CLINICAL STUDY PROTOCOL

Amendment #5

Protocol Title: **A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy**

Protocol Number:	VBP15-BMD-001
Document Number:	VBP15-BMD-001-A5
FDA IND No.:	152,881
EudraCT No:	2022-000844-31
Investigational Product:	Vamorolone
Sponsor:	ReveraGen BioPharma, Inc. 155 Gibbs St. Suite 433 Rockville, MD 20850
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Document Date:	21 April 2025

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SIGNATURES OF AGREEMENT FOR VBP15-BMD-001-A5

A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy

Reviewed and approved by:



Electronically signed by: Eric Hoffman Reason: approval Date: Apr 23, 2025 11:08 EDT

Eric Hoffman, Ph.D. Date
CEO
ReveraGen BioPharma, Inc.



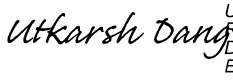
Electronically signed by: Paula Clemens Reason: approve document Date: Apr 23, 2025 11:23 EDT

Paula Clemens, M.D. Date
Study Chair
University of Pittsburgh



Electronically signed by: Johannes van den Anker Reason: Approve Date: Apr 23, 2025 11:33 EDT

John Van Den Anker, M.D., Ph.D. Date
Medical Monitor
ReveraGen BioPharma, Inc.



Electronically signed by: Utkarsh Dang Reason: Review online Date: Apr 23, 2025 11:57 EDT

Utkarsh Dang, Ph.D. Date
Statistician
Carleton University

INVESTIGATOR PROTOCOL AGREEMENT

Amendment #5 for A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy

PROTOCOL NUMBER: **VBP15-BMD-001**

DOCUMENT NUMBER: **VBP15-BMD-001-A5**

SPONSOR: **ReveraGen BioPharma, Inc.**

DOCUMENT DATE: **21 April 2025**

By my signature, I confirm that my staff and I have carefully read and understand this protocol, protocol amendment, amended protocol, or revised protocol and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by ReveraGen BioPharma, Inc.
I agree to conduct the study according to this protocol and the obligations and requirements of clinical Investigators and all other requirements set out in the Declaration of Helsinki listed in 21 CFR part 312, and ICH principles of Good Clinical Practice (GCP) and in accordance with all applicable laws, guidances and directives of the jurisdiction where the study is being conducted. I will not initiate this study without the approval of an Institutional ReviewBoard (IRB) or Independent Ethics Committee (IEC).
I understand that, should the decision be made by ReveraGen BioPharma, Inc. to terminate prematurely or suspend the study at any time for whatever reason, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate immediately such decision in writing to ReveraGen BioPharma, Inc.
For protocol amendments, I agree not to implement the amendment without agreement from ReveraGen BioPharma, Inc. and prior submission to and written approval (where required) from the IRB/IEC, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

_____ _____
Investigator's Signature Date

_____
Investigator's Name (Please print)
Address (Please print):

RETAIN THE ORIGINAL SIGNED AGREEMENT AT YOUR SITE AND RETURN AN ELECTRONIC SIGNED COPY TO REVERAGEN BIOPHARMA, INC., OR DESIGNEE

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of a serious adverse event (SAE) (see Section 7.6), the Investigator will complete the SAE electronic case report form within 24 hours of first awareness of the event. In the unlikely event that the electronic study database is inaccessible and the Investigator is unable to complete the SAE electronic case report form within 24 hours, the SAE Notification Form (pdf) should be completed and emailed or printed/faxed to the PRA safety management team within 24 hours, using the contact information below:

In North/South America:

Email: CHOSafety@prahs.com

Drug Safety Fax: 1 888 772 6919 or 1 434 951 3482

SAE Questions: Drug Safety Helpline: 1 800 772 2215

In Europe, Asia-Pacific and Africa (EAPA):

Email: MHGSafety@prahs.com

Drug Safety Fax: +44 1792 525720

SAE Questions: Drug Safety Helpline: +49 621 878 2154

PROTOCOL AMENDMENT TRACKING

Original Protocol	VBP15-BMD-001	29 September 2020
Amendment #1	VBP15-BMD-001-A1	08 June 2021
Amendment #2	VBP15-BMD-001-A2	26 October 2021
Amendment #3	VBP15-BMD-001-A3	27 June 2022
Amendment #4	VBP15-BMD-001-A4	20 March 2023
Amendment #5	VBP15-BMD-001-A5	21 April 2025

Reasons for Protocol Amendment #1:

1. To change study design to a randomized, double blind, placebo-controlled study
2. To add an NSAA score ≤ 32 to the inclusion criteria
3. To add an TTRW ≤ 30 seconds to the inclusion criteria #4
4. To add contraceptive use during the subject's participation to the inclusion criteria.
5. To add the NSAA assessment at the Screening Visit.
6. To add the TTRW assessment at the Screening Visit
7. To add glutamate dehydrogenase (GLDH) and gamma glutamyl transferase (GGT) to the clinical safety labs.
8. To add pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with BMD to the secondary objectives.
9. To update drug dose and dispensing calculation presented in section 15.1 Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide to adjust to the daily dose of 500mg (250mg if <50kg body weight) administered as a 4.0% oral suspension.

The Sections changed by Amendment #1 are listed in Section 15.2.1

Reasons for Protocol Amendment #2:

1. To change inclusion criteria #3 – Subject is ≥18 of age and <65 years
2. To remove miR146a and CK biomarker to evaluate response to vamorolone treatment
3. To add CD23 biomarker to evaluate response to vamorolone treatment
4. To remove exclusion criterion #5 and #7
5. To update section 1.2 Nonclinical Experience
6. To update section 1.3- Clinical Experience
7. To update section 1.5- Overall Benefit/Risk

The Sections changed by Amendment #2 are listed in Section 15.2.2

Reasons for Protocol Amendment #3:

1. To change inclusion criteria #3 – Subject is ≥18 of age at the time of consent
2. To remove duplicated inclusion criteria #7
3. To update inclusion criteria #10
4. To remove the Legally Authorized representative
5. To update breakfast diet
6. To update the CTCAE version to v 5.0
7. To remove the GLDH test
8. To update MedDRA version to v 25.0
9. To add information regarding NIAMS
10. To add information related to the COVID-19 pandemic
11. To remove the coordinating center
12. To update prior steroid use information
13. To clarify "stress dosing" of hydrocortisone
14. To update Table 6. Schedule of Study Activities
15. To update the visit dispensing of the saliva collection kit
16. To update section 7.2.8 and Table 11, blood volume required
17. To add a definition of Unanticipated Problems
18. To update section 7.6 AE, SAE, and UP
19. To update section 7.6.6 SAE
20. To update section 8.2 information regarding the DSMB
21. To update section 9.2 eCRF completion
22. To update section 11.3.2 reporting important protocol deviations
23. To update section 12.2 Publication

The Sections changed by Amendment #3 are listed in Section 15.2.3

Reasons for Protocol Amendment #4:

1. To add EUDRA No
2. To update inclusion criteria item# 1
3. To update inclusion criteria item# 6
4. To update exclusion criteria item# 1
5. To add a Prescreening visit

6. To change the term “expanded access or compassionate use program” to “another program” or “separate program”
7. To update synopsis, section Study Drug Formulation, Dosage & Administration
8. To update synopsis, section Study Summary
9. To update section 1.5 Overall benefit/Risk
10. To add section 2.2.3 Secondary Endpoints
11. To update section 2.2.3.1 Pharmacokinetics Analysis
12. To update section 2.2.3.2 Pharmacodynamic Safety Endpoints
13. To revise the title of section 2.2.3.3
14. To update section 2.2.4 Exploratory endpoints
15. To update section 3.1 Overall Study Design
16. To update section 3.2 Randomization
17. To update section 4.1 Subject Enrollment and Identification Log
18. To update section 5.1 Study Medication Administered
19. To update section 5.4 rationale for Dose Selection
20. To update section 6.1 Time and Events Schedule
21. To update Table 6. Schedule of Study Activities
22. To update section 6.2 Informed Consent Procedures
23. To add section 6.3.1 Prescreening Visit
24. To update section 6.3.2 Screening Period
25. To revise section 6.3.3 – Activities prior to first dose administration
26. To update section 6.3.5 Treatment Period (Weeks 1-24)
27. To add hemoglobin A1c at week 12
28. To update section 6.3.6 Dose-tapering Period
29. To update section 7.2.1 Medical History
30. To update section 7.2.6 Pharmacodynamic Biomarker Panel
31. To update the reference ‘c’ of table 11
32. To revise section 7.6.6 – SAE reporting

Reasons for Protocol Amendment #5:

1. To add clinical efficacy of vamorolone over 24 weeks treatment to the secondary objectives
2. To change the exploratory objective of evaluation of clinical efficacy of vamorolone to 12 weeks of treatment, in place of 24 weeks of treatment.
3. To revise EC#1: definition of uncontrolled diabetes

4. To remove height from analysis of safety measurements over 24 weeks
5. To update the date of last subject last visit
6. To update section 2.2.1 Body weight change.
7. To add NSAA and TTRW to Section 2.2.3
8. To add section 2.2.3.4 Efficacy Motor Endpoints
9. To remove Week 6 from the Section 10.7.1

STUDY SYNOPSIS

Protocol Title	A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy
Name of Sponsor	ReveraGen BioPharma, Inc.
Protocol Number	VBP15-BMD-001-A5
Drug Substance	delta-1,4,9(11)-pregnatriene-17-alpha,21-dihydroxy-16-alpha-methyl-3,20-dione
Investigational Drug Product	Vamorolone, 4.0% wt/wt suspension for oral dosing
Phase of Development	Phase II
Indication	Treatment of Becker muscular dystrophy (BMD)
Primary Objective	• To evaluate the safety and tolerability of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.
Secondary Objectives	• To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy. • To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy. • To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.
Exploratory Objectives	• To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 12-week treatment period in subjects with Becker dystrophy. • To evaluate the effect on patient-reported outcomes of treatment response of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.
Study Design	This Phase II pilot study is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg/day (250mg if <50kg body weight) compared to placebo administered

	daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory subjects with Becker dystrophy, ages ≥18 and <65. The study is comprised of a 1-day Prescreening visit (optional), 35-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in a separate program for treatment with vamorolone). Subjects will be randomized to one of two treatment groups in a 1:2 ratio (placebo: vamorolone 500mg/day [250mg if <50kg body weight]). Subjects will be enrolled into the study at the Screening Visit, at the time written main informed consent is obtained. All subjects will begin study medication (vamorolone or placebo) treatment on Treatment Period Day 1 and will continue to receive study medication treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24). At the end of the 24-week Treatment Period (Week 24), all subjects may be given the option to receive vamorolone in another program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into another program providing vamorolone will not need to taper their study medication dose prior to participation in a separate program providing vamorolone. All subjects who will not transition directly to vamorolone treatment will begin a 4-week Dose-tapering Period to taper study medication prior to discharge from the study.
Planned Sample Size	A total of approximately 39 subjects will be enrolled and randomized 1:2 to treatment with placebo or vamorolone 500mg/day (250mg if <50kg body weight) administered orally
Inclusion Criteria	1. Subject or Subject's parent(s) or legal guardian (s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures~~;~~ 2. Subject is a male and has a confirmed diagnosis of Becker dystrophy as defined as: a. Identifiable mutation within the *DMD* gene (deletion/duplication of one or more exons), where reading frame can be predicted as 'in-frame', and clinical picture consistent with Becker dystrophy, OR b. Complete dystrophin gene sequencing showing an alteration (small mutation, duplication, other) that is expected to allow

	production of an internally deleted dystrophin protein, with a typical clinical picture of Becker dystrophy; 3. Subject is ≥ 18 years of age and <65 years of age at time of informed consent; 4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) in ≤ 30 sec at screening; assistive devices, cane or walker, are allowed. 5. Subject has an NSAA score ≤ 32 at screening. 6. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit). While AST and ALT can be elevated due to disease of muscle or liver, the study PI will review any increases of AST or ALT. If above upper limit of normal (ULN), then study PI will assess whether the increases are likely of muscle origin to determine inclusion. 7. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study]; 8. Subject has evidence of chicken pox immunity as determined by: a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication; 9. Subject is willing and able to comply with scheduled visits, study medication administration plan, and study procedures. 10. Subject agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed.
Exclusion Criteria	1. Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with hemoglobin A1C level > 8.0 at screening) or immunosuppression;

	2. Subject has current or history of chronic systemic fungal or viral infections; 3. Subject has had an acute illness within 4 weeks prior to the first dose of study medication 4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication; 5. Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary unless cardiac ejection fraction is less than 40%]; 6. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents; 7. Subject has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the Investigator; 8. Subject has previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up will be correctly completed or impair the assessment of study results, in the opinion of the Investigator; 9. Subject is taking (or has taken within 4 weeks prior to first dose of study medication) herbal remedies and supplements which can impact muscle strength and function (e.g., Co-enzyme Q10, creatine, etc); 10. Subject has been administered a live attenuated vaccine within 14 days prior to the first dose of study medication; 11. Subject is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to first dose of study medication; or 12. Subject has previously been enrolled in the VBP15-BMD-001 study or any other vamorolone study. Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result.
Number of Centers	The study will be conducted at the University of Pittsburgh and the Azienda Ospedale-University of Padova.
Study Period	First subject screened: 3 Q 2022 Last subject last visit: 3 Q 2025
Study Duration	Approximately 36 months total duration

Individual Subject Study Duration	Prescreening visit (optional): 1 day Screening Period: up to 5 weeks (unless extended for varicella vaccine administration) Baseline Period: 1 day Treatment Period: 24 weeks (Weeks 1-24) Dose-tapering Period: 4 weeks (only for subjects who will not transition directly to vamorolone in another program) Subjects who complete the Treatment Period Week 24 assessments might be given the option of receiving vamorolone treatment in another program, if possible. Subjects who continue directly with vamorolone treatment in another program will be discharged from the VBP15-BMD-001 study following completion of all Week 24 assessments and will not participate in the Dose-tapering Period.
Study Drug Formulation, Dosage & Administration	**Treatment Period and Dose-tapering Period** Subjects will be administered vamorolone 4.0% wt/wt oral suspension or a matched placebo as the study medication. All subjects will be administered study medication once daily over the 24-week Treatment Period (Weeks 1-24) and during the 4-week Dose-tapering Period, as applicable. The site will dispense study medication in 120 mL bottles sufficient for 12 weeks of dosing (4 weeks for Dose-tapering Period) plus overage to subjects at the Day 1 and Week 12 Visits (and Week 24 Visit to subjects participating in the Dose-tapering Period), according to the subject's body weight (500mg/day if ≥ 50 kg or 250mg if <50kg) recorded at the dispensing visit (Day -1 weight for Day 1 dispensing). As needed, study medication bottles will be shipped to the subject's mail address. The oral suspension study medication will be administered to the subject in the study unit at the Day 1, Week 12, and Week 24 study visits; all other doses will be administered at home. Study medication oral suspension will be administered by mouth using a volumetric syringe. Following administration of the dose of study medication, the syringe will be filled once with water and the water will be administered by mouth using the volumetric syringe. The subject will then drink approximately 50 mL (approximately 2 ounces) of water to ensure the full dose has been ingested. The daily dose of study medication should be taken with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food. There are no other food or drink restrictions before or after dosing.

Study Summary	This Phase II pilot study is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, PD, and exploratory clinical efficacy of vamorolone 500mg (250mg for body weight <50 kg) daily administered orally compared to placebo over a treatment period of 24 weeks in males with Becker dystrophy. The study is comprised of a 1-day Prescreening visit (optional), a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period, and a 4-week Dose-tapering Period (for subjects not continuing directly with vamorolone treatment in another program). Subjects will be enrolled into this study at the time written main informed consent is given during the screening visit. Subjects will be administered study medication only after completion of all Pretreatment Screening assessments to confirm eligibility. Subjects will be assessed for safety, tolerability, PK, PD, and effect on physical functioning at scheduled visits throughout the study. Screening assessments will be performed prior to baseline assessments on Day -1 and first administration of study medication on Day 1. After completion of Screening and Baseline assessments, subjects will return to the study clinic on Day 1 for safety, PK and PD assessments prior to administration of the first dose of study medication. Additional on-site study visits will occur at Week 4, Week 12, Week 24, and Week 28 (for subjects participating in the Dose-tapering Period). Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the NIAMS regarding study conduct. The Study Team will receive the recommendations through the NIAMS Executive Secretary and share them with ReveraGen. Subject diaries will be dispensed at the Day 1, Week 12, and Week 24 (for subjects participating in the Dose-tapering Period) Visits to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication. The scheduled Week 12 and Week 24 assessments may be completed on a different day within the timeframe of +/- 1 week to the Week 12 or Week 24, to facilitate scheduling.

	Subjects who complete the VBP15-BMD-001 study assessments through the Week 24 Visit may be given the opportunity to receive vamorolone as part of another program. Subjects who complete the VBP15-BMD-001 study and will enroll directly into another program to receive vamorolone treatment will be discharged from the VBP15-BMD-001 study following completion of all Week 24 assessments. Subjects who will not enter another program for vamorolone treatment will have their study medication dose tapered during a 4-week Dose-tapering Period prior to discharge from the study. For these subjects, site study staff will contact the subject by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms of adrenal insufficiency, and to address any questions the subject may have. The subject should return to the study site for scheduled Week 28 assessments. In the event that any clinical or laboratory parameters remain abnormal at the time of discharge from the study, the subject will be followed medically, as clinically indicated. Any subject who discontinues the study prior to the Week 24 Visit should return to the study site for scheduled Week 24 assessments at the time of early withdrawal and a Week 28 Visit following the taper, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun should undergo dose-tapering following early completion of the Week 24 assessments and a Week 28 Visit following the taper.
Dose-Limiting Toxicities, and Stopping Criteria	If dose-limiting toxicities occur at any time during the Treatment Period, the study may be stopped or the study design may be modified, in consultation with the Study Chair, Medical Monitor, Data and Safety Monitoring Board (DSMB), and ReveraGen, depending on the timing and nature of the toxicities. Clinical AEs and clinical laboratory AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, dated November 27, 2021. Dose-limiting toxicities will be defined as follows: The presence of a CTCAE Grade ≥ 3 AE, considered to be probably or definitely related to study drug, in the opinion of the Investigator; The presence of a CTCAE Grade ≥ 3 clinical laboratory AE considered to be probably or definitely related to study drug, in the opinion of the Investigator; or

	deterioration of the muscle condition, unexpected for the natural course of Becker dystrophy and without other clear cause, in the opinion of the Investigator. The possibility to consider the event as a dose-limiting toxicity will be discussed by the Study Chair, the Medical Monitor and the DSMB. The SAE data collection tool must be completed if the event also meets the criteria for an SAE.
Safety Measures	Weight Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature [modality for determining temperature should be consistent for each subject at all assessment time points throughout the study]) Physical examination Clinical laboratory tests: Hematology and clinical chemistry CK GGT Urinalysis (urine protein and glucose) Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]) First morning cortisol (secondary endpoint) Bone biomarker (secondary endpoint) Fasting glucose and insulin (secondary endpoints) 12-lead electrocardiogram (ECG) Clinical signs and symptoms (AEs and SAEs) Grading of clinical and clinical laboratory AEs will be according to the Common Terminology Criteria for Adverse Events (CTCAE), v.5.0
Pharmacokinetic (PK) Measures **(Secondary endpoint)**	Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis.

Pharmacodynamic Measures **(Secondary endpoint)**	Blood will be collected for serum PD biomarker analysis to evaluate effects of vamorolone on biomarkers of safety associated with insulin resistance [fasting glucose and insulin, and hemoglobin A1c {HbA1c}], and bone turnover (osteocalcin) and additional exploratory biomarkers. Blood will also be collected for serum PD biomarker analysis to evaluate effects of vamorolone on biomarkers of efficacy, CD23 and MDC). Blood samples for analysis of PD biomarkers will be collected prior to the first dose of study medication at the Day 1 Visit and prior to the dose of study medication at the Week 12 and Week 24 Visit. Saliva for morning cortisol (biomarker associated with adrenal suppression) will also be collected at home and brought to the study site at the Day 1, Week 12 and Week 24 Visit. Blood samples for PD biomarkers will be collected after subjects have fasted for ≥ 8 hours, and prior to the daily dose of study medication.
Clinical Efficacy Measures	Time to run/walk 10 meters (TTRW) North Star Ambulatory Assessment (NSAA)
Patient-reported Outcome Measures	NeuroQOL patient-reported outcome measures for fatigue, upper and lower extremity function, and sleep
Statistical Methods	**Sample Size:** The primary objective is to evaluate safety and tolerability of vamorolone in Becker dystrophy, for which this is the pilot study and no effect sizes are available. A sample of 26 Becker dystrophy subjects on vamorolone will be large enough to have a confidence interval of no wider than 39% for the proportion of treatment emergent adverse events assessed or any other event outcome in the vamorolone group. We also assessed power for motor efficacy comparisons of vamorolone to placebo and present these calculations needed to detect a similar effect as that observed for TTRW velocity in DMD subjects, in Becker dystrophy. We conducted a sample size calculation based on observed TTRW values from the VBP15-003 DMD vamorolone trial (11 subjects for 24 weeks on 6.0 mg/kg/day) and VBP15-004 (25 subjects for 24 weeks on 6.0 mg/kg/day). Using observed baseline and 24-week measurements for TTRW velocities, we estimate that 39 subjects (randomized 1:2 placebo:vamorolone) will ensure that a two-sided t-test with alpha=0.05 has 83% power to detect a pooled mean difference of 0.275 m/s (sd=0.2715) in Becker dystrophy subjects on vamorolone vs. no mean change in subjects on placebo (sd=0.2715). Assuming dropout of 5%, we have 80% power. Note that subjects who withdraw early from the study may be replaced. Given our sample size calculations and that we aim to recruit 39 subjects, we should have enough power to detect a difference in TTRW velocities.

	Analysis Populations: Four populations will be defined for data analysis: Safety Population, a modified Intent-to-Treat Population, per protocol population, and a PK population Safety Population All subjects who receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety and PD assessments. Results will be presented "as treated." Modified Intent-to-Treat (mITT) Population All subjects who receive at least one dose of study medication and have at least one post-baseline efficacy assessment will be included in the mITT Population. The mITT Population is the primary analysis population for clinical efficacy. Subjects who receive at least one dose of study medication but never have post-baseline assessments will be excluded. Results will be presented "as randomized." Per Protocol Population The Per Protocol Population will be those subjects in the mITT Population who had no important protocol deviations and will be the secondary analysis population for analysis of the efficacy data PK Population The PK Population consisted of all subjects who received a dose of vamorolone on Day 1 and had sufficient quantifiable plasma concentration data for PK analysis. **General Statistical Considerations:** All measurements will be analyzed based upon the type of distribution and descriptive statistics presented by treatment group and time point, as appropriate. No formal interim statistical analyses are planned, apart from the interim safety data views and presentations to be created for the DSMB. The Week 24 analyses are the primary analyses for this study and will be performed after all subjects have completed Week 24. Missing values for safety outcomes will be treated as missing, unless stated otherwise.

	Baseline measurement is defined as the last non-missing value prior to the first dose of study drug. Analyses will be summarized by two treatment groups: Vamorolone (n=26) Placebo (n=13) A secondary efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. Another secondary efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24. For the efficacy motor endpoint, TTRW (velocity), change from baseline to Week 24 will be compared between the vamorolone dose group and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, baseline age, and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 12 and 24) along with the treatment-by-week interaction. Within this model, the comparison (using least squares [LS] mean contrasts) will be made to compare TTRW velocity at 24 weeks for the vamorolone group with placebo. For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline age and outcome, and treatment-by-week interaction). An unstructured covariance matrix will be used, and underlying modelling assumptions will be checked. If differences between baseline characteristics exist between the treatment groups, it will be investigated if adjustment for these characteristics is clinically relevant and necessary. **Safety and Tolerability Analyses:** All evaluations of clinical safety will be listed and presented using descriptive statistics by time point. Safety data will include weight, vital signs, and ECG results, and these will be presented using descriptive statistics. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed. Adverse events will be summarized overall and by system organ class (SOC) and preferred term (PT) (using the Medical Dictionary for Regulatory Activities

	[MedDRA], version 25.0) and by relationship to study medication and intensity (CTCAE grade, version 5.0) and AE outcome. **Pharmacokinetic Analyses**: Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects **Biomarkers Analyses:** Saliva and serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers. Change from Day 1 will be presented through paired t-test analyses for the serum safety pharmacodynamic biomarkers (Day 1 and Week 24) and for insulin, glucose, (Week 24 vs Day 1 and Week 12 vs. Day 1). For safety endpoints cortisol and osteocalcin, and efficacy endpoints, CD23 and MDC data, these may be used on the log scale (in case of skewness) and MMRM approach will be used and change from Day 1 compared between vamorolone and placebo dose groups. **Clinical Efficacy Analyses:** The clinical efficacy outcomes are the time to run/walk 10 meters velocity and the NSAA. Standard descriptive statistics will be used to summarize the clinical efficacy endpoints. TTRW velocities and NSAA score will be modeled via MMRM approach and change from baseline presented. **Patient-reported Outcome Analyses:** Patient-reported Outcomes will be listed and presented using descriptive statistics and ANCOVA modeling.

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL 1
SIGNATURES OF AGREEMENT FOR VBP15-BMD-001-A5 2
INVESTIGATOR PROTOCOL AGREEMENT 3
SERIOUS ADVERSE EVENT CONTACT INFORMATION 4
PROTOCOL AMENDMENT TRACKING 5
STUDY SYNOPSIS 9
TABLE OF CONTENTS 21
LIST OF TABLES 25
LIST OF FIGURES 26
LIST OF ABBREVIATIONS 27
1 INTRODUCTION 31
1.1 Background and Unmet Need 31
1.2 Nonclinical Experience 33
1.2.1 Safety Pharmacology 33
1.2.2 Pharmacokinetics and Metabolism 35
1.2.3 Toxicology 38
1.3 Clinical Experience 47
1.3.1 Phase I Study in Healthy Adult Male Volunteers (VBP15-001) 47
1.3.2 Pharmacokinetics in Phase IIa Study in 4 to <7 years Duchenne Muscular Dystrophy Boys (VBP15-002) 55
1.3.3 Safety in Phase II Studies in 4 to7 years Duchenne Muscular Dystrophy Boys (VBP15-002, VBP15-003, VBP15-LTE, and VBP15-004) 58
1.4 Rationale for Study Design 60
1.5 Overall Benefit/Risk 61
2 STUDY OBJECTIVES AND ENDPOINTS 65
2.1 Study Objectives 65
2.1.1 Primary Objective 65
2.1.2 Secondary Objective 65
2.1.3 Exploratory Objectives 65
2.2 Study Endpoints 65
2.2.1 Safety Endpoints 65
2.2.2 Tolerability Endpoint 66
2.2.3 Secondary endpoints 66
2.2.4 Exploratory Endpoints 67
3 STUDY DESIGN 68
3.1 Overall Study Design 68
3.2 Randomization 69
3.3 Blinding 70
3.4 Unblinding 70
4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS 72
4.1 Subject Enrollment and Identification Log 72
4.2 Inclusion Criteria 72
4.3 Exclusion Criteria 73
4.4 Withdrawal of Subjects from Study 74
4.5 Termination of Study 75

5 TREATMENT OF STUDY SUBJECTS 76
5.1 Study Medication Administered 76
5.2 Identity of Investigational Product 76
5.3 Dosage Schedule and Administration of Study Medication 76
5.4 Rationale for Dose Selection 78
5.5 Treatment Compliance 79
5.6 Study Drug Dose Interruption or Discontinuation 79
5.7 Prior and Concomitant Medications and Therapies 80
5.7.1 Prior Therapy 80
5.7.2 Concomitant Therapies 80
5.7.3 Prohibited Therapies 80
5.7.4 Permitted Therapies 81
5.7.5 Hydrocortisone 81
5.8 Study Medication Management 81
5.8.1 Packaging and Labeling of Study Medication 81
5.8.2 Storage of Study Medication 82
5.8.3 Study Medication Shipping and Handling 82
5.8.4 Study Medication Accountability 83
5.9 Procedures for Assigning Subject Identification Numbers 84
6 STUDY SCHEDULE 85
6.1 Time and Events Schedule 85
6.2 Informed Consent Procedures 90
6.3 Visit Schedule and Procedures 90
6.3.1 Prescreening Visit 91
6.3.2 Screening Period (Day -35 to -3) 91
6.3.3 Baseline Period (Day -1) Visit 92
6.3.4 Treatment Period Day 1 Visit 93
6.3.5 Treatment Period (Weeks 1-24) 94
6.3.6 Dose-tapering Period (Weeks 25-28) 95
6.4 Subject Discontinuation 96
6.5 Subject and Study Completion 97
7 STUDY ASSESSMENTS AND MEASUREMENTS 98
7.1 Demographic Assessments 98
7.2 Safety and Tolerability Assessments 98
7.2.1 Medical History 98
7.2.2 Physical Examination, Cushingoid Features, Weight, and Height 98
7.2.3 Vital Signs 99
7.2.4 Clinical Laboratory Tests 99
7.2.5 Chicken Pox Immunity 101
7.2.6 Pharmacodynamic Biomarker Panel 102
7.2.7 PK Assessment 103
7.2.8 Total Blood Volume Required 103
7.2.9 12-Lead ECG 104
7.3 Assessment of Muscle Function 104
7.3.1 North Star Ambulatory Assessment (NSAA) 105
7.4 Patient-Reported Outcome Measures 105

7.5 Subject Diary 105
7.6 Adverse Events, Serious Adverse Events and Unanticipated Problems 105
7.6.1 Intensity 107
7.6.2 Relationship 107
7.6.3 Clinical Laboratory Test Abnormalities 108
7.6.4 Follow-Up of Adverse Events 109
7.6.5 Dosing Error 109
7.6.6 Serious Adverse Events 109
8 STUDY COMMITTEES 113
9 DATA COLLECTION 114
9.1 Source Documents 114
9.2 Electronic Case Report Form Completion 114
9.3 Data Processing 115
9.4 Subject Diaries 115
10 STATISTICAL METHODS AND PLANNED ANALYSES 116
10.1 Sample Size Determination 116
10.2 Statistical and Analytical Plan (SAP) 116
10.2.1 Deviations from the Statistical Analysis Plan 116
10.3 Analysis Populations 116
10.3.1 Safety Population 117
10.3.2 Modified Intent-to-Treat (mITT) Population 117
10.3.3 Per Protocol Population 117
10.3.4 PK Population 117
10.4 Measures Taken to Avoid/Minimize Bias 117
10.5 Interim Analysis 117
10.6 Missing, Unused, and Spurious Data 117
10.7 Statistical Analysis 117
10.7.1 General Considerations 117
10.7.2 Subject Disposition, Demographics, and Baseline Characteristics 118
10.7.3 Safety and Tolerability Analyses 118
10.7.4 Pharmacokinetic Analyses 119
10.7.5 Pharmacodynamic Analyses 119
10.7.6 Clinical Efficacy Analyses 119
10.7.7 Patient-Reported Outcome Analyses 120
10.7.8 Concurrent Medications 120
11 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS 121
11.1 Regulatory Approval and Good Clinical Practice 121
11.2 Investigator Responsibilities 121
11.2.1 Subject Information and Informed Consent 121
11.2.2 Institutional Review Board/Independent Ethics Committee Approval and Other Institutional Requirements 121
11.2.3 Study Documentation 122
11.2.4 Delegation of Investigator Responsibilities 124
11.3 Protocol Deviations 124
11.3.1 Protocol Deviation Definitions 124

11.3.2 Reporting Important Protocol Deviations 124
11.4 Study Records Retention and Direct Access to Source Documents 125
11.5 Study Monitoring 125
11.6 Quality Assurance 126
11.7 Study Termination and Site Closure 127
11.8 Site Termination 127
11.9 Discontinuation of Study 128
12 DISCLOSURE OF DATA 129
12.1 Confidentiality 129
12.2 Publication 129
13 INVESTIGATOR PROTOCOL AGREEMENT 131
14 REFERENCES 132
15 APPENDICES 136
15.1 Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide 136
15.1.1 Dose Calculation Worksheet 136
15.1.2 Vamorolone 4.0% Suspension Dispensing Guide 136
15.2 Protocol Amendments Complete List of Changes 137
15.2.1 Protocol Amendment #1 Complete List of Changes 137
15.2.2 Protocol Amendment #2 Complete List of Changes 177
15.2.3 Protocol Amendment #3 Complete List of Changes 226
15.2.4 Protocol Amendment #4 Complete List of Changes 251
15.2.5 Protocol Amendment #5 Complete List of Changes 266

LIST OF TABLES

Table 1. $AUC_{0\text{-}24hr}$ in Mice after 179 Days Treatment with 3 Dose Levels (5, 15 and 45 mg/kg/day) 42
Table 2. Summary of Pharmacokinetic Parameters for Vamorolone after Oral Administration of Single Doses of 0.1, 0.3, 1.0, 3.0, 8.0, and 20.0 mg/kg to Healthy Subjects Under Fasted Conditions 49
Table 3. Summary of Pharmacokinetic Parameters for Vamorolone During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions 50
Table 4. Summary of Pharmacokinetic Parameters for Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0 and 6.0 mg/kg Doses to DMD Boys 57
Table 5. Overall Summary of Adverse Events (Safety Population) 63
Table 6. Schedule of Study Activities 87
Table 7. Study Medication Dose Tapering 96
Table 8. Hematology, Chemistry, GGT, and Lipids Clinical Laboratory Tests 100
Table 9. Urinalysis Clinical Laboratory Tests 101
Table 10. Pharmacodynamic Biomarkers - Exploratory Safety Outcomes 103
Table 11. Blood Sample Number and Volume by Study Visit 104

LIST OF FIGURES

Figure 1. Liver Function Enzymes in GLP Chronic Toxicology Study in Mice (26 weeks).....43
Figure 2. Plasma Concentrations of Vamorolone (VBP15) after Oral Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to Healthy Subjects Under Fasted Conditions 48
Figure 3. Relationship Between Individual Subject Vamorolone AUC($_{Inf}$) and Dose After Oral Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to Healthy Subjects Under Fasted Conditions.....49
Figure 4. Plasma Concentrations of Vamorolone (VBP15) on Days 1 and 14 During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions.....51
Figure 5. Morning Cortisol Measurements in the Vamorolone Phase I Healthy Subjects.....53
Figure 6. Fasting Serum Glucose During the Phase I MAD Period (Two Weeks Daily Treatment).....54
Figure 7. Mean Plasma Concentrations of Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0, and 6.0 mg/kg Doses.....56
Figure 8. Regression Analysis of Cmax and AUCinf versus Dose 58

LIST OF ABBREVIATIONS

Abbreviation	Definition/Term
%CV	percent coefficient of variation
ACTH	adrenocorticotropic hormone
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-24hr	area under the concentration-time curve from time 0 to 24 hours
AUC(0-t)	area under the concentration-time curve from time 0 to time t
AUC(inf)	area under the concentration-time curve from time 0 to infinity
AUClast	area under the concentration-time curve from time 0 to the last observed measurable concentration
Bayley-III	Bayley Scales of Infant and Toddler Development-III
BCRP	breast cancer resistance protein
BMI	body mass index
BSEP	bile salt export pump
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CK	creatine kinase
CL	clearance
ConA	Concanavalin A
cm	centimeter
Cmax	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Material
CTMS	Clinical Trial Management Software
CTX	C-terminal peptide fragment of collagen 1
CYP	cytochrome P450
dL	deciliter
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DNHS	Duchenne Natural History Study
DSMB	Data and Safety Monitoring Board
E50	50% of maximum effect
ECG	electrocardiogram
eCRF	electronic case report form

EAP	Expanded Access Program
EDC	electronic data capture
EK2	Egen Klassification 2 (Checklist)
EMA	European Medicines Agency
Emax	maximum effect
F%	percent bioavailability
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GALT	gut-associated lymphoid tissue
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
IC50	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
kg	kilogram
L	liter
LLC	Limited Liability Company
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LS	least squares
µg	microgram
m	meter
m2	square meter
MAD	multiple ascending dose (study)
MATE1	multidrug and toxin extrusion 1
MATE2-K	multidrug and toxin extrusion 2
MD	Medical Doctor (physician)
Mdx	mouse model lacking dystrophin

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	modified Intent-to-Treat
mL	milliliter
MTD	maximum tolerated dose
N, No.	number
NADPH	nicotinamide adenine dinucleotide phosphate
NCA	noncompartmental analytical (methods)
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
ng	nanogram
NIAMS	The National Institute of Arthritis and Musculoskeletal and Skin Diseases
nM	nanomolar
nmol	nanomole
NOAEL	no observed adverse effect level
NSAA	North Star Ambulatory Assessment
OATP1B1	organic anion transporting polypeptide B1
OATP1B3	organic anion transporting polypeptide B3
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OCT2	organic cation transporter 2
OECD	Organisation for Economic Cooperation and Development
OTC	over-the-counter (non-prescription medication)
oz	Ounce
P1NP	aminoterminal propeptide of type I collagen
PARS III	Personal Adjustment and Role Skills Scale III
PBL	peripheral blood leukocytes
PD	pharmacodynamics
PEF	Peak Expiratory Flow
P-gp	permeable-glycoprotein
PHI	Protected Health Information
PK	pharmacokinetics
PND	Postnatal Day
PODCI	Pediatric Outcomes Data Collection Instrument
PR [PQ]	time from onset of P wave to start of the QRS complex
PUL	Performance of Upper Limb (Test)
QD	once daily (dosing)
QRS	in electrocardiography, the complex consisting of Q, R, and S waves, corresponding to depolarization of ventricles [complex]
QSAR	quantitative structure-activity relationship

QT	in cardiology, the time between the start of the Q wave and end of the T wave
QTc	corrected QT interval
QTcF	Fridericia corrected QT interval
QWBA	quantitative whole-body autoradiography
RBC	Red Blood Cell
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
SD	standard deviation
SOC	system organ class
SOP	standard operating procedures
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	terminal half-life
TDI	time-dependent inhibition
TEAE	treatment-emergent adverse event
Tmax	time to maximum observed plasma concentration
TRiNDS	Therapeutic Research in Neuromuscular Disorders Solutions
TTCLIMB	Time to Climb (Test)
TTRW	Time to Run/Walk (Test)
TTSTAND	Time to Stand (Test)
ULN	Upper limit of Normal
UGT	uridine 5’-diphospho-glucuronosyltransferase
UP	Unanticipated Problem
US	United States
vs.	versus
Vss	volume of distribution at steady state
WBC	White Blood Cell
WHO	World Health Organization
wt	weight

1 INTRODUCTION

1.1 Background and Unmet Need

Becker dystrophy is a genetic neuromuscular condition that causes significant progressive disability over a lifetime. Becker dystrophy is caused by recessive mutations in the *DMD* gene at Xp21, the same gene that causes the more clinically severe Duchenne dystrophy. Whereas Duchenne dystrophy is caused by loss of dystrophin protein due to loss-of-function mutations in the *DMD* gene (cross-reactive material [CRM]-negative), Becker dystrophy shows residual dystrophin in muscle (CRM-positive). Residual dystrophin in Becker dystrophy patient muscle is abnormal in quality (molecular weight), quantity (reduced amounts), or both (Hoffman et al., 1987; Hoffman et al., 1989). Thus, the biochemical basis of Becker dystrophy is a partial deficiency of dystrophin protein in striated muscle due to mutations in the dystrophin gene. The prevalence of Duchenne dystrophy (2.48 per 100,000) and Becker dystrophy (2.38 per 100,000) are similar (Bushby et al., 1991; Lefter et al., 2017). However, Becker dystrophy can be compatible with longer lifespan, which explains the higher incidence of Duchenne dystrophy, about 2- to 3-fold higher than Becker dystrophy.

There is significant understanding of the molecular basis of partial dystrophin deficiency in Becker dystrophy, genotype/phenotype correlations, and identified a molecular mechanism underlying variable dystrophin levels via inflammation-associated dystrophin-targeting microRNAs (Hoffman et al., 1989; Beggs et al., 1991; Kesari et al., 2008; Fiorillo et al., 2015; Fiorillo et al., 2018; Clemens et al., 2020). Despite a mature understanding of the genetic basis and muscle pathophysiology of Becker dystrophy, there are no disease-modifying treatments for patients with this disorder.

Becker dystrophy demonstrates high clinical variability, with patients across the age span, and both ambulatory and non-ambulatory patients, ranging from nearly as severe as Duchenne dystrophy, to asymptomatic. This clinical variability and relatively slow progression of Becker dystrophy has hindered the development of robust clinical outcome measures that can measure efficacy across the heterogeneous Becker dystrophy patient population. Indeed, there are generally few currently enrolling clinical trials in Becker dystrophy, in contrast to often approximately 30 currently enrolling trials in Duchenne dystrophy (ClinicalTrials.gov). For Becker dystrophy, there is no pharmacological standard of care beyond non-specific cardioprotective approaches if cardiomyopathy develops.

Corticosteroids (prednisone, deflazacort) are considered standard of care for Duchenne dystrophy despite the side effects. However, in Becker dystrophy the severe side effects of chronic corticosteroid treatment over the longer lifespan for Becker dystrophy are generally considered to outweigh the clinical benefit for this disorder. As a result, treatment of Becker dystrophy patients with corticosteroids is generally limited to the most severe Becker dystrophy phenotypes that present with similar severity to Duchenne dystrophy.

Vamorolone is a first-generation delta-9,11 chemical compound belonging to the structural class of synthetic steroidal drugs, which includes the glucocorticoids prednisone, prednisolone, methylprednisolone, and dexamethasone. The chemical structure of vamorolone has optimized four subactivities of traditional glucocorticoid drugs, namely transactivation, transrepression, physiochemical membrane properties, and mineralocorticoid receptor antagonism (Heier et al., 2013; Heier et al., 2019; Liu et al., 2020). By reducing transactivation subproperties, retaining transrepression, imparting membrane stabilizing properties, and inhibiting the mineralocorticoid receptor pathway, vamorolone has favorable efficacy and adverse effect profiles relative to classic glucocorticoids in nonclinical models and is anticipated to be an attractive candidate for the treatment of patients with Becker dystrophy.

To date, glucocorticoid treatment has not been used extensively in patients with Becker dystrophy. In a recent natural history study of Becker dystrophy, only 9% of participants in the observational study were treated with glucocorticoids clinically (Clemens et al., 2020). The cumulative adverse effects of glucocorticoids, including excess weight, delayed puberty, fragile skin, loss of bone mineral density, bruising, and cushingoid appearance have significant potential to negatively impact on quality of life (Bello et al., 2015; Griggs et al., 2016). Glucocorticoids also contribute to further muscle damage with long-term administration. Vamorolone has shown few if any of the adverse effects of traditional glucocorticoids in mouse models of dystrophin deficiency (Heier et al., 2013).
This study proposes a single dose (500mg/day [250mg if <50kg body weight]) 24-week trial with a 4-week taper or continuation of therapy in another program.

The study will test 3 hypotheses:

1. Vamorolone, will prove to be safe and tolerable in a first-in-Becker dystrophy treatment study.
2. Vamorolone will demonstrate PK profile in Becker dystrophy similar to in Duchenne dystrophy and healthy controls
3. Serum biomarkers of inflammation that have been identified as candidate biomarkers in Duchenne dystrophy research, macrophage derived chemokine (MDC) and CD23, will respond to treatment with vamorolone in patients with Becker dystrophy.

The impact of the proposed study will be to provide initial testing of a promising candidate treatment for a disorder that has no current treatments, and to test candidate serum biomarkers that will facilitate future studies of treatments for a disorder with high clinical variability.
In addition to the anti-inflammatory properties of vamorolone as a result of NF-κB pathway inhibition, vamorolone may also improve efficacy over conventional glucocorticoids due to the lack of interference in the AKT1/FOXO pathway, a key feature of glucocorticoid therapy which leads in the long term to muscle wasting and atrophy (Dillingham et al., 2015). Further, vamorolone has been recently demonstrated to improve asynchronous remodeling, believed to be a component of progressive muscle weakness and wasting in dystrophin deficiency (Dadgar et

al., 2014). Vamorolone is an antagonist to the mineralocorticoid receptor, with the potential to ameliorate heart function similar to eplerenone (Heier et al., 2019; Raman et al., 2015; Raman et al., 2019). Finally, vamorolone imparts physical stability to myofiber plasma membranes, whereas prednisolone destabilizes membranes (Sreetama et al., 2018). This property addresses the primary defect of membrane instability in dystrophin deficient myofibers in DMD.
An additional mechanism of action of vamorolone could increase dystrophin expression in muscle and thus enhance clinical benefit to Becker dystrophy. The dystrophin mRNA includes a 3,600 base pair 3' untranslated region (3'UTR) that includes about 80 potential microRNA binding sites (Fiorillo et al., 2015). Specific microRNAs that are well-documented to be induced in tissue inflammation, such as miR146a, have been found to directly bind to the dystrophin 3'UTR and inhibit dystrophin protein expression (Fiorillo et al., 2015; Fiorillo et al., 2018). Vamorolone inhibits these inflammation-associated microRNAs, and in turn leads to increased dystrophin protein levels in mouse models (Fiorillo et al., 2018; Kinder et al., 2020). Indeed, the levels of dystrophin protein in muscle biopsies from Becker dystrophy patients are strongly inversely correlated with inflammatory microRNA expression (Fiorillo et al., 2015). Thus, it is anticipated that treatment of Becker dystrophy patients with vamorolone may lead to increased dystrophin content in patient muscle, and improvement in disease outcomes.

1.2 Nonclinical Experience

The safety pharmacology, pharmacokinetics (PK) and metabolism, and toxicology of vamorolone have been evaluated in multiple nonclinical studies *in vitro* and in mice, rats, beagle dogs, and cynomolgus monkeys *in vivo*.

All Good Clinical Laboratory (GLP) studies were conducted in, or inspected by, a country that has implemented the Organisation for Economic Cooperation and Development (OECD) Mutual Acceptance of Data system.

1.2.1 Safety Pharmacology

Stunted growth is a significant side effect of chronic glucocorticoid use in children (Aviolli et al., 1993; Wolthers et al., 1990) Chronic treatment with glucocorticoids negatively affects bone growth and development and can cause osteoporosis (Bircan et al., 1997; Manolagas et al., 1999).

The effect of vamorolone as compared to prednisolone on bone growth and development was evaluated in the *mdx* mouse model of DMD that lacks dystrophin due to a premature chain-terminating mutation in the mouse homologue of the dystrophin gene. In the pre-symptomatic *mdx* study, tibia length was measured to determine if vamorolone inhibited bone growth. Prednisolone significantly decreased tibia length whereas vamorolone did not affect tibia length at any concentration tested. Micro-computed tomography was performed on femurs to examine bone density and structure. Comparison of vehicle, prednisolone, and the highest vamorolone

dose showed prednisolone to significantly reduce trabecular thickness compared to vehicle, while vamorolone did not (Bello et al., 2015)

In normal, male CD-1® mice, these effects were reproduced. Unlike CD-1 mice treated with prednisolone, CD-1 mice receiving vamorolone did not experience tibia length shortening (Damsker et al., 2013). However, at the highest vamorolone dose tested, mice did have significantly reduced body length, though to a lesser extent as compared to prednisolone.

Duchenne muscular dystrophy is associated with cardiomyopathy that can become life threatening, and increased fibrosis with prednisolone treatment in heart muscle of the *mdx* mouse has been reported (Sali et al., 2012) Histologically, definitive fibrosis was evident in 50% of young (8-week) prednisolone-treated mouse hearts compared to no incidence of fibrosis identified in the other groups (wild type; *mdx* vehicle, and vamorolone-treated).

Pharmacologically, glucocorticoids show immunosuppressive and immunotoxic properties that limit therapeutic windows and long-term use. Vamorolone (5, 15, 30 mg/kg/day) was benchmarked against prednisolone (5 mg/kg/day) to determine if similar properties were observed (Bello et al., 2015) Untreated *mdx* mice showed increased numbers of peripheral blood leukocytes (PBL) and enlarged spleens resulting from ongoing muscle damage compared to wild type mice. Vamorolone treatment reduced spleen mass and PBL counts in a dose-dependent manner. This finding is attributed to a reduction in muscle damage by vamorolone that decreases spleen size to levels resembling those in wild type mice. Prednisolone reduced these measures below wild type, suggesting immunosuppressive and/or immunotoxic properties. Further, prednisolone significantly decreased viable splenocytes per gram of tissue ($p<0.005$), whereas this decrease was not observed for any vamorolone dose tested (ReveraGen Report No. MDX-RBP-VBP15-02) (Bello et al., 2015).

To further query the potential immune modulation, the effects of vamorolone and prednisolone on counts of splenic B and T-lymphocytes isolated from treated *mdx* mice were examined. CD4+ T-cell activation was assayed by stimulation of splenocytes with the T-cell mitogen, concanavalin A (ConA). Splenocytes obtained from prednisolone-treated mice displayed a significant reduction of the percentage of splenic activated CD4+CD25+ T-cells upon ConA stimulation while splenocytes derived from vamorolone-treated mice did not (ReveraGen Report No. MDX-RBP-VBP15-02).

Taken together, these findings suggest that while prednisolone treatment leads to a reduction in T-cell number and activation status, vamorolone modulates inflamed *mdx* immune systems towards a wild type state without compromising T-cell activation status.

1.2.2 Pharmacokinetics and Metabolism

1.2.2.1 Single Dose

Vamorolone PK profiles were determined in male CD-1 mice, Sprague Dawley rats and beagle dogs after a single intravenous injection of 10 mg/kg and after a single oral dose of 50 mg/kg in mice and rats and 30 mg/kg in dogs.

Pharmacokinetic results for vamorolone following a single intravenous administration of 10 mg/kg in Crl:CD1(ICR) mice demonstrated a clearance (CL) of 18.8 mL/min/kg. The terminal half-life ($t_{½}$) was 0.35 hours. Volume of distribution at steady state (V_{ss}) was 0.76 L/kg. Following oral administration of 50 mg/kg in mice, the maximum observed plasma concentration (C_{max}) of 6787 ng/mL was observed at 2 hours (time to maximum observed plasma concentration [T_{max}]) after drug administration, and percent bioavailability (F%) was 74.5%. Following oral administration of 15 mg/kg via cherry syrup, the C_{max} of 1527 ng/mL was observed at 2 hours after drug administration and bioavailability was 47.7% (ReveraGen Report No. PH-DPMK-VBP-10-004).

Pharmacokinetic results for vamorolone following a single intravenous administration of 50 mg/kg in Sprague Dawley rats indicated a CL of 20.2 mL/min/kg. The $t_{½}$ was 0.58 hours. V_{ss} was 0.77 L/kg, which was similar to that observed in mice. After oral administration of 50 mg/kg in rats, a C_{max} of 2543 ng/mL was observed at 4 hours after dose administration, and bioavailability was 47.8% (ReveraGen Report No. PH-DPMK-VBP-10-007).

In beagle dogs, vamorolone had a CL of 24.7 mL/min/kg. The $t_{½}$ was 5.42 hours and V_{ss} was 1.93 L/kg. After oral administration of 30 mg/kg in dogs, a C_{max} of 814 ng/mL was observed at 6 hours after dose administration and bioavailability was 53.2% (ReveraGen Report No. 48504-10-464).

Vamorolone clearance was therefore comparable in all 3 species studied (19-25 mL/min/kg). Bioavailability ranged from approximately 50% in mouse (cherry syrup), rat, and dog to 75% in the mouse (30% Labrafil) (ReveraGen Report Nos. PH-DPMK-VBP-10-004, PH-DPMK-VBP-10-007, 48504-10-464).

1.2.2.2 Multiple Dose

Crl:CD1(ICR) mice were administered vamorolone or vehicle once daily (QD) for 28 consecutive days. Vamorolone exposure (as assessed by the C_{max} and area under the plasma concentration-time curve from time 0 to the last observed measurable concentration [AUC_{last}]) increased with increasing dose on Study Days 1 and 28. Repeated dosing of vamorolone over a 28-day duration was associated with decreases in mean vamorolone AUC_{last} values in the 30 and 100 mg/kg dose groups compared to Day 1, indicating possible enzyme induction. On Study Day 28, mean AUC_{last} values were 1.81-fold and 5.02-fold lower compared to Study Day 1 for the 30 and 100 mg/kg dose groups, respectively. The observed difference in exposure relative to

Day 1 increased with the increase in administered dose of vamorolone (ReveraGen Report No. 1998-009).

Beagle dogs were either administered vamorolone or vehicle QD for 28 consecutive days. Vamorolone exposure in dogs (as assessed by C_{max} and AUC_{last}) generally increased with increasing dose on Study Days 1 and 28. For the 2 and 10 mg/kg dose groups, exposure on Day 28 was generally higher than on Day 1, indicating possible inhibition of metabolism of vamorolone at these dose levels. On Day 28, mean AUC_{last} values were 2.35-fold and 2.43-fold (males) and 3.03-fold and 3.23-fold (females) higher compared to Study Day 1 for the 2 and 10 mg/kg/day dose groups, respectively. For the 50 mg/kg dose group, exposure on Day 28 was similar to that on Day 1. At the 50 mg/kg dose, AUC_{last} values in males were 1.71-fold lower whereas females were 1.22 higher on Day 28 compared to Day 1 (ReveraGen Report No. 031302).

Beagle dogs were administered vehicle or vamorolone at doses of 2 mg/kg/day, 10 mg/kg/day, or 50 mg/kg/day for 39 weeks. Systemic exposure (area under the plasma concentration-time curve from time 0 to 24 hours [$AUC_{0\text{-}24hr}$]) to vamorolone appeared to be independent of sex. Mean $AUC_{0\text{-}24hr}$ and C_{max} values for vamorolone increased with increasing dose in an approximately dose proportional manner on Days 1 and 270. Mean systemic exposure ($AUC_{0\text{-}24hr}$) to vamorolone appeared to increase following repeated administration of vamorolone. Due to the alterations in the feeding regimen, changes in systemic exposure following repeated administration should be viewed with caution due the influence of feeding on exposure. For the 2 and 10 mg/kg/day dose groups, exposure on Day 270 was generally higher than on Day 1, indicating possible inhibition of metabolism of vamorolone at these dose levels. On Day 270, mean $AUC_{0\text{-}24hr}$ values were 2.34-fold and 2.98-fold higher compared to Study Day 1 for the 2 and 10 mg/kg/day dose groups, respectively. For the 50 mg/kg dose group, exposure on Day 270 was 2.07-fold higher compared to that on Day 1 (ReveraGen Report No. 1998-014).

Non-naïve cynomolgus monkeys were administered vamorolone (300 and 600 mg/kg/day) or vehicle once daily for 7 consecutive days. Vamorolone exposure (as assessed by C_{max} and AUC_{last}) generally increased with increasing dose on Study Days 1 and 7 with the exception of male monkeys on Day 7, which showed no clear increase in exposure between the 300 and 600 mg/kg/day dose levels. Repeated dosing over the 7-day study duration was associated with decreases in mean plasma vamorolone AUC_{last} values for female and male monkeys indicating possible metabolic induction. On Day 7, mean AUC_{last} values were 1.60-fold, 2.19-fold, and 2.02-fold lower in females and 1.20-fold, 2.09-fold, and 2.88-fold lower in males compared to Study Day 1 for the 100, 300 and 600 mg/kg/day dose groups, respectively (ReveraGen Report Nos. 1998-001, SW11-0418).

1.2.2.3 Distribution

In the plasma protein binding studies, percent bound was similar in human and mouse cells in culture (88.06% and 86.71%, respectively). In the blood partition experiment done *ex vivo*, the

blood to plasma ratio was similar between human and mouse (0.87 and 0.68, respectively), but the red blood cell to plasma ratio for the mouse (0.33) was less than half that of the human (0.74). Human *in vivo* data are presented in Section 1.3 (VBP15-001). In the blood/brain concentration mouse experiment *in vivo*, the plasma concentrations of vamorolone were higher than brain concentrations with the area under the plasma concentration-time curve (AUC) and C_{max} approximately 2-fold higher in plasma than in brain (ReveraGen Report Nos. ADME-NCG-PPB-NC135, ADME-VBP-PPB-V002, ADME-NCG-BP-NC134, NCATS 2013-38).

1.2.2.4 Metabolism

The *in vitro* and *in vivo* data demonstrate that vamorolone can be metabolized via multiple metabolic pathways, including glucuronidation, hydroxylation, and reduction. Glucuronidation appeared to be the major metabolic pathway in human cells *in vitro*. All metabolites observed in human *in vitro* were observed in monkey *in vitro*. Most human metabolites identified *in vitro* were also found in mouse and dog. Thus, there is no unique human metabolite identified for vamorolone.

The metabolic stability of vamorolone was assessed in non-Good Laboratory Practice (GLP) studies. Based on the data generated, vamorolone was highly stable for up to 60 minutes in human, monkey, dog, and mouse liver microsomes in the presence or absence of nicotinamide adenine dinucleotide phosphate (NADPH) and stable for up to 60 minutes in rat liver in the absence of NADPH. Moderate metabolism was apparent in rat liver microsomes in the presence of NADPH stimulation (35% remaining), suggesting that rat was a high metabolizer of vamorolone relative to other species (mouse, dog, human) (ReveraGen Report Nos. NIH-R2526, and ADME-VBP-LM-V003).

Vamorolone did not significantly inhibit any of the cytochrome P450 (CYP) enzyme isoforms tested (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). Vamorolone moderately induced CYP3A4 (24% to 42%), indicating that vamorolone is a potential inducer of CYP3A4 (ReveraGen Report Nos. ADME-VBP-Inhibition-V005, ADME-VBP-Induction-V006, ADME-VBP-Induction-V009).

1.2.2.5 Excretion

Vamorolone showed high plasma clearance in rats but, consistent with the extensive metabolism in hepatocytes from this species, the biliary and urinary excretion of the parent compound was low with an average of <0.05% of the dose recovered in bile and approximately 0.1% in urine. Overall, vamorolone showed high plasma clearance and extremely low biliary and urinary excretion (ReveraGen Report No. NCATS 2013-44).

1.2.3 Toxicology

1.2.3.1 Single Dose

Crl:CD1(ICR) mice were administered vamorolone once via oral gavage at 50, 125, 250, and 500 mg/kg and observed for abnormalities. All animals survived to their scheduled termination, and there were no significant abnormalities observed. However, a slight decrease in body weight related to vamorolone was observed in males and females at doses above 125 mg/kg. A dose dependent decrease in food consumption related to vamorolone was also observed in males and females. There were no other clinical observations (ReveraGen Report No. 1998-002).

Beagle dogs received single 60, 180, 360, and 750 mg/kg doses of vamorolone using an escalation study design with a 4-day washout period between doses. All animals survived dose escalation. Clinical signs attributed to vamorolone (750 mg/kg) included red discoloration of the ears and face. This effect occurred within a few hours of dosing and was transient. The highest dose also resulted in increased white blood cell count (increased neutrophils and monocytes [female only] and decreased lymphocytes and eosinophils [male and female]). At the 360 and 750 mg/kg dose levels, slight elevations in albumin were observed. A mild elevation in cholesterol at the 750 mg/kg (and possibly 360 mg/kg) dose level was also observed (ReveraGen Report No. 13788.01.01).

In cynomolgus monkeys, single oral doses of up to 500 mg/kg were well tolerated with no significant clinical observations (ReveraGen Report No. 1998-001).

1.2.3.2 Multiple Dose

Acute Toxicity Studies

Vamorolone or vehicle was administered to Crl:CD1(ICR) mice QD for 28 consecutive days at doses of 10, 30 and 100 mg/kg/day. All animals survived to their scheduled necropsy with the exception of a female mouse (100 mg/kg/day dose group) that was found dead on Day 16. The cause of death was considered incidental and attributed to a dosing injury based on the amount of red fluid in the thoracic cavity.

No effects attributable to vamorolone were observed on clinical observations, food consumption, ophthalmic examination, or urinalysis during the study. A dose-dependent decrease in body weight gain was observed at all doses; however, weight was fully regained during the recovery period. Adrenal gland weights were variable between groups and generally decreased, but without a dose response relationship, and correlated microscopically with minimal to moderate vacuolar degeneration and cortical atrophy. After the 2-week recovery period there was evidence of vacuolar degeneration. Liver weights were significantly increased at the 100 mg/kg/day dose level. Hepatocellular hypertrophy, increased vacuolation, and necrosis (single cell) were seen in a few male mice at 30 mg/kg/day. There was evidence of lipid and glycogen accumulation. Serum alanine aminotransferase and aspartate aminotransferase levels were

higher with associated microscopic hypertrophy/vacuolation/necrosis at 100 mg/kg/day. Spleen weights decreased in a dose-dependent manner and correlated with a decreased number of lymphocytes in spleen. Thymus weights decreased in a dose dependent manner and were associated microscopically with lymphoid atrophy. Mice had dose-dependent reductions in serum lymphocytes which were significant in the 100 mg/kg dose group. After the recovery period, all parameters returned to normal (untreated) except for thymus weights, which were increased.

Based on the liver-related findings in this study, the no observed adverse effect level (NOAEL) for vamorolone in mice is 30 mg/kg/day (ReveraGen Report No. 1998-009).

Vamorolone or vehicle was administered to beagle dogs QD for 28 consecutive days at doses of 2, 10 and 50 mg/kg/day. All animals survived to their scheduled termination and no effect of vamorolone was noted on body weight, body temperature, food consumption, ophthalmology, electrocardiography, macroscopic, or urinalysis parameters at necropsy. A dose-dependent decrease in body weight gain was observed at all doses but weights generally returned to normal during the recovery period.

Adrenal gland weights decreased which correlated with mild or moderate diffuse bilateral atrophy of the adrenal cortex, mild multifocal bilateral vacuolation of the adrenal cortex, increased white blood cell and neutrophil counts, and decreased eosinophil counts. Liver weights increased in the 50 mg/kg/day dose group, which correlated with diffuse hypertrophy and vacuolation and increased levels of alkaline phosphatase and gamma glutamyltransferase. Spleen weights decreased, which correlated with lymphoid depletion. Thymus weights decreased, which corresponded to diffuse lymphoid depletion. With the exception of diffuse depletion of lymphocytes in thymus in the 50 mg/kg group, all abnormal parameters returned to normal during the recovery period.

The NOAEL was considered by the study director to be 10 mg/kg/day. Although reversible, the liver changes were considered adverse at 50 mg/kg/day because the severity score was moderate and the changes were diffuse in nature in all animals treated at the high dose. This is in contrast to the conclusion drawn by the study pathologist, who considered the NOAEL to be 50 mg/kg/day due to reversibility following cessation of dosing (ReveraGen Report No. 31302).

Non-naive cynomolgus monkeys were administered vamorolone or vehicle QD for 7 consecutive days at doses of 100, 300, and 600 mg/kg. All animals survived until the end of the study period. There were effects on clinical observations, food consumption, and urinalysis attributable to vamorolone.

There was a dose proportional decrease in body weight gain observed in males and females at each dose (up to 11% and 9% respectively) related to vamorolone. A cessation of the body weight loss in treatment was observed during the recovery phase but no recovery of body weight lost during the 7 days of dosing was observed.

At termination there were non-significant increases in red cell mass and decreases in lymphocytes (up to 56%) in the 600 mg/kg/day dose group. However, most individual animals, including controls, had decreases in lymphocytes (up to 81%) at termination relative to their respective pretest. They had resolved by the recovery interval in both sexes.

In both sexes receiving ≥ 300 mg/kg/day, there was increased urea nitrogen (up to 141%), creatinine (up to 58%), total protein (up to 15%), albumin (up to 11%), globulin (up to 25%), and/or potassium (up to 39%) with concurrent decreases in sodium (up to 10%) and chloride (up to 10%) relative to controls. At the recovery interval, the majority of these effects had resolved (ReveraGen Report No. 1998-001).

Chronic toxicity studies

26-week chronic toxicity study in mice

A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article.

There were no vamorolone-related effects on mortality, detailed clinical observations, food consumption, ophthalmology, sperm evaluations, or bone lengths (femur or tibia).

Five test article-treated mice were unscheduled deaths (euthanized *in extremis* or found dead) during the dosing phase. Three of these were considered to be potentially due to dosing injury based on microscopic findings in mediastinum, epicardium, or lung. One of these unscheduled deaths was attributed to moderate progressive nephropathy; a spontaneous background finding. The death of one male at 5 mg/kg/day was undetermined since there were no major pathologic findings to explain the unscheduled death of this animal; there was no target organ toxicity in the mouse. Target organ toxicity was not considered a contributor to the death of these animals and there was no dose-relationship in incidence.

A vamorolone-related increase in body weight gain was observed relative to controls in males (+14%) and females (+23%) at 45 mg/kg/day. Increases in body weights at 45 mg/kg/day were not considered to be adverse due to the general health of the animals overall. During the recovery phase, bodyweights in males returned to comparable levels with controls, however female body weights remained increased compared to female controls.

Evidence of a minimal to mild vamorolone-related hepatic effects were observed in males at ≥ 5 mg/kg/day and females at 45 mg/kg/day, indicated by mild to moderate increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase activities, and/or total bilirubin, as related to microscopic hepatocellular vacuolation, inflammation, and/or necrosis in males at ≥ 15 mg/kg/day and females at 45 mg/kg/day; these changes had generally resolved at

recovery collections with the exception of minimal increases in alanine aminotransferase activity in females at 45 mg/kg/day, which may have correlated to microscopic liver pathology.

A mild vamorolone-related increase in neutrophil counts was observed in both sexes at 45 mg/kg/day with concurrent decreases in lymphocyte counts in females at 45 mg/kg/day consistent with a glucocorticoid-like effect, as related to microscopic lymphoid depletion, although an inflammatory stimulus may have contributed to increases in neutrophil counts, as related to microscopic liver inflammation; these changes had generally resolved at recovery collections.

A mild vamorolone-related decrease in chloride was observed in males at ≥ 5 mg/kg/day and females at ≥ 15 mg/kg/day that lacked correlative findings among other study endpoints; resolution for this endpoint could not be determined.

A mild vamorolone-related increase in albumin was observed in males at ≥ 5 mg/kg/day and females at 45 mg/kg/day with concurrent mild increases in globulin in females at 45 mg/kg/day; these changes had resolved at recovery collections.

A minor vamorolone-related alteration in lipid metabolism was observed in both sexes at 45 mg/kg/day and females at 15 mg/kg/day indicated by increases in triglyceride and/or cholesterol; these changes had resolved at recovery collections.

Vamorolone-related macroscopic findings occurred in the liver of mice at 45 mg/kg/day. Tan discoloration occurred in one female and four males at this dose in the dosing phase. This correlated with microvesicular/macrovesicular hepatocyte vacuolation. There were no test article-related macroscopic findings in recovery animals.

Test article-related microscopic findings occurred in adrenal gland (cortical atrophy- with correlating decreases in adrenal weights in females), liver (increased severity of centrilobular hypertrophy; hepatocyte vacuolation; hepatocyte vacuolation; and inflammation/necrosis), lymphoid tissues (thymus, spleen, mandibular lymph node, mesenteric lymph node, and gut-associated lymphoid tissue [GALT]) skin, and pancreatic islets (minimal to mild hypertrophy). Observed changes in these tissues are considered pharmacologically-mediated and not adverse.

An increased incidence of decreased anagen hair follicles occurred in mice at 45 mg/kg/day. Decreased anagen hair follicles was documented for individual animals when there were no anagen hair follicles in the section of skin. Incidence in controls and mice at 5 and 15 mg/kg/day were similar. A severity score was not given to the decrease as this may have been somewhat dependent on size of skin sample. This change is not considered adverse.

There was full reversibility of lymphoid changes in thymus, spleen, mesenteric lymph node, mandibular lymph node, and GALT. There were no meaningful differences between treated and controls at the end of the recovery tissues for these lymphoid tissues. There was recovery of adrenal gland findings in females and partial recovery of adrenal gland findings in males. In

addition, there was partial reversibility of liver findings for males and females. Minor changes persisted in the pancreas and skin.

Systemic exposure to vamorolone appeared to be sex-dependent on Day 1 (males > females) and appeared to be independent of sex on Day 179. Following daily administration of vamorolone in females and males, systemic exposure ($AUC_{0\text{-}24hr}$) and C_{max} values of vamorolone increased with increasing dose in a greater than dose proportional manner on Day 1 and in an approximately dose proportional manner on Day 179. Systemic exposure to vamorolone in females appeared to increase following repeated administration of vamorolone at 5 mg/kg, did not appear to change following repeated administration of vamorolone at 15 mg/kg, and appeared to decrease following repeated administration of vamorolone at 45 mg/kg. Systemic exposure to vamorolone in males appeared to decrease following repeated administration of vamorolone (Table 1).

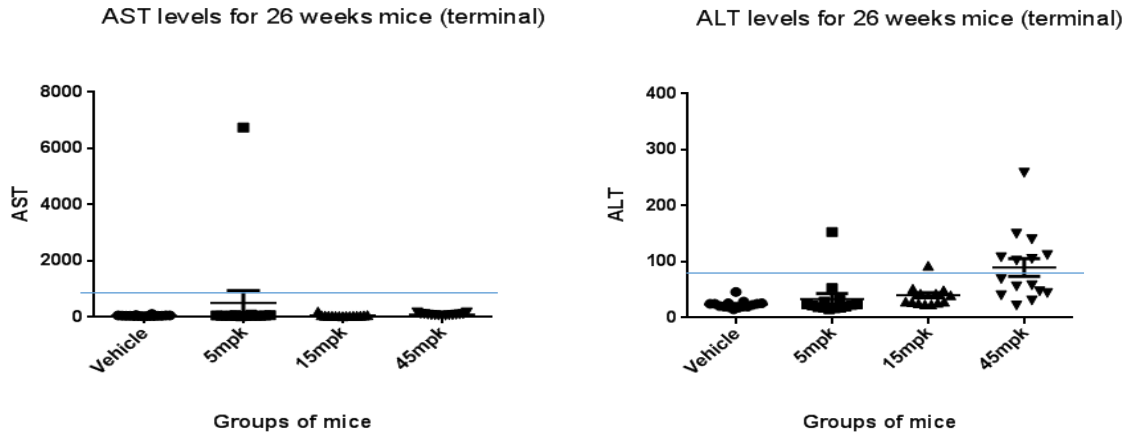
Table 1. $AUC_{0\text{-}24hr}$ in Mice after 179 Days Treatment with 3 Dose Levels (5, 15 and 45 mg/kg/day)

Average $AUC_{0\text{-}24hr}$ (hr*ng/mL)				
Dose (mg/kg/day)	Male		Female	
	Day 1	Day 179	Day 1	Day 179
5	5700	1150	159	991
15	11600	3710	3450	4240
45	50700	10200	27000	12700

The once daily administration of vamorolone via oral gavage to mice for 26 weeks at 5, 15, and 45 mg/kg/day did not produce any adverse effects. Therefore, the No-Observable-Adverse-Effect Level (NOAEL) is considered to be 45 mg/kg/day under the conditions of this study.

As liver is considered a primary target organ, the liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) of mice in this study were studied at study termination (Figure 1).

Figure 1. Liver Function Enzymes in GLP Chronic Toxicology Study in Mice (26 weeks)



There were no differences between male and female mice regarding liver function enzymes. There were no drug-related elevations of AST at any dose. The highest dose tested (45 mg/kg/day) showed mild elevations of ALT with about half of values above the upper limit of normal range. The mild elevations of ALT were reversible, returning to within normal range after cessation of drug.

The Study Director concluded that the once daily administration of vamorolone via oral gavage to mice for 26 weeks at 5, 15, and 45 mg/kg/day did not produce any adverse effects. Therefore, the No-Observable-Adverse-Effect Level (NOAEL) is considered to be 45 mg/kg/day under the conditions of this study.

39-week chronic toxicity study in beagle dogs

Vamorolone or vehicle was administered to beagle dogs once daily for 39 weeks at doses of 2, 10 and 50 mg/kg/day. Six dogs of each sex received each dose or placebo, and two of the six dogs of each sex at each dose or placebo were followed for an additional 4 weeks to evaluate reversibility, progression, or delayed appearance of any observed changes. One male dog that received 50 mg/kg/day was euthanized in extremis on Day 273 due to paraphimosis (an extended penis). All other animals survived to their scheduled termination.

Detailed clinical observations considered test article-related at 50 mg/kg/day, and reversible, included decreased activity (considered adverse), struggling during dosing, feces soft, limb function impaired, interdigital cysts, and unkempt appearance (considered adverse). Test article-related, dose-dependent increases in body weight gains correlating with increases in food consumption were observed relative to controls in males at all dose levels and in females at 10 and 50 mg/kg/day. Test article-related, reversible increases in average mean food consumption were observed relative to controls over the course of the 39-week dose phase in both sexes at 10 and 50 mg/kg/day.

No test article-related ophthalmological effects were noted. No test-article-related changes were noted in respiratory rates or rectal temperatures. There may have been a mild dose-related reversible increase in the heart rate at the terminal post-dose interval that was significantly different from vehicle in both sexes following the 50 mg/kg/day dose. Semen analysis/evaluation for test article affects could not be conducted as there were not enough viable samples collected.

Test article-related effects on clinical pathology endpoints with microscopic correlates included the following:

- A hepatocellular and hepatobiliary effect in males at 10 mg/kg/day and both sexes at 50 mg/kg/day, which included increased alkaline phosphatase, gamma glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase activity. These changes correlated with microscopic changes in the liver, bile duct, and gall bladder. This spectrum of changes was considered adverse in both sexes at 50 mg/kg/day.
- There was also evidence of an inflammatory response in both sexes at 50 mg/kg/day, which included increased total leukocyte, neutrophil, and monocyte counts, and increased fibrinogen and/or globulin concentrations. The inflammatory response was likely secondary to inflammation in the liver associated with hepatocellular necrosis. Platelet counts were also increased in both sexes at 50 mg/kg/day and may have been secondary to the inflammatory response.

Following a 4-week recovery period, all noted clinical pathological changes resolved, with the exceptions of increased alanine aminotransferase activity in both sexes at 50 mg/kg/day, and increased globulin in males at 50 mg/kg/day.

Reversible, test article-related macroscopic findings included mildly to moderately enlarged livers in males and females at 50 mg/kg/day, which correlated microscopically with panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation; hemorrhage in the gall bladder of one 50 mg/kg/day female, that was associated with moderate acute inflammation and mild vascular necrosis, and considered to be adverse; red focus/foci within the pylorus of the stomach of one 50 mg/kg/day female and one male at 10 mg/kg/day, which correlated microscopically with mild acute inflammation in the female.

Test article-related organ weight changes at the terminal necropsy included decreases in adrenal gland weights in both sexes at ≥ 2 mg/kg/day (microscopic correlate of bilateral cortical atrophy); increases in liver weights in both sexes at ≥ 10 mg/kg/day (microscopic correlates of panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation); increases in kidney weights in females at ≥ 10 mg/kg/day and males at 50 mg/kg/day (microscopic correlate of bilateral tubular vacuolation); decreases in prostate gland weights in males at 50 mg/kg/day (microscopic correlate of decreased secretory product). These organ weight changes were all reversible, except for the decreases in the prostate gland. Microscopic evaluation revealed the

following test article-related changes: adrenal glands (atrophy of the zona fasciculata and zona reticularis and hypertrophy/hyperplasia of the zona glomerulosa in both sexes at ≥ 10 mg/kg/day and atrophy was considered adverse); esophagus and pylorus of the stomach (erosion/ulceration in a few animals of both sexes at 50 mg/kg/day); gallbladder (hypertrophy/hyperplasia of the mucosal epithelium in both sexes at ≥ 10 mg/kg/day and cytoplasmic vacuolation of the mucosal epithelium in males at ≥ 10 mg/kg/day and females at ≥ 2 mg/kg/day); liver (hepatocellular vacuolation in males at ≥ 10 mg/kg/day and females at ≥ 2 mg/kg/day, panlobular hypertrophy in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day, and inflammation/necrosis in both sexes at 50 mg/kg/day and considered adverse, bile duct hyperplasia in both sexes at 50 mg/kg/day, bile duct hypertrophy in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day, and cytoplasmic vacuolation of the bile duct epithelium in both sexes at ≥ 10 mg/kg/day); kidneys (bilateral tubular vacuolation in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day and an increased incidence of bilateral basophilic tubules in males and females at 50 mg/kg/day); lymphoid depletion in both sexes at 50 mg/kg/day in mandibular and mesenteric lymph nodes, thymus and spleen (with extramedullary hematopoiesis in 50 mg/kg/day females); bone marrow in the sternum (increased adipocytes in males at ≥ 2 mg/kg/day and females at 50 mg/kg/day); testes (spermatocyte/spermatid degeneration in males at 50 mg/kg/day); epididymides (oligospermia/germ cell debris in males at 50 mg/kg/day); ovaries (absent corpora lutea in females at ≥ 2 mg/kg/day and considered adverse); the mammary gland and other tissues in the female reproductive tract (uterus, cervix, and vagina) of these animals were consistent with animals that have not ovulated; vacuolation in the epithelium of the mammary gland duct in females at 50 mg/kg/day; parotid salivary gland (cytoplasmic alteration in both sexes at ≥ 10 mg/kg/day); biceps femoris (atrophy of the skeletal muscle in both sexes at 50 mg/kg/day); skin (atrophy and alopecia/hypotrichosis in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day); prostate gland (decreased secretory product in males at 50 mg/kg/day); thyroid glands (bilateral increased colloid in males at ≥ 10 mg/kg/day).

Many of the findings were considered by the Study Director to be consistent with the pharmacology of the test article including cortical atrophy of the adrenal glands (affecting the zona fasciculata and reticularis), generalized lymphoid depletion in lymphoid tissues (thymus, spleen, and lymph nodes), increased adipocytes in the bone marrow, atrophy of the skeletal muscle, alopecia/hypotrichosis and atrophy of the skin (thinning of the dermal collagen and atrophy of hair follicles and adnexa), an absence of corpora lutea in the ovary (likely indicative of delayed puberty), decreased secretory product in the prostate gland, and multiple changes in the liver. The liver had panlobular hypertrophy and vacuolation of hepatocytes consistent with glycogen accumulation. Due to the magnitude of hypertrophy and vacuolation, there were (likely secondary) foci of hepatocellular necrosis and inflammation.

Test article-related microscopic findings at the recovery necropsy were present in the adrenal glands, liver, gallbladder, kidneys, stomach (pylorus), female reproductive tract (ovaries), male reproductive tract (testes, epididymides, prostate gland), mesenteric lymph node, skeletal muscle (biceps femoris), and parotid salivary gland.

The No Observed Adverse Effect Level was 2 mg/kg/day for males; a No Observed Adverse Effect Level was not observed for females (ReveraGen Report No. 1998-014).

7-day study in cynomolgus monkeys

Non-naive cynomolgus monkeys were administered vamorolone or vehicle QD for 7 consecutive days at doses of 100, 300, and 600 mg/kg. All animals survived until the end of the study period. There were effects on clinical observations, food consumption, and urinalysis attributable to vamorolone that are described below.

There was a dose proportional decrease in body weight gain observed in males and females at each dose (up to 11% and 9% respectively) related to vamorolone. A cessation of the body weight loss in treatment was observed during the recovery phase but no recovery of body weight lost during the 7 days of dosing was observed.

At termination there were nonsignificant increases in red cell mass and decreases in lymphocytes (up to 56%) in the 600 mg/kg/day dose group. However, most individual animals, including controls, had decreases in lymphocytes (up to 81%) at termination relative to their respective pretest. These decreases had resolved by the recovery interval in both sexes.

In both sexes receiving ≥ 300 mg/kg/day, there was increased urea nitrogen (up to 141%), creatinine (up to 58%), total protein (up to 15%), albumin (up to 11%), globulin (up to 25%), and/or potassium (up to 39%) with concurrent decreases in sodium (up to 10%) and chloride (up to 10%) relative to controls. At the recovery interval, the majority of these effects had resolved (ReveraGen Report No. 1998-001).

1.2.3.3 Genotoxicity

The mutagenic and genotoxic potential of vamorolone was assessed in several assays. A non-GLP Ames screen was negative for bacterial mutations (ReveraGen Report No. BIO-VBP-001-AMES). In a GLP Ames test, no background lawn toxicity was observed; however, a reduction in revertant counts was observed (ReveraGen Report No. AD79DT.502ICH.BTL). Vamorolone was negative for inducing chromosomal aberrations in cultured mouse lymphocytes without and with metabolic activation (ReveraGen Report No. AD79DT.704.BTL).

Femoral bone marrow was microscopically evaluated for the presence of polychromatic erythrocytes (PCEs) containing micronuclei. No significant reductions in the PCEs/EC (total erythrocytes) ratio were observed in the vamorolone groups compared to the vehicle control group. Although statistically significant increases in the incidence of micronucleated PCEs in the vamorolone treated groups were observed, no dose response was observed with respect to other groups and the values of micronuclei for the individual animals were within the historical range. Therefore, the statistically significant increase was considered as biologically insignificant (ReveraGen Report No. AD76BK.123012ICH.BTL).

A study was performed to evaluate the potential mutagenicity of two theoretical epoxide impurities related to the drug substance vamorolone (formerly VBP15), which is a steroid-like structure containing a delta 9,11 double bond. The delta 9,11 epoxide structures evaluated were VBP15-B-3, which is structurally similar to vamorolone except for the epoxide moiety, and VBP15-B-2, which has a 21-acetate substitution (vamorolone and VBP15-B-3 contain a 21-hydroxy moiety). Two validated and complementary *in silico* prediction methodologies were used for assessing mutagenic potential. The statistics-based quantitative structure-activity relationship (QSAR) program MultiCASE CASE Ultra was used, employing four different modules (GT1_A7B, GT1_AT_ECOLI, PHARM_ECOLI, and PHARM_SAL) designed to cover a wide range of molecular substructures collected from both proprietary and public compounds. In addition, the expert rule-based SAR program Derek Nexus was used to determine if the theoretical impurities contained structural alerts associated with known genotoxicants. CASE Ultra predicted both VBP15-B-2 and VBP15-B-3 as negative for mutagenicity (ReveraGen Report "In Silico Mutagenicity Evaluation of Delta 9,11 Epoxide Structures of VBP15: VBP15-B-2 [21-Acetate] and VBP15-B-3 [21-Hydroxy]").

Taken together, these data indicate vamorolone is negative for any mutagenic signal.

1.3 Clinical Experience

Clinical experience with vamorolone is comprised of a completed Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001), completed Phase IIa (VBP15-002) and Phase II extension (VBP15-003) trials in DMD boys, completed Phase II long-term extension (VBP15-LTE) trial in DMD boys, and a completed Phase IIb active- and placebo-controlled trial in DMD boys (VBP15-004). Furthermore, two relative bioavailability (BA) and food effect (FE) studies have been conducted (VBP15-PKFORM and VBP15-PKFORM-002) comparing the formulation used in clinical studies (ROS1) with the to-be-marketed formulation (ROS2).

1.3.1 Phase I Study in Healthy Adult Male Volunteers (VBP15-001)

1.3.1.1 Study Design and Objectives

The safety, tolerability, and PK of vamorolone were initially evaluated in a Phase I , placebo-controlled, double-blind, single ascending dose (SAD) and multiple ascending dose (MAD) study. In the SAD portion of the study, Cohorts 1 through 5 and Cohort 7 were comprised of eight subjects each; six subjects in each cohort received a single oral dose of vamorolone (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 8.0 mg/kg, and 20 mg/kg, respectively) and two subjects in each cohort received placebo under fasted conditions. In Cohort 6, six subjects received a single oral dose of 8.0 mg/kg vamorolone within 30 minutes of beginning a high fat/high calorie meal. The MAD portion of the study had four cohorts of 8 subjects each; six subjects in each cohort received 14 daily doses of vamorolone (1.0, 3.0, 9.0 and 20.0 mg/kg/day) and two subjects in each cohort received placebo.

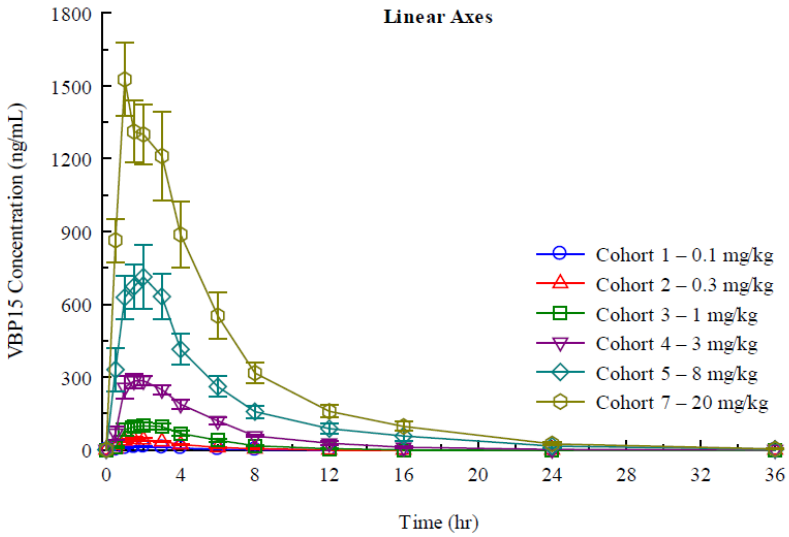
The primary objectives of the Phase I study were to evaluate the safety and tolerability of single and multiple oral doses of vamorolone, and to evaluate the PK of single doses and multiple doses of vamorolone. A secondary objective was to evaluate the effect of food on the absorption and PK of vamorolone. Other objectives were to obtain samples from subjects on Day 1 (pre-dose) and Day 14 of the MAD cohorts for use in Metabolites in Safety Testing (MIST) assessments, and to test back-up PK samples from a subset of MAD subjects for pharmacodynamic (PD) biomarkers.

1.3.1.2 Pharmacokinetics

SAD Cohorts – Pharmacokinetics (Fasted)

Vamorolone PK data shows strong adherence to dose linearity and dose proportionality, with relatively little subject-subject variation (Figure 2, Table 2, Figure 3). The half-life was about 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0 and 20.0 mg/kg showed an extended tail, increasing half-life to 2.5, 3.3 and 4.3 hours, respectively (Figure 2, Table 2).

Figure 2. Plasma Concentrations of Vamorolone (VBP15) after Oral Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to Healthy Subjects Under Fasted Conditions



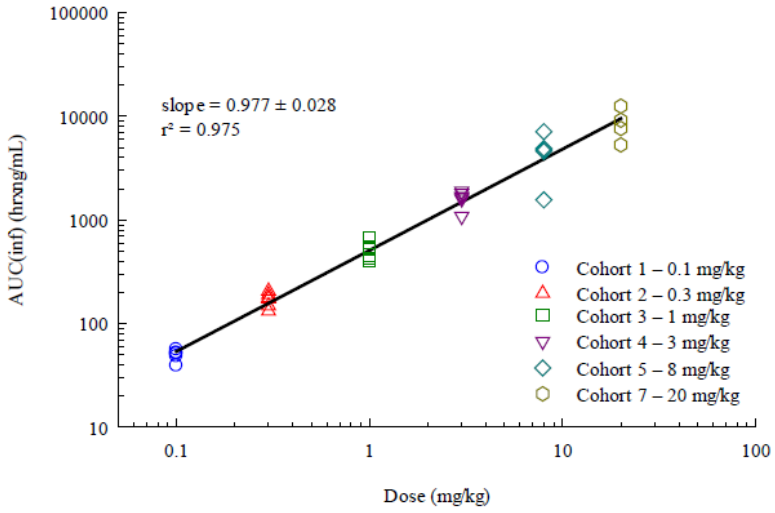
Data presented as arithmetic mean ± standard error

Table 2. Summary of Pharmacokinetic Parameters for Vamorolone after Oral Administration of Single Doses of 0.1, 0.3, 1.0, 3.0, 8.0, and 20.0 mg/kg to Healthy Subjects Under Fasted Conditions

Parameter*	Dose					
	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	8 mg/kg	20 mg/kg
Cmax (ng/mL)	13.1 (12.8) (6)	50.8 (16.5) (6)	122 (32.8) (6)	305 (24.4) (6)	718 (42.5) (6)	1,648 (16.7) (6)
Tmax (hr)	1.50 (6)	1.50 (6)	1.75 (6)	1.75 (6)	1.78 (6)	1.50 (6)
	[1.50 – 2.03]	[1.00 – 3.00]	[1.00 – 3.00]	[1.00 – 2.00]	[1.00 – 2.00]	[1.00 – 3.03]
AUC(0-t) (hr×ng/mL)	41.9 (16.8) (6)	161 (15.9) (6)	486 (19.7) (6)	1,577 (20.7) (6)	3,997 (55.0) (6)	8,545 (29.5) (6)
AUC(inf) (hr×ng/mL)	49.5 (12.5) (6)	170 (16.5) (6)	500 (19.2) (6)	1,600 (20.3) (6)	3,602 (60.2) (4)	8,653 (37.0) (4)
λz (1/hr)	0.4060 (12.5) (6)	0.4325 (17.8) (6)	0.3828 (17.9) (6)	0.2773 (16.3) (6)	0.2136 (40.9) (4)	0.1629 (25.2) (4)
t½ (hr)	1.71 (12.5) (6)	1.60 (17.8) (6)	1.81 (17.9) (6)	2.50 (16.3) (6)	3.25 (40.9) (4)	4.26 (25.2) (4)
CL/F						
(L/hr/kg)	2.02 (12.5) (6)	1.76 (16.5) (6)	2.00 (19.2) (6)	1.88 (20.3) (6)	2.22 (60.2) (4)	2.31 (37.0) (4)
(L/hr)	168 (20.8) (6)	142 (14.4) (6)	165 (12.0) (6)	152 (18.5) (6)	196 (57.6) (4)	180 (29.8) (4)
Vz/F						
(L/kg)	4.98 (6.14) (6)	4.07 (20.5) (6)	5.22 (18.5) (6)	6.76 (28.7) (6)	10.4 (61.8) (4)	14.2 (37.2) (4)
(L)	415 (17.4) (6)	329 (19.6) (6)	432 (22.8) (6)	550 (28.7) (6)	919 (63.1) (4)	1,107 (34.6) (4)

*Geometric mean (%CV) (N) except T_{max} for which the median (N) [Range] is reported.
C_{max} = maximum observed plasma concentration; T_{max} = time to maximum observed plasma concentration; $AUC_{(0-t)}$ = area under concentration-time curve from time 0 to time t; $AUC_{(inf)}$ = area under concentration-time curve from time 0 to infinity; λ_z = elimination rate constant; $t_{½}$ = terminal half-life; CL/F = apparent total clearance from plasma; V_z/F = apparent volume of distribution during terminal phase.

Figure 3. Relationship Between Individual Subject Vamorolone $AUC_{(Inf)}$ and Dose After Oral Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to Healthy Subjects Under Fasted Conditions



MAD Cohorts

The relatively short half-life of vamorolone (2-4 hours), coupled with the planned daily dose schedule, was expected to give PK data on each single dose, not cumulative dose, as the dosing interval was > 5 × $t_{½}$. The MAD component was therefore a study of individual daily doses, rather than dose-related accumulation and pharmacodistribution related to cumulative drug exposure. Thus, with the short half-life of vamorolone, useful information to determine steady

state drug levels was not expected. Safety and tolerability were additional goals of the MAD study.

MAD Cohorts – Pharmacokinetics Fasted

The original design for the Phase I MAD was modified to remove the two lowest doses (0.1, 0.3 mg/kg/day), and to begin dosing at 1.0 mg/kg/day. Four cohorts were completed (1.0 mg/kg/day, 3.0 mg/kg/day, 9.0 mg/kg/day, 20.0 mg/kg/day) for the MAD study (Table 3).

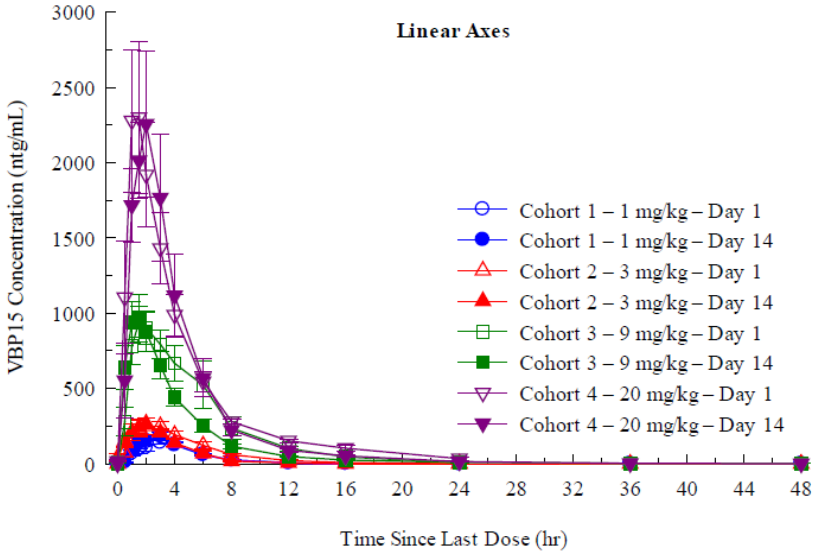
Table 3. Summary of Pharmacokinetic Parameters for Vamorolone During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions

	Vamorolone Dose			
	1 mg/kg	**3 mg/kg**	**9 mg/kg**	**20 mg/kg**
Day 1 C_{max} (ng/mL)	153 (15.9)	281 (36.9)	1,082 (23.3)	2,416 (51.1)
T_{max} (hr)	3.04 [1.50 – 4.00]	2.01 [1.00 – 3.00]	1.75 [1.00 – 6.00]	1.00 [0.50 – 3.00]
$AUC_{(0-t)}$ (hr_xng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)
$AUC_{(0-24)}$ (hr_xng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)
$AUC_{(inf)}$ (hr_xng/mL)	695 (22.1)	1,487 (23.7)	5,745 (29.5)	10,190 (27.0)
λ_z (1/hr)	0.3848 (10.9)	0.2918 (18.1)	0.2317 (22.6)	0.1747 (44.3)
$t_{½}$ (hr)	1.80 (10.9)	2.38 (18.1)	2.99 (22.6)	3.97 (44.3)
CL/F (L/hr/kg)	1.44 (22.1)	2.02 (23.7)	1.57 (29.5)	1.96 (27.0)
V_z/F (L/kg)	3.74 (16.9)	6.91 (34.8)	6.76 (46.9)	11.2 (77.6)
Day 14 C_{max} (ng/mL)	203 (30.1)	276 (35.6)	935 (48.3)	2,491 (27.9)
T_{max} (hr)	2.96 [1.50 – 3.00]	2.50 [1.00 – 4.00]	1.25 [0.55 – 3.00]	2.00 [1.00 – 2.00]
$AUC_{(0-24)}$ (hr_xng/mL)	794 (22.3)	1,494 (18.6)	4,366 (20.2)	9,309 (38.8)
λ_z (1/hr)	0.3993 (20.4)	0.3273 (25.2)	0.1629 (63.5)	0.1879 (31.6)
$t_{½}$ (hr)	1.74 (20.4)	2.12 (25.2)	4.25 (63.5)	3.69 (31.6)
CL/F (L/hr/kg)	1.26 (22.3)	2.01 (18.6)	2.06 (20.2)	2.15 (38.8)
V_z/F (L/kg)	3.15 (20.6)	6.14 (39.7)	12.7 (79.9)	11.4 (49.1)

C_{max} = maximum observed plasma concentration; T_{max} = time to maximum observed plasma concentration; $AUC_{(0-t)}$ = area under concentration-time curve from time 0 to time t; $AUC_{(0-24)}$ = area under concentration-time curve from time 0 to 24 hours; $AUC_{(inf)}$ = area under concentration-time curve from time 0 to infinity; λ_z = elimination rate constant; $t_{½}$ = terminal half-life; CL/F = apparent total clearance from plasma; V_z/F = apparent volume of distribution during terminal phase.

Taking into account the small numbers and different subjects, the geometric mean values for C_{max}, $AUC_{(0-t)}$, and $AUC_{(inf)}$ are not different for the SAD and MAD cohorts. Within the MAD, there is good agreement between Days 1 and 14 at all dose groups. There is no accumulation — the geometric mean C_{max} and $AUC_{(0-24)}$ on Days 1 and 14 are not different, consistent with the $t_{½}$ (~2-4 hours) and dosing interval (24 hours) (Figure 4; Table 3).

Figure 4. Plasma Concentrations of Vamorolone (VBP15) on Days 1 and 14 During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions



Data presented as arithmetic mean ± standard error

1.3.1.3 Safety

SAD Cohorts

In the SAD part, overall, 6 subjects (11%) administered vamorolone experienced a total of 10 treatment-emergent adverse events (TEAEs); no subject in the placebo group experienced any TEAEs. There was no dose-related trend in the incidence or severity of TEAEs; the dose group with the highest number of subjects reporting TEAEs was the 0.1 mg/kg dose group (2 subjects, 33%), and the highest number of TEAEs (3 events) was reported by 1 subject in the 1.0 mg/kg vamorolone dose group. In the 0.3 and 3.0 mg/kg vamorolone fasted and the 8.0 mg/kg fed dose groups, 1 subject per group (17%) experienced TEAEs, and no subjects in the 8.0 mg/kg and 20 mg/kg, fasted, dose groups experienced any TEAEs. The most common TEAEs were dizziness and headache, each reported by 2 subjects overall (4%); all other TEAEs were reported by only 1 subject (2%) and included ear pain, nausea, non-cardiac chest pain, and blood bilirubin increased. Three subjects (6%) had TEAEs that were considered possibly related to treatment. Possibly related TEAEs included nausea (1 subject, 2%), dizziness (2 subjects, 4%), and headache (2 subjects, 4%). One subject (2%) had a moderate TEAE of blood bilirubin increased, which was considered unrelated to study drug. All other TEAEs were mild in severity.

MAD Cohorts

In the MAD part, overall, a total of 6 subjects (19%) administered vamorolone or placebo experienced a total of 10 TEAEs: 2 subjects each in the 1.0 mg/kg vamorolone, 20 mg/kg

vamorolone, and placebo groups, and none in the 3.0 mg/kg and 9.0 mg/kg dose groups. There was no dose-related trend in the incidence or severity of TEAEs. The most common TEAE was headache (2 subjects, 6%); all other TEAEs occurred in only 1 subject (3%) per group, and included nausea, toothache, vomiting, ALT increased, hepatic enzyme increased, arthralgia, dizziness, and syncope. TEAEs were considered possibly related in 2 subjects (6%) and remotely related in 1 subject (3%). Possibly related AEs were ALT increased and hepatic enzyme increased, occurring in 1 subject in the 20 mg/kg vamorolone and placebo groups, respectively. The remotely related TEAEs were dizziness and syncope, both occurring in the same subject (1.0 mg/kg vamorolone). All TEAEs were mild in severity.

With the exception of the AEs related to hepatic enzymes, there were no other meaningful changes in clinical laboratory parameters. Of note, glucose levels remained stable at all doses of vamorolone in both the SAD and MAD parts, suggesting that vamorolone does not induce insulin resistance at the doses and dosing duration studied; in addition, no changes in the white blood cell count differential were observed, suggesting that vamorolone did not induce immunosuppressive effects in this study population.

1.3.1.3.1 Pharmacodynamic Safety Biomarkers

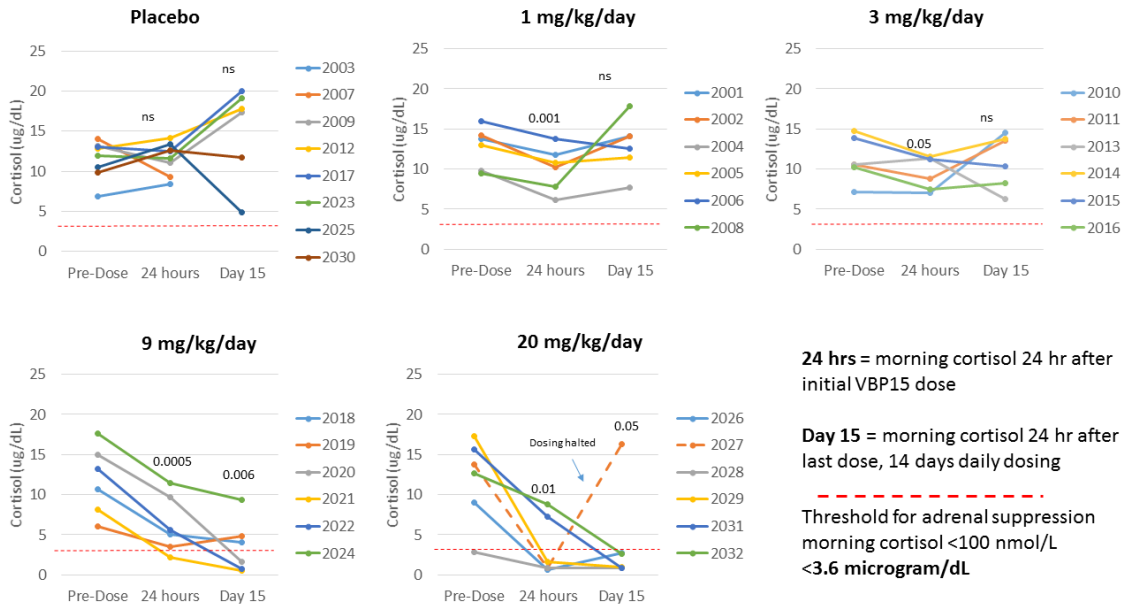
Vamorolone has shown improved safety profiles relative to prednisone in nonclinical testing, both *in vitro* and *in vivo* (Bello et al., 2015; Dillingham et al., 2015). Safety concerns with glucocorticoids include suppression of the adrenal axis and insulin resistance. Pharmacodynamic biomarker assays of suppression of the adrenal axis (serum cortisol) and insulin resistance (serum glucose) were measured in the Phase I MAD studies of vamorolone.

Suppression of the adrenal axis. Prednisone directly impinges on cortisol regulatory pathways (adrenal axis) both acutely and chronically. Acute suppression of adrenal function is seen within hours of doses of a single 0.1 mg/kg/day (approximate) dose of prednisone, as evidenced by reductions in adrenocorticotropic hormone (ACTH) levels in normal volunteers (Kauh et al., 2012) More chronic suppression of the adrenal axis, characterized as severe, is typically diagnosed when morning cortisol is < 100 nmol/L (< 3.6 µg/dL) when drawn > 24 hrs after the last dose of pharmacological steroids.

Morning serum cortisol levels were measured in the vamorolone Phase I MAD cohorts, at baseline (prior to drug administration), 24 hours after the first dose (Day 1), and 24 hours after the 14-day dose (Day 15) (Figure 5). Volunteers receiving vamorolone at four MAD dose levels are shown (1.0 mg/kg/day; 3.0 mg/kg/day; 9.0 mg/kg/day; 20.0 mg/kg/day); all subjects were treated for 14 days with daily dosing. The red hatched line on each graph shows a typical threshold for adrenal axis suppression (< 100 nmol/L, or < 3.6 µg/dL). P values shown are for paired T test, indicating significance of the consistency of longitudinal changes of subjects relative to their own individual baseline values. Acute adrenal axis suppression is measured at

24 hours (after first dose), whereas chronic adrenal axis suppression is measured after 14 days of daily dosing (24 hours after last dose).

Figure 5. Morning Cortisol Measurements in the Vamorolone Phase I Healthy Subjects



Note: Placebo subjects from each of the four MAD cohorts are graphed together.

Vamorolone showed little evidence of either acute (24-hour data), or chronic (Day 15 data) suppression of the adrenal axis at doses of either 1.0 mg/kg/day or 3.0 mg/kg/day. The data suggest that vamorolone induces variable, mild, acute and chronic suppression of the adrenal axis at 9.0 mg/kg/day, and stronger evidence of both acute and chronic adrenal axis suppression at 20.0 mg/kg/day. Prednisone typically shows both acute and chronic adrenal axis suppression approximately at 0.1 mg/kg/day (Kauh et al., 2012), suggesting that vamorolone has an improved safety window regarding adrenal axis suppression.

Vamorolone thus shows approximately a 10-fold improvement in safety window compared to prednisone on a mg/kg comparative basis. These data are consistent with *in vitro* and *ex vivo* nonclinical mouse data comparing vamorolone to prednisone for adrenal suppression (Bello et al., 2015).

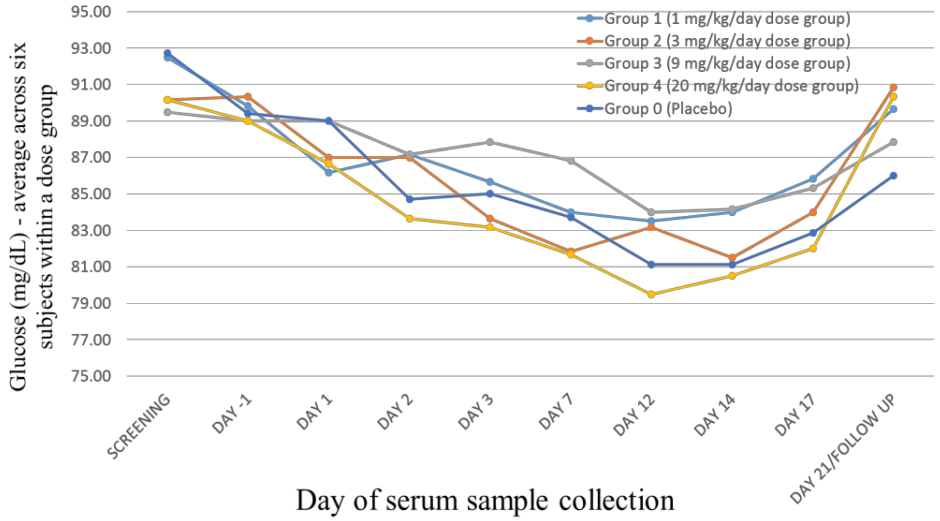
Insulin resistance. Prednisone induces the safety signal of insulin resistance, where glucose is not efficiently taken up from the blood by target tissues, such as muscle and liver, leading to hyperglycemia (Kauh et al., 2012) Insulin resistance may be an important safety signal for dystrophic muscle, where the dysfunctional myofibers have been shown to have inadequate energy stores (Dadgar et al., 2014; Wehling-Henricks et al., 2009) and insulin resistance likely

limits availability of glycogen substrates for glycolysis. The hyperglycemia, in turn, leads to chronic increases in insulin levels (hyperinsulinemia).

Levels of fasting glucose and insulin are reasonably sensitive and reliable measures of insulin resistance in non-diabetic individuals. Glucose is acutely (single dose) and chronically (multiple doses) elevated after treatment with pharmacological glucocorticoids. Glucose is elevated 24 hours after a single administration of glucocorticoids (2.0 mg/kg) (Younes et al., 2007; Moon et al., 2014)

In the Phase I MAD of vamorolone, fasting serum glucose was measured at 10 time points during the 2-week study; each sample was taken 24 hours after the previous dose of vamorolone (Figure 6).

Figure 6. Fasting Serum Glucose During the Phase I MAD Period (Two Weeks Daily Treatment)



Glucose levels for all vamorolone dose groups were similar to those of the placebo group. There was no evidence of elevations of glucose levels at any time point or any dose of vamorolone, suggesting that the side effect of insulin resistance was not seen with vamorolone. These data are consistent with a nonclinical study in a dystrophin-deficient mouse model, where chronic treatment of prednisolone (5 mg/kg/day) versus vamorolone (15 mg/kg/day; 30 mg/kg/day) showed development of insulin resistance with prednisolone, but not vamorolone.

1.3.1.4 Summary of Phase I Data

Pharmacokinetics

- Vamorolone PK data show strong adherence to dose linearity and dose proportionality, with relatively little subject-subject variation (both SAD and MAD).

- The half-life was approximately 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0, and 20.0 mg/kg showed an extended tail, increasing half-life to 2.5, 3.8, and 3.8 hours, respectively. The PK for the MAD cohorts was very similar to the SAD cohorts, showing little if any drug accumulation, consistent with the short half-life and daily dosing schedule.
- There were no apparent relationships between CL/F and body size, either in terms of body weight or BMI.
- For the food effect group, a high fat meal was given to a cohort of Phase I SAD volunteers with the 8.0 mg/kg dose of vamorolone. Comparison of the data from the high fat meal with the fasted 8.0 mg/kg cohort data showed that absorption was increased by 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone (steroidal compound).

Safety

- Single and multiple daily doses of vamorolone up to 20 mg/kg were well tolerated by healthy subjects, and a maximum tolerated dose (MTD) was not identified.
- Regarding the primary target organ, liver, one subject in the 20 mg/kg vamorolone MAD dose group who had an elevation of serum bilirubin at baseline (pre-dose) experienced an AE of ALT increased after 9 days of dosing; this AE was judged to be possibly related to vamorolone and drug dosing was halted. No other subjects in the vamorolone dose groups experienced AEs related to liver function.
- Results of post-dose morning cortisol levels suggest that vamorolone causes acute adrenal suppression after single dosing and chronic adrenal suppression after multiple dosing, but only at the higher (≥ 8.0 mg/kg) single and multiple doses studied.
- Safety PD biomarker studies showed that vamorolone had an improved safety window for adrenal axis suppression (100-fold increase in therapeutic window), no evidence of insulin resistance, no changes in bone turnover markers (osteocalcin, C-terminal peptide fragment of collagen 1 [CTX]), compared to prednisone studies reported in the literature (Kauh et al., 2012; Hoffman et al., 2018)
- There were no clinically significant changes in vital signs, electrocardiograms (ECGs), or physical examinations.

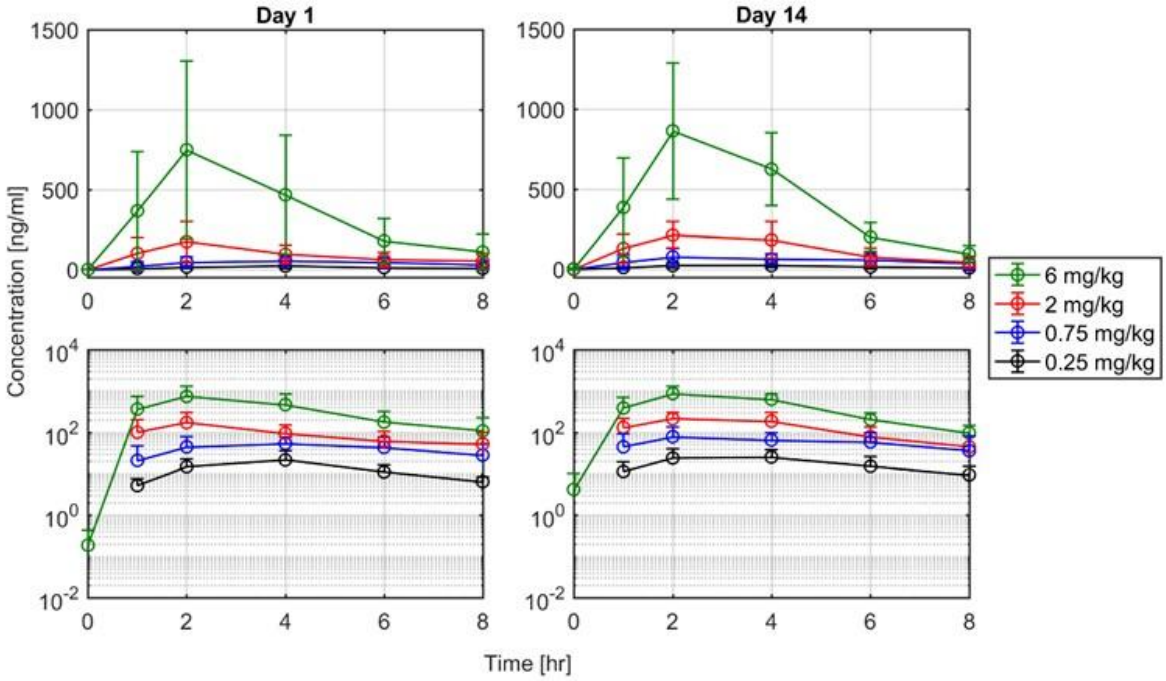
1.3.2 Pharmacokinetics in Phase IIa Study in 4 to <7 years Duchenne Muscular Dystrophy Boys (VBP15-002)

Forty-eight boys with DMD received oral doses of vamorolone once daily for 14 days at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day, 12 subjects receiving vamorolone at each dose level. The drug was administered with a glass of whole milk or other high-fat food. Six blood samples were collected on Day 1 and Day 14 at 0, 1, 2, 4, 6, and 8 hours post-dose and plasma was analyzed for vamorolone. The time-course of plasma drug

concentrations was assessed using noncompartmental analytical (NCA) methods using the WinNonlin software (Certara).

Of the 48 DMD subjects enrolled in the study (12 at each dosing level), 47 had evaluable PK data. The average Day 1 and Day 14 vamorolone concentration versus time profiles are shown in Figure 7 for the four dose levels. Overall, as expected, higher doses resulted in higher plasma concentrations of vamorolone. In particular, plasma vamorolone concentrations versus time showed a rapid to moderate rate of absorption, a maximum concentration (C_{max}) at a T_{max} of 2 to 4 hours, and a decline phase with a typical half-life ($t_{1/2}$) of 2 hours. For all 4 doses, the mean PK profiles on Day 1 and Day14 appear similar. Many individual subjects had closely matching Day 1 and Day 14 profiles, but several did not. There was no accumulation of drug owing to the relatively short half-life and once-daily (morning) dosing.

Figure 7. Mean Plasma Concentrations of Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0, and 6.0 mg/kg Doses



Vamorolone concentrations shown as mean ± standard deviation on linear (top panel) and semi-logarithmic (bottom panel) graphs.

A summary of the observed (C_{max} and T_{max}) and calculated (AUC, $t_{1/2}$, and CL) PK parameters for all doses on Day 1 and Day 14 is provided in Table 4. Even with only 6 blood samples collected from each subject, the PK profiles adequately capture the overall exposures, but must be considered approximate. This particularly applies to the peak values and the half-lives. Nevertheless, there is good consistency in the data with moderate variability as standard

deviation (SD) values are reasonable and the coefficient of variation values are typically less than 50%.

The drug is absorbed at a moderate rate with peak concentrations typically occurring at 2 to 4 hours on both Days 1 and 14. The median T_{max} across all doses is typically 2 or 4 hours. The half-lives were similar on both days, averaging about 2 hours, although some subjects had irregular profiles without a clear decline phase. The apparent clearance (CL and CL/F) values were consistent across the dose levels for Day 1 as well as for Day 14, but the latter tended to average slightly lower (about 2400 mL/hr/kg on Day 1 and 1900 mL/hr/kg on Day 14).

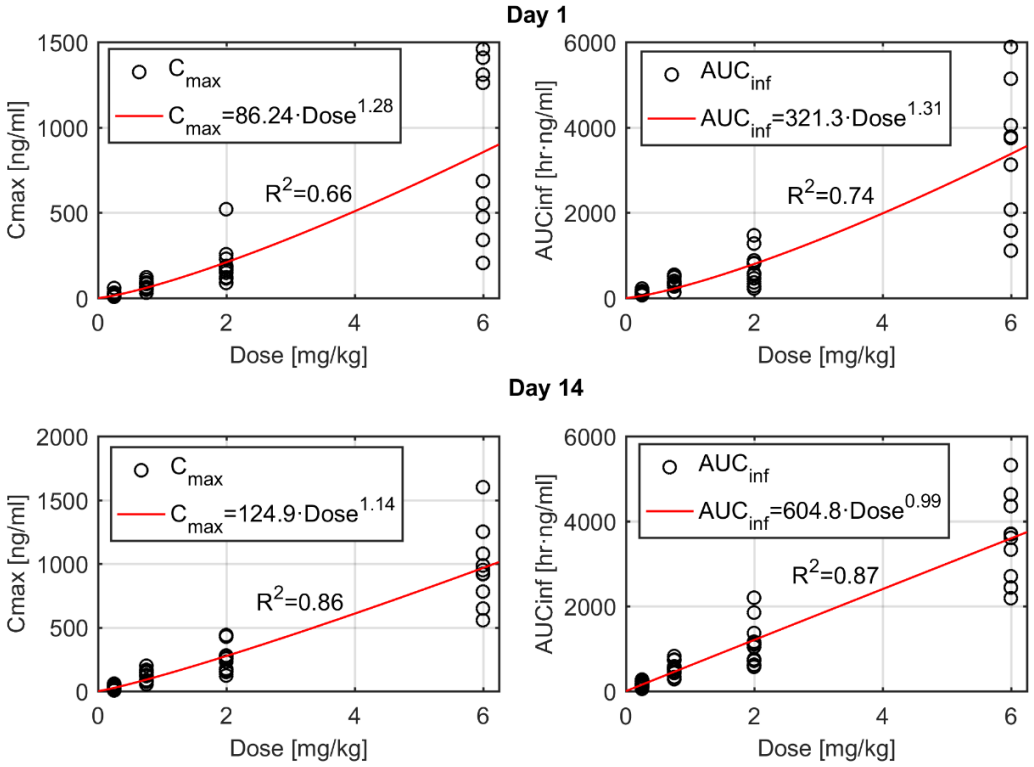
Table 4. Summary of Pharmacokinetic Parameters for Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0 and 6.0 mg/kg Doses to DMD Boys

Parameters	Day 1 Dose, mg/kg/day				Day 14 Dose, mg/kg/day			
	0.25	**0.75**	**2.0**	**6.0**	**0.25**	**0.75**	**2.0**	**6.0**
Cmax [ng/ml]	22.9 (13.4)	75.9 (25.9)	199 (111)	855.6 (471)	32.2 (15.2)	124.7 (42.5)	252.5 (96)	970 (270)
T_{max} [h]	3.6 [4] (1.2)	4.6 [4] (2.1)	2.5 [2] (1.3)	2.7 [2] (1.3)	3.8 [4] (1.8)	3.8 [4] (2.2)	2.8 [2] (1)	2.3 [2] (0.86)
AUC_{inf} [hr·ng/ml]	118 (48)	379 (117)	761 (352)	3279 (1693)	164 (61)	544 (155)	1138 (467)	3606 (897)
$t_{1/2}$ [h]	2.1 (0.85)	1.8 (0.43)	1.9 (0.79)	1.9 (0.95)	1.9 (0.96)	2.1 (0.8)	1.9 (1.02)	1.4 (0.35)
CL [ml/hr/kg]	2459 (897)	2285 (1103)	2697 (1285)	2320 (1375)	1828 (919)	1509 (482)	2047 (771)	1777 (476)

Values are mean (standard deviation) and for T_{max}, which are shown as mean [median] (standard deviation).

An assessment of the linearity of the PKwith dose using C_{max} and AUC is shown in Figure 8. Data for all individual subjects were used which also depict the variability for each dose level. While larger doses appear to present greater variability, this is a visual size distortion as the standard deviation is similar at each dose level (Table 4) Fitting the power equation of the form (C_{max} , $AUC_{inf} = a \, x \cdot Dose^{b}$) resulted in 95% confidence intervals for *b* values that include 1.0 for C_{max} and AUC_{inf} for both Days 1 and 14 indicative of linear relationships across this range of dose levels.

Figure 8. Regression Analysis of Cmax and AUCinf versus Dose



Regression was performed by fitting the indicated power equations to the data for Day 1 and Day 14. The fitted parameters are shown in the figure boxes.

Compared with fasting healthy adult volunteers (Section 1.3.1), the boys with DMD showed lower C_{max} values and more variation in the time to reach the maximal concentration of vamorolone for any given dose. This observation might be due to the fact that the boys with DMD received vamorolone after 8 ounces of whole milk or other high fat food and a so-called food effect might have played a role. The apparent clearance of vamorolone seems higher in the boys with DMD but this finding is not significant.

1.3.3 Safety in Phase II Studies in 4 to7 years Duchenne Muscular Dystrophy Boys (VBP15-002, VBP15-003, VBP15-LTE, and VBP15-004)

Adverse events: There were no serious adverse events (SAEs) reported over the 14-day treatment in the Phase I clinical trial in healthy adult volunteers, nor in the four cohorts (0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg) of the Phase IIa study (VBP15-002; 14-day treatment) in boys ages 4 to <7 years with DMD. There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in the same subject receiving

6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study. In the completed VBP15-003 study, there were a total of 218 TEAEs among 42 of the 48 subjects (87.5%). In VBP15-003 study, the TEAEs with the highest incidence were viral upper respiratory tract infection (41.7%); pyrexia (35.4%); cough (18.8%); vomiting (14.6%); and diarrhea (10.4%).

Body Mass Index (BMI): Body Mass Index was measured throughout the VBP15-003 study. The mean change from baseline to Week 24 for BMI was 0.03, 0.20, 0.23, and 1.15 for the 0.25, 0.75, 2.0, and 6.0 mg/kg/day dose level groups, respectively. Body Mass Index increases generally reflect an increase in weight. Body Mass Index z-score was monitored in the VBP15-003 study. The mean change from baseline to Week 24 for BMI z-score for the 6.0 mg/kg/day group showed a statistically significant increase compared to the mean change from baseline to Week 24 for the 0.25 mg/kg/day and 0.75 mg/kg/day dose level groups. In contrast, the mean change from baseline to Week 24 for the 2.0 mg/kg/day dose level group in BMI z-score was minimal and comparisons with the other vamorolone dose level groups lacked statistical significance. The mean increase from baseline to Week 24 for BMI z-score was similar for the 6.0 mg/kg/day group and a daily prednisone-treated historical control group.

Potential liver toxicity: In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state, and dosing was halted. All DMD subjects have elevated serum ALT and AST enzymes because of the muscle condition. For that reason, two enzymes, glutamate dehydrogenase (GLDH) and gamma glutamyl transferase (GTT), that are preferentially expressed in liver were evaluated in the VBP15-003 study. None of the mean changes in GLDH from baseline to any of the VBP15-003 on-treatment assessment time points were statistically significant for any dose level group. Although the mean changes from baseline to Week 8, Week 16, and Week 24 in GLDH levels did not show a dose response, shift analysis of GLDH levels did suggest a possible dose-related shift to higher GLDH levels at 2.0 mg/kg/day and 6.0 mg/kg/day at Weeks 16 and 24. Mean GGT levels and individual subject values at each VBP15-003 assessment time point across the four dose level groups remained at or below the normal range. On the basis of these mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day does not appear to induce liver toxicity over a 24-week treatment period.

Adrenal suppression: In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μg/dL [100 nM]) consistent with chronic adrenal suppression.

Insulin resistance: In the VBP15-003 study, mean changes from baseline for fasting insulin showed dose-and time-related changes for all dose level groups at Week 12 and Week 24.

Statistical significance was observed for mean increase from baseline for the 6.0 mg/kg/day dose level group at Week 12 and Week 24.

Bone Turnover: In the VBP15-003 study, pharmacodynamic biomarker testing for bone turnover markers suggested that vamorolone does not have the detrimental bone effects observed with prednisone and deflazacort.

1.4 Rationale for Study Design

This Phase II pilot study is a randomized, double-blind, placebo-controlled study design to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg (250mg if <50kg body weight) vs. placebo administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory patients age 18 - <65 years with Becker dystrophy.

The study is comprised of a 1-day Prescreening visit (optional), 35-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in the separate program to continue treatment with vamorolone).

Subjects will be enrolled into the study at the Screening Visit, at the time written main informed consent is obtained. Subjects who meet all eligibility criteria in this study will be randomized to vamorolone or placebo treatment group. All subjects will begin study medication treatment on Treatment Period Day 1 and will continue to receive study medication treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24).

At the end of the 24-week Treatment Period (Week 24), subjects might be given the option to receive vamorolone in another program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into another program providing vamorolone will not need to taper their study medication dose prior to participation in the additional protocol. All subjects who will not transition directly to further vamorolone treatment will begin a 4-week Dose tapering Period during which the dose of study medication will be progressively reduced and discontinued.

Key safety parameters will be evaluated during the course of the study to assess vamorolone safety and tolerability. Safety parameters will include weight, vital signs, assessment of cushingoid features, clinical laboratory tests, first morning cortisol to assess adrenal suppression, bone biomarker osteocalcin and fasting glucose and insulin to assess glucose handling.
To evaluate clinical efficacy, the effect of vamorolone 500mg/day (250mg/day if <50kg body weight) on muscle function will be assessed using the time to run/walk 10 meters (TTRW) test and the North Star Ambulatory Assessments (NSAA). Patient-reported outcomes will be assessed with the NeuroQOL for fatigue, upper and lower extremity function, and sleep.

Pharmacodynamic safety biomarker findings will be assessed in BMD patients receiving vamorolone 500mg/day (250mg/day if <50kg body weight) over 24 weeks. Serum PD biomarkers bridged to later clinical safety concerns will be assessed over time as exploratory safety measures. These PD biomarkers include:

1. **Adrenal suppression.** Pharmacological doses of glucocorticoids cause suppression of the hypothalamo-pituitary-adrenal axis, leading to low concentration of endogenous cortisol and other steroidal hormones in serum. Adrenal suppression is directly associated with risk of adrenal crisis, delay of puberty and stunting of growth. Measurement of morning cortisol concentrations will reflect the degree of adrenal suppression. Plasma cortisol secretion typically follows a circadian pattern with the highest concentrations early in the morning; a morning serum cortisol concentration less than 3.6 µg/dL (or 100 nM) is highly suggestive of adrenal suppression.
2. **Bone turnover.** Pharmacological doses of glucocorticoids cause an imbalance of bone formation and bone resorption, leading to later osteopenia and bone fragility. Bone fragility is a significant adverse effect of chronic pharmacologic glucocorticoids as this can lead to fracture, which increases the likelihood of premature loss of ambulation. Serum biomarker osteocalcin (bone resorption; glucocorticoids increase serum levels) will be assessed. Increases of osteocalcin are reflective of abnormal bone turnover, a risk factor bridged to later bone fragility.
3. **Insulin resistance.** Insulin resistance is the metabolic state where increased blood glucose triggers increased insulin secretion from the pancreatic islet cells, but the elevated serum insulin fails to sufficiently trigger glucose uptake by muscle and/or liver. Thus, peripheral tissues are resistant to insulin signaling (insulin resistance). Insulin resistance has been bridged to later clinical outcomes, including heart disease, type 2 diabetes, and vascular disease. Serum biomarkers that are accepted as measures of insulin resistance are increased serum glucose and insulin. This can be measured after acute (hours after first dose) or chronic (after weeks or months of dosing) glucocorticoid treatment.

This trial will be conducted in compliance with this protocol, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements, and the recently issued FDA guidance on developing drugs for treatment for DMD and related dystrophinopathies (FDA 2015).

It is obligatory that the Investigator become familiar with all sections of the vamorolone Investigator's Brochure (Investigator's Brochure, June 2020).

1.5 Overall Benefit/Risk

There were no serious adverse events (SAEs) reported over the 14-day treatment in the Phase I clinical trial in healthy adult volunteers, nor in the four cohorts (0.25 mg/kg, 0.75 mg/kg,

2.0 mg/kg, and 6.0 mg/kg) of the Phase IIa study (VBP15-002; 14-day treatment) in boys ages 4 to <7 years with DMD. There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza-associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in a subject receiving 6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study. In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state. On the basis of mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day did not appear to induce liver toxicity over a 24-week treatment period in the VBP15-003 study. In the VBP15-002 study, after 2 weeks of treatment, 0 of 11 tested participants who received vamorolone 0.25 mg/kg/day, 0 of 11 tested participants who received vamorolone 0.75 mg/kg/day, 2 of 11 (18.2%) tested participants who received vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested participants who received vamorolone 6 mg/kg/day had a depressed morning cortisol (<3.6 µg/dL [100 nmol/L]) consistent with chronic adrenal suppression. In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 µg/dL [100 nM]) consistent with chronic adrenal suppression. Instructions for detecting adrenal crisis and the circumstances in which stress dose steroids should be provided will be included in the Informed Consent Form (ICF) and Manual of Operations, and Investigators should monitor clinical study participants closely to identify elevations in liver-specific enzymes.

In the VBP15-004 double-blind, placebo- and prednisone-controlled study, a lower proportion of subjects in the Safety Population who experienced at least one TEAE during Treatment Period #1 was observed for subjects in the placebo group (79.3%) compared to subjects in the prednisone 0.75 mg/kg/day (83.9%), vamorolone 2.0 mg/kg/day (83.3%), and vamorolone 6.0 mg/kg/day (89.3%) groups: 23 subjects (79.3%) in the placebo group experienced a total of 77 TEAEs; 26 subjects (83.9%) in the prednisone 0.75 mg/kg/day group experienced a total of 121 TEAEs; 25 subjects (83.3%) in the vamorolone 2.0 mg/kg/day group experienced a total of 97 TEAEs; and 25 subjects (89.3%) in the vamorolone 6.0 mg/kg/day group experienced a total of 91 TEAEs; a greater total number of TEAEs was experienced by subjects in the prednisone group (121), with fewer TEAEs experienced by subjects in the placebo (77), vamorolone 2.0 mg/kg/day (97), and vamorolone 6.0 mg/kg/day (91) groups (Table 5).

A total of 51 subjects (43.2%) in the Safety Population experienced at least one treatment-related TEAE: eight subjects (27.6%) in the placebo group; 14 subjects (45.2%) in the prednisone 0.75 mg/kg/day group; 10 subjects (33.3%) in the vamorolone 2.0 mg/kg/day group; and 19 subjects

(67.9%) in the vamorolone 6.0 mg/kg/day group. None of the treatment-related TEAEs was serious.

One subject (3.2%) in the prednisone 0.75 mg/kg/day group reported a TEAE with CTCAE grade ≥ 3.

One subject (3.2%) in the prednisone 0.75 mg/kg/day group experienced a TEAE leading to study drug and study discontinuation.

One subject (3.3%) in the vamorolone 2.0 mg/kg/day group experienced one serious TEAE during Treatment Period #1 of the study.

No subject experienced a TEAE considered by the Investigator to be life-threatening or which resulted in death during Treatment Period #1 of the study.

Table 5. Overall Summary of Adverse Events (Safety Population)

	Treatment Group				
	Placebo (N = 29)	**Prednisone 0.75 mg/kg/day (N = 31)**	**Vamorolone 2.0 mg/kg/day (N = 30)**	**Vamorolone 6.0 mg/kg/day (N = 28)**	**Total (N = 118)**
Total Number of AEs	82	133	108	105	428
Total Number of TEAEs	77	121	97	91	386
Subjects with [n (%)]					
Any TEAE	23 (79.3)	26 (83.9)	25 (83.3)	25 (89.3)	99 (83.9)
Any Treatment-related TEAE[a]	8 (27.6)	14 (45.2)	10 (33.3)	19 (67.9)	51 (43.2)
Any TEAE with CTCAE Grade ≥ 3[b]	0	1 (3.2)	0	0	1 (0.8)
Any TEAE Leading to Discontinuation of Study Drug	0	1 (3.2)	0	0	1 (0.8)
Any TEAE Leading to Discontinuation of Study	0	1 (3.2)	0	0	1 (0.8)
Any SAE	0	0	1 (3.3)	0	1 (0.8)
Any Serious TEAE	0	0	1 (3.3)	0	1 (0.8)
Death[c]	0	0	0	0	0

Abbreviations: AE = adverse event; CTCAE = Terminology Criteria for Adverse Events; F/U = Follow-up (Visit); kg = kilogram; mg = milligram; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: AEs are defined starting at the date of written informed consent. TEAEs are defined as any AE starting or worsening after initiation of study drug dosing through the subject's final visit (study completion or early termination). For Treatment Period #1 analyses, AEs and TEAEs with onset through the Week 24 F/U Visit are included. SAEs were recorded for up to 30 days after the final administration of study drug; for the Treatment Period #1 analyses, SAEs with onset through the Week 24 F/U Visit are included.

a. Related TEAEs include Possibly, Probably, and Definitely related to study medication.
b. Grade: 3=Severe, 4=Life threatening, 5=Death.
c. Deaths are defined as deaths that occur during the study and ≤ 30 days after the last dose of study drug.

Potential Health Benefits: Subjects may or may not receive direct health benefit from participating in the study Subjects will be treated with vamorolone at 500 mg/day (250mg if <50kg body weight) over the course of the 24-week trial. In the VBP15-003 study, clinical efficacy was assessed by Timed Function Tests. Improvement in Time to Stand, Time to Climb,

Time to Run/Walk 10 Meters, and 6-Minute Walk Test were seen predominantly for the 2.0 and 6.0 mg/kg/day dose level groups, with many of the improvements showing statistical significance compared to an untreated Duchenne Natural History Group. In the VBP15-004 double-blind study, both 2.0 and 6.0 mg/kg/day vamorolone groups showed significant improvement vs. placebo on motor outcomes, and improvements were comparable to the prednisone group.

Individuals with Becker muscular dystrophy show progressive muscle weakness and wasting, with a variable onset and progression. The anticipated benefit to patients with Becker dystrophy is what we have observed in patients with the related (but more severe) Duchenne muscular dystrophy; namely, an acute improvement of motor outcomes, and subsequent slowing of the decline in muscle function relative to untreated peers. The anticipated mechanism of action of vamorolone underlying this anticipated benefit is the documented anti-inflammatory mechanism of vamorolone, and the potential increase in dystrophin protein levels seen in animal models. The beneficial effects would be expected to parallel those seen in the allelic disorder, Duchenne dystrophy, and they are allelic disorders involving the same dystrophin gene and protein.

Vamorolone is a dissociative steroidal anti-inflammatory drug and glucocorticoid receptor (GR) selective agonist with differences from corticosteroids in terms of chemical structure, mechanism of action, and physiologic effects. Because it exerts part of its pharmacological effect through an agonistic action on the Glucocorticoid Receptor (GR), the typical risks associated with glucocorticoids (GC) should be considered as potential risks also for vamorolone. The clinical data obtained with vamorolone to date in controlled and uncontrolled studies have shown that AEs which are typical for GC like Adrenal Suppression, Adrenal Insufficiency, Hypercortisolism (Cushingoïd symptoms, Weight gain, skin and hair changes), Behavioural problems and GI symptoms can also occur with vamorolone but in most cases are only of mild to moderate severity and should not be considered important risks for the drug. As for Behavioural changes and GI symptoms, a weak safety signal could only be concluded for respectively irritability and abdominal pain upper, vomiting and diarrhoea in controlled clinical trials with vamorolone.

In clinical experience with Duchenne muscular dystrophy, mild cushingoid features are the most frequently reported adverse reaction with vamorolone. Weight gain was commonly observed in clinical trials with vamorolone. Laboratory measurement of adrenal suppression shows all patients to show vamorolone-related adrenal suppression, although overt symptoms of this condition are rare, and all patients are provided with medical alert cards noting risk for adrenal insufficiency and adrenal crisis (and need for supplemental cortisone if trauma, surgery or acute illness).

In view of the initial clinical evidence of safety, the improvements observed in the assessments of efficacy, and the nature of potential adverse effects that can be monitored, the data support an acceptable benefit/risk profile for vamorolone.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is:

1. To evaluate the safety and tolerability of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy;

2.1.2 Secondary Objective

The secondary objective of this study is:

1. To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy
2. To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.
3. To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.

2.1.3 Exploratory Objectives

The exploratory objectives of this study are:

1. To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 12-week treatment period in subjects with Becker dystrophy.
2. To evaluate the effect on patient-reported outcomes of treatment response of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.

2.2 Study Endpoints

2.2.1 Safety Endpoints

The following endpoints will be evaluated for all participants.

1. Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC and PT): Overall by treatment, by treatment and relationship, and by treatment and intensity (see Section 7.6);
2. Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points;

3. Body weight: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
4. Clinical laboratory values: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points in:
    a. Hematology and clinical chemistry;
    b. GGT;
    c. CK;
    d. Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]); and
    e. Urinalysis
5. 12-lead ECG: Change from baseline to Week 12 and Week 24; Data for the following additional safety outcome will be listed only:

Physical examination findings at each of the pretreatment, on-treatment, and post-treatment assessment time points.

2.2.2 Tolerability Endpoint

Premature discontinuation of study treatment due to adverse event.

2.2.3 Secondary endpoints

The following secondary endpoints will be evaluated for all participants, and are detailed in the subsections (2.2.3.1, 2.2.3.2, 2.2.3.3 and 2.2.3.4)

- Vamorolone PK analysis
- Cortisol
- Osteocalcin
- Fasting glucose, insulin; Hb1Ac
- MDC and CD23
- NSAA and TTRW

2.2.3.1 Pharmacokinetics Analysis

Blood (plasma) will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis, and stored. Once all samples are collected from the trial, the samples will be sent to ICON (Lenexa, KS, USA) for determination of drug levels using established and validated LC-MS methods. The pharmacokinetic parameters of the treated Becker muscular dystrophy patients will be compared to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects. Only single dose (Day 1) PK parameters are measured due to the short half-life of vamorolone (~2 hours), and lack of any drug accumulation between daily doses. In previous pop-

PK models there have been no significant differences between single dose and multiple dose PK parameters.

2.2.3.2 Pharmacodynamic safety Endpoints

The following pharmacodynamic biomarkers reflective of safety concerns of glucocorticoids will be evaluated:

1. Adrenal suppression. First-in-morning salivary cortisol levels will be measured. Cortisol measures falling below 3.6 µg/dL (or 100 nM) will be considered to be indicative of the development of adrenal suppression;
2. Bone turnover. Measure of serum osteocalcin is reflective of bone turnover and will be assessed for all participants;
3. Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance, with serum elevations of both insulin and glucose. Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose, fasting insulin, and Hb1Ac will be measured as biomarkers of insulin resistance;

2.2.3.3 Pharmacodynamic efficacy Endpoints

1. Exploratory biomarkers for treatment response including MDC and CD23 (Fiorillo et al., 2015; Conklin et al., 2018a; Conklin et al., 2018b): Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points.

2.2.3.4 Efficacy Motor Endpoints

1. For the clinical efficacy motor endpoint, TTRW (velocity) and NSAA (score): change from baseline to Week 24 will be compared between vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo

2.2.4 Exploratory Endpoints

The following endpoints will be evaluated for all participants.

2. For the clinical efficacy motor endpoint, TTRW (velocity) and NSAA (score): change from baseline to Week 12 will be compared between vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo

3. Participants will be asked to complete the NeuroQOL scales for fatigue, mobility and sleep

3 STUDY DESIGN

3.1 Overall Study Design

This Phase II pilot study is a randomized, double-blind, placebo-controlled study design to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg (250mg if <50kg body weight) compared to placebo administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory male subjects with Becker dystrophy.
A total of approximately 39 subjects ages 18 to <65 years will be enrolled in the study
The study is comprised of a 1-day Prescreening Visit (optional), a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1 day Pretreatment Baseline Period, a 24- week Treatment Period, and a 4-week Dose tapering Period (for subjects not continuing directly with further vamorolone treatment).

After providing prescreening informed consent, subjects will provide authorization to release medical records including a genetic report confirming the diagnosis of BMD. Based on the review of the subject's medical records, the subject might be asked to sign the main consent form to continue his participation in the study.

Subjects will be enrolled into this study at the time written main informed consent is given during the Screening visit. After completion of Screening assessments subjects who meet all eligibility criteria in this study will be randomized to vamorolone or placebo treatment group.

After completion of Screening and Baseline assessments, subjects will return to the study clinic on Day 1 for safety and PD assessments prior to administration of the first dose of study medication. Additional onsite study visits will occur at Week 4, Week 12, and Week 24. Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the NIAMS regarding study conduct. The Study Team will receive the recommendations through the NIAMS Executive Secretary and share them with ReveraGen.

Subject diaries will be dispensed at the Day 1, Week 12, and Week 24 (for subjects participating in the Dose-tapering Period) Visits to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication. Study drug dosing will occur at home on all days except dates of the Day 1, Week 12, and Week 24 Visits, when dosing will occur at the study site.
The scheduled Week 12 and Week 24 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling. For the Week 24 assessments, the scheduled 12-lead ECG and patient-reported outcomes may be completed on the day prior to the final Week 24 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 24 dose of study medication. The scheduled physical examination, weight, height, vital signs,

clinical laboratory tests, blood draws for PD biomarker analysis, functional assessments (TTRW and NSAA), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 24 dose of study medication.

Subjects who complete the VBP15-BMD-001 study assessments through the Week 24 Visit may be given the opportunity to receive vamorolone as part of another program if the subject wishes to receive vamorolone dosing and if the Investigator feels that it is in the best interest of the subject.

Subjects who complete the VBP15-BMD-001 study and will enroll directly into another program to receive vamorolone treatment will be discharged from the VBP15 BMD-001 study following completion of all Week 24 assessments. Subjects who will not enter another program will have their study medication dose tapered during a 4-week Dose-tapering Period prior to discharge from the study. For these subjects, site study staff will contact the subject by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms of adrenal suppression, and to address any questions the subject may have. These subjects will have a final visit at Week 28 after the completion of the dose taper for a final physical exam, safety assessment, and return of remaining study medication and final subject diary.

In the event that any clinical or laboratory parameters remain abnormal at the time of discharge from the study, the subject will be followed medically, as clinically indicated.
Any subject who discontinues the study prior to the Week 24 Visit should return to the study unit for scheduled Week 24 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun should undergo dose-tapering and follow up as described above following early completion of the Week 24 assessments.

To ensure the safety of trial participants, maintain compliance with good clinical practice (GCP), and minimize risks to trial integrity relating to the COVID-19 pandemic, the investigators, study team staff, and participants of the VBP15-BMD-001 study should follow the guidelines around social/behavioral interactions consistent with national, local and institutional COVID-19 prevention guidance (U.S. Food and Drug Administration, 2020).

3.2 Randomization

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

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

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

3.3 Blinding

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

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

3.4 Unblinding

Every attempt should be made to preserve the integrity of study drug blinding. All subjects will be provided with a card, to be carried at all times, stating "I am taking part in a clinical trial" (in the local language) to be presented to medical staff in the event of routine treatment or a medical emergency. Investigational medications can usually be withdrawn without the need for unblinding in a subject experiencing an AE that requires study medication withdrawal. In this case, the site investigator should provide adequate and necessary support to the subject without unblinding study treatment.

Subjects who experience a medical emergency, whether their treatment remains blinded or is unblinded, should be covered with stress-dose steroids, except for unblinded subjects who were receiving placebo.

All subjects who have study medication withdrawn without unblinding will need to undergo dose-tapering according to the schedule in Section 6.3.6.

In the event that unblinding is necessary, an emergency unblinding procedure is provided to allow site investigators to disclose a treatment assignment for an individual subject if clinical circumstances should require this.

Unblinding will be performed and treatment assignment obtained through Almac's-WebEZ™ system with username and password code. The expectation is that emergency unblinding will occur only very rarely; for example, when the subject needs emergency surgery and information about all treatment interventions is required. In the exceptional circumstance that knowledge of the study drug assignment appears essential for providing appropriate medical management, the site investigator should make every effort to contact the study chair or the independent Medical Monitor to discuss the rationale for breaking the blind. If the site investigator still believes that unblinding is needed, or the study chair and independent Medical Monitor are not available for contact, the site investigator will follow Almac's-WebEZ™ unblinding procedures for unblinding the subject in question (see the Manual of Operations for details on how to unblind a subject using Almac's-WebEZ™ system).
After breaking the blind, the site staff should record details regarding the reasons for breaking the blind, including any AEs leading to the unblinding, in the source documents and electronic case report form (eCRF). Once the blind is broken for a given subject, the site will need to use the WebEZ™ discontinuation module to withdraw the patient in the system, then study drug will be discontinued, and the subject will be withdrawn from the study. Furthermore, as the subject might have received vamorolone as part of the study and as vamorolone appears to affect the adrenal axis, vamorolone should not be discontinued without a dose-tapering period.

Any subject whose treatment is unblinded prior to the Week 24 Visit should return to the clinic for Week 24 assessments at the time of unblinding, whenever possible, assuming the subject has not withdrawn consent; any subject whose treatment is unblinded after Week 24 and prior to the Week 28 Visit should return to the clinic for Week 28 assessments at the time of unblinding, whenever possible, assuming the subject has not withdrawn consent. Any subject whose treatment, upon unblinding, is revealed to be vamorolone will need to follow the dose-tapering protocol (Section 6.3.5 specific to the time of unblinding); these subjects will also be asked to return to the clinic at the end of the tapering period for final Dose-tapering Period assessments, whenever possible. If the subject was taking placebo prior to unblinding, study drug tapering will not be required; however, the subject should return for final Week 24 assessments at the time of unblinding and withdrawal from the study.

Subjects who discontinue the study for any reason other than a medical emergency will not be unblinded.

4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Subject Enrollment and Identification Log

Subjects will be recruited through the clinics of participating site investigators and other mechanisms including patient registries, national and international networks, and patient foundations. After identification of a possible subject, the site investigator will discuss the study with the subject. The subject will be provided with a copy of the informed consent document and allowed time to consider participation prior to signing. Individuals interested in participating will be asked to complete an optional prescreening visit or come to one of the participating study sites to complete the main informed consent process with a site investigator or designee prior to initiation of screening procedures. Subjects will not be excluded on the basis of race, ethnicity, or age, except that the target population for the trial is 18 - <65 years of age.

A subject enrollment log will be maintained at each investigational site for all subjects who are screened for the study, including those not assigned to treatment. Limited data will be collected for these subjects, including date of birth and reason for exclusion from the study. Subject enrollment logs will be maintained for all subjects enrolled in the study. This record will also include the dates of subject enrollment and completion/termination.
The Site Investigator will keep a record relating the names of the subjects to their enrollment numbers (subject identification log) to permit efficient verification of data subject files, when required. These logs will be reviewed during routine monitoring calls and/or visits.

4.2 Inclusion Criteria

To qualify for treatment assignment in this study, the subject must satisfy the following inclusion criteria:

1. Subject or Subject's parent(s) or legal guardian (s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures;
2. Subject is a male and has a confirmed diagnosis of Becker dystrophy as defined as:
   a. Identifiable mutation within the DMD gene (deletion/duplication of one or more exons), where reading frame can be predicted as 'in-frame', and clinical picture consistent with Becker dystrophy, OR
   b. Complete dystrophin gene sequencing showing an alteration (small mutation, duplication, other) that is expected to allow production of an internally deleted dystrophin protein, with a typical clinical picture of Becker dystrophy;
3. Subject is ≥ 18 years of age and <65 years of age at time of informed consent;
4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) ≤ 30 sec at screening; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32 at screening.
6. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum

gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit). While AST and ALT can be elevated due to disease of muscle or liver, the study PI will review any increases of AST or ALT. If above upper limit of normal (ULN), then study PI will assess whether the increases are likely of muscle origin to determine inclusion.

7. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
8. Subject has evidence of chicken pox immunity as determined by:
    a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
    b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;
9. Subject is willing and able to comply with scheduled visits, study medication administration plan, and study procedures.
10. Subject agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed

4.3 Exclusion Criteria

A subject will be excluded from randomization in this study if he meets any of the following exclusion criteria:

1. Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with hemoglobin A1C level > 8.0 at screening) or immunosuppression;
2. Subject has current or history of chronic systemic fungal or viral infections;
3. Subject has had an acute illness within 4 weeks prior to the first dose of study medication;

4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;
5. Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary unless cardiac ejection fraction is less than 40%];
6. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;

7. Subject has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the Investigator;
8. Subject has previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up will be correctly completed or impair the assessment of study results, in the opinion of the Investigator;
9. Subject is taking (or has taken within 4 weeks prior to first dose of study medication) herbal remedies and supplements which can impact muscle strength and function (e.g., Co-enzyme Q10, creatine, etc);
10. Subject has been administered a live attenuated vaccine within 14 days prior to the first dose of study medication;
11. Subject is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to first dose of study medication; or
12. Subject has previously been enrolled in the VBP15-BMD-001 study or any other vamorolone study.

Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result.

4.4 Withdrawal of Subjects from Study

A subject may withdraw from the study at any time without the need to justify the decision. The Investigator has the right to terminate participation of a subject in the study for any of the following reasons:

- The subject is uncooperative/noncompliant and does not adhere to study responsibilities, including failure to attend study visits;
- Difficulty in obtaining blood samples from the subject for safety monitoring;
- The subject experiences an unmanageable or non-tolerable AE/SAE which is considered to be possibly, probably, or definitely related to study drug, in the opinion of the Investigator, and may jeopardize the subject's health;
- ReveraGen terminates the study;
- Any other reason relating to subject safety or integrity of the study data.

In the event a subject is withdrawn from the study, ReveraGen or designee (e.g., Study Project Manager) will be informed within one business day. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until resolution of the event. Any subject who discontinues the study prior to the Week 24 Visit should return to the study unit for scheduled Week 24 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun should undergo dose-tapering following early completion of the Week 24 assessments. Subjects will also be asked to return to the study unit at

the end of the tapering period for a final study visit. In the event a subject withdraws informed consent, no further study procedures should be performed and no additional data should be collected. Any data collected up to the point of withdrawal of informed consent may be used by ReveraGen.

4.5 Termination of Study

This study may be prematurely terminated if, in the opinion of ReveraGen, there is sufficient reasonable cause. An example of a circumstance that may warrant termination is determination of unexpected, significant, or unacceptable risks to participants.

If the study is prematurely terminated or suspended, ReveraGen will promptly inform the site Investigators and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The Institutional Review Board(s) (IRB[s])/Independent Ethics Committee(s) (IEC[s]) will also be informed promptly by the Investigator/institution or ReveraGen and provided the reason(s) for the termination or suspension.

Subject enrollment at a given site may be terminated by ReveraGen. Possible reasons for termination of the study at a given site include, but are not limited to:

1. Unsatisfactory enrollment with respect to quantity or quality
2. Inaccurate or incomplete data collection
3. Falsification of records
4. Failure to adhere to the protocol.

Subjects who are participating at a given site at the time it is terminated by ReveraGen will need to undergo dose tapering at the time the site is terminated according to the dose-tapering schedule (see Section 6.3.6).

5 TREATMENT OF STUDY SUBJECTS

5.1 Study Medication Administered

Planned vamorolone dose level 500mg/day (250mg/day if <50kg body weight) or a matched placebo. A defined daily dose (definition by World Health Organization) of 500mg/day was chosen because this is typical procedure for adult drug dosing and most closely approximates the 6mg/kg/day dose identified for children with DMD. A dose of 500mg/day equates to approximately 6mg/kg/day for an 83kg male. In the event of a subject who is <50kg, the protocol specifies administering a half dose of 250mg/day (equivalent to 5mg/kg/day for a 50kg male).

Study medication will be administered to all subjects as an oral liquid suspension.

A total of approximately 39 subjects will be administered vamorolone 4.0% wt/wt oral suspension or a matched placebo.

Vamorolone 4.0% wt/wt or placebo oral suspension will be administered to all subjects once daily for 24 weeks, from Study Day 1 until the Week 24 Visit. At the end of the 24-week Treatment Period, a subset of subjects may receive additional study medication treatment in a dose-tapering manner during a 4-week Dose-tapering Period prior to discharge from the study (see Section 6.3.6).

5.2 Identity of Investigational Product

ReveraGen BioPharma, Inc. will supply the following investigational study medication:

Vamorolone:

Active Substance:	Vamorolone
Strength:	4.0% wt/wt
Dosage Form:	Oral suspension
Manufacturer:	Velesco Pharmaceutical Services

Placebo to Match Vamorolone:

Dosage Form:	Oral suspension
Manufacturer:	Velesco Pharmaceutical Services

The clinical trials supplies companies will manufacture identical liquid formulation of vamorolone and placebo to maintain the blind.

5.3 Dosage Schedule and Administration of Study Medication

The site pharmacist or designated site study staff will dispense blinded study medication to each subject randomized in the study. Subjects will be administered vamorolone 4.0% wt/wt or placebo oral suspension.

All subjects will receive study medication, administered orally once daily for 24 weeks, from Study Day 1 to the Week 24 Visit. At the end of the 24-week Treatment Period, subjects who will not continue directly with further vamorolone treatment at the end of the study will be tapered off suspension study medication over a 4-week Dose-tapering Period, prior to discharge from the study (see Section 6.3.6).

The site pharmacist or designated site study staff will dispense study medication to each randomized subject in 120 mL bottles sufficient for 12 weeks of dosing (4 weeks for Dose-tapering Period) plus overage at the Day 1 Visit, just prior to dosing, and at the Week 12 Visit (and Week 24 Visit to subjects participating in the Dose-tapering Period), according to the subject body weight (in kg) recorded at the Baseline visit (Day -1 weight for Day 1 dispensing) (see Section 15.1 for a dose calculation worksheet).

Each subject's dose (in mL) will be calculated and written on the labels of the bottles to be dispensed at a given visit by trained site staff based on the weight of the subject (in kg) recorded at the dispensing visit. The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled study visit. For interim compliance monitoring, the subject will bring to the Week 4 visit any empty study medication bottles and also the current bottle in use that was dispensed at the Day 1 Visit. The bottle of study medication in use will be returned to the subject at the end of the Week 4 Visit for continued dosing; new study medication will not be dispensed at the Week 4 Visit.

Dosing is to occur at home throughout the 24-week Treatment Period, except at the Day 1, Week 12, and Week 24 Visits when dosing will occur at the study site to accommodate morning fasted blood collections. Subjects should receive each dose of study medication in the morning and at approximately the same time of day.

Vamorolone suspension will be administered orally using a volumetric syringe supplied by the site. Following administration of the dose of study drug suspension, the syringe will be filled once with water and the water will be administered by mouth using the volumetric syringe. The subject will then drink approximately 50 mL (approximately 2 ounces) of water to ensure the full dose has been ingested. The daily dose of study medication should be taken with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food. There are no other food or drink restrictions before or after dosing.
At the Day 1, Week 12, and Week 24 study visits, subjects will arrive at the study clinic after having fasted for ≥ 8 hours, and will eat breakfast at the study site. On Day 1, food will be taken within 30 minutes prior to administration of the dose of study medication.

Any missed or incomplete doses of study medication should be recorded in the Subject Diary and reported immediately to the site Investigator.

5.4 Rationale for Dose Selection

The dose level of the investigational medication were chosen for this study to ensure the safety of subjects participating in the study, to allow demonstration of PD effects, and to evaluate clinical efficacy.

Vamorolone at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day has been demonstrated to be safe and well-tolerated in 48 DMD boys 4 to <7 years (12 subjects at each dose level) in a 2-week Phase IIa study (VBP15-002), a 24-week Phase II extension study (VBP15-003), and a 24-month extension study (VBP15-LTE). The safety of the 2.0 mg/kg/day and 6.0 mg/kg/day doses is also being studied in a recently completed 52-week double-blind, comparator- and placebo-controlled study (VBP15-004) in 120 subjects receiving vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo for the first 24 weeks of the study, and then vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for the final 24 weeks of the study.

There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza-associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in a subject receiving 6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study.

One subject receiving vamorolone 6.0 mg/kg in the Phase II extension study (VBP15-003) who had an incidental early morning cortisol drawn following an AE of presyncope had evidence of adrenal suppression. In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12

(41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants

(6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μg/dL [100 nM]) consistent with chronic adrenal suppression (Hoffman et al., 2018). Thus, based on the available data in the VBP15-003 study regarding the safety signal of suppression of the adrenal axis, the possibility of adrenal suppression is present in subjects at the 2.0 and 6.0 mg/kg/day dose levels.

The results of the VBP15-003 24-week extension study and of the 24-month VBP15-LTE study suggest that doses of vamorolone of 2.0 mg/kg/day and 6.0 mg/kg/day produced significant enhancement of muscle strength, mobility, and functional exercise capacity.

The results of the VBP15-004 24-week double-blind, placebo- and prednisone-controlled study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day showed significant

enhancement of muscle strength, mobility, and functional exercise capacity vs. placebo. This study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day did not cause the growth retardation and deleterious changes in bone biomarkers seen with prednisone in this head-to-head comparison.

A defined daily dose (definition by World Health Organization) of 500mg/day was chosen because this is typical procedure for adult drug dosing and most closely approximates the 6mg/kg/day dose identified for children with DMD. A dose of 500mg/day equates to approximately 6mg/kg/day for an 83kg male. In the event of a subject who is <50kg, the protocol specifies administering a half dose of 250mg/day (equivalent to 5mg/kg/day for a 50kg male). Vamorolone will be administered with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food.

5.5 Treatment Compliance

Subject compliance with the dosing schedule will be assessed by site maintenance of accurate study drug dispensing and return records, and accurate recording of incomplete or missed doses by completion of a diary by the subject. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. The Investigator or designee will instruct the subject with regard to proper dosing of study medication and completion of subject diaries and will reinforce the importance of taking all study medication per protocol instructions. Doses of study drug on the days of the Day 1, Week 12, and Week 24 Visits will be administered at the participating study site by a trained investigational staff member. All incomplete or missed doses are to be documented in the source document and on the appropriate eCRF page. The volume of unused study medication remaining in each bottle returned, as measured by the weight of returned bottles, will be documented in the source documents and on the appropriate eCRF page.

5.6 Study Drug Dose Interruption or Discontinuation

Subjects whose study medication is interrupted should continue to follow the original schedule and timing of study visits. Study staff should contact the Study Chair or Medical Monitor at the time of dose interruption for any additional instructions for visit-specific assessments.

In the event any clinical observation suggests an intolerability of an individual subject to the study medication, in the opinion of the Investigator, the case should be discussed with the Study Chair and Medical Monitor within 24 hours and study drug discontinuation should be considered. In view of the potential effect of the study drugs on adrenal glands, the study drugs cannot be discontinued suddenly. In case study drug needs to be discontinued, for whatever reason, the dose tapering process described for the end of the treatment period should be followed. If a subject discontinues study drug due to intolerability, the subject will be withdrawn from the study. The subject should return to the study site for completion of Week 24 assessments at the time of early withdrawal, prior to participation in the Dose-tapering Period, as appropriate. Any AE still ongoing at the time of study drug discontinuation will be monitored

until it has returned to baseline status, stabilized, or the Investigator, Study Chair, Medical Monitor and ReveraGen agree that follow-up is no longer needed.

5.7 Prior and Concomitant Medications and Therapies

5.7.1 Prior Therapy

All medications (prescription and over-the-counter [OTC]) taken within 3 months prior to the Screening Visit through Baseline Day -1 (until just prior to administration of the first dose of study medication) will be captured as prior medications (Medication History) in the source

document and the eCRF, including the name of the medication (or device or procedure), the dosage and regimen, the indication, and the treatment start and stop dates. Steroid use within the last 12 months will be recorded. Any earlier steroid use that the subject recalls can also be recorded.

5.7.2 Concomitant Therapies

Any medications that are taken after administration of the first dose of study medication will be recorded as concomitant medications on the appropriate eCRF page. Subject diaries will be provided to subjects to record any concomitant medication changes during the study (see Section 7.5).

All medications (prescription and OTC) taken during the study must be recorded in the source documents and in the eCRF, including the name of the medication, dosage and regimen, reason for therapy, and treatment start and stop dates. Furthermore, each change in concomitant medication (e.g., new treatment, discontinuation of treatment, or change in dosage/regimen) during the study must be documented in the same manner. Details of any non-pharmacological therapies (e.g., devices, procedures), including name, reason for therapy, and dates of therapy will also be recorded. Site personnel will review the information with the subject for completeness and accuracy at each study visit.

5.7.3 Prohibited Therapies

Subjects must discontinue use of the following medications prior to participation in the study, as indicated, and refrain from using these medications throughout the duration of the study:

- Mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), and mexrenone (mexrenoate potassium): use must be discontinued at least 4 weeks prior to enrollment;

- Oral glucocorticoids or other immunosuppressive agents. Subjects must have discontinued all use of oral glucocorticoids or other immunosuppressive agents at least 3 months prior to enrollment. [Note: Inhaled and/or topical glucocorticoids are permitted but must be administered at stable dose beginning at least 4 weeks prior to enrollment, and anticipated to be used at the stable dose regimen for the duration of the study.]

- Live attenuated vaccines: use must be avoided within 14 days prior to first dose of study medication and for the duration of participation in the study;
- Any investigational medications other than vamorolone: use must be discontinued at least 3 months prior to enrollment;
- Any approved medications or herbal remedies which can impact strength and function (including, but not limited to, Co-enzyme Q10 and creatine): use must be discontinued at least 4 weeks prior to enrollment.

In addition, vamorolone should be used with caution with any drug metabolized by cytochrome P450 3A4 (CYP3A4).

The Investigator should contact the Study Chair and Medical Monitor concerning individual medications or therapies not listed that may be of concern.

5.7.4 Permitted Therapies

Every effort should be made NOT to start any prescription or OTC medications during the study. Concomitant medications should be maintained on the same dose and regimen throughout the study whenever possible. However, all other medications other than those specifically prohibited above may be taken during the study, if clinically indicated, provided they are recorded in the source documents and in the eCRF.

5.7.5 Hydrocortisone

All subjects should be covered with "stress dosing" of hydrocortisone (or prednisone) during times of illness, injury, or surgery. Hydrocortisone dosing will be recorded in the source document and in the eCRF.

5.8 Study Medication Management

5.8.1 Packaging and Labeling of Study Medication

When all entry criteria are met, and prior to the Baseline Day -1 Visit, subjects will be randomized to treatment via the Almac's-WebEZ™ system. The sites will be pre-seeded with individual, uniquely numbered bottles labeled with a write-in area to add the patient number after the bottles are assigned. The subject will be supplied with sufficient study drug for the first twelve weeks of the Treatment Period.

Investigational medication suspension and matching placebo suspension will be packaged in sterile 120 mL (4 oz) amber bottles with a 107 mL fill volume with child-resistant cap with a 24 mm bottle press-in adapter. Bottles are filled with 107 mL of suspension in order to guarantee a delivery of 100 mL.

Bottles of investigational medication suspension will contain 4.0 grams of vamorolone/100 mL (4.0% orange-flavored suspension). The matching placebo suspension will be identical in

appearance and taste to the vamorolone suspensions. The volume per dose to be administered to each subject depends on the subject's weight (in kg) recorded at the visit prior to each study drug dispensing visit. Each subject will receive a volume of 12.5 ml/day (6.25 ml/day if <50kg body weight) of a vamorolone suspension or matching placebo suspension. Instructions for the calculation of each dose of liquid formulation are given in the Pharmacy Manual.

Bulk drug supplies will be labeled with ReveraGen, protocol number, lot number, expiration or retest date, and other appropriate study information. Carton and bottle labels will be written in accordance with all applicable laws, guidance and directives of the jurisdiction where the study is being conducted.

The volume per dose to be administered to each subject depends on the subject's weight (≥ 50 kg or <50kg) recorded at the dispensing visit; see Section 15.1 for complete instructions on calculating dose volume.

Trained site staff will write the dose level, dose volume in mL, and dispense date on the bottle label, prior to dispensing to subjects. Clinical supplies dispensed by the study site staff and ready for administration to subjects will be labeled with the dispense date, vamorolone/placebo dose level, volume to be administered per dose, protocol number, and additional information as required by all applicable laws, guidance and directives of the jurisdiction where the study is being conducted.

Study medication will be dispensed to the subject for Treatment Period dosing at the Day 1 Visit and at the Week 12 and Week 24 Visits. At the Week 24 Follow-up Visit, study medication for the Dose-tapering Period will be dispensed. Dispensed bottles of study medication will be returned at each subsequent study visit, prior to dispensing bottle(s) for the next dispensing interval.

Each study medication bottle may be used for a single subject only.

5.8.2 Storage of Study Medication

All Clinical Trial Materials (CTM) for use in the trial must be stored in a locked container/cabinet free from environmental extremes, under the responsibility of the institutional pharmacist or Principal Investigator. Bulk CTM should be stored at refrigerated temperature (2^oC - 8^oC; 36^oF – 46^oF). Excursions to ambient temperature are allowed (see Pharmacy Manual for details).

Access to study medication stored at the study site must be limited to authorized clinic personnel.

5.8.3 Study Medication Shipping and Handling

CTM will be shipped to the study sites only after receipt of required documents in accordance with applicable regulatory requirements and ReveraGen procedures. Study sites will receive CTM in bulk in sufficient quantity to satisfy the protocol requirements.

When all entry criteria are met, prior to the Baseline Visit, subjects will be randomized to treatment via the Almac's-WebEZ™ system. Study medication will be packaged with individual, uniquely numbered bottles labeled with a write-in area to add the patient number after the bottles are assigned. At the Day 1 Visit, the trained site staff will record the volume in mL per suspension dose (bottles) on the bottle. Study drug supplies sufficient to last until the Week 12 Visit will be dispensed to each subject. The first dose of study medication will be administered in clinic on Study Day 1. The initial drug supply will be sufficient to allow for the Week 12 Visit to occur on the latest date permissible within the protocol-specified visit window (12 weeks ± 7 days). No additional study drug supplies will be dispensed at the Week 4 Visit.

Prior to the subsequent study drug dispensing visits (i.e., Week 12, Week 24, Dose-tapering Period), additional study drug supplies will be ordered using the Almac's-WebEZ™ system. Additional labeled study drug supplies sufficient to last from Week 12 until the Week 24 Visit will be assigned via WebEZ™ and dispensed to each subject at the Week 12 Visit; and additional labeled study drug supplies sufficient to last from Week 24 through the duration of the Dose-tapering Period will be dispensed at the Week 24 Visit to subjects participating in the Dose-tapering Period.

CTM will only be dispensed to the subject once the subject has (1) a signed informed consent form (ICF) and HIPAA (as applicable) authorization on file, (2) met all eligibility criteria for entry into the study, and (3) completed all Pretreatment requirements.

It is essential to this study that all CTM be accounted for during the study period. All unused (i.e., undispensed; dispensed and returned) study medication will be retained at the study site for reconciliation by ReveraGen's study monitors (or designees) during routine monitoring visits.

Final disposition of all unused CTM will be coordinated by ReveraGen's study monitors (or designees) throughout and at the end of the study (see Section 5.8.4).

CTM must be dispensed and administered according to the procedures described in this protocol. Only subjects enrolled in the study may receive study medication, in accordance with all applicable regulatory requirements. Only authorized study personnel may supply CTM. Authorized study personnel refers to the Investigator (or designee) and hospital pharmacists, in accordance with all applicable regulatory requirements and the Site Signature Log/Delegation of Authority. Only authorized study personnel or the subject may administer CTM.

5.8.4 Study Medication Accountability

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The Subject Identification (ID) number of the subject to whom the study drug was dispensed
- The MED ID number of the dispensed kit
- The date(s) and quantity of the study drug dispensed to the subject
- The weight (g) of the dispensed bottle(s)
- The date(s) and quantity of the study drug returned by the subject
- The weight (g) of the returned bottle(s).

All records and drug supplies must be available for inspection by the Study Monitor at every monitoring visit. Unused CTM will be returned to ReveraGen Inc. or its designee or destroyed on site at the end of the study or at a specific time in agreement with ReveraGen, as coordinated between the site and ReveraGen or its designee. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to ReveraGen Inc or its designee. The Investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to ReveraGen Inc. or its designee.

5.9 Procedures for Assigning Subject Identification Numbers

Following the signing of the main written ICF, subjects will be assigned a unique site-specific 6-digit subject ID number in sequential order of screening into the study.

The site will notify the SPM of the newly assigned subject number.

All data for subjects who sign the main Informed Consent Form (ICF) for the study will be identified using the unique 6-digit subject ID number. Subjects are considered to be enrolled in the study when the subject signs the study main ICF at Screening. These subject ID numbers assigned upon signing of the written ICF will be retained through enrollment and throughout participation in the study. Subject ID numbers assigned to subjects who fail screening may not be used again.

The Site Investigator will keep a record relating the names of the subjects to their ID numbers (subject identification log) to permit efficient verification of data subject files, when required. A subject enrollment log will include the dates of subject enrollment and completion/termination.

6 STUDY SCHEDULE

6.1 Time and Events Schedule

The study procedures to be conducted for each subject are divided into the following study periods:

- **Prescreening visit**: At the optional prescreening visit, subjects will provide written prescreening informed consent/HIPPA authorization to release medical records including a genetic report confirming the diagnosis of BMD. Based on the review of the subject's medical records, the subject might be asked to sign the main consent form to continue his participation in the study.

- **Pretreatment Screening Period:** During the screening period (up-to-35-day interval, unless extended to accommodate varicella vaccine), the subject will sign the main Informed Consent/HIPAA authorization, and will complete all designated screening procedures, at least 24 hours prior to the first dose of study medication. All screening procedures must be completed by Day -1. The screening procedures related to eligibility criteria must be completed by Day -11. Subjects meeting all eligibility criteria will be randomized by Day -11, prior to the Baseline Day -1 Visit.

- **Pretreatment Baseline Period:** The 24-hour period immediately prior to administration of the first dose of study medication, also designated as Day -1.

- **Treatment Period:** The 24-week interval starting with administration of the first dose of study medication on Study Day 1 and continuing through the time of completion of all scheduled Week 24 Visit assessments. Subjects who will continue directly with vamorolone treatment will be discharged from the study following completion of all scheduled Week 24 assessments.

- **Dose-tapering Period:** The 4-week interval following the end of the 24-week Treatment Period during which subjects who will not transition directly to vamorolone treatment will begin a 4-week open-label Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued (see Section 6.3.6). Subjects participating in the Dose-tapering Period will be discharged from the study following completion of all final Dose-tapering Period assessments.

The procedures to be completed at each visit during each study period are presented in the Schedule of Study Activities in Table 6 and in the sections that follow. (Note: In Table 6, each visit with the acceptable time window around the planned visit date, where applicable, is provided.) Detailed descriptions of the assessments and the definitions of study endpoints are provided in Section 7 and Section 2, respectively. Any deviation from study procedures should be noted in the source documents and in the Clinical Trial Management Software (CTMS), and significant deviations should be reported immediately to ReveraGen.

Overall, up to approximately 33 weeks are allocated for each subject to complete the main study, including a 1-day Prescreening visit (optional), 35-day Pretreatment Screening Period, a one-day Pretreatment Baseline Period, a 24-week Treatment Period, plus a 4-week Dose-Tapering Period, as applicable. Upon the completion of the study, subjects may have the option to receive vamorolone treatment by enrolling in another program providing vamorolone.

Subjects who continue directly with vamorolone treatment by another program will be discharged from the VBP15-BMD-001 study following completion of all Week 24 assessments and will not participate in the Dose-tapering Period.

Subjects who do not enroll directly into another program providing vamorolone will participate in the 4-week Dose-tapering Period and will be discharged from the VBP15-BMD- 001 study following completion of all Dose-tapering Period assessments.

Table 6. Schedule of Study Activities

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

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

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

a. After signing the optional Prescreening Visit informed consent, participants will provide HIPPA authorization to release medical records, including a genetic report confirming the diagnosis of BMD
b. Randomization occurs by Almac's-WebEZ™ System after subjects are confirmed to have met all study entry criteria, prior to the Baseline Day -1 Visit.
c. NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep
d. Clinical safety labs: chemistry, hematology, CK, GGT, lipids; urinalysis by dipstick and microscopic
e. Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose
f. Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin
g. Only hemoglobin A1c (HbA1c)
h. Serum efficacy pharmacodynamic biomarkers: MDC and CD23
i. Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic
j. Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening
k. On week 4, only empty bottles of study medication and the current bottle in use will be returned

l. The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home
m. Only for subjects participating in the Dose-tapering Period
n. At Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication
o. Discharge from the study will be after Week 24 visit for those who enter another program for administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication

6.2 Informed Consent Procedures

Subjects are considered to be enrolled in the study at the time written main informed consent is obtained.

The subjects are to give prescreening (if participating in the optional prescreening visit) and main informed consent in accordance within the Declaration of Helsinki, US 21 Code of Federal Regulations (CFR) Part 50, International Conference on Harmonisation (ICH) guidelines on GCP and all applicable laws, guidances, and directives of the jurisdiction where the study is being conducted.

The subject who chooses to participate in this study will give written informed consent. The Investigator (or designated staff) will obtain the written informed consent from the subject prior to performing any study-related procedures. Each subject will receive an explanation of the nature and purposes of the study from the Investigator or designee. Time will be given to the subject to ask questions and make their decision as to whether they would like to participate. The Investigator or designee will ensure the study is appropriate for the subject.

Reasons for exclusion will be documented for subjects found ineligible during the Pretreatment Period. The subject will be asked if he understands that the study is for research purposes only and that it may not provide any therapeutic benefit to the subject. Each subject will be asked if he understands that the subject is free to withdraw from the study at any time without prejudice. Each subject will be required to sign a study main ICF (and HIPAA authorization, if applicable) before any procedures are performed for the study.

The Investigator or designee will obtain written informed consent from each subject prior to the subject's participation in the study using prescreening (if participating in the optional prescreening visit) and main ICFs approved by the appropriate IRB/IEC at each site. Consent must be obtained in accordance with the principles outlined in the current version of the Declaration of Helsinki. Informed Consent Forms must be dated and signed by the Investigator or designee and the subject and the original signed consent form must be kept by the Investigator in the study subject's file.

HIPAA and Protected Health Information

In the applicable countries, during the informed consent procedure, the Investigator or designee will review the elements of the HIPAA and Protected Health Information (PHI) with each subject, and each subject will confirm that he understands HIPAA authorization and PHI. The Investigator (or designated staff) will obtain HIPAA authorization from the subject on the appropriate IRB/IEC-approved form at each site, prior to any study-related procedures.

6.3 Visit Schedule and Procedures

During the study, there will be an optional prescreening visit and total of up to seven study site visits: Pretreatment Screening Visit (screening procedures can be performed on more than one day if necessary); Pretreatment Baseline Day -1 Visit; Treatment Period Day 1 and Week 4, Week 12, and Week 24 Visits; and a final Dose-tapering Period Week 28 Visit. In addition, a

telephone call from site staff to the subject will occur at Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication. To facilitate completion of all required Week 12 and Week 24 assessments, some of the assessments scheduled for the Week 12 and Week 24 Visits may be completed on a different day within the timeframe of +/- 1 week to the Week 12 or Week 24 (see Section 6.3.5).

Each subject will receive the double-blind study medication at 500mg (250mg if <50kg body weight) daily dose for a period of 24 weeks. Following completion of the 24-week Treatment Period, all subjects who will not be continuing directly to receive vamorolone in another program will taper their study medication during the 4-week Dose-tapering Period. See Section 7 for a detailed description of the safety, clinical efficacy, PK, PD, and patient-reported outcomes to be performed during this study.

6.3.1 Prescreening Visit

At the optional prescreening visit, the Investigator or study staff will discuss with each subject the nature and purpose of the study and the required study procedures. The subject's medical records will be reviewed after the subject sign the prescreening consent form/HIPAA Authorization. The subject's dystrophin genetic test report will be reviewed by the site PI for confirmation that the subject meets the Becker dystrophy diagnostic inclusion criteria. The subject's medical history and medication history will be reviewed to determine initial eligibility for participation in the study.

6.3.2 Screening Period (Day -35 to -3)

Following the signing of the written, main ICF, subjects will be considered to be enrolled in the study, and will be assigned a unique site-specific 6-digit subject ID number that will be comprised of protocol, site, and subject numbers in sequential order of screening into the study. All data will be identified using the unique subject ID number. The site Investigator will keep a record relating the names of the subjects to their subject ID numbers (subject identification log) to permit efficient verification of data subject files, when required. This record will also include the dates of subject enrollment and completion/termination.

The subject's medical history and medication history will be reviewed to determine eligibility for enrollment in the study. Demographic information will be collected.

Subjects will undergo the procedures in the bulleted list below and in Table 6 during the Screening Period. The procedures may be completed over the course of several visits, if necessary, but all scheduled Screening procedures must be completed within the timeframe of Day -35 to Day -3, and the actual date each procedure is performed must be recorded in the source document and eCRF. Any parameter/test may be repeated at the Investigator's discretion during Pretreatment Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result.

The following procedures will be completed at the Screening Visit:

- Main Informed Consent (see Section 6.2)
- Enrollment (see Section 5.9)
- Review of the Inclusion and Exclusion Criteria (see Section 4.2 and Section 4.3)
- Recording of the medical history, including any toxicities or allergy-related events to prior treatments (see Section 7.2.1)
- Recording of prior medications (Medication History) (see Section 5.7.1)
- Complete physical examination, including weight (in kilograms), height (in cm), and assessment of cushingoid features (see Section 7.2.2)
- Confirmation of chicken pox immunity (see Section 7.2.5)
- Recording of vital signs (sitting blood pressure, heart rate, body temperature, respiratory rate) (see Section 7.2.3)
- Collection of blood for clinical laboratory testing (hematology, clinical chemistry, GGT, and lipids) and collection of urine for urinalysis (see Section 7.2.4)
- NSAA including TTRW (see Section 7.3.1)
- Recording of AEs and SAEs beginning at the time written informed consent is obtained (see Section 7.6)

Subjects meeting all Screening eligibility tests will be randomized to treatment during the Screening Period.

6.3.3 Baseline Period (Day -1) Visit

Subjects who have met all study eligibility criteria and been randomized to treatment via Almac-WebEZ during the Screening Period, and for whom blinded study medication has been shipped to and received by the study site will return to the study site during the Pretreatment Baseline Period (Day -1, the 24-hour interval immediately preceding administration of the first dose of study medication) for baseline assessments, and will be assigned to treatment at the Baseline Day -1 Visit. Subjects will retain their 6-digit study identification number which was assigned during the Screening Period.

The following procedures will be completed at the Baseline Day -1 Visit:

- Review of the Inclusion and Exclusion Criteria (see Section 4.2 and Section 4.3)
- Recording of prior medications (Medication History) (see Section 5.7.1)
- Physical examination including weight (in kilograms) and assessment of cushingoid features (see Section 7.2.2)

- Recording of vital signs (sitting blood pressure, heart rate, body temperature, respiratory rate) (see Section 7.2.3)
- The patient-reported outcomes (Neuro-QOL for fatigue, upper and lower extremity function, and sleep)
- NSAA including TTRW (see Section 7.3.1)
- 12-lead ECG (see Section 7.2.8)
- Recording of AEs and SAEs; review of all AEs for resolution status and date (see Section 7.6)
- Dispensing of saliva collection kit to measure cortisol.

6.3.4 Treatment Period Day 1 Visit

At the Treatment Period Day 1 Visit, certain procedures must be performed prior to administration of the first dose of study medication and are so noted in this section. Treatment Period Day 1, for purposes of the study analyses, begins with administration of the first dose of study medication.

Subjects will take the first dose of study medication in clinic on the day after the Pretreatment Baseline (Day -1) Visit. Subjects must have fasted ≥ 8 hours prior to arrival at the study site for the Day 1 Visit. Subjects will bring a saliva sample to measure cortisol that they collect on first awakening the morning of the Treatment Period Day 1 Visit. Breakfast will be served at the study site after the blood collections for clinical laboratory tests and PD biomarkers, and within 30 minutes prior to administration of the dose of study medication. Urine must be collected prior to administration of the first dose of study medication.

Subjects will receive a medical “alert” card stating that participation in the study may increase the subjects’ risk of adrenal suppression. The card will include instructions for subjects and clinicians regarding management of possible adrenal suppression during emergencies, including coverage with “stress doses” of hydrocortisone (or prednisone) during times of illness, injury, or surgery.

The following procedures will be completed at the Treatment Period Day 1 Visit:

- Recording of vital signs (sitting blood pressure, heart rate, body temperature, respiratory rate) prior to administration of first dose of study drug (see Section 7.2.3)
- Clinical laboratory evaluation including hematology, clinical chemistry, GGT, lipids, and urinalysis tests, prior to administration of first dose of study drug (see Section 7.2.4).The study PI should review the clinical laboratory report prior to the administration of the first dose of the study medication.
- Blood samples for, PK, PD biomarkers including fasting glucose and insulin, osteocalcin and HbA1c, prior to administration of first dose of study drug (see Section 7.2.6).

Subjects will bring to the study site a saliva sample for cortisol collected at home on first awakening on the Treatment Period Day 1 Visit. Blood remaining from collected samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies.

- Dispensing of study medication and administration of first dose (see Section 5.8.1 and Section 5.3, respectively)
- Dispensing of subject diary (see Section 7.5)
- Recording of AEs and SAEs; review of all AEs for resolution status and date (see Section 7.6)
- Recording of concomitant medications (see Section 5.7)

On Day 1, the subject will be discharged from the clinic after completion of all scheduled assessments.

6.3.5 Treatment Period (Weeks 1-24)

Subjects will return to the study site for safety, clinical efficacy, PD and patient-related outcome assessments beginning at Week 4 and continuing through the Week 24 Visit, according to the schedule of assessments in Table 6.

Subjects will continue to receive daily oral administration of study medication suspension throughout the 24-week Treatment Period. The daily dose of study medication should be taken with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food.

Dosing is to occur at home throughout the 24-week Treatment Period, except at the Weeks 12 and 24 study visits, when dosing will occur at the study site. Subjects must have fasted ≥ 8 hours prior to arrival at the study site for the Weeks 12, and 24 study visits. Upon awakening on these 2 study visit days, the subject will collect a saliva sample to measure first-in-morning cortisol level. The subject will bring the sample to the study site. Breakfast will be served at the study site after the blood collections for clinical laboratory tests (Weeks 12 and 24) and blood draws for PD biomarkers, including insulin, glucose and HbA1c Weeks 12 and 24), and osteocalcin (Week 24 only); and within 30 minutes prior to administration of the dose of study medication.

Study medication will be dispensed at Weeks 12 and 24 (for subjects participating in the Dose-tapering Period) Visits. Empty study medication bottles and the bottle in use will be brought by the subject to the visits at Weeks 4 and 12; unused bottles will be left at home. The empty bottles will be retained by the site and the bottle in use will be re-dispensed at the end of the Week 4 or Week 12 visit. Subjects will receive subject diaries at each on-site study visit beginning at Day 1 and up to and including Week 12, and will return the diaries at each subsequent on-site visit. Diaries will be reviewed with the subject by the study staff to assess AEs, changes to concomitant medications/therapies, any missed or incomplete doses of study medication.

Clinical efficacy assessments (TTRW and NSAA) and the patient-reported outcomes (NeuroQOL for fatigue, mobility and sleep) will be conducted as specified in the schedule of study activities (Table 6).

Weight and height will be measured at the Weeks 12 and 24 Visits. Vital signs will be recorded at each on-site study visit. A physical examination including assessment of cushingoid features will be performed at Weeks 12 and 24. A 12-lead ECG will be recorded at Weeks 12 and 24.

Blood and urine samples for clinical laboratory tests and blood for the serum PD biomarker panel will be collected at scheduled visits throughout the study (Table 6). Adverse events, including SAEs, and concomitant medications will be assessed at each study visit and recorded throughout the study.

The scheduled Week 12 and Week 24 assessments may be performed over a 1 week period, if necessary, to facilitate scheduling. For the Week 24 assessments, the scheduled 12-lead ECG and NeuroQOL patient-reported outcomes may be completed on the day prior to the final Week 24 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 24 dose of study medication. The scheduled physical examination, weight, height, vital signs, clinical laboratory tests and blood draws for PD biomarker analysis, functional assessments (TTRW, NSAA), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 24 dose of study medication.

Subjects who complete the VBP15-BMD-001 study and will enroll directly into another program to receive vamorolone treatment will be discharged from the VBP15-BMD-001 study following completion of all Week 24 assessments. Subjects who will not continue into another program will have their study medication dose tapered during a 4-week Dose-tapering Period prior to discharge from the study (see Section 6.3.6). Site study staff will contact the subject by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms of adrenal suppression, and to address any questions the subject may have.

6.3.6 Dose-tapering Period (Weeks 25-28)

All subjects who complete the study and do not continue directly into another program to receive vamorolone, will participate in a 4-week Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued prior to discharge from the study. In addition, subjects who discontinue study medication after the first dose and prior to Week 24 will also participate in the Dose-tapering Period if possible and if, in the opinion of the Investigator, it is safe to do so.

The purpose of dose-tapering is to aid in re-establishment of adrenal function if adrenal suppression has occurred during vamorolone treatment. Dose tapering will be performed in a stepwise manner, according to the subject's most recent calculated liquid formulation dose during the 24-week Treatment Period.

Dose tapering for study medication will be performed as outlined in Table 7.

Table 7. Study Medication Dose Tapering

Treatment Period Dose Level	Week 25 Dose Level	Week 26 Dose Level	Week 27 Dose Level	Week 28 Dose Level
Formulation: 100%	50%	25%	10%	0%

Subjects will take the first dose of study medication in the Dose-tapering Period (Week 25 dose level) with a meal on the day following the Week 24 dose of study medication.

Site study staff will contact the subject by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal insufficiency, and to address any questions the subject may have. In addition, subjects will be assessed promptly for adrenal insufficiency if unwell at any time during the Dose-tapering Period. There will be a low threshold for recommending commencement of daily oral prednisone or hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these circumstances.

Following completion of the dose taper, the subject will return to the study site for a Week 28 visit. Adverse events, including SAEs, and concomitant medications will be assessed. Subjects

will have non-fasting blood and urine samples collected for clinical laboratory tests at the final Early Termination/Week 28 Visit. Subject diaries will be returned and reviewed with site staff. Study medication will be returned to the site for compliance monitoring.

Subjects participating in the Dose-tapering Period will be discharged from the study following completion of all Dose-tapering Period assessments.

6.4 Subject Discontinuation

Any subject who chooses to withdraw from the study after Day 1 and prior to the Week 24 Visit should return to the study site for Week 24 assessments at the time of early withdrawal, whenever possible (see Section 6.3.5), assuming the subject has not withdrawn consent, and should participate in the 4-week Dose-tapering Period whenever possible. Site personnel will document all assessments, including any AEs, in the source documents and eCRF.

In the event that a subject withdraws early from the study prior to the Week 24 Visit, the reason for discontinuation must be fully documented in the source documents and the eCRF.

In the event a subject withdraws informed consent, no further study procedures should be performed and no additional data should be collected. Any data collected up to the point of withdrawal of consent may be used by ReveraGen. Every effort will be made to ensure that subjects who withdraw consent undergo dose-tapering, as appropriate, prior to the date of withdrawal of consent. Subjects who withdraw early from the study may be replaced, at the discretion of ReveraGen.

Subjects who discontinue study medication should follow the procedures for dose-tapering, as outlined in Section 6.3.6 and Table 7, whenever possible. Dose tapering will be performed in a stepwise manner.

Subjects who discontinue early from the study and participate in the Dose-tapering Period will take the first dose of study medication in the Dose-tapering Period with a meal on the day after the last dose of Treatment Period study medication.

Dose-tapering for subjects who discontinue the study early is to aid in re-establishment of adrenal function if adrenal suppression has occurred with vamorolone treatment.

Subjects will be assessed promptly if unwell during the tapering phase or in the weeks following study medication cessation due to the risk of adrenal suppression. There will be a low threshold for recommending commencement of daily oral prednisone or hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these circumstances.

The final end-of-study visit will be scheduled during week 28 (final dose tapering to 0 mg/kg). Each subject will return to the study site for final study assessments when he has completed all administration of study medication.

Subjects will have non-fasting blood and urine samples collected for clinical laboratory tests at the final Early Termination/Week 28 Visit. Subjects will also have a physical examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including SAEs, and concomitant medications will be assessed. Subject diaries will be returned and reviewed with site staff.

Subjects will be discharged from the study following final Early Termination/Week 28 assessments.

6.5 Subject and Study Completion

A completed subject is defined as a subject who has completed the Treatment Period, through the Week 24 Visit assessments, and Dose-tapering Period, if applicable, and has not prematurely withdrawn from the study for any reason. The study will be completed when the final subject has completed his final study visit (“last subject, last visit”).

7 STUDY ASSESSMENTS AND MEASUREMENTS

7.1 Demographic Assessments

Demographic information (age, race, and ethnicity) will be collected during the Pretreatment Screening Period and will be recorded on the appropriate eCRF page.

7.2 Safety and Tolerability Assessments

7.2.1 Medical History

The medical history will be reviewed after the subject signs the prescreening consent form, if the subject is participating in the optional prescreening visit.

After the subject signs the main inform consent, the medical history will be recorded at the Screening Visit and will include significant past medical or surgical procedures as well as previous and current co-existent diseases. It should include the date (month/year) the subject was diagnosed with Becker dystrophy, initial symptoms of Becker dystrophy and the age at which they were first identified, and any toxicities or allergies to prior treatments. It should include relevant medical history for the following body systems: head, eyes, ears, nose and throat (HEENT), respiratory, cardiovascular, gastrointestinal, endocrine, hematological, dermatological, genital-urinary, neurological, musculoskeletal, psychological/psychiatric, and any other history of medical significance. The medical history will be recorded in the source document and on the appropriate eCRF page.

7.2.2 Physical Examination, Cushingoid Features, Weight, and Height

A complete physical examination will be performed at Screening, Baseline Day -1, Week 12, and Week 24, and at the final Week 28 Dose-tapering Period Visit, and will include examination of the following: head, eyes, ears, nose, and throat, neck *(including an examination of the thyroid),* heart, lungs, abdomen *(including an examination of the liver and spleen),* lymph nodes, extremities, nervous system, and skin. Clinically significant changes from baseline should be recorded as AEs. Particular attention will be paid in identifying any sign of cushingoid features, which should also be recorded as AEs if they first appear or worsen during the study.

Additional unscheduled symptom-directed physical examinations may be conducted at any time at the Investigator's discretion.

Height (in cm) will be recorded at Screening, Week 12, and Week 24. Both standing height and ulnar length will be measured on all subjects. Ulnar length will be measured on the non-dominant arm, measured from the olecranon (point of elbow) to the styloid process (prominent bone of the wrist).

Weight (in kg) will be collected at the study center using a calibrated scale at Screening, Baseline Day -1, Week 12, Week 24, and at the final Week 28 Dose-tapering Visit (Table 6). Weight recorded at the dispensing visit will be used to calculate the study medication dose for the subsequent dispensing interval (see Section 5.3).

Results will be recorded in the source document and on the appropriate eCRF page.

7.2.3 Vital Signs

Vital signs (sitting blood pressure, heart rate, respiration rate, and body temperature) will be recorded at Screening, Baseline Day -1, Day 1 pre-dose, Week 4, Week 12, and Week 24, and at the final Week 28 Dose-tapering Visit. Vital signs should be recorded after the subject has been resting for at least 5 minutes. Body temperature may be measured using oral, tympanic, or temporal recording devices; however, the same methodology must be used for all assessments of a given subject.

Results will be recorded in the source document and on the appropriate eCRF page.

If vital signs are recorded at the same study visit as blood collection and ECG recording, at least 15 minutes should elapse after collection of blood samples and before performing ECG and recording vital signs.

7.2.4 Clinical Laboratory Tests

Each subject will have blood drawn and urine collected for the hematology, chemistry, GGT, lipids, and urinalysis clinical laboratory tests listed in Table 8 and Table 9, below, during the Screening Period, Week 4, Week 12, Week 24, and Week 28 Visits, as specified in Table 6. Fasted blood samples for clinical laboratory tests will be collected pre-dose at the Day 1, Week12, and Week 24 Visits. Non-fasted blood samples for clinical laboratory tests will be collected at the Screening, and Week 4 and Week 28 Visits. Urine samples should be collected pre-dose on Day 1 and may be collected non-fasting at all scheduled visits.

All blood and urine samples will be sent to the local laboratory for testing.

For the hematology, chemistry, GGT, and lipids laboratory tests, blood will be collected by direct venipuncture of peripheral veins. A total of approximately 30 mL of blood will be collected over the course of this study for clinical safety laboratory evaluation (see Section 7.2.8 for details of blood volumes to be collected).

If blood collection is performed at the same study visit as vital signs assessment and ECG recording, at least 15 minutes should elapse after collection of blood samples and before performing ECG and recording vital signs.

Any abnormal hematology, chemistry, lipid, or urinalysis test result deemed clinically significant by the Investigator or medically qualified sub-investigator may be repeated, including test results obtained on the final study day.

Any treatment-emergent abnormal laboratory test result that is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE section of the eCRF:

- Accompanied by clinical symptoms
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)
- Is otherwise considered clinically significant by the Investigator

Any clinically significant test abnormality as defined above should be recorded as an AE (unless it was considered spurious), and repeat analysis performed until resolution or until the Investigator or medically qualified sub-investigator determines that resolution of the abnormality is not expected.

Table 8. Hematology, Chemistry, GGT, and Lipids Clinical Laboratory Tests

Hematology	
Red Blood Cells (RBC)	Platelets
Hemoglobin	White Blood Cells (WBC)
Hematocrit	
Chemistry	
Sodium	Total Bilirubin[a]
Potassium	Glucose
Chloride	Alkaline phosphatase (ALP)
Calcium	Aspartate aminotransferase (AST)
Blood Urea Nitrogen (BUN)	Alanine aminotransferase (ALT)
Creatinine	Creatine kinase (CK)
Total Protein	Bicarbonate
Albumin	Gamma glutamyl transferase (GGT)
Lipids	
Triglycerides	Low Density Lipoprotein (LDL)
Total cholesterol	High Density Lipoprotein (HDL)

a. If outside normal range, direct bilirubin will be measured and reported.

Urine will be collected for routine analysis, by dipstick and microscopic analysis, for the tests described in Table 9.

Table 9. Urinalysis Clinical Laboratory Tests

Urinalysis (including microscopic examination)	
Dipstick[a]	**Microscopic Analysis**
Protein	WBC/hpf
Glucose	RBC/hpf
Ketones	Casts
pH	Bacteria
Leukocyte esterase	
Blood	

a. A midstream clean-catch urine specimen will be collected for dipstick analysis.

Clinical laboratory tests will be performed by the local laboratory; results will be reported to the study site and manually entered into the clinical study database.

7.2.4.1 Follow-up of Abnormal Laboratory Test Results

In the event of a medically significant, unexplained, or abnormal clinical laboratory test value, the test(s) may be repeated, evaluated by the Investigator for sustainability and reproducibility, and followed-up until the results have returned to the normal range, stabilized, and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate which of these deviations are clinically significant. These clinically significant deviating laboratory results will then be further described as AEs, and the relationship to the treatment, in the Investigator's opinion, will be assessed (see Section 7.6).

7.2.5 Chicken Pox Immunity

Subjects must provide evidence of immunity to varicella zoster virus to be eligible for assignment to treatment. Evidence of immunity may be determined by either a positive anti-varicella IgG antibody test result obtained during the Screening Period, or documentation, provided at the Screening Visit, that the subject has had 2 doses of varicella vaccine, with or without serologic immunity, with the second of the 2 doses given at least 14 days prior to randomization. For subjects whose anti-varicella antibody titer will be measured at Screening, a 2 mL blood sample will be collected for antibodies (IgG) to Varicella Zoster virus to confirm immunity. The blood sample will be sent to the local laboratory for testing.

If antibodies are not detected in the blood sample sent to the local laboratory, and documentation of the required previous vaccination(s) against varicella cannot be provided, immunization before starting the trial will be advised and the immunization status must be re-checked prior to assignment (see Manual of Operations for details). Lack of willingness to immunize a subject who is not already immune to chicken pox will be a reason for exclusion of the subject from the trial.

7.2.6 Pharmacodynamic Biomarker Panel

Saliva and blood samples will be collected to explore the effect of vamorolone on biomarkers associated with glucocorticoid safety concerns (exploratory outcomes for anti-inflammatory efficacy, and safety outcomes of adrenal suppression, insulin resistance, and bone turnover), as listed in Table 10.

Blood samples will be collected pre-dose at the Day 1, Week 12, and Week 24 Visits for analysis of biomarkers bridged to safety measures of insulin resistance and bone turnover.

Approximately 6 mL of blood will be collected for the safety PD biomarker panel (osteocalcin at Day 1 and Week 24, and hemoglobin A1c (HbA1c) and fasting insulin [insulin resistance] at Day 1, Week 12 and Week 24). Samples collected at the Day 1 , Week 12, and Week 24 Visits will be collected after the subject has fasted for ≥ 8 hours and prior to administration of the daily dose of study medication.

Approximately 6 mL of blood will be collected for the efficacy PD biomarker panel (MDC and CD23) at Day 1, Week 12 and Week 24.

Saliva for first morning cortisol will be collected by subjects at home before coming to the study site on Day 1, Week 12, and Week 24, for analysis of biomarkers for exploratory outcome measures of adrenal suppression.

Blood remaining from collected samples not needed for protocol-specified analyses at each of the blood collection time points may be stored for future exploratory biomarker studies for aspects of safety and efficacy. These remaining blood samples may be released to scientists worldwide for research purposes, including research on biomarkers in Becker dystrophy. Any released samples will have no identifying subject information.

Additional blood samples for HbA1c determination should be collected if urine glucose is positive and/or fasted glucose levels are above normal limits at any of the scheduled assessment time points.

A total of approximately 42 mL of blood will be collected for safety and efficacy PD biomarkers (fasting insulin, osteocalcin, HbA1c, MDC and CD23) over the course of the 33-week study (see Section 7.2.7).

Table 10. Pharmacodynamic Biomarkers - Exploratory Safety Outcomes

Adrenal Suppression
Cortisol – first morning
Insulin Resistance
Glucose – fasting
Insulin – fasting
HbA1c
Bone Turnover
Osteocalcin
Drug target (inflammatory)
CD23
MDC

7.2.7 PK Assessment

At the Day 1 Visit, all subjects will have blood collected for PK assessments at 1, 2 and 3 hours post-dose. Approximately 2 mL of blood will be collected into K2-EDTA tubes at the assessment time points.

Plasma concentrations of vamorolone will be measured using a specific and validated liquid chromatography tandem mass spectrometry assay. PK assessments will be performed by a central laboratory. The procedures for the collection, handling, and shipping of laboratory samples will be specified in the VBP15-BMD-001_GUIDELINES for Biological Specimen Collection provided to the study sites.

The exact time of blood sampling will be recorded in the source document and eCRF.

If PK and PD or clinical laboratory blood samples are to be collected at the same time point, the PK blood sample should be collected prior to the PD blood sample(s), which in turn should be collected prior to the clinical laboratory blood samples.

7.2.8 Total Blood Volume Required

The number and volume of blood samples and total volume of blood to be collected from each subject throughout the duration of the up-to-33-week study are summarized in Table 11. A total of 86 mL of blood will be collected from each subject over the course of the up-to-33-week study.

Table 11. Blood Sample Number and Volume by Study Visit

Test	Blood Volume (mL)						
	SCR	Day 1	Week 4	Week 12	Week 24	Week 28	Total Volume
Varicella Zoster IgG	2						2
Clinical Lab tests[a]	6	6	6	6[f]	6	6	36
Safety PD Biomarker Panel[c]		6			6		12
Efficacy PD Biomarker Panel[d]		6		6	6		18
Fasting blood for insulin and glucose[b]		4		4	4		12
PK[e]		6					6
Total Volume by Visit (mL)	8	28	6	16	22	6	86
Total Volume: 86 mL							

SCR = Screening

a. Hematology, Chemistry, CK, GGT and Lipids.
b. Subjects must have fasted ≥ 8 hours prior to blood draws.
c. Osteocalcin, hemoglobin A1c (HbA1c), insulin. (HbA1c) will also measured on Week 12
d. MDC and CD23
e. Blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

7.2.9 12-Lead ECG

12-lead ECGs will be recorded at Baseline Day -1, Week 12, and Week 24 Visits. All ECG recordings must be performed using a standard high-quality, high-fidelity machine equipped with computer-based interval measurements. Digital ECG recording is recommended. Automated ECG intervals (QRS duration, PR [PQ] interval, RR interval [interbeat interval], QT interval, QTc, and heart rate) will be captured or calculated.

12-lead ECGs will be obtained over a 3- to 5-minute period after the subject has been resting quietly in a supine position for at least 5 minutes.

If blood collection, vital signs assessment, and ECG recordings are scheduled at the same study visits, at least 15 minutes should elapse between collection of blood samples and before performing ECG and recording vital signs.

ECG results will be read locally. Results must be interpreted. ECG reports must be retained in the source document, and results recorded on the appropriate eCRF page.

7.3 Assessment of Muscle Function

Muscle function assessments should be performed in the morning and at approximately the same time of day, whenever possible.

7.3.1 North Star Ambulatory Assessment (NSAA)

The North Star Ambulatory Assessment (NSAA) is a clinical assessment scale designed to measure functional ability in ambulant boys and men with Becker dystrophy. The NSAA consists of 17 scored items including 2 timed tests, namely the Time to Run/Walk test (TTRW) and the Time to Stand test (TTSTAND). The NSAA will be completed for subjects at the Screening, Baseline, Week 12 and Week 24 Visits.

Subjects should be barefoot and wear comfortable clothing. Complete instructions for administering and scoring the NSAA are given in the Clinical Evaluator Manual to be supplied to the sites prior to study start.

Results will be recorded in the source documents and in the eCRF.

7.4 Patient-Reported Outcome Measures

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

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

7.5 Subject Diary

The subject will be given a subject diary at the Day 1 Visit in which to record any new concomitant medications and any changes to existing concomitant medications taken during the study, any AEs experienced by the subject during the study, and any missed or incomplete doses of study medication. The subject will be instructed in how to record information in the diary and will be instructed to bring the diary with them to each study visit for review by study staff for completeness and accuracy. A new diary will be dispensed at each on-site visit for use through the time of the next scheduled on-site visit. Collection of final diaries will occur at discharge from the study at the Week 24 Visit, for those subjects not entering the Dose-tapering Period, or at the Week 28 Visit, at the end of the Dose-tapering Period.

7.6 Adverse Events, Serious Adverse Events and Unanticipated Problems

The condition of the subjects will be monitored throughout the duration of the study by the clinical site study team and by recording of AEs in subject diaries. An AE is any untoward medical occurrence in a subject and does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the drug. Pre-existing conditions that worsen during a study are to be reported as AEs. Signs and symptoms of Becker dystrophy should not be recorded as AEs, unless their nature or severity is unexpected for the course of the disease.

The Investigator is responsible for reporting AEs and SAEs to ReveraGen or designee. For reported death of a participant, the Investigator shall supply ReveraGen and the IRB/IEC with any additional information requested. All AEs should be reported in aggregate to the NIAMS and the DSMB (through the NIAMS Executive Secretary) as part of the routine data and safety monitoring report provided for DSMB meetings.

Adverse events will be recorded from the date of informed consent and through the time of the subject's last study visit (study completion or early discontinuation). 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. In addition, subjects will be questioned by study staff at each study visit for any new signs or symptoms or changes in existing signs or symptoms.

All AEs and SAEs that are spontaneously reported, identified during questioning, or are apparent from a subject's physical appearance, will be recorded in the source document and in the subject's eCRF. The date of onset will be recorded. Any laboratory abnormality that is outside the normal range and is considered an AE (see Section 7.2.4) should be recorded as an AE on the appropriate eCRF page. The details recorded shall include the nature, date of onset, final outcome and its date, intensity assessment (Common Terminology Criteria for Adverse Events [CTCAE] grade), and a determination of the relationship of the event to administration of the study drug (i.e., causality). The intensity of all AEs will be graded by CTCAE, Version 5.0.

Details of any medications given to the subject to abate the AE should be recorded on the appropriate eCRF page.

Unanticipated Problems (UPs) can be either AE/SAEs, which are unexpected events that relate directly to participant safety, or protocol deviations that put patient privacy at risk or put patients at risk in some way that does not have an impact on their health and safety.

Unanticipated problems are defined as any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If UPs occur during the study, they will be reported to the IRB, the NIAMS and the DSMB (through the NIAMS Executive Secretary) by the study team. The UP report for the Monitoring

Body and NIAMS will be completed and submitted to the NIAMS Executive Secretary within 48 hours of the Study Chair becoming aware of the event.

7.6.1 Intensity

All AEs encountered during the clinical study will be recorded in the eCRF. Intensity of AEs will be graded using the most current version of the CTCAE, version v 5.0, 5-point scale, and reported in detail as indicated in the eCRF. A description of the intensity scales can be found below:

Mild (Grade 1): Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.

Moderate (Grade 2): Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Severe (Grade 3): Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;

Life-Threatening (Grade 4): Life-threatening consequences; urgent intervention indicated.

Death (Grade 5): Death related to AE.

7.6.2 Relationship

Relationship to study drug will be graded on a 5-point scale (definite, probable, possible, remote, or unrelated). A description of the relationship scale can be found below:

Definite: This category applies to an AE that meets at least criteria 1, 2, and 4 of the "Probable" category.

Probable: This category applies to those AEs that are considered, with a high degree of certainty, to be related to the study drug. An AE may be considered probable, if (must include first 3):

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases after dosing is complete. (There are important exceptions when an AE does not disappear upon discontinuation of study drug, yet drug relatedness clearly exists, e.g., [1] bone marrow depression and [2] tardive dyskinesia.)
4. It follows a known pattern of response to the suspected study drug.

Possible: This category applies to those AEs for which the connection with study drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related to study drug if or when (must include first 2):

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the suspected study drug.

Remote: In general, this category is applicable to an AE that meets the following criteria (must include the first 2):

1. It does not follow a reasonable temporal sequence from administration of the study drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the suspected study drug.

Unrelated: This category is applicable to those AEs which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for study drug relationship listed under remote, possible, or probable.

7.6.3 Clinical Laboratory Test Abnormalities

Clinical laboratory test results will be recorded on the designated eCRF page. The intensity of abnormal clinical laboratory test results that are AEs will also be graded using the most current version of the CTCAE, version 5.0, 5-point scale and reported in detail as indicated in the eCRF. A description of the intensity scale can be found above.

Any treatment-emergent abnormal clinical laboratory test result that is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE section of the eCRF:

- Accompanied by clinical symptoms
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)
- Is otherwise considered clinically significant by the Investigator

This applies to any protocol and non-protocol-specified safety laboratory result from tests performed after the first dose of study drug, which falls outside the laboratory reference range and meets the clinical significance criteria per Investigator standard operating procedures (SOPs).

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range, but does not meet the clinical significance criteria (which will be analyzed and reported as laboratory abnormalities); those that are considered AEs of the type explicitly exempted by the protocol; or those that are the result of an AE which has already been reported.

Please Note: any clinical laboratory abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

7.6.4 Follow-Up of Adverse Events

Adverse events will be followed until they have returned to baseline status, stabilized, or the Investigator, Study Chair, Medical Monitor and ReveraGen agree that follow-up is no longer needed. If a clear explanation of cause is established, it should be recorded in the source document and eCRF. In the event of unexplained abnormal laboratory test values, the tests may be repeated as soon as possible and followed up until they have returned to the normal range or baseline value and/or an adequate explanation of the abnormality is found. In case of ongoing AEs at the time of database closure, the data obtained at the time of database closure will be used in the statistical analysis. The further follow-up of AEs will be documented in the source document and will be described in the final report only if considered relevant by the Investigator, the Study Chair, the Medical Monitor and/or ReveraGen.

In addition, the Medical Monitor may request additional blood tests, diagnostic imaging studies, or specialist physician consultations in order to further evaluate any AE or test abnormality considered to be clinically significant by Reveragen.

7.6.5 Dosing Error

For the purposes of this study, a dosing error is defined as a dose exceeding or less than the scheduled dose of vamorolone suspension. Such occurrences will be reported as a Protocol Deviation, and recorded in the dosing page of the eCRF and as follows:

- Use of study medication in doses in excess or less of that specified in the protocol will not be recorded as an AE unless there are associated signs or symptoms.
- A dosing error with associated non-serious AEs will be recorded as AEs on the relevant AE forms in the eCRF.
- A dosing error with an associated SAE will be recorded as an SAE.
- Details of all dosing errors, including actual dose administered, will be documented in the source document and recorded in the appropriate documentation.

7.6.6 Serious Adverse Events

Serious adverse events will be collected and reported during the study from the time informed consent is obtained through 30 days after the final dose of study medication, according to the protocol and applicable regulations. For subjects who do not receive vamorolone in another program providing vamorolone, site staff will make a phone call to the home 31-35 days after the final dose of study medication in the VBP15-BMD-001 study to confirm the final SAE status of the subject.

All SAEs, including those that continue beyond the normal AE collection period (i.e., are ongoing at the subject's last study visit), will be followed until resolution or until stabilized without sequelae. All SAEs, both related and unrelated, that begin within 30 days after the subject's final dose of study medication will be reported to ReveraGen within 24 hours of discovery by the Investigator.

During the SAE collection period, the Investigator or clinical site personnel should notify ICON of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event. All SAE reports should be completed within the EDC; both the AE and SAE eCRF within 24 hours of first awarenessof the event. This triggers alerts to the ICON safety management team. The ICON safety management team works directly with sites to receive follow-up information after initial SAE notification and notify other study parties including the Medical Monitor, Study Chair, and ReveraGen.

In addition, notification is sent by the Investigator to the IRB/IEC, following local reporting requirements.

The study chair or designee should also report to the NIAMS and the DSMB Safety Officer (through the NIAMS Executive Secretary) within 48 hours of the Investigator becoming aware of all SAEs (regardless of relatedness or expectedness).

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or ReveraGen, it results in any of the following outcomes:

- Is fatal (results in the outcome of death)
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The terms death and sudden death are clearly distinct and must not be used interchangeably.

Any AE (including treatment-emergent, clinically significant, abnormal laboratory test values), as determined by the Investigator, that is serious and which occurs during the course of the study (as defined above) must be reported within the EDC. The ICON safety management team will notify the Study Chair, ReveraGen and the Medical Monitor, within 24 hours of the Investigator becoming aware of the event. Additional information that becomes available for an SAE after the initial report is submitted will be reported to the ICON safety management team, who will notify the Study Chair, ReveraGen and the Medical Monitor, within 24 hours of the Investigator becoming aware of the new information.

All SAEs must be collected and reported during the study from the time of informed consent through 30 days after the final dose of study medication. All SAEs, related and unrelated, must be reported to ReveraGen within 24 hours of first awareness.

If at any time during the study a subject experiences an SAE, appropriate care should be instituted.

In the event of an SAE, the Investigator will complete the SAE electronic case report form within 24 hours of first awareness of the event. In the unlikely event that the electronic study database is inaccessible and the Investigator is unable to complete the SAE electronic case report form within 24 hours, the SAE Notification Form (pdf) should be completed and emailed or printed/faxed to the PRA safety management team within 24 hours, using the contact information below:

In North/South America:

Email: CHOSafety@prahs.com
Drug Safety Fax: 1 888 772 6919 or 1 434 951 3482
SAE Questions: Drug Safety Helpline: 1 800 772 2215

In Europe, Asia-Pacific and Africa (EAPA):

Email: MHGSafety@prahs.com
Drug Safety Fax: +44 1792 525720
SAE Questions: Drug Safety Helpline: +49 621 878 2154

Serious Adverse Events will be recorded from the time the subject's written informed consent is obtained. Serious adverse events that occur within 30 days of study drug dosing must continue to be recorded and reported to ReveraGen or its designee. Should there be an SAE that occurs that suggests an increased risk to the participants, the following steps will be considered, depending on the number and severity of the SAE(s): modification of the protocol, investigation of the relationship of the SAE(s) to study drug, suspension of the study, and/or discontinuation of the study.

Suspected Unexpected Serious Adverse Reaction (SUSAR) Identification and Reporting

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected (not identified in the Investigator's Brochure). ReveraGen will evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event. Reveragen will notify all participating investigators of SUSARs in a manner and timeframe consistent with applicable national regulatory requirements.

Under the former 21 CFR 312.32 (Investigational new Drug (IND) Safety Report), ReveraGen must report to the FDA any unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following ReveraGen's initial receipt of the information. Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as

possible but no later than within 15 calendar days following ReveraGen's initial receipt of the information.

The study will comply with all local regulatory requirements. This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.

8 STUDY COMMITTEES

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB), operating autonomously from ReveraGen and the site investigators, will be responsible for providing independent recommendations to the NIAMS about risk-benefit of the study and for any modification affecting safety or data integrity required during the course of the study. The DSMB members must not be actively involved in study design, conduct or daily management of this study and must not have financial, propriety, professional, or other interests that may affect impartial, independent decision-making.

Specialists may be invited to participate as non-voting members at any time if additional expertise is desired. The DSMB will formally interact with the NIAMS through the sharing of DSMB meeting minutes. The NIAMS (through the NIAMS Executive Secretary) will share any DSMB recommendation.

The DSMB will be responsible for:

- Examining accumulating safety and other relevant data at pre-specified points during the course of the study in order to make recommendations concerning continuation, termination, or modification of the study;
- Reviewing important protocol deviations;
- Providing expert advice to the NIAMS on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects;
- Based on the results of its deliberations, the DSMB can recommend continuation of the studies unchanged, study interruption, study termination, modification of the studies, or alteration in the DSMB monitoring plan.

9 DATA COLLECTION

9.1 Source Documents

Source documents are defined as original documents, data, and records. These documents may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded in the appropriate source documents.

Investigators will keep a record relating the names of the subjects to their enrollment numbers (subject identification log) to permit efficient verification of data subject files, when required.

A subject enrollment log is to be completed at each study site. Data recorded on the enrollment log are to include a subject identifier, the dates of enrollment and completion/termination, and the reason the subject was not entered (if applicable).

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data documents.

9.2 Electronic Case Report Form Completion

Subject data will be collected in this study using an EDC system. The EDC and database system will be OpenClinica by Akaza Research, LLC. OpenClinica is a web-based (https://www.openclinica.com) data entry system utilizing a high security environment. The underlying storage facility will be PostgreSQL, whose structure permits the linking of subject information across all tables in relational databases. OpenClinica uses secure socket layers (SSL) and in its Enterprise version used in this study is 21 CFR Part 11 compliant. Once an eCRF is created in the database, a data dictionary exists and the data team creates compatible paper source documentation.

TRiNDS data management team will design an electronic database in OpenClinica for this study. Access rights to the EDC system for the study site team members will need to be requested. Every user of the system will be made aware of the fact that username and password should never be shared, and their electronic signature constitutes the legally binding equivalent of a handwritten signature. Only trained personnel certified by TRiNDS will receive a username and password.

All data will be directly entered or collected on a source document and then entered into OpenClinica or transferred electronically to the study database (e.g., clinical laboratory results).

TRiNDS data management team will monitor the eCRFs for completeness and acceptability throughout the course of the study. ReveraGen personnel (or their representatives) will be allowed read-only access to all source documents in order to verify eCRF entries.

9.3 Data Processing

A clinical study database will be constructed from the eCRFs and any data merged electronically, and the data will be validated both manually and electronically. Clarification of data will be requested from the study site as required. The database will be quality assured in accordance to the data management plan and will be available for statistical analysis according to the methods outlined in Section 10.7 and the Statistical Analysis Plan (SAP).

9.4 Subject Diaries

The information recorded in the diary will be considered source documentation, and any relevant requested information recorded in the diary should be transcribed by study staff to the appropriate eCRF page.

10 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 Sample Size Determination

The primary objective is to evaluate safety and tolerability in this Becker dystrophy population, for which this is the pilot study and no effect sizes are available.

A sample of 26 Becker dystrophy subjects on vamorolone will be large enough to have a confidence interval of no wider than 39% for the proportion of treatment emergent adverse events assessed or any other event outcome in the vamorolone group.

We also assessed power for motor efficacy comparisons of vamorolone to placebo and present these calculations needed to detect a similar effect as that observed for TTRW velocity in DMD subjects in Becker dystrophy.

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

Given our sample size calculations and that we aim to recruit 39 subjects, we should have enough power to detect a difference in TTRW velocities.

10.2 Statistical and Analytical Plan (SAP)

The sections below summarize the intended statistical methods and analyses for this study. A more detailed SAP will be written and finalized prior to any lock of the study database (final or interim, if applicable) and any analysis performed. The SAP will give a detailed description of the summaries and analyses that will be performed and will clearly describe when these analyses will take place.

10.2.1 Deviations from the Statistical Analysis Plan

Any deviation(s) from the original SAP will be described and justified in the clinical study report.

10.3 Analysis Populations

Four populations will be defined for data analysis: Safety Population, a modified Intent-to- Treat (mITT) Population, per protocol population, and a PK population

10.3.1 Safety Population

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

10.3.2 Modified Intent-to-Treat (mITT) Population

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

10.3.3 Per Protocol Population

The Per Protocol Population will be those subjects in the mITT Population who had no important protocol deviations and will be the secondary analysis population for analysis of the efficacy data.

10.3.4 PK Population

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

10.4 Measures Taken to Avoid/Minimize Bias

Not applicable.

10.5 Interim Analysis

No formal interim statistical analyses are planned, apart from the interim data views and presentations to be created for the DSMB.

10.6 Missing, Unused, and Spurious Data

The possibility of bias from missing data of subjects who prematurely discontinue will be addressed in the clinical study report. Missing values for safety and exploratory outcomes will be treated as missing, unless stated otherwise. Full details are presented in the SAP.

10.7 Statistical Analysis

10.7.1 General Considerations

Statistical analyses will be performed using SAS® version 9.4 or later.

All measurements will be analyzed based upon the type of distribution, and descriptive statistics will be presented by assessment time point, as appropriate.

No formal interim statistical analyses are planned at the mid-point of the study (after week 12 visit for 39 participants), apart from the interim unblinded safety data views and presentations to be created for the Data and Safety Monitoring Board (DSMB). An interim analysis will follow

interim database lock, subsequent to last patient last visit, and preceding the final database lock and final primary analysis. The Week 24 analyses are the primary analyses for this study and will be performed after all subjects have completed Week 24. Missing values for safety outcomes will be treated as missing, unless stated otherwise. Baseline measurement is defined as the last non-missing value prior to the first dose of study drug.

Analyses will be summarized by two treatment groups:

Vamorolone (n=26)

Placebo (n=13)

The secondary efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. Another secondary efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.

For the efficacy motor endpoint, TTRW (velocity), change from baseline to Week 24 will be compared between the vamorolone dose group and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, baseline age, and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 12 and 24) along with the treatment-by-week interaction. Within this model, the comparison (using least squares [LS] mean contrasts) will be made to compare TTRW velocity at 24 weeks for the vamorolone group with placebo.

For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline age and outcome, and treatment-by-week interaction).

An unstructured covariance matrix will be used, and underlying modelling assumptions will be checked. If differences between baseline characteristics exist between the treatment groups, it will be investigated if adjustment for these characteristics is clinically relevant and necessary.

10.7.2 Subject Disposition, Demographics, and Baseline Characteristics

Subject disposition will be summarized by analysis population. The number of subjects enrolled, the number in each population, and the reason for discontinuation from the study will be summarized and listed.

Subject demographics (e.g., age, race, and ethnicity) and baseline characteristics (e.g., height, weight, and months/years since BMD diagnosis) will be summarized descriptively.

10.7.3 Safety and Tolerability Analyses

The Safety Population will be used for presentations and analyses of the safety and tolerability parameters. Analyses will be done as per actual treatment received.

In general, all evaluations of clinical safety will be listed and presented using descriptive statistics by time point. In addition, individual subject listings of all safety data will be created and sorted by age and time point and will be reviewed for any evidence of differences or trends in the safety profile of vamorolone. Where considered relevant, plots will be created.

Safety data will include weight, vital signs and ECG results, and these will be presented using descriptive statistics. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed.

Adverse events will be summarized overall and by SOC, and Preferred Term (PT) (using the Medical Dictionary for Regulatory Activities [MedDRA], version 25.0) and by relationship to study medication and intensity (CTCAE grade, version 5.0) and AE outcome. Number of subjects who discontinue study medication due to AEs will be summarized.

Physical examination results will be listed only.

10.7.4 Pharmacokinetic Analyses

Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects.

10.7.5 Pharmacodynamic Analyses

The evaluations of PD biomarkers will be performed using the Safety Population. Analyses will be done as per treatment actually received.

All PD biomarker results will be summarized and listed.

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers. Change from baseline will be presented through paired t-test analyses for the serum safety pharmacodynamic biomarkers (baseline and week 24) and for insulin, glucose~~, cortisol, and osteocalcin~~ (week 24 vs baseline and week 12 vs baseline). For safety endpoints cortisol and osteocalcin, and efficacy endpoints, CD23 and MDC data, these may be used on the log scale (in case of skewness) and MMRM approach will be used and change from Day 1 compared between vamorolone and placebo dose groups.

Full details will be provided in the SAP.

10.7.6 Clinical Efficacy Analyses

The evaluations of clinical efficacy will be performed using the mITT Population.

All efficacy data will be summarized and listed. Where considered relevant, plots will be created.

The clinical efficacy outcomes are the time to run/walk 10 meters velocity, the NSAA and serum biomarkers of CD23 and MDC. Standard descriptive statistics will be used to summarize the clinical efficacy endpoints. TTRW velocities and NSAA score will be modeled via MMRM approach and change from baseline presented. Full details will be provided in the SAP.

10.7.7 Patient-Reported Outcome Analyses

Patient-reported Outcomes will be listed and presented using descriptive statistics and ANCOVA comparisons between vamorolone and placebo dose groups. Full details will be provided in the SAP.

10.7.8 Concurrent Medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the World Health Organization (WHO) Drug classification (Version 4.03). All concomitant medications will be detailed in the subject data listings.

11 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

11.1 Regulatory Approval and Good Clinical Practice

This study will be conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, June 1964), and amendments of the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, 1996), 52nd (Edinburgh, 2000), 53rd

(Washington, 2002), 55th (Tokyo, 2004), 59th (Seoul, 2008), and 64th (Fortaleza, 2013) World Medical Assemblies and ICH E6 Guideline for Good Clinical Practice (GCP).

Further, the trial will be conducted in accordance with all applicable laws, guidances and directives of the jurisdiction where the study is being conducted.

11.2 Investigator Responsibilities

11.2.1 Subject Information and Informed Consent

It is the Investigator's responsibility to ensure that subjects give informed consent before the subject is admitted to the study, in accordance with ICH guidelines on GCP and all applicable laws, guidances and directives of the jurisdiction where the study is being conducted.

An approved ICF will be given to each subject written in a language they understand.

The Investigator or designee will review the study with the subject. The review will include the nature, scope, procedures, and possible consequences of the subject's participation in the study. The consent, assent, and review must be in a form understandable to the subject. The Investigator or designee and the subject must both sign and date the ICF after review and before the subject can participate in the study. The subject will receive a copy of the signed and dated form, and the original will be retained in the site study files. The Investigator or designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

11.2.2 Institutional Review Board/Independent Ethics Committee Approval and Other Institutional Requirements

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/IEC for review and approval. Per institutional requirements, the study protocol and any other appropriate documents will be submitted to relevant committees for approval.

The Investigator will forward to ReveraGen, or designee a copy of the IRB/IEC's approval of this protocol, amendments, ICF and any changes to the ICF, as per ICH guidelines on GCP and

all applicable laws, guidances and directives of the jurisdiction where the study is being conducted. The Investigator will also keep documentation of study approval by internal committees per institutional requirements.

It is the responsibility of ReveraGen to notify the competent authority of the Member State concerned and/or the IEC of any substantial amendment(s) to the protocol.

Study medication can only be supplied to the Investigator after documentation of all ethical and legal requirements for starting the study has been received by the ReveraGen or designee. This documentation must also include an IRB/IEC membership list that contains members' occupations and qualifications. If the IRB/IEC will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP.

The Investigator will keep the IRB/IEC informed regarding the progress of the study, per institutional requirements. No changes will be made in the study without IRB/IEC approval, except when required to eliminate apparent immediate hazards to the subjects. In cases where any implemented deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants is implemented without prior IRB/IEC approval, the implemented deviation should be notified as soon as possible not only to the IRB/IEC for review and approval/favorable opinion but also to the regulatory authority(ies).

While the study is ongoing and at study completion/discontinuation, the Investigator must submit to the IRB/IEC the following information in accordance with applicable regulatory requirements where the study is being conducted:

1. Information on serious or unexpected AEs, showing due diligence in providing this information as soon as possible
2. Periodic reports on the progress of the study
3. Final Study Summary upon study completion or closure.

Notification of the end of the trial will be sent to the IRB/IEC within 30 days after completion of the study close-out visit. In case the study is ended prematurely, the IRB/IEC will be notified within 15 days, including the reasons for the premature termination. The end of the trial is defined as the date of final analysis of the study data according to the SAP.

11.2.3 Study Documentation

11.2.3.1 Before the Start of the Study

The following study documentation will be in place at the study site prior to the first administration of study drug:

- Fully signed protocol and protocol-supporting manuals
- Investigator's Brochure
- Investigator Protocol Agreement form signed by the Investigator
- IRB/IEC-approved copy of the ICF
- Curriculum vitae of the Investigator and all sub-investigators listed on the FDA Form 1572
- A letter of IRB/IEC approval for protocol
- A list of members of the IRB/IEC and their affiliations
- A copy of the Investigator-signed FDA 1572 form
- An Investigator-signed financial disclosure form
- Investigator/site study contract.

11.2.3.2 During the Study

The following documentation should be added to the site study file during study conduct:

- Any paper source forms completed and subsequently entered into the study database. An explanation should be given for all missing data and any protocol deviations documented in the site study file
- Any changes to the documentation identified above (see Section 11.2.3.1)
- Shipping documents relating to shipment of medication (drug accountability) and bioanalytical samples
- Copies of relevant correspondence such as letters, emails, meeting notes, and telephone calls.

11.2.3.3 After the Study

After completion or premature termination of the trial, all of the documents identified should be in the file, together with the following:

- Study drug accountability documents
- Audit certificates (if applicable)
- Investigator delegation of responsibilities log
- Site signature log
- Subject enrollment log
- Subject identification log

- Substantive correspondence with the ReveraGen and IRB/IEC
- Notification of the end of the trial to the IRB/IEC.

11.2.4 Delegation of Investigator Responsibilities

The Investigator must (a) ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and licensure, if relevant) to perform the task; and

(b) provide adequate supervision. The Investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant

study-related duties.

11.3 Protocol Deviations

11.3.1 Protocol Deviation Definitions

Protocol deviations should be documented in accordance with the Manual of Operations.

11.3.1.1 Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB/IEC.

Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered minor protocol deviations.

11.3.1.2 Important Protocol Deviation

An important protocol deviation is a deviation from the IRB/IEC-approved protocol that may significantly affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. This includes examples such as inappropriate consent, errors in drug dosing, or lack of reporting of safety data.

11.3.2 Reporting Important Protocol Deviations

Upon discovery of an important protocol deviation, the Investigator is responsible for reporting the important protocol deviation to the ReveraGen or designee within 24 hours of discovery, or according to local site requirements.

Protocol deviations that may impact participant safety will be reported to the the NIAMS and the DSMB (through the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event. Protocol deviations that do not impact participant safety will be reported in aggregate as part of the routine data and safety monitoring report sent to the DSMB and NIAMS.

Protocol deviations are reported to the IRB in accordance to their policy, within 10 days of identification of the event.

All deviations must be recorded in the CTMS.

11.4 Study Records Retention and Direct Access to Source Documents

Following completion of the clinical study, the medical files of trial subjects as well as other essential documents shall be retained by the ReveraGen and the Investigator for at least 10 years after completion of the clinical trial, or for a period of time as required by the applicable regulatory authority.

The Investigator must maintain a copy of all data collected for each subject treated (including eCRFs and source data). In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of ReveraGen, or designee, as well as representatives of health authorities have direct access to original source documents (e.g., subject records, subject charts, and laboratory reports). During the review of these documents, the anonymity of the subject will be respected with strict adherence to professional standards of confidentiality.

ReveraGen reserves the right to terminate the study for refusal of the Investigator to supply source documentation of work performed in this clinical study.

The following includes, but is not limited to, the records that must be retained by the Investigator:

1. Signed informed consent documents for all subjects
2. Subject identification log
3. Subject enrollment log
4. Record of all relevant communications between the Investigator and the IRB/IEC
5. Composition of the IRB/IEC
6. Record of all relevant communications between the Investigator and ReveraGen (or designee)
7. List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study and their signatures
8. Drug accountability records (see Section 5.8.4)
9. Record of any body fluids or tissue samples retained
10. All other source documents (subject records, hospital records, laboratory records, etc.)
11. All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

11.5 Study Monitoring

In accordance with applicable regulations, GCP, and the procedures of ReveraGen or its designees, the Study Monitor will periodically contact the site and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on enrollment rate and data quality at the site. Through frequent communications (e.g., letter, e-mail, and telephone), the Study

Monitor will ensure that the investigation is conducted according to protocol and regulatory requirements.

During these contacts, the monitoring activities will include:

1. Checking and assessing the progress of the study
2. Reviewing study data collected to date for completeness and accuracy
3. Reviewing compliance with protocol assessments
4. Conducting source document verification by reviewing eCRF database data against source documents when available (e.g., medical records, subject diaries, ICF [and assent, if applicable], laboratory result reports, raw data collection forms)
5. Identifying any issues and addressing resolutions.

These activities will be done in order to verify that the:

1. Data are authentic, accurate, and complete
2. Safety and rights of the subjects are being protected
3. Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents, and allocate his/her time and the time of his/her staff to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

At study closure, Study Monitors will conduct all activities as indicated in Section 11.7.

11.6 Quality Assurance

At its discretion, ReveraGen or its designee may conduct a quality assurance audit of this study. Auditing procedures of ReveraGen and/or its designee will be followed in order to comply with GCP guidelines and ensure acceptability of the study data for registration purposes. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents, and will allocate his/her time and the time of his/her staff to the auditor as may be required to discuss findings and any relevant issues.

In addition, regulatory authorities and/or the IRB/IEC may conduct an inspection of this study. If such an inspection occurs, the Investigator will allow the inspector direct access to all source documents, eCRFs, and other study documentation for source data check and/or on-site audit inspection. The Investigator must allocate his/her time and the time of his/her staff to the inspector to discuss findings of any relevant issues.

An explanation will be given for all missing, unused, and spurious data in the relevant section of the study report.

11.7 Study Termination and Site Closure

Upon completion of the study, the following activities, when applicable, must be conducted by the Study Monitor in conjunction with the Investigator, as appropriate:

1. Provision of all study data to ReveraGen
2. Data clarifications and/or resolutions
3. Accounting, reconciliation, and final disposition of used and unused study medication
4. Review of site study records for completeness.

In addition, ReveraGen reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reason(s), ReveraGen will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB/IEC, and providing the reason(s) for the suspension or termination of the study.

If the study is prematurely terminated, all study data must be returned to ReveraGen. In addition, the site must conduct final disposition of all unused study medications in accordance with ReveraGen procedures for the study.

11.8 Site Termination

ReveraGen may at any time, at its sole discretion, terminate the study site for various reasons, including, without limitation, the following:

1. Failure of the Investigator to enroll subjects into the study
2. Failure of the Investigator to comply with applicable laws and/or pertinent regulations
3. Submission of knowingly false information from the research facility to ReveraGen, Study Monitor, or regulatory authorities
4. Insufficient adherence to protocol requirements.

If participation of a study site is terminated, ReveraGen and Study Chair will issue a written notice to the Investigator. The written notice will contain the reasons for taking such action. If the study site is terminated for noncompliance, appropriate regulatory authorities will also be notified by ReveraGen. Study termination and follow-up will be performed in compliance with relevant regulations where the study is being conducted.

11.9 Discontinuation of Study

ReveraGen reserves the right to discontinue the study for any reason at any time. In addition, the study may be stopped at any time if, in the opinion of ReveraGen and Medical Monitor, safety data suggest that the medical safety of subjects is being or may become compromised.

12 DISCLOSURE OF DATA

12.1 Confidentiality

The rights and privacy of participants in this study will be protected at all times. All personal details of subjects will be treated as confidential by the Investigator. All applicable data protection laws in the relevant countries will be adhered to at all times.

Subject names will remain confidential and will not be included in the database. Only enrollment number and age will be recorded on the eCRF. If the subject's name appears on any other document collected (e.g., hospital discharge summary), the name must be redacted before the document is transmitted to ReveraGen or its designee. All study findings will be stored in electronic databases. The subject will give explicit permission for representatives of ReveraGen, regulatory authorities, and the IRB/IEC to inspect the subjects' medical records to verify the information collected. The subject will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all applicable data protection / privacy laws in the relevant countries.

The subjects will provide written country-specific authorization to disclose private health information either as a part of the written ICF or as a separate authorization form. The authorization will contain all required elements specified by 21 CFR 50. The authorization will remain valid and in full force and effect until the first to occur of (1) the expiration of 2 years after the study medication is approved for the indication being studied, or (2) the expiration of 2 years after the research program is discontinued. Individual subject medical information obtained during this study is confidential, and its disclosure to third parties (other than those mentioned in this section) is strictly prohibited. In addition, medical information obtained during this study may be provided to the subject's personal physician or to other appropriate medical personnel when required in connection with the subject's continued health and welfare.

The study Investigator will maintain a subject identification log (enrollment numbers and corresponding subject names) to enable records to be identified.

12.2 Publication

ReveraGen BioPharma, Inc. retains the ownership of all data and results collected during this study. Therefore, ReveraGen reserves the right to use the data from this present study, either in the form of eCRFs (or copies of these), or in the form of a report, with or without comments and analysis in order to submit them to Health Authorities of any country.

Furthermore, in the event that the clinical research leads to patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s). Patent applications will be filed by ReveraGen BioPharma, Inc. or another entity delegated by ReveraGen BioPharma, Inc.

All information concerning the product as well as any information such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have

been provided by ReveraGen or designee, and are unpublished, are confidential and must remain the sole property of ReveraGen. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from ReveraGen is obtained. ReveraGen has full ownership of the eCRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by ReveraGen. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

ReveraGen or designee will prepare a final report on the study. The Investigator may not publish or present any information on this study without the express written approval of ReveraGen. Additionally, ReveraGen, may, for any reason, withhold approval for publication or presentation.

ReveraGen will observe the NIH policy on enhancing public access to archived publications resulting from NIH-funded research. NIH-funded investigators will submit to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) an electronic version of the author's final manuscript upon acceptance for publication, resulting from research supported, in whole or in part, with direct costs from NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

13 INVESTIGATOR PROTOCOL AGREEMENT

The Investigator Protocol Agreement at the front of this document must be signed by the study site Principal Investigator. The Investigator must retain the original and an electronic signed copy must be kept on file by ReveraGen. The completed Protocol Agreement signifies review and acceptance of the protocol amendment by the Principal Investigator prior to initiation of the study.

14 REFERENCES

Avioli LV. Glucocorticoid effects on statural growth. *Br J Rheumatol* 1993; 32 Suppl 2:27-30.

Beggs AH, Hoffman EP, Snyder JR, Arahata K, Specht L, Shapiro F, et al. Exploring the molecular basis for variability among patients with Becker muscular dystrophy: dystrophin gene and protein studies. *Am J Hum Gen.* 1991; 49: 54-67.

Bello L, Gordish-Dressman H, Morgenroth LP, Henricson EK, Duong T, Hoffman EP, et al. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurol* 2015; 85: 1048-55.

Bircan Z, Soran M, Yildirim I, et al. The effect of alternate-day low dose prednisolone on bone age in children with steroid dependent nephrotic syndrome. *Int Urol Nephrol*. 1997; 29(3): 357-61

Bushby KM, Thambyayah M and Gardner-Medwin D. Prevalence and incidence of Becker muscular dystrophy. *Lancet* 1991; 337: 1022-4.

Clemens PR, Niizawa G, Feng J, *et al.* The CINRG Becker Natural History Study: Baseline characteristics. *Muscle Nerve* 2020; 62: 369-76.

Conklin LS, Damsker JM, Hoffman EP, et al. Phase IIa trial in Duchenne muscular dystrophy shows vamorolone is a first-in-class dissociative steroidal anti-inflammatory drug. *Pharmacol R*es 2018a (Sep 13); 136: 140-50.

Conklin LS, Merkel PA, Pachman LM, Parikh H, Tawalbeh S, Damsker JM, et al. Serum biomarkers of glucocorticoid response and safety in anti-neutrophil cytoplasmic antibody-associated vasculitis and juvenile dermatomyositis. *Steroids* 2018b; 140: 159-66.

Dadgar S, Wang Z, Johnston H, Dillingham BC, Huynh T, Van der Meulen JH, et al. Asynchronous remodeling is a driver of failed regeneration in Duchenne muscular dystrophy. *J Cell Biol* 2014; 207: 139-58.

Damsker JM, Dillingham BC, Rose MC, et al. VBP15, a glucocorticoid analogue, is effective at reducing allergic lung inflammation in mice. *Plos One*. 2013; 8(5): e63871.

Damsker JM, Conklin LS, Sadri S, Dillingham BC, Panchapakesan K, Heier CR, et al. VBP15, a novel dissociative steroid compound, reduces NFkB-induced expression of inflammatory cytokines in vitro and symptoms of murine trinitrobenzene sulfonic acid-induced colitis. *Inflamm Res* 2016; 65: 737-43.

Dillingham BC, Knoblach SM, Many GM, et al. VBP15, a novel anti-inflammatory, is effective at reducing the severity of murine experimental autoimmune encephalomyelitis. *Cell Mol Neurobiol* 2015; 35(3): 377-87.

FDA Draft Guidance for Industry: Duchenne muscular dystrophy and related dystrophinopathies: developing drugs for treatment. June 2015.

Fiorillo AA, Heier CR, Novak JS, Tully CB, Brown KJ, Uaesoontrachoon K, et al. TNF-α-Induced microRNAs Control Dystrophin Expression in Becker Muscular Dystrophy. *Cell Rep* 2015; 12: 1678-90.

Fiorillo AA, Tully CB, Damsker JM, Nagaraju K, Hoffman EP, Heier CR. Muscle miRNAome shows suppression of chronic inflammatory miRNAs with both prednisone and vamorolone.

Physiol Genomics 2018; 50: 735-45.

Fleishaker DL, Mukherjee A, Whaley FS, Daniel S, Zeiher BG. Safety and pharmacodynamic dose response of short-term prednisone in healthy adult subjects: a dose ranging, randomized, placebo-controlled, crossover study. *BMC Musculoskelet Disord* 2016 (Jul 16); 17: 293.

Griggs RC, Miller JP, Greenberg CR, Fehlings DL, Pestronk A, Mendell JR, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. *Neurol* 2016; 87: 2123-32.

Heier CR, Damsker JM, Yu Q, Dillingham BC, Huynh T, Van der Meulen JH, et al. VBP15, a novel anti-inflammatory and membrane-stabilizer, improves muscular dystrophy without side effects. *EMBO Mol Med;* 2013; 5: 1569-85.

Heier CR, Yu Q, Fiorillo AA, Tully CB, Tucker A, Mazala DA, et al. Vamorolone targets dual nuclear receptors to treat inflammation and dystrophic cardiomyopathy. *Life Sci Alliance* 2019 (Feb 11); 2(1): pii: e201800186. doi: 10.26508/lsa.201800186.

Hoffman EP, Brown RH and Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell* 1987; 51: 919-28.

Hoffman EP, Kunkel LM, Angelini C, Clarke A, Johnson M, Harris JB. Improved diagnosis of Becker muscular dystrophy by dystrophin testing. *Neurol* 1989; 39(8): 1011-7.

Hoffman EP, Riddle V, Siegler MA, Dickerson D, Backonja M, Kramer WG, et al. Phase 1 trial of vamorolone, a first-in-class steroid, shows improvements in side effects via biomarkers bridged to clinical outcomes. *Steroids* 2018; 134: 43-52.

Hoffman EP, Schwartz BD, Mengle-Gaw LJ, et al. Vamorolone trial in Duchenne muscular dystrophy shows dose-related improvement of muscle function. *Neurol* 2019; 93(13): e1312-23.

Investigator's Brochure, Version 9, Vamorolone (VBP15) (17α, 21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione) 1.33% and 4% Oral Suspension, ReveraGen BioPharma, Inc., June 29, 2020.

Kauh E, Mixson L, Malice M-P, et al. Prednisone affects inflammation, glucose tolerance, and bone turnover within hours of treatment in healthy individuals. *European J Endocrinol* 2012; 166: 459-67.

Kesari A, Pirra LN, Bremadesam L, McIntyre O, Gordon E, Dubrovsky AL, et al. Integrated DNA, cDNA, and protein studies in Becker muscular dystrophy show high exception to the reading frame rule. *Hum Mutat* 2008; 29: 728-37.

Kinder TB, Heier CR, Tully CB, Van der Muelen JH, Hoffman EP, Nagaraju K, Fiorillo AA. Muscle weakness in Myositis: MicroRNA-mediated dystrophin reduction in a myositis mouse model and human muscle biopsies. *Arthritis Rheumatol* 2020; 72: 1170-83.

Lefter S, Hardiman O and Ryan AM. A population-based epidemiologic study of adult neuromuscular disease in the Republic of Ireland. *Neurol* 2017; 88: 304-13.

Li X, Conklin LS, van den Anker J, Hoffman EP, Clemens PR, Jusko WJ. Exposure-response analysis of vamorolone (VBP15) in boys with Duchenne muscular dystrophy [published online ahead of print, 2020 May 20]. *J Clin Pharmacol* 2020; 10. 1002/jcph.1632. doi:10.1002/jcph.1632.

Liu X, Wang Y, Gutierreza JS, Damsker JM, Nagaraju K, Hoffman EP, Ortlund EA. Disruption of a key ligand-H-bond network drives dissociative properties in vamorolone for Duchenne muscular dystrophy treatment. *Proc Natl Acad Sci USA*, 2020, *in press.*

Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. J Bone Miner Res. 1999; 14(7): 1061 6.

Mavroudis PD, van den Anker J, Conklin LS, Damsker JM, Hoffman EP, Nagaraju K, Clemens PR, Jusko WJ. Population pharmacokinetics of vamorolone (VBP15) in healthy men and boys with Duchenne muscular dystrophy. *J Clin Pharmacol* 2019; 59: 979-88.

Moon HJ, Choi KH, Lee SI, Lee OJ, Shin JW, and Kim TW. Changes in blood glucose and cortisol levels after epidural or shoulder intra-articular glucocorticoid injections in diabetic or nondiabetic patients. *Am J Phys Med Rehabil*. 2014; 93(5): 372-8.

Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015; 14(2): 153-61.

Raman SV, Hor KN, Mazur W, et al. Stabilization of early Duchenne cardiomyopathy with Aldosterone Inhibition: results of the multicenter DMD trial. *J Am Heart Assoc* 2019; 8: e013501.

Sali A, Guerron AD, Gordish-Dressman H, et al. Glucocorticoid-treated mice are an inappropriate positive control for long-term preclinical studies in the mdx mouse. Plos One. 2012; 7(4): e34204.8

Smith EC, Conklin LS, Hoffman EP, Clemens PR, Mah JK, Finkel RS, et al. Efficacy and safety of vamorolone in Duchenne muscular dystrophy: an 18-month interim analysis of a non-randomized open-label extension study. *PLOS Med*, 2020*, in press.*

Sreetama SC, Chandra G, Van der Meulen JH, Ahmad MM, Suzuki P, Bhuvanendran S, et al. Membrane stabilization by modified steroid offers a potential therapy for muscular dystrophy due to dysferlin deficit. *Mol Ther* 2018; 26: 2231-42.

U.S. Food and Drug Administration. 2020. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. Washington,

DC. Retrieved 04May2020 from https://www.fda.gov/media/136238/downloadff

van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatol (Oxford)* 2000 (Dec); 39(12): 1383- 9.

Wehling-Henricks M, Oltmann M, Rinaldi C, Myung KH, and Tidball JG. Loss of positive allosteric interactions between neuronal nitric oxide synthase and phosphofructokinase contributes to defects in glycolysis and increased fatigability in muscular dystrophy. *Hum Mol Genet*. 2009; 18(18): 3439-51

Wolthers OD and Pedersen S. Short term linear growth in asthmatic children during treatment with prednisolone. BMJ. 1990; 301(6744): 145-8.

Younes M, Neffati F, Touzi M, et al. Systemic effects of epidural and intraarticular glucocorticoid injections in diabetic and non-diabetic patients. *Joint Bone Spine*. 2007; 74(5): 472-6.

15 APPENDICES

15.1 Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide

15.1.1 Dose Calculation Worksheet

Vamorolone is administered once daily as a 4.0% oral suspension. The volume per dose is determined by the subject's dosing level and body weight (500mg if ≥ 50 kg OR 250mg if <50kg) at each study medication dispensing visit.

Example 1: Dose volume calculation for a subject receiving **500 mg**/day with a body weight ≥ 50kg:

$$\frac{\textbf{Dose Level (500.0 mg)}}{\textbf{40 mg/mL}} = \textbf{12.5 mL}$$

The subject will receive a daily dose volume of **12.5** mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a **10** mL volumetric syringe rounded to the nearest 0.2 mL daily.

15.1.2 Vamorolone 4.0% Suspension Dispensing Guide

Each subject enrolled in the study will be dispensed 120 ml bottle(s), each containing at least 107 mL of vamorolone 4.0% or matching placebo suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Additional supplies will be dispensed at the Week 12 Visit, sufficient for dosing through the time of the scheduled Week 24 Visit. Subjects whose study medication dose is tapered during the Dose-tapering Period will be dispensed additional study medication at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see Section 6.3.6).

The number of bottles to be dispensed at each dispensing visit for the following 12-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 1*) by 95 days (84 days in the dosing period + 11 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 2*, below:

Equation 1

$$\frac{\textbf{Daily Dose (mL/Day) x 95 Days}}{\textbf{100 mL for 12 Weeks Dosing}} = \textbf{\# Bottles to be Dispensed}$$

Example 2: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of **12.5** mL (from Example 1 above):

$$\frac{\textbf{Daily Dose (12.5 mL/Day) x 95 Days}}{\textbf{100 mL}} = \textbf{11.9 Bottles}$$

The number of bottles dispensed is rounded up to the nearest whole integer, or 12 bottles to be dispensed.

Each bulk bottle should be used for one subject only. Each bottle dispensed to the subject and ready for administration to subjects will be labeled with subject number, dispense date, protocol number, dose level, and volume to be administered per dose.

Any unused or partially used drug product should be returned at the Week 12 and Week 24 Visits, respectively, and at the end of the Dose-tapering Period, if applicable, and retained at the clinical study site for investigational drug accountability monitoring.

15.2 Protocol Amendments Complete List of Changes

15.2.1 Protocol Amendment #1 Complete List of Changes

The following changes have been incorporated into the protocol under this protocol amendment, as summarized in Protocol Amendment Tracking, Reasons for Protocol Amendment #1. Protocol sections that have been changed are itemized below with the original and revised text.

Section Changed:
Protocol Title
Original Text:
A Phase II Pilot Trial of Vamorolone for the Treatment of Becker Muscular Dystrophy
Revised Text:
A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy

Section Changed:
Synopsis: Primary Objective
Original Text:
To evaluate the safety and tolerability of vamorolone administered orally at daily dose of 6.0 mg/kg over a 24-week treatment period in patients with BMD.
Revised Text:
To evaluate the safety and tolerability of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with BMD

Section Changed:
Synopsis: Secondary Objective
Original Text:
To evaluate the pharmacodynamic response of biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, insulin resistance) to vamorolone administered orally at daily dose of 6.0 mg/kg in patients with BMD.
Revised Text:
To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with BMD .
To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (miR146aCD23, MDC and CK) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with BMD.

Section Changed:
Synopsis: Exploratory Objective
Original Text:
To evaluate timed function outcomes of treatment response.
To evaluate patient-reported outcomes of treatment response
To evaluate pharmacodynamic biomarkers of treatment response.
Revised Text:
To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with BMD.
To evaluate the effect on patient-reported outcomes of treatment response of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with BMD

Section Changed:
Synopsis: Study Design
Original Text:
This Phase II study is an open-label, single dose study to evaluate the safety, tolerability, PD, and clinical efficacy of vamorolone (the investigational study medication) 6.0 mg/kg administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory, steroid-naïve patients age 12-<65 years with BMD.
The study is comprised of a 35-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in the separate expanded access or compassionate use program to continue treatment with vamorolone).
Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained. All subjects will begin vamorolone treatment on Treatment Period Day 1 and will continue to receive vamorolone treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24).
At the end of the 24-week Treatment Period (Week 24), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into the expanded access or compassionate use program will not need to taper their vamorolone dose prior to participation in the expanded access or compassionate use program. All subjects who will not transition directly to further vamorolone treatment will begin a 4-week open-label Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.

Revised Text:
This Phase II pilot study is a randomized, double-blind, placebo-controlled study design to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg/day (250mg if <50kg body weight) compare to placebo administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory subjects with BMD, ages 12 and <65.
The study is comprised of a 35-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in a separate expanded access or compassionate use program to continue treatment with vamorolone).
Subjects will be randomized to one of two treatment groups in a 1:2 ratio (placebo: vamorolone 500mg/day [250mg if <50kg body weight]).
Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained. All subjects will begin study medication (vamorolone or placebo) treatment on Treatment Period Day 1 and will continue to receive study medication treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24).
At the end of the 24-week Treatment Period (Week 24), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into the expanded access or compassionate use program will not need to taper their study medication dose prior to participation in the expanded access or compassionate use program. All subjects who will not transition directly to further vamorolone treatment will begin a 4-week open-label Dose-tapering Period to taper study medication prior to discharge from the study.

Section Changed:
Synopsis: Planned Sample Size
Original Text:
A total of approximately 30 subjects will be enrolled.
Revised Text:
A total of approximately 39 subjects will be enrolled and randomized 1:2 to treatment with placebo or vamorolone 500mg/day (250mg if <50kg body weight) administered orally

Section Changed:
Synopsis: Inclusion Criteria # 2, 4-11
Original Text:
2. Subject has a confirmed diagnosis of BMD as defined as:
4. Subject is able to perform the timed run/walk 10 meters assessment; assistive devices, cane or walker, are allowed.
5. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit); and
6. Subject is willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
7. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
8. Subject has evidence of chicken pox immunity as determined by:

a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;

9. Subject and parent(s)/guardian(s) (if subject is <18 years of age) are is willing and able to comply with scheduled visits, study medication administration plan, and study procedures.

Revised Text:

2. Subject is a male and has a confirmed diagnosis of BMD as defined as:
4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) ≤ 30 sec; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32
6. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit); and
7. Subject is willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
8. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
9. Subject has evidence of chicken pox immunity as determined by:
   a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
   b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;
10. Subject and parent(s)/guardian(s) (if subject is <18 years of age) are willing and able to comply with scheduled visits, study medication administration plan, and study procedures.
11. Subject of childbearing potential agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed.

Section Changed:
Synopsis: Exclusion Criteria # 3 and 4

Original Text:

3. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;
4. Subject has a history of primary hyperaldosteronism;

Revised Text:

3. Subject has had an acute illness within 4 weeks prior to the first dose of study medication
4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;

Section Changed:
Synopsis: Study Period
Original Text:
First subject screened: 1Q 2021
Last subject last visit: 3Q 2022
Revised Text:
First subject screened: 1Q 2022
Last subject last visit: 3Q 2024

Section Changed:
Synopsis: Study Duration
Original Text:
Approximately 18 months total duration
Revised Text:
Approximately 24 months total duration

Section Changed:
Synopsis: Study Drug Formulation, Dosage & Administration
Original Text:
Subjects will be administered vamorolone 4.0% wt/wt oral suspension.
All subjects will be administered vamorolone once daily over the 24-week Treatment Period (Weeks 1-24) and during the 4-week Dose-tapering Period, as applicable. The site will dispense study medication in 110 mL bottles sufficient for 12 weeks of dosing (4 weeks for Dose-tapering Period) plus overage to subjects at the Day 1 and Week 12 Visits (and Week 24 Visit to subjects participating in the Dose-tapering Period), according to the subject's body weight recorded at the dispensing visit (Day -1 weight for Day 1 dispensing).
Revised Text:
Subjects will be administered vamorolone 4.0% wt/wt oral suspension or a matched placebo as the study medication.
All subjects will be administered vamorolone once daily over the 24-week Treatment Period (Weeks 1-24) and during the 4-week Dose-tapering Period, as applicable. The site will dispense study medication in 110 mL bottles sufficient for 12 weeks of dosing (4 weeks for Dose-tapering Period) plus overage to subjects at the Day 1 and Week 12 Visits (and Week 24 Visit to subjects participating in the Dose-tapering Period), according to the subject's body weight (500mg/day if ≥ 50 kg or 250mg if <50kg) recorded at the dispensing visit (Day -1 weight for Day 1 dispensing).

Section Changed:
Synopsis: Dose-Limiting Toxicities, and Stopping Criteria
Original Text:
None
Revised Text:
If dose-limiting toxicities occur at any time during the Treatment Period, the study may be stopped or the study design may be modified, in consultation with the Study Chair, Medical Monitor, Data and Safety Monitoring Board (DSMB), and the Sponsor, depending on the timing and nature of the toxicities.
Clinical AEs and clinical laboratory AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, dated June 14, 2010.
Dose-limiting toxicities will be defined as follows:
1. The presence of a CTCAE Grade ≥ 3 AE, considered to be probably or definitely related to study drug, in the opinion of the Investigator;
2. The presence of a CTCAE Grade ≥ 3 clinical laboratory AE considered to be probably or definitely related to study drug, in the opinion of the Investigator; or

3. Deterioration of the muscle condition, unexpected for the natural course of BMD and without other clear cause, in the opinion of the Investigator. The possibility to consider the event as a dose-limiting toxicity will be discussed by the Study Chair, the Medical Monitor and the DSMB. The SAE data collection tool must be completed if the event also meets the criteria for an SAE.

Section Changed:
Synopsis: Safety Measures
Original Text:
- Clinical laboratory tests:
  - Hematology and clinical chemistry
  - Urinalysis (urine protein and glucose)
  - Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])
  - First morning cortisol
  - Bone biomarkers
  - Fasting glucose and insulin

Revised Text:
- Clinical laboratory tests:
  - Hematology and clinical chemistry
  - GLDH
  - GGT
  - Urinalysis (urine protein and glucose)
  - Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])
  - First morning cortisol
  - Bone biomarkers
  - Fasting glucose and insulin

Section Changed:
Synopsis: Pharmacokinetic (PK) Measures
Original Text:
None
Revised Text:
Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis.

Section Changed:
Synopsis: Pharmacodynamic Measures
Original Text:
… and bone turnover (osteocalcin) and additional exploratory biomarkers. Blood samples for analysis of PD biomarkers …
Revised Text:
… and bone turnover (osteocalcin) and additional exploratory biomarkers. Blood will also be collected for serum PD biomarker analysis to evaluate effects of vamorolone on biomarkers of efficacy (miR146a, MDC and CK). Blood samples for analysis of PD biomarkers …

Section Changed:
Synopsis: Statistical Methods: Sample Size
Original Text:
We present sample size calculations needed to detect a similar effect as that observed for TTRW in DMD subjects in Becker dystrophy. We conducted a sample size calculation based on observed TTRW values

from the VBP15-003 DMD vamorolone trial (11 subjects for 24 weeks for 6.0 mg/kg/day only). Using observed baseline and 24-week measurements for TTRW velocities, we estimate that 13 subjects will ensure that a two-sided test with alpha=0.05 has 90% power to detect a mean difference of 0.255 m/s. Assuming attrition of 10%, we need to recruit 15 ambulatory subjects. A sample of 30 will be large enough to have a confidence interval of no wider than 36% for the proportion of treatment emergent adverse events assessed or any other event outcome. Given our sample size calculations and that we aim to recruit 30 subjects, we should have enough power to detect a difference in TTRW velocities. Subjects who withdraw early from the study may be replaced.

Revised Text:

The primary objective is to evaluate safety and tolerability in this BMD population, for which this is the pilot study and no effect sizes are available. A sample of 26 BMD subjects on vamorolone will be large enough to have a confidence interval of no wider than 39% for the proportion of treatment emergent adverse events assessed or any other event outcome in the vamolorone group. We also assessed power for motor efficacy comparisons of vamorolone to placebo and present these calculations needed to detect a similar effect as that observed for TTRW velocity in DMD subjects in Becker dystrophy. We conducted a sample size calculation based on observed TTRW values from the VBP15-003 DMD vamorolone trial (11 subjects for 24 weeks on 6.0 mg/kg/day) and VBP15-004 (25 subjects for 24 weeks on 6.0 mg/kg/day). Using observed baseline and 24-week measurements for TTRW velocities, we estimate that 39 subjects (randomized 1:2 placebo:vamorolone) will ensure that a two-sided t-test with alpha=0.05 has 83% power to detect a pooled mean difference of 0.275 m/s (sd=0.2715) in BMD subjects on vamorolone vs. no mean change in subjects on placebo (sd=0.2715). Assuming dropout of 5%, we have 80% power. Note that subjects who withdraw early from the study may be replaced. Given our sample size calculations and that we aim to recruit 39 subjects, we should have enough power to detect a difference in TTRW velocities.

Section Changed:

Synopsis: Statistical Methods: Analysis Populations

Original Text:

Three populations will be defined for data analysis: Safety Population and a modified Intent-to-Treat Population.

Safety Population

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

Modified Intent-to-Treat (mITT) Population

All subjects who receive at least one dose of study medication and have at least one post-baseline assessment will be included in the mITT Population. The mITT Population is the primary analysis population for clinical efficacy.

Subjects who receive at least one dose of study medication but never have post-baseline assessments will be excluded. Results will be presented “as treated.”

Revised Text:

Four populations will be defined for data analysis: Safety Population, a modified Intent-to-Treat Population, per protocol population, and a PK population

Safety Population

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

Modified Intent-to-Treat (mITT) Population

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

Per Protocol Population
The Per Protocol Population will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data

PK Population
The PK Population consisted of all subjects who received at least one dose of study medication and had sufficient quantifiable plasma concentration data for PK analysis.

Section Changed:
Synopsis: Statistical Methods: General Statistical Considerations
Original Text:
No formal interim statistical analyses are planned, apart from the interim safety data views and presentations to be created for the DSMB. Missing values for safety outcomes will be treated as missing, unless stated otherwise. Baseline measurement is defined as the last non-missing value prior to the first dose of study drug.
Revised Text:
All measurements will be analyzed based upon the type of distribution and descriptive statistics presented by treatment group and time point, as appropriate. No formal interim statistical analyses are planned, apart from the interim safety data views and presentations to be created for the DSMB. The Week 24 analyses are the primary analyses for this study and will be performed after all subjects have completed Week 24. Missing values for safety outcomes will be treated as missing, unless stated otherwise. Baseline measurement is defined as the last non-missing value prior to the first dose of study drug.
Analyses will be summarized by two treatment groups:
- Vamorolone (n=26)
- Placebo (n=13)

The exploratory efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. The motor efficacy endpoint supports the exploratory motor efficacy objective of this study. Another efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.
For the efficacy motor endpoint, TTRW (velocity), change from baseline to Week 24 will be compared between the vamorolone dose group and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, the comparison (using least squares [LS] mean contrasts) will be made to compare TTRW velocity at 24 weeks for the vamorolone group with placebo. For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline, and treatment-by-week interaction).

An unstructured covariance matrix will be used, and underlying modelling assumptions will be checked. If differences between baseline characteristics exist between the treatment groups, it will be investigated if adjustment for these characteristics is clinically relevant and necessary.

Section Changed:
Synopsis: Statistical Methods: Pharmacokinetic Analyses
Original Text:
none
Revised Text:
Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects

Section Changed:
LIST OF ABBREVIATIONS
Original Text:
NOAEL no observed adverse effect level
OATP1B1 organic anion transporting polypeptide B1
Revised Text:
NOAEL no observed adverse effect level
NSAA North Star Ambulatory Assessment
OATP1B1 organic anion transporting polypeptide B1

Section Changed:
INTRODUCTION: 1.1 Background and Unmet Need - paragraph #8
Original Text:
This study proposes a single dose (6 mg/kg/day) 24-week trial with a 4-week taper or continuation of therapy in an expanded access protocol or by compassionate use.
Revised Text:
This study proposes a single dose (500mg/day [250mg if <50kg body weight]) 24-week trial with a 4-week taper or continuation of therapy in an expanded access protocol or by compassionate use.

Section Changed:
INTRODUCTION: 1.4 Rationale for Study Design
Original Text:
This Phase II study is an open-label, single dose study to evaluate the safety, tolerability, PD, and clinical efficacy of vamorolone 6.0 mg/kg administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory, steroid-naïve patients age 12-65 years with BMD.
The study is comprised of a 26-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in the separate expanded access or compassionate use program to continue treatment with vamorolone).
Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained. All subjects will begin vamorolone treatment on Treatment Period Day 1 and will continue to receive vamorolone treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24).
At the end of the 24-week Treatment Period (Week 24), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into the expanded access or compassionate use program will not need to taper their vamorolone dose prior to participation in the expanded access or compassionate use program. All subjects who will not transition directly to further vamorolone treatment will begin a 4-week open label Dose tapering Period during which the dose of study medication will be progressively reduced and discontinued.

Key safety parameters will be evaluated during the course of the study to assess vamorolone safety and tolerability. Safety parameters will include weight, vital signs, assessment of cushingoid features, clinical laboratory tests, first morning cortisol to assess adrenal suppression, bone biomarker osteocalcin and fasting glucose and insulin to assess glucose handling.
To evaluate clinical efficacy, the effect of vamorolone 6.0 mg/kg/day on muscle function will be assessed using the time to run/walk 10 meters (TTRW) test and the North Star Ambulatory Assessments (NSAA). Patient-reported outcomes will be assessed with the NeuroQOL for fatigue, mobility and sleep.
Pharmacodynamic safety biomarker findings will be assessed in BMD patients receiving vamorolone 6.0 mg/kg/day over 24 weeks. Serum PD biomarkers bridged to later clinical safety concerns will be assessed over time as exploratory safety measures. These PD biomarkers include:
Revised Text:
This Phase II pilot study is a randomized, double-blind, placebo-controlled study desing to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg (250mg if <50kg body weight) vs. placebo administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory patients age 12-65 years with BMD.
The study is comprised of a 35-day Pretreatment Screening Period (which can be extended if varicella vaccination is required), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period and a 4-week Post-treatment Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in the separate expanded access or compassionate use program to continue treatment with vamorolone).
Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained. Subjects who meet all eligibility criteria in this study will be randomized to vamorolone or placebo treatment group.
All subjects will begin study medication treatment on Treatment Period Day 1 and will continue to receive study medication treatment throughout the duration of the 24-week Treatment Period (Weeks 1-24)
At the end of the 24-week Treatment Period (Week 24), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into the expanded access or compassionate use program will not need to taper their study medication dose prior to participation in the expanded access or compassionate use program. All subjects who will not transition directly to further vamorolone treatment will begin a 4-week open label Dose tapering Period during which the dose of study medication will be progressively reduced and discontinued.
Key safety parameters will be evaluated during the course of the study to assess vamorolone safety and tolerability. Safety parameters will include weight, vital signs, assessment of cushingoid features, clinical laboratory tests, first morning cortisol to assess adrenal suppression, bone biomarker osteocalcin and fasting glucose and insulin to assess glucose handling.
To evaluate clinical efficacy, the effect of vamorolone 500mg/day (250mg/day if <50kg body weight) on muscle function will be assessed using the time to run/walk 10 meters (TTRW) test and the North Star Ambulatory Assessments (NSAA). Patient-reported outcomes will be assessed with the NeuroQOL for fatigue, mobility and sleep.
Pharmacodynamic safety biomarker findings will be assessed in BMD patients receiving vamorolone 500mg/day (250mg/day if <50kg body weight) over 24 weeks. Serum PD biomarkers bridged to later clinical safety concerns will be assessed over time as exploratory safety measures. These PD biomarkers include:

Section Changed:
INTRODUCTION: 1.5 Overall Benefit/Risk- Potential Health Benefits
Original Text:
Subjects may or may not receive direct health benefit from participating in the study. Subjects will be treated with vamorolone at 6.0 mg/kg/day over the course of the 24-week trial

Revised Text:
Subjects may or may not receive direct health benefit from participating in the study. Subjects will be treated with vamorolone at 500 mg/day (250mg if <50kg body weight) over the course of the 24-week trial.

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.1.1 Primary Objective
Original Text:
1. To evaluate the safety and tolerability of vamorolone administered orally at daily dose of 6.0 mg/kg over a 24-week treatment period in patients with BMD;

Revised Text:
1. To evaluate the safety and tolerability of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with BMD;

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.1.2 Secondary Objective
Original Text:
1. To evaluate the pharmcodynamic response of biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, insulin resistance) to vamorolone administered orally at daily dose of 6.0 mg/kg in patients with BMD.

Revised Text:
1. To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with BMD
2. To evaluate the pharmcodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, insulin resistance) and efficacy (miR146a, MDC and CK) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with BMD

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.1.3 Exploratory Objectives
Original Text:
1. To evaluate timed function outcomes of treatment response.
2. To evaluate patient-reported outcomes of treatment response
3. To evaluate pharmacodynamic biomarkers of treatment response

Revised Text:
1. To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with BMD.
2. To evaluate the effect on patient-reported outcomes of treatment response of vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with BMD

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.2.1 Clinical Efficacy Endpoints
Original Text:
None

Revised Text:
1. Exploratory biomarkers for treatment response including CK, MDC and mIR146a (Fiorillo et al., 2015; Conklin et al., 2018a; Conklin et al., 2018b): Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points.

2. For the efficacy motor endpoint, TTRW (velocity) and NSAA (score): change from baseline to Week 24 will be compared between vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.2.2 Safety Endpoints
Original Text:
4. Clinical laboratory values: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points in:
   - Hematology and clinical chemistry;
   - Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]); and
   - Urinalysis

Revised Text:
4. Clinical laboratory values: Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points in:
   - Hematology and clinical chemistry;
   - GLDH
   - GGT
   - Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]); and
   - Urinalysis

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.2.4 Exploratory Endpoints
Original Text:
1. Clinical efficacy assessments: Change from baseline to Week 12 and Week 24 in TTRW test and NSAA; and
2. Patient-reported outcomes by NeuroQOL scales for fatigue, mobility and sleep

Revised Text:
1. Participants or participants' parent(s)/legal guardian(s) will be asked to complete the NeuroQOL scales for fatigue, mobility and sleep

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.2.5 Pharmacokinetics Analysis
Original Text:
None
Revised Text:
Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects

Section Changed:
STUDY OBJECTIVES AND ENDPOINTS: 2.2.6 Pharmacodynamic Endpoints
Original Text:
4. Exploratory biomarkers for treatment response including CK, MDC and mIR146a (Fiorillo et al., 2015; Conklin et al., 2018a; Conklin et al., 2018b).

Revised Text:
Item #4 removed

Section Changed:
STUDY DESIGN: 3.1 Overall Study Design
Original Text:
This Phase II study is an open-label, single dose study to evaluate the safety, tolerability, PD, and effect on physical functioning of vamorolone over a treatment period of 24 weeks in males with BMD.
The study is comprised of a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1 day Pretreatment Baseline Period, a 24- week Treatment Period, and a 4-week Dose tapering Period (for subjects not continuing directly with further vamorolone treatment). Subjects will be enrolled into this study at the time written informed consent is given, and administered study medication only after completion of all Pretreatment Screening assessments to confirm eligibility.
Subjects will be assessed for safety and tolerability, PD, and effect on physical functioning at scheduled visits throughout the study. Screening assessments will be performed prior to baseline assessments on Day -1 and first administration of study medication on Day 1.
After completion of Screening and Baseline assessments, subjects will return to the study clinic on Day -1 for safety and PD assessments prior to administration of the first dose of study medication. Additional onsite study visits will occur at Week 4, Week 12, and Week 24.
Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor and Study Team regarding study conduct.
Subject diaries will be dispensed at the Day 1, Week 12, and Week 24 (for subjects participating in the Dose-tapering Period) Visits to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication.
The scheduled Week 12 and Week 24 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling.
Subjects who complete the VBP15-BMD-001 study assessments through the Week 24 Visit may be given the opportunity to continue to receive vamorolone as part of an expanded access or compassionate use program.
Subjects who complete the VBP15-BMD-001 study and will enroll directly into the expanded access or compassionate use program to continue vamorolone treatment will be discharged from the VBP15 BMD-001 study following completion of all Week 24 assessments. Subjects who will not continue vamorolone treatment in the expanded access or compassionate use program will have their vamorolone dose tapered during a
4-week Dose-tapering Period prior to discharge from the study. For these subjects, site study staff will contact the subject or parent(s)/guardian(s) by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms of adrenal suppression, and to address any questions the subject or parent(s)/guardian(s) may have. These subjects will have a final visit at Week 28 after the completion of the dose taper for a final physical exam, safety assessment, and return of remaining vamorolone and final subject diary.
In the event that any clinical or laboratory parameters remain abnormal at the time of discharge from the study, the subject will be followed medically, as clinically indicated.
Any subject who discontinues the study prior to the Week 24 Visit should return to the study unit for scheduled Week 24 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun should undergo dose-tapering and follow up as described above following early completion of the Week 24 assessments
Revised Text:
This Phase II pilot study is a randomized, double-blind, placebo-controlled study design to evaluate the safety, tolerability, PK, PD, and clinical efficacy of vamorolone 500mg (250mg if <50kg body weight)

compare to placebo administered daily by liquid oral suspension over a treatment period of 24 weeks in ambulatory male subjects with BMD.
A total of approximately 39 subjects ages 12 to <65 years will be enrolled in the study
The study is comprised of a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1 day Pretreatment Baseline Period, a 24- week Treatment Period, and a 4-week Dose tapering Period (for subjects not continuing directly with further vamorolone treatment).
Subjects will be enrolled into this study at the time written informed consent is given. After completion of Screening assessments subjects who meet all eligibility criteria in this study will be randomized to vamorolone or placebo treatment group.
After completion of Screening and Baseline assessments, subjects will return to the study clinic on Day 1 for safety and PD assessments prior to administration of the first dose of study medication. Additional onsite study visits will occur at Week 4, Week 12, and Week 24.
Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor and Study Team regarding study conduct.
Subject diaries will be dispensed at the Day 1, Week 12, and Week 24 (for subjects participating in the Dose-tapering Period) Visits to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication. Study drug dosing will occur at home on all days except dates of the Day 1, Week 12, and Week 24 Visits, when dosing will occur at the study site.
The scheduled Week 12 and Week 24 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling. For the Week 24 assessments, the scheduled 12-lead ECG and patient-reported outcomes may be completed on the day prior to the final Week 24 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 24 dose of study medication. The scheduled physical examination, weight, height, vital signs, clinical laboratory tests, blood draws for PD biomarker analysis, functional assessments (TTRW and NSAA), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 24 dose of study medication.
Subjects who complete the VBP15-BMD-001 study assessments through the Week 24 Visit may be given the opportunity to continue to receive vamorolone as part of an expanded access or compassionate use program if the subject wishes to continue vamorolone dosing and if the Investigator feels that it is in the best interest of the subject.
Subjects who complete the VBP15-BMD-001 study and will enroll directly into the expanded access or compassionate use program to continue vamorolone treatment will be discharged from the VBP15 BMD-001 study following completion of all Week 24 assessments. Subjects who will not continue vamorolone treatment in the expanded access or compassionate use program will have their study medication dose tapered during a 4-week Dose-tapering Period prior to discharge from the study. For these subjects, site study staff will contact the subject or parent(s)/guardian(s) by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms of adrenal suppression, and to address any questions the subject or parent(s)/guardian(s) may have. These subjects will have a final visit at Week 28 after the completion of the dose taper for a final physical exam, safety assessment, and return of remaining study medication and final subject diary.
In the event that any clinical or laboratory parameters remain abnormal at the time of discharge from the study, the subject will be followed medically, as clinically indicated.
Any subject who discontinues the study prior to the Week 24 Visit should return to the study unit for scheduled Week 24 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun should undergo dose-tapering and follow up as described above following early completion of the Week 24 assessments.

Section Changed:
STUDY DESIGN: 3.2 Study Summary
Original Text:
This Phase II study is an open-label, single dose study to evaluate the safety, tolerability, PD and clinical efficacy of vamorolone over a treatment period of 24 weeks in ambulatory boys and men with BMD.
A total of approximately 30 subjects ages 12 to <65 years will be enrolled in the study.

The study is comprised of a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1 day Pretreatment Baseline Period, a 24- week Treatment Period, and a 4-week Dose tapering Period (for subjects not continuing directly with further vamorolone treatment). Subjects will be enrolled into this study at the time written informed consent is given.

After completion of Screening and Baseline assessments, subjects will return to the study clinic on Day 1 for safety and PD assessments prior to administration of the first dose of study medication. Additional onsite study visits will occur at Week 4, Week 12, and Week 24.
Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor and Study Team regarding study conduct.
For all subjects, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 24 Visit (see Section 5.3). Study drug dosing will occur at home on all days except dates of the Day 1, Week 12, and Week 24 Visits, when dosing will occur at the study site. Subject diaries will be dispensed at the Day 1, Week 4, Week 12, and Week 24 (for subjects participating in the Dose-tapering Period) Visits to record AEs, changes to concomitant medications taken during the study and any missed or incomplete doses of study medication.
The scheduled Week 12 and Week 24 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling. For the Week 24 assessments, the scheduled 12-lead ECG and patient-reported outcomes may be completed on the day prior to the final Week 24 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 24 dose of study medication. The scheduled physical examination, weight, height, vital signs, clinical laboratory tests, blood draws for PD biomarker analysis, functional assessments (TTRW and NSAA), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 24 dose of study medication.
Subjects who complete the VBP15-BMD-001 study assessments through the Week 24 Visit may be given the opportunity to continue to receive vamorolone as part of an expanded access or compassionate use program if the subject wishes to continue vamorolone dosing and if the Investigator feels that it is in the best interest of the subject.
Subjects who complete the VBP15-BMD-001 study and will enroll directly into the expanded access or compassionate use program to continue vamorolone treatment will be discharged from the VBP15-BMD-001 study following completion of all Week 24 assessments. Subjects who will not continue vamorolone treatment in the expanded access or compassionate use program,

will have their vamorolone dose tapered during a 4-week Dose-tapering Period prior to discharge from the study. For these subjects, site study staff will contact the subject or subjects' parent(s)/guardian(s) by telephone at Week 26 to ensure that the dose tapering is proceeding according to protocol (see Section 6.3.5), to assess potential signs or symptoms of adrenal suppression, and to address any questions the subject or subject's parent(s)/guardian(s) may have. These subjects will have a final visit at Week 28 after the completion of the dose taper for a final safety assessment, safety lab studies and return of remaining vamorolone and final subject diary.
In the event that any clinical or laboratory parameters remain abnormal at the time of discharge from the study, the subject will be followed medically, as clinically indicated.

Any subject who discontinues the study prior to the Week 24 Visit should return to the study unit for scheduled Week 24 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun should undergo dose-tapering (see Section 6.3.5) following early completion of the Week 24 assessments and follow up as described above following early completion of the Week 24 assessments.

Revised Text:

Section removed

Section Changed:

STUDY DESIGN: 3.2 Randomization

Original Text:

None

Revised Text:

Following consent and review of study entry criteria to confirm subject eligibility for the study, the subject can be randomized to treatment. Randomization should be performed at least 10 days prior to the baseline visit and will be achieved via the Interactive Voice/Web Response System (IXRS) system with user name and password access. Randomization will be stratified by participant's age (<6 vs. ≥ 6 years). Randomization will be stratified only by age; randomization will not be stratified by investigational site. Randomization will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study, and to verify that the child has not previously been randomized. The following information will need to be entered into the IXRS system in order to assign the subject to a treatment group and the appropriate age stratification group:

- Participant's Study Subject Identification Number
- Participant's Date of Birth
- Participant's weight, as recorded at the Screening Visit

When the site investigator/designee completes the randomization procedures via the IXRS system, an e-mail report with the randomization number and age stratification group will be generated and sent to the clinical trials supply company confirming randomization into the trial.
The randomization number will be assigned by the IXRS system and will only be used for study drug supply and shipment. Once the information has been received, the clinical trials supply company will prepare a subject-specific kit of study medication and ship it to the pharmacy at the study site. Randomization procedures should be completed at least 10 days prior to the Baseline Visit in order to allow study drug supply to be shipped to the site in time to be dispensed to the participant by the site investigator for Day 1 dosing.

Section Changed:

STUDY DESIGN: 3.3 Blinding

Original Text:

None

Revised Text:

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

To blind the liquid formulation, the supplies company will manufacture 4.0% wt/wt vamorolone suspension formulations, and placebo suspension formulation, identical in appearance. Subjects who are randomized to receive vamorolone 500mg/day (250mg/day if <50kg body weight) will receive the 4.0% vamorolone suspension. Study medication will be shipped to the sites in 100 mL bottles labeled with

subject-specific identifiers. Trained site study staff will calculate study medication dose volume based on subject body weight for all subjects as 0.15 mL/kg, regardless of treatment assignment.
Subjects, parents/guardians, site investigators and all other site study staff will not know to which treatment group the subject has been assigned and will remain blinded to the identity of the treatment assignment until the end of the study (last subject last visit) and the database has been locked

Section Changed:
STUDY DESIGN: 3.4 Unblinding
Original Text:
None
Revised Text:
Every attempt should be made to preserve the integrity of study drug blinding. All subjects will be provided with a card, to be carried at all times, stating "I am taking part in a clinical trial" (in the local language) to be presented to medical staff in the event of routine treatment or a medical emergency. Investigational medications can usually be withdrawn without the need for unblinding in a subject experiencing an AE that requires study medication withdrawal. In this case, the site investigator should provide adequate and necessary support to the subject without unblinding study treatment.

Subjects who experience a medical emergency, whether their treatment remains blinded or is unblinded, should be covered with stress steroids, except for unblinded subjects who were receiving placebo.

All subjects who have study medication withdrawn without unblinding will need to undergo dose-tapering according to the schedule in Section 6.3.5

In the event that unblinding is necessary, an emergency unblinding procedure is provided to allow site investigators to disclose a treatment assignment for an individual subject if clinical circumstances should require this.

Unblinding will be performed and treatment assignment obtained through the IXRS system with username and password code. The expectation is that emergency unblinding will occur only very rarely; for example, when the subject needs emergency surgery and information about all treatment interventions is required. In the exceptional circumstance that knowledge of the study drug assignment appears essential for providing appropriate medical management, the site investigator should make every effort to contact the study chair or the independent Medical Monitor to discuss the rationale for breaking the blind. If the site investigator still believes that unblinding is needed, or the study chair and independent Medical Monitor are not available for contact, the site investigator will follow the IXRS unblinding procedures for unblinding the subject in question (see the Manual of Operations for details on how to unblind a subject using the IXRS system).
After breaking the blind, the site staff should record details regarding the reasons for breaking the blind, including any AEs leading to the unblinding, in the source documents and electronic case report form (eCRF). Once the blind is broken for a given subject, study drug will be discontinued and the subject will be withdrawn from the study. Furthermore, as the subject might have received glucocorticoids (prednisone) as part of the study and as vamorolone appears to affect the adrenal axis, prednisone and vamorolone cannot be discontinued without a proper dose-tapering period.

Any subject whose treatment is unblinded prior to the Week 24 Visit should return to the clinic for Week 24 assessments at the time of unblinding, whenever possible, assuming the subject has not withdrawn consent; any subject whose treatment is unblinded after Week 24 and prior to the Week 28 Visit should return to the clinic for Week 28 assessments at the time of unblinding, whenever possible, assuming the subject has not withdrawn consent. Any subject whose treatment, upon unblinding, is revealed to be vamorolone will need to follow the dose-tapering protocol (Section 6.3.5 specific to the time of

unblinding); these subjects will also be asked to return to the clinic at the end of the tapering period for final Dose-tapering Period assessments, whenever possible. If the subject was taking placebo prior to unblinding, study drug tapering will not be required; however, the subject should return for final Week 24 assessments at the time of unblinding and withdrawal from the study. After unblinding, a subject may be prescribed standard of care glucocorticoids, if clinically indicated.

Subjects who discontinue the study for any reason other than a medical emergency will not be unblinded

Section Changed:
SELECTION AND WITHDRAWAL OF STUDY SUBJECTS: 4.2 Inclusion Criteria-Inclusion Criteria # 2, 4-11
Original Text:

2. Subject has a confirmed diagnosis of BMD as defined as:
4. Subject is able to perform the timed run/walk 10 meters assessment; assistive devices, cane or walker, are allowed.
5. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit); and
6. Subject is willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
7. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
8. Subject has evidence of chicken pox immunity as determined by:
    a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
    b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;
9. Subject and parent(s)/guardian(s) (if subject is <18 years of age) are willing and able to comply with scheduled visits, study medication administration plan, and study procedures.

Revised Text:

2. Subject is a male and has a confirmed diagnosis of BMD as defined as:
4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) ≤ 30 sec; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32
6. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit); and
7. Subject is willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
8. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first

administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];

9. Subject has evidence of chicken pox immunity as determined by:
   a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
   b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;
10. Subject and parent(s)/guardian(s) (if subject is <18 years of age) are willing and able to comply with scheduled visits, study medication administration plan, and study procedures.
11. Subject of childbearing potential agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed.

Section Changed:
SELECTION AND WITHDRAWAL OF STUDY SUBJECTS: 4.3 Exclusion Criteria # 3 and 4
Original Text:

3. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;
4. Subject has a history of primary hyperaldosteronism;

Revised Text:

3. Subject has had an acute illness within 4 weeks prior to the first dose of study medication
4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.1 Study Medication Administered
Original Text:

Planned vamorolone dose level: 6.0 mg/kg.
Vamorolone will be administered to all subjects as an oral liquid suspension.
A total of approximately 30 subjects will be administered vamorolone 4.0% wt/wt oral suspension.
Vamorolone 4.0% wt/wt oral suspension (investigational medicine) will be administered to all subjects once daily for 24 weeks, from Study Day 1 until the Week 24 Visit. At the end of the 24-week Treatment Period, a subset of subjects may receive additional vamorolone treatment in a dose-tapering manner during a 4-week Dose-tapering Period prior to discharge from the study (see Section 6.3.5).

Revised Text:

Planned vamorolone dose level 500mg/day (250mg/day if <50kg body weight) or a matched placebo.
Study medication will be administered to all subjects as an oral liquid suspension.
A total of approximately 39 subjects will be administered vamorolone 4.0% wt/wt oral suspension.
Vamorolone 4.0% wt/wt or placebo oral suspension will be administered to all subjects once daily for 24 weeks, from Study Day 1 until the Week 24 Visit. At the end of the 24-week Treatment Period, a subset of subjects may receive additional study medication treatment in a dose-tapering manner during a 4-week Dose-tapering Period prior to discharge from the study (see Section 6.3.5).

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.2 Identity of Investigational Product
Original Text:

Active Substance: Vamorolone
Strength: 4.0% wt/wt
Dosage Form: Oral suspension

Manufacturer: Velesco Pharmaceutical Services
Revised Text:
Vamorolone:
Active Substance: Vamorolone
Strength: 4.0% wt/wt
Dosage Form: Oral suspension
Manufacturer: Velesco Pharmaceutical Services

Placebo to Match Vamorolone:

Dosage Form: Oral suspension
Manufacturer: Velesco Pharmaceutical Services
The clinical trials supplies companies will manufacture identical liquid formulation of vamorolone and placebo to maintain the blind.

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.3 Dosage Schedule and Administration of Study Medication - paragraph #1
Original Text:
Subjects will be administered vamorolone 4.0% wt/wt oral suspension
Revised Text:
The site pharmacist or designated site study staff will dispense blinded study medication to each subject randomized in the study. Subjects will be administered vamorolone 4.0% wt/wt or placebo oral suspension.

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.4 Rationale for Dose Selection- paragraph #6
Original Text:
Based on the safety and efficacy results observed in these earlier studies, the dose of vamorolone at 6.0 mg/kg/day was chosen for evaluation in the current study.
Revised Text:
Based on the safety and efficacy results observed in these earlier studies, the dose of vamorolone at 500mg/day (250mg/day if <50kg body weight) was chosen for evaluation in the current study.

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.8.1 Packaging and Labeling of Study Medication
Original Text:
The site pharmacist or designated study staff will receive clinical trial material (CTM) when all regulatory requirements have been completed by the site. Additional CTM will be available upon request. The Study Sponsor through the designated central pharmacy will provide CTM in bulk quantities sufficient to satisfy the protocol requirement. Vamorolone will be shipped in bulk to the study site's registered pharmacist or designated study staff in suitably labeled study cartons. Cartons will contain study medication packaged in sterile 110 mL (4 oz) amber bottles

with a 110 mL fill volume with child-resistant cap with a 24 mm bottle press-in adapter. Bottles are filled with 110 mL of suspension in order to guarantee a delivery of 100 mL.
Bottles of investigational medication suspension will contain 4.0 grams of vamorolone/100 mL (4.0% orange-flavored suspension).
Bulk drug supplies will be labeled with the Sponsor name, protocol number, lot number, expiration or retest date, and other appropriate study information. Carton and bottle labels will be written in accordance with all applicable laws, guidance and directives of the jurisdiction where the study is being conducted.

The volume per dose to be administered to each subject depends on the subject's weight (in kg) recorded at the dispensing visit; see Appendix 15.1 for complete instructions on calculating dose volume.
Trained site staff will write the dose level, dose volume in mL, and dispense date on the bottle label, prior to dispensing to subjects. Clinical supplies dispensed by the study site staff and ready for administration to subjects will be labeled with the dispense date, vamorolone dose level, volume to be administered per dose, protocol number, and additional information as required by all applicable laws, guidance and directives of the jurisdiction where the study is being conducted.
Each study medication bottle may be used for a single subject only

Revised Text:

When all entry criteria are met, and at least 10 days prior to the Baseline Day -1 Visit, subjects will be randomized to treatment via the IXRS system. Subject-specific suspension study drug supplies sufficient for the first six weeks of Treatment Period will be packaged, labeled (with MED ID number and other protocol-specific information) and couriered to the pharmacy at the recruiting site prior to the Baseline Visit for the subject.
Investigational medication suspension and matching placebo suspension will be packaged in sterile 110 mL (4 oz) amber bottles with a 100 mL fill volume with child-resistant cap with a 24 mm bottle press-in adapter. Bottles are filled with 110 mL of suspension in order to guarantee a delivery of 100 mL
Bottles of investigational medication suspension will contain 4.0 grams of vamorolone/100 mL (4.0% orange-flavored suspension). The matching placebo suspension will be identical in appearance and taste to the vamorolone suspensions. The volume per dose to be administered to each subject depends on the subject's weight (in kg) recorded at the visit prior to each study drug dispensing visit. Each subject will receive a volume of 12.5 ml/day (6.25 ml/day if <50kg body weight) of a vamorolone suspension or matching placebo suspension. Instructions for the calculation of each dose of liquid formulation are given in the Pharmacy Manual
Bulk drug supplies will be labeled with the Sponsor name, protocol number, lot number, expiration or retest date, and other appropriate study information. Carton and bottle labels will be written in accordance with all applicable laws, guidance and directives of the jurisdiction where the study is being conducted.
The volume per dose to be administered to each subject depends on the subject's weight (≥ 50 kg or <50kg) recorded at the dispensing visit; see Appendix 15.1 for complete instructions on calculating dose volume.
Trained site staff will write the dose level, dose volume in mL, and dispense date on the bottle label, prior to dispensing to subjects. Clinical supplies dispensed by the study site staff and ready for administration to subjects will be labeled with the dispense date, vamorolone dose level, volume to be administered per dose, protocol number, and additional information as required by all applicable laws, guidance and directives of the jurisdiction where the study is being conducted.
Study medication will be dispensed to the subject's parent or legal guardian for Treatment Period dosing at the Day 1 Visit and at the Week 12 and Week 24 Visits. At the Week 24 Follow-up Visit, study medication or placebo for the Dose-tapering Period will be dispensed. Dispensed bottles and unused tablets of study medication will be returned at each subsequent study visit, prior to dispensing bottle(s)/blister pack(s) for the next dispensing interval.
Each study medication bottle may be used for a single subject only.

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.8.2 Storage of Study Medication

Original Text:

All CTM for use in the trial must be stored in a locked container/cabinet free from environmental extremes, under the responsibility of the institutional pharmacist or Principal Investigator

Revised Text:

All Clinical Trial Materials (CTM) for use in the trial must be stored in a locked container/cabinet free from environmental extremes, under the responsibility of the institutional pharmacist or Principal Investigator.

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.8.3 Study Medication Shipping and Handling – paragraph #2-5
Original Text:
It is essential to this study that all CTM be accounted for during the study period. All unused (i.e., undispensed; dispensed and returned) study medication will be retained at the study site for reconciliation by the Sponsor's study monitors (or designees) during routine monitoring visits.
Final disposition of all unused CTM will be coordinated by the Sponsor's study monitors (or designees) throughout and at the end of the study (see Section 5.8.4).

Clinical trial material must be dispensed and administered according to the procedures described in this protocol. Only subjects enrolled in the study may receive study medication, in accordance with all applicable regulatory requirements. Only authorized study personnel may supply CTM. Authorized study personnel refers to the Investigator (or designee) and hospital pharmacists, in accordance with all applicable regulatory requirements and the Site Signature Log/Delegation of Authority. Only authorized study personnel or the subject or subject's parent or legal guardian may administer CTM.

At the Baseline (Day -1) Visit, subjects will be assigned to treatment (see Section 3.3). At the Day 1 Visit, the trained site staff will record the dose level, volume in mL per suspension dose, and dispense date on the bottle label(s). Labeled study drug supplies sufficient to last until the Week 12 Visit will be dispensed to each subject. The first dose of study medication will be administered in clinic on Study Day 1. The initial drug supply will be sufficient to allow for the Week 12 Visit to occur on the latest date permissible within the protocol-specified visit window (12 weeks ± 7 days). No additional study drug supplies will be dispensed at the Week 4 Visit. Additional labeled study drug supplies sufficient to last from Week 12 until the Week 24 Visit will be dispensed to each subject at the Week 12 Visit; and additional labeled study drug supplies sufficient to last from Week 24 through the duration of the Dose-tapering Period will be dispensed at the Week 24 Visit to subjects participating in the Dose-tapering Period.
Additional bulk CTM supply will be packaged, labeled (as described above) and couriered to the site as needed to satisfy enrollment.
Revised Text:
When all entry criteria are met, at least 10 days prior to the Baseline Visit, subjects will be randomized to treatment via the IXRS system. Subject-specific will be packaged, labeled (with MED ID number and other protocol-specific information) and couriered to the pharmacy at the study site prior to the Baseline Visit for the subject. At the Day 1 Visit, the trained site staff will record the volume in mL per suspension dose (bottles) on the bottle. Labeled study drug supplies sufficient to last until the Week 12 Visit will be dispensed to each subject. The first dose of study medication will be administered in clinic on Study Day 1. The initial drug supply will be sufficient to allow for the Week 12 Visit to occur on the latest date permissible within the protocol-specified visit window (12 weeks ± 7 days). No additional study drug supplies will be dispensed at the Week 4 Visit.
Prior to the subsequent study drug dispensing visits (i.e., Week 12, Week 24, Dose-tapering Period), additional study drug supplies will be ordered using the IXRS system. Additional labeled study drug supplies sufficient to last from Week 12 until the Week 24 Visit will be dispensed to each subject at the Week 12 Visit; and additional labeled study drug supplies sufficient to last from Week 24 through the duration of the Dose-tapering Period will be dispensed at the Week 24 Visit to subjects participating in the Dose-tapering Period.
Clinical trial material will only be dispensed to the subject once the subject or subject's parent/guardian has (1) a signed informed consent form (ICF) and HIPAA (as applicable) authorization on file, (2) met all eligibility criteria for entry into the study, and (3) completed all Pretreatment requirements.

It is essential to this study that all CTM be accounted for during the study period. All unused (i.e., undispensed; dispensed and returned) study medication will be retained at the study site for reconciliation by the Sponsor's study monitors (or designees) during routine monitoring visits.
Final disposition of all unused CTM will be coordinated by the Sponsor's study monitors (or designees) throughout and at the end of the study (see Section 5.8.4).
Clinical trial material must be dispensed and administered according to the procedures described in this protocol. Only subjects enrolled in the study may receive study medication, in accordance with all applicable regulatory requirements. Only authorized study personnel may supply CTM. Authorized study personnel refers to the Investigator (or designee) and hospital pharmacists, in accordance with all applicable regulatory requirements and the Site Signature Log/Delegation of Authority. Only authorized study personnel or the subject or subject's parent or legal guardian may administer CTM.

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.8.4 Study Medication Accountability
Original Text:
The Subject Identification (ID) number of the subject to whom the study drug was dispensed
The date(s) and quantity of the study drug dispensed to the subject
Revised Text:
The Subject Identification (ID) number of the subject to whom the study drug was dispensed
The MED ID number of the dispensed kit
The date(s) and quantity of the study drug dispensed to the subject

Section Changed:
TREATMENT OF STUDY SUBJECTS: 5.9 Procedures for Assigning Subject Identification Numbers
Original Text:
This is an open-label study. Following the signing of the written ICF, subjects will be assigned a unique site-specific 6-digit subject ID number in sequential order of screening into the study.
Revised Text:
Following the signing of the written ICF, subjects will be assigned a unique site-specific 6-digit subject ID number in sequential order of screening into the study.

Section Changed:
STUDY SCHEDULE: 6.1 Time and Events Schedule
Original Text:
Pretreatment Screening Period: The up-to-35-day interval (unless extended to accommodate varicella vaccine), from the subject or subject's parent(s) or guardian(s) signing of the Informed Consent/HIPAA authorization until completion of all designated screening procedures, at least 24 hours prior to the first dose of study medication. All screening procedures must be completed by Day -1.
Pretreatment Baseline Period: The 24-hour period immediately prior to administration of the first dose of study medication, also designated as Day -1. Subjects meeting all eligibility criteria will be assigned to study medication treatment on Baseline Day -1, within 24 hours prior to administration of the first dose of study medication.
Revised Text:
Pretreatment Screening Period: The up-to-35-day interval (unless extended to accommodate varicella vaccine), from the subject or subject's parent(s) or guardian(s) signing of the Informed Consent/HIPAA authorization until completion of all designated screening procedures, at least 24 hours prior to the first dose of study medication. All screening procedures must be completed by Day -1. The screening procedures related to eligibility criteria must be completed by Day -11. Subjects meeting all eligibility criteria will be randomized by Day -11, at least 10 days prior to the Baseline Day -1 Visit

Pretreatment Baseline Period: The 24-hour period immediately prior to administration of the first dose of study medication, also designated as Day -1.

Section Changed:
STUDY SCHEDULE: Table 2. Schedule of Study Activities
Original Text:

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Inclusion/Exclusion Criteria	X	X					
Informed Consent	X						
Enrollment	X						
Medical History	X						
Medication History	X	X					
Physical Examination	X	X			X	X	X
Varicella immunity	X						
Height	X				X	X	
Weight	X	X			X	X	X
Vital Signs	X	X	X	X	X	X	X
Neuro-QOL questionnaires[a]		X				X	
TTRW	X	X			X	X	
NSAA		X			X	X	
Blood for Clinical Labs[b]	X			X	X	X	
Urinalysis[b]	X			X	X	X	
Blood for Safety PD Biomarker Panel[c]			X,			X	
Blood and urine for Efficacy PD Biomarker Panel[d]			X		X	X	
Fasting blood for insulin and glucose [e]			X		X	X	
Saliva for cortisol[f]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	

Return Study Medication/ Compliance Monitoring					X	X	
Study Medication Dosing[g]			X		X	X	
Vamorolone dose tapering[h]							X
Dispense Subject Diaries			X		X		
Return Subject Diaries				X	X	X	
AE/SAE Recording	X					▶	
Concomitant Medications			X				
Discharge from Study[h]						X	X

w = week; TTRW = time to run/walk 10 meters test; NSAA = North Star Ambulatory Assessment
NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep
Clinical safety labs: chemistry, hematology, lipids; urinalysis by dipstick and microscopic
Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin
Serum efficacy pharmacodynamic biomarkers: CK, MDC and mIR146a; urine efficacy pharmacodynamic biomarker: mIR146a
Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic
Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening
The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home.
Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use to continue administration of vamorolone, or will be after completing the dose taper followed by a final study visit for those who discontinue vamorolone.

Revised Text:

Study Day or Week/Visit	**Pretreatment Period**		**Treatment Period**				**Dose-tapering Period**
	Screening -35 to -3 days	**Baseline -1 day**	**Day 1**	**Week 4 (±1w)**	**Week 12 (±1w)**	**Week 24 (±1w)**	**Week 25-28 (±1w)**
Informed Consent	X						
Enrollment	X						
Inclusion/exclusion criteria	X	X					
Randomization[a]	X						
Medical History	X						
Medication History	X	X					
Physical Examination	X	X			X	X	X
Varicella immunity	X						
Height	X				X	X	

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Weight	X	X			X	X	X
Vital Signs	X	X	X	X	X	X	X
Neuro-QOL questionnaires[b]		X				X	
TTRW	X	X			X	X	
NSAA	X	X			X	X	
Blood for Clinical Labs[c]	X			X	X	X	
Urinalysis[c]	X			X	X	X	
Blood for PK[d]			X				
Blood for Safety PD Biomarker Panel[e]			X,			X	
Blood and urine for Efficacy PD Biomarker Panel[f]			X		X	X	
Fasting blood for insulin and glucose [g]			X		X	X	
Saliva for cortisol[h]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	
Return Study Medication/ Compliance Monitoring					X	X	
Study Medication Dosing[i]			X		X	X	
Study Medication dose tapering[j]							X
Dispense Subject Diaries			X		X		
Return Subject Diaries				X	X	X	
AE/SAE Recording	X						
Concomitant Medications			X				
Discharge from Study[j]						X	X

w = week; TTRW = time to run/walk 10 meters test; NSAA = North Star Ambulatory Assessment
Randomization occurs by Interactive Voice/Web Response System (IXRS) after subjects are confirmed to have met all study entry criteria, at least 10 days prior to the Baseline Day -1 Visit.
NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep
Clinical safety labs: chemistry, hematology, GLDH, GGT, lipids; urinalysis by dipstick and microscopic
Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin
Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose
Serum efficacy pharmacodynamic biomarkers: CK, MDC and mIR146a; urine efficacy pharmacodynamic biomarker: mIR146a
Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic
Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening

The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home.

Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use to continue administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication.

Section Changed:
STUDY SCHEDULE: 6.3 Visit Schedule and Procedures – paragraph #2
Original Text:
Each subject will receive the open-label study medication at 6 mg/kg daily dose for a period of 24 weeks. Following completion of the 24-week Treatment Period, all subjects who will not be continuing directly to receive vamorolone by expanded access or compassionate use will taper their study medication during the 4-week open-label Dose-tapering Period. See Section 7 for a detailed description of the safety, clinical efficacy, PD, and patient-reported outcomes to be performed during this study.
Revised Text:
Each subject will receive the double-blind study medication at 500mg (250mg if <50kg body weight) daily dose for a period of 24 weeks. Following completion of the 24-week Treatment Period, all subjects who will not be continuing directly to receive vamorolone by expanded access or compassionate use will taper their study medication during the 4-week open-label Dose-tapering Period. See Section 7 for a detailed description of the safety, clinical efficacy, PK, PD, and patient-reported outcomes to be performed during this study.

Section Changed:
STUDY SCHEDULE: 6.3.1 Screening Period (Day -35 to -3) – paragraph #4 Bullet #7 and 9
Original Text:
Collection of blood for clinical laboratory testing (hematology, clinical chemistry, and lipids) and collection of urine for urinalysis (see Section 7.2.4)
TTRW (see Section 7.3.1)
Revised Text:
Collection of blood for clinical laboratory testing (hematology, clinical chemistry, GLDH, GGT, and lipids) and collection of urine for urinalysis (see Section 7.2.4)
NSAA including TTRW (see Section 7.3.1)

Section Changed:
STUDY SCHEDULE: 6.3.2 Baseline Period (Day -1) Visit– paragraph #1
Original Text:
Subjects who have met all study eligibility criteria will return to the study site during the Pretreatment Baseline Period (Day -1, the 24-hour interval immediately preceding administration of the first dose of study medication) for baseline assessments, and will be assigned to treatment at the Baseline Day -1 Visit.
Revised Text:
Subjects who have met all study eligibility criteria and been randomized to treatment via IXRS during the Screening Period, and for whom subject-specific blinded study medication has been shipped to and received by the study site will return to the study site during the Pretreatment Baseline Period (Day -1, the 24-hour interval immediately preceding administration of the first dose of study medication) for baseline assessments, and will be assigned to treatment at the Baseline Day -1 Visit.

Section Changed:
STUDY SCHEDULE: 6.3.3 Treatment Period Day 1 Visit – paragraph #4 Bullet #2 and 3
Original Text:
Clinical laboratory evaluation including hematology, clinical chemistry, lipids, and urinalysis tests, prior to administration of first dose of study drug (see Section 7.2.4)
Blood samples for, PD biomarkers including fasting glucose and insulin, osteocalcin and HbA1c, prior to administration of first dose of study drug (see Section 7.2.6).
Revised Text:
Clinical laboratory evaluation including hematology, clinical chemistry, GLDH, GGT, lipids, and urinalysis tests, prior to administration of first dose of study drug (see Section 7.2.4)

Blood samples for, PK, PD biomarkers including fasting glucose and insulin, osteocalcin and HbA1c, prior to administration of first dose of study drug (see Section 7.2.6).

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS: 7.2.4 Clinical Laboratory Tests– paragraph #1 and 2
Original Text:
for the hematology, chemistry, lipids,
Revised Text:
for the hematology, chemistry, GLDH, GGT, lipids,

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS: 7.2.4 Clinical Laboratory Tests– Table 4
Original Text:
Table 4. Hematology, Chemistry, and Lipids Clinical Laboratory Tests
Revised Text:
Table 4. Hematology, Chemistry, GLDH, GGT, and Lipids Clinical Laboratory Tests
Chemistry Tests added to Table 4.
Glutamate dehydrogenase (GLDH)
Gamma glutamyl transferase (GGT)

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS: 7.2.7 PK Assessment
Original Text:
none
Revised Text:
At the Day 1 Visit, all subjects will have blood collected for PK assessments at 1, 2 and 3 hours post-dose. Approximately 2 mL of blood will be collected into K2-EDTA tubes at the single assessment time point.
Plasma concentrations of vamorolone will be measured using a specific and validated liquid chromatography tandem mass spectrometry assay. PK assessments will be performed by a central laboratory. The procedures for the collection, handling, and shipping of laboratory samples will be specified in the Laboratory Manual(s) provided to the study sites.
The exact time of blood sampling will be recorded in the source document and eCRF.
If PK and PD or clinical laboratory blood samples are to be collected at the same time point, the PK blood sample should be collected prior to the PD blood sample(s), which in turn should be collected prior to the clinical laboratory blood samples

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS: 7.2.8 Total Blood Volume Required
Original Text:
A total of 70 mL of blood will be collected from each subject over the course of the up-to-33-week study.
Revised Text:
A total of 76 mL of blood will be collected from each subject over the course of the up-to-33-week study.

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS: 7.2.8 Total Blood Volume Required – Table7
Original Text:

Test	Blood Volume (mL)						
	SCR	Day 1	Week 4	Week 12	Week 24	Week 28	Total Volume
Varicella Zoster IgG	2						2
Clinical Lab tests[a,b]	6		6	6b	6b	6	30
Safety PD Biomarker Panel[c]		6b			6b		12
Efficay PD Biomarker Panel[d]		6		6	6		18
Fasting blood for insulin and glucose		4		4			8
Total Volume by Visit (mL)	8	16	6	16	18	6	70
Total Volume: 70 mL							

SCR = Screening
[a] Hematology, Chemistry, and Lipids.
[b] Subjects must have fasted ≥ 8 hours prior to blood draws.
[c] Osteocalcin, hemoglobin A1c (HbA1c), insulin
[d] CK, MDC and mIR146a

Revised Text:

Test	Blood Volume (mL)						
	SCR	Day 1	Week 4	Week 12	Week 24	Week 28	Total Volume
Varicella Zoster IgG	2						2
Clinical Lab tests[a,b]	6		6	6b	6b	6	30
Safety PD Biomarker Panel[c]		6b			6b		12
Efficay PD Biomarker Panel[d]		6		6	6		18
Fasting blood for insulin and glucose		4		4			8
PK[e]		6					6
Total Volume by Visit (mL)	8	22	6	16	18	6	76
Total Volume: 70 mL							

SCR = Screening
[a] Hematology, Chemistry, GLDH, GGT and Lipids.
[b] Subjects must have fasted ≥ 8 hours prior to blood draws.
[c] Osteocalcin, hemoglobin A1c (HbA1c), insulin
[d] CK, MDC and mIR146a
[e.] Blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS: 7.3.1 North Star Ambulatory Assessment (NSAA)
Original Text:
The NSAA will be completed for subjects at Baseline Day -1, and at the Week 12, and Week 24 Visits. At the Screening visit only TTRW will be completed.

Revised Text:
The NSAA will be completed for subjects at the Screening, Baseline Week 12, and Week 24 Visits

Section Changed:
STUDY ASSESSMENTS AND MEASUREMENTS 7.6.6 Serious Adverse Events
Original Text:
For subjects who do not continue to receive vamorolone in an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in the VBP15-BMD-006 study to confirm the final SAE status of the subject.
Revised Text:
For subjects who do not continue to receive vamorolone in an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in the VBP15-BMD-001 study to confirm the final SAE status of the subject.

Section Changed:
DATA COLLECTION: 9.2 Electronic Case Report Form Completion
Original Text:
Subject data will be collected in this study using RedCap.

The Coordinating Center will design an electronic database in RedCap for this study. Access rights to the EDC system for the study site team members will need to be requested. Every user of the system will be made aware of the fact that username and password should never be shared, and their electronic signature constitutes the legally binding equivalent of a handwritten signature. Only trained personnel certified by the Coordinating Center will receive a username and password.
All data will be directly entered or collected on a source document and then entered into RedCap or transferred electronically to the study database (e.g., clinical laboratory results)..
Revised Text:
Subject data will be collected in this study using an EDC system. The EDC and database system will be OpenClinica by Akaza Research, LLC. OpenClinica is a web-based (https://www.openclinica.com) data entry system utilizing a high security environment. The underlying storage facility will be PostgreSQL, whose structure permits the linking of subject information across all tables in relational databases. OpenClinica uses secure socket layers (SSL) and in its Enterprise version used in this study is 21 CFR Part 11 compliant. Once an eCRF is created in the database, a data dictionary exists and the data team creates compatible paper source documentation.
The Coordinating Center will design an electronic database in OpenClinica for this study. Access rights to the EDC system for the study site team members will need to be requested. Every user of the system will be made aware of the fact that username and password should never be shared, and their electronic signature constitutes the legally binding equivalent of a handwritten signature. Only trained personnel certified by the Coordinating Center will receive a username and password.
All data will be directly entered or collected on a source document and then entered into OpenClinica or transferred electronically to the study database (e.g., clinical laboratory results).

Section Changed:
STATISTICAL METHODS AND PLANNED ANALYSES: 10.1 Sample Size Determination
Original Text:
This is a randomized, open-label, single dose study. Study medication is administered daily in this Phase II trial. A total of approximately 30 subjects will be enrolled.
We present sample size calculations needed to detect a similar effect as that observed for TTRW in DMD subjects in Becker dystrophy. We conducted a sample size calculation based on observed TTRW values from the VBP15-003 DMD vamorolone trial (11 subjects for 24 weeks for 6.0 mg/kg/day only). Using observed baseline and 24-week measurements for TTRW velocities, we estimate that 13 subjects will

ensure that a two-sided test with alpha=0.05 has 90% power to detect a mean difference of 0.255 m/s. Assuming attrition of 10%, we need to recruit 15 ambulatory subjects. A sample of 30 will be large enough to have a confidence interval of no wider than 36% for the proportion of treatment emergent adverse events assessed or any other event outcome. Given our sample size calculations and that we aim to recruit 30 subjects, we should have enough power to detect a difference in TTRW velocities.
A drop-out rate is not considered; subjects who withdraw early from the study may be replaced

Revised Text:

The primary objective is to evaluate safety and tolerability in this BMD population, for which this is the pilot study and no effect sizes are available.
A sample of 26 BMD subjects on vamorolone will be large enough to have a confidence interval of no wider than 39% for the proportion of treatment emergent adverse events assessed or any other event outcome in the vamorolone group.
We also assessed power for motor efficacy comparisons of vamorolone to placebo and present these calculations needed to detect a similar effect as that observed for TTRW velocity in DMD subjects in Becker dystrophy.
We conducted a sample size calculation based on observed TTRW values from the VBP15-003 DMD vamorolone trial (11 subjects for 24 weeks on 6.0 mg/kg/day) and VBP15-004 (25 subjects for 24 weeks on 6.0 mg/kg/day). Using observed baseline and 24-week measurements for TTRW velocities, we estimate that 39 subjects (randomized 1:2 placebo:vamorolone) will ensure that a two-sided t-test with alpha=0.05 has 83% power to detect a pooled mean difference of 0.275 m/s (sd=0.2715) in BMD subjects on vamorolone vs. no mean change in subjects on placebo (sd=0.2715). Assuming dropout of 5%, we have 80% power. Note that subjects who withdraw early from the study may be replaced.
Given our sample size calculations and that we aim to recruit 39 subjects, we should have enough power to detect a difference in TTRW velocities.

Section Changed:
STATISTICAL METHODS AND PLANNED ANALYSES: 10.3 Analysis Populations

Original Text:

Two populations will be defined for data analysis: Safety Population and a modified Intent-to- Treat (mITT) Population.
10.3.2 Modified Intent-to-Treat (mITT) Population
All subjects who receive at least one dose of study medication and have at least one post-baseline assessment will be included in the mITT Population. The mITT Population is the primary analysis population for clinical efficacy. Subjects who receive at least one dose of study medication but never have post-baseline assessments will be excluded. Results will be presented “as treated.”

Revised text:

Four populations will be defined for data analysis: Safety Population, a modified Intent-to- Treat (mITT) Population , per protocol population, and a PK population
10.3.2 Modified Intent-to-Treat (mITT) Population
All subjects who receive at least one dose of study medication and have at least one post-baseline assessment will be included in the mITT Population. The mITT Population is the primary analysis population for clinical efficacy. Subjects who receive at least one dose of study medication but never have post-baseline assessments will be excluded. Results will be presented “as randomized.”
10.3.3 Per Protocol population
The Per Protocol Population will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data
10.3.4 PK Population
The PK Population consisted of all subjects who received at least one dose of study medication and had sufficient quantifiable plasma concentration data for PK analysis.

Section Changed:
STATISTICAL METHODS AND PLANNED ANALYSES: 10.7.1 General Considerations
Original Text:
Statistical analyses will be performed using SAS® version 9.4 or later.
All measurements will be analyzed based upon the type of distribution, and descriptive statistics will be presented by assessment time point, as appropriate. Descriptive statistics for continuous variables (number [N], mean, median, standard deviation [SD], minimum, and maximum), descriptive statistics for categorical variables (N and percentage), and individual subject profiles will be presented, as appropriate.
All statistical tests will be performed at the 0.05 level. Paired t-tests will be utilized for select variables.
Baseline measurement is defined as the last non-missing value prior to the first dose of study drug in the study.
Revised text:
Statistical analyses will be performed using SAS® version 9.4 or later.
All measurements will be analyzed based upon the type of distribution, and descriptive statistics will be presented by assessment time point, as appropriate.
No formal interim statistical analyses are planned, apart from the interim unblinded safety data views and presentations to be created for the Data and Safety Monitoring Board (DSMB). The Week 24 analyses are the primary analyses for this study and will be performed after all subjects have completed Week 24.
Missing values for safety outcomes will be treated as missing, unless stated otherwise.
Baseline measurement is defined as the last non-missing value prior to the first dose of study drug.
Analyses will be summarized by two treatment groups:
Vamorolone (n=26)
Placebo (n=13)
The exploratory efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. The motor efficacy endpoint supports the exploratory motor efficacy objective of this study.
Another efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.
For the efficacy motor endpoint, TTRW (velocity), change from baseline to Week 24 will be compared between the vamorolone dose group and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, the comparison (using least squares [LS] mean contrasts) will be made to compare TTRW velocity at 24 weeks for the vamorolone group with placebo.
For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline, and treatment-by-week interaction).
An unstructured covariance matrix will be used, and underlying modelling assumptions will be checked.
If differences between baseline characteristics exist between the treatment groups, it will be investigated if adjustment for these characteristics is clinically relevant and necessary.

Section Changed:
STATISTICAL METHODS AND PLANNED ANALYSES: 10.7.4 Pharmacokinetic Analyses
Original Text:
None
Revised text:
Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects

Section Changed:
15 APPENDICES: 15.1 Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide
Original Text:
Subjects 2 to <4 years of Age

Dose Calculation Worksheet

Vamorolone is administered once daily as a 1.33% oral suspension. The volume per dose is determined by the subject's dosing level and body weight (in kg) at each study medication dispensing visit, as shown by *Equation 1*:

Equation 1

$$\frac{\text{Subject Weight (kg)} \times \text{Dose Level (mg/kg)}}{13.3\ \text{mg/mL}} = \text{Subject Dose (in mL)}$$

Subject weight (in kg) should be rounded to the nearest whole integer for the calculation of volume per dose.
Calculated dose volume will be rounded to the nearest 0.01 mL (1 mL syringe), 0.1 mL (3 mL syringe), 0.2 mL (5 mL syringe), or 0.2 mL (10 mL syringe) depending upon the total dose volume and calibration of the volumetric syringe to be used for administration of dose, as shown in the examples below:
Example 1: Dose volume calculation for a subject receiving 2.0 mg/kg/day with a body weight of 13 kg:

$$\frac{\textit{Subject Weight (13 kg)} \times \textit{Dose Level (2.0 mg/kg)}}{13.3\ \text{mg/mL}} = \textit{1.95 mL}$$

The subject will receive a daily dose volume of 1.95 mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a 3 mL volumetric syringe rounded to the nearest 0.1 mL, or 2.0 mL daily.

Example 2: Dose volume calculation for a subject receiving 6.0 mg/kg/day with a body weight of 16 kg:

$$\frac{\textit{Subject Weight (16 kg)} \times \textit{Dose Level (6.0 mg/kg)}}{13.3\ \text{mg/mL}} = \textit{7.22 m}$$

The subject will receive a daily dose volume of 7.22 mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a 10 mL volumetric syringe rounded to the nearest 0.2 mL, or 7.2 mL daily.

Vamorolone 1.33% Suspension Dispensing Guide

Each subject enrolled in the study will be dispensed 100 ml bottle(s) of vamorolone 1.33% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Additional supplies will be dispensed at the Week 12 Visit, sufficient for dosing through the time of the scheduled Week 24 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 1.33% suspension at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see Section 6.3.5).
The number of bottles to be dispensed at each dispensing visit for the following 12-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 1*) by 91 days (84 days in the dosing period + 7 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 2*, below:

Equation 2 $\frac{\text{Daily Dose (mL/day) x 91 Days}}{\text{100 mL}}$ = #Bottles to be Dispensed for 12 weeks dosing

Example 3: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of 2.0 mL (from Example 1 above):

$\frac{\text{Daily Dose (2.0 mL/day) x 91 Days}}{\text{100 mL}}$ = 1.82 Bottles

The number of bottles dispensed is rounded up to the nearest whole integer, or 2 bottles to be dispensed.

Example 4: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of 7.2 mL (from Example 2 above):

$\frac{\text{Daily Dose (7.2 mL/day) x 91 Days}}{\text{100 mL}}$ = 6.55 Bottles

The number of bottles dispensed is rounded up to the nearest whole integer, or 7 bottles to be dispensed. Each bulk bottle should be used for one subject only. Each bottle dispensed to the subject and ready for administration to subjects will be labeled with subject number, dispense date, protocol number, dose level, and volume to be administered per dose.
Any unused or partially used drug product should be returned at the Week 12 and Week 24 Visits, respectively, and at the end of the Dose-tapering Period, if applicable, and retained at the clinical study site for investigational drug accountability monitoring.

Subjects 7 to <18 Years of Age

Dose Calculation Worksheet

Vamorolone is administered once daily as a 4.0% oral suspension. The volume per dose is determined by the subject's dosing level and body weight (in kg) at each study medication dispensing visit, as shown by *Equation 3*:

Equation 3

$$\frac{\text{Subject Weight (kg)} \times \text{Dose Level (mg/kg)}}{40 \text{ mg/mL}} = \text{Subject Dose (in mL)}$$

Subject weight (in kg) should be rounded to the nearest whole integer for the calculation of volume per dose.
Calculated dose volume will be rounded to the nearest 0.01 mL (1 mL syringe), 0.1 mL (3 mL syringe), 0.2 mL (5 mL syringe), or 0.2 mL (10 mL syringe) depending upon the total dose volume and calibration of the volumetric syringe to be used for administration of dose, as shown in the examples below:
Example 5: Dose volume calculation for a subject receiving 2.0 mg/kg/day with a body weight of 23 kg:

$$\frac{\textit{Subject Weight (23 kg)} \times \textit{Dose Level (2.0 mg/kg)}}{40 \text{ mg/mL}} = \textit{1.15 mL}$$

The subject will receive a daily dose volume of 1.15 mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a 3 mL volumetric syringe rounded to the nearest 0.1 mL, or 1.2 mL daily.
Example 6: Dose volume calculation for a subject receiving 6.0 mg/kg/day with a body weight of 66 kg:

$$\frac{\text{Subject Weight (66 kg)} \times \text{Dose Level (6.0 mg/kg)}}{\text{40 mg/mL}} = 9.90\ mL$$

The subject will receive a daily dose volume of 9.90 mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a 10 mL volumetric syringe rounded to the nearest 0.2 mL, or 10 mL daily.

Vamorolone 4.0% Suspension Dispensing Guide

Each subject enrolled in the study will be dispensed 100 ml bottle(s) of vamorolone 4.0% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Additional supplies will be dispensed at the Week 12 Visit, sufficient for dosing through the time of the scheduled Week 24 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4.0% suspension at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see Section 6.3.5).
The number of bottles to be dispensed at each dispensing visit for the following 12-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 3*) by 91 days (84 days in the dosing period + 7 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 4*, below:

Equation 4

$$\frac{\text{Daily Dose (mL/day)} \times \text{91 Days}}{\text{100 mL}} = \#\text{Bottles to be Dispensed for 12 weeks dosing}$$

Example 7: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of 1.2 mL (from Example 5 above):

$$\frac{\text{Daily Dose (1.2 mL/day)} \times \text{91 Days}}{\text{100 mL}} = 1.09\ \text{Bottles}$$

The number of bottles dispensed is rounded up to the nearest whole integer, or 2 bottles to be dispensed.
Example 8: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of 10 mL (from Example 6 above):

$$\frac{\text{Daily Dose (10 mL/day)} \times \text{91 Days}}{\text{100 mL}} = \text{9.1 Bottles}$$

Revised Text:
Dose Calculation Worksheet

Vamorolone is administered once daily as a 4.0% oral suspension. The volume per dose is determined by the subject's dosing level and body weight (500mg if ♀≥ 50 kg OR 250mg if <50kg) at each study medication dispensing visit, as shown by *Equation 1*:

Equation 1

$$\frac{\text{Dose Level (mg)}}{\text{40 mg/mL}} = \text{Subject Dose (in mL)}$$

Subject weight (in kg) should be rounded to the nearest whole integer for the calculation of volume per dose.
Calculated dose volume will be rounded to the nearest 0.01 mL (1 mL syringe), 0.1 mL (3 mL syringe), 0.2 mL (5 mL syringe), or 0.2 mL (10 mL syringe) depending upon the total dose volume and calibration of the volumetric syringe to be used for administration of dose, as shown in the examples below:
Example 1: Dose volume calculation for a subject receiving 500 mg/day with a body weight ♀≥ 50kg:

$$\frac{\textit{Dose Level (500.0 mg)}}{\text{40 mg/mL}} = \textit{12.5 mL}$$

The subject will receive a daily dose volume of 12.5 mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a 10 mL volumetric syringe rounded to the nearest 0.2 mL daily.

Vamorolone 4.0% Suspension Dispensing Guide

Each subject enrolled in the study will be dispensed 100 ml bottle(s) of vamorolone 4.0% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Additional supplies will be dispensed at the Week 12 Visit, sufficient for dosing through the time of the scheduled Week 24 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4.0% suspension at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see Section 6.3.5).
The number of bottles to be dispensed at each dispensing visit for the following 12-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 1*) by 91 days (84 days in the dosing period + 7 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 2*, below:

$$\frac{\text{Daily Dose (mL/day)} \times \text{91 Days}}{\text{100 mL}} = \text{\#Bottles to be Dispensed for 12 weeks dosing}$$

Example 2: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of 12.5 mL (from Example 1 above):

$$\frac{\text{Daily Dose(12.5mL/day) x 91 Days}}{\text{100 mL}} = 11.40 \text{ Bottles}$$

The number of bottles dispensed is rounded up to the nearest whole integer, or 12 bottles to be dispensed.

15.2.2 Protocol Amendment #2 Complete List of Changes

The following changes have been incorporated into the protocol under this protocol amendment, as summarized in Protocol Amendment Tracking, Reasons for Protocol Amendment #2. Protocol sections that have been changed are itemized below with the original and revised text.

Original Text:
BMD
Revised Text:
Becker dystrophy

Section Changed:
STUDY SYNOPSIS - Secondary Objective
Original Text:
To evaluate the pharmcodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (miR146a, MDC and CK) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with BMD.
Revised Text:
To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.

STUDY SYNOPSIS - Study Design – paragraph #1
Original Text:
ambulatory subjects with BMD, ages 12 and <65.
Revised Text:
ambulatory subjects with Becker dystrophy, ages ≥18 and <65.

STUDY SYNOPSIS - Study Design – paragraph #5
Original Text:
All subjects who will not transition directly to further vamorolone treatment will begin a 4-week open-label Dose-tapering Period to taper study medication prior to discharge from the study.
Revised Text:
All subjects who will not transition directly to vamorolone treatment will begin a 4-week Dose-tapering Period to taper study medication prior to discharge from the study.

STUDY SYNOPSIS - Inclusion Criteria #1, 3-5
Original Text:
1. Subject or Subject's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements;
3. Subject is ≥ 12 years of age and <65 years of age at time of first dose of study drug;
4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) ≤ 30 sec; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32

Revised Text:
1. Subject has provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements.
3. Subject is ≥ 18 years of age and <65 years of age at time of first dose of study drug;

4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) in ≤ 30 sec at screening; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32 at screening.

STUDY SYNOPSIS - Exclusion Criteria #6, 3-5
Original Text:
6. Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents [Note: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 6 months cumulative, with last use at least 3 months prior to first dose of study medication, will be considered for eligibility on a case- by-case basis. Inhaled and/or topical corticosteroids prescribed for an indication other than BMD are permitted but must be administered at stable dose for at least 4 weeks prior to study drug administration and anticipated to be continued at a stable dose for the duration of the study];
8. Subject has used idebenone within 4 weeks prior to the first dose of study medication
Revised Text:
None

STUDY SYNOPSIS - Safety Measures
Original Text*:*
None
Revised Text:
CK

STUDY SYNOPSIS - Pharmacodynamic Measures
Original Text:
Blood will also be collected for serum PD biomarker analysis to evaluate effects of vamorolone on biomarkers of efficacy (miR146a, MDC and CK).
Revised Text:
Blood will also be collected for serum PD biomarker analysis to evaluate effects of vamorolone on biomarkers of efficacy (CD23 and MDC)

STUDY SYNOPSIS - Statistical Methods - Safety and Tolerability Analyses - Biomarkers Analyses
Original Text:
For the efficacy assessment, miR146a, MDC, and CK data will be used on the log scale and linear mixed effect models will be used and change from Day 1 presented.
Revised Text:
For the efficacy assessment, CD23 and MDC data will be used on the log scale and linear mixed effect models will be used and change from Day 1 presented.

1. INTRODUCTION- 1.1 Background and Unmet Need – paragraph#8
Original Text:
The study will test 2 hypotheses:
1. Vamorolone, will prove to be safe and tolerable in a first-in-Becker dystrophy treatment study.
2. Serum biomarkers of inflammation that have been identified as candidate biomarkers in Duchenne dystrophy research, creatine kinase (CK), macrophage derived chemokine (MDC) and micro RNA 146a (miR146a) will respond to treatment with vamorolone in patients with Becker dystrophy.

Revised Text:
The study will test 3 hypotheses:
1. Vamorolone, will prove to be safe and tolerable in a first-in-Becker dystrophy treatment study.

2. Vamorolone will demonstrate PK profile in Becker dystrophy similar to in Duchenne dystrophy and healthy controls
3. Serum biomarkers of inflammation that have been identified as candidate biomarkers in Duchenne dystrophy research, macrophage derived chemokine (MDC) and CD23, will respond to treatment with vamorolone in patients with Becker dystrophy.

1. INTRODUCTION- 1.2.1 Safety Pharmacology – paragraph #4

Original Text:

None

Revised Text:

Duchenne muscular dystrophy is associated with cardiomyopathy that can become life threatening, and increased fibrosis with prednisolone treatment in heart muscle of the *mdx* mouse has been reported (Sali et al., 2012) Histologically, definitive fibrosis was evident in 50% of young (8-week) prednisolone-treated mouse hearts compared to no incidence of fibrosis identified in the other groups (wild type; *mdx* vehicle, and vamorolone-treated).

1. INTRODUCTION- 1.2.2 Distribution and Metabolism

Original Text:

1.2.2 Distribution and Metabolism

1.2.2.1 Distribution

A quantitative whole-body autoradiography (QWBA) and mass balance study was conducted with [14C]-vamorolone in male Long Evans rats. The biodistribution of [14C]-vamorolone in rats was examined to determine sites of concentration that may contribute to its toxicological and pharmacokinetic characteristics. QWBA was assessed at 1 hour, 2-hour, 6-hour, 1-day, 5-day and 10-day time points. Internally, [14C]-vamorolone showed a widespread distribution among body organs with a peak absorption between 2-6 hours for most organs. Furthermore, the mass balance study in the rats showed 91% recovery of vamorolone by 1 day (81% feces), and 97% recovery of vamorolone by 7 days after a single dose administration (87% and 10% in feces and
urine, respectively). These results show that vamorolone is rapidly metabolized and excreted, with no evidence of retention or accumulation in specific organs (ReveraGen Report No. Metis Labs ML10100).

In plasma protein binding studies, percent bound was similar in human and mouse cells in culture (88.06% and 86.71%, respectively). In a blood partition experiment done ex vivo, the blood to plasma ratio was similar between human and mouse (0.87 and 0.68, respectively), but the red blood cell to plasma ratio for the mouse (0.33) was less than half that of the human (0.74). Human in vivo data are presented in Section 1.3 (VBP15-001). In a blood/brain concentration experiment performed in vivo in mice, the plasma concentrations of vamorolone were higher than brain concentrations with the area under the plasma concentration-time curve (AUC) and Cmax approximately 2-fold higher in plasma than in brain (ReveraGen Report Nos. ADME-NCG-PPB-NC135, ADME-VBP-PPB-V002, ADME-NCG-BP-NC134, NCATS 2013- 38).

1.2.2.2 Metabolism

The in vitro and in vivo data demonstrate that vamorolone can be metabolized via multiple metabolic pathways, including glucuronidation, hydroxylation, and reduction. Glucuronidation appears to be the major metabolic pathway in vitro in human cells. All metabolites observed in vitro in human were observed in vitro in monkey. Most human metabolites identified in vitro were also found in mouse and dog. Thus, there is no unique human metabolite identified for vamorolone.

The metabolic stability of vamorolone was assessed in non-Good Laboratory Practice (GLP) studies. Based on the data generated, vamorolone is highly stable for up to 60 minutes in human, monkey, dog, and mouse liver microsomes in the presence or absence of nicotinamide adenine dinucleotide phosphate

(NADPH) and stable for up to 60 minutes in rat liver in the absence of NADPH. Moderate metabolism was apparent in rat liver microsomes in the presence of NADPH stimulation (35% remaining), suggesting that rat is a high metabolizer of vamorolone relative to other species (mouse, dog, human) (ReveraGen Report Nos. NIH-R2526, and ADME-VBP-LM- V003).

Vamorolone was screened against a panel of recombinantly expressed Cytochrome P450 (CYP) enzymes to determine the CYP isoforms that contribute to metabolism of this drug. Studies using specific inhibitors of CYP enzymes and pooled human liver microsomes were also conducted to determine which isoform was most likely to be involved in metabolism and clearance of this drug in vivo. The following CYP isoforms were screened in this study: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5. CYP 3A4 and CYP3A5 were determined
to be the major isoforms involved in the metabolism of vamorolone, with minor contributions from CYP2C8 and possibly CYP2C9. The metabolite observed was consistent with hydroxylation. The potential of vamorolone to inhibit major CYP enzymes through time dependent inhibition (TDI) was assessed through half-maximal inhibitory concentration (IC50) shifts. There was no significant time dependent inhibition of any of the CYP isoforms tested (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5). The potential for vamorolone to induce CYP 1A2, 2B6, 2C8, 2C9, and 2C19, and 3A4 was also assessed. Induction of CYP1A2 and 2B6 by vamorolone was not observed over the concentration range 0.15 to 50 μM in hepatocytes of 3 donors. Induction was also not observed for CYP2C8, CYP2C9, or CYP2C19 over a vamorolone concentration range of 2-25 μM. Induction of CYP3A4 by vamorolone at concentration of 50 μM was observed in hepatocytes of 2 donors with mean-fold induction of >4.76 and >6.85, and the effect was dose-dependent (ReveraGen Report Nos. ADME-VBP- Inhibition-V005, ADME-VBP-Induction-V006, ADME-VBP-Induction-V009, ADME-VBP- 190730-CYP Phenotyping, NBAA-0002-DV-DA, ADME-VBP-161118-Induction, ADME-VBP-190730-CYP Phenotyping).

A panel of recombinantly expressed uridine 5'-diphospho-glucuronosyltransferases (UGTs) isoforms were also assessed for phase II metabolism of vamorolone. The following isoforms were included in this screen: 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15. No direct conjugation of vamorolone was observed following incubation with the UGT panel. However, there remains the potential of sequential phase II metabolism of a vamorolone metabolite by UGTs 1A3 and 2B7.

Additionally, inhibition assays of both UGTs and transporters (breast cancer resistance protein [BCRP], bile salt export pump [BSEP], multidrug and toxin extrusion 1 [MATE1], multidrug and toxin extrusion 2 [MATE2-K], permeable-glycoprotein [P-gp], organic anion transporter 1 [OAT1], organic anion transporter 3 [OAT3], organic cation transporter 2 [OCT2], organic and transporting polypeptide B1 [OATP1B1], and organic anion transporting polypeptide B3 [OATP1B3]) were performed. Vamorolone does not inhibit transporters at in vitro IC50 concentrations of 40 μM and higher with the exceptions of MATE2K (12.9 μM) and OAT3 (16.9 μM) (ReveraGen Report Nos. ADME-VBP-161118-BCRP Inhibition, ADME-VBP- 161118-BCRP Substrate, ADME-VBP-161118-SLC Inhibition, ADME-VBP-161118-SLC
Substrate, ADME-VBP-161118-UGT Inhibition, ADME-VBP-190730-BSEP Substrate, ADME- VBP-190730-SLC Inhibition, ADME-VBP-190730-SLC Substrate, ADME-VBP-190730-UGT Phenotyping.)

1.2.2.3 Excretion

The Sponsor conducted a second study entitled "Metabolite Profiling of [14C]VBP15 in Human Urine, Feces and Plasma" (n=6 healthy adults; single dose of 6 mg/kg). Plasma, whole blood, urine, and fecal samples were collected to measure total radioactivity (all samples), metabolic profiling (plasma, urine and feces only) for at least 96 hours post dose (Day 5).

Mean recovery in urine and feces by interval, along with total mass balance is shown in the following figure. Most of the total radioactivity associated with the oral suspension dose of [14C]-vamorolone was recovered in the urine by 48 hours postdose (48.2%) with a total recovered in urine mean of 56.7%. Most of the total radioactivity in feces was recovered by 96 hours post dose (27.9%) with a mean total recovered of 30.3% at discharge. Therefore 87.0% of the dose was recovered on average, with individual subjects' total recoveries ranging from 77.1% to 92.9%.

Plasma total radioactivity was generally quantifiable in most subjects for 168 hours postdose, and subjects began to meet discharge criteria or had levels below quantitation thereafter. Mean total radioactivity peaked at 8 hours postdose at a mean concentration of 9239 ng eq/mL. At
36 hours post dose, concentrations appeared to decline in a monophasic manner. Whole blood to plasma ratios of total radioactivity averaged approximately 0.52 to 0.57, indicating that vamorolone-related radioactivity is not distributed into red blood cells to an appreciable extent.
Twelve metabolites were observed in human urine, one (M1) which was not identified. The major metabolic pathway was glucuronidation, including direct glucuronidation (M5), hydrogenation in combination with glucuronidation (M2, M4, M6, M8, M9, and M10) and
oxidation with hydrogenation in combination with glucuronidation (M3). The minor metabolic pathways were oxidation (M11), oxidation with dehydrogenation (M7) and hydrogenation (M12).

The major component observed in feces was unchanged parent. The five late eluting radio peaks are not identified; these could be due to the binding of parent to endogenous materials.
Four glucuronide metabolites (M5, M6, M8 and M10) were observed at greater than 10% of drug related material in human plasma.

Revised Text:

1.2.2 Pharmacokinetics and Metabolism

1.2.2.1 Single Dose

Vamorolone PK profiles were determined in male CD-1 mice, Sprague Dawley rats and beagle dogs after a single intravenous injection of 10 mg/kg and after a single oral dose of 50 mg/kg in mice and rats and 30 mg/kg in dogs.

Pharmacokinetic results for vamorolone following a single intravenous administration of 10 mg/kg in Crl:CD1(ICR) mice demonstrated a clearance (CL) of 18.8 mL/min/kg. The terminal half-life (t½) was 0.35 hours. Volume of distribution at steady state (Vss) was 0.76 L/kg. Following oral administration of 50 mg/kg in mice, the maximum observed plasma concentration (Cmax) of 6787 ng/mL was observed at 2 hours (time to maximum observed plasma concentration [Tmax]) after drug administration, and percent bioavailability (F%) was 74.5%. Following oral administration of 15 mg/kg via cherry syrup, the Cmax of 1527 ng/mL was observed at 2 hours after drug administration and bioavailability was 47.7% (ReveraGen Report No. PH-DPMK-VBP-10-004).

Pharmacokinetic results for vamorolone following a single intravenous administration of 50 mg/kg in Sprague Dawley rats indicated a CL of 20.2 mL/min/kg. The t½ was 0.58 hours. Vss was 0.77 L/kg, which was similar to that observed in mice. After oral administration of 50 mg/kg in rats, a Cmax of 2543 ng/mL was observed at 4 hours after dose administration, and bioavailability was 47.8% (ReveraGen Report No. PH DPMK-VBP-10-007).
In beagle dogs, vamorolone had a CL of 24.7 mL/min/kg. The t½ was 5.42 hours and Vss was 1.93 L/kg. After oral administration of 30 mg/kg in dogs, a Cmax of 814 ng/mL was observed at 6 hours after dose administration and bioavailability was 53.2% (ReveraGen Report No. 48504-10-464).

Vamorolone clearance was therefore comparable in all 3 species studied (19 25 mL/min/kg). Bioavailability ranged from approximately 50% in mouse (cherry syrup), rat, and dog to 75% in the

mouse (30% Labrafil) (ReveraGen Report Nos. PH DPMK-VBP-10-004, PH DPMK-VBP-10-007, 48504-10-464).

1.2.2.2 Multiple Dose

Crl:CD1(ICR) mice were administered vamorolone or vehicle once daily (QD) for 28 consecutive days. Vamorolone exposure (as assessed by the Cmax and area under the plasma concentration-time curve from time 0 to the last observed measurable concentration [AUClast]) increased with increasing dose on Study Days 1 and 28. Repeated dosing of vamorolone over a 28 day duration was associated with decreases in mean vamorolone AUClast values in the 30 and 100 mg/kg dose groups compared to Day 1, indicating possible enzyme induction. On Study Day 28, mean AUClast values were 1.81-fold and 5.02 fold lower compared to Study Day 1 for the 30 and 100 mg/kg dose groups, respectively. The observed difference in exposure relative to Day 1 increased with the increase in administered dose of vamorolone (ReveraGen Report No. 1998-009).

Beagle dogs were either administered vamorolone or vehicle QD for 28 consecutive days. Vamorolone exposure in dogs (as assessed by Cmax and AUClast) generally increased with increasing dose on Study Days 1 and 28. For the 2 and 10 mg/kg dose groups, exposure on Day 28 was generally higher than on Day 1, indicating possible inhibition of metabolism of vamorolone at these dose levels. On Day 28, mean AUClast values were 2.35 fold and 2.43-fold (males) and 3.03-fold and 3.23-fold (females) higher compared to Study Day 1 for the 2 and 10 mg/kg/day dose groups, respectively. For the 50 mg/kg dose group, exposure on Day 28 was similar to that on Day 1. At the 50 mg/kg dose, AUClast values in males were 1.71-fold lower whereas females were 1.22 higher on Day 28 compared to Day 1 (ReveraGen Report No. 031302).

Beagle dogs were administered vehicle or vamorolone at doses of 2 mg/kg/day, 10 mg/kg/day, or 50 mg/kg/day for 39 weeks. Systemic exposure (area under the plasma concentration-time curve from time 0 to 24 hours [AUC0 24hr]) to vamorolone appeared to be independent of sex. Mean AUC0 24hr and Cmax values for vamorolone increased with increasing dose in an approximately dose proportional manner on Days 1 and 270. Mean systemic exposure (AUC0 24hr) to vamorolone appeared to increase following repeated administration of vamorolone. Due to the alterations in the feeding regimen, changes in systemic exposure following repeated administration should be viewed with caution due the influence of feeding on exposure. For the 2 and 10 mg/kg/day dose groups, exposure on Day 270 was generally higher than on Day 1, indicating possible inhibition of metabolism of vamorolone at these dose levels. On Day 270, mean AUC0 24hr values were 2.34 fold and 2.98-fold higher compared to Study Day 1 for the 2 and 10 mg/kg/day dose groups, respectively. For the 50 mg/kg dose group, exposure on Day 270 was 2.07 fold higher compared to that on Day 1 (ReveraGen Report No. 1998 014).
Non-naïve cynomolgus monkeys were administered vamorolone (300 and 600 mg/kg/day) or vehicle once daily for 7 consecutive days. Vamorolone exposure (as assessed by Cmax and AUClast) generally increased with increasing dose on Study Days 1 and 7 with the exception of male monkeys on Day 7, which showed no clear increase in exposure between the 300 and 600 mg/kg/day dose levels. Repeated dosing over the 7 day study duration was associated with decreases in mean plasma vamorolone AUClast values for female and male monkeys indicating possible metabolic induction. On Day 7, mean AUClast values were 1.60-fold, 2.19-fold, and 2.02-fold lower in females and 1.20 fold, 2.09 fold, and 2.88 fold lower in males compared to Study Day 1 for the 100, 300 and 600 mg/kg/day dose groups, respectively (ReveraGen Report Nos. 1998-001, SW11-0418).

1.2.2.3 Distribution

In the plasma protein binding studies, percent bound was similar in human and mouse cells in culture (88.06% and 86.71%, respectively). In the blood partition experiment done ex vivo, the blood to plasma ratio was similar between human and mouse (0.87 and 0.68, respectively), but the red blood cell to plasma ratio for the mouse (0.33) was less than half that of the human (0.74). Human in vivo data are presented in Section 1.3 (VBP15-001). In the blood/brain concentration mouse experiment in vivo, the

plasma concentrations of vamorolone were higher than brain concentrations with the area under the plasma concentration-time curve (AUC) and Cmax approximately 2-fold higher in plasma than in brain (ReveraGen Report Nos. ADME-NCG-PPB-NC135, ADME-VBP-PPB-V002, ADME-NCG-BP-NC134, NCATS 2013-38).

1.2.2.4 Metabolism

The in vitro and in vivo data demonstrate that vamorolone can be metabolized via multiple metabolic pathways, including glucuronidation, hydroxylation, and reduction. Glucuronidation appeared to be the major metabolic pathway in human cells in vitro. All metabolites observed in human in vitro were observed in monkey in vitro. Most human metabolites identified in vitro were also found in mouse and dog. Thus, there is no unique human metabolite identified for vamorolone.

The metabolic stability of vamorolone was assessed in non-Good Laboratory Practice (GLP) studies. Based on the data generated, vamorolone was highly stable for up to 60 minutes in human, monkey, dog, and mouse liver microsomes in the presence or absence of nicotinamide adenine dinucleotide phosphate (NADPH) and stable for up to 60 minutes in rat liver in the absence of NADPH. Moderate metabolism was apparent in rat liver microsomes in the presence of NADPH stimulation (35% remaining), suggesting that rat was a high metabolizer of vamorolone relative to other species (mouse, dog, human) (ReveraGen Report Nos. NIH-R2526, and ADME-VBP-LM-V003).

Vamorolone did not significantly inhibit any of the cytochrome P450 (CYP) enzyme isoforms tested (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). Vamorolone moderately induced CYP3A4 (24% to 42%), indicating that vamorolone is a potential inducer of CYP3A4 (ReveraGen Report Nos. ADME-VBP-Inhibition-V005, ADME-VBP-Induction-V006, ADME-VBP-Induction-V009).

1.2.2.5 Excretion

Vamorolone showed high plasma clearance in rats but, consistent with the extensive metabolism in hepatocytes from this species, the biliary and urinary excretion of the parent compound was low with an average of <0.05% of the dose recovered in bile and approximately 0.1% in urine. Overall, vamorolone showed high plasma clearance and extremely low biliary and urinary excretion (ReveraGen Report No. NCATS 2013-44).

1. INTRODUCTION- 1.2.3 Toxicology

***Original Text**:*

Vamorolone has been evaluated in a comprehensive series of toxicology studies in laboratory animals and in vitro test systems. The repeated-dose toxicology studies include three GLP studies in mice (a 4-week oral toxicity study with a 2-week recovery period in adult mice, a
26-week oral toxicity study with a 4-week recovery period in adult mice, and a 10-week toxicity study with a 4-week recovery period in juvenile mice), two GLP studies in dogs (a 4-week oral toxicity and toxicokinetics study with a 2-week recovery period and a 39-week oral toxicity study with a 4-week recovery period) and an exploratory study in cynomolgus monkeys (1-week oral toxicity study with a 1-week recovery period).

1.2.3.1 Nonclinical Toxicology: Summary of Major Findings in the Mouse and Dog Chronic Toxicology Studies and Juvenile Mouse Toxicity Study

1.2.3.1.1 Mouse Chronic Toxicity Study

In the 26-week mouse GLP-compliant toxicity study with a 4-week recovery period, vamorolone was evaluated at oral daily doses of 0, 5, 15, and 45 mg/kg/day. A vamorolone-related increase in body weight gain was observed relative to controls in males (+14%) and females (+23%) at 45 mg/kg/day, which correlated with an increase (+5%) in food consumption in both sexes at that dose level. During the recovery phase, mean body weights in males returned to comparable levels with controls, as well as

females at 5 and 15 mg/kg/day; however mean body weights for 45 mg/kg/day females were +25% compared to female controls.

Evidence of minimal to mild vamorolone-related hepatic effects were observed in males at ≥ 5 mg/kg/day and females at 45 mg/kg/day, indicated by mild to moderate increases in ALP, ALT, AST, and/or total bilirubin, as related to microscopic hepatocellular vacuolation, inflammation, and/or necrosis in males at ≥ 15 mg/kg/day and females at 45 mg/kg/day. These changes had generally resolved at recovery collections with the exception of minimal increases in ALT in females at 45 mg/kg/day, which may have correlated to microscopic liver pathology. A mild vamorolone-related increase in neutrophil counts was observed in both sexes at 45 mg/kg/day with concurrent decreases in lymphocyte counts in females at 45 mg/kg/day, consistent with a glucocorticoid-like effect, as related to microscopic lymphoid depletion; these changes had generally resolved at recovery collections. Vamorolone-related microscopic findings occurred in the adrenal gland (cortical atrophy- with correlating decreases in adrenal weights in females), liver (increased severity of centrilobular hypertrophy; hepatocyte vacuolation; and inflammation/ necrosis), lymphoid tissues (thymus, spleen, mandibular lymph node, mesenteric lymph node, and GALT) skin, and pancreatic islets (minimal to mild hypertrophy). Observed changes in these tissues are considered pharmacologically-mediated and not adverse. There was full reversibility of lymphoid changes in thymus, spleen, mesenteric lymph node, mandibular lymph node, and gut-associated lymphoid tissue (GALT). There were no meaningful differences between vamorolone-treated and control mice at the end of the recovery for these lymphoid tissues. There was recovery from the adrenal gland findings in females and partial recovery from the adrenal gland findings in males. In addition, there was partial reversibility of liver findings for males and females.

The conclusion from the study was that vamorolone at all doses tested in mice did not produce any adverse effects. The NOAEL was considered to be 45 mg/kg/day (ReveraGen Report No. 1998-013).

1.2.3.1.2 Dog Chronic Toxicity Study

In the 39-week dog GLP-compliant toxicity study with a 4-week recovery period, vamorolone was evaluated at oral daily doses of 0, 2, 10, and 50 mg/kg/day. Vamorolone-related, dose- dependent increases in body weight gains were observed relative to controls in males at all dose levels (+5 to +46%) and in females at 10 and 50 mg/kg/day (+10% to +21%). These increases in body weights correlated with increases in food consumption.

There was a hepatocellular and hepatobiliary effect in males at 10 mg/kg/day and both sexes at 50 mg/kg/day, which included increased ALP, GGT, ALT and AST. These changes correlated with microscopic changes in the liver, bile duct and gall bladder. This spectrum of changes was considered adverse in both sexes at 50 mg/kg/day. There was also evidence of an inflammatory response in both sexes at 50 mg/kg/day, which included increased total leukocyte, neutrophil and monocyte counts, increased fibrinogen and/or globulin concentrations, and increased platelet counts. Following a 4-week recovery period, all previously noted changes resolved, except for increases in platelet counts which persisted in one male and one female at 50 mg/kg/day; increased ALT which persisted in both sexes at 50 mg/kg/day, and increased globulin which persisted in males at 50 mg/kg/day. Reversible vamorolone-related macroscopic findings included mildly to moderately enlarged livers in males and females at 50 mg/kg/day.

Microscopic evaluation included the following vamorolone-related changes: adrenal glands (atrophy of the zona fasciculata and zona reticularis and hypertrophy/hyperplasia of the zona glomerulosa in both sexes at ≥ 10 mg/kg/day; the atrophy was considered adverse); liver (hepatocellular vacuolation in males at ≥ 10 mg/kg/day and females at ≥ 2 mg/kg/day, panlobular hypertrophy in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day, and inflammation/necrosis in both sexes at 50 mg/kg/day, considered adverse); kidneys (bilateral tubular vacuolation in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day and an increased incidence of bilateral basophilic tubules in males and females at 50 mg/kg/day);

lymphoid depletion in both sexes at 50 mg/kg/day in mandibular and mesenteric lymph nodes, thymus and spleen (with extramedullary hematopoiesis in 50 mg/kg/day females); testes (spermatocyte/spermatid degeneration in males at 50 mg/kg/day); epididymides (oligospermia/germ cell debris in males at 50 mg/kg/day); and ovaries (absent corpora lutea in females at ≥ 2 mg/kg/day and considered adverse). Many of the findings are likely consistent with the pharmacology of vamorolone.
The conclusion from the study was that many of the adverse changes seen in dogs at all dose levels of vamorolone (2, 10, and 50 mg/kg/day) were consistent with expected and exaggerated pharmacology. In males, the NOAEL was considered to be 2 mg/kg/day; a NOAEL was not established in females (ReveraGen Report No. 1998-014).

1.2.3.1.3 Juvenile Mouse Toxicity Study

In the 10-week juvenile mouse GLP-compliant toxicity study with a 29-day recovery period, vamorolone was evaluated at oral doses of 0, 15, 30, and 100 mg/kg/day starting at Postnatal Day (PND) 21. The study included the standard battery of toxicology assessments along with
study phases assessing reproductive, immunological, neurobehavioral and neurohistopathological endpoints.

Systemic exposure to vamorolone appeared to be independent of sex. Following daily oral administration of vamorolone, Cmax values increased with increasing dose in an approximately dose proportional manner on Day 1 and in a less than dose proportional manner on Day 70.
Following daily oral administration of vamorolone, AUC values increased with increasing dose in a greater than dose proportional manner on Day 1 and in a less than dose proportional manner on Day 70. Systemic exposure to vamorolone did not appear to change following repeated administration of 15 mg/kg/day, however, systemic exposure appeared to decrease following repeated administration at 30 and 100 mg/kg/day.

Vamorolone-related decreases in mean body weights were observed in males at ≥ 30 mg/kg/day and females at ≥ 15 mg/kg/day, but these were not considered adverse as these animals continued to gain weight throughout the treatment period, albeit at a slower rate relative to concurrent controls.
Vamorolone-related microscopic findings at the end of the 10-week terminal interval (Day 71) were limited to the liver of males at ≥ 30 mg/kg/day and females at ≥ 100 mg/kg/day, the adrenal glands of males and females at ≥ 15 mg/kg/day, the spleen and mandibular lymph nodes of males and of females at ≥ 15 mg/kg/day, the GALT of males at ≥ 15 mg/kg/day and a single female at 100 mg/kg/day, the thymus of males and females at ≥ 15 mg/kg/day, and the salivary gland in females at ≥ 15 mg/kg/day. Findings in the liver were limited to hepatocellular degeneration/necrosis in the liver of males at ≥ 30 mg/kg/day and females at 100 mg/kg/day, hepatocellular vacuolation in the liver of males and females at ≥ 15 mg/kg/day, hepatocellular hypertrophy in males at ≥ 15 mg/kg/day and females at ≥ 30 mg/kg/day. Adverse vamorolone- related findings were limited to the degeneration/necrosis noted in the liver that was of increased incidence and/or severity in males at ≥ 30 mg/kg/day and females at 100 mg/kg/day. Cortical atrophy was noted within the adrenal glands of males and females at ≥15 mg/kg/day. Decreased lymphocytes were noted in the spleen and mandibular lymph nodes of males and of females at ≥ 15 mg/kg/day, the GALT of males at ≥ 15 mg/kg/day and a single female at 100 mg/kg/day, and thymus of males and females at ≥ 15 mg/kg/day. Minimal to moderate reversible increases were observed in mean ALT activities in males at ≥ 15 mg/kg/day and females at 100 mg/kg/day with concurrent mild to moderate increases in mean AST activities and minimal increases in mean total bilirubin concentrations in females at 100 mg/kg/day; males at ≥ 30 mg/kg/day also
had minimal to mild increases in mean ALP activities. These changes were considered indicative of hepatocellular and/or hepatobiliary effects, as related to microscopic hepatocellular findings including degeneration/necrosis, vacuolation, and/or hypertrophy.

No effect of vamorolone was observed from neurobehavioral testing (motor activity, auditory startle habituation or Morris water swim maze) or neurohistopathological evaluations.
In the reproductive phase, no vamorolone-related mortality was observed, and no significant effect of vamorolone was observed from clinical observations, food consumption, sexual maturation, first day of estrous, estrous cyclicity, reproductive and fertility indices, uterine examinations, sperm evaluations, macroscopic observation or organ weights.

Thus, in this 10-week mice toxicity study with vamorolone administered orally once daily and treatment starting on PND 21, the NOAEL in females was 30 mg/kg/day based on microscopic observation of degeneration/necrosis in the liver at 100 mg/kg/day, with increases in mean ALT, increases in mean AST, and increases in mean total bilirubin concentrations. In males, the NOAEL was 15 mg/kg/day based on degeneration/necrosis in the liver at ≥ 30 mg/kg/day, including increases in mean ALT, increases in mean AST (100 mg/kg/day males only), increases in mean total bilirubin concentrations (100 mg/kg/day males only), and increases in mean ALP (ReveraGen Report No. 1998-020).

1.2.3.2 Genotoxicity
The mutagenic and genotoxic potential of vamorolone was assessed in several assays. A non- GLP Ames screen was negative for bacterial mutations (ReveraGen Report No. BIO-VBP-001- AMES). In a GLP Ames test, no background lawn toxicity was observed; however, a reduction in revertant counts was observed (ReveraGen Report No. AD79DT.502ICH.BTL). Vamorolone was negative for inducing chromosomal aberrations in cultured mouse lymphocytes without and with metabolic activation (ReveraGen Report No. AD79DT.704.BTL).

Femoral bone marrow was microscopically evaluated for the presence of polychromatic erythrocytes (PCEs) containing micronuclei. No significant reductions in the PCEs/EC (total erythrocytes) ratio were observed in the vamorolone groups compared to the vehicle control group. Although statistically significant increases in the incidence of micronucleated PCEs in the vamorolone treated groups were observed, no dose response was observed with respect to
other groups and the values of micronuclei for the individual animals were within the historical range. Therefore, the statistically significant increase was considered as biologically insignificant (ReveraGen Report No. AD76BK.123012ICH.BTL).

A study was performed to evaluate the potential mutagenicity of two theoretical epoxide impurities related to the drug substance vamorolone (formerly VBP15), which is a steroid-like structure containing a delta 9,11 double bond. The delta 9,11 epoxide structures evaluated were VBP15-B-3, which is structurally similar to vamorolone except for the epoxide moiety, and VBP15-B-2, which has a 21-acetate substitution (vamorolone and VBP15-B-3 contain a 21- hydroxy moiety). Two validated and complementary in silico prediction methodologies were used for assessing mutagenic potential. The statistics-based quantitative structure-activity relationship (QSAR) program MultiCASE CASE Ultra was used, employing four different modules (GT1_A7B, GT1_AT_ECOLI, PHARM_ECOLI, and PHARM_SAL) designed to cover a wide range of molecular substructures collected from both proprietary and public compounds. In addition, the expert rule-based SAR program Derek Nexus was used to determine if the theoretical impurities contained structural alerts associated with known genotoxicants. CASE Ultra predicted both VBP15-B-2 and VBP15-B-3 as negative for mutagenicity (ReveraGen Report “In Silico Mutagenicity Evaluation of Delta 9,11 Epoxide Structures of VBP15: VBP15-B-2 [21-Acetate] and VBP15-B-3 [21-Hydroxy]”). Taken together, these data indicate vamorolone is negative for any mutagenic signal.
***Revised Text**:*
1.2.3.1 Single Dose
Crl:CD1(ICR) mice were administered vamorolone once via oral gavage at 50, 125, 250, and 500 mg/kg and observed for abnormalities. All animals survived to their scheduled termination, and there were no

significant abnormalities observed. However, a slight decrease in body weight related to vamorolone was observed in males and females at doses above 125 mg/kg. A dose dependent decrease in food consumption related to vamorolone was also observed in males and females. There were no other clinical observations (ReveraGen Report No. 1998-002).
Beagle dogs received single 60, 180, 360, and 750 mg/kg doses of vamorolone using an escalation study design with a 4 day washout period between doses. All animals survived dose escalation. Clinical signs attributed to vamorolone (750 mg/kg) included red discoloration of the ears and face. This effect occurred within a few hours of dosing and was transient. The highest dose also resulted in increased white blood cell count (increased neutrophils and monocytes [female only] and decreased lymphocytes and eosinophils [male and female]). At the 360 and 750 mg/kg dose levels, slight elevations in albumin were observed. A mild elevation in cholesterol at the 750 mg/kg (and possibly 360 mg/kg) dose level was also observed (ReveraGen Report No. 13788.01.01).

In cynomolgus monkeys, single oral doses of up to 500 mg/kg were well tolerated with no significant clinical observations (ReveraGen Report No. 1998-001).

1.2.3.2 Multiple Dose

Acute Toxicity Studies

Vamorolone or vehicle was administered to Crl:CD1(ICR) mice QD for 28 consecutive days at doses of 10, 30 and 100 mg/kg/day. All animals survived to their scheduled necropsy with the exception of a female mouse (100 mg/kg/day dose group) that was found dead on Day 16. The cause of death was considered incidental and attributed to a dosing injury based on the amount of red fluid in the thoracic cavity.

No effects attributable to vamorolone were observed on clinical observations, food consumption, ophthalmic examination, or urinalysis during the study. A dose dependent decrease in body weight gain was observed at all doses; however, weight was fully regained during the recovery period. Adrenal gland weights were variable between groups and generally decreased, but without a dose response relationship, and correlated microscopically with minimal to moderate vacuolar degeneration and cortical atrophy. After the 2-week recovery period there was evidence of vacuolar degeneration. Liver weights were significantly increased at the 100 mg/kg/day dose level. Hepatocellular hypertrophy, increased vacuolation, and necrosis (single cell) were seen in a few male mice at 30 mg/kg/day. There was evidence of lipid and glycogen accumulation. Serum alanine aminotransferase and aspartate aminotransferase levels were higher with associated microscopic hypertrophy/vacuolation/necrosis at 100 mg/kg/day. Spleen weights decreased in a dose-dependent manner and correlated with a decreased number of lymphocytes in spleen. Thymus weights decreased in a dose dependent manner and were associated microscopically with lymphoid atrophy. Mice had dose dependent reductions in serum lymphocytes which were significant in the 100 mg/kg dose group. After the recovery period, all parameters returned to normal (untreated) except for thymus weights, which were increased.

Based on the liver-related findings in this study, the no observed adverse effect level (NOAEL) for vamorolone in mice is 30 mg/kg/day (ReveraGen Report No. 1998-009).

Vamorolone or vehicle was administered to beagle dogs QD for 28 consecutive days at doses of 2, 10 and 50 mg/kg/day. All animals survived to their scheduled termination and no effect of vamorolone was noted on body weight, body temperature, food consumption, ophthalmology, electrocardiography, macroscopic, or urinalysis parameters at necropsy. A dose-dependent decrease in body weight gain was observed at all doses but weights generally returned to normal during the recovery period.

Adrenal gland weights decreased which correlated with mild or moderate diffuse bilateral atrophy of the adrenal cortex, mild multifocal bilateral vacuolation of the adrenal cortex, increased white blood cell and

neutrophil counts, and decreased eosinophil counts. Liver weights increased in the 50 mg/kg/day dose group, which correlated with diffuse hypertrophy and vacuolation and increased levels of alkaline phosphatase and gamma glutamyltransferase. Spleen weights decreased, which correlated with lymphoid depletion. Thymus weights decreased, which corresponded to diffuse lymphoid depletion. With the exception of diffuse depletion of lymphocytes in thymus in the 50 mg/kg group, all abnormal parameters returned to normal during the recovery period.

The NOAEL was considered by the study director to be 10 mg/kg/day. Although reversible, the liver changes were considered adverse at 50 mg/kg/day because the severity score was moderate and the changes were diffuse in nature in all animals treated at the high dose. This is in contrast to the conclusion drawn by the study pathologist, who considered the NOAEL to be 50 mg/kg/day due to reversibility following cessation of dosing (ReveraGen Report No. 31302).
Non-naive cynomolgus monkeys were administered vamorolone or vehicle QD for 7 consecutive days at doses of 100, 300, and 600 mg/kg. All animals survived until the end of the study period. There were effects on clinical observations, food consumption, and urinalysis attributable to vamorolone.

There was a dose proportional decrease in body weight gain observed in males and females at each dose (up to 11% and 9% respectively) related to vamorolone. A cessation of the body weight loss in treatment was observed during the recovery phase but no recovery of body weight lost during the 7 days of dosing was observed.

At termination there were non-significant increases in red cell mass and decreases in lymphocytes (up to 56%) in the 600 mg/kg/day dose group. However, most individual animals, including controls, had decreases in lymphocytes (up to 81%) at termination relative to their respective pretest. They had resolved by the recovery interval in both sexes.
In both sexes receiving ≥ 300 mg/kg/day, there was increased urea nitrogen (up to 141%), creatinine (up to 58%), total protein (up to 15%), albumin (up to 11%), globulin (up to 25%), and/or potassium (up to 39%) with concurrent decreases in sodium (up to 10%) and chloride (up to 10%) relative to controls. At the recovery interval, the majority of these effects had resolved (ReveraGen Report No. 1998-001).

Chronic toxicity studies
26-week chronic toxicity study in mice
A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4 week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article.

There were no vamorolone-related effects on mortality, detailed clinical observations, food consumption, ophthalmology, sperm evaluations, or bone lengths (femur or tibia).
Five test article-treated mice were unscheduled deaths (euthanized in extremis or found dead) during the dosing phase. Three of these were considered to be potentially due to dosing injury based on microscopic findings in mediastinum, epicardium, or lung. One of these unscheduled deaths was attributed to moderate progressive nephropathy; a spontaneous background finding. The death of one male at 5 mg/kg/day was undetermined since there were no major pathologic findings to explain the unscheduled death of this animal; there was no target organ toxicity in the mouse. Target organ toxicity was not considered a contributor to the death of these animals and there was no dose-relationship in incidence.

A vamorolone related increase in body weight gain was observed relative to controls in males (+14%) and females (+23%) at 45 mg/kg/day. Increases in body weights at 45 mg/kg/day were not considered to be adverse due to the general health of the animals overall. During the recovery phase, bodyweights in

males returned to comparable levels with controls, however female body weights remained increased compared to female controls.
Evidence of a minimal to mild vamorolone-related hepatic effects were observed in males at ≥ 5 mg/kg/day and females at 45 mg/kg/day, indicated by mild to moderate increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase activities, and/or total bilirubin, as related to microscopic hepatocellular vacuolation, inflammation, and/or necrosis in males at ≥ 15 mg/kg/day and females at 45 mg/kg/day; these changes had generally resolved at recovery collections with the exception of minimal increases in alanine aminotransferase activity in females at 45 mg/kg/day, which may have correlated to microscopic liver pathology.
A mild vamorolone-related increase in neutrophil counts was observed in both sexes at 45 mg/kg/day with concurrent decreases in lymphocyte counts in females at 45 mg/kg/day consistent with a glucocorticoid-like effect, as related to microscopic lymphoid depletion, although an inflammatory stimulus may have contributed to increases in neutrophil counts, as related to microscopic liver inflammation; these changes had generally resolved at recovery collections.

A mild vamorolone-related decrease in chloride was observed in males at ≥ 5 mg/kg/day and females at ≥ 15 mg/kg/day that lacked correlative findings among other study endpoints; resolution for this endpoint could not be determined.

A mild vamorolone-related increase in albumin was observed in males at ≥ 5 mg/kg/day and females at 45 mg/kg/day with concurrent mild increases in globulin in females at 45 mg/kg/day; these changes had resolved at recovery collections.

A minor vamorolone-related alteration in lipid metabolism was observed in both sexes at 45 mg/kg/day and females at 15 mg/kg/day indicated by increases in triglyceride and/or cholesterol; these changes had resolved at recovery collections.

Vamorolone-related macroscopic findings occurred in the liver of mice at 45 mg/kg/day. Tan discoloration occurred in one female and four males at this dose in the dosing phase. This correlated with microvesicular/macrovesicular hepatocyte vacuolation. There were no test article-related macroscopic findings in recovery animals.

Test article-related microscopic findings occurred in adrenal gland (cortical atrophy- with correlating decreases in adrenal weights in females), liver (increased severity of centrilobular hypertrophy; hepatocyte vacuolation; hepatocyte vacuolation; and inflammation/necrosis), lymphoid tissues (thymus, spleen, mandibular lymph node, mesenteric lymph node, and gut-associated lymphoid tissue [GALT]) skin, and pancreatic islets (minimal to mild hypertrophy). Observed changes in these tissues are considered pharmacologically-mediated and not adverse.
An increased incidence of decreased anagen hair follicles occurred in mice at 45 mg/kg/day. Decreased anagen hair follicles was documented for individual animals when there were no anagen hair follicles in the section of skin. Incidence in controls and mice at 5 and 15 mg/kg/day were similar. A severity score was not given to the decrease as this may have been somewhat dependent on size of skin sample. This change is not considered adverse.

There was full reversibility of lymphoid changes in thymus, spleen, mesenteric lymph node, mandibular lymph node, and GALT. There were no meaningful differences between treated and controls at the end of the recovery tissues for these lymphoid tissues. There was recovery of adrenal gland findings in females and partial recovery of adrenal gland findings in males. In addition, there was partial reversibility of liver findings for males and females. Minor changes persisted in the pancreas and skin.

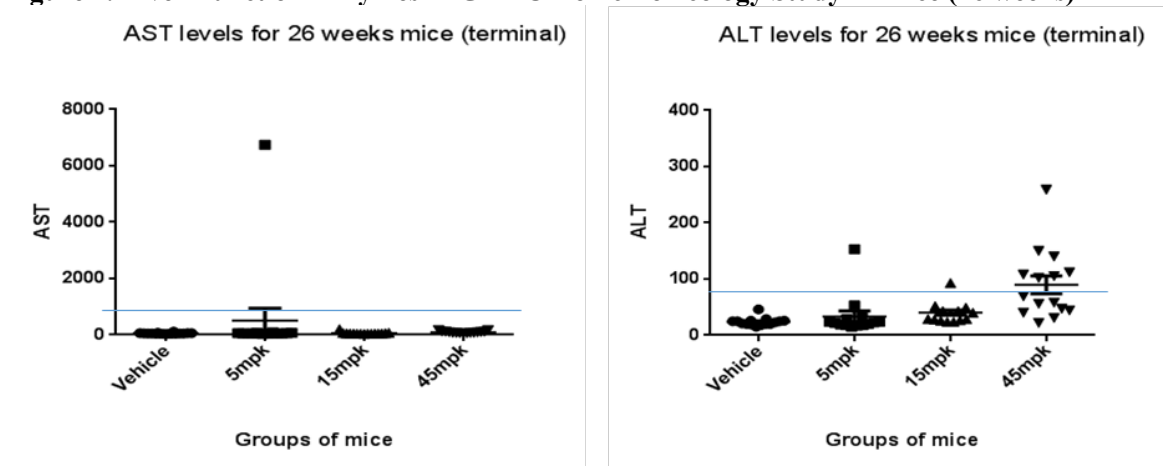
Systemic exposure to vamorolone appeared to be sex-dependent on Day 1 (males > females) and appeared to be independent of sex on Day 179. Following daily administration of vamorolone in females and males, systemic exposure (AUC0-24hr) and Cmax values of vamorolone increased with increasing dose in a greater than dose proportional manner on Day 1 and in an approximately dose proportional manner on Day 179. Systemic exposure to vamorolone in females appeared to increase following repeated administration of vamorolone at 5 mg/kg, did not appear to change following repeated administration of vamorolone at 15 mg/kg, and appeared to decrease following repeated administration of vamorolone at 45 mg/kg. Systemic exposure to vamorolone in males appeared to decrease following repeated administration of vamorolone (Table 1).

Table 1. AUC0-24hr in Mice after 179 Days Treatment with 3 Dose Levels (5, 15 and 45 mg/kg/day)

Average $AUC_{0\text{-}24hr}$ (hr*ng/mL)				
Dose (mg/kg/day)	Male		Female	
	Day 1	Day 179	Day 1	Day 179
5	5700	1150	159	991
15	11600	3710	3450	4240
45	50700	10200	27000	12700

The once daily administration of vamorolone via oral gavage to mice for 26 weeks at 5, 15, and 45 mg/kg/day did not produce any adverse effects. Therefore, the No-Observable-Adverse-Effect Level (NOAEL) is considered to be 45 mg/kg/day under the conditions of this study.
As liver is considered a primary target organ, the liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) of mice in this study were studied at study termination (Figure 1).

Figure 1. Liver Function Enzymes in GLP Chronic Toxicology Study in Mice (26 weeks)



There were no differences between male and female mice regarding liver function enzymes. There were no drug-related elevations of AST at any dose. The highest dose tested (45 mg/kg/day) showed mild elevations of ALT with about half of values above the upper limit of normal range. The mild elevations of ALT were reversible, returning to within normal range after cessation of drug.

The Study Director concluded that the once daily administration of vamorolone via oral gavage to mice for 26 weeks at 5, 15, and 45 mg/kg/day did not produce any adverse effects. Therefore, the No Observable-Adverse-Effect Level (NOAEL) is considered to be 45 mg/kg/day under the conditions of this study.

39-week chronic toxicity study in beagle dogs

Vamorolone or vehicle was administered to beagle dogs once daily for 39 weeks at doses of 2, 10 and 50 mg/kg/day. Six dogs of each sex received each dose or placebo, and two of the six dogs of each sex at each dose or placebo were followed for an additional 4 weeks to evaluate reversibility, progression, or delayed appearance of any observed changes. One male dog that received 50 mg/kg/day was euthanized in extremis on Day 273 due to paraphimosis (an extended penis). All other animals survived to their scheduled termination.

Detailed clinical observations considered test article related at 50 mg/kg/day, and reversible, included decreased activity (considered adverse), struggling during dosing, feces soft, limb function impaired, interdigital cysts, and unkempt appearance (considered adverse). Test article related, dose-dependent increases in body weight gains correlating with increases in food consumption were observed relative to controls in males at all dose levels and in females at 10 and 50 mg/kg/day. Test article-related, reversible increases in average mean food consumption were observed relative to controls over the course of the 39-week dose phase in both sexes at 10 and 50 mg/kg/day.

No test article-related ophthalmological effects were noted. No test-article-related changes were noted in respiratory rates or rectal temperatures. There may have been a mild dose-related reversible increase in the heart rate at the terminal post-dose interval that was significantly different from vehicle in both sexes following the 50 mg/kg/day dose. Semen analysis/evaluation for test article affects could not be conducted as there were not enough viable samples collected.
Test article-related effects on clinical pathology endpoints with microscopic correlates included the following:

- A hepatocellular and hepatobiliary effect in males at 10 mg/kg/day and both sexes at 50 mg/kg/day, which included increased alkaline phosphatase, gamma glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase activity. These changes correlated with microscopic changes in the liver, bile duct, and gall bladder. This spectrum of changes was considered adverse in both sexes at 50 mg/kg/day.
- There was also evidence of an inflammatory response in both sexes at 50 mg/kg/day, which included increased total leukocyte, neutrophil, and monocyte counts, and increased fibrinogen and/or globulin concentrations. The inflammatory response was likely secondary to inflammation in the liver associated with hepatocellular necrosis. Platelet counts were also increased in both sexes at 50 mg/kg/day and may have been secondary to the inflammatory response.

Following a 4-week recovery period, all noted clinical pathological changes resolved, with the exceptions of increased alanine aminotransferase activity in both sexes at 50 mg/kg/day, and increased globulin in males at 50 mg/kg/day.

Reversible, test article-related macroscopic findings included mildly to moderately enlarged livers in males and females at 50 mg/kg/day, which correlated microscopically with panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation; hemorrhage in the gall bladder of one 50 mg/kg/day female, that was associated with moderate acute inflammation and mild vascular necrosis, and considered to be adverse; red focus/foci within the pylorus of the stomach of one 50 mg/kg/day female and one male at 10 mg/kg/day, which correlated microscopically with mild acute inflammation in the female.

Test article-related organ weight changes at the terminal necropsy included decreases in adrenal gland weights in both sexes at ≥ 2 mg/kg/day (microscopic correlate of bilateral cortical atrophy); increases in liver weights in both sexes at ≥ 10 mg/kg/day (microscopic correlates of panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation); increases in kidney weights in females at ≥ 10 mg/kg/day and males at 50 mg/kg/day (microscopic correlate of bilateral tubular vacuolation); decreases in prostate gland weights in males at 50 mg/kg/day (microscopic correlate of decreased secretory product). These organ weight changes were all reversible, except for the decreases in the prostate gland. Microscopic evaluation revealed the following test article-related changes: adrenal glands (atrophy of the zona

fasciculata and zona reticularis and hypertrophy/hyperplasia of the zona glomerulosa in both sexes at ≥ 10 mg/kg/day and atrophy was considered adverse); esophagus and pylorus of the stomach (erosion/ulceration in a few animals of both sexes at 50 mg/kg/day); gallbladder (hypertrophy/hyperplasia of the mucosal epithelium in both sexes at ≥ 10 mg/kg/day and cytoplasmic vacuolation of the mucosal epithelium in males at ≥ 10 mg/kg/day and females at ≥ 2 mg/kg/day); liver (hepatocellular vacuolation in males at ≥ 10 mg/kg/day and females at ≥ 2 mg/kg/day, panlobular hypertrophy in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day, and inflammation/necrosis in both sexes at 50 mg/kg/day and considered adverse, bile duct hyperplasia in both sexes at 50 mg/kg/day, bile duct hypertrophy in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day, and cytoplasmic vacuolation of the bile duct epithelium in both sexes at ≥ 10 mg/kg/day); kidneys (bilateral tubular vacuolation in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day and an increased incidence of bilateral basophilic tubules in males and females at 50 mg/kg/day); lymphoid depletion in both sexes at 50 mg/kg/day in mandibular and mesenteric lymph nodes, thymus and spleen (with extramedullary hematopoiesis in 50 mg/kg/day females); bone marrow in the sternum (increased adipocytes in males at ≥ 2 mg/kg/day and females at 50 mg/kg/day); testes (spermatocyte/spermatid degeneration in males at 50 mg/kg/day); epididymides (oligospermia/germ cell debris in males at 50 mg/kg/day); ovaries (absent corpora lutea in females at ≥ 2 mg/kg/day and considered adverse); the mammary gland and other tissues in the female reproductive tract (uterus, cervix, and vagina) of these animals were consistent with animals that have not ovulated; vacuolation in the epithelium of the mammary gland duct in females at 50 mg/kg/day; parotid salivary gland (cytoplasmic alteration in both sexes at ≥ 10 mg/kg/day); biceps femoris (atrophy of the skeletal muscle in both sexes at 50 mg/kg/day); skin (atrophy and alopecia/hypotrichosis in males at 50 mg/kg/day and females at ≥ 10 mg/kg/day); prostate gland (decreased secretory product in males at 50 mg/kg/day); thyroid glands (bilateral increased colloid in males at ≥ 10 mg/kg/day).
Many of the findings were considered by the Study Director to be consistent with the pharmacology of the test article including cortical atrophy of the adrenal glands (affecting the zona fasciculata and reticularis), generalized lymphoid depletion in lymphoid tissues (thymus, spleen, and lymph nodes), increased adipocytes in the bone marrow, atrophy of the skeletal muscle, alopecia/hypotrichosis and atrophy of the skin (thinning of the dermal collagen and atrophy of hair follicles and adnexa), an absence of corpora lutea in the ovary (likely indicative of delayed puberty), decreased secretory product in the prostate gland, and multiple changes in the liver. The liver had panlobular hypertrophy and vacuolation of hepatocytes consistent with glycogen accumulation. Due to the magnitude of hypertrophy and vacuolation, there were (likely secondary) foci of hepatocellular necrosis and inflammation.

Test article-related microscopic findings at the recovery necropsy were present in the adrenal glands, liver, gallbladder, kidneys, stomach (pylorus), female reproductive tract (ovaries), male reproductive tract (testes, epididymides, prostate gland), mesenteric lymph node, skeletal muscle (biceps femoris), and parotid salivary gland.

The No Observed Adverse Effect Level was 2 mg/kg/day for males; a No Observed Adverse Effect Level was not observed for females (ReveraGen Report No. 1998 014).

7-day study in cynomolgus monkeys
Non-naive cynomolgus monkeys were administered vamorolone or vehicle QD for 7 consecutive days at doses of 100, 300, and 600 mg/kg. All animals survived until the end of the study period. There were effects on clinical observations, food consumption, and urinalysis attributable to vamorolone that are described below.

There was a dose proportional decrease in body weight gain observed in males and females at each dose (up to 11% and 9% respectively) related to vamorolone. A cessation of the body weight loss in treatment was observed during the recovery phase but no recovery of body weight lost during the 7 days of dosing was observed.

At termination there were nonsignificant increases in red cell mass and decreases in lymphocytes (up to 56%) in the 600 mg/kg/day dose group. However, most individual animals, including controls, had decreases in lymphocytes (up to 81%) at termination relative to their respective pretest. These decreases had resolved by the recovery interval in both sexes.

In both sexes receiving ≥ 300 mg/kg/day, there was increased urea nitrogen (up to 141%), creatinine (up to 58%), total protein (up to 15%), albumin (up to 11%), globulin (up to 25%), and/or potassium (up to 39%) with concurrent decreases in sodium (up to 10%) and chloride (up to 10%) relative to controls. At the recovery interval, the majority of these effects had resolved (ReveraGen Report No. 1998-001).

1.2.3.3 Genotoxicity

The mutagenic and genotoxic potential of vamorolone was assessed in several assays. A non-GLP Ames screen was negative for bacterial mutations (ReveraGen Report No. BIO VBP-001-AMES). In a GLP Ames test, no background lawn toxicity was observed; however, a reduction in revertant counts was observed (ReveraGen Report No. AD79DT.502ICH.BTL). Vamorolone was negative for inducing chromosomal aberrations in cultured mouse lymphocytes without and with metabolic activation (ReveraGen Report No. AD79DT.704.BTL).

Femoral bone marrow was microscopically evaluated for the presence of polychromatic erythrocytes (PCEs) containing micronuclei. No significant reductions in the PCEs/EC (total erythrocytes) ratio were observed in the vamorolone groups compared to the vehicle control group. Although statistically significant increases in the incidence of micronucleated PCEs in the vamorolone treated groups were observed, no dose response was observed with respect to other groups and the values of micronuclei for the individual animals were within the historical range. Therefore, the statistically significant increase was considered as biologically insignificant (ReveraGen Report No. AD76BK.123012ICH.BTL).

A study was performed to evaluate the potential mutagenicity of two theoretical epoxide impurities related to the drug substance vamorolone (formerly VBP15), which is a steroid-like structure containing a delta 9,11 double bond. The delta 9,11 epoxide structures evaluated were VBP15-B-3, which is structurally similar to vamorolone except for the epoxide moiety, and VBP15-B-2, which has a 21-acetate substitution (vamorolone and VBP15-B-3 contain a 21-hydroxy moiety). Two validated and complementary in silico prediction methodologies were used for assessing mutagenic potential. The statistics-based quantitative structure-activity relationship (QSAR) program MultiCASE CASE Ultra was used, employing four different modules (GT1_A7B, GT1_AT_ECOLI, PHARM_ECOLI, and PHARM_SAL) designed to cover a wide range of molecular substructures collected from both proprietary and public compounds. In addition, the expert rule-based SAR program Derek Nexus was used to determine if the theoretical impurities contained structural alerts associated with known genotoxicants. CASE Ultra predicted both VBP15-B-2 and VBP15-B-3 as negative for mutagenicity (ReveraGen Report "In Silico Mutagenicity Evaluation of Delta 9,11 Epoxide Structures of VBP15: VBP15-B-2 [21-Acetate] and VBP15-B-3 [21-Hydroxy]").
Taken together, these data indicate vamorolone is negative for any mutagenic signal.

1. INTRODUCTION- 1.3 Clinical Experience

Original Text:

Clinical experience with vamorolone is comprised of a completed Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001), completed Phase IIa (VBP15-002) and Phase II extension (VBP15-003) trials in DMD boys, an ongoing Phase II long-term extension (VBP15-LTE) trial in DMD boys in which the clinical conduct has been completed, and an ongoing Phase IIb active- and placebo-controlled trial in DMD boys (VBP15-004).

1.3.1 Phase I Study in Healthy Adult Male Volunteers (VBP15-001)

A Phase I first-in-human study (VBP15-001) entitled, "A Phase I Randomized, Placebo- Controlled, Double-Blind, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Vamorolone in Health Adult Subjects" was completed in 2015 (Hoffman et al., 2018).

The single ascending dose (SAD) component of the study included 6 cohorts of 8 subjects each (6 vamorolone and 2 placebo) at dose levels of 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 8.0 mg/kg, and 20 mg/kg administered orally under fasted conditions. A seventh cohort of 6 subjects, all receiving vamorolone following a high fat, high calorie meal, were also enrolled and dosed at 8.0 mg/kg administered orally. The dose level for this fed cohort was determined after review of the safety and pharmacokinetic (PK) data from SAD cohorts dosed through 8.0 mg/kg.

The multiple ascending dose (MAD) component of the study enrolled 4 cohorts of 8 subjects each (6 vamorolone and 2 placebo) at dose levels of 1.0 mg/kg, 3.0 mg/kg, 9.0 mg/kg and 20.0 mg/kg, each dosed orally once daily for 14 days with follow-up through Day 21.

1.3.1.1 Pharmacokinetics

SAD Cohorts – Pharmacokinetics (Fasted)

Vamorolone PK data shows strong adherence to dose linearity and dose proportionality, with relatively little subject-subject variation. The half-life was about 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0 and 20.0 mg/kg showed an extended tail, increasing half-life to 2.5, 3.3 and 4.3 hours, respectively.

SAD Cohorts – Pharmacokinetics (Fed)

For the food effect group, a high fat meal (45 grams fat) was given to a cohort of Phase I SAD volunteers with the 8.0 mg/kg dose of vamorolone. These data were then compared to the fasted 8.0 mg/kg cohort data. This showed that absorption was increased by 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone (steroidal compound).

MAD Cohorts

The relatively short half-life of vamorolone (2-4 hours), coupled with the planned daily dose schedule, was expected to give PK data on each single dose, not cumulative dose, as the dosing interval was > 5 × t½. The MAD component was therefore a study of individual daily doses, rather than dose-related accumulation and pharmacodistribution related to cumulative drug exposure. Thus, with the short half-life of vamorolone, useful information to determine steady state drug levels was not expected. Safety and tolerability were additional goals of the MAD study.

MAD Cohorts – Pharmacokinetics Fasted

Four cohorts were completed (1.0 mg/kg/day, 3.0 mg/kg/day, 9.0 mg/kg/day, 20.0 mg/kg/day) for the MAD study.

Taking into account the small numbers and different subjects, the geometric mean values for Cmax, AUC(0-t), and AUC(inf) were not different for the SAD and MAD cohorts. Within the MAD, there is good agreement between Days 1 and 14 at all dose groups. There was no accumulation - the geometric mean Cmax and AUC(0-24) on Days 1 and 14 are not different, consistent with the t½ (~2-4 hours) and dosing interval (24 hours).

1.3.1.2 Safety

Single and multiple daily doses of vamorolone up to 20 mg/kg were well tolerated by healthy subjects, and a maximum tolerated dose (MTD) was not identified.

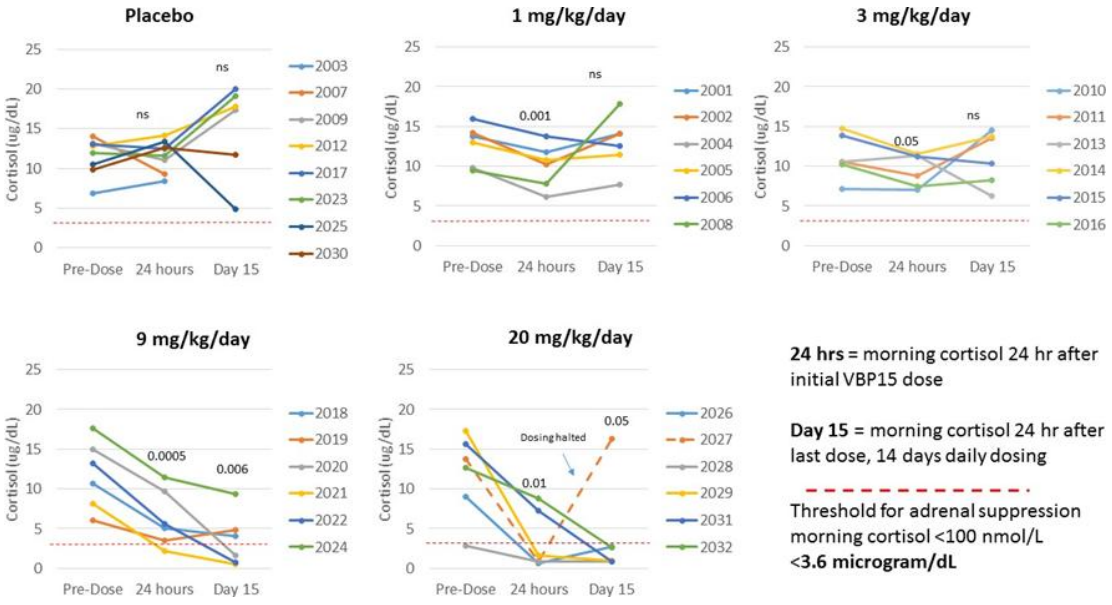
One subject in the 20 mg/kg vamorolone MAD dose group who had an elevation of serum bilirubin at baseline (pre-dose) experienced an AE of ALT increased after 9 days of dosing; this AE was judged to be possibly related to vamorolone and drug dosing was halted. No other subjects in the vamorolone dose groups experienced AEs related to liver function.
There were no clinically significant changes in vital signs, electrocardiograms (ECGs), or physical examinations.

1.3.1.2.1 Pharmacodynamic Safety Biomarkers
Safety concerns with glucocorticoids include suppression of the adrenal axis and insulin resistance. Pharmacodynamic biomarker assays of suppression of the adrenal axis (serum cortisol) and insulin resistance (serum glucose) were measured in the Phase I MAD studies of vamorolone.

Suppression of the adrenal axis: Prednisone directly impinges on cortisol regulatory pathways (adrenal axis) both acutely and chronically. Acute suppression of adrenal function is seen within hours of doses of a single 0.1 mg/kg/day (approximate) dose of prednisone, as evidenced by reductions in adrenocorticotropic hormone (ACTH) levels in normal volunteers (Kauh et al., 2012). More chronic suppression of the adrenal axis, characterized as severe, is typically diagnosed when morning cortisol is < 100 nmol/L (< 3.6 µg/dL) when drawn > 24 hrs after the last dose of pharmacological steroids.

Morning serum cortisol levels were measured in the vamorolone Phase I MAD cohorts, at baseline (prior to drug administration), 24 hours after the first dose (Day 1), and 24 hours after the 14-day dose (Day 15) (Figure 1). Volunteers receiving vamorolone at four MAD dose levels are shown (1.0 mg/kg/day; 3.0 mg/kg/day; 9.0 mg/kg/day; 20.0 mg/kg/day); all subjects were treated for 14 days with daily dosing. The red hatched line on each graph shows a typical threshold for adrenal axis suppression (< 100 nmol/L, or < 3.6 µg/dL). P values shown are for paired T test, indicating significance of the consistency of longitudinal changes of subjects relative to their own individual baseline values. Acute adrenal axis suppression is measured at 24 hours (after first dose), whereas chronic adrenal axis suppression is measured after 14 days of daily dosing (24 hours after last dose).

Figure 1. Morning Cortisol Measurements in the Vamorolone Phase I Healthy Subjects Placebo subjects from each of the four MAD cohorts are graphed together.



Vamorolone showed little evidence of either acute (24-hour data), or chronic (Day 15 data) suppression of the adrenal axis at doses of either 1.0 mg/kg/day or 3.0 mg/kg/day. The data suggest that vamorolone induces variable, mild, acute and chronic suppression of the adrenal axis at 9.0 mg/kg/day, and stronger evidence of both acute and chronic adrenal axis suppression at 20.0 mg/kg/day. Prednisone typically shows both acute and chronic adrenal axis suppression approximately at 0.1 mg/kg/day (Fleishaker et al., 2016), suggesting that vamorolone has an improved safety window regarding adrenal axis suppression.

Insulin resistance: Prednisone induces the safety signal of insulin resistance, where glucose is not efficiently taken up from the blood by target tissues, such as muscle and liver, leading to hyperglycemia. Insulin resistance may be an important safety signal for dystrophic muscle, where the dysfunctional myofibers have been shown to have inadequate energy stores, and insulin resistance likely limits availability of glycogen substrates for glycolysis. The hyperglycemia, in turn, leads to chronic increases in insulin levels (hyperinsulinemia).
Levels of fasting glucose and insulin are reasonably sensitive and reliable measures of insulin resistance in non-diabetic individuals. Glucose is acutely (single dose) and chronically (multiple doses) elevated after treatment with pharmacological glucocorticoids. Glucose is elevated 24 hours after a single administration of glucocorticoids (2.0 mg/kg) (Kauh et al., 2012; Fleishaker et al., 2016).

In the Phase I MAD of vamorolone, fasting serum glucose was measured at 10 time points during the 2-week study; each sample was taken 24 hours after the previous dose of vamorolone. Glucose levels for all vamorolone dose groups were similar to those of the placebo group. There was no evidence of elevations of glucose levels at any time point or any dose of vamorolone, suggesting that the side effect of insulin resistance was not seen with vamorolone. These data are consistent with a nonclinical study in a dystrophin-deficient mouse model, where chronic treatment of prednisolone (5 mg/kg/day) versus vamorolone (15 mg/kg/day; 30 mg/kg/day) showed development of insulin resistance with prednisolone, but not vamorolone (Heier et al., 2013).

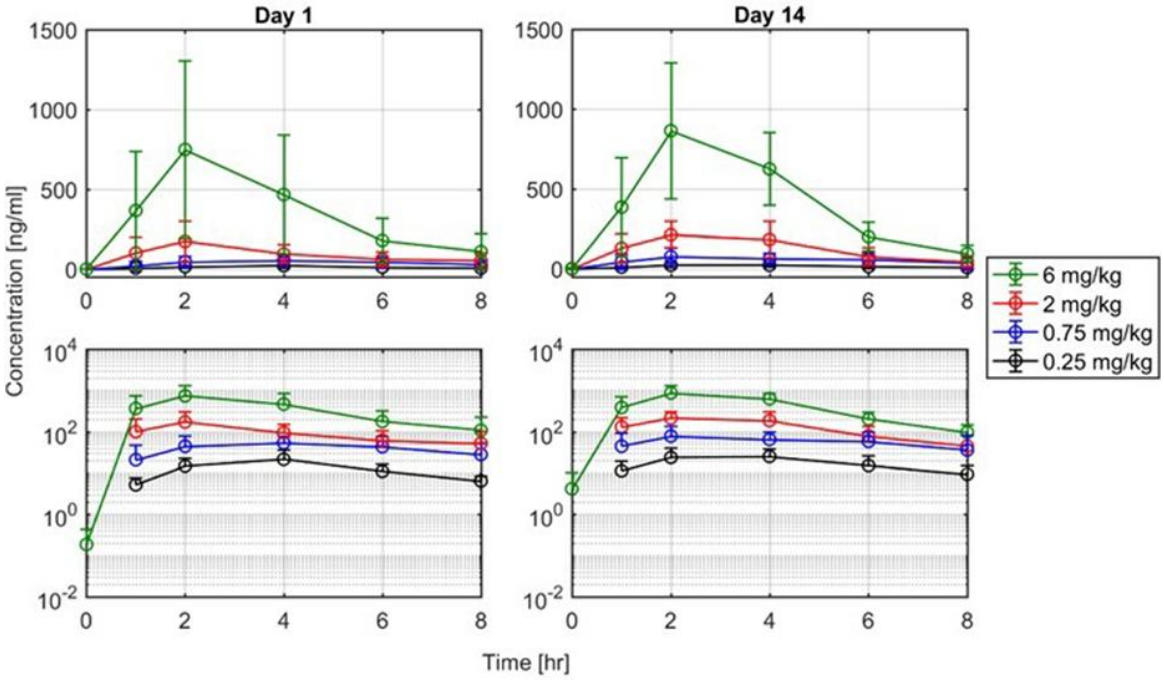
Bone turnover: Safety PD biomarker studies showed that vamorolone had no effect on bone turnover markers (osteocalcin, C-terminal peptide fragment of collagen 1 [CTX]), in contrast to prednisone studies reported in the literature (Hoffman et al., 2018; Conklin et al., 2018a).

1.3.2 Phase IIa Study in 4 to <7 years Duchenne Muscular Dystrophy Boys (VBP15-002)

A Phase IIa first-in-patient study (VBP15-002) to evaluate safety, tolerability, and pharmacokinetics has been completed and results have been published (Conklin et al., 2018a). Forty-eight boys with DMD received oral doses of vamorolone once daily for 14 days at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day, 12 subjects receiving vamorolone at each dose level. The drug was administered with a glass of whole milk or other high-fat food. Six blood samples were collected on Day 1 and Day 14 at 0, 1, 2, 4, 6, and 8 hours post-dose and plasma was analyzed for vamorolone. The time-course of plasma drug concentrations was assessed using noncompartmental analytical (NCA) methods using the WinNonlin software (Certara).

Of the 48 DMD subjects enrolled in the study (12 at each dosing level), 47 had evaluable PK data. The average Day 1 and Day 14 vamorolone concentration versus time profiles are shown in Figure 2 for the four dose levels. Overall, as expected, higher doses resulted in higher plasma concentrations of vamorolone. In particular, plasma vamorolone concentrations versus time showed a rapid to moderate rate of absorption, a maximum concentration (Cmax) at a Tmax of 2 to 4 hours, and a decline phase with a typical half-life (t1/2) of 2 hours. For all 4 dose levels, the mean PK profiles on Day 1 and Day14 appear similar. Many individual subjects had closely matching Day 1 and Day 14 profiles, but several did not. There was no accumulation of drug owing to the relatively short half-life and once-daily (morning) dosing.

Figure 2. Mean Plasma Concentrations of Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0, and 6.0 mg/kg Doses



Vamorolone concentrations shown as mean ± standard deviation on linear (top panel) and semi-logarithmic (bottom panel) graphs.

A summary of the observed (Cmax and Tmax) and calculated (AUC, t1/2, and CL) PK parameters for all doses on Day 1 and Day 14 is provided in Table 1. Even with only 6 blood samples collected from each subject, the PK profiles adequately capture the overall exposures, but must be considered approximate. This particularly applies to the peak values and the half-lives.
Nevertheless, there is good consistency in the data with moderate variability as standard deviation (SD) values are reasonable and the coefficient of variation values are typically less than 50%.

The drug is absorbed at a moderate rate with peak concentrations typically occurring at 2 to 4 hours on both Days 1 and 14. The median Tmax across all doses is typically 2 or 4 hours. The half-lives were similar on both days, averaging about 2 hours, although some subjects had irregular profiles without a clear decline phase. The apparent clearance (CL and CL/F) values were consistent across the dose levels for Day 1 as well as for Day 14, but the latter tended to average slightly lower (about 2400 mL/hr/kg on Day 1 and 1900 mL/hr/kg on Day 14).

Table 1. Summary of Pharmacokinetic Parameters for Vamorone after Once Daily Oral Administration of 0.25, 0.75, 2.0 and 6.0 mg/kg Doses to DMD Boys

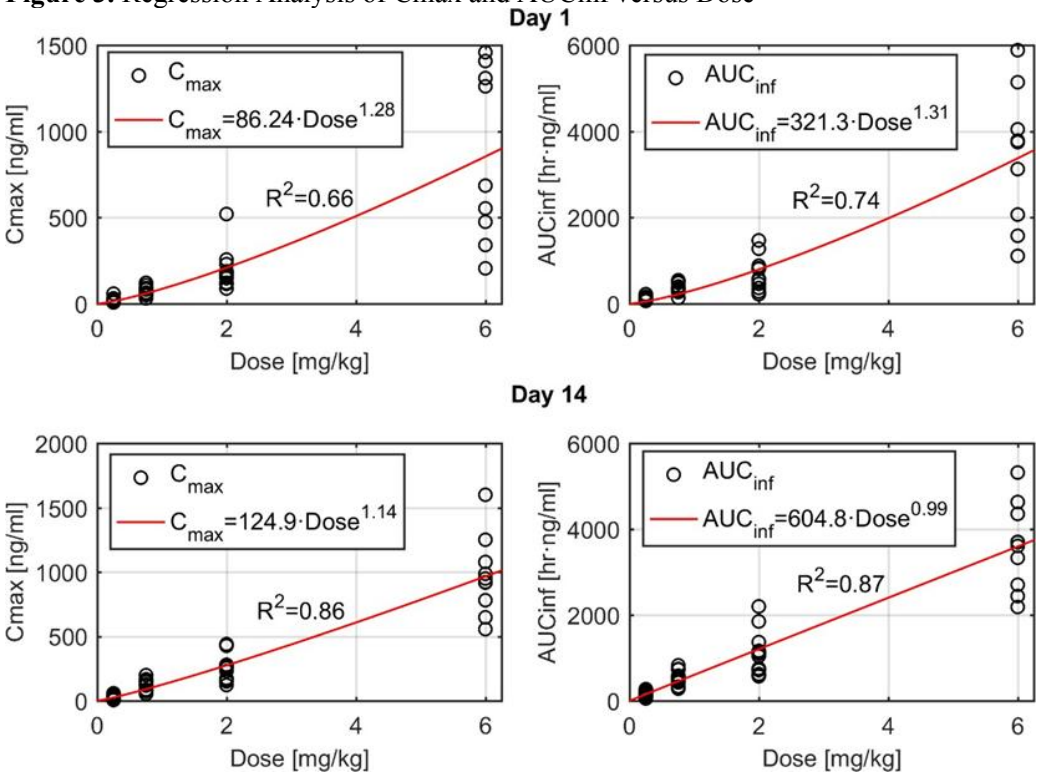
Parameters	**Day 1 Dose, mg/kg/day**				**Day 14 Dose, mg/kg/day**			
	0.25	**0.75**	**2.0**	**6.0**	**0.25**	**0.75**	**2.0**	**6.0**
Cmax [ng/ml]	22.9 (13.4)	75.9 (25.9)	199 (111)	855.6 (471)	32.2 (15.2)	124.7 (42.5)	252.5 (96)	970 (270)

Tmax [h]	3.6 [4] (1.2)	4.6 [4] (2.1)	2.5 [2] (1.3)	2.7 [2] (1.3)	3.8 [4] (1.8)	3.8 [4] (2.2)	2.8 [2] (1)	2.3 [2] (0.86)
AUCinf [hr·ng/ml]	118 (48)	379 (117)	761 (352)	3279 (1693)	164 (61)	544 (155)	1138 (467)	3606 (897)
t1/2 [h]	2.1 (0.85)	1.8 (0.43)	1.9 (0.79)	1.9 (0.95)	1.9 (0.96)	2.1 (0.8)	1.9 (1.02)	1.4 (0.35)
CL [ml/hr/kg]	2459 (897)	2285 (1103)	2697 (1285)	2320 (1375)	1828 (919)	1509 (482)	2047 (771)	1777 (476)

Values are mean (standard deviation) and for Tmax, which are shown as mean [median] (standard deviation).

An assessment of the linearity of the PKwith dose using Cmax and AUC is shown in Figure 3. Data for all individual subjects were used which also depict the variability for each dose level. While larger doses appear to present greater variability, this is a visual size distortion as the standard deviation is similar at each dose level (Table 1). Fitting the power equation of the form (Cmax , AUCinf = a x·Doseb) resulted in 95% confidence intervals for b values that include 1.0 for Cmax and AUCinf for both Days 1 and 14 indicative of linear relationships across this range of dose levels.

Figure 3. Regression Analysis of Cmax and AUCinf versus Dose



Regression was performed by fitting the indicated power equations to the data for Day 1 and Day 14. The fitted parameters are shown in the figure boxes.

Compared with fasting healthy adult volunteers (Section 1.3.4), the boys with DMD showed lower Cmax values and more variation in the time to reach the maximal concentration of vamorolone for any given dose. This observation might be due to the fact that the boys with DMD received vamorolone after 8

ounces of whole milk or other high fat food and a so-called food effect might have played a role. The apparent clearance of vamorolone seems higher in the boys with DMD but this finding is not significant.

1.3.3 Population Pharmacokinetics

The PK of oral vamorolone were assessed in parallel group studies in healthy men (Phase I, n=86) and boys with DMD (Phase IIa, n=48) during 14 days of once-daily dosing over a range of doses (Mavroudis et al., 2019). Vamorolone exhibited moderate variability in PK, with the Cmax usually occurring at 2-4 hours and a half-life of approximately 2 hours for all doses and days examined. Population PK modeling of all data together indicated that the PK of vamorolone can be well described by a 1-compartment model with zero-order absorption. Both men and boys

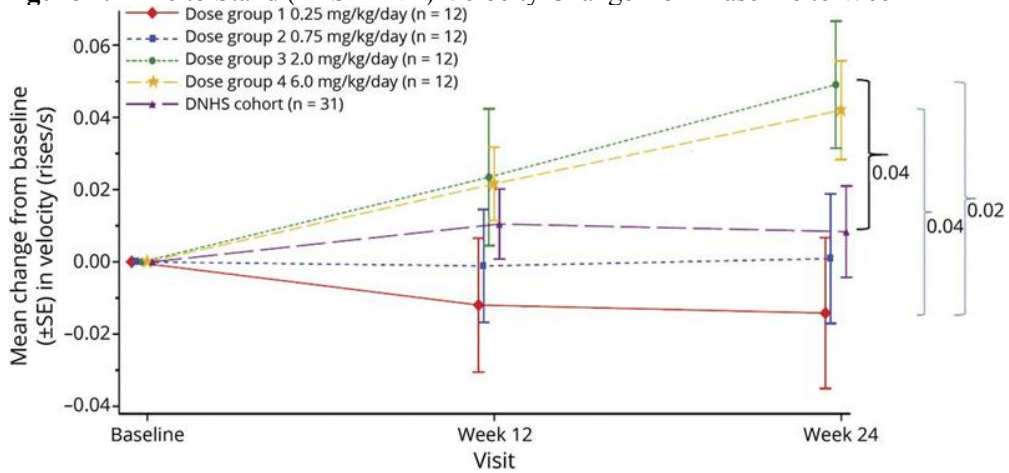
showed a dose-linearity of PK parameters for the doses examined, with no accumulation of the drug during daily dosing. Ingestion with food resulted in markedly enhanced absorption of the drug, as tested in healthy men. There was similar PK of vamorolone in healthy men and DMD boys with apparent clearance averaging 2.0 L/hr/kg in men and 1.7 L/hr/kg in boys. Overall, vamorolone exhibited well-behaved linear PK, with similar profiles in healthy men and boys with DMD, moderate variability in PK parameters, and absorption and disposition profiles similar to those of classical glucocorticoids.

1.3.4 Phase II Extension Study in 4 to <7 years Duchenne Muscular Dystrophy Boys (VBP15-003)

After completion of the Phase IIa VBP15-002 study, each subject was able to enroll in a Phase II 24-week extension study (VBP15-003) at the same dose level he received in VBP15-002, and preliminary efficacy was evaluated. The study has been completed and results have been published (Hoffman et al., 2019; Smith et al., 2020).

Clinical efficacy was assessed by Timed Function Tests. The primary study clinical efficacy endpoint was TTSTAND velocity (rises/second) change from baseline to Week 24 for vamorolone compared to an untreated Duchenne Natural History Study (DNHS) control group. Time to Stand (TTSTAND) velocity showed dose- and time-related increases, with greater increases observed for the 2.0 mg/kg/day and 6.0 mg/kg/day dose level groups, and greater increases at Week 24 compared to Week 12. Statistically significant increases in mean change from baseline to Week 24 for TTSTAND velocity were observed for the 2.0 mg/kg/day dose level group compared to the untreated DNHS cohort and for the 2.0 mg/kg/day and
6.0 mg/kg/day dose level groups compared to the 0.25 mg/kg/day dose level group (Figure 4).

Figure 4. Time to Stand (TTSTAND) Velocity Change from Baseline to Week 24 in DMD Boys



Data shown as mean ± standard error (SE)

Brackets indicate mixed-model repeated-measures p values (black for comparisons to Cooperative International Neuromuscular Research Group Duchenne Natural History Study [DNHS] external comparator; blue for within-trial dose group comparisons).

Time to Climb (TTCLIMB) velocity (tasks/second) mean changes from baseline to Week 24 showed dose-related increases, with greater increases observed for the 2.0 mg/kg/day and 6.0 mg/kg/day dose level groups. Mean change from baseline to Week 24 lacked statistical significance for comparison of each vamorolone dose level group to the untreated DNHS cohort; however, comparison of the 6.0 mg/kg/day dose level group to the untreated DNHS cohort almost achieved statistical significance at an alpha level of 0.05 ($p = 0.0507$).

Time to Run/Walk 10 Meters (TTRW) velocity (meters/second) mean changes from baseline to Week 12 and Week 24 showed dose-related increases, with greater increases observed for the 2.0 mg/kg/day and 6.0 mg/kg/day dose level groups. The mean changes from baseline for each dose level group were generally similar at Week 12 and Week 24. Statistically significant increases in mean change from baseline to VBP15-003 Week 12 and Week 24 for TTRW velocity were observed for the 6.0 mg/kg/day dose level group compared to the untreated DNHS cohort.

Six-minute Walk Test (6MWT) results showed mean increases in meters walked at Week 12 compared to baseline for all dose level groups, and at Week 24 compared to baseline for the 0.75, 2.0, and 6.0 mg/kg/day dose level groups, the increases correlating with increase in dose level. Statistically significant increases in mean change from baseline to Week 24 for 6MWT were observed.

1.3.5 Exposure-Response Relationships

Exposure-response relationships of vamorolone were investigated in the VBP15-002 and VBP15-003 trials, and the results have been published (Li et al., 2020). Variables were clinical outcome measures, Fridericia-corrected QT interval (QTcF), and PD biomarkers. Exposure metrics were AUC and Cmax, with a sigmoid maximum effect (Emax) model applied. Significant improvement in clinical efficacy outcomes was observed after 24 weeks of daily dosing. The primary outcome, TTSTAND from supine velocity, exhibited the highest sensitivity to vamorolone, with the lowest AUC value providing 50% of maximum effect ([E50] = 186 ng·hr/mL), followed by TTCLIMB 4 stairs (E50 = 478 ng·hr/mL), TTRW 10 m (E50 = 1220 ng·hr/mL), and 6MWT (E50 = 1770 ng·hr/mL). Week 2 changes of pro-inflammatory PD biomarkers showed exposure-dependent decreases. The E50 was 260 ng·hr/mL for insulin-like growth factor-binding protein 2, 1200 ng·hr/mL for matrix metalloproteinase 12, 1260 ng·hr/mL for lymphotoxin α1/β2, 1340 ng·hr/mL for CD23, 1420 ng·hr/mL for interleukin-22-binding protein, and 1600 ng·hr/mL for macrophage-derived chemokine/C-C motif chemokine 22. No relationship was found between QTcF interval changes from baseline and Cmax at Weeks 2 or 24. This analysis showed that improvements in clinical efficacy end points in Week 24 and PD biomarkers in Week 2 were achieved at typical vamorolone exposure of 2 mg/kg daily dose with a median AUC dose of 6 mg/kg (3651 ng·hr/mL), corresponding to approximately 95% of maximum effects for most response variables.

1.3.6 Phase II VBP15-LTE Study

On completion of the VBP15-003 study, subjects were eligible to enroll in a 24-month long-term extension study, VBP15-LTE. All (100%) subjects completing VBP15-003 elected to enroll in VBP15-LTE (46 of 46 subjects). Each subject entered LTE at the same dose level he had received in the VBP15-002 and VBP15-003 studies. Subjects were eligible to escalate to the next higher dose up to 3 times up to 6.0 mg/kg/day after they had been on each previous dose level for at least one month, with the approval of the study chair and medical monitor. The clinical conduct of the study has been completed, and analysis is ongoing. Of the 46 subjects initially enrolled in VBP15-LTE, 41 completed the final visit. The majority of subjects completed the study at the highest possible dose (6 mg/kg/day). Cumulative drug exposure at 2.0

or 6.0 mg/kg/day was 24 subject-years in VBP15-003, and 82 subject-years in VPB15-LTE, for a total cumulative exposure of 106 patient-years.

1.3.7 Phase IIb VBP15-004 Study

The VBP15-004 study is an ongoing double-blind, randomized trial which includes two Treatment Periods, Treatment Period #1, during which subjects are randomized to vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo, and Treatment Period #2, during which subjects are randomized to vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day.

1.3.8 Safety in Phase II Studies in 4 to7 years Duchenne Muscular Dystrophy Boys (VBP15- 002, VBP15-003, VBP15-LTE, and VBP15-004)

Adverse Events: There has been a total of 11 SAEs in the vamorolone program to date: a total of 4 SAEs in the VBP15-003 study, a total of 3 SAEs in the VBP15-LTE study, a total of 3 SAEs in the VBP15-004 study, and 1 SAE in the VBP15-EAP program. There have been two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day); one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day; one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day; two SAEs of acute myoglobulinemia in the same subject receiving 6.0 mg/kg/day; one SAE of viral gastroenteritis with secondary dehydration in a subject receiving blinded study drug; one SAE of asthma exacerbation in the setting of respiratory syncytial virus and bronchiolitis in a subject receiving vamorolone at either 2.0 mg/kg/day or 6.0 mg/kg/day; one SAE of perforated appendicitis occurring with 30 days after the subject completed the VBP15-004 study, and one SAE of viral gastroenteritis requiring hospitalization for hydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study. In the completed VBP15-003 study, there were a total of 218 TEAEs among 42 of the 48 subjects (87.5%). In VBP15-003 study, the TEAEs with the highest incidence were viral upper respiratory tract infection (41.7%); pyrexia (35.4%); cough (18.8%); vomiting (14.6%); and diarrhea (10.4%).

Body Mass Index (BMI): Body Mass Index was measured throughout the VBP15-003 study. The mean change from baseline to Week 24 for BMI was 0.03, 0.20, 0.23, and 1.15 for the 0.25, 0.75, 2.0, and 6.0 mg/kg/day dose level groups, respectively. Body Mass Index increases generally reflect an increase in weight. Body Mass Index z-score was monitored in the VBP15- 003 study. The mean change from baseline to Week 24 for BMI z-score for the 6.0 mg/kg/day group showed a statistically significant increase compared to the mean change from baseline to Week 24 for the 0.25 mg/kg/day and 0.75 mg/kg/day dose level groups. In contrast, the mean change from baseline to Week 24 for the 2.0 mg/kg/day dose level group in BMI z-score was minimal and comparisons with the other vamorolone dose level groups lacked statistical significance. The mean increase from baseline to Week 24 for BMI z-score was similar for the 6.0 mg/kg/day group and a daily prednisone-treated historical control group.

Potential liver toxicity: In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state, and dosing was halted. All DMD subjects have elevated serum ALT and AST enzymes because of the muscle condition. For that reason, two enzymes, GLDH and gamma glutamyl transferase (GTT), that are preferentially expressed in liver were evaluated in the VBP15-003 study. None of the mean changes in GLDH from baseline to any of the VBP15-003 on-treatment assessment time points were statistically significant for any dose level group.

Although the mean changes from baseline to Week 8, Week 16, and Week 24 in GLDH levels did not show a dose response, shift analysis of GLDH levels did suggest a possible dose-related shift to higher GLDH levels at 2.0 mg/kg/day and 6.0 mg/kg/day at Weeks 16 and 24. Mean GGT levels and individual

subject values at each VBP15-003 assessment time point across the four dose level groups remained at or below the normal range. On the basis of these mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day does not appear to induce liver toxicity over a 24-week treatment period. However, one subject participating in VBP15- 004 developed an AE of acute cholestatic hepatitis manifested by elevated transaminases, direct bilirubin, ALP and GGT during Treatment Period #1 (blinded study drug) which caused interruption of study drug. After return of all laboratory values to baseline levels and subsequently restarting study drug during Treatment Period #2 (vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day), he had a second episode of acute cholestatic hepatitis again manifested by elevated transaminases, direct bilirubin, ALP and GGT which led to discontinuation of the subject from the study. After discontinuation of study drug, the elevated laboratory values returned to pre-dosing levels. In both instances, serum albumin was unaffected. Unblinding of the treatment assignment for this subject, to facilitate decisions regarding subsequent standard of care corticosteroid therapy, indicated that the subject had been on vamorolone 6.0 mg/kg/day in both Treatment Period #1 and Treatment Period #2.

Adrenal suppression: In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μg/dL [100 nM]) consistent with chronic adrenal suppression.

Insulin resistance: In the VBP15-003 study, mean changes from baseline for fasting insulin showed dose- and time-related changes for all dose level groups at Week 12 and Week 24.
Statistical significance was observed for mean increase from baseline for the 6.0 mg/kg/day dose level group at Week 12 and Week 24.

Bone Turnover: In the VBP15-003 study, pharmacodynamic biomarker testing for bone turnover markers suggested that vamorolone does not have the detrimental bone effects observed with prednisone and deflazacort.

Revised text:
Clinical experience with vamorolone is comprised of a completed Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001), completed Phase IIa (VBP15-002) and Phase II extension (VBP15-003) trials in DMD boys, completed Phase II long-term extension (VBP15-LTE) trial in DMD boys, and a completed Phase IIb active- and placebo-controlled trial in DMD boys (VBP15-004). Furthermore, two relative bioavailability (BA) and food effect (FE) studies have been conducted (VBP15-PKFORM and VBP15-PKFORM-002) comparing the formulation used in clinical studies (ROS1) with the to-be-marketed formulation (ROS2).

1.3.1 Phase I Study in Healthy Adult Male Volunteers (VBP15-001)

1.3.1.1 Study Design and Objectives

The safety, tolerability, and PK of vamorolone were initially evaluated in a Phase I , placebo-controlled, double-blind, single ascending dose (SAD) and multiple ascending dose (MAD) study. In the SAD portion of the study, Cohorts 1 through 5 and Cohort 7 were comprised of eight subjects each; six subjects in each cohort received a single oral dose of vamorolone (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 8.0 mg/kg, and 20 mg/kg, respectively) and two subjects in each cohort received placebo under fasted conditions. In Cohort 6, six subjects received a single oral dose of 8.0 mg/kg vamorolone within 30 minutes of beginning a high fat/high calorie meal. The MAD portion of the study had four cohorts of 8 subjects each; six subjects in each cohort received 14 daily doses of vamorolone (1.0, 3.0, 9.0 and 20.0 mg/kg/day) and two subjects in each cohort received placebo.
The primary objectives of the Phase I study were to evaluate the safety and tolerability of single and multiple oral doses of vamorolone, and to evaluate the PK of single doses and multiple doses of

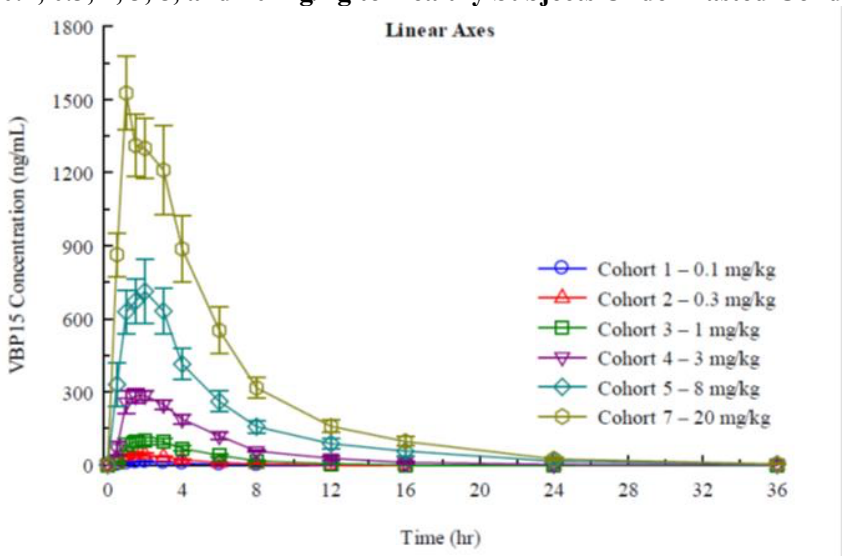
vamorolone. A secondary objective was to evaluate the effect of food on the absorption and PK of vamorolone. Other objectives were to obtain samples from subjects on Day 1 (pre-dose) and Day 14 of the MAD cohorts for use in Metabolites in Safety Testing (MIST) assessments, and to test back-up PK samples from a subset of MAD subjects for pharmacodynamic (PD) biomarkers.

1.3.1.2 Pharmacokinetics

SAD Cohorts – Pharmacokinetics (Fasted)

Vamorolone PK data shows strong adherence to dose linearity and dose proportionality, with relatively little subject-subject variation (Figure 2, Table 2, Figure 3). The half-life was about 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0 and 20.0 mg/kg showed an extended tail, increasing half-life to 2.5, 3.3 and 4.3 hours, respectively (Figure 2, Table 2).

Figure 2. Plasma Concentrations of Vamorolone (VBP15) after Oral Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to Healthy Subjects Under Fasted Conditions



Data presented as arithmetic mean ± standard error

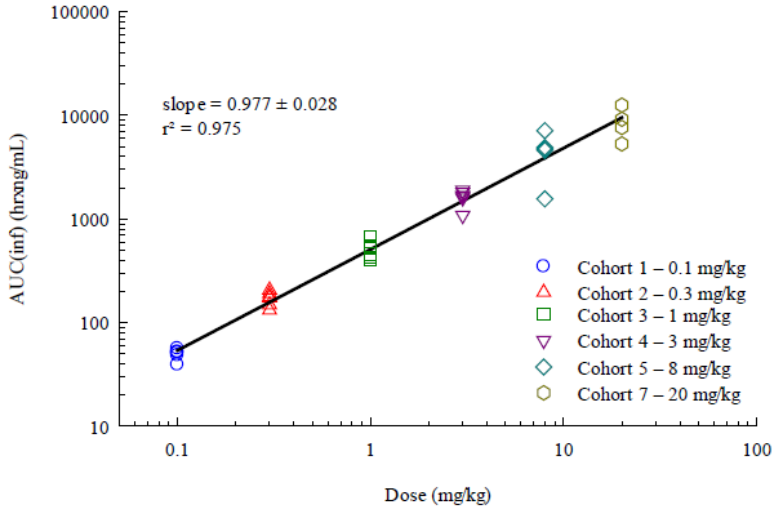
Table 2. Summary of Pharmacokinetic Parameters for Vamorolone after Oral Administration of Single Doses of 0.1, 0.3, 1.0, 3.0, 8.0, and 20.0 mg/kg to Healthy Subjects Under Fasted Conditions

	Dose					
Parameter*	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	8 mg/kg	20 mg/kg
Cmax (ng/mL)	13.1 (12.8) (6)	50.8 (16.5) (6)	122 (32.8) (6)	305 (24.4) (6)	718 (42.5) (6)	1,648 (16.7) (6)
Tmax (hr)	1.50 (6) [1.50 – 2.03]	1.50 (6) [1.00 – 3.00]	1.75 (6) [1.00 – 3.00]	1.75 (6) [1.00 – 2.00]	1.78 (6) [1.00 – 2.00]	1.50 (6) [1.00 – 3.03]
AUC(0-t) (hr×ng/mL)	41.9 (16.8) (6)	161 (15.9) (6)	486 (19.7) (6)	1,577 (20.7) (6)	3,997 (55.0) (6)	8,545 (29.5) (6)
AUC(inf) (hr×ng/mL)	49.5 (12.5) (6)	170 (16.5) (6)	500 (19.2) (6)	1,600 (20.3) (6)	3,602 (60.2) (4)	8,653 (37.0) (4)
λz (1/hr)	0.4060 (12.5) (6)	0.4325 (17.8) (6)	0.3828 (17.9) (6)	0.2773 (16.3) (6)	0.2136 (40.9) (4)	0.1629 (25.2) (4)
t½ (hr)	1.71 (12.5) (6)	1.60 (17.8) (6)	1.81 (17.9) (6)	2.50 (16.3) (6)	3.25 (40.9) (4)	4.26 (25.2) (4)
CL/F						
(L/hr/kg)	2.02 (12.5) (6)	1.76 (16.5) (6)	2.00 (19.2) (6)	1.88 (20.3) (6)	2.22 (60.2) (4)	2.31 (37.0) (4)
(L/hr)	168 (20.8) (6)	142 (14.4) (6)	165 (12.0) (6)	152 (18.5) (6)	196 (57.6) (4)	180 (29.8) (4)
Vz/F						
(L/kg)	4.98 (6.14) (6)	4.07 (20.5) (6)	5.22 (18.5) (6)	6.76 (28.7) (6)	10.4 (61.8) (4)	14.2 (37.2) (4)
(L)	415 (17.4) (6)	329 (19.6) (6)	432 (22.8) (6)	550 (28.7) (6)	919 (63.1) (4)	1,107 (34.6) (4)

*Geometric mean (%CV) (N) except Tmax for which the median (N) [Range] is reported.
Cmax = maximum observed plasma concentration; Tmax = time to maximum observed plasma concentration; AUC(0-t) = area under concentration-time curve from time 0 to time t; AUC(inf) = area

under concentration-time curve from time 0 to infinity; □z = elimination rate constant; t½ = terminal half-life; CL/F = apparent total clearance from plasma; Vz/F = apparent volume of distribution during terminal phase.

Figure 3. Relationship Between Individual Subject Vamorolone AUC(Inf) and Dose After Oral Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to Healthy Subjects Under Fasted Conditions



MAD Cohorts

The relatively short half-life of vamorolone (2-4 hours), coupled with the planned daily dose schedule, was expected to give PK data on each single dose, not cumulative dose, as the dosing interval was > 5 × t½. The MAD component was therefore a study of individual daily doses, rather than dose-related accumulation and pharmacodistribution related to cumulative drug exposure. Thus, with the short half-life of vamorolone, useful information to determine steady state drug levels was not expected. Safety and tolerability were additional goals of the MAD study.

MAD Cohorts – Pharmacokinetics Fasted

The original design for the Phase I MAD was modified to remove the two lowest doses (0.1, 0.3 mg/kg/day), and to begin dosing at 1.0 mg/kg/day. Four cohorts were completed (1.0 mg/kg/day, 3.0 mg/kg/day, 9.0 mg/kg/day, 20.0 mg/kg/day) for the MAD study (Table 4).

Table 4. Summary of Pharmacokinetic Parameters for Vamorolone During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions

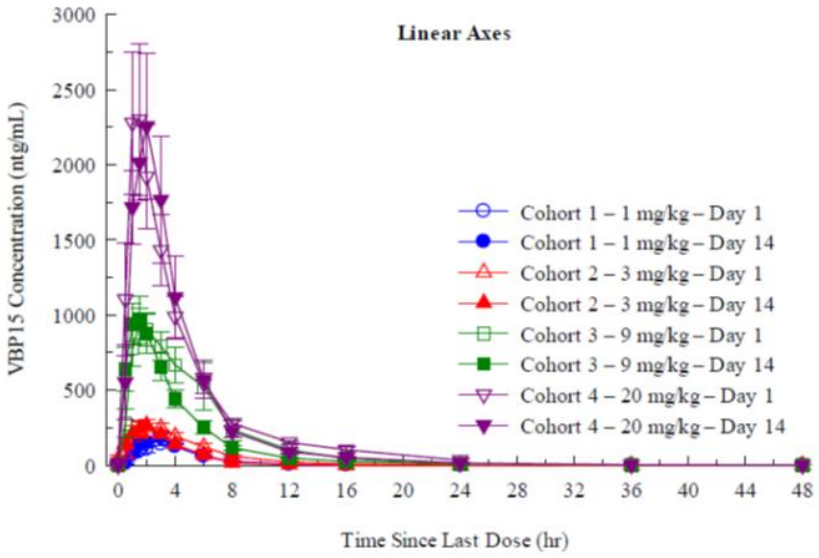
	Vamorolone Dose			
	1 mg/kg	**3 mg/kg**	**9 mg/kg**	**20 mg/kg**
Day 1 C_{max} (ng/mL)	153 (15.9)	281 (36.9)	1,082 (23.3)	2,416 (51.1)
T_{max} (hr)	3.04 [1.50 – 4.00]	2.01 [1.00 – 3.00]	1.75 [1.00 – 6.00]	1.00 [0.50 – 3.00]
$AUC_{(0\text{-}t)}$ (hr_xng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)
$AUC_{(0\text{-}24)}$ ($hr_{\times}$ng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)
$AUC_{(inf)}$ ($hr_{\times}$ng/mL)	695 (22.1)	1,487 (23.7)	5,745 (29.5)	10,190 (27.0)
λ_z (1/hr)	0.3848 (10.9)	0.2918 (18.1)	0.2317 (22.6)	0.1747 (44.3)
$t_{½}$ (hr)	1.80 (10.9)	2.38 (18.1)	2.99 (22.6)	3.97 (44.3)
CL/F (L/hr/kg)	1.44 (22.1)	2.02 (23.7)	1.57 (29.5)	1.96 (27.0)
V_z/F (L/kg)	3.74 (16.9)	6.91 (34.8)	6.76 (46.9)	11.2 (77.6)
Day 14	203 (30.1)	276 (35.6)	935 (48.3)	2,491 (27.9)

C_{max} (ng/mL)				
T_{max} (hr)	2.96 [1.50 – 3.00]	2.50 [1.00 – 4.00]	1.25 [0.55 – 3.00]	2.00 [1.00 – 2.00]
$AUC_{(0-24)}$ (hr×ng/mL)	794 (22.3)	1,494 (18.6)	4,366 (20.2)	9,309 (38.8)
λ_z (1/hr)	0.3993 (20.4)	0.3273 (25.2)	0.1629 (63.5)	0.1879 (31.6)
$t_{½}$ (hr)	1.74 (20.4)	2.12 (25.2)	4.25 (63.5)	3.69 (31.6)
CL/F (L/hr/kg)	1.26 (22.3)	2.01 (18.6)	2.06 (20.2)	2.15 (38.8)
V_z/F (L/kg)	3.15 (20.6)	6.14 (39.7)	12.7 (79.9)	11.4 (49.1)

Cmax = maximum observed plasma concentration; Tmax = time to maximum observed plasma concentration; AUC(0-t) = area under concentration-time curve from time 0 to time t; AUC(0-24) = area under concentration-time curve from time 0 to 24 hours; AUC(inf) = area under concentration-time curve from time 0 to infinity; □z = elimination rate constant; t½ = terminal half-life; CL/F = apparent total clearance from plasma; Vz/F = apparent volume of distribution during terminal phase.

Taking into account the small numbers and different subjects, the geometric mean values for Cmax, AUC(0-t), and AUC(inf) are not different for the SAD and MAD cohorts. Within the MAD, there is good agreement between Days 1 and 14 at all dose groups. There is no accumulation — the geometric mean Cmax and AUC(0-24) on Days 1 and 14 are not different, consistent with the t½ (~2-4 hours) and dosing interval (24 hours) (Figure 5; Table 4).

Figure 5. Plasma Concentrations of Vamorolone (VBP15) on Days 1 and 14 During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions



Data presented as arithmetic mean ± standard error

1.3.1.3 Safety

SAD Cohorts

In the SAD part, overall, 6 subjects (11%) administered vamorolone experienced a total of 10 treatment-emergent adverse events (TEAEs); no subject in the placebo group experienced any TEAEs. There was no dose-related trend in the incidence or severity of TEAEs; the dose group with the highest number of

subjects reporting TEAEs was the 0.1 mg/kg dose group (2 subjects, 33%), and the highest number of TEAEs (3 events) was reported by 1 subject in the 1.0 mg/kg vamorolone dose group. In the 0.3 and 3.0 mg/kg vamorolone fasted and the 8.0 mg/kg fed dose groups, 1 subject per group (17%) experienced TEAEs, and no subjects in the 8.0 mg/kg and 20 mg/kg, fasted, dose groups experienced any TEAEs. The most common TEAEs were dizziness and headache, each reported by 2 subjects overall (4%); all other TEAEs were reported by only 1 subject (2%) and included ear pain, nausea, non-cardiac chest pain, and blood bilirubin increased. Three subjects (6%) had TEAEs that were considered possibly related to treatment. Possibly related TEAEs included nausea (1 subject, 2%), dizziness (2 subjects, 4%), and headache (2 subjects, 4%). One subject (2%) had a moderate TEAE of blood bilirubin increased, which was considered unrelated to study drug. All other TEAEs were mild in severity.

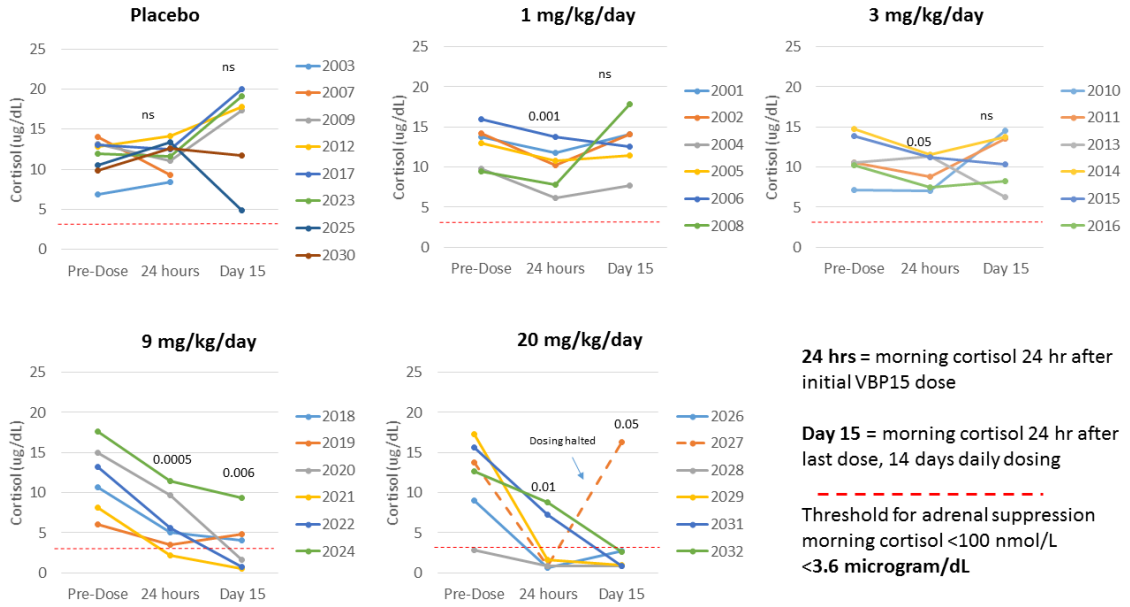
MAD Cohorts
In the MAD part, overall, a total of 6 subjects (19%) administered vamorolone or placebo experienced a total of 10 TEAEs: 2 subjects each in the 1.0 mg/kg vamorolone, 20 mg/kg vamorolone, and placebo groups, and none in the 3.0 mg/kg and 9.0 mg/kg dose groups. There was no dose-related trend in the incidence or severity of TEAEs. The most common TEAE was headache (2 subjects, 6%); all other TEAEs occurred in only 1 subject (3%) per group, and included nausea, toothache, vomiting, ALT increased, hepatic enzyme increased, arthralgia, dizziness, and syncope. TEAEs were considered possibly related in 2 subjects (6%) and remotely related in 1 subject (3%). Possibly related AEs were ALT increased and hepatic enzyme increased, occurring in 1 subject in the 20 mg/kg vamorolone and placebo groups, respectively. The remotely related TEAEs were dizziness and syncope, both occurring in the same subject (1.0 mg/kg vamorolone). All TEAEs were mild in severity.
With the exception of the AEs related to hepatic enzymes, there were no other meaningful changes in clinical laboratory parameters. Of note, glucose levels remained stable at all doses of vamorolone in both the SAD and MAD parts, suggesting that vamorolone does not induce insulin resistance at the doses and dosing duration studied; in addition, no changes in the white blood cell count differential were observed, suggesting that vamorolone did not induce immunosuppressive effects in this study population.

1.3.1.3.1 Pharmacodynamic Safety Biomarkers
Vamorolone has shown improved safety profiles relative to prednisone in nonclinical testing, both in vitro and in vivo (Bello et al., 2015; Dillingham et al., 2015) Safety concerns with glucocorticoids include suppression of the adrenal axis and insulin resistance. Pharmacodynamic biomarker assays of suppression of the adrenal axis (serum cortisol) and insulin resistance (serum glucose) were measured in the Phase I MAD studies of vamorolone.

Suppression of the adrenal axis. Prednisone directly impinges on cortisol regulatory pathways (adrenal axis) both acutely and chronically. Acute suppression of adrenal function is seen within hours of doses of a single 0.1 mg/kg/day (approximate) dose of prednisone, as evidenced by reductions in adrenocorticotropic hormone (ACTH) levels in normal volunteers (Kauh et al., 2012) More chronic suppression of the adrenal axis, characterized as severe, is typically diagnosed when morning cortisol is < 100 nmol/L (< 3.6 µg/dL) when drawn > 24 hrs after the last dose of pharmacological steroids.

Morning serum cortisol levels were measured in the vamorolone Phase I MAD cohorts, at baseline (prior to drug administration), 24 hours after the first dose (Day 1), and 24 hours after the 14-day dose (Day 15) (Figure 6). Volunteers receiving vamorolone at four MAD dose levels are shown (1.0 mg/kg/day; 3.0 mg/kg/day; 9.0 mg/kg/day; 20.0 mg/kg/day); all subjects were treated for 14 days with daily dosing. The red hatched line on each graph shows a typical threshold for adrenal axis suppression (< 100 nmol/L, or < 3.6 µg/dL). P values shown are for paired T test, indicating significance of the consistency of longitudinal changes of subjects relative to their own individual baseline values. Acute adrenal axis suppression is measured at 24 hours (after first dose), whereas chronic adrenal axis suppression is measured after 14 days of daily dosing (24 hours after last dose).

Figure 6. Morning Cortisol Measurements in the Vamorolone Phase I Healthy Subjects



Note: Placebo subjects from each of the four MAD cohorts are graphed together.

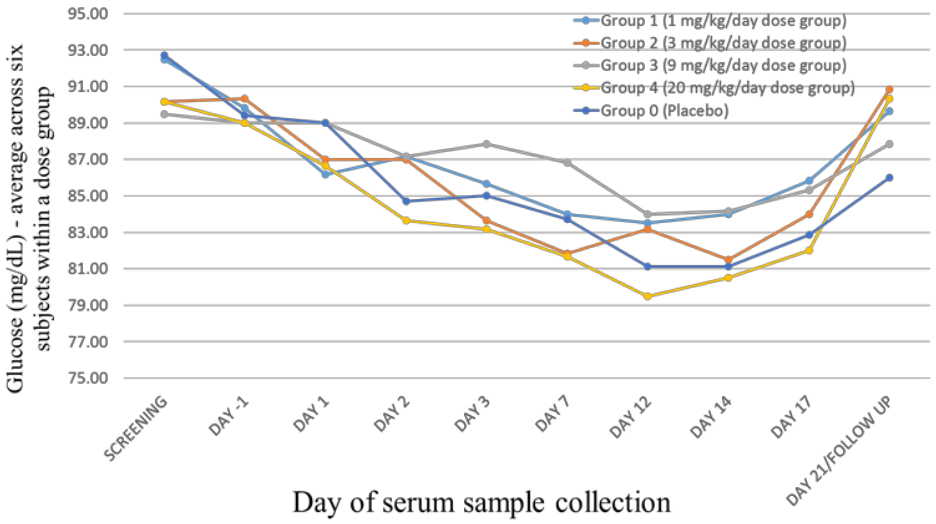
Vamorolone showed little evidence of either acute (24-hour data), or chronic (Day 15 data) suppression of the adrenal axis at doses of either 1.0 mg/kg/day or 3.0 mg/kg/day. The data suggest that vamorolone induces variable, mild, acute and chronic suppression of the adrenal axis at 9.0 mg/kg/day, and stronger evidence of both acute and chronic adrenal axis suppression at 20.0 mg/kg/day. Prednisone typically shows both acute and chronic adrenal axis suppression approximately at 0.1 mg/kg/day (Kauh et al., 2012), suggesting that vamorolone has an improved safety window regarding adrenal axis suppression.

Vamorolone thus shows approximately a 10-fold improvement in safety window compared to prednisone on a mg/kg comparative basis. These data are consistent with in vitro and ex vivo nonclinical mouse data comparing vamorolone to prednisone for adrenal suppression (Bello et al., 2015).

Insulin resistance. Prednisone induces the safety signal of insulin resistance, where glucose is not efficiently taken up from the blood by target tissues, such as muscle and liver, leading to hyperglycemia (Kauh et al., 2012) Insulin resistance may be an important safety signal for dystrophic muscle, where the dysfunctional myofibers have been shown to have inadequate energy stores (Dadgar et al., 2014; Wehling-Henricks et al., 2009) and insulin resistance likely limits availability of glycogen substrates for glycolysis. The hyperglycemia, in turn, leads to chronic increases in insulin levels (hyperinsulinemia).

Levels of fasting glucose and insulin are reasonably sensitive and reliable measures of insulin resistance in non-diabetic individuals. Glucose is acutely (single dose) and chronically (multiple doses) elevated after treatment with pharmacological glucocorticoids. Glucose is elevated 24 hours after a single administration of glucocorticoids (2.0 mg/kg) (Younes et al., 2007; Moon et al., 2014)
In the Phase I MAD of vamorolone, fasting serum glucose was measured at 10 time points during the 2-week study; each sample was taken 24 hours after the previous dose of vamorolone (Figure 7).

Figure 7. Fasting Serum Glucose During the Phase I MAD Period (Two Weeks Daily Treatment)



Glucose levels for all vamorolone dose groups were similar to those of the placebo group. There was no evidence of elevations of glucose levels at any time point or any dose of vamorolone, suggesting that the side effect of insulin resistance was not seen with vamorolone. These data are consistent with a nonclinical study in a dystrophin-deficient mouse model, where chronic treatment of prednisolone (5 mg/kg/day) versus vamorolone (15 mg/kg/day; 30 mg/kg/day) showed development of insulin resistance with prednisolone, but not vamorolone.30

1.3.1.4 Summary of Phase I Data

Pharmacokinetics

- Vamorolone PK data show strong adherence to dose linearity and dose proportionality, with relatively little subject-subject variation (both SAD and MAD).
- The half-life was approximately 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0, and 20.0 mg/kg showed an extended tail, increasing half-life to 2.5, 3.8, and 3.8 hours, respectively. The PK for the MAD cohorts was very similar to the SAD cohorts, showing little if any drug accumulation, consistent with the short half-life and daily dosing schedule.
- There were no apparent relationships between CL/F and body size, either in terms of body weight or BMI.
- For the food effect group, a high fat meal was given to a cohort of Phase I SAD volunteers with the 8.0 mg/kg dose of vamorolone. Comparison of the data from the high fat meal with the fasted 8.0 mg/kg cohort data showed that absorption was increased by 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone (steroidal compound).

Safety

- Single and multiple daily doses of vamorolone up to 20 mg/kg were well tolerated by healthy subjects, and a maximum tolerated dose (MTD) was not identified.
- Regarding the primary target organ, liver, one subject in the 20 mg/kg vamorolone MAD dose group who had an elevation of serum bilirubin at baseline (pre-dose) experienced an AE of ALT increased after 9 days of dosing; this AE was judged to be possibly related to vamorolone and drug dosing was halted. No other subjects in the vamorolone dose groups experienced AEs related to liver function.
- Results of post-dose morning cortisol levels suggest that vamorolone causes acute adrenal suppression after single dosing and chronic adrenal suppression after multiple dosing, but only at the higher (≥ 8.0 mg/kg) single and multiple doses studied.

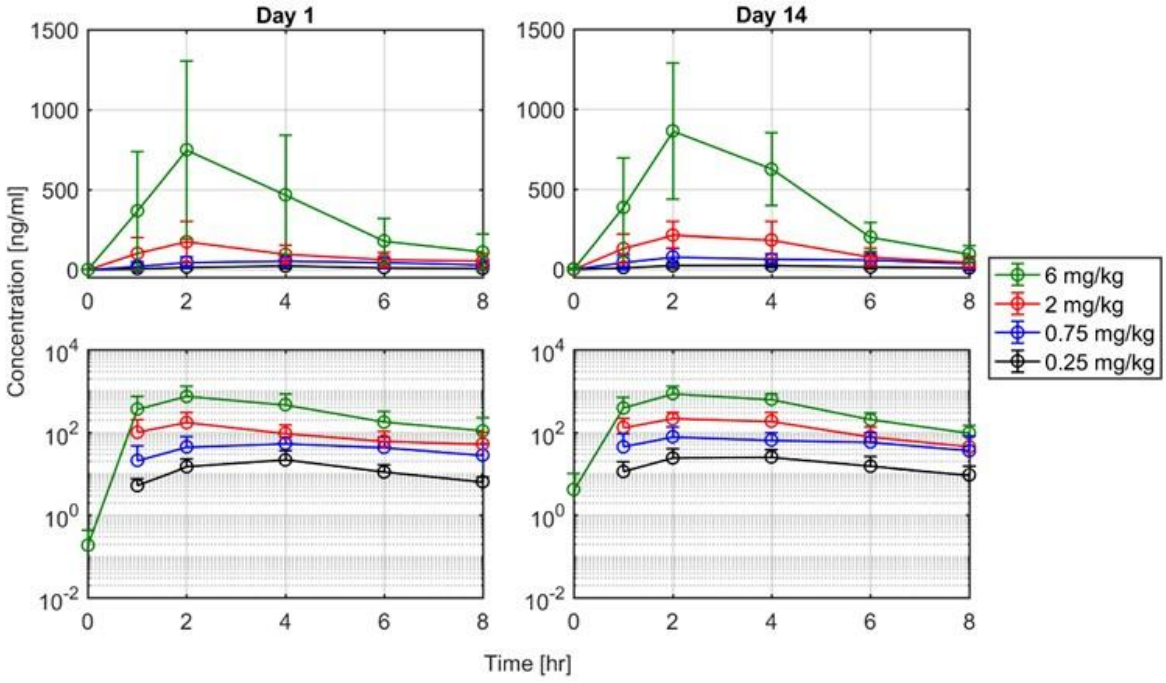
- Safety PD biomarker studies showed that vamorolone had an improved safety window for adrenal axis suppression (100-fold increase in therapeutic window), no evidence of insulin resistance, no changes in bone turnover markers (osteocalcin, C terminal peptide fragment of collagen 1 [CTX]), compared to prednisone studies reported in the literature (Kauh et al., 2012; Hoffman et al., 2018)
- There were no clinically significant changes in vital signs, electrocardiograms (ECGs), or physical examinations.

1.3.2 Pharmacokinetics in Phase IIa Study in 4 to <7 years Duchenne Muscular Dystrophy Boys (VBP15 002)

Forty-eight boys with DMD received oral doses of vamorolone once daily for 14 days at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day, 12 subjects receiving vamorolone at each dose level. The drug was administered with a glass of whole milk or other high-fat food. Six blood samples were collected on Day 1 and Day 14 at 0, 1, 2, 4, 6, and 8 hours post-dose and plasma was analyzed for vamorolone. The time-course of plasma drug concentrations was assessed using noncompartmental analytical (NCA) methods using the WinNonlin software (Certara).

Of the 48 DMD subjects enrolled in the study (12 at each dosing level), 47 had evaluable PK data. The average Day 1 and Day 14 vamorolone concentration versus time profiles are shown in Figure 8 for the four dose levels. Overall, as expected, higher doses resulted in higher plasma concentrations of vamorolone. In particular, plasma vamorolone concentrations versus time showed a rapid to moderate rate of absorption, a maximum concentration (Cmax) at a Tmax of 2 to 4 hours, and a decline phase with a typical half-life (t1/2) of 2 hours. For all 4 doses, the mean PK profiles on Day 1 and Day14 appear similar. Many individual subjects had closely matching Day 1 and Day 14 profiles, but several did not. There was no accumulation of drug owing to the relatively short half-life and once-daily (morning) dosing.

Figure 8.Mean Plasma Concentrations of Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0, and 6.0 mg/kg Doses



Vamorolone concentrations shown as mean ± standard deviation on linear (top panel) and semi-logarithmic (bottom panel) graphs.

A summary of the observed (Cmax and Tmax) and calculated (AUC, t1/2, and CL) PK parameters for all doses on Day 1 and Day 14 is provided in Table 5. Even with only 6 blood samples collected from each subject, the PK profiles adequately capture the overall exposures, but must be considered approximate. This particularly applies to the peak values and the half-lives. Nevertheless, there is good consistency in the data with moderate variability as standard deviation (SD) values are reasonable and the coefficient of variation values are typically less than 50%.

The drug is absorbed at a moderate rate with peak concentrations typically occurring at 2 to 4 hours on both Days 1 and 14. The median Tmax across all doses is typically 2 or 4 hours. The half-lives were similar on both days, averaging about 2 hours, although some subjects had irregular profiles without a clear decline phase. The apparent clearance (CL and CL/F) values were consistent across the dose levels for Day 1 as well as for Day 14, but the latter tended to average slightly lower (about 2400 mL/hr/kg on Day 1 and 1900 mL/hr/kg on Day 14).

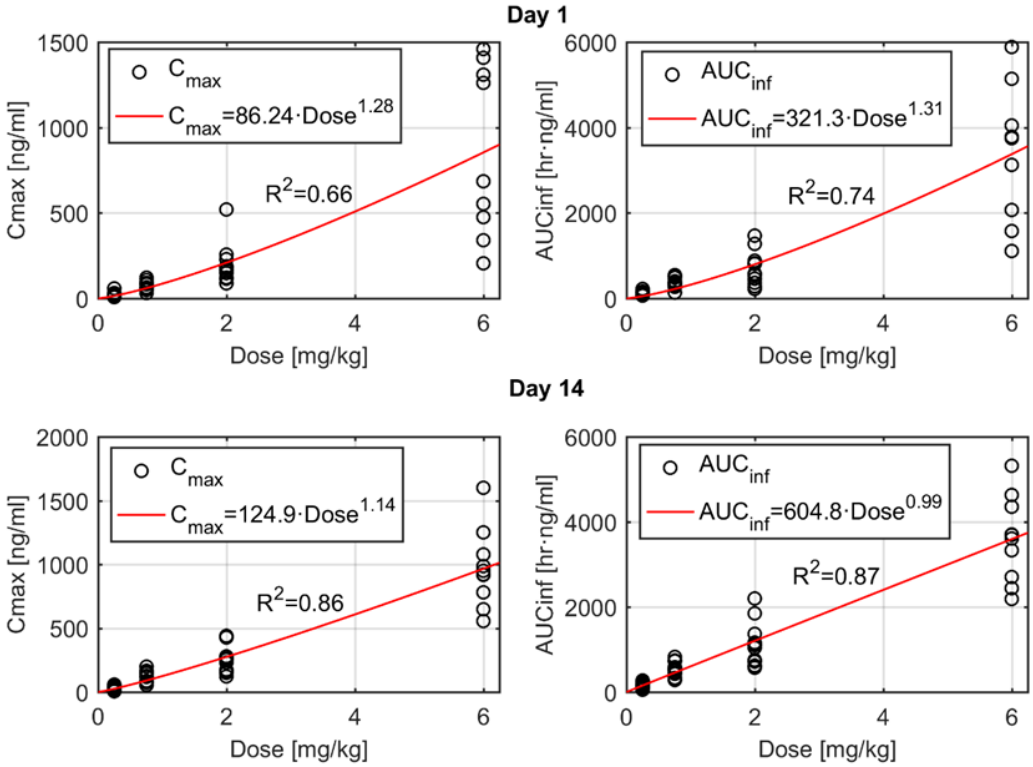
Table 5. Summary of Pharmacokinetic Parameters for Vamorolone after Once Daily Oral Administration of 0.25, 0.75, 2.0 and 6.0 mg/kg Doses to DMD Boys

	Day 1 Dose, mg/kg/day				**Day 14 Dose, mg/kg/day**			
Parameters	**0.25**	**0.75**	**2.0**	**6.0**	**0.25**	**0.75**	**2.0**	**6.0**
Cmax [ng/ml]	22.9 (13.4)	75.9 (25.9)	199 (111)	855.6 (471)	32.2 (15.2)	124.7 (42.5)	252.5 (96)	970 (270)
T_{max} [h]	3.6 [4] (1.2)	4.6 [4] (2.1)	2.5 [2] (1.3)	2.7 [2] (1.3)	3.8 [4] (1.8)	3.8 [4] (2.2)	2.8 [2] (1)	2.3 [2] (0.86)
AUC_{inf} [hr·ng/ml]	118 (48)	379 (117)	761 (352)	3279 (1693)	164 (61)	544 (155)	1138 (467)	3606 (897)
$t_{1/2}$ [h]	2.1 (0.85)	1.8 (0.43)	1.9 (0.79)	1.9 (0.95)	1.9 (0.96)	2.1 (0.8)	1.9 (1.02)	1.4 (0.35)
CL [ml/hr/kg]	2459 (897)	2285 (1103)	2697 (1285)	2320 (1375)	1828 (919)	1509 (482)	2047 (771)	1777 (476)

Values are mean (standard deviation) and for Tmax, which are shown as mean [median] (standard deviation).

An assessment of the linearity of the PKwith dose using Cmax and AUC is shown in Figure 9. Data for all individual subjects were used which also depict the variability for each dose level. While larger doses appear to present greater variability, this is a visual size distortion as the standard deviation is similar at each dose level (Table 5). Fitting the power equation of the form (Cmax , AUCinf = a x·Doseb) resulted in 95% confidence intervals for b values that include 1.0 for Cmax and AUCinf for both Days 1 and 14 indicative of linear relationships across this range of dose levels.

Figure 9. Regression Analysis of Cmax and AUCinf versus Dose



Regression was performed by fitting the indicated power equations to the data for Day 1 and Day 14. The fitted parameters are shown in the figure boxes.

Compared with fasting healthy adult volunteers (Section 1.3.1), the boys with DMD showed lower Cmax values and more variation in the time to reach the maximal concentration of vamorolone for any given dose. This observation might be due to the fact that the boys with DMD received vamorolone after 8 ounces of whole milk or other high fat food and a so-called food effect might have played a role. The apparent clearance of vamorolone seems higher in the boys with DMD but this finding is not significant.

1.3.3 Safety in Phase II Studies in 4 to7 years Duchenne Muscular Dystrophy Boys (VBP15-002, VBP15-003, VBP15-LTE, and VBP15-004)

Adverse events: There were no serious adverse events (SAEs) reported over the 14-day treatment in the Phase I clinical trial in healthy adult volunteers, nor in the four cohorts (0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg) of the Phase IIa study (VBP15-002; 14-day treatment) in boys ages 4 to <7 years with DMD. There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in the same subject receiving 6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study. In the completed VBP15 003 study, there were a total of 218 TEAEs among 42 of the 48 subjects (87.5%). In VBP15 003 study, the TEAEs with the highest incidence were viral upper respiratory tract infection (41.7%); pyrexia (35.4%); cough (18.8%); vomiting (14.6%); and diarrhea (10.4%).

Body Mass Index (BMI): Body Mass Index was measured throughout the VBP15-003 study. The mean change from baseline to Week 24 for BMI was 0.03, 0.20, 0.23, and 1.15 for the 0.25, 0.75, 2.0, and 6.0 mg/kg/day dose level groups, respectively. Body Mass Index increases generally reflect an increase in weight. Body Mass Index z-score was monitored in the VBP15-003 study. The mean change from baseline to Week 24 for BMI z-score for the 6.0 mg/kg/day group showed a statistically significant increase compared to the mean change from baseline to Week 24 for the 0.25 mg/kg/day and 0.75 mg/kg/day dose level groups. In contrast, the mean change from baseline to Week 24 for the 2.0 mg/kg/day dose level group in BMI z score was minimal and comparisons with the other vamorolone dose level groups lacked statistical significance. The mean increase from baseline to Week 24 for BMI z-score was similar for the 6.0 mg/kg/day group and a daily prednisone-treated historical control group.
Potential liver toxicity: In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state, and dosing was halted. All DMD subjects have elevated serum ALT and AST enzymes because of the muscle condition. For that reason, two enzymes, glutamate dehydrogenase (GLDH) and gamma glutamyl transferase (GTT), that are preferentially expressed in liver were evaluated in the VBP15-003 study. None of the mean changes in GLDH from baseline to any of the VBP15-003 on treatment assessment time points were statistically significant for any dose level group. Although the mean changes from baseline to Week 8, Week 16, and Week 24 in GLDH levels did not show a dose response, shift analysis of GLDH levels did suggest a possible dose-related shift to higher GLDH levels at 2.0 mg/kg/day and 6.0 mg/kg/day at Weeks 16 and 24. Mean GGT levels and individual subject values at each VBP15-003 assessment time point across the four dose level groups remained at or below the normal range. On the basis of these mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day does not appear to induce liver toxicity over a 24-week treatment period.
Adrenal suppression: In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μg/dL [100 nM]) consistent with chronic adrenal suppression.
Insulin resistance: In the VBP15-003 study, mean changes from baseline for fasting insulin showed dose- and time-related changes for all dose level groups at Week 12 and Week 24. Statistical significance was observed for mean increase from baseline for the 6.0 mg/kg/day dose level group at Week 12 and Week 24.
Bone Turnover: In the VBP15-003 study, pharmacodynamic biomarker testing for bone turnover markers suggested that vamorolone does not have the detrimental bone effects observed with prednisone and deflazacort.

INTRODUCTION - 1.4 Rationale for Study Design
Original Text:
ambulatory subjects with BMD, ages 12 and <65.

Revised Text:
in ambulatory patients age 18 - <65 years with Becker dystrophy.

INTRODUCTION - 1.5 Overall Benefit/Risk
Original Text:
It is anticipated that the adverse effect profile of the investigational product will be more favorable than standard of care glucocorticoids in the long term. There has been a total of 11 SAEs in the vamorolone program to date: a total of 4 SAEs in the VBP15-003 study, a total of 3 SAEs in the VBP15-LTE study, a total of 3 SAEs in the VBP15-004 study, and 1 SAE in the VBP15-EAP program. There have been two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day); one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day;

one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day; two SAEs of acute myoglobulinemia in the
same subject receiving 6.0 mg/kg/day; one SAE of viral gastroenteritis with secondary dehydration in a subject receiving blinded study drug; one SAE of asthma exacerbation in the setting of respiratory syncytial virus and bronchiolitis in a subject receiving vamorolone at either
2.0 mg/kg/day or 6.0 mg/kg/day; one SAE of perforated appendicitis occurring with 30 days after the subject completed the VBP15-004 study, and one SAE of viral gastroenteritis requiring hospitalization for hydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study.

In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state. On the basis of mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day did not appear to induce liver toxicity over a 24-week treatment period in the VBP15-003 study. However, one subject receiving 6.0 mg/kg/day vamorolone in VBP15-004 developed an AE of acute cholestatic hepatitis manifested by elevated transaminases, direct bilirubin, ALP and GGT which led to discontinuation from the study.

In the VBP15-002 study, after 2 weeks of treatment, 0 of 11 tested participants who received vamorolone 0.25 mg/kg/day, 0 of 11 tested participants who received vamorolone
0.75 mg/kg/day, 2 of 11 (18.2%) tested participants who received vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested participants who received vamorolone 6 mg/kg/day had a depressed morning cortisol (<3.6 µg/dL [100 nmol/L]) consistent with chronic adrenal suppression. In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 µg/dL [100 nM]) consistent with chronic adrenal suppression. Instructions for detecting adrenal crisis and the circumstances in which stress dose steroids should be provided will be included in the Informed Consent Form (ICF) and Manual of Operations, and Investigators should monitor clinical study participants closely to identify elevations in liver- specific enzymes.

Potential Health Benefits: Subjects may or may not receive direct health benefit from participating in the study. Subjects will be treated with vamorolone at 500 mg/day (250mg if <50kg body weight) over the course of the 24-week trial. In the VBP15-003 study, clinical efficacy was assessed by Time Function Tests. Improvement in Time to Stand, Time to Climb, Time to Run/Walk 10 Meters, and 6-Minute Walk Test were seen predominantly for the 2.0 and 6.0 mg/kg/day dose level groups, with many of the improvements showing statistical significance compared to an untreated Duchenne Natural History Group. In view of the clinical evidence of safety collected to date, the improvements observed in the assessments of efficacy, and the nature of potential adverse effects that can be monitored, the data support an acceptable benefit/risk profile for vamorolone.

Revised Text:
There were no serious adverse events (SAEs) reported over the 14-day treatment in the Phase I clinical trial in healthy adult volunteers, nor in the four cohorts (0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg) of the Phase IIa study (VBP15-002; 14-day treatment) in boys ages 4 to <7 years with DMD. There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza-associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in a subject receiving 6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and

none of them resulted in discontinuation from the study. In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state. On the basis of mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day did not appear to induce liver toxicity over a 24 week treatment period in the VBP15-003 study. In the VBP15-002 study, after 2 weeks of treatment, 0 of 11 tested participants who received vamorolone 0.25 mg/kg/day, 0 of 11 tested participants who received vamorolone 0.75 mg/kg/day, 2 of 11 (18.2%) tested participants who received vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested participants who received vamorolone 6 mg/kg/day had a depressed morning cortisol (<3.6 μg/dL [100 nmol/L]) consistent with chronic adrenal suppression. In the VBP15 003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μg/dL [100 nM]) consistent with chronic adrenal suppression. Instructions for detecting adrenal crisis and the circumstances in which stress dose steroids should be provided will be included in the Informed Consent Form (ICF) and Manual of Operations, and Investigators should monitor clinical study participants closely to identify elevations in liver-specific enzymes.

In the VBP15-004 double-blind, placebo- and prednisone-controlled study, a lower proportion of subjects in the Safety Population who experienced at least one TEAE during Treatment Period #1 was observed for subjects in the placebo group (79.3%) compared to subjects in the prednisone 0.75 mg/kg/day (83.9%), vamorolone 2.0 mg/kg/day (83.3%), and vamorolone 6.0 mg/kg/day (89.3%) groups: 23 subjects (79.3%) in the placebo group experienced a total of 77 TEAEs; 26 subjects (83.9%) in the prednisone 0.75 mg/kg/day group experienced a total of 121 TEAEs; 25 subjects (83.3%) in the vamorolone 2.0 mg/kg/day group experienced a total of 97 TEAEs; and 25 subjects (89.3%) in the vamorolone 6.0 mg/kg/day group experienced a total of 91 TEAEs; a greater total number of TEAEs was experienced by subjects in the prednisone group (121), with fewer TEAEs experienced by subjects in the placebo (77), vamorolone 2.0 mg/kg/day (97), and vamorolone 6.0 mg/kg/day (91) groups (Table 6).

A total of 51 subjects (43.2%) in the Safety Population experienced at least one treatment-related TEAE: eight subjects (27.6%) in the placebo group; 14 subjects (45.2%) in the prednisone 0.75 mg/kg/day group; 10 subjects (33.3%) in the vamorolone 2.0 mg/kg/day group; and 19 subjects (67.9%) in the vamorolone 6.0 mg/kg/day group. None of the treatment-related TEAEs was serious.

One subject (3.2%) in the prednisone 0.75 mg/kg/day group reported a TEAE with CTCAE grade ≥ 3.

One subject (3.2%) in the prednisone 0.75 mg/kg/day group experienced a TEAE leading to study drug and study discontinuation.

One subject (3.3%) in the vamorolone 2.0 mg/kg/day group experienced one serious TEAE during Treatment Period #1 of the study.

No subject experienced a TEAE considered by the Investigator to be life-threatening or which resulted in death during Treatment Period #1 of the study.

Table 6. Overall Summary of Adverse Events (Safety Population)

	Treatment Group				
	Placebo (N = 29)	**Prednisone 0.75 mg/kg/day (N = 31)**	**Vamorolone 2.0 mg/kg/day (N = 30)**	**Vamorolone 6.0 mg/kg/day (N = 28)**	**Total (N = 118)**
Total Number of AEs	82	133	108	105	428
Total Number of TEAEs	77	121	97	91	386
Subjects with [n (%)]					
Any TEAE	23 (79.3)	26 (83.9)	25 (83.3)	25 (89.3)	99 (83.9)

Any Treatment-related TEAE[a]	8 (27.6)	14 (45.2)	10 (33.3)	19 (67.9)	51 (43.2)
Any TEAE with CTCAE Grade ≥ 3[b]	0	1 (3.2)	0	0	1 (0.8)
Any TEAE Leading to Discontinuation of Study Drug	0	1 (3.2)	0	0	1 (0.8)
Any TEAE Leading to Discontinuation of Study	0	1 (3.2)	0	0	1 (0.8)
Any SAE	0	0	1 (3.3)	0	1 (0.8)
Any Serious TEAE	0	0	1 (3.3)	0	1 (0.8)
Death[c]	0	0	0	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; F/U = Follow-up (Visit); kg = kilogram; mg = milligram; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: AEs are defined starting at the date of written informed consent. TEAEs are defined as any AE starting or worsening after initiation of study drug dosing through the subject's final visit (study completion or early termination). For Treatment Period #1 analyses, AEs and TEAEs with onset through the Week 24 F/U Visit are included. SAEs were recorded for up to 30 days after the final administration of study drug; for the Treatment Period #1 analyses, SAEs with onset through the Week 24 F/U Visit are included.
Related TEAEs include Possibly, Probably, and Definitely related to study medication.
Grade: 3=Severe, 4=Life threatening, 5=Death.
Deaths are defined as deaths that occur during the study and ≤ 30 days after the last dose of study drug.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; F/U = Follow-up (Visit); kg = kilogram; mg = milligram; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: AEs are defined starting at the date of written informed consent. TEAEs are defined as any AE starting or worsening after initiation of study drug dosing through the subject's final visit (study completion or early termination). For Treatment Period #1 analyses, AEs and TEAEs with onset through the Week 24 F/U Visit are included. SAEs were recorded for up to 30 days after the final administration of study drug; for the Treatment Period #1 analyses, SAEs with onset through the Week 24 F/U Visit are included.
a. Related TEAEs include Possibly, Probably, and Definitely related to study medication.
b. Grade: 3=Severe, 4=Life threatening, 5=Death.
c. Deaths are defined as deaths that occur during the study and ≤ 30 days after the last dose of study drug.

Potential Health Benefits: Subjects may or may not receive direct health benefit from participating in the study Subjects will be treated with vamorolone at 500 mg/day (250mg if <50kg body weight) over the course of the 24-week trial. In the VBP15-003 study, clinical efficacy was assessed by Timed Function Tests. Improvement in Time to Stand, Time to Climb, Time to Run/Walk 10 Meters, and 6 Minute Walk Test were seen predominantly for the 2.0 and 6.0 mg/kg/day dose level groups, with many of the improvements showing statistical significance compared to an untreated Duchenne Natural History Group. In the VBP15-004 double-blind study, both 2.0 and 6.0 mg/kg/day vamorolone groups showed significant improvement vs. placebo on motor outcomes, and improvements were comparable to the

prednisone group. In view of the initial clinical evidence of safety, the improvements observed in the assessments of efficacy, and the nature of potential adverse effects that can be monitored, the data support an acceptable benefit/risk profile for vamorolone.

2 STUDY OBJECTIVES AND ENDPOINTS - 2.1.2 Secondary Objective

Original Text:
and efficacy (miR146a, MDC and CK)
Revised Text:
and efficacy (CD23 and MDC)

2 STUDY OBJECTIVES AND ENDPOINTS - 2.2.1Clinical Efficacy Endpoints

Original Text:
Exploratory biomarkers for treatment response including CK, MDC and mIR146a
Revised Text:
Exploratory biomarkers for treatment response including MDC and CD23

2. STUDY OBJECTIVES AND ENDPOINTS - 2.2.2 Safety Endpoints – item#4
Original Text:
Hematology and clinical chemistry;
GLDH;
GGT;
Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]); and
Urinalysis
Revised Text:
Hematology and clinical chemistry;
GLDH;
GGT;
CK;
Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]); and
Urinalysis

3. STUDY DESIGN - 3.1 Overall Study Design
Original Text:
A total of approximately 39 subjects ages 12 to <65 years will be enrolled in the study
Revised Text:
Exploratory biomarkers for treatment response including MDC and CD23

3. STUDY DESIGN - 3.2 Randomization – paragraph #1, 2, 3
Original Text:
Following consent and review of study entry criteria to confirm subject eligibility for the study, the subject can be randomized to treatment. Randomization should be performed at least 10 days prior to the baseline visit and will be achieved via the Interactive Voice/Web Response System (IXRS) system with user name and password access. Randomization will be stratified only by age; randomization will not be stratified by investigational site. Randomization will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study, and to verify that the child has not previously been randomized. The following information will need to be entered into the IXRS system in order to assign the subject to a treatment group and the appropriate age stratification group:

• Participant's Study Subject Identification Number
• Participant's Date of Birth
• Participant's weight, as recorded at the Screening Visit

When the site investigator/designee completes the randomization procedures via the IXRS system, an e-mail report with the randomization number and age stratification group will be generated and sent to the clinical trials supply company confirming randomization into the trial.
The randomization number will be assigned by the IXRS system and will only be used for study drug supply and shipment. Once the information has been received, the clinical trials supply company will prepare a subject-specific kit of study medication and ship it to the pharmacy at the study site.

Randomization procedures should be completed at least 10 days prior to the Baseline Visit in order to allow study drug supply to be shipped to the site in time to be dispensed to the participant by the site investigator for Day 1 dosing.

Revised Text:
Following consent and review of study entry criteria to confirm subject eligibility for the study, the subject can be randomized to treatment. Randomization should be performed at least 10 days prior to the baseline visit and will be achieved using Almac's-WebEZTM system with user name and password access. Randomization will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study, and to verify that the subject has not previously been randomized.

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

The sites will be pre-seeded with individual, uniquely numbered bottles labeled with a write-in area to add the patient number after the bottles are assigned. Almac's-WebEZTM will assign 6 bottles at a time.

3. STUDY DESIGN - 3.3 Blinding – paragraph #2
Original Text:
Study medication will be shipped to the sites in 100 mL bottles labeled with subject-specific identifiers.
Revised Text:
Study medication will be shipped to the sites in 120 mL bottles labeled with a write-in area to add the patient number after the bottles are assigned.

4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS - 4.1 Subject Enrollment and Identification Log
Original Text:
Subjects will not be excluded on the basis of race, ethnicity, or age, except that the target population for the trial is 12 - <65 years of age.
Revised Text:
Subjects will not be excluded on the basis of race, ethnicity, or age, except that the target population for the trial is 18 - <65 years of age.

4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS - 4.2 Inclusion Criteria
Original Text:

1. Subject or Subject's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements;
3. Subject is ≥ 12 years of age and <65 years of age at time of first dose of study drug;
4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) ≤ 30 sec; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32

Revised Text:

1. Subject has provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements.
3. Subject is ≥ 18 years of age and <65 years of age at time of first dose of study drug;
4. Subject is able to perform the timed run/walk 10 meters assessment (TTRW) in ≤ 30 sec at screening; assistive devices, cane or walker, are allowed.
5. Subject has an NSAA score ≤ 32 at screening.

4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS - 4.3 Exclusion Criteria

Original Text:

6. Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents [Note: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 6 months cumulative, with last use at least 3 months prior to first dose of study medication, will be considered for eligibility on a case- by-case basis. Inhaled and/or topical corticosteroids prescribed for an indication other than BMD are permitted but must be administered at stable dose for at least 4 weeks prior to study drug administration and anticipated to be continued at a stable dose for the duration of the study];
8. Subject has used idebenone within 4 weeks prior to the first dose of study medication

Revised Text:

None

4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS - 4.4 Withdrawal of Subjects from Study

Original Text:

A subject may withdraw from the study, or may be withdrawn by his parent or guardian at any time without the need to justify the decision

The subject or the subject's parent/legal guardian are uncooperative/noncompliant and do not adhere to study responsibilities, including failure to attend study visits;

Revised Text:

A subject may withdraw from the study at any time without the need to justify the decision.

- The subject is uncooperative/noncompliant and does not adhere to study responsibilities, including failure to attend study visits;

5 TREATMENT OF STUDY SUBJECTS - 5.4 Rationale for Dose Selection - paragraph#2 and 3

Original Text:

Vamorolone at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day has been demonstrated to be safe and well-tolerated in 48 DMD boys 4 to <7 years (12 subjects at each dose level) in a 2-week Phase IIa study (VBP15-002), and a 24-week Phase II extension study (VBP15-003). The

safety of these doses continues to be evaluated in the same subjects in the recently completed VBP15-LTE 24-month extension study. The safety of the 2.0 mg/kg/day and 6.0 mg/kg/day doses is also being studied in an ongoing 52-week double-blind, comparator- and placebo-controlled study (VBP15-004) in approximately 120 subjects randomized to receive
vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo for the first 24 weeks of the study, and then vamorolone 2.0 mg/kg/day or vamorolone
6.0 mg/kg/day for the final 20 weeks of the study.
There has been a total of 11 SAEs to date in the vamorolone program, none related to study drug. One subject receiving 6.0 mg/kg/day vamorolone in VBP15-004 developed an AE of acute cholestatic hepatitis manifested by elevated transaminases, direct bilirubin, ALP and GGT which led to discontinuation from the study.
Revised Text:
Vamorolone at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day has been demonstrated to be safe and well-tolerated in 48 DMD boys 4 to <7 years (12 subjects at each dose level) in a 2-week Phase IIa study (VBP15-002), a 24-week Phase II extension study (VBP15-003), and a 24-month extension study (VBP15-LTE). The safety of the 2.0 mg/kg/day and 6.0 mg/kg/day doses is also being studied in a recently completed 52-week double-blind, comparator- and placebo controlled study (VBP15 004) in 120 subjects receiving vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo for the first 24 weeks of the study, and then vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for the final 24 weeks of the study.

There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza-associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in a subject receiving 6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study.

5 TREATMENT OF STUDY SUBJECTS - 5.4 Rationale for Dose Selection
Original Text:
None
Revised Text:
The results of the VBP15-004 24-week double-blind, placebo- and prednisone-controlled study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day showed significant enhancement of muscle strength, mobility, and functional exercise capacity vs. placebo. This study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day did not cause the growth retardation and deleterious changes in bone biomarkers seen with prednisone in this head-to-head comparison.

5 TREATMENT OF STUDY SUBJECTS - 5.5 Treatment Compliance
Original Text:
or the subject's parent(s) or guardian(s)
Revised Text:
None

5 TREATMENT OF STUDY SUBJECTS - 5.7.3 Prohibited Therapies
Original Text:
- Idebenone: use must be discontinued at least 4 weeks prior to enrollment

Revised Text:

None

5 TREATMENT OF STUDY SUBJECTS - 5.8.1 Packaging and Labeling of Study Medication

Original Text:

When all entry criteria are met, and at least 10 days prior to the Baseline Day -1 Visit, subjects will be randomized to treatment via the IXRS system. Subject-specific suspension study drug supplies sufficient for the first six weeks of Treatment Period will be packaged, labeled (with MED ID number and other protocol-specific information) and couriered to the pharmacy at the recruiting site prior to the Baseline Visit for the subject.

Investigational medication suspension and matching placebo suspension will be packaged in sterile 120 mL (4 oz) amber bottles with a 100 mL fill volume with child-resistant cap with a 24 mm bottle press-in adapter. Bottles are filled with 110 mL of suspension in order to guarantee a delivery of 100 mL.

Revised Text:

When all entry criteria are met, and at least 10 days prior to the Baseline Day -1 Visit, subjects will be randomized to treatment via the Almac's-WebEZTM system. The sites will be pre-seeded with individual, uniquely numbered bottles labeled with a write-in area to add the patient number after the bottles are assigned. The subject will be supplied with sufficient study drug for the first twelve weeks of the Treatment Period.

Investigational medication suspension and matching placebo suspension will be packaged in sterile 120 mL (4 oz) amber bottles with a 107 mL fill volume with child-resistant cap with a 24 mm bottle press-in adapter. Bottles are filled with 107 mL of suspension in order to guarantee a delivery of 100 mL.

6 STUDY SCHEDULE- 6.1 Time and Events Schedule

Original Text:

Table 2. Schedule of Study Activities

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25- (±1w)
Informed Consent	X						
Enrollment	X						
Inclusion/exclusion criteria	X	X					
Randomization[a]	X						
Medical History	X						
Medication History	X	X					
Physical Examination	X	X			X	X	X
Varicella immunity	X						
Height	X				X	X	
Weight	X	X			X	X	X
Vital Signs	X	X	X	X	X	X	X
Neuro-QOL questionnaires[b]		X				X	
TTRW	X	X			X	X	
NSAA	X	X			X	X	
Blood for Clinical Labs[c]	X			X	X	X	
Urinalysis[c]	X			X	X	X	
Blood for PK[d]			X				
Blood for Safety PD Biomarker Panel[e]			X			X	
Blood and urine for Efficacy PD Biomarker Panel[f]			X		X	X	
Fasting blood for insulin and glucose [g]			X		X	X	
Saliva for cortisol[h]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	
Return Study Medication/ Compliance Monitoring					X	X	
Study Medication Dosing[i]			X		X	X	
Study Medication dose tapering[j]							X
Dispense Subject Diaries			X		X		
Return Subject Diaries				X	X	X	
AE/SAE Recording	X	→	→	→	→	→	
Concomitant Medications			X	→	→	→	→
Discharge from Study[j]						X	X

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

[a] Randomization occurs by Interactive Voice/Web Response System (IXRS) after subjects are confirmed to have met all study entry criteria, at least 10 days prior to the Baseline Day -1 Visit.

[b] NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep

[c] Clinical safety labs: chemistry, hematology, GLDH, GGT, lipids; urinalysis by dipstick and microscopic

[d] Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin

[e] Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

[f] Serum efficacy pharmacodynamic biomarkers: CK, MDC and mIR146a; urine efficacy pharmacodynamic biomarker: mIR146a

[g] Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic

[h] Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening

[I] The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home.

[j] Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use to continue administration of vamorolone or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication

Revised Text:

Table 7. Schedule of Study Activities

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25- (±1w)
Informed Consent	X						
Enrollment	X						
Inclusion/exclusion criteria	X	X					
Randomization[a]	X						
Medical History	X						
Medication History	X	X					
Physical Examination	X	X			X	X	X
Varicella immunity	X						
Height	X				X	X	
Weight	X	X			X	X	X
Vital Signs	X	X	X	X	X	X	X
Neuro-QOL questionnaires[b]		X				X	
TTRW	X	X			X	X	
NSAA	X	X			X	X	
Blood for Clinical Labs[c]	X			X	X	X	
Urinalysis[c]	X			X	X	X	
Blood for PK[d]			X				
Blood for Safety PD Biomarker Panel[e]			X			X	
Blood for Efficacy PD Biomarker Panel[f]			X		X	X	
Fasting blood for insulin and glucose [g]			X		X	X	
Saliva for cortisol[h]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	
Return Study Medication/ Compliance Monitoring					X	X	
Study Medication Dosing[i]			X →	→	→	→	
Study Medication dose tapering[j]							X
Dispense Subject Diaries			X		X	X[k]	
Return Subject Diaries				X	X	X	X[k]
AE/SAE Recording	X →	→	→	→	→	→	→
Concomitant Medications			X →	→	→	→	→
Discharge from Study[j]						X	X[k]

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

[a] Randomization occurs by Almac-WebEZ System after subjects are confirmed to have met all study entry criteria, at least 10 days prior to the Baseline Day -1 Visit.

[b] NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep

[c] Clinical safety labs: chemistry, hematology, GLDH, GGT, lipids; urinalysis by dipstick and microscopic

[d] Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

[e] Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin

[f] Serum efficacy pharmacodynamic biomarkers: MDC and CD23

[g] Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic

[h] Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening

[i] The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home.

[j] Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use protocol for administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication.

[k] Only for subjects participating in the Dose-tapering Period

6 STUDY SCHEDULE- 6.2 Informed Consent and Assent Procedures

Original Text:

or the parent (s)
or the subject's parent(s)

Revised Text:

None
None

6 STUDY SCHEDULE- 6.2.1 HIPAA and Protected Health Information
Original Text:
subject's parent or guardian
Revised Text:
None

6 STUDY SCHEDULE- 6.3 Visit Schedule and Procedures
Original Text:
, some of the assessments scheduled for the Week 12 and Week 24 Visits may be completed on the day prior to the Week 12 or Week 24 dose of study medication, respectively, if needed

Revised Text:
, some of the assessments scheduled for the Week 12 and Week 24 Visits may be completed on a different day within the timeframe of +/- 1 week to the Week 12 or Week 24

6 STUDY SCHEDULE- 6.3.1 Screening Period (Day -35 to -3) – paragraph #4
Original Text:
None
Revised Text:
• Dispensing of saliva collection kit to measure cortisol (if subject meet all screening eligibility criteria)

6 STUDY SCHEDULE- 6.3.2Baseline Period (Day -1) Visit
Original Text:
IXRS
Revised Text:
Almac-WebEZ

6 STUDY SCHEDULE- 6.3.4 Treatment Period (Weeks 1-24) – paragraph #3
Original Text:
Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the Weeks 12, and 24 study visits
Revised Text:
Subjects must have fasted ≥ 8 hours prior to arrival at the study site for the Weeks 12, and 24 study visits

6 STUDY SCHEDULE- 6.3.4 Treatment Period (Weeks 1-24) – paragraph #6
Original Text:
The scheduled Week 12 and Week 24 assessments may be performed over a 2-day period, if necessary,
Revised Text:
The scheduled Week 12 and Week 24 assessments may be performed over a 1 week period, if necessary,

6 STUDY SCHEDULE- 6.3.5 Dose-tapering Period (Weeks 25-28)
Original Text:
Table 3
Revised Text:
Table 8

7 STUDY ASSESSMENTS AND MEASUREMENTS - 7.2.2 Physical Examination, Cushingoid Features, Weight, and Height – paragraph #2

Original Text:
Standing height will be measured for subjects in the 2-<4 years age group.
Revised Text:
None

7 STUDY ASSESSMENTS AND MEASUREMENTS - 7.2.4 Clinical Laboratory Tests
Original Text:
Table 4
Table 5
Revised Text:
Table 9
Table 10

7 STUDY ASSESSMENTS AND MEASUREMENTS - 7.2.6 Pharmacodynamic Biomarker Panel
Original Text:
Table 6

Drug target (inflammatory)
miR146a/b
MDC
CK

Revised Text:
Table 11

Drug target (inflammatory)
CD23
MDC

7 STUDY ASSESSMENTS AND MEASUREMENTS - 7.2.8 Total Blood Volume Required
Original Text:
Table 7
[d] CK, MDC and mIR146a

Revised Text:
Table 12
[d] MDC and CD23

7 STUDY ASSESSMENTS AND MEASUREMENTS – 7.4, 7.5, 7.6
Original Text:
or the subject's parent(s) or guardian(s)
or their parent(s) or legal guardian(s)
Revised Text:
None
None

15. APPENDICES - 15.2 Vamorolone 4.0% Suspension Dispensing Guide
Original text:

Each subject enrolled in the study will be dispensed 100 ml bottle(s) of vamorolone 4.0% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit.

Additional supplies will be dispensed at the Week 12 Visit, sufficient for dosing through the time of the scheduled Week 24 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4.0% suspension at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see Section 6.3.5).
The number of bottles to be dispensed at each dispensing visit for the following 12-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 1*) by 91 days (84 days in the dosing period + 7 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 2*, below:

Equation 2 $\dfrac{\textbf{Daily Dose (mL/Day) x 91 Days}}{\textbf{100 mL for 12 Weeks Dosing}}$ **= # Bottles to be Dispensed**

Example 2: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of **12.5** mL (from Example 1 above):

$$\frac{\textbf{Daily Dose (12.5 mL/Day) x 91 Days}}{\textbf{100 mL}} = \textbf{11.40 Bottles}$$

The number of bottles dispensed is rounded up to the nearest whole integer, or 1**2** bottles to be dispensed.

Revised text:
Each subject enrolled in the study will be dispensed 120 ml bottle(s), each containing at least 107 mL of vamorolone 4.0% or matching placebo suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Additional supplies will be dispensed at the Week 12 Visit, sufficient for dosing through the time of the scheduled Week 24 Visit. Subjects whose study medication dose is tapered during the Dose-tapering Period will be dispensed additional study medication at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see Section 6.3.5).
The number of bottles to be dispensed at each dispensing visit for the following 12-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 1*) by 95 days (84 days in the dosing period + 11 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 2*, below:

Equation 1 $\dfrac{\textbf{Daily Dose (mL/Day) x 95 Days}}{\textbf{100 mL for 12 Weeks Dosing}}$ **= # Bottles to be Dispensed**

Example 2: Calculation of number of bottles to be dispensed for 12-week dosing for a subject taking a daily dose of **12.5** mL (from Example 1 above):

$$\frac{\textbf{Daily Dose (12.5 mL/Day) x 95 Days}}{\textbf{100 mL}} = \textbf{11.9 Bottles}$$

The number of bottles dispensed is rounded up to the nearest whole integer, or 12 bottles to be dispensed

15.2.3 Protocol Amendment #3 Complete List of Changes

The following changes have been incorporated into the protocol under this protocol amendment, as summarized in Protocol Amendment Tracking, Reasons for Protocol Amendment #3. Protocol sections that have been changed are itemized below with the original and revised text

SERIOUS ADVERSE EVENT CONTACT INFORMATION
Original text:
In United States and Canada:
In Europe, Asia-Pacific and Africa (EAPA):
Revised text:
In North/South America:
In Europe, Asia-Pacific and Africa (EAPA):

SYNOPSIS: Protocol Title
Original text:
A Phase II Pilot Trial of Vamorolone for the Treatment of Becker Muscular Dystrophy
Revised text:
A Phase II Pilot Trial of Vamorolone vs. Placebo for the Treatment of Becker Muscular Dystrophy

SYNOPSIS: Inclusion Criteria
Original text:
1. Subject has provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements
3. Subject is ≥ 18 years of age and <65 years of age at time of first dose of study drug
7. Subject is willing and able to comply with scheduled visits, study drug administration plan, and study procedures
8. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
9. Subject has evidence of chicken pox immunity as determined by:

- Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR

- Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;

10. Subject is willing and able to comply with scheduled visits, study medication administration plan, and study procedures.

11. Subject of childbearing potential agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed.

Revised text:

1. Subject has provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures

3. Subject is ≥ 18 years of age and <65 years of age at time of informed consent

7. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];

8. Subject has evidence of chicken pox immunity as determined by:

a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR

b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;

9. Subject is willing and able to comply with scheduled visits, study medication administration plan, and study procedures.

10. Subject agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed.

SYNOPSIS: Exclusion Criteria

Original text:

Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility

Revised text:
Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result.

SYNOPSIS: Study Period
Original text:
First subject screened: 1Q 2022
Last subject last visit: 1Q 2024
Revised text:
First subject screened: 3 Q 2022
Last subject last visit: 3 Q 2024.

SYNOPSIS: Study Drug Formulation, Dosage & Administration
Original text:
The daily dose of study medication should be taken with breakfast including at least 8 g of fat (approximately 8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).

Revised text:
The daily dose of study medication should be taken with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food.

SYNOPSIS: Study Summary
Original text:
A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study, and make recommendations to the Sponsor and Study Team regarding study conduct
Revised text:
A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the NIAMS regarding study conduct. The Study Team will receive the recommendations through the NIAMS Executive Secretary and share them with ReveraGen.

SYNOPSIS: Dose-Limiting Toxicities, and Stopping Criteria
Original text:
The sponsor
Revised text:
ReveraGen

SYNOPSIS: Dose-Limiting Toxicities, and Stopping Criteria
Original text:
Clinical AEs and clinical laboratory AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, dated June 14, 2010
Revised text:
Clinical AEs and clinical laboratory AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 , dated November 27, 2021

SYNOPSIS: Safety Measures
Original text*:*
- o Hematology and clinical chemistry
- o GLDH
- o CK

Revised text:
- o Hematology and clinical chemistry
- o CK

SYNOPSIS: Patient-reported Outcome Measures
Original text:
NeuroQOL patient-reported outcome measures for fatigue, mobility and sleep
Revised text:
NeuroQOL patient-reported outcome measures for fatigue, upper and lower extremity function, and sleep

SYNOPSIS: Statistical Methods – Analysis Population
Original text:
The Per Protocol Population will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data
The PK Population consisted of all subjects who received at least one dose of study medication and had sufficient quantifiable plasma concentration data for PK analysis
Revised text:
The Per Protocol Population will be those subjects in the mITT Population who had no important protocol deviations and will be the secondary analysis population for analysis of the efficacy data
The PK Population consisted of all subjects who received a dose of vamorolone on Day 1 and had sufficient quantifiable plasma concentration data for PK analysis.

SYNOPSIS: Statistical Methods – Safety and Tolerability Analyses
Original text:
Adverse events will be summarized overall and by system organ class (SOC) and preferred term (PT) (using the Medical Dictionary for Regulatory Activities [MedDRA], version 20.0) and by relationship to study medication and intensity (CTCAE grade, version 4.03) and AE outcome
Revised text:
Adverse events will be summarized overall and by system organ class (SOC) and preferred term (PT) (using the Medical Dictionary for Regulatory Activities [MedDRA], version 25.0) and by relationship to study medication and intensity (CTCAE grade, version 5.0) and AE outcome.

LIST OF ABBREVIATIONS
Original text:
6MWT – Six Minute walk test
Revised text:
Deleted 6MWT
Added NIAMS - The National Institute of Arthritis and Musculoskeletal and Skin Diseases
Added UP - Unanticipated Problem

INTRODUCTION – Section 1.4 Rationale for Study Design
Original text:
Paragraph 5:
Patient-reported outcomes will be assessed with the NeuroQOL for fatigue, mobility and sleep.
Revised text:
Paragraph 5:
Patient-reported outcomes will be assessed with the NeuroQOL for fatigue, upper and lower extremity function, and sleep.

STUDY OBJECTIVES AND ENDPOINTS – Section 2.2 Study Endpoints
Original text:
2.2.1 Clinical Efficacy Endpoints
2.2.2 Safety Endpoints
Hematology and clinical chemistry;
GLDH;
GGT;

2.2.3 Tolerability Endpoint
2.2.4 Exploratory Endpoints
2.2.5 Pharmacokinetics Analysis
2.2.6 Pharmacodynamic Endpoints

Revised text:

2.2.1 Safety Endpoints
a. Hematology and clinical chemistry;
b. GGT;
2.2.2 Tolerability Endpoint
2.2.3 Pharmacokinetics Analysis
2.2.4 Pharmacodynamic Endpoints
2.2.5 Clinical Efficacy Endpoints
2.2.6 Exploratory Endpoints

STUDY DESIGN – Section 3.1 Overall Study Design

Original text:

Paragraph 3:

A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor and Study Team regarding study conduct.

Revised text:

Paragraph 3:

A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the NIAMS regarding study conduct. The Study Team will receive the recommendations through the NIAMS Executive Secretary and share them with ReveraGen

STUDY DESIGN – Section 3.1 Overall Study Design

Original text:

Paragraph 8:

None

Revised text:

Paragraph 8:

To ensure the safety of trial participants, maintain compliance with good clinical practice (GCP), and minimize risks to trial integrity relating to the COVID-19 pandemic, the investigators, study team staff, and participants of the VBP15-BMD-001 study should follow the guidelines around social/behavioral interactions consistent with national, local and institutional COVID-19 prevention guidance (U.S. Food and Drug Administration, 2020).

STUDY DESIGN – Section 3.2 Randomization

Original text:

Paragraph 3:

The sites will be pre-seeded with individual, uniquely numbered bottles labeled with a write-in area to add the patient number after the bottles are assigned. Almac's-WebEZTM will assign 6 bottles at a time.

Revised text:

Paragraph 3:

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

bottles will be sufficient supply for 12 weeks of dosing

SELECTION AND WITHDRAWAL OF STUDY SUBJECTS – Section 4.2 Inclusion Criteria
Original text:
1. Subject has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements
3. Subject is ≥ 18 years of age and <65 years of age at time of first dose of study drug;
7. Subject is willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
8. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
9. Subject has evidence of chicken pox immunity as determined by:
a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;
10. Subject is willing and able to comply with scheduled visits, study medication administration plan, and study procedures.
11. Subject of childbearing potential agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed
Revised text:
1. Subject has provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures
3. Subject is ≥ 18 years of age and <65 years of age at time of informed consent
7. Subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to first administration of study medication. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to first administration of study medication or if administered at stable dose beginning at least 4 weeks prior to first administration of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
8. Subject has evidence of chicken pox immunity as determined by:
a. Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR
b. Documentation, provided at the Screening Visit, that the subject has received 2 doses of varicella vaccine, with or without serologic evidence of immunity, with the second of the 2 immunizations given at least 14 days prior to first administration of study medication;
9. Subject is willing and able to comply with scheduled visits, study medication administration plan, and study procedures.
10. Subject agrees to use barrier contraception methods during his participation in this study and for 30 days after the tapering dose is completed

SELECTION AND WITHDRAWAL OF STUDY SUBJECTS – Section 4.3 Exclusion Criteria
Original text:
3. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;

4. Subject has a history of primary hyperaldosteronism

Revised text:

3. Subject has had an acute illness within 4 weeks prior to the first dose of study medication;

4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to administration of study medication;

SELECTION AND WITHDRAWAL OF STUDY SUBJECTS – Section 4.4 Withdrawal of Subjects from Study

Original text:

the Sponsor
Coordinating Center

Revised text:

ReveraGen
Study Project Manager

SELECTION AND WITHDRAWAL OF STUDY SUBJECTS – Section 4.5 Termination of Study

Original text:

the Sponsor

Revised text:

ReveraGen

TREATMENT OF STUDY SUBJECTS – Section 5.3 Dosage Schedule and Administration of Study Medication

Original text:

Paragraph 6
The daily dose of study medication should be taken with breakfast, including at least 8 g of fat (approximately 8 ounces [240 mL] of full-fat milk or equivalent high- fat food portion).
Paragraph 7
At the Day 1, Week 12, and Week 24 study visits, subjects will arrive at the study clinic after having fasted for ≥ 8 hours, and will eat breakfast at the study site within 30 minutes prior to administration of the dose of study medication; breakfast at the site will include at least 8 g of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).

Revised text:

Paragraph 6
The daily dose of study medication should be taken with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food.
Paragraph 7
At the Day 1, Week 12, and Week 24 study visits, subjects will arrive at the study clinic after having fasted for ≥ 8 hours, and will eat breakfast at the study site. On Day 1, food will be taken within 30 minutes prior to administration of the dose of study medication.

TREATMENT OF STUDY SUBJECTS – Section 5.4 Rationale for Dose Selection – paragraph 6

Original text:

Paragraph 6
Vamorolone will be administered in the morning with breakfast, including at least 8 g of fat (approximately 8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).

Revised text:

Paragraph 6

Vamorolone will be administered with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food.

TREATMENT OF STUDY SUBJECTS – Section 5.6 Study Drug Dose Interruption or Discontinuation
Original text:
the Sponsor
Revised text:
ReveraGen

TREATMENT OF STUDY SUBJECTS – Section 5.7.1 Prior Therapy
Original text:
All past (lifetime) steroid use will be recorded.
Revised text:
Steroid use within the last 12 months will be recorded. Any earlier steroid use that the subject recalls can also be recorded.

TREATMENT OF STUDY SUBJECTS – Section 5.8.1, 5.8.3, 5.8.4
Original text:
the Sponsor
Revised text:
ReveraGen

TREATMENT OF STUDY SUBJECTS – Section 5.9
Original text:
Coordinating Center
Revised text:
SPM

STUDY SCHEDULE
Original text:
Table 12. Schedule of Study Activities

Study Day or Week/Visit	**Pretreatment Period**		**Treatment Period**				**Dose-tapering Period**
	Screening -35 to -3 days	**Baseline -1 day**	**Day 1**	**Week 4 (±1w)**	**Week 12 (±1w)**	**Week 24 (±1w)**	**Week 25-28 (±1w)**
Informed Consent	X						
Enrollment	X						
Inclusion/exclusion criteria	X	X					
Randomization[a]	X						

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Medical History	X						
Medication History	X	X					
Physical Examination	X	X			X	X	X
Varicella immunity	X						
Height	X				X	X	
Weight	X	X			X	X	X
Vital Signs	X	X	X	X	X	X	X
Neuro-QOL questionnaires[b]		X				X	
TTRW	X	X			X	X	
NSAA	X	X			X	X	
Blood for Clinical Labs[c]	X			X	X	X	
Urinalysis[c]	X			X	X	X	
Blood for PK[d]			X				
Blood for Safety PD Biomarker Panel[e]			X,			X	
Blood for Efficacy PD Biomarker Panel[f]			X		X	X	
Fasting blood for insulin and glucose [g]			X		X	X	
Saliva for cortisol[h]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Return Study Medication/ Compliance Monitoring					X	X	
Study Medication Dosing[i]			X	→	X	X	→
Study Medication dose tapering[j]							X
Dispense Subject Diaries			X		X	X[k]	
Return Subject Diaries				X	X	X	X[k]
AE/SAE Recording	X	→	→	→	→	→	→
Concomitant Medications			X	→	→	→	→
Discharge from Study[j]						X	X[k]

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

[a] Randomization occurs by Almac's-WebEZ™ System after subjects are confirmed to have met all study entry criteria, prior to the Baseline Day -1 Visit.

[b] NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep

[c] Clinical safety labs: chemistry, hematology, GLDH, GGT, lipids; urinalysis by dipstick and microscopic

[d] Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

[e] Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin

[f] Serum efficacy pharmacodynamic biomarkers: MDC and CD23

[g] Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic

[h] Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening

[i] The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home.

[j] Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use protocol for administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication.

[k] Only for subjects participating in the Dose-tapering Period

Revised text:

Table 6. Schedule of Study Activities

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

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Blood for Clinical Labs[c]	X		X	X	X	X	X
Urinalysis[c]	X		X	X	X	X	X
Blood for PK[d]			X				
Blood for Safety PD Biomarker Panel[e]			X,			X	
Blood for Efficacy PD Biomarker Panel[f]			X		X	X	
Fasting blood for insulin and glucose[g]			X		X	X	
Saliva for cortisol[h]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	
Return Study Medication/ Compliance Monitoring				X	X	X	
Study Medication Dosing[i]			X →	→	X →	X →	
Study Medication dose tapering[j]							X

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25-28 (±1w)
Dispense Subject Diaries			X		X	X[j]	
Return Subject Diaries				X	X	X	X[j]
AE/SAE Recording	X →	→	→	→	→	→	→
Concomitant Medications			X →	→	→	→	→
Follow up phone call							x[k]
Discharge from Study[l]						X	X

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

[a] Randomization occurs by Almac's-WebEZ™ System after subjects are confirmed to have met all study entry criteria, prior to the Baseline Day -1 Visit.

[b] NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep

[c] Clinical safety labs: chemistry, hematology, CK, GGT, lipids; urinalysis by dipstick and microscopic

[d] Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

[e] Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin

[f] Serum efficacy pharmacodynamic biomarkers: MDC and CD23

[g] Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic

[h] Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening

[i] The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home

[j] Only for subjects participating in the Dose-tapering Period

[k] At Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication

[l] Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use protocol for administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication

STUDY SCHEDULE – Section 6.2 Informed Consent Procedures

Original text:

Paragraph 4

Informed Consent Forms must be dated and signed by the Investigator or designee and the subject or subject's legal representative(s) and the original signed consent form must be kept by the Investigator in the study subject's file. "Legal representative" means an individual whom a judicial or other body has authorized under applicable law to consent on behalf of a prospective study subject to the subject's participation in the procedure(s) involved in the research. The Study Monitor will ensure that the ICF has been signed by the subject or subject's legal representative(s). The subject or study subject's legal representative(s) will receive a copy of the signed consent form.

Revised text:

Paragraph 4

Informed Consent Forms must be dated and signed by the Investigator or designee and the subject and the original signed consent form must be kept by the Investigator in the study subject's file.

STUDY SCHEDULE – Section 6.3 Visit Schedule and Procedures

Original text:

In addition, a telephone call from site staff to the subject will occur at Week 26 for subjects participating in the Dose-tapering Period

Revised text:

In addition, a telephone call from site staff to the subject will occur at Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication.

STUDY SCHEDULE – Section 6.3.1 Screening Period (Day -35 to -3)

Original text:

and the subject's de- identified dystrophin genetic test report will be reviewed by the Coordinating Center for confirmation that the subject meets the Becker dystrophy diagnostic inclusion criteria

The following procedures will be completed at the Screening Visit:

- Collection of blood for clinical laboratory testing (hematology, clinical chemistry, GLDH, GGT, and lipids) and collection of urine for urinalysis (see Section 7.2.4)
- Dispensing of saliva collection kit to measure cortisol (if subject meet all screening eligibility criteria)

Revised text:

The subject's dystrophin genetic test report will be reviewed by the site PI for confirmation that the subject meets the Becker dystrophy diagnostic inclusion criteria
The following procedures will be completed at the Screening Visit:
- Informed Consent (see Section 6.2)
- Collection of blood for clinical laboratory testing (hematology, clinical chemistry, GGT, and lipids) and collection of urine for urinalysis (see Section 7.2.4)

STUDY SCHEDULE – Section 6.3.2 Baseline Period (Day -1) Visit
Original text:
The following procedures will be completed at the Baseline Day -1 Visit:
Revised text:
The following procedures will be completed at the Baseline Day -1 Visit:
- Recording of prior medications (Medication History) (see Section 5.7.1)• Collection of blood for clinical laboratory testing (hematology, clinical chemistry, GGT, and lipids) and collection of urine for urinalysis (see Section 7.2.4)
- The patient-reported outcomes (Neuro-QOL for fatigue, upper and lower extremity function, and sleep)
- Dispensing of saliva collection kit to measure cortisol.

STUDY SCHEDULE – Section 6.3.3 Treatment Period Day 1 Visit
Original text:
Breakfast, including at least 8 g of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion) will be served at the study site after the blood collections for clinical laboratory tests and PD biomarkers, and within 30 minutes prior to administration of the dose of study medication
The following procedures will be completed at the Treatment Period Day 1 Visit:
- Clinical laboratory evaluation including hematology, clinical chemistry, GLDH, GGT, lipids, and urinalysis tests, prior to administration of first dose of study drug (see Section 7.2.4)

Revised text:
Breakfast will be served at the study site after the blood collections for clinical laboratory tests and PD biomarkers, and within 30 minutes prior to administration of the dose of study medication
The following procedures will be completed at the Treatment Period Day 1 Visit:
- Clinical laboratory evaluation including hematology, clinical chemistry, GGT, lipids, and urinalysis tests, prior to administration of first dose of study drug (see Section 7.2.4)

STUDY SCHEDULE – Section 6.3.4 Treatment Period (Weeks 1-24)
Original text:
The daily dose of study medication should be taken with breakfast, including at least 8 g of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).
Breakfast, including at least 8 g of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion) will be served at the study site after the blood collections for clinical laboratory tests (Weeks 12 and 24)
Revised text:
The daily dose of study medication should be taken with food at approximately the same time each morning; the study drug is not absorbed well if not taken with food.
Breakfast will be served at the study site after the blood collections for clinical laboratory tests (Weeks 12 and 24).

STUDY SCHEDULE – Section 6.3.5 Dose-tapering Period (Weeks 25-28)
Original text

Subjects will take the first dose of study medication in the Dose-tapering Period (Week 25 dose level) with a high-fat meal
Revised text:
Subjects will take the first dose of study medication in the Dose-tapering Period (Week 25 dose level) with a meal

STUDY SCHEDULE – Section 6.4 Subject Discontinuation
Original text*:*
the Sponsor
Revised text:
ReveraGen

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.2.4 Clinical Laboratory Tests
Original text:
For the hematology, chemistry, GLDH, GGT, and lipids laboratory tests, blood will be collected by direct venipuncture of peripheral veins. A total of approximately 22 mL of blood will be collected over the course of this study for clinical safety laboratory evaluation
Table 8. Hematology, Chemistry, GGT, and Lipids Clinical Laboratory Tests

Hematology	
Red Blood Cells (RBC)	Platelets
Hemoglobin	White Blood Cells (WBC)
Hematocrit	
Chemistry	
Sodium	Total Bilirubin[a]
Potassium	Glucose
Chloride	Alkaline phosphatase (ALP)
Calcium	Aspartate aminotransferase (AST)
Blood Urea Nitrogen (BUN)	Alanine aminotransferase (ALT)
Creatinine	Creatine kinase (CK)
Total Protein	Bicarbonate
Albumin	Glutamate dehydrogenase (GLDH)
	Gamma glutamyl transferase (GGT)
Lipids	
Triglycerides	Low Density Lipoprotein (LDL)

Total cholesterol	High Density Lipoprotein (HDL)

Revised text:
For the hematology, chemistry, GGT, and lipids laboratory tests, blood will be collected by direct venipuncture of peripheral veins. A total of approximately 30 mL of blood will be collected over the course of this study for clinical safety laboratory evaluation
Table 8. Hematology, Chemistry, GGT, and Lipids Clinical Laboratory Tests

Hematology	
Red Blood Cells (RBC)	Platelets
Hemoglobin	White Blood Cells (WBC)
Hematocrit	
Chemistry	
Sodium	Total Bilirubin[a]
Potassium	Glucose
Chloride	Alkaline phosphatase (ALP)
Calcium	Aspartate aminotransferase (AST)
Blood Urea Nitrogen (BUN)	Alanine aminotransferase (ALT)
Creatinine	Creatine kinase (CK)
Total Protein	Bicarbonate
Albumin	Gamma glutamyl transferase (GGT)
Lipids	
Triglycerides	Low Density Lipoprotein (LDL)
Total cholesterol	High Density Lipoprotein (HDL)

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.2.6 Pharmacodynamic Biomarker Panel
Original text:
None
A total of approximately 20 mL of blood will be collected for safety PD biomarkers (fasting insulin, osteocalcin, HbA1c) over the course of the 33-week study
Revised text:

Added paragraph 3: Approximately 6 mL of blood will be collected for the efficacy PD biomarker panel (MDC and CD23) at Day 1, Week 12 and Week 24.
A total of approximately 42 mL of blood will be collected for safety and efficacy PD biomarkers (fasting insulin, osteocalcin, HbA1c, MDC and CD23) over the course of the 33-week study

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.2.7 PK Assessment
Original text:
The procedures for the collection, handling, and shipping of laboratory samples will be specified in the Laboratory Manual(s) provided to the study sites
Revised text:
The procedures for the collection, handling, and shipping of laboratory samples will be specified in the VBP15-BMD-001_GUIDELINES for Biological Specimen Collection provided to the study sites

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.2.8 Total Blood Volume Required
Original text:
A total of 76 mL of blood will be collected from each subject over the course of the up-to-33-week study.
Table 11. Blood Sample Number and Volume by Study Visit

Test	Blood Volume (mL)						
	SCR	**Day 1**	**Week 4**	**Week 12**	**Week 24**	**Week 28**	**Total Volume**
Varicella Zoster IgG	2						2
Clinical Lab tests[a,b]	6		6	6	6	6	30
Safety PD Biomarker Panel[c]		6			6		12
Efficacy PD Biomarker Panel[d]		6		6	6		18
Fasting blood for insulin and glucose[b]		4		4			8
PK[e]		**6**					**6**
Total Volume by Visit (mL)	8	22	6	16	18	6	76
Total Volume: 76 mL							

Revised text:

A total of 86 mL of blood will be collected from each subject over the course of the up-to-33-week study.
Table 11. Blood Sample Number and Volume by Study Visit

Test	Blood Volume (mL)						
	SCR	**Day 1**	**Week 4**	**Week 12**	**Week 24**	**Week 28**	**Total Volume**
Varicella Zoster IgG	2						2
Clinical Lab tests[a]	6	6	6	6	6	6	36
Safety PD Biomarker Panel[c]		6			6		12
Efficacy PD Biomarker Panel[d]		6		6	6		18
Fasting blood for insulin and glucose[b]		4		4	4		12
PK[e]		6					6
Total Volume by Visit (mL)	8	28	6	16	22	6	86
Total Volume: 86 mL							

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.4 Patient-Reported Outcome Measures

Original text:

Physical functioning will be assessed by completion of the NeuroQOL scales for fatigue, mobility and sleep. The subject will be asked to complete this instrument at Day -1 and Week 24 Visits

Revised text:

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

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.6 Adverse Events, Serious Adverse Events Outcome Measures

Original text:

Section title: Adverse Events, Serious Adverse Events
Paragraph 2:

The Investigator is responsible for reporting AEs and SAEs to the Sponsor or designee. For reported death of a participant, the Investigator shall supply the Sponsor and the IRB/IEC with any additional information requested
Paragraph 5:
None
Revised text:
Section title: Adverse Events, Serious Adverse Events and Unanticipated Problems
Paragraph 2:
The Investigator is responsible for reporting AEs and SAEs to ReveraGen or designee. For reported death of a participant, the Investigator shall supply ReveraGen and the IRB/IEC with any additional information requested. All AEs should be reported in aggregate to the NIAMS and the DSMB (through the NIAMS Executive Secretary) as part of the routine data and safety monitoring report provided for DSMB meetings.
Paragraph 5:
Unanticipated Problems (UPs) can be either AE/SAEs, which are unexpected events that relate directly to participant safety, or protocol deviations that put patient privacy at risk or put patients at risk in some way that does not have an impact on their health and safety.
Unanticipated problems are defined as any incident, experience, or outcome that meets all of the following criteria:
unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
If UPs occur during the study, they will be reported to the IRB, the NIAMS and the DSMB (through the NIAMS Executive Secretary) by the study team. The UP report for the Monitoring Body and NIAMS will be completed and submitted to the NIAMS Executive Secretary within 48 hours of the Study Chair becoming aware of the event.

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.6.1 Intensity
Original text:
Intensity of AEs will be graded using the most current version of the CTCAE, version 4.03
Life-Threatening (Grade 4): Urgent intervention indicated.
Revised text:
Intensity of AEs will be graded using the most current version of the CTCAE, version v 5.0
Life-Threatening (Grade 4): Life-threatening consequences; urgent intervention indicated.

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.6.3 Clinical Laboratory Test Abnormalities
Original text:
The intensity of abnormal clinical laboratory test results that are AEs will also be graded using the most current version of the CTCAE, version 4.03.
Revised text:
The intensity of abnormal clinical laboratory test results that are AEs will also be graded using the most current version of the CTCAE, version 5.0.

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.6.4 Follow-Up of Adverse Events
Original text:
the Sponsor
Revised text:
ReveraGen

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.6.5 Dosing Error
Original text:
Such occurrences will be reported and recorded in the dosing page of the eCRF and as follows:
Use of study medication in doses in excess of that specified in the protocol will not be recorded as an AE unless there are associated signs or symptoms
Revised text:
Such occurrences will be reported as a Protocol Deviation, and recorded in the dosing page of the eCRF and as follows:
Use of study medication in doses in excess or less of that specified in the protocol will not be recorded as an AE unless there are associated signs or symptoms.

STUDY ASSESSMENTS AND MEASUREMENTS – Section 7.6.6 Serious Adverse Events
Original text:
the Sponsor
Paragraph 3:
During the SAE collection period, the Investigator or clinical site personnel should notify the Coordinating Center of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event; notification to the Coordinating Center will trigger alerts to the Study Chair, the Sponsor, and the Medical Monitor. The Investigator will provide the initial notification by completing the SAE Report Form in the electronic data capture (EDC) system, which must include the Investigator's assessment of the relationship of the event to investigational drug, and must be signed by the Investigator.
Paragraph 6:
Any AE (including treatment-emergent, clinically significant, abnormal laboratory test values), as determined by the Investigator, that is serious and which occurs during the course of the study (as defined above) must be reported to the Coordinating Center, who will notify the Study Chair, the Sponsor and the Medical Monitor, within 24 hours of the Investigator becoming aware of the event. Additional information that becomes available for an SAE after the initial report is submitted will be reported to the Coordinating Center, who will notify the Study Chair, the Sponsor and the Medical Monitor, within 24 hours of the Investigator becoming aware of the new information.
Paragraph 12:
Suspected Unexpected Serious Adverse Reaction (SUSAR) Identification and Reporting
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected (not identified in the Investigator's Brochure). Sponsor will inform Investigators of SUSARs in a manner and timeframe consistent with applicable national regulatory requirements
Revised text:
ReveraGen
Paragraph 3:
During the SAE collection period, the Investigator or clinical site personnel should notify all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event. All SAE reports should be completed within the EDC; both the AE and SAE eCRF within 24 hours of first awareness of the event. This triggers alerts to the ICON safety management team. The ICON safety management team works directly with sites to receive follow-up information after initial SAE notification and notify other study parties including the Medical Monitor, Study Chair, and ReveraGen

Paragraph 7:
Any AE (including treatment-emergent, clinically significant, abnormal laboratory test values), as determined by the Investigator, that is serious and which occurs during the course of the study (as defined above) must be reported within the EDC. The ICON safety management team will notify the Study Chair, ReveraGen and the Medical Monitor, within 24 hours of the Investigator becoming aware of the event. Additional information that becomes available for an SAE after the initial report is submitted will be reported to the ICON safety management team, who will notify the Study Chair, ReveraGen and the Medical Monitor, within 24 hours of the Investigator becoming aware of the new information
Paragraph 12:
Suspected Unexpected Serious Adverse Reaction (SUSAR) Identification and Reporting
Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event.
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected (not identified in the Investigator's Brochure). ReveraGen will evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event. Reveragen will notify all participating investigators of SUSARs in a manner and timeframe consistent with applicable national regulatory requirements.
Under the former 21 CFR 312.32(Investigational new Drug (IND) Safety Report), ReveraGen must report to the FDA any unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following ReveraGen's initial receipt of the information. Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within 15 calendar days following ReveraGen's initial receipt of the information.

STUDY COMMITTEES – Section 8.1Study Steering Committee
Original text*:*
A Study Steering Committee (SSC – VISION-DMD) will be responsible for protocol development, review of any study amendments, and coordination of study conduct and interpretation of study results. The SSC comprises the Sponsor, study chair and medical monitor for the VBP15-BMD-001 study, and, as applicable, the project managers, and the patient representatives.
Revised text:
None

STUDY COMMITTEES – Section 8.2 Data and Safety Monitoring Board
Original text:
A Data and Safety Monitoring Board (DSMB), operating autonomously from the Sponsor and the site investigators, will be responsible for providing independent recommendations to the Sponsor about risk-benefit of the study and for any modification affecting safety or data integrity required during the course of the study. The DSMB members must not be actively involved in study design, conduct or daily management of this study and must not have financial, propriety, professional, or other interests that may affect impartial, independent decision-making.
Specialists may be invited to participate as non-voting members at any time if additional expertise is desired. The DSMB will formally interact with the Sponsor through the sharing of DSMB meeting minutes.
The DSMB will be responsible for:
Providing expert advice to the sponsor on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects
Revised text:
A Data and Safety Monitoring Board (DSMB), operating autonomously from ReveraGen and the site investigators, will be responsible for providing independent recommendations to the NIAMS about risk-

benefit of the study and for any modification affecting safety or data integrity required during the course of the study. The DSMB members must not be actively involved in study design, conduct or daily management of this study and must not have financial, propriety, professional, or other interests that may affect impartial, independent decision-making.
Specialists may be invited to participate as non-voting members at any time if additional expertise is desired. The DSMB will formally interact with the NIAMS through the sharing of DSMB meeting minutes. The NIAMS (through the NIAMS Executive Secretary) will share any DSMB recommendation.
The DSMB will be responsible for:
Providing expert advice to the NIAMS on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects

DATA COLLECTION – Section 9.2 Electronic Case Report Form Completion
Original text:
The Coordinating Center
Revised text:
TRiNDS

STATISTICAL METHODS AND PLANNED ANALYSES– Section 10.3.2 Modified Intent-to-Treat (mITT) Population
Original text:
All subjects who receive at least one dose of study medication and have at least one post-baseline assessment will be included in the mITT Population
Revised text:
All subjects who receive at least one dose of study medication and have at least one post-baseline efficacy assessment will be included in the mITT Population

STATISTICAL METHODS AND PLANNED ANALYSES– Section 10.3.3 Per Protocol Population
Original text:
The Per Protocol Population will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data.
Revised text:
The Per Protocol Population will be those subjects in the mITT Population who had no important protocol deviations and will be the secondary analysis population for analysis of the efficacy data.

STATISTICAL METHODS AND PLANNED ANALYSES– Section 10.3.4 PK Population
Original text:
The PK Population consisted of all subjects who received at least one dose of study medication and had sufficient quantifiable plasma concentration data for PK analysis
Revised text:
The PK Population consisted of all subjects who received a dose of vamorolone on Day 1 and had sufficient quantifiable plasma concentration data for PK analysis.

STATISTICAL METHODS AND PLANNED ANALYSES– Section 10.7.1 General Considerations
Original text:
No formal interim statistical analyses are planned, apart from the interim unblinded safety data views and presentations to be created for the Data and Safety Monitoring Board (DSMB). ***Revised text:***
No formal interim statistical analyses are planned at the mid-point of the study (after week 12 visit for 39 participants), apart from the interim unblinded safety data views and presentations to be created for the Data and Safety Monitoring Board (DSMB). An interim analysis will follow interim database lock, subsequent to last patient last visit, and preceding the final database lock and final primary analysis

STATISTICAL METHODS AND PLANNED ANALYSES– Section 10.7.3 Safety and Tolerability Analyses

Original text:

Adverse events will be summarized overall and by SOC, and Preferred Term (PT) (using the Medical Dictionary for Regulatory Activities [MedDRA], version 20.0) and by relationship to study medication and intensity (CTCAE grade, version 4.03) and AE outcome

Revised text:

Adverse events will be summarized overall and by SOC, and Preferred Term (PT) (using the Medical Dictionary for Regulatory Activities [MedDRA], version 25.0) and by relationship to study medication and intensity (CTCAE grade, version 5.0) and AE outcome

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.2.2 Institutional Review Board/Independent Ethics Committee Approval and Other Institutional Requirements

Original text*:*

the Sponsor

Revised text:

ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.2.3.3 After the Study

Original text:

the Sponsor

Revised text:

ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.3.2 Reporting Important Protocol Deviations

Original text*:*

the Sponsor

Revised text:

ReveraGen

Protocol deviations that may impact participant safety will be reported to the the NIAMS and the DSMB (through the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event. Protocol deviations that do not impact participant safety will be reported in aggregate as part of the routine data and safety monitoring report sent to the DSMB and NIAMS.

Protocol deviations are reported to the IRB in accordance to their policy, within 10 days of identification of the event

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.4 Study Records Retention and Direct Access to Source Documents

Original text:

the Sponsor

Revised text:

ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.5 Study Monitoring

Original text*:*

the Sponsor

Revised text:

ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.6 Quality Assurance
***Original text**:*
the Sponsor
Revised text:
ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.7 Study Termination and Site Closure
Original text:
the Sponsor
Revised text:
ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.8 Site Termination
Original text:
the Sponsor
Revised text:
ReveraGen

STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS – Section 11.9 Discontinuation of Study
Original text:
the Sponsor
Revised text:
ReveraGen

DISCLOSURE OF DATA – Section 12.1 Confidentiality
Original text:
the Sponsor
Revised text:
ReveraGen

DISCLOSURE OF DATA – Section 12.2 Publication
Original text:
the Sponsor
Revised text:
ReveraGen
ReveraGen will observe the NIH policy on enhancing public access to archived publications resulting from NIH-funded research. NIH-funded investigators will submit to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) an electronic version of the author's final manuscript upon acceptance for publication, resulting from research supported, in whole or in part, with direct costs from NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

INVESTIGATOR PROTOCOL AGREEMENT
Original text:
the Sponsor

Revised text:
ReveraGen

15.2.4 Protocol Amendment #4 Complete List of Changes

The following changes have been incorporated into the protocol under this protocol amendment, as summarized in Protocol Amendment Tracking, Reasons for Protocol Amendment #4. Protocol sections that have been changed are itemized below with the original and revised text

Section Changed:
CLINICAL STUDY PROTOCOL information – Page 1 and Page 3.
Original Text:
Amendment #4
Document Number:VBP15-BMD-001-A3
Document Date:27 June 2022
Revised Text:
Amendment #4
Document Number:VBP15-BMD-001-A4
Document Date:20 Mar 2023

Section Changed:
CLINICAL STUDY PROTOCOL information – Page 1
Original Text:
N/A
Revised Text:
EudraCT No: 2022-000844-31

Section Changed:
PROTOCOL AMENDMENT TRACKING table – Page 5
Original Text:

Original Protocol	VBP15-BMD-001	29 September 2020
Amendment #1	VBP15-BMD-001-A1	08 June 2021
Amendment #2	VBP15-BMD-001-A2	26 October 2021
Amendment #3	VBP15-BMD-001-A3	27 June 2022

Revised Text:

Original Protocol	VBP15-BMD-001	29 September 2020
Amendment #1	VBP15-BMD-001-A1	08 June 2021
Amendment #2	VBP15-BMD-001-A2	26 October 2021
Amendment #3	VBP15-BMD-001-A3	27 June 2022
Amendment #4	VBP15-BMD-001-A4	20 March 2023

Section Changed:
Reasons for Protocol Amendment #4- Page 6
Original Text:
None
Revised Text:
1. To add EUDRA No
2. To update inclusion criteria item# 1
3. To update inclusion criteria item# 6
4. To update exclusion criteria item# 1
5. To add a Prescreening visit
6. To change the term “expanded access or compassionate use program” to “another program” or “separate program”
7. To update synopsis, section Study Drug Formulation, Dosage & Administration
8. To update synopsis, section Study Summary
9. To update section 1.5 Overall benefit/Risk
10. To add section 2.2.3 Secondary Endpoints
11. To update section 2.2.3.1 Pharmacokinetics Analysis
12. To update section 2.2.3.2 Pharmacodynamic Safety Endpoints
13. To revise the title of section 2.2.3.3
14. To update section 2.2.4 Exploratory endpoints
15. To update section 3.1 Overall Study Design
16. To update section 3.2 Randomization
17. To update section 4.1 Subject Enrollment and Identification Log
18. To update section 5.1 Study Medication Administered
19. To update section 5.4 rationale for Dose Selection
20. To update section 6.1 Time and Events Schedule
21. To update Table 6. Schedule of Study Activities
22. To update section 6.2 Informed Consent Procedures
23. To add section 6.3.1 Prescreening Visit
24. To update section 6.3.2 Screening Period
25. To revise section 6.3.3 – Activities prior to first dose administration
26. To update section 6.3.5 Treatment Period (Weeks 1-24)
27. To add hemoglobin A1c at week 12
28. To update section 6.3.6 Dose-tapering Period
29. To update section 7.2.1 Medical History
30. To update section 7.2.6 Pharmacodynamic Biomarker Panel
31. To update the reference ‘c’ of table 11
32. To revise section 7.6.6 – SAE reporting

To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.

Section Changed:
Starting on STUDY SYNOPSIS - Study Design through the rest of the protocol
Original Text:
The study is comprised of a 35-day Pretreatment Screening Period
Revised Text:
The study is comprised of a 1-day Prescreening visit (optional), 35-day Pretreatment Screening Period

Section Changed:
STUDY SYNOPSIS - Study Design
Original Text:
Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in a separate expanded access or compassionate use program for treatment with vamorolone).

At the end of the 24-week Treatment Period (Week 24), all subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into the expanded access or compassionate use program will not need to taper their study medication dose prior to participation in the expanded access or compassionate use program
Revised Text:
Dose Tapering Period (post-treatment dose tapering period only for those participants who do not enroll in a separate program for treatment with vamorolone).

At the end of the 24-week Treatment Period (Week 24), all subjects may be given the option to receive vamorolone in another program, if possible. Subjects completing VBP15-BMD-001 and enrolling directly into another program providing vamorolone will not need to taper their study medication dose prior to participation in a separate program providing vamorolone

Section Changed:
STUDY SYNOPSIS - Inclusion Criteria
Original Text:
1.Subject has provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures

6.Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit)
Revised Text
1.Subject or Subject's parent(s) or legal guardian (s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures

6.Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit). While AST and ALT can be elevated due to disease of muscle or liver, the study PI will review any increases of AST or ALT. If above upper limit of normal (ULN), then study PI will assess whether the increases are likely of muscle origin to determine inclusion.

Section Changed:
STUDY SYNOPSIS - Exclusion Criteria
Original Text:
1.Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression
Revised Text
1.Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with random glucose more than 1.5x ULN at screening and the patient has symptoms of polyuria or polydipsia) or immunosuppression

Section Changed:
STUDY SYNOPSIS - Individual Subject Study Duration
Original Text:
None
Revised Text
- Prescreening visit (optional): 1 day

Section Changed:
Starting on STUDY SYNOPSIS - Individual Subject Study Duration through the rest of the protocol
Original Text:
by expanded access or compassionate use.
Revised Text
another program

Section Changed:
STUDY SYNOPSIS - Study Drug Formulation, Dosage & Administration – 2nd paragraph
Original Text:
- recorded at the dispensing visit (Day -1 weight for Day 1 dispensing).
Revised Text
- recorded at the dispensing visit (Day -1 weight for Day 1 dispensing). As needed, study medication bottles will be shipped to the subject's mail address.

Section Changed:
STUDY SYNOPSIS - Study Summary - 2nd paragraph
Original Text:
The study is comprised of a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period, and a 4-week Dose-tapering Period (for subjects not continuing directly with vamorolone treatment in an expanded access or compassionate use protocol). Subjects will be enrolled into this study at the time written informed consent is given, and administered study medication only after completion of all Pretreatment Screening assessments to confirm eligibility.
Revised Text
The study is comprised of a 1-day Prescreening visit (optional), a Pretreatment Screening Period of up to 5 weeks duration (unless extended to accommodate varicella vaccination), a 1-day Pretreatment Baseline Period, a 24-week Treatment Period, and a 4-week Dose-tapering Period (for subjects not continuing directly with vamorolone treatment in another program). Subjects will be enrolled into this study at the time written main informed consent is given during the screening visit. Subjects will be administered study medication only after completion of all Pretreatment Screening assessments to confirm eligibility..

Section Changed:
STUDY SYNOPSIS - Study Summary – 4th paragraph
Original Text:
Additional on-site study visits will occur at Week 4, Week 12, and Week 24.
Revised Text
Additional on-site study visits will occur at Week 4, Week 12, Week 24, and Week 28 (for subjects participating in the Dose-tapering Period).

Section Changed:
STUDY SYNOPSIS - Study Summary – 9th paragraph

Original Text:
-to assess potential signs or symptoms of adrenal insufficiency, and to address any questions the subject may have.
Revised Text
-to assess potential signs or symptoms of adrenal insufficiency, and to address any questions the subject may have. The subject should return to the study site for scheduled Week 28 assessments.

Section Changed:
STUDY SYNOPSIS - Safety Measures
Original Text:
First morning cortisol

Bone biomarkers

Fasting glucose and insulin
Revised Text
First morning cortisol (secondary endpoint)

Bone biomarker (secondary endpoint)

Fasting glucose and insulin (secondary endpoints)

Section Changed:
LIST OF ABBREVIATIONS – Page 28
Original Text:
None
Revised Text
ULN Upper limit of Normal

Section Changed:
1.4 Rationale for Study Design – 3rd paragraph
Original Text:
at the time written informed consent is obtained
Revised Text
at the time written main informed consent is obtained

Section Changed:
1.4 Rationale for Study Design – 4th paragraph
Original Text:
subjects will be given the option to receive vamorolone in
Revised Text
subjects will be given the option to receive vamorolone in an expanded access or compassionate use program

Section Changed:
1.5 Overall Benefit/Risk – Page 64
Original Text:
None
Revised Text

Individuals with Becker muscular dystrophy show progressive muscle weakness and wasting, with a variable onset and progression. The anticipated benefit to patients with Becker dystrophy is what we have observed in patients with the related (but more severe) Duchenne muscular dystrophy; namely, an acute improvement of motor outcomes, and subsequent slowing of the decline in muscle function relative to untreated peers. The anticipated mechanism of action of vamorolone underlying this anticipated benefit is the documented anti-inflammatory mechanism of vamorolone, and the potential increase in dystrophin protein levels seen in animal models. The beneficial effects would be expected to parallel those seen in the allelic disorder, Duchenne dystrophy, and they are allelic disorders involving the same dystrophin gene and protein.

Vamorolone is a dissociative steroidal anti-inflammatory drug and glucocorticoid receptor (GR) selective agonist with differences from corticosteroids in terms of chemical structure, mechanism of action, and physiologic effects. Because it exerts part of its pharmacological effect through an agonistic action on the Glucocorticoid Receptor (GR), the typical risks associated with glucocorticoids (GC) should be considered as potential risks also for vamorolone. The clinical data obtained with vamorolone to date in controlled and uncontrolled studies have shown that AEs which are typical for GC like Adrenal Suppression, Adrenal Insufficiency, Hypercortisolism (Cushingoïd symptoms, Weight gain, skin and hair changes), Behavioural problems and GI symptoms can also occur with vamorolone but in most cases are only of mild to moderate severity and should not be considered important risks for the drug. As for Behavioural changes and GI symptoms, a weak safety signal could only be concluded for respectively irritability and abdominal pain upper, vomiting and diarrhoea in controlled clinical trials with vamorolone.

In clinical experience with Duchenne muscular dystrophy, mild cushingoid features are the most frequently reported adverse reaction with vamorolone. Weight gain was commonly observed in clinical trials with vamorolone. Laboratory measurement of adrenal suppression shows all patients to show vamorolone-related adrenal suppression, although overt symptoms of this condition are rare, and all patients are provided with medical alert cards noting risk for adrenal insufficiency and adrenal crisis (and need for supplemental cortisone if trauma, surgery or acute illness).

Section Changed:
2.2.3 Secondary endpoints
Original Text:
None
Revised Text
The following secondary endpoints will be evaluated for all participants, and are detailed in the subsections (2.2.3.1, 2.2.3.2, and 2.2.3.3)

- Vamorolone PK analysis
- Cortisol
- Osteocalcin
- Fasting glucose, insulin; Hb1Ac
- MDC and CD23

Section Changed:
2.2.3 Pharmacokinetics Analysis
Original Text:
Blood will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis. The data will be added to PK data from previous studies in DMD boys for comparison with

measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects.

Revised Text

Blood (plasma) will be collected from all subjects at the Day 1 Visit, at 1, 2 and 3 hours post-dose, for vamorolone PK analysis, and stored. Once all samples are collected from the trial, the samples will be sent to ICON (Lenexa, KS, USA) for determination of drug levels using established and validated LC-MS methods. The pharmacokinetic parameters of the treated Becker muscular dystrophy patients will be compared to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects. Only single dose (Day 1) PK parameters are measured due to the short half-life of vamorolone (~2 hours), and lack of any drug accumulation between daily doses. In previous pop-PK models there have been no significant differences between single dose and multiple dose PK parameters.

Section Changed:

2.2.4 Pharmacodynamic Endpoints

Original Text:

2.2.4 Pharmacodynamic Endpoints

3. Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance, with serum elevations of both insulin and glucose. Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose and insulin will be measured;

Revised Text

2.2.3.2 Pharmacodynamic safety Endpoints

4. Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance, with serum elevations of both insulin and glucose. Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose, fasting insulin, and Hb1Ac will be measured as biomarkers of insulin resistance;

Section Changed:

2.2.5 Clinical Efficacy Endpoints

Original Text:

2.2.5 Clinical Efficacy Endpoints

2. Exploratory biomarkers for treatment response including MDC and CD23 (Fiorillo et al., 2015; Conklin et al., 2018a; Conklin et al., 2018b): Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points.

3. For the efficacy motor endpoint, TTRW (velocity) and NSAA (score): change from baseline to Week 24 will be compared between vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo

Revised Text

2.2.3.3 Pharmacodynamic efficacy Endpoints

1. Exploratory biomarkers for treatment response including MDC and CD23 (Fiorillo et al., 2015; Conklin et al., 2018a; Conklin et al., 2018b): Change from Day 1 to each of the scheduled on-treatment and post-treatment assessment time points.

Section Changed:
2.2.6 Exploratory Endpoints
Original Text:
2.2.6 Exploratory Endpoints
1.Participants will be asked to complete the NeuroQOL scales for fatigue, mobility and sleep
Revised Text

2.2.4 Exploratory Endpoints
1.The following endpoints will be evaluated for all participants.
For the clinical efficacy motor endpoint, TTRW (velocity) and NSAA (score): change from baseline to Week 24 will be compared between vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo
2.Participants will be asked to complete the NeuroQOL scales for fatigue, mobility and sleep

Section Changed:
3.1 Overall Study Design – 2nd paragraph
Original Text:
None
Revised Text
After providing prescreening informed consent, subjects will provide authorization to release medical records including a genetic report confirming the diagnosis of BMD. Based on the review of the subject's medical records, the subject might be asked to sign the main consent form to continue his participation in the study.

Section Changed:
4.1 Subject Enrollment and Identification Log– 1st paragraph
Original Text:
Individuals interested in participating will be asked to come to one of the participating study sites to complete the informed consent process with a site investigator or designee prior to initiation of screening procedures
Revised Text
Individuals interested in participating will be asked to complete an optional prescreening visit or come to one of the participating study sites to complete the main informed consent process with a site investigator or designee prior to initiation of screening procedures

Section Changed:
4.2 Inclusion Criteria
Original Text:
1.Subject has provided written informed consent and Health Insurance Portability and Accountability Act-
6.Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit);
Revised Text
1.Subject or Subject's parent(s) or legal guardian (s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act -
6.Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. (Note: Serum gamma glutamyl transferase [GGT], creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit). While

AST and ALT can be elevated due to disease of muscle or liver, the study PI will review any increases of AST or ALT. If above upper limit of normal (ULN), then study PI will assess whether the increases are likely of muscle origin to determine inclusion

Section Changed:
4.3 Exclusion Criteria
Original Text:
1. Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression
Revised Text
1. Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with random glucose more than 1.5x ULN at screening and the patient has symptoms of polyuria or polydipsia) or immunosuppression;

Section Changed:
5.1 Study Medication Administered
Original Text:
Planned vamorolone dose level 500mg/day (250mg/day if <50kg body weight) or a matched placebo.
Revised Text
Planned vamorolone dose level 500mg/day (250mg/day if <50kg body weight) or a matched placebo. A defined daily dose (definition by World Health Organization) of 500mg/day was chosen because this is typical procedure for adult drug dosing and most closely approximates the 6mg/kg/day dose identified for children with DMD. A dose of 500mg/day equates to approximately 6mg/kg/day for an 83kg male. In the event of a subject who is <50kg, the protocol specifies administering a half dose of 250mg/day (equivalent to 5mg/kg/day for a 50kg male).

Section Changed:
5.3 Dosage Schedule and Administration of Study Medication – 4th paragraph
Original Text:
The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled study visit. Study medication suspension dispensed at the Day 1 Visit should be brought in with the subject to the Week 4 Visit, for interim compliance monitoring; this study medication will be returned to the subject at the end of the Week 4 Visit for continued dosing through the Week 12 Visit; new study medication will not be dispensed at the Week 4 Visit.
Revised Text
The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled study visit. For interim compliance monitoring, the subject will bring to the Week 4 visit any empty study medication bottles and also the current bottle in use that was dispensed at the Day 1 Visit. The bottle of study medication in use will be returned to the subject at the end of the Week 4 Visit for continued dosing; new study medication will not be dispensed at the Week 4 Visit

Section Changed:
5.4 Rationale for Dose Selection– 7th paragraph
Original Text:
Based on the safety and efficacy results observed in these earlier studies, the dose of vamorolone at 500mg/day (250mg/day if <50kg body weight) was chosen for evaluation in the current study.
Revised Text
A defined daily dose (definition by World Health Organization) of 500mg/day was chosen because this is typical procedure for adult drug dosing and most closely approximates the 6mg/kg/day dose identified for children with DMD. A dose of 500mg/day equates to approximately 6mg/kg/day for an 83kg male. In the

event of a subject who is <50kg, the protocol specifies administering a half dose of 250mg/day (equivalent to 5mg/kg/day for a 50kg male).

Section Changed:
6.1 Time and Events Schedule
Original Text:
None
Revised Text
• Prescreening visit: At the optional prescreening visit, subjects will provide written prescreening informed consent/HIPPA authorization to release medical records including a genetic report confirming the diagnosis of BMD. Based on the review of the subject's medical records, the subject might be asked to sign the main consent form to continue his participation in the study.

Section Changed:
6.1 Time and Events Schedule – 7th paragraph
Original Text:
Overall, up to approximately 33 weeks are allocated for each subject to complete the study, including a 35-day Pretreatment Screening Period
Revised Text
Overall, up to approximately 33 weeks are allocated for each subject to complete the main study, including a 1-day Prescreening visit (optional), 35-day Pretreatment Screening Period

Section Changed:
Table 6: Schedule of Study Activities
Original Text:

Study Day or Week/Visit	Pretreatment Period		Treatment Period				Dose-tapering Period
	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25- (±1w)
Informed Consent	X						
Enrollment	X						
Inclusion/exclusion criteria	X	X					
Randomization[a]	X						
Medical History	X						
Medication History	X	X					
Physical Examination	X	X			X	X	X
Varicella immunity	X						
Height	X				X	X	
Weight	X	X			X	X	X
Vital Signs	X	X	X	X	X	X	X
Neuro-QOL questionnaires[b]		X				X	
TTRW	X	X			X	X	
NSAA	X	X			X	X	
Blood for Clinical Labs[c]	X		X	X	X	X	X
Urinalysis[c]	X		X	X	X	X	X
Blood for PK[d]			X				
Blood for Safety PD Biomarker Panel[e]			X			X	
Blood for Efficacy PD Biomarker Panel[f]			X		X	X	
Fasting blood for insulin and glucose[g]			X		X	X	
Saliva for cortisol[h]			X		X	X	
12-lead ECG		X			X	X	
Dispense Study Medication			X		X	X	
Return Study Medication/ Compliance Monitoring				X	X	X	
Study Medication Dosing[i]			X	→	X	X	
Study Medication dose tapering[j]							X
Dispense Subject Diaries			X		X	X[j]	
Return Subject Diaries				X	X	X	X[j]
AE/SAE Recording	X	→	→	→	→	→	→
Concomitant Medications			X	→	→	→	→
Follow up phone call							x[k]

Revised Text

Study Day or Week/Visit	Pretreatment Period			Treatment Period				Dose-tapering Period
	Prescreening	Screening -35 to -3 days	Baseline -1 day	Day 1	Week 4 (±1w)	Week 12 (±1w)	Week 24 (±1w)	Week 25- (±1w)
Prescreening Consent	X[a]							
Main Informed Consent		X						
Enrollment		X						
Inclusion/exclusion criteria		X	X					
Randomization[b]		X						
Medical History	X	X						
Medication History	X	X	X					
Physical Examination		X	X			X	X	X
Varicella immunity		X						
Height		X				X	X	
Weight		X	X			X	X	X
Vital Signs		X	X	X	X	X	X	X
Neuro-QOL questionnaires[c]			X				X	
TTRW		X	X			X	X	
NSAA		X	X			X	X	
Blood for Clinical Labs[d]		X		X	X	X	X	X
Urinalysis[d]		X		X	X	X	X	X
Blood for PK[e]				X				
Blood for Safety PD Biomarker Panel[f]				X		X[g]	X	
Blood for Efficacy PD Biomarker Panel[h]				X		X	X	
Fasting blood for insulin and glucose[i]				X		X	X	
Saliva for cortisol[j]				X		X	X	
12-lead ECG			X			X	X	
Dispense Study Medication				X		X	X	
Return Study Medication/ Compliance Monitoring					X[k]	X	X	X[m]
Study Medication Dosing[l]				X →	→	→	→	
Study Medication dose tapering[m]								X
Dispense Subject Diaries				X		X	X[m]	
Return Subject Diaries					X	X	X	X[n]
AE/SAE Recording		X →	→	→	→	→	→	→
Concomitant Medications				X →	→	→	→	→

Section Changed:

Table 6: Schedule of Study Activities - references

Original Text:

Randomization occurs by Almac's-WebEZ™ System after subjects are confirmed to have met all study entry criteria, prior to the Baseline Day -1 Visit.

b NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep

c Clinical safety labs: chemistry, hematology, CK, GGT, lipids; urinalysis by dipstick and microscopic

d Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose

e Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin

f Serum efficacy pharmacodynamic biomarkers: MDC and CD23

g Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic

h Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening

i The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home

j Only for subjects participating in the Dose-tapering Period

k At Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication

[l] Discharge from the study will be after Week 24 visit for those who enter the Expanded Access Protocol or compassionate use protocol for administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication

Revised Text

a. After signing the optional Prescreening Visit informed consent, participants will provide HIPPA authorization to release medical records, including a genetic report confirming the diagnosis of BMD
b. Randomization occurs by Almac's-WebEZ™ System after subjects are confirmed to have met all study entry criteria, prior to the Baseline Day -1 Visit.
c. NeuroQOL patient-reported outcome measures: fatigue, upper and lower extremities function, and sleep
d. Clinical safety labs: chemistry, hematology, CK, GGT, lipids; urinalysis by dipstick and microscopic
e. Vamorolone PK analysis: blood samples will be collected from all subjects at 1, 2 and 3 hours post-dose
f. Serum safety pharmacodynamic biomarkers: osteocalcin, hemoglobin A1c (HbA1c), insulin
g. Only hemoglobin A1c (HbA1c)
h. Serum efficacy pharmacodynamic biomarkers: MDC and CD23
i. Subjects will be fasting for this blood draw, and then take their dose of medication in the clinic
j. Saliva safety pharmacodynamic biomarkers: first morning cortisol awakening. Saliva will be collected immediately after awakening
k. On week 4, only empty bottles of study medication and the current bottle in use will be returned
l. The first dose of study medication on Day 1 and the dose of study medication on Week 12 and Week 24 will be administered in the study clinic; all other doses will be taken at home
m. Only for subjects participating in the Dose-tapering Period
n. At Week 26 for subjects participating in the Dose-tapering Period and 31-35 days after the final dose of study medication
o. Discharge from the study will be after Week 24 visit for those who enter another program for administration of vamorolone, or will be after completing the dose-tapering period followed by a final study visit for those who discontinue study medication

Section Changed:

6.2 Informed Consent Procedures– 2nd paragraph

Original Text:

The subjects are to give informed consent in accordance within the Declaration of Helsinki

Revised Text

The subjects are to give prescreening (if participating in the optional prescreening visit) and main informed consent in accordance within the Declaration of Helsinki

Section Changed:

6.2 Informed Consent Procedures– 5th paragraph

Original Text:

The Investigator or designee will obtain written informed consent from each subject prior to the subject's participation in the study using ICFs approved by the appropriate IRB/IEC at each site.

Revised Text

The Investigator or designee will obtain written informed consent from each subject prior to the subject's participation in the study using prescreening (if participating in the optional prescreening visit) and main ICFs approved by the appropriate IRB/IEC at each site.

Section Changed:

6.3 Visit Schedule and Procedures– 1st paragraph

Original Text:

During the study, there will be a total of up to seven study site visits

Revised Text

During the study, there will be an optional prescreening visit and total of up to seven study site visits

Section Changed:
6.3.1 Screening Period (Day -35 to -3)
Original Text:
6.3.1 Screening Period (Day -35 to -3)
The Investigator or study staff will discuss with each subject the nature and purpose of the study and the required study procedures. The subject's medical history and medication history will be reviewed to determine initial eligibility for participation in the study
Revised Text
6.3.1 Prescreening Visit
At the optional prescreening visit, the Investigator or study staff will discuss with each subject the nature and purpose of the study and the required study procedures. The subject's medical records will be reviewed after the subject sign the prescreening consent form/HIPAA Authorization.

Section Changed:
6.3.1 Screening Period (Day -35 to -3)
Original Text:
6.3.1 Screening Period (Day -35 to -3)

Revised Text
6.3.2 Screening Period (Day -35 to -3)
Added: The subject's medical history and medication history will be reviewed to determine eligibility for enrollment in the study. Demographic information will be collected

Section Changed:
6.3.4 Treatment Period (Weeks 1-24) – 3rd paragraph
Original Text:
6.3.4 Treatment Period (Weeks 1-24)
and blood draws for PD biomarkers, including insulin, glucose Weeks 12 and 24)
Revised Text
6.3.5 Treatment Period (Weeks 1-24)
and blood draws for PD biomarkers, including insulin, glucose and HbA1c Weeks 12 and 24)

Section Changed:
6.3.4 Treatment Period (Weeks 1-24) – 4th paragraph
Original Text:
6.3.4 Treatment Period (Weeks 1-24)
Study medication will be dispensed at Weeks 12 and 24 (for subjects participating in the Dose- tapering Period) Visits and returned at Weeks 4 (compliance monitoring only; will be redispensed at end of visit), 12 and 24 for all subjects. Subjects will receive subject diaries at each on-site study visit beginning at Day 1 and up to and including Week 12, and will return the diaries at each subsequent on-site visit.
Revised Text
6.3.5 Treatment Period (Weeks 1-24)
Study medication will be dispensed at Weeks 12 and 24 (for subjects participating in the Dose- tapering Period) Visits. Empty study medication bottles and the bottle in use will be brought by the subject to the visits at Weeks 4 and 12; unused bottles will be left at home. The empty bottles will be retained by the site and the bottle in use will be re-dispensed at the end of the Week 4 or Week 12 visit. Subjects will receive subject diaries at each on-site study visit beginning at Day 1 and up to and including Week 12, and will return the diaries at each subsequent on-site visit

Section Changed:
6.3.5 Dose-tapering Period (Weeks 25-28)– 1st paragraph
Original Text:
6.3.5 Dose-tapering Period (Weeks 25-28)
All subjects who complete the study and opt not to continue directly with vamorolone treatment in an expanded access or compassionate use program.
Revised Text
6.3.6 Dose-tapering Period (Weeks 25-28)
All subjects who complete the study and do not continue directly into another program to receive vamorolone.

Section Changed:
6.3.5 Dose-tapering Period (Weeks 25-28)– 4th paragraph
Original Text:
6.3.5 Dose-tapering Period (Weeks 25-28)
to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the subject may have. In addition, subjects will be assessed promptly for adrenal suppression if unwell at any time during the Dose-tapering Period
Revised Text
6.3.6 Dose-tapering Period (Weeks 25-28)
to assess potential signs or symptoms indicative of adrenal insufficiency, and to address any questions the subject may have. In addition, subjects will be assessed promptly for adrenal insufficiency if unwell at any time during the Dose-tapering

Section Changed:
7.2.1 Medical History– 1st paragraph
Original Text:
The medical history will be recorded at the Screening Visit and will include significant past medical or surgical procedures as well as previous and current co-existent diseases
Revised Text
The medical history will be reviewed after the subject signs the prescreening consent form, if the subject is participating in the optional prescreening visit.
After the subject signs the main inform consent, the medical history will be recorded at the Screening Visit and will include significant past medical or surgical procedures as well as previous and current co-existent diseases

Section Changed:
7.2.6 Pharmacodynamic Biomarker Panel – 3rd paragraph
Original Text:
Approximately 6 mL of blood will be collected for the safety PD biomarker panel (osteocalcin at Day 1 and Week 24, and fasting insulin [insulin resistance] at Day 1, Week 12 and Week 24).
Revised Text
Approximately 6 mL of blood will be collected for the safety PD biomarker panel (osteocalcin at Day 1 and Week 24, and hemoglobin A1c (HbA1c) and fasting insulin [insulin resistance] at Day 1, Week 12 and Week 24).

Section Changed:
Table 11:Blood Sample Number and Volume by Study Visit -References
Original Text:

c. Osteocalcin, hemoglobin A1c (HbA1c), insulin.

Revised Text

c. Osteocalcin, hemoglobin A1c (HbA1c), insulin. (HbA1c) will also measured on Week 12

Section Changed:

7.6.6 Serious Adverse Events – 3rd paragraph

Original Text:

During the SAE collection period, the Investigator or clinical site personnel should notify all SAEs.

Revised Text

During the SAE collection period, the Investigator or clinical site personnel should notify ICON of all SAEs

Section Changed:

7.6.6 Serious Adverse Events – 4th paragraph

Original Text:

In addition, notification is sent by the Investigator to the IRB/IEC

Revised Text

In addition, notification is sent by the Investigator to the IRB/IEC, following local reporting requirements.

The study chair or designee should also report to the NIAMS and the DSMB Safety Officer (through the NIAMS Executive Secretary) within 48 hours of the Investigator becoming aware of all SAEs (regardless of relatedness or expectedness).

15.2.5 Protocol Amendment #5 Complete List of Changes

Section Changed:

Reasons for Protocol Amendment #5- Page 7

Original Text:

None

Revised Text:

Reasons for Protocol Amendment #5:

1. To add clinical efficacy of vamorolone over 24 weeks treatment to the secondary objectives
2. To change the exploratory objective of evaluation of clinical efficacy of vamorolone to 12 weeks of treatment, in place of 24 weeks of treatment.
3. To revise EC#1: definition of uncontrolled diabetes
4. To remove height from analysis of safety measurements over 24 weeks
5. To update the date of last subject last visit
6. To update section 2.2.1 Body weight change.
7. To add NSAA and TTRW to Section 2.2.3
8. To add section 2.2.3.4 Efficacy Motor Endpoints
9. To remove Week 6 from the Section 10.7.1

Section Changed:
STUDY SYNOPSIS - Secondary Objective
Original Text:

- To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy.
- To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.

Revised Text

- To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy.
- To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.
- To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy.

Section Changed:
STUDY SYNOPSIS – Exploratory Objectives
Original Text:
To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy
Revised Text
To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 12-week treatment period in subjects with Becker dystrophy

Section Changed:
STUDY SYNOPSIS - Exclusion Criteria
Original Text:

1. Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with random glucose more than 1.5x ULN at screening and the patient has symptoms of polyuria or polydipsia) or immunosuppression;

Revised Text

1. Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with hemoglobin A1C level > 8.0 at screening) or immunosuppression;

Section Changed:
STUDY SYNOPSIS - Study Period
Original Text:
Last subject last visit: 3 Q 2024
Revised Text
Last subject last visit: 3 Q 2025

Section Changed:
STUDY SYNOPSIS - Study Duration
Original Text:
Approximately 24 months total duration
Revised Text
Approximately 36 months total duration

Section Changed:
STUDY SYNOPSIS - Safety Measures
Original Text:

Weight and Height
Revised Text
Weight

Section Changed:
STUDY SYNOPSIS - Statistical Methods- General Statistical Considerations
Original Text:
The exploratory efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. The motor efficacy endpoint supports the exploratory motor efficacy objective of this study. Another exploratory efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.

This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, and the treatment-by-week interaction.

For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline, and treatment-by-week interaction).

Revised Text

A secondary efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. Another secondary efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.

This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, baseline age, and the treatment-by-week interaction.

For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline age and outcome, and treatment-by-week interaction).

Section Changed:
STUDY SYNOPSIS - Statistical Methods- Safety and Tolerability Analyses
Original Text:
Safety data will include weight, height, vital signs, and ECG results

Revised Text

Safety data will include weight, vital signs, and ECG results

Section Changed:
STUDY SYNOPSIS - Statistical Methods- Biomarkers Analyses
Original Text:
Saliva and serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers. Change from Day 1 will be presented through paired t-test analyses for the serum safety pharmacodynamic biomarkers (Day 1 and Week 24) and for insulin, glucose, cortisol, and osteocalcin (Week 24 vs Day 1 and Week 12 vs. Day 1)

Revised Text

Saliva and serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers. Change from Day 1 will be presented through paired t-test analyses for the serum safety pharmacodynamic biomarkers (Day 1 and Week 24) and for insulin, glucose (Week 24 vs Day 1 and Week 12 vs. Day 1). For safety endpoints cortisol and osteocalcin, and efficacy endpoints, CD23 and MDC data, these may be used on the log scale (in case of skewness) and MMRM approach will be used and change from Day 1 compared between vamorolone and placebo dose groups.

Section Changed:
STUDY SYNOPSIS - Statistical Methods- Clinical Efficacy Analyses
Original Text:
The clinical efficacy outcomes are the time to run/walk 10 meters and the NSAA. Standard descriptive statistics will be used to summarize the clinical efficacy endpoints. TTRW velocities and NSAA score will be modeled via linear mixed effect models and change from baseline presented.

Revised Text
The clinical efficacy outcomes are the time to run/walk 10 meters velocity and the NSAA. Standard descriptive statistics will be used to summarize the clinical efficacy endpoints. TTRW velocities and NSAA score will be modeled via MMRM approach and change from baseline presented

Section Changed:
STUDY SYNOPSIS - Statistical Methods- Patient-reported Outcome Analyses
Original Text:
Patient-reported Outcomes will be listed and presented using descriptive statistics.

Revised Text
Patient-reported Outcomes will be listed and presented using descriptive statistics and ANCOVA modeling.

Section Changed:
2.1.2 Secondary Objectives
Original Text:

- To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy.
- To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to

vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.

Revised Text

- To evaluate the pharmacokinetics (PK) of vamorolone 500mg (250mg if <50kg body weight) daily administered orally in subjects with Becker dystrophy.
- To evaluate the pharmacodynamic response using biomarkers bridged to clinical safety outcomes (adrenal suppression, bone turnover, and insulin resistance) and efficacy (CD23 and MDC) to vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo in subjects with Becker dystrophy.
- To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy

Section Changed:

2.1.3 Exploratory Objectives

Original Text:

To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy

Revised Text

To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 12-week treatment period in subjects with Becker dystrophy

Section Changed:

2.2.1 Safety Endpoints

Original Text:

3. Body weight and height: Change from Screening

Revised Text

3.Body weight: Change from Baseline

Section Changed:

2.2.3 Secondary Endpoints

Original Text:

None

Revised Text

NSAA and TTRW

Section Changed:

2.2.3.4 Efficacy Motor Endpoints

Original Text:

None

Revised Text

For the clinical efficacy motor endpoint, TTRW (velocity) and NSAA (score): change from baseline to Week 24 will be compared between vamorolone 500mg (250mg if <50kg body weight) daily administered orally vs. placebo.

Section Changed:

2.2.4 Exploratory Endpoints

Original Text:

To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 24-week treatment period in subjects with Becker dystrophy

Revised Text

To evaluate clinical efficacy of vamorolone 500 mg (250mg if <50kg body weight) daily administered orally vs. placebo over a 12-week treatment period in subjects with Becker dystrophy

Section Changed:

4.3 Exclusion Criteria

Original Text:

1.Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with random glucose more than 1.5x ULN at screening and the patient has symptoms of polyuria or polydipsia) or immunosuppression;

Revised Text

1.Subject has current or history of major renal or hepatic impairment, uncontrolled diabetes mellitus (defined as a diagnosis of diabetes with hemoglobin A1C level > 8.0 at screening) or immunosuppression;

Section Changed:

10.7.1 General Considerations

Original Text:

The exploratory efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. The motor efficacy endpoint supports the exploratory motor efficacy objective of this study. Another exploratory efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.

This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, and the treatment-by-week interaction.

For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline, and treatment-by-week interaction).

Revised Text

A secondary efficacy motor endpoint tests vamorolone vs. placebo using change in TTRW velocity at Week 24. Another secondary efficacy endpoint tests vamorolone vs. placebo using change in NSAA score at Week 24.

This model includes fixed effects for treatment (vamorolone, and placebo), week, baseline TTRW, baseline age, and the treatment-by-week interaction.

For NSAA, the same models will be used as for the TTRW velocity (REML-based MMRM including fixed effects for treatment [vamorolone, and placebo], week, baseline age and outcome, and treatment-by-week interaction).

Section Changed:

10.7.3 Safety and Tolerability Analyses

Original Text:
Safety data will include weight, height, vital signs, and ECG results

Revised Text

Safety data will include weight, vital signs, and ECG results

Section Changed:
10.7.5 Pharmacodynamic Analyses
Original Text:
Saliva and serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers. Change from Day 1 will be presented through paired t-test analyses for the serum safety pharmacodynamic biomarkers (Day 1 and Week 24) and for insulin, glucose, cortisol, and osteocalcin (Week 24 vs Day 1 and Week 12 vs. Day 1)

Revised Text

Saliva and serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers. Change from Day 1 will be presented through paired t-test analyses for the serum safety pharmacodynamic biomarkers (Day 1 and Week 24) and for insulin, glucose (Week 24 vs Day 1 and Week 12 vs. Day 1). For safety endpoints cortisol and osteocalcin, and efficacy endpoints, CD23 and MDC data, these may be used on the log scale (in case of skewness) and MMRM approach will be used and change from Day 1 compared between vamorolone and placebo dose groups.

Section Changed:
10.7.6 Clinical Efficacy Analyses
Original Text:
The clinical efficacy outcomes are the time to run/walk 10 meters and the NSAA. Standard descriptive statistics will be used to summarize the clinical efficacy endpoints. TTRW velocities and NSAA score will be modeled via linear mixed effect models and change from baseline presented.

Revised Text
The clinical efficacy outcomes are the time to run/walk 10 meters velocity and the NSAA. Standard descriptive statistics will be used to summarize the clinical efficacy endpoints. TTRW velocities and NSAA score will be modeled via MMRM approach and change from baseline presented

Section Changed:
10.7.7 Patient-Reported Outcome Analyses
Original Text:
Patient-reported Outcomes will be listed and presented using descriptive statistics.

Revised Text
Patient-reported Outcomes will be listed and presented using descriptive statistics and ANCOVA modeling.