ReveraGen BioPharma, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase IIa, Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)
Protocol Number	VBP15-002
Phase:	Phase IIa
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SAP Date:	2018-01-31
Status:	FINAL V1.0

SUMMITANALYTICAL	**Statistical Analysis Plan Approval Form**

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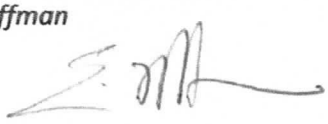
SAP Version: Final v1.0
SAP Date: 31JAN2018

The statistical analysis plan has been reviewed and approved.

Sponsor: *ReveraGen BioPharma, Inc.*
Eric Hoffman
CEO



Signature — 31 January 2018 — Date

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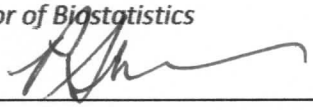

Signature — 31 JAN 2018 — Date

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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
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
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)

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
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 VBP15-002, (*A Phase IIa Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory 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 exploratory efficacy information. A separate PK Analysis plan, and report, will be developed for this study that provides the details and methods for the analysis and reporting of pharmacokinetic (PK) and Metabolite in Safety Testing (MIST) analyses.

Reference materials for this statistical plan include the protocol VBP15-002 (Revision #2 Dated: 20 January 2017) and Case Report Forms (Version 1.0, 1.1, and 1.2).

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 safety, tolerability, pharmacodynamics, and exploratory efficacy of multiple ascending oral doses of vamorolone in ambulant boys ages 4-< 7 years with DMD, and to investigate exploratory muscle strength and flexibility endpoints. Results from the analyses completed will be included in the final clinical study report for VBP15-002, 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.

Safety lab and PD biomarker results will be tested inferentially using paired t-tests. The protocol states that no inferential statistics will be presented.

Laboratory endpoints that will be included in this SAP that are not included in the protocol include GLDH, serum creatine kinase, and safety pharmacodynamic biomarkers (, cortisone, androstenedione, progesterone, DHEA, Leptin, MMP-3, Angiotensinogen, Afamin, IGFBP-5, GHBP), and efficacy pharmacodynamic biomarkers (CD23, MDC/CCL22, IL-22RA2/IL-22BP, Lymphototoxin a1/b2, IGFBP-2, CD49a/ITGa1/b1, MMP-12, Protein C, ANGPT2, FGG, LY9.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy endpoints. Objectives and pre-specified endpoints are as follows:

4.1. Study Objectives

4.1.1. Primary Objective

- To evaluate the safety and tolerability of multiple ascending oral doses of vamorolone in ambulant boys ages 4-< 7 years with DMD.

4.1.2. Secondary Objectives

- To investigate the single-dose and multiple-dose pharmacokinetics (PK) of oral vamorolone at multiple dose levels in ambulant boys ages 4-< 7 years with DMD;

- To investigate the effects of single and multiple oral doses of vamorolone on serum pharmacodynamic (PD) biomarkers bridged to later clinical safety concerns (adrenal suppression [first in morning cortisol], bone turnover [osteocalcin, CTX, P1NP], insulin resistance [fasting insulin, glucose; HbA1c]) in ambulant boys ages 4-< 7 years with DMD;

- To evaluate metabolites of vamorolone in Metabolites in Safety Testing (MIST) assessments following administration of multiple ascending oral doses.

Note: Secondary objectives associated with the characterization of PK parameter estimates, and MIST will be specified in a separate PK analysis plan and report.

4.1.3. Exploratory Objectives

- To investigate the effect of multiple oral doses of vamorolone on muscle strength, mobility, and functional exercise capacity, as measured by Quantitative Muscle Testing (QMT), Time to Run/Walk 10 meters Test (TTRW), Time to Stand Test (TTSTAND), Time to Climb Test (TTCLIMB), North Star Ambulatory Assessment (NSAA), and Six-minute Walk Test (6MWT) in ambulant boys ages 4-< 7 years with DMD.

- To investigate the effect of multiple oral doses of vamorolone on pharmacodynamic biomarkers for safety and efficacy, not bridged to later clinical safety or efficacy endpoints.

These exploratory endpoints are to assess the potential efficacy and provide signal information that may be used for planning future efficacy studies with vamorolone

4.2. Study Endpoints

4.2.1. Primary Endpoints

Primary endpoints from the protocol include the following:

- Adverse events
- Vital Signs
    - Supine blood pressure
    - Heart rate
    - Respiratory rate
    - Oral temperature
- Body weight
- Laboratory tests
    - Hematology
        - Red blood cell (RBC) count
        - Hemoglobin
        - Hematocrit
        - Numerical platelet count
        - WBC count and differential
            - White blood cell counts
            - Neutrophils cell counts
            - Lymphocytes cell counts
            - Eosinophils cell counts
    - Chemistry
        - Sodium
        - Potassium
        - Chloride
        - Calcium
        - Inorganic phosphorus
        - Blood urea nitrogen (BUN)
        - Creatinine
        - Total protein
        - Albumin
        - Bicarbonate
        - Lactate dehydrogenase (LDH)
        - Total Bilirubin (if out of normal range, direct bilirubin will be reported)
        - Uric acid
        - Glucose

        - Alkaline phosphatase (ALP)
        - Gamma glutamyl transferase (GGT)
        - Aspartate aminotransferase (AST)
        - Alanine aminotransferase (ALT)
        - Glutamte dehydrogenase (GLDH)
        - Lipase
        - Amylase
    - Urinalysis
        - Urine glucose
        - Urine protein
        - Ketones
        - pH
        - Leukocyte esterase
        - Blood
        - WBC/hpf
        - RBC/hpf
        - Casts
        - Bacteria
    - Lipid profile
        - Triglycerides
        - Total cholesterol
        - Low density lipoprotein (LDL)
        - High density lipoprotein (HDL)
    - Liver Safety
        - GLDH
- 12-lead electrocardiogram (ECG)
    - QRS duration
    - PR [PQ] interval
    - RR interval [interbeat interval]
    - QT interval
    - QTc
    - QTcF
    - Heart rate
- Physical exam findings of abnormality
- Subject assessment of vamorolone acceptability by a 5-point hedonic scale

4.2.2. Secondary Endpoints

Secondary endpoints from the protocol include the following:

- PK
    - plasma concentration levels of vamorolone and metabolites (Metabolites in Safety Testing – MIST) (Addendum – Separate report).

- pharmacokinetic parameter estimates for vamorolone (Addendum – Separate report).

- PD
  - Bone turnover marker immunoassay
    - Osteocalcin
    - Serum aminoterminal propeptide of type I collagen (P1NP)
    - Carboxy-terminal telopeptide (CTX)
  - Adrenal axis suppression immunoassay
    - Cortisol (first in morning)
    - 11-deoxycortisol (daytime)
    - 17-hydroxyprogesterone (daytime)
    - Adrenocorticotropic hormone (daytime)
    - Corticosterone (daytime)
    - Testosterone (daytime)
    - Cortisol (daytime)
  - Insulin resistance
    - Fasting insulin
    - Fasting glucose
    - HbA1C

4.2.3. Exploratory Endpoints

- Efficacy
  - QMT
  - TTSTAND
  - TTCLIMB
  - TTRW
  - NSAA
  - 6MWT
- Biomarker (Addendum – separate report)
  - SOMAscan aptamers for safety
    - Insulin
    - Leptin
    - MMP-3
    - Angiotensinogen
    - Afamin
    - IGFBP-5
    - GHBP
  - SOMAscan aptamers for efficacy
    - CD23
    - MDC or CCL22
    - IL-22RA2 or IL-22BP
    - Lymphototoxin a1/b2
    - IGFBP-2

        - CD49a or ITGa1/b1
        - MMP-12
        - Protein C
        - ANGPT2
        - FGG
        - LY9
    - Serum chemistry markers for efficacy
        - Serum Creatine Kinase

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 is a Phase IIa, multiple site, open-label, multiple ascending dose study to evaluate the safety, tolerability, PK, PD biomarker responsiveness, and exploratory clinical efficacy of vamorolone administered once daily by liquid oral suspension over a Treatment Period of 14 days to ambulant boys ages 4-< 7 years with DMD.

The study is comprised of a Pretreatment Screening Period of up to 26 days duration, a 1-day Pretreatment Baseline Period, a 14-day Treatment Period, and a 14-day Follow-up Period. Four dose level groups of approximately 12 subjects each will receive vamorolone once daily for 14 days (Table 1). 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). Treatment of the approximately 12-subjects in each dose level group will be completed and safety results evaluated prior to enrollment of subjects in each subsequent dose level group. The process of dose escalation will be based on the appearance of dose-limiting toxicities.

Table 1: Dose level group composition

Planned Dose Level Group	No. Subjects in Dose Level Group	Vamorolone Dose	Treatment Duration
1	12	0.25 mg/kg	14 days
2	12	0.75 mg/kg	14 days
3	12	2.0 mg/kg	14 days
4	12	6.0 mg/kg	14 days

Table 2 presents the schedule of study procedures.

Table 2 Schedule of Time and Events

	Pretreatment Period		Treatment Period			Post-treatment Follow-up	
	SCR	BL					
	Day		Day	Week		Week	
Visit/Contact	-28 to -3	-1	1	1 (7±1d)	2[a] (14±1d)	3 (21±2d)	4[b] (28±3d)
Informed Consent[c]	X						
Medical History	X						
Medication History	X	X					
Blood for Chicken Pox Immunity	X[d]						
Inclusion/Exclusion Criteria	X	X					
Physical Examination	X				X		X
Height	X						
Weight	X	X			X		X
Vital Signs[e]	X	X[f]	X[f]	X	X[f]		X
Blood for Clinical Labs[g]	X				X		X
Urinalysis[g]	X				X		X
12-lead ECG	X[h]				X[h]		X[h]
Enrollment		X					
Dispense Study Medication			X				
Return Study Medication					X		
Study Medication Dosing[i]			X →		X		
Blood for Plasma PK		X[j]	X[j]		X[j]		
Blood for Metabolites in Safety Testing (MIST)[q]					X[q]		
Blood for Serum PD Biomarker Panel	X[k]	X[l]	X[m]		X[l,n]		X[n]
Quantitative Muscle Testing (QMT)	X	X			X[o]		X
Time to Run/Walk 10 Meters Test (TTRW)	X	X			X[o]		X
Time to Stand Test (TTSTAND)	X	X			X[o]		X
Time to Climb Test (TTCLIMB)	X	X			X[o]		X
North Star Ambulatory Assessment (NSAA)	X	X			X[o]		X
Six-minute Walk Test (6MWT)	X	X			X[o]		X
Study Medication Acceptability Assessment			X[p]		X[p]		

	Pretreatment Period		Treatment Period			Post-treatment Follow-up	
	SCR	BL					
	Day		Day	Week		Week	
Visit/Contact	-28 to -3	-1	1	1 (7±1d)	2[a] (14±1d)	3 (21±2d)	4[b] (28±3d)
Study Medication Accountability					X		
Safety Monitoring			X	X	X	X	X
AE/SAE Recording	X	X	X	X	X	X	X
Concomitant Medications			X	X	X	X	X
Telephone Contact						X	
Discharge from Study							X

SCR=Screening Period; BL=Baseline Period, within 24 hours prior to administration of the first dose of study drug.

a. Subjects who prematurely discontinue from the study prior to Week 2 (Day 14) should complete the Week 2 (Days 13 and 14) procedures at the time of early discontinuation and enter the 14-day Follow-up Period.
b. Subjects who prematurely discontinue from the study after Week 2 (Day 14) but prior to the scheduled Week 4 (Day 28) Follow-up Visit should return to the study site for Week 4 (Day 28) procedures.
c. Informed Consent must be obtained prior to any study-related procedures.
d. All subjects will have blood collected at the Screening Visit for testing for IgG antibodies to varicella. Eligibility for study enrollment is dependent upon availability of positive result prior to enrollment.
e. Supine blood pressure, oral temperature, respiratory rate, and heart rate. At visits where blood is also drawn, vital signs must be recorded prior to blood draws.
f. On Days 1 and 14, vital signs will be recorded at 0.5 hour pre-dose and 0.5, 1, 2, 4, 6, and 8 hours post-dose, prior to PK blood draws where time points coincide.
g. Blood for chemistry, hematology, lipids; urinalysis by dipstick and microscopic analysis.
h. ECG must be conducted prior to vital signs.
i. The first dose of study medication on Day 1 and the final dose of study medication on Day 14 will be administered in the study clinic; all other doses will be taken at home.
j. Blood collected for plasma PK analysis on Day -1 (0.5 hour pre-dose) and 1, 2, 4, 6, and 8 hours post-dose on Day 1; and 0.5 hour pre-dose and 1, 2, 4, 6, and 8 hours post-dose on Day 14. Subjects must be fasting at the time of collection of Day 1 and Day 14 pre-dose samples.
k. cortisol, ACTH, P1NP, osteocalcin, CTX, 17- hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, hemoglobin A1c (HbA1c), SomaScan, and proteomics testing.
l. Blood collected for insulin and glucose during Screening (0.5 hour pre-dose) and on Day 14 (0.5 hour pre-dose). Subjects must be fasting at the time of blood collection.
m. Day 1, 6 hours post dose: cortisol, ACTH, P1NP, osteocalcin, CTX, 17- hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol.
n. Day 14, 6 hours post-dose:): cortisol, ACTH, P1NP, osteocalcin, CTX, 17- hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, SomaScan, and proteomics testing. Week 4 (Day 28): cortisol, ACTH, P1NP, osteocalcin, CTX, 17- hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, and proteomics testing.
o. Week 2 clinical efficacy assessments to be completed on Day 13.
p. Study medication acceptability assessment performed immediately pre-dose (smell) and post-dose (taste).
q. MIST assessment will be performed on portions of the blood samples collected for PK analysis; no additional blood will be collected.

5.2. Inclusion – Exclusion Criteria and General Study Population

Approximately 12 subjects with confirmed diagnosis of DMD (4-<7 years of age) will be enrolled into each of the four cohorts (48 subjects total). The inclusion and exclusion criteria defined in the protocol apply to all subjects and are not repeated herein the SAP.

5.3. Randomization and Blinding

This is an open-label study, and no randomization schedule or blinding of study medication is applicable. 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, efficacy variables, PK variables (observed and predicted concentration levels and estimated pharmacokinetic parameters), etc. as described throughout this SAP. Derived variables from study endpoints are described with the sections describing the analyses for these endpoints.

Unless otherwise noted, baseline is defined as the last measurement taken prior to first exposure to study drug, including Day 1 measurements taken pre-dosing.

6. SAMPLE SIZE

A sample of 12 in each cohort is large enough to have a confidence interval of no wider than 50% for the proportion of adverse events assessed or any other event outcome. For the continuous outcomes such as safety laboratory markers or pharmacodynamics markers, a two-sided 95.0% confidence interval for the mean will be no wider than 0.8 standard deviation (SD) from the observed mean, with 90.0% coverage probability, based on the t statistic; thus, the total confidence interval will be approximately 1.6 SDs wide for any continuous parameter if its underlying distribution is approximately normal.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

There will be two (2) analysis populations defined for this study.

7.1.1. Safety Population

All subjects who receive at least one dose of vamorolone study medication will be included in the Safety Population.

7.1.2. Pharmacokinetic Population (PK)

All subjects who receive at least one dose of vamorolone study medication and have sufficient quantifiable plasma concentration data for PK analysis will be included in the PK population. [Note that the PK population will be determined by the study pharmacokineticist upon review of the concentration information for each subject in each cohort. Inclusion or exclusion into the PK population will be fully documented.]

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

No covariates will be included in statistical analyses.

7.2.2. Planned Subgroups

Descriptive summaries for BMI and efficacy endpoints will be presented by age of study subjects (4 to 5 years and 6 to <7 years).

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.

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

No data will be imputed for this study. All data will be observed cases, 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 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.

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 body system).

Prior and Concomitant medications will be coded using World Health Organization (WHO) Drug classification (Version 4.3).

7.3.6. Baseline Visits

Baseline for the following endpoints is defined as the last response during Screening prior to Study Day -1: physical exam; blood for chemistry, hematology, lipids; urinalysis by dipstick and microscopic analysis; 12-lead ECG; serum PD biomarkers (cortisol (daytime), cortisone, 17- hydroxyprogesterone, ACTH, testosterone, corticosterone, 11- deoxycortisol, androstenedione, progesterone, DHEA, osteocalcin, serum aminoterminal propeptide of type I collagen (P1NP), carboxy-terminal telopeptide (CTX), HbA1c); and SOMAscan aptamers.

Baseline for the following endpoints is defined as Study Day -1: weight; blood for serum PK; and strength and flexibility testing (QMT, TTRW, TTSTAND, TTCLIMB, NSAA, and 6MWT).

Baseline for the following endpoints is defined as the last response prior to dosing on Study Day 1: vital signs, and PD biomarkers fasting insulin and glucose.

7.3.7. Analysis Software

Data manipulation, tabulation of descriptive statistics, and graphical representations will be performed primarily using SAS (release 9.2 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.

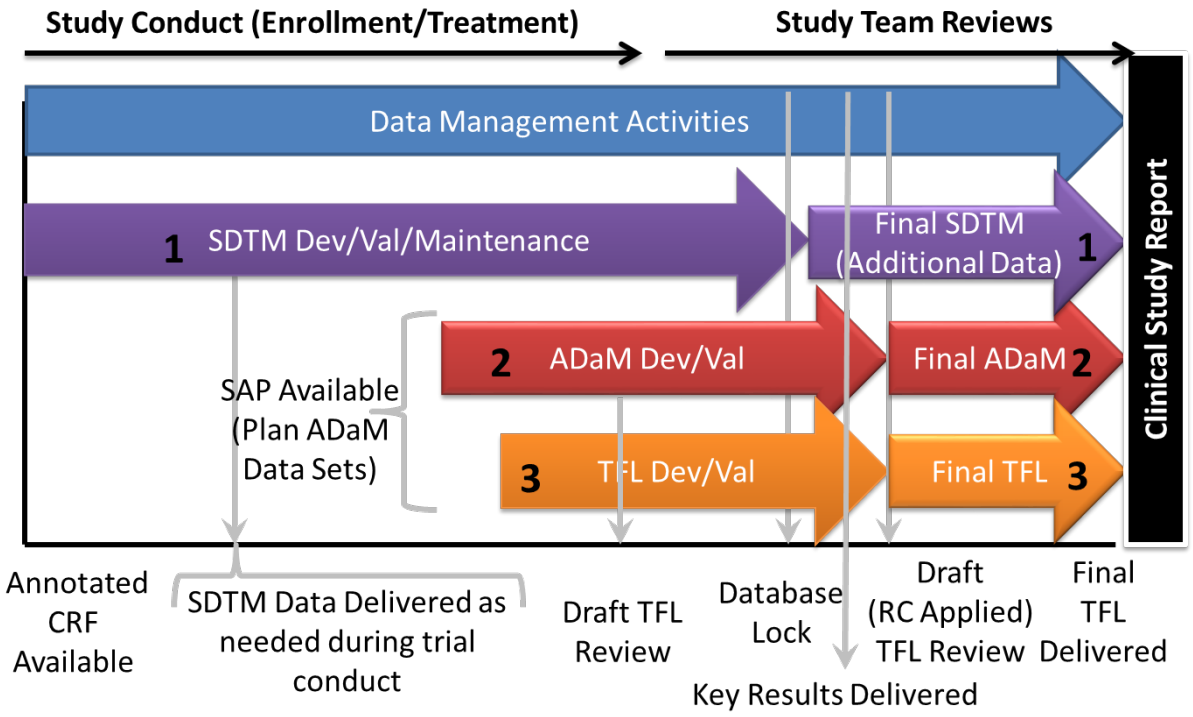
7.3.8. Study Data

Study data identified in the schedule for time and events (Table 2) are collected, and source verified, on the electronic data capture tool OpenClinica v3.12.2. Laboratory data, including PK and 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 independent Data and Safety Monitoring Board (DSMB) will be consulted to review the safety data from each dose level group. The DSMB will receive reports when it is assessed that a dose level group is completed and no more de-escalations to that dose are expected, but no less frequently than every 6 months. The DSMB will meet at regular intervals to review all pertinent safety data. The DSMB will also be notified at any point where a dose de-escalation occurs and the dose is deemed to have unacceptable toxicity. 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 2 (Day 14) should complete the Week 2 (Days 13 and 14) procedures at the time of early discontinuation and enter the 14-day Follow-up Period. Subjects who prematurely discontinue from the study after Week 2 (Day 14) but prior to the scheduled Week 4 (Day 28) Follow-up Visit should return to the study site for Week 4 (Day 28) procedures.

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, data summaries will be presented by study cohort: Dose Level Group 1, Dose Level Group 2, Dose Level Group 3, or Dose Level Group 4.

8.2. Patient 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 and whether they occurred before the Week 2 visit or after the Week 2 visit but before the Week 4 visit and whether the Week 4 visit assessments were completed 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/Violations

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

All protocol deviations and violations 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) will be summarized descriptively, either continuously or categorically. The summaries will be compared visually by cohort dose level group and reviewed for any differences among the dose level groups.

All demographic and baseline information will be listed by subject.

8.5. Medical History

Subject medical, surgical, medication and treatment history will be collected during the screening phase and reviewed throughout the study. 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 (Version 4.3).

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 up until Week 4 treatment follow-up.

Prior medications are defined as any medication that is taken prior to the day of first exposure to any study drug, collected from up to 30 days prior to Screening.

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

8.7. Treatment Compliance

Continuous descriptive summaries will be presented for the Safety Population by dose level and will include number of doses, number of doses missed, and total exposure to study drug.

9. EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will be exploratory and be completed using the Safety Population. All efficacy analyses will be completed using the planned dose that the subject received.

In general, and unless otherwise noted, data summaries will be presented by study cohort: Dose Level Group 1, Dose Level Group 2, Dose Level Group 3, or Dose Level Group 4. If, due to dose limiting toxicity, 2 or more study cohorts are dosed at the same level, then summaries will also be grouped by treatment dose level.

Since change in strength is not expected from a two-week treatment period, the main purpose of collecting these strength and mobility data is to provide baseline responses for the VBP15-003 six month extension study as well as potentially provide coefficients of variation to assess reliability in this age group.

9.1. Clinical Efficacy

The evaluations of exploratory clinical efficacy will be performed using the Safety Population. The last non-missing value prior to the first dose of study medication will be used as the baseline value for analyses. Data will be summarized by planned treatment.

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.

The descriptive summaries will include continuous descriptive statistics and box and whisker plots on observed and change from baseline responses at each time point by dose level.

Subject data reliability over testing visits may be explored if necessary by examining plots of the coefficient of variation and would be presented in the CSR as post hoc.

All QMT data will be presented in a listing.

The same approach described for QMT will be taken for all timed function tests (TTRW, TTSTAND, TTCLIMB, 6MWT) and the NSAA total score (note that NSAA total score is only calculated if all subscores are non-missing).

For TTRW, TTSTAND, 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.

Note that serum creatine kinase is considered an exploratory efficacy endpoint. However, for convenience, it is presented with the other chemistry laboratory results described in Section 10.2.

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, then the time of first dose, collected from the vitals CRF or PK CRF, will be compared to the time of onset to determine if the AE is treatment-emergent.

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 (ex. 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 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 highest relationship level to study drug by SOC and PT
- Summary table of TEAEs by maximum intensity by SOC and PT
- Summary table of TEAEs leading to study 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 weight and BMI, 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. BMI observed and change from baseline will also be presented using box and whisker plots.

Paired t-tests will be used to statistically test the change from Baseline to Week 2 and the change from Week 2 to Week 4 within each dose level (and overall) for all **lab parameters**, where applicable.

Note that vital signs will be gathered before and after dosing at Day 1. All change from baseline calculations for all time points following will be relative to the pre-dose vital signs response at Day 1.

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.

12-lead ECG interval parameters will only be presented in subject listings. Overall ECG assessment will be summarized via shift table presenting Normal/Abnormal Not Clinically Significant/Abnormal Clinically Significant, and will be presented in subject listings also.

10.3. Physical Exam

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

10.4. Other Safety Measures

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.

11. PHARMACOKINETIC (PK) ANALYSES

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

12. PHARMACODYNAMIC (PD) SERUM AND OTHER BIOMARKERS

The evaluations of PD will be performed using the Safety Population. The last non-missing value prior to the first dose of study medication will be used as the baseline value for analyses. Data will be summarized by planned treatment.

The descriptive summaries will include continuous descriptive statistics and box and whisker plots on observed and change from baseline responses at each time point by dose level.

Paired t-tests will be used to statistically test the change from Baseline to Week 2 and the change from Week 2 to Week 4 within each dose level (and overall), where applicable (note that the insulin resistance endpoints fasting glucose and fasting insulin are collected at Screening, Day 1, and Week 2, but will only have a paired t-test performed to test change from baseline at Week 2).

A single time series plot will be created presenting individual subject's change from baseline response over time by dose level. Each dose level will be presented on a separate figure.

Percentage change from baseline in serum PD biomarker concentrations will also be summarized in a table over time by dose level. Continuous descriptive statistics will be provided along with interquartile range. Percentage change is defined as 100*(change from baseline/baseline).

Note that adrenal suppression immunoassay (first in-morning cortisol) endpoint will only be collected at Week 2 and will only be summarized as count data. The summary table will tabulate the number and percentage of subjects with less than 100 nmol/L (3.6 micrograms/dL) at 002 Week 2 pre-dose.

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 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.

13. 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

13.1. 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 (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

ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline, September 1998

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
14.2.1	Treatment Administration\ Safety Population
14.3.1	Summary of Study Drug Exposure\ Safety Population
14.2.4.1	Summary of Time to Stand (TTSTAND) in Seconds \ Safety Population
14.2.4.1.1	Summary of Time to Stand (TTSTAND) in Seconds by Age Group\ Safety Population
14.2.4.2	Summary of Time to Stand (TTSTAND) Velocity in Rises/Second \ Safety Population
14.2.4.2.1	Summary of Time to Stand (TTSTAND) Velocity in Rises/Second by Age Group\ Safety Population
14.2.5.1	Summary of Time to Climb (TTCLIMB) in Seconds\ Safety Population
14.2.5.1.1	Summary of Time to Climb (TTCLIMB) in Seconds by Age Group\ Safety Population
14.2.5.2	Summary of Time to Climb (TTCLIMB) Velocity in Tasks/Second \ Safety Population
14.2.5.2.1	Summary of Time to Climb (TTCLIMB) Velocity in Tasks/Second by Age Group\ Safety Population
14.2.6.1	Summary of Time to Run/Walk 10 Meters (TTRW) in Seconds\ Safety Population
14.2.6.1.1	Summary of Time to Run/Walk 10 Meters (TTRW) in Seconds by Age Group\ Safety Population
14.2.6.2	Summary of Time to Run/Walk 10 Meters (TTRW) Velocity in Meters/Second\ Safety Population
14.2.6.2.1	Summary of Time to Run/Walk 10 Meters (TTRW) Velocity in Meters/Second by Age Group\ Safety Population
14.2.7.1	Summary of 6 Minute Walk Test (6MWT) in Meters\ Safety Population
14.2.7.1.1	Summary of 6 Minute Walk Test (6MWT) in Meters by Age Group\ Safety Population

14.2.8.1	Summary of Quantitative Muscle Testing (QMT) Elbow Flexors in Pounds\ Safety Population
14.2.8.1.1	Summary of Quantitative Muscle Testing (QMT) Elbow Flexors in Pounds by Age Group\ Safety Population
14.2.8.2	Summary of Quantitative Muscle Testing (QMT) Elbow Extensors in Pounds \ Safety Population
14.2.8.2.1	Summary of Quantitative Muscle Testing (QMT) Elbow Extensors in Pounds by Age Group\ Safety Population
14.2.8.3	Summary of Quantitative Muscle Testing (QMT) Knee Flexors in Pounds \ Safety Population
14.2.8.3.1	Summary of Quantitative Muscle Testing (QMT) Knee Flexors in Pounds by Age Group\ Safety Population
14.2.8.4	Summary of Quantitative Muscle Testing (QMT) Knee Extensors in Pounds \ Safety Population
14.2.8.4.1	Summary of Quantitative Muscle Testing (QMT) Knee Extensors in Pounds by Age Group\ Safety Population
14.2.9.1	Summary of North Star Ambulatory Assessment (NSAA) Total Score \ Safety Population
14.2.9.1.1	Summary of North Star Ambulatory Assessment (NSAA) Total Score by Age Group\ Safety Population
14.2.10.1	Summary of Pharmacodynamic Parameters - Bone Turnover\ Safety Population
14.2.10.2	Summary of Pharmacodynamic Parameters - Adrenal Axis Suppression Mass Spectrometry\ Safety Population
14.2.10.3	Summary of Pharmacodynamic Parameters - Insulin Resistance \ Safety Population
14.2.10.4	Adrenal Axis Suppression Immunoassay (Cortisol (First in Morning) \ 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

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 Medication Log\ All Subjects
16.2.5.4	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

16.2.9.1.1	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

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 (seconds) \ Safety Population
14.2.4.1.2	Time to Stand (seconds) Change from Baseline\ Safety Population
14.2.4.2.1	Time to Stand Velocity (rise/seconds) \ Safety Population
14.2.4.2.2	Time to Stand Velocity (rise/seconds) Change from Baseline\ Safety Population
14.2.5.1.1	Time to Climb (seconds) \ Safety Population
14.2.5.1.2	Time to Climb (seconds) Change from Baseline\ Safety Population
14.2.5.2.1	Time to Climb Velocity (tasks/seconds) \ Safety Population
14.2.5.2.2	Time to Climb Velocity (tasks/seconds) Change from Baseline\ Safety Population
14.2.6.1.1	Time to Run/Walk 10 Meters (seconds) \ Safety Population
14.2.6.1.2	Time to Run/Walk 10 Meters (seconds) Change from Baseline\ Safety Population
14.2.6.2.1	Time to Run/Walk 10 Meters Velocity (meters/second) \ Safety Population
14.2.6.2.2	Time to Run/Walk 10 Meters Velocity (meters/second) Change from Baseline\ Safety Population
14.2.7.1.1	6 Minute Walk Test (meters) \ Safety Population
14.2.7.1.2	6 Minute Walk Test (meters) Change from Baseline\ Safety Population
14.2.8.1.1	QMT Elbow Flexors \ Safety Population
14.2.8.1.2	QMT Elbow Flexors Change from Baseline\ Safety Population
14.2.8.2.1	QMT Elbow Extensors \ Safety Population
14.2.8.2.2	QMT Elbow Extensors Change from Baseline\ Safety Population
14.2.8.3.1	QMT Knee Flexors \ Safety Population
14.2.8.3.2	QMT Knee Flexors Change from Baseline\ Safety Population
14.2.8.4.1	QMT Knee Extensors \ Safety Population
14.2.8.4.2	QMT Knee Extensors Change from Baseline\ Safety Population
14.2.9.1.1	NSAA Total Score \ Safety Population
14.2.9.1.2	NSAA Total Score Change from Baseline\ Safety Population
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
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14.2.10.3.1	Pharmacodynamic Parameters - Insulin Resistance\ Safety Population
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14.3.3.3.1	Serum Creatine Kinase\ Safety Population
14.3.3.3.2	Serum Creatine Kinase Change from Baseline\ Safety Population
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14.3.4.2.1	Body Mass Index (kg/m2) \ Safety Population
14.3.4.2.2	Body Mass Index (kg/m2) 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