manipulation, tabulation of descriptive 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.

7.3.8. Study Data

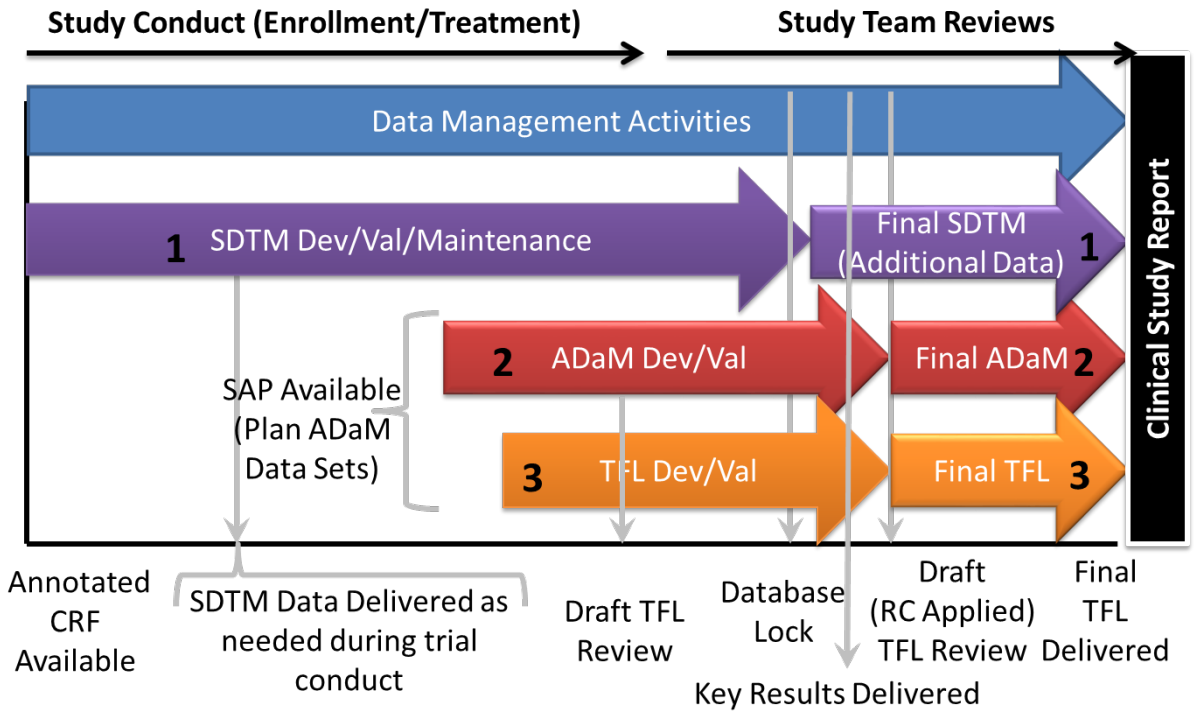
Study data identified in the schedule for time and events (Table 2) are collected, and source verified, on the electronic data capture tool OpenClinica v3.13. Laboratory data, including PD test results, are not collected in the EDC tool and are provided from external laboratories.

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 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.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, Validation, and Maintenance of SDTM domains
2. Development and Validation of Analysis Data Sets (ADaM), with input source the appropriate SDTM domains.
3. Development and Validation of draft and then final Tables, Figures, and Listings (TFL), with input data source the SDTM domains and analysis specific ADaM data sets and randomization code (RC) applied.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

All statistical tests will be two-sided and a resultant p-value of less than or equal to 0.05 will be considered statistically significant. 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.

Descriptive summaries of variables will be provided where appropriate. In general, for continuous variables, the number of non-missing values (n) and the mean, standard deviation, median, minimum, and maximum will be tabulated. For categorical variables, the counts and proportions of each value will be tabulated.

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

7.4.2. Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

The DSMB will meet at regular intervals to review all pertinent safety data. The DSMB may request summaries at other points in time. In addition, the Medical Monitor may request at any time that the DSMB review safety data if the Medical Monitor has specific concerns.

In all cases, data will be compiled by the Coordinating Center and presented to the DSMB in a format that allows for complete review of all compiled safety data. The DSMB can recommend to the Sponsor altering or terminating the trial for safety or other study integrity-related issues.

The primary safety endpoints that the DSMB will review are safety labs and adverse events. Refer to the DSMB charter for complete details. Analysis and reporting of safety endpoint information is specified in the DSMB Charter, and not repeated herein. Note that all DSMB reports will be included in the final CSR.

7.4.3. Final Analysis

The final study analysis will be completed following complete enrollment and the database locked after all subjects have completed their final follow-up assessments. Subjects who prematurely discontinue from the study prior to Week 24 should complete the Week 24 procedures at the time of early discontinuation and enter the 4-week Dose-tapering Period.

7.5. Multiple Testing Procedures

No adjustments for multiplicity on inferential statistics will be presented in this SAP.

8. SUMMARY OF STUDY DATA

8.1. Subject Summary Grouping

In general, and unless otherwise noted, summaries of VBP15-003 data will be presented by study cohort: Dose Group 1 0.25 mg/kg/day, Dose Group 2 0.75 mg/kg/day, Dose Group 3 2.0 mg/kg/day, or Dose Group 4 6.0 mg/kg/day. Data from the untreated and prednisone-treated DMD historical control studies will be presented in separate columns when the data align with the VBP15-003 data.

8.2. Subject Disposition

The number of subjects at each cohort dose level, and the compliance and completion rates of dosing at each dose level will be summarized. The number of discontinuations (if any) and reason for discontinuation will be summarized by dose level group.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

8.3. Protocol Deviations

A summary listing of protocol deviations will be provided by dose level group and by study site.

All protocol deviations will be presented in a by-subject data listing.

8.4. Demographics and Baseline Characteristics

Subject demographics (age, race, and ethnicity) and baseline characteristics (height, weight, body mass index [BMI] and BMI percentile (see Appendix13.4 for a description and example of BMI percentile calculation given BMI score; see Centers for Disease Control and Prevention [CDC] webpage https://www.cdc.gov/growthcharts/percentile_data_files.htm for a detailed discussion on the derivation of the computational algorithm), and months/years since DMD diagnosis) are collected in VBP15-002 and will be displayed descriptively from this preceding study.

All demographic and baseline information will be listed by subject.

8.5. Medical History

Subject medical, surgical, medication and treatment history were collected during the screening phase for the VBP15-002 study; interim medical history will be collected on Day -1 of the VBP15-003 study and will be merged with the initial VBP15-002 medical history data. The dates and descriptions of past events will be documented in source

documents and captured in the relevant eCRF. Medical history will be coded using the MedDRA (version 19.0).

Subject medical history data will be presented in a by-subject listing.

8.6. Prior and Concomitant Medications

A categorical summary of all prior and concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name (brand name where generic name is unavailable) using the World Health Organization (WHO) Drug classification (June 1st, 20a7).

All prior and concomitant medications will be detailed in the subject data listings.

A concomitant medication is defined as any medication taken on or after the day of first exposure to study drug in the VBP15-003 study through the Dose-tapering Period ending on Week 29.

Prior medications are defined as any changes in non-study medication/therapy, including administration of new medication(s), change of dose, or discontinuation of medication, that occur after completion of the VBP15-002 core study Week 4 assessments and prior to administration of the first dose of study medication in the VBP15-003 study. Medications that start during the VBP15-002 study will be considered prior medications for the VBP15-003 study.

All prior and concomitant medications will be presented in by-subject listings.

8.7. Treatment Compliance and Study Drug Exposure

Descriptive statistics (n, mean, median, min, max) for treatment compliance percentage will be summarized.

A summary table will also include number and percentage of subjects with overall (Weeks 1-24) treatment compliance 80-120% by dose level group. The denominator for the treatment compliance calculation will be the number of subjects with reliable treatment compliance data. Treatment compliance is calculated as described in the equations below and following examples:

Total scheduled dose (in mL) is calculated as subject weight (kg) at the dispensing visit x assigned daily dose in mg/kg/day x days in the dosing interval ÷ 40 mg/mL for each dosing interval (Day 1 through Week 12 and Week 12 through Week 24), using the following conventions:

The actual visit dates for the 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 are instances where they do not match the visit dates of interest.

As an example, assume a subject weighed 15 kg at the start of the study and 18 kg at 12 weeks and was to receive 2 mg/kg/day every day over each of the dosing intervals (dosing interval is the actual number of days between the Day 1 visit and the Week 12 visit, inclusive, and 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 mL in the dosing interval = (15 kg x 2.0 mg/kg/day x 80 days ÷ 40 mg/mL) = 60 mL, and for the Week 12 to Week 24 interval, total scheduled mL in the dosing interval = (18 kg x 2.0 mg/kg/day x 82 days ÷ 40 mg/mL) = 73.8 mL. The total scheduled mL overall is 133.8 mL.

Actual total dose taken in mL is calculated as (dispensed volume) – (returned volume).

For illustrative purposes, assume the subject was dispensed 2 bottles (each bottle is filled with 110 mL) which gives the dispensed volume of 220 mL, and returned 100 mL. The actual total dose taken = 120 mL. (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 mL ÷ total scheduled mL (Day 1 to Week 12 scheduled mL + Week 12 to Week 24 scheduled mL).

In this example, % compliance is 120 mL ÷ 133.8 mL = 89.7.1% for Overall Compliance.

Descriptive statistics (n, mean, median, min, 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.

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

9. EFFICACY ANALYSES

The evaluations of clinical efficacy will be performed using the FAS for VBP15-003 study subjects (including VBP15-002 baseline data), and the control populations from the DNHS study. Data will be summarized by planned treatment.

The primary efficacy outcome is TTSTAND velocity. The descriptive summaries will include continuous descriptive statistics on observed values and change from VBP15-002 baseline values at each time point by dose level.

TTSTAND velocity change from baseline (VBP15-002 baseline) results will be compared between vamorolone dose groups and historical untreated controls (CINRG DNHS) using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) analysis with treatment group, week of the visit, and the treatment-by-week interaction as factors, and age at study entry and baseline response as covariates. Week will be included in the model as a categorical variable (Week 12 and 24) along with the treatment-by-week interaction. An unstructured within-subject covariance matrix will be used. 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. The primary treatment comparison will be the LS means contrasts between the dose groups and historical untreated controls (CINRG DHNS) at Week 24. Additional exploratory analyses will include pairwise comparisons between the 4 vamorolone dose groups within the VBP15-003 trial (0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day).

The same approach described for TTSTAND velocity will be taken for TTSTAND raw, TTRW velocity and raw, and TTCLIMB velocity and raw; 6MWT, except no comparison to DNHS will be done; NSAA total score (note that NSAA total score is only calculated if all subscores are non-missing), except no comparison to DNHS will be done; and QMT. The QMT measurements will be done unilaterally using the dominant side, if known. For each muscle group (knee extension/flexion, elbow extension/flexion) the better of two collected test results at each visit will be summarized.

For TTSTAND, TTRW, and TTCLIMB, results will also be converted to velocities and analyzed as described above using the following transformation formulas:

- TTSTAND velocity = 1 / TTSTAND and is expressed as rises/sec.
- TTCLIMB velocity = 1 / TTCLIMB and is expressed as tasks/sec.
- TTRW velocity = 10 / TTRW and is expressed as meters/sec.

Subject data reliability over testing visits may be explored if necessary and would be presented in the CSR as post hoc.

All efficacy data will be presented in by-subject listings.

10. SAFETY ANALYSES

Safety analyses will be performed using the Safety Population and will be completed using the actual treatment a subject received and will address the primary objective of the study.

All safety data will be presented in by-subject listings as well as in tables and figures as described below.

10.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event or worsening of an existing condition after initiation of the investigational product and through the subject's last study visit (study completion or early termination). Serious adverse events will be recorded from the date of informed consent, throughout the clinical trial, and for up to 30 days after the final administration of study drug. If the onset of an AE is on Day 1 and its relationship to time of study drug administration is unknown, then the AE will be counted as treatment-emergent. If the onset of the AE is on Day 1 but is known to have onset prior to the time of the first administration of study drug, the AE will not be considered treatment-emergent.

Adverse events that start during the VBP15-002 study and are ongoing at the end of the 002 study will be placed in the Interim Medical History CRF for the VBP15-003 study−they will not be presented as AEs in the VBP15-003 study unless they worsen during the VBP15-003 study, in which case they would be treated as new AEs. Similarly, events that occur after the VBP15-002 study and before initiation of the investigational product for the VBP15-003 study will be counted as medical history in the VBP15-003 study.

The number and percent of subjects with any TEAEs will be summarized by system organ class and preferred term by dose level (and overall). At each level of tabulation (e.g., at the preferred term level) subjects will be counted only once if they had more than one such event reported during the AE collection period.

Level of intensity will be assessed using the CTCAE grading.

The following summary tables and subject level listings will be presented for TEAE data:

- Overall summary of TEAEs
- Summary table of TEAE by descending incidence by PT
- Summary table of TEAEs by SOC and PT
- Summary table of serious TEAEs by SOC and PT
- Summary table of TEAEs by maximum relatedness to treatment by SOC and PT
- Summary table of TEAEs by maximum intensity by SOC and PT
- Summary table of TEAEs leading to study drug discontinuation by SOC and PT
- Summary table of TEAEs by worst outcome (recovered/resolved vs. recovering/resolving vs. not recovered/not resolved vs. recovered/resolved with sequelae vs. fatal vs. unknown) by SOC and PT
- Table listing of SAEs
- Table listing of related SAEs

- Table listing of all AEs leading to death
- Table listing of all AEs leading to study discontinuation

10.2. Vital Signs, 12-Lead ECG, and Laboratory Outcomes

Vital signs, including height, weight and BMI and BMI z-score, clinical laboratory test results, and other laboratory test results not detailed elsewhere in this SAP will be summarized at each time point by dose level (and overall) using descriptive statistics and presented for observed response as well as change from baseline. Descriptive statistics will include the typical statistics for continuous endpoints described in this SAP as well as interquartile range.

The primary safety variable will be BMI z-score. BMI z-score change from baseline (VBP15-002 baseline) results will be compared between vamorolone dose groups and daily prednisone treated subjects (CINRG prednisone trial) using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) analysis with treatment group, week of the visit, and the treatment-by-week interaction as factors, and baseline response as a covariate. Week will be included in the model as a categorical variable (Week 12 and 24) along with the treatment-by-week interaction. An unstructured within-subject covariance matrix will be used. 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. The primary treatment comparison will be the LS means contrasts between the vamorolone dose groups and daily prednisone treated subjects (CINRG prednisone trial) at Week 24. Additional exploratory analyses will include pairwise comparisons between the 4 vamorolone dose groups within the VBP15-003 trial (0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day).

Change from baseline in continuous clinical laboratory test results will be tested using one-sample t-tests within each vamorolone treatment group. Clinical laboratory test results will also be presented in shift tables for all laboratory parameters where low/normal/high or abnormal/normal status can be ascertained. Abnormal clinical lab test results will be presented in a table listing where low/normal/high or abnormal/normal status can be ascertained.

Except for lab results, data gathered at unscheduled visits will not be summarized but will be included in by-subject data listings. See Section 7.3.1 for unscheduled or repeated lab tests.

Lab results will be presented using U.S. conventional units.

For by-subject listings, normal/abnormal flags will be imputed on local lab data only if the normal flag is missing and both a lower and upper normal range are provided in the raw data

for the observation so that the lab response can be assessed as normal or abnormal depending on whether it falls within the provided normal range.

Also, for by-subject listings, clinically significant response (yes/no) will only be presented in the listings for local labs if the response is abnormal.

Overall ECG interpretation will be summarized categorically by assessment response and via shift table presenting Normal/Abnormal Not Clinically Significant/Abnormal Clinically Significant and will also be presented in subject listings.

10.3. Physical Exam

CRF physical exam results will be presented in by-subject listings.

10.4. Other Safety Measures

Acceptability of the study medication will be assessed using a 5-point hedonic scale immediately before (smell) and after (taste) dosing at the Week 12 and Week 24 Visits. Drug acceptability will be summarized descriptively as a continuous endpoint by study cohort at each time point collected and presented in a by-subject listing.

Quality of life will be assessed by completion of the Pediatric Outcomes Data Collection Instrument (PODCI). Two subscales (Upper Extremity and Physical Function; Transfer and Basic Mobility) will be summarized descriptively as a continuous endpoint by study cohort at each time point collected. Observed scores and change from baseline will be presented. Standardized scores will be used for the analyses. All PODCI data will be presented in a by-subject listing.

11. PHARMACODYNAMIC (PD) SERUM AND OTHER BIOMARKERS

The evaluations of PD will be performed using the Safety Population. The baseline values will come from the baseline assessment in the VBP15-002 study.

The descriptive summaries will include continuous descriptive statistics on observed, change from baseline, and percent change from baseline responses at each time point by dose level. Continuous descriptive statistics will be provided along with interquartile range. Percentage change is defined as 100*(change from baseline/baseline). One sample t-tests will be provided to test if the change from baseline mean values are different from zero within the vamorolone dose groups.

PD biomarker change from baseline (VBP15-002 baseline) results will be analyzed using restricted maximum likelihood (REML)-based mixed models for repeated measures

(MMRM) analysis with treatment group, week of the visit, and the treatment-by-week interaction as factors, and age at study entry and baseline response as a covariate. Week will be included in the model as a categorical variable (Week 8, 12, 16, and/or 24) along with the treatment-by-week interaction. An unstructured within-subject covariance matrix will be used. 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. Pairwise comparisons of LS means between the 4 vamorolone dose groups within the VBP15-003 trial (0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day) will be presented.

All PD biomarker data will be presented in by-subject listings. The listings will include normal range data, where available. Furthermore, a listing of out of range observations will be presented.

SomaScan data, if available, will be presented in an addendum report.

Proteomics profiling data will be collected for potential analysis in future studies. These data will not be included in any by subject listing or in the CSR for this study. Any analysis of the proteomics profiling information will be reported in separate reports.

12. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations

12.1. General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in presented in color with treatment groups distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.

- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Graph status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.
- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

11.1 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "Population: <name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.

- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: N, mean, SD, median, minimum, and maximum. Other summaries (e.g. number missing, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. For categorical summaries presenting "n (%)", a count of 0 will be presented as "0". For continuous results, an estimated % of 0 will be presented as "0%".
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (e.g., 0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version 9.2 or later) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000.

12 REFERENCES

Bello L, Gordish-Dressman H, Morgenroth LP, Henricson EK, Duong T, Hoffman EP, Cnaan A, McDonald CM; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology. 2015 Sep 22;85(12):1048-55. doi: 10.1212/WNL.0000000000001950. Epub 2015 Aug 26. PubMed PMID: 26311750; PubMed Central PMCID: PMC4603595.

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McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H; CINRG Investigators. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018 Feb 3;391(10119):451-461.

13 APPENDICES

13.1 List of Planned Tables

This list of planned tables includes all of the main tables to be presented for the study. Other tables may be presented and will be described in a TLF shell document.

NUMBER	TITLES
14.1.1.1	Subject Disposition \ All Subjects
14.1.2	Demographic and Baseline Characteristics \ Safety Population
14.1.4.1	Prior Medications \ Safety Population
14.1.4.2	Concomitant Medications\ Safety Population
14.2.4.1	Summary of Time to Stand (TTSTAND) in Seconds \ Full Analysis Set
14.2.4.1.1	Summary of Time to Stand (TTSTAND) in Seconds - w/o ET\ Full Analysis Set
14.2.4.2	Summary of Time to Stand (TTSTAND) Velocity in Rises/Second \ Full Analysis Set
14.2.4.2.1	Summary of Time to Stand (TTSTAND) Velocity in Rises/Second - w/o ET\ Full Analysis Set
14.2.4.3	Time to Stand (TTSTAND) in Seconds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.4.3.1	Time to Stand (TTSTAND) in Seconds Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis\ Full Analysis Set
14.2.4.4	Time to Stand (TTSTAND) Velocity in Rises/Second Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.4.4.1	Time to Stand (TTSTAND) Velocity in Rises/Second Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis\ Full Analysis Set
14.2.5.1	Summary of Time to Climb (TTCLIMB) in Seconds\ Full Analysis Set

14.2.5.1.1	Summary of Time to Climb (TTCLIMB) in Seconds - w/o ET\ Full Analysis Set
14.2.5.2	Summary of Time to Climb (TTCLIMB) Velocity in Tasks/Second \ Full Analysis Set
14.2.5.2.1	Summary of Time to Climb (TTCLIMB) Velocity in Tasks/Second - w/o ET\ Full Analysis Set
14.2.5.3	Time to Climb (TTCLIMB) in Seconds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.5.3.1	Time to Climb (TTCLIMB) in Seconds Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis\ Full Analysis Set
14.2.5.4	Time to Climb (TTCLIMB) Velocity in Tasks/Second Change from Baseline at Week 12 and Week 24 - MMRM Analysis \ Full Analysis Set
14.2.5.4.1	Time to Climb (TTCLIMB) Velocity in Tasks/Second Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis \ Full Analysis Set
14.2.6.1	Summary of Time to Run/Walk 10 Meters (TTRW) in Seconds\ Full Analysis Set
14.2.6.1.1	Summary of Time to Run/Walk 10 Meters (TTRW) in Seconds - w/o ET\ Full Analysis Set
14.2.6.2	Summary of Time to Run/Walk 10 Meters (TTRW) Velocity in Meters/Second\ Full Analysis Set
14.2.6.2.1	Summary of Time to Run/Walk 10 Meters (TTRW) Velocity in Meters/Second - w/o ET\ Full Analysis Set
14.2.6.3	Time to Run/Walk 10 Meters (TTRW) in Seconds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.6.3.1	Time to Run/Walk 10 Meters (TTRW) in Seconds Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis\ Full Analysis Set
14.2.6.4	Time to Run/Walk 10 Meters (TTRW) Velocity in Meters/Second Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set

14.2.6.4.1	Time to Run/Walk 10 Meters (TTRW) Velocity in Meters/Second Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis\ Full Analysis Set
14.2.7.1	Summary of 6 Minute Walk Test (6MWT) in Meters\ Full Analysis Set
14.2.7.1.1	Summary of 6 Minute Walk Test (6MWT) in Meters - w/o ET\ Full Analysis Set
14.2.7.2	Summary of 6 Minute Walk Test (6MWT) in Meters - MMRM Analysis\ Full Analysis Set
14.2.7.2.1	Summary of 6 Minute Walk Test (6MWT) in Meters - w/o ET - MMRM Analysis\ Full Analysis Set
14.2.8.1	Summary of Quantitative Muscle Testing (QMT) Elbow Flexors in Pounds\ Full Analysis Set
14.2.8.2	Summary of Quantitative Muscle Testing (QMT) Elbow Extensors in Pounds \ Full Analysis Set
14.2.8.3	Summary of Quantitative Muscle Testing (QMT) Knee Flexors in Pounds \ Full Analysis Set
14.2.8.4	Summary of Quantitative Muscle Testing (QMT) Knee Extensors in Pounds \ Full Analysis Set
14.2.8.5	Quantitative Muscle Testing (QMT) Elbow Flexors in Pounds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.8.6	Quantitative Muscle Testing (QMT) Elbow Extensors in Pounds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.8.7	Quantitative Muscle Testing (QMT) Knee Flexors in Pounds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.8.8	Quantitative Muscle Testing (QMT) Knee Extensors in Pounds Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Full Analysis Set
14.2.9.1	Summary of North Star Ambulatory Assessment (NSAA) Total Score \ Full Analysis Set
14.2.9.2	Summary of North Star Ambulatory Assessment (NSAA) Total Score - MMRM Analysis\ Full Analysis Set

14.2.10.1	Summary of Pharmacodynamic Parameters - Bone Turnover\ Safety Population
14.2.10.1.1	Summary of Pharmacodynamic Parameters - Bone Turnover - w/o ET \ Safety Population
14.2.10.2	Summary of Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry\ Safety Population
14.2.10.2.1	Summary of Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry - w/o ET \ Safety Population
14.2.10.3	Summary of Pharmacodynamic Parameters - Insulin Resistance \ Safety Population
14.2.10.3.1	Summary of Pharmacodynamic Parameters - Insulin Resistance - w/o ET \ Safety Population
14.2.10.4	Summary of Pharmacodynamic Parameters - Bone Turnover - MMRM Analysis\ Safety Population
14.2.10.4.1	Summary of Pharmacodynamic Parameters - Bone Turnover - w/o ET - MMRM Analysis\ Safety Population
14.2.10.5	Summary of Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry - MMRM Analysis\ Safety Population
14.2.10.5.1	Summary of Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry - w/o ET - MMRM Analysis\ Safety Population
14.2.10.6	Summary of Pharmacodynamic Parameters - Insulin Resistance - MMRM Analysis\ Safety Population
14.2.10.6.1	Summary of Pharmacodynamic Parameters - Insulin Resistance - w/o ET - MMRM Analysis\ Safety Population
14.3.1	Study Drug Exposure\ Safety Population
14.3.1.1	Overall Summary of Adverse Events \ Safety Population
14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term\ Safety Population
14.3.1.3	Summary of Treatment Emergent Adverse Events by Descending Incidence of Preferred Term\ Safety Population

14.3.1.4	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term\ Safety Population
14.3.1.5	Summary of Treatment Emergent Adverse Events by Maximum Relatedness to Treatment by System Organ Class and Preferred Term\ Safety Population
14.3.1.6	Summary of Treatment Emergent Adverse Events by Maximum Severity by System Organ Class and Preferred Term\ Safety Population
14.3.1.7	Summary of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term\ Safety Population
14.3.1.8	Summary of Treatment Emergent Adverse Events by Worst Outcome by System Organ Class and Preferred Term\ Safety Population
14.3.2.1	Table Listing of Serious Treatment Emergent Adverse Events\ Safety Population
14.3.2.2	Table Listing of Related Serious Treatment Emergent Adverse Events \ Safety Population
14.3.2.3	Table Listing of Treatment Emergent Serious Adverse Events Leading to Death\ Safety Population
14.3.2.4	Table Listing of Treatment Emergent Adverse Events Leading to Study Discontinuation\ Safety Population
14.3.3.1	Summary of Laboratory Parameters: Hematology\ Safety Population
14.3.3.2	Laboratory Shift from Baseline: Hematology \ Safety Population
14.3.3.3	Summary of Laboratory Parameters: Chemistry\ Safety Population
14.3.3.4	Laboratory Shift from Baseline: Chemistry \ Safety Population
14.3.3.5	Summary of Laboratory Parameters: Urinalysis\ Safety Population
14.3.3.6	Laboratory Shift from Baseline: Urinalysis- Random Urine\ Safety Population
14.3.3.7	Summary of Laboratory Parameters: Lipid Profile\ Safety Population
14.3.3.8	Laboratory Shift from Baseline: Lipid Profile\ Safety Population
14.3.3.9	Table Listing of Abnormal Lab Results by Subject and Visit\ Safety Population

14.3.3.10	Table of Normal Laboratory Ranges
14.3.3.11	Table of Normal Biomarker Ranges
14.3.4.1	Summary of Vital Signs\ Safety Population
14.3.4.2	Summary of Anthropometrics\ Safety Population
14.3.4.3	Summary of 12-Lead ECG Interpretation\ Safety Population
14.3.4.4	12-Lead ECG Interpretation Shift from Baseline\ Safety Population
14.3.4.5	Summary of Study Medication Acceptability \ Safety Population
14.3.4.6	Summary of Pediatric Outcomes Data Collection Instrument \Safety Population
14.3.4.7	Summary of BMI Z-score \ Safety Population
14.3.4.7.1	Summary of BMI Z-score - w/o ET\ Safety Population
14.3.4.8	Summary of BMI Z-score Change from Baseline at Week 12 and Week 24 - MMRM Analysis\ Safety Population
14.3.4.8.1	Summary of BMI Z-score Change from Baseline at Week 12 and Week 24 - w/o ET - MMRM Analysis\ Safety Population

13.2 List of Planned Listings

This list of planned listings includes all of the main listings to be presented for the study. Other listings may be presented and will be described in a TLF shell document.

NUMBER	TITLES
16.2.1	Subject Disposition \ All Subjects
16.2.2.1.1	Inclusion/Exclusion Criteria
16.2.2.1.2	Inclusion/Exclusion Listing\ All Subjects
16.2.2.2	Protocol Deviations\ All Subjects
16.2.4.1	Demographic and Baseline Information\ All Subjects
16.2.4.2	Medical History\ All Subjects
16.2.4.3	DMD History\ All Subjects
16.2.4.4	Genetic Confirmation by Muscle Biopsy\ All Subjects
16.2.4.5.1	Genetic Confirmation by DNA\ All Subjects
16.2.4.5.2	Genetic Confirmation by DNA Continued\ All Subjects
16.2.5.1	Study Drug Administration\ All Subjects
16.2.5.2	Study Drug Exposure\ All Subjects
16.2.5.3	Study Drug Accountability\ All Subjects
16.2.6.1	Timed Tests\ All Subjects
16.2.6.2	Time to Stand (TTSTAND)\ All Subjects
16.2.6.3	Time to Climb (TTCLIMB)\ All Subjects
16.2.6.4	Time to Run/Walk (TTRW)\ All Subjects
16.2.6.5	Quantitative Muscle Testing (QMT)\ All Subjects
16.2.6.6	6 Minute Walk Test (6MWT) Pre-Test\ All Subjects

16.2.6.7	6 Minute Walk Test (6MWT) \ All Subjects
16.2.6.8	6 Minute Walk Test (6MWT) Post-Test\ All Subjects
16.2.6.9	North Star Ambulatory Assessment (NSAA)\ All Subjects
16.2.7.1	Adverse Events\ All Subjects
16.2.7.2	Adverse Events by System Organ Class and Preferred Term\ All Subjects
16.2.7.3	Serious Adverse Events\ All Subjects
16.2.7.4	Serious Adverse Events Leading to Death\ All Subjects
16.2.8.1	Hematology Laboratory Evaluations by Subject and Visit\ All Subjects
16.2.8.2	Chemistry Laboratory Evaluations by Subject and Visit\ All Subjects
16.2.8.3	Urinalysis Laboratory Evaluations by Subject and Visit\ All Subjects
16.2.8.4	Biomarker Laboratory Evaluations by Subject and Visit\ All Subjects
16.2.8.5	Lipids Laboratory Evaluations by Subject and Visit\ All Subjects
16.2.8.6	Laboratory Evaluations collected on the CRF by Subject and Visit\ All Subjects
16.2.9.1.1	Prior and Concomitant Medications\ All Subjects
16.2.9.1.2	Prior and Concomitant Medications - Steroids\ All Subjects
16.2.9.1.3	Concurrent Assistive, Orthotic, Night Splint, and Respiratory Devices\ All Subjects
16.2.9.1.4	Concurrent Occupational and Physical Therapy\ All Subjects
16.2.9.2	Vital Signs\ All Subjects
16.2.9.3	Physical Examination\ All Subjects
16.2.9.4.1	12-Lead Electrocardiogram (ECG) Results\ All Subjects
16.2.9.4.2	12-Lead Electrocardiogram (ECG) Interpretation\ All Subjects
16.2.10	Study Drug Acceptability\ All Subjects

16.2.11.1	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 1 (Questions 1-8)\ All Subjects
16.2.11.2	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 2 (Questions 9-14)\ All Subjects
16.2.11.3	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 3 (Questions 15-25) \ All Subjects
16.2.11.4	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 4 (Questions 26-33) \ All Subjects
16.2.11.5	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 5 (Questions 34-43) \ All Subjects
16.2.11.6	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 6 (Questions 44-51) \ All Subjects
16.2.11.7	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 7 (Questions 52-65) \ All Subjects
16.2.11.8	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 8 (Questions 66-76) \ All Subjects
16.2.11.9	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 9 (Questions 77-86) \ All Subjects
16.2.11.10	Pediatric Outcomes Data Collection Instrument (PODCI) - Part 10 (Derived Standardized Scores) \ All Subjects

13.3 List of Planned Figures

This list of planned figures includes all of the main figures to be presented for the study. Other figures may be presented and will be described in a TLF shell document.

NUMBER	TITLES
14.2.4.1.1	Time to Stand (TTSTAND) in Seconds\ Full Analysis Set
14.2.4.1.2	Time to Stand (TTSTAND) Change from Baseline in Seconds\ Full Analysis Set
14.2.4.2.1	Time to Stand (TTSTAND) Velocity \ Full Analysis Set
14.2.4.2.2	Time to Stand (TTSTAND) Velocity Change from Baseline\ Full Analysis Set
14.2.5.1.1	Time to Climb (TTCLIMB) in Seconds\ Full Analysis Set
14.2.5.1.2	Time to Climb (TTCLIMB) Change from Baseline in Seconds\ Full Analysis Set
14.2.5.2.1	Time to Climb (TTCLIMB) Velocity \ Full Analysis Set
14.2.5.2.2	Time to Climb (TTCLIMB) Velocity Change from Baseline\ Full Analysis Set
14.2.6.1.1	Time to Run/Walk 10 Meters (TTRW) in Seconds\ Full Analysis Set
14.2.6.1.2	Time to Run/Walk 10 Meters (TTRW) Change from Baseline in Seconds\ Full Analysis Set
14.2.6.2.1	Time to Run/Walk 10 Meters (TTRW) Velocity \ Full Analysis Set
14.2.6.2.2	Time to Run/Walk 10 Meters (TTRW) Velocity Change from Baseline\ Full Analysis Set
14.2.7.1.1	6 Minute Walk Test (6MWT) \ Full Analysis Set
14.2.7.1.2	6 Minute Walk Test (6MWT) Change from Baseline\ Full Analysis Set
14.2.8.1.1	Quantitative Muscle Testing (QMT) Elbow Flexors \ Full Analysis Set
14.2.8.1.2	Quantitative Muscle Testing (QMT) Elbow Flexors Change from Baseline\ Full Analysis Set
14.2.8.2.1	Quantitative Muscle Testing (QMT) Elbow Extensors \ Full Analysis Set

14.2.8.2.2	Quantitative Muscle Testing (QMT) Elbow Extensors Change from Baseline\ Full Analysis Set
14.2.8.3.1	Quantitative Muscle Testing (QMT) Knee Flexors \ Full Analysis Set
14.2.8.3.2	Quantitative Muscle Testing (QMT) Knee Flexors Change from Baseline\ Full Analysis Set
14.2.8.4.1	Quantitative Muscle Testing (QMT) Knee Extensors\ Full Analysis Set
14.2.8.4.2	Quantitative Muscle Testing (QMT) Knee Extensors Change from Baseline\ Full Analysis Set
14.2.9.1.1	North Star Ambulatory Assessment (NSAA) Total Score \ Full Analysis Set
14.2.9.1.2	North Star Ambulatory Assessment (NSAA) Total Score Change from Baseline\ Full Analysis Set
14.2.10.1.1	Pharmacodynamic Parameters - Bone Turnover\ Safety Population
14.2.10.1.2	Pharmacodynamic Parameters - Bone Turnover Change from Baseline\ Safety Population
14.2.10.1.3	Pharmacodynamic Parameters - Bone Turnover Change from Baseline by Subject\ Safety Population
14.2.10.2.1	Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry\ Safety Population
14.2.10.2.2	Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry Change from Baseline\ Safety Population
14.2.10.2.3	Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry Change from Baseline by Subject\ Safety Population
14.2.10.3.1	Pharmacodynamic Parameters - Insulin Resistance\ Safety Population
14.2.10.3.2	Pharmacodynamic Parameters - Insulin Resistance Change from Baseline\ Safety Population
14.2.10.3.3	Pharmacodynamic Parameters - Insulin Resistance Change from Baseline by Subject\ Safety Population
14.3.3.3.1	Serum Creatine Kinase\ Safety Population

14.3.3.3.2	Serum Creatine Kinase Change from Baseline\ Safety Population
14.3.3.3.3	Serum Creatine Kinase Change from Baseline by Subject\ Safety Population
14.3.4.1.1	Body Mass Index (BMI) \ Safety Population
14.3.4.1.2	Body Mass Index (BMI) Change from Baseline\ Safety Population
14.3.4.1.3	Body Mass Index Z-score \ Safety Population
14.3.4.1.4	Body Mass Index Z-score Change from Baseline\ Safety Population

13.4 Calculating BMI Z-Scores

The following example for computing BMI z-scores given age and sex for children aged 2 to 20 years uses the computational algorithm presented on the Centers for Disease Control and Prevention (CDC) webpage "Percentile Data Files with LMS Values". For a detailed discussion on the derivation of the computational algorithm and reference materials, visit the webpage at https://www.cdc.gov/growthcharts/percentile_data_files.htm.

To obtain the z-score (Z) for a given BMI measurement X, use the following equation:

$Z= [((X/M)^{\wedge L}) - 1] / (LS)$, where $L \neq 0$

or

$Z = \ln(X/M)/S$, where $L=0$

where L, M, and S are the values from the BMIAGE.xls reference table (growth chart 8 linked to on the aforementioned CDC webpage).

For example, for a 24 month old male (coded sex value = 1) who has a BMI of 17.2864, the BMIAGE.xls reference table presents values of L=-2.01118, M=16.57503, and S=0.080592. Plugging those parameter values into the Z formula above results in a Z-score of 0.5.

13.5 SAP Amendment Summary of Changes

Page Number	Section	Description of Change