

## REVISED CLINICAL STUDY PROTOCOL

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**Document Title:** Revised Clinical Protocol #2 for a Phase II Open-label, Multicenter Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)

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**Protocol Number:** VBP15-003

**Document Number:** VBP15-003-R2

**FDA IND No.:** 118,942

**Investigational Product:** Vamorolone (VBP15)

**Sponsor:** ReveraGen BioPharma, Inc.  
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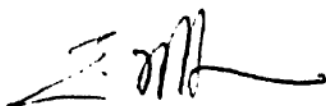
**Document Date:** 22 February 2017

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**SIGNATURES OF AGREEMENT FOR VBP15-003-R2**

**Revised Clinical Protocol #2 for a Phase II Open-label, Multicenter Extension Study  
to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne  
Muscular Dystrophy (DMD)**

**Reviewed and Approved by:**



Eric Hoffman, Ph.D.  
Chief Executive Officer  
ReveraGen BioPharma, Inc.

25 February 2017

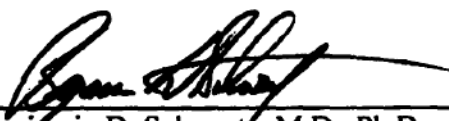
Date



Paula R. Clemens, M.D.  
Study Chair  
University of Pittsburgh School of Medicine

28 February 2017.

Date



Benjamin D. Schwartz, M.D., Ph.D.  
Consulting Medical Monitor  
The Camden Group, LLC

24 February 2017

Date



Laurel J. Mengle-Gaw, Ph.D.  
Consulting Clinical Monitor  
The Camden Group, LLC

24 February 2017

Date



Avital Cnaan, Ph.D.  
TRiNDS, LLC

2 March 2017

Date

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**INVESTIGATOR REVISED PROTOCOL AGREEMENT**

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**Revised Clinical Protocol #2 for a Phase II Open-label, Multicenter Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)**

**Protocol Number:** VBP15-003  
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*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 listed in 21 CFR part 312 and all applicable local, state, and federal regulations and ICH guidelines. I will not initiate this study without the approval of an Institutional Review Board (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 and amended protocols, 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).*

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Investigator's Signature

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Date

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Investigator's Name (Please print)

Address (Please print):

**RETURN THE ORIGINAL SIGNED COPY TO REVERAGEN BIOPHARMA, INC. OR DESIGNEE AND KEEP A XEROX COPY AT YOUR SITE.**

### **SERIOUS ADVERSE EVENT CONTACT INFORMATION**

**In the event of a serious adverse event (SAE) (see [Section 7.2.6.1](#)), 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:**

**Email [CHOSafety@prahs.com](mailto:CHOSafety@prahs.com)**

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

**SAE Questions: Drug Safety Hotline: 1-800-772-2215 or 1-434-951-3489**

## PROTOCOL AMENDMENT TRACKING

Document	Document Number	Approval Date
Original Protocol	VBP15-003	07 March 2016
Amended Protocol #1	VBP15-003-A1	31 May 2016
Revised Protocol #1	VBP15-003-R1	01 August 2016
Amended Protocol #2	VBP15-003-A2	21 February 2017
Revised Protocol #2	VBP15-003-R2	22 February 2017

**Note: Amended protocols show all changes from previous version in bold/strike-through format.**

### Reason for Revised Protocol #2:

1. to incorporate all changes from Amended Protocol #2 into a new protocol document.

### Reasons for Amended Protocol #2:

1. to update the nonclinical toxicology information with results of a 26-week toxicology study in mice;
2. to update the study medication dispensing schedule to reflect a 12-week supply to be dispensed at each Treatment Period dispensing visit;
3. to remove the requirement that QT<sub>c</sub> must be calculated using Fredericia's formula;
4. to clarify the role of the DSMB in safety data review, including removal of the requirement that SAE information be forwarded to the DSMB within 24 hours of first awareness;
5. to update the blood volumes required for clinical laboratory and PD biomarker analysis; and
6. to correct typographical errors.

## STUDY SYNOPSIS

<b>Protocol Title</b>	A Phase II Open-label, Multicenter Extension Study to Assess the Long-term Safety and Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)
<b>Protocol Number</b>	VBP15-003
<b>Name of Sponsor</b>	ReveraGen BioPharma, Inc.
<b>Drug Substance</b>	delta-1,4,9(11)-pregnatriene-17-alpha,21-dihydroxy-16-alpha-methyl-3,20-dione
<b>Investigational Drug Product</b>	Vamorolone, 4% suspension for oral dosing
<b>Phase of Development</b>	Phase II
<b>Indication</b>	Treatment of Duchenne muscular dystrophy (DMD)
<b>Objectives</b>	<p><i>Primary:</i></p> <ol style="list-style-type: none"> <li>To evaluate the long-term safety and tolerability of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period, in boys ages 4-7 years with DMD;</li> <li>To compare the efficacy, as measured by the Time to Stand Test (TTSTAND), of vamorolone administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. untreated DMD historical controls in boys ages 4-7 years with DMD; and</li> <li>To compare the safety, as measured by body mass index (BMI) z-score, of vamorolone administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. prednisone-treated historical controls in boys ages 4-7 years with DMD.</li> </ol> <p><i>Secondary:</i></p> <ol style="list-style-type: none"> <li>To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. prednisone-treated historical controls, on serum pharmacodynamic (PD) biomarkers of safety (insulin resistance, adrenal axis suppression, and bone turnover);</li> <li>To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week treatment period vs. untreated historical controls, on serum PD biomarkers of efficacy (inflammatory protein suppression); and</li> <li>To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period, on muscle strength, mobility and functional exercise capacity vs. historical controls as measured by Quantitative Muscle Testing (QMT), Time to Run/Walk Test (TTRW), North Star Ambulatory Assessment (NSAA), Time to Climb Test (TTCLIMB), and 6-minute Walk Test (6MWT) in boys ages 4-7 years with DMD.</li> </ol> <p><i>Exploratory:</i></p> <ol style="list-style-type: none"> <li>To investigate the effects of vamorolone administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period on an extended panel of</li> </ol>

	PD biomarkers using SomaScan aptamer arrays, and proteomic profiling.
<b>Study Design</b>	<p>This Phase IIa extension study is an open-label, multicenter study to evaluate the long-term safety, tolerability, clinical efficacy, and PD of vamorolone at dose levels up to 6.0 mg/kg administered daily by liquid oral suspension over a Treatment Period of 24 weeks to boys ages 4-7 years with DMD. Subjects who have completed the Phase IIa VBP15-002 Study Week 4 Follow-up assessments within 8 weeks prior to enrollment are eligible.</p> <p>The study is comprised of a Pretreatment Baseline Period of up to 24 hours, which begins with the signing of the extension study-specific informed consent form (ICF), a 24-week Treatment Period, and a 2- to 5-week Dose-tapering Period for subjects who elect to transition off vamorolone treatment at the end of the study.</p> <p>Subjects are enrolled at the time of ICF signing. Parents or guardians of eligible subjects may provide written informed consent for VBP15-003 extension study participation, and subjects may undergo Baseline assessments, at the final VBP15-002 Week 4 Visit, following completion of all VBP15-002 Week 4 assessments.</p>
<b>Planned Sample Size</b>	Up to approximately 48 subjects who complete the VBP15-002 core study will be enrolled; approximately 12 subjects may be eligible for extension study dosing at each of the dose levels tolerated in the Phase IIa core study.
<b>Population</b>	<p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Subject's parent or legal guardian has provided written informed consent/HIPAA authorization prior to any extension study-specific procedures;</li> <li>2. Subject has previously completed study VBP15-002 up to and including the Week 4 Follow-up assessments within 8 weeks prior to enrollment; and</li> <li>3. Subject and parent/guardian are willing and able to comply with scheduled visits, study drug administration plan, and study procedures.</li> </ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Subject had a serious or severe adverse event in study VBP15-002 that, in the opinion of the Investigator, was probably or definitely related to vamorolone use and precludes safe use of vamorolone for the subject in this study;</li> <li>2. Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression;</li> <li>3. Subject has current or history of chronic systemic fungal or viral infections;</li> <li>4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prerenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication;</li> <li>5. Subject has evidence of symptomatic cardiomyopathy. [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary];</li> <li>6. Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents. [Notes: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 3 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</li> </ol>

	<p>prescribed for an indication other than DMD are permitted but must be administered at stable dose for at least 3 months prior to study drug administration];</p> <p>7. Subject has used idebenone within 4 weeks prior to the first dose of study medication;</p> <p>8. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;</p> <p>9. Subject has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the Investigator;</p> <p>10. 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; or</p> <p>11. Subject is currently taking any investigational drug, or has taken any investigational drug other than vamorolone within 3 months prior to the start of study treatment.</p> <p><b>Note:</b> Subjects may be re-evaluated if ineligible due to a transient condition which would prevent the subject from participating.</p>
<b>Number of Centers</b>	The study will be conducted at approximately 10 United States (US) and non-US study sites.
<b>Study Period</b>	First subject enrolled: 2Q 2016 Last subject last visit: 4Q 2017
<b>Study Duration</b>	Up to approximately 24 months total duration
<b>Individual Subject Study Duration</b>	<p>Approximately 24-29 weeks:</p> <ul style="list-style-type: none"> <li>• Baseline Period: up to 24 hours immediately prior to administration of first dose of study medication in VBP15-003 extension study</li> <li>• Treatment Period: 24 weeks</li> <li>• Dose-tapering Period: 2-5 weeks (only for subjects who will transition off vamorolone at end of study)</li> </ul>
<b>Study Drug Formulation, Dosage &amp; Administration</b>	<p>Vamorolone 4% oral suspension will be administered once daily over a 24-week Treatment Period, at the following planned dose levels: 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, or 6.0 mg/kg/day. Subjects will receive vamorolone throughout the 24-week Treatment Period in this study at the same dose level they received in the Phase IIa VBP15-002 study. Subjects who elect to transition off vamorolone treatment at the end of the Treatment Period will receive vamorolone for an additional 1-4 weeks according to a dose-tapering protocol following the end of the Treatment Period.</p> <p>The Week 12 and Week 24 doses will be administered at the study site; all other doses, including the first dose administered on Study Day 1, will be administered at home under the supervision of the parent or guardian. Study drug will be administered by mouth using a volumetric syringe. Following administration of the dose of study drug, 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.</p> <p>The daily dose of study medication should be taken with 8 ounces of whole milk. If whole milk is not tolerable to the subject, a serving of another high fat food can be substituted. . There are no food or drink restrictions before or after</p>



	dosing.
<b>Study Summary</b>	<p>This Phase IIa extension study is an open-label, multiple-dose study to evaluate the long-term safety, tolerability, efficacy and PD of vamorolone administered once daily by liquid oral suspension over a Treatment Period of 24 weeks to boys ages 4-7 years with DMD.</p> <p>Only subjects who have completed Phase IIa core study VBP15-002 Week 4 Follow-up Visit assessments will be eligible for participation in this open-label extension study. Participation in this extension study will be discussed with the subject's parent or guardian prior to the VBP15-002 Week 4 Visit. Standard of care treatment (glucocorticoids) for DMD may be offered to the subject following completion of the Phase IIa VBP15-002 study, if the subject's parent or guardian does not wish to enroll the subject in the extension study and/or the Investigator feels it to be in the best interest of the subject. A total of up to approximately 48 subjects will be enrolled into this extension study.</p> <p>The parents or legal guardians of subjects who choose to enroll in this extension study will give written informed consent for the extension study at the VBP15-003 Baseline Day -1 Visit. The Baseline Day -1 Visit, including signing of the ICF, may occur at the conclusion of the VBP15-002 Week 4 Visit following completion of all Week 4 assessments; alternatively, the Baseline Day -1 Visit and VBP15-003-specific ICF signing may occur up to 8 weeks after the date of the final VBP15-002 Week 4 Visit, at the convenience of the subject's parent or legal guardian and discretion of the Investigator. Subjects are considered to be enrolled in the VBP15-003 extension study after the parent or guardian has signed the VBP15-003-specific ICF at the Baseline Day -1 Visit. Each subject will retain the study identification number assigned to him at the start of the Phase IIa core study.</p> <p>For subjects who enroll in the VBP15-003 extension study within 28 days after completion of all final VBP15-002 Week 4 assessments, many of the safety, efficacy, and PD assessments performed for the VBP15-002 study at the final Week 4 Visit will be used to determine extension study eligibility or to provide baseline study data for the extension study and do not need to be repeated at the VBP15-003 Baseline Visit. For these subjects, additional extension study procedures will still be performed at the Baseline Day -1 Visit, within 24 hours prior to administration of the first dose of study drug in the extension study. Subjects who enroll in the VBP15-003 extension study &gt;28 days after the date of the final VBP15-002 Week 4 Visit must have all scheduled Baseline Day -1 assessments performed.</p> <p>Subjects will begin dosing in this study on Study Day 1 at the same vamorolone dose level they received in the Phase IIa core study. Subjects will continue to receive vamorolone at the dose received in the Phase IIa core study for the duration of the 24-week Treatment Period, unless new safety data indicate the dose level should be de-escalated.</p> <p>The planned dose levels are 0.25 mg /kg (Dose Level Group 1), 0.75 mg/kg (Dose Level 2), 2.0 mg/kg (Dose Level Group 3), and 6.0 mg/kg (Dose Level Group 4). A total of approximately 48 subjects will be enrolled; a maximum of 12 subjects may be eligible for extension study dosing at each of the dose levels tolerated in the Phase IIa study.</p> <p>If dose limiting toxicities are identified in the Phase IIa core study which preclude confirmation of safety of all four planned dose levels, the dose levels in this extension study will be modified, as needed.</p> <p>In the event any clinical observation suggests an intolerability for an individual subject to the study medication, in the opinion of the Investigator, the subject's</p>

	<p>dose level may be decreased to the next lower dose level (e.g., a subject taking 6.0 mg/kg/day decreased to 2.0 mg/kg/day) and maintained at that lower dose level throughout the duration of the Treatment Period. In the event the next lower dose level is also not tolerated and is considered a safety risk to the subject, in the opinion of the Investigator, Study Chair, and Medical Monitor, the subject should be withdrawn from the study.</p> <p>Subjects will be assessed for safety and tolerability, clinical efficacy, and PD at scheduled visits throughout the 24-week Treatment Period. Treatment Period study visits will occur at Week 2, Week 4, and every 4 weeks thereafter through Week 24. Adverse events (AEs), including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study.</p> <p>Once daily Treatment Period study drug dosing will occur from Day 1 until the Week 24 Visit. Study drug dosing will occur at home on all days except the days of the Week 12 and Week 24 Visits, when dosing will occur at the study site.</p> <p>Subject diaries will be dispensed at Baseline Day -1 and at each monthly study visit to record AEs and concomitant medications taken during the study.</p> <p>All subjects will return to the clinical site for Week 24 assessments. Following completion of the 24-week Treatment Period, subjects may be offered further extended treatment with vamorolone in a separate extension study, or switch to standard of care treatment (e.g., glucocorticoids) for DMD, as deemed appropriate for each subject. Alternatively, subjects may choose to discontinue vamorolone and not begin standard of care glucocorticoid treatment for DMD. Subjects who switch to standard of care glucocorticoids for DMD or who discontinue treatment will participate in a Dose-tapering Period of 2-5 weeks in duration, following the end of the Treatment Period and prior to discharge from the study; subjects who elect to receive further vamorolone treatment will be discharged from the VBP-003 study after completion of final VBP-003 study assessments at the Week 24 Visit, prior to enrollment in a subsequent extension study. Subjects will be discharged from the study following completion of all final Week 24 or Dose-tapering Period assessments, as appropriate.</p> <p>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 final Week 24 safety and efficacy assessments at the time of early discontinuation.</p>
<p><b>Safety Measures</b></p>	<ul style="list-style-type: none"> <li>▪ Physical examination</li> <li>▪ Weight</li> <li>▪ Body Mass Index (BMI)</li> <li>▪ Vital signs (supine blood pressure, heart rate, respiratory rate, oral temperature)</li> <li>▪ Clinical laboratory tests                         <ul style="list-style-type: none"> <li>○ Hematology and biochemistry</li> <li>○ Urinalysis (by dipstick and microscopic analysis)</li> <li>○ Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])</li> </ul> </li> <li>▪ 12-lead electrocardiogram (ECG)</li> <li>▪ Clinical signs and symptoms (AEs and SAEs)</li> <li>▪ Grading of clinical and clinical laboratory AEs will be according to the Common Terminology Criteria for Adverse Events (CTCAE), v4.0.3</li> </ul>
<p><b>Pharmacodynamic Measures</b></p>	<ul style="list-style-type: none"> <li>▪ Blood will be drawn for a serum PD biomarker panel at Day -1, Week 8, Week 12, Week 16, Week 24, and at the end of the Dose-tapering Period,</li> </ul>

	if applicable, to explore the effect of vamorolone on biomarkers of adrenal axis suppression, bone turnover, and insulin resistance.
<b>Clinical Efficacy Measures</b>	<ul style="list-style-type: none"> <li>▪ Quantitative Muscle Testing (QMT)</li> <li>▪ Time to Stand Test (TTSTAND)</li> <li>▪ Time to Climb Test (TTCLIMB)</li> <li>▪ Time to Run/Walk Test (TTRW)</li> <li>▪ North Star Ambulatory Assessment (NSAA)</li> <li>▪ Six-minute Walk Test (6MWT)</li> </ul>
<b>Exploratory Measures</b>	<ul style="list-style-type: none"> <li>▪ Measures of serum proteins (SomaScan aptamer panel; proteomics profiling)</li> </ul>
<b>Statistical Methods</b>	<p><b>Sample Size:</b></p> <p>This is an open-label extension study with no placebo arm. Historical control data are available for the same age range (4-7 years), largely collected at the same study sites, with the same outcome measures. Untreated natural history control population data are from the ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study of approximately 400 DMD boys. Prednisone-treated historical control data are from a clinical trial of prednisone carried out by the CINRG group (CINRG Prednisone study). Vamorolone is administered daily in this Phase IIa extension trial. To more accurately determine the sample size necessary to detect a glucocorticoid effect on efficacy, sample size calculations were limited to the daily prednisone treatment arm of the CINRG Prednisone study (n = 11-13), at 6 or 12 months, for three clinical efficacy outcomes (TTSTAND, TTRW, TTCLIMB) (<b>Synopsis Table 1</b>). Sample size was also calculated assuming the observed effect of vamorolone was 100%, 80% or 60% of that observed with daily glucocorticoids (<b>Synopsis Table 1</b>).</p> <p>The primary pharmacological safety outcome proposed in the Phase IIa extension trial is change in BMI z-score. Daily glucocorticoids show a relatively rapid increase in BMI z-score (6-month change in non-treated = -0.14; 6-month change in prednisone-treated = +0.54) (<b>Synopsis Table 1</b>). Vamorolone is not anticipated to show an increase in BMI.</p>

**Synopsis Table 1. 6-month and 12-month changes in outcomes in 4-<7 years old (at study start).**

Outcome	Time (months)	Untreated – Natural history study		Treated – Prednisone trial		N needed per group to detect a significant difference – Using observed changes	N needed per group to detect a significant difference – Using conservative change estimates <sup>^</sup>	N needed per group to detect a significant difference – Using conservative change estimates <sup>^^</sup>
		N	Mean ± SD	N	Mean ± SD			
BMI (Z-score)	6	40	-0.14 ± 0.78	13	0.54 ± 0.66	12	15	
	12	26	-0.25 ± 0.83	13	0.63 ± 0.45	7	6	
Time to run/walk 10 m velocity (m/s)	6	39	0.02 ± 0.31	13	0.35 ± 0.32	12	19	28
	12	26	0.01 ± 0.25	12	0.42 ± 0.23	5	7	11
Time to climb 4 stairs velocity (climb/s)	6	40	0.01 ± 0.07	13	0.11 ± 0.08	7	11	17
	12	26	0.01 ± 0.06	12	0.16 ± 0.10	5	7	10
Time to stand from supine velocity (rise/s)	6	38	0.004 ± 0.07	12	0.10 ± 0.10	10	16	23
	12	26	-0.01 ± 0.06	11	0.11 ± 0.09	5	8	9

- Notes: a) Data for untreated subjects from the CINRG Duchenne Natural History Study; data for prednisone-treated subjects from the CINRG Prednisone study.  
 b) All comparisons are of daily dose prednisone-treated patients to untreated patients.  
 c) All calculations assume a repeated measures ANOVA model with one pre- and one post-measurement. Correlation between repeated measures was used as follows: 0.75 for height changes, 0.70 for 6 month BMI changes, and 0.65 for 12 month BMI z-score changes, and 0.575 for 6 and 12 month velocity changes. Power = 0.80 and alpha = 0.025 for all calculations to account for multiple group comparisons (i.e. two vamorolone doses, each compared to prednisone for safety and placebo for efficacy).

<sup>^</sup> Conservative change estimates were defined as follows: For BMI z-score, the expected change in vamorolone was set to 0.0 rather than the observed decrease. For timed tests, the expected change in vamorolone was set to 80% of the observed change in the prednisone group.

<sup>^^</sup> Conservative change estimates were defined as follows: For timed tests, the expected change in vamorolone was set to 60% of the observed change in the prednisone group (with SD at 80%).

**Analysis Populations:**

All analyses will be based on the actual treatment each subject received. Four populations will be defined for data analysis: the Safety Population, the Full Analysis Set, the control population CINRG Duchenne Natural History Study, and the control population CINRG Prednisone study.

Safety Population

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

Full Analysis Set (FAS)

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

Control Population CINRG Duchenne Natural History Study

The control population from the CINRG Duchenne Natural History Study will include all subjects who were observed as part of the study in ages ≥ 4 years and <7 years of age at a start of an interval of observation; observed for at least one year with at least two visits in a time interval of no more than 15 months

	<p>with TTSTAND, TTCLIMB, TTRW, NSAA, 6MWT and QMT measured; remained glucocorticoid-naive during the entire observation period; and were able to walk independently without assistive devices, able to complete the TTSTAND; and lacked any history of disease, impairment, or medications that would have made them ineligible to receive the vamorolone intervention as defined by the Phase IIa study exclusion criteria at the start of the interval.</p> <p><u>Control Population CINRG Prednisone Study</u></p> <p>The control population from the CINRG Prednisone study will include all subjects who were younger than 7 years old at entry and who were randomized to the daily prednisone arm.</p> <p><b>General Statistical Considerations:</b></p> <p>All measurements will be analyzed based upon the type of distribution and descriptive statistics presented by treatment group and time point, as appropriate. No interim statistical analyses are planned. Missing values for safety and exploratory outcomes will be treated as missing.</p> <p>Baseline measurement is defined as the last non-missing value prior to the first dose of study drug in the extension study.</p> <p><b>Efficacy Analyses:</b></p> <p>The primary efficacy outcome is TTSTAND. Secondary efficacy outcomes are the NSAA assessment, TTCLIMB, TTRW, QMT, and the 6MWT. The primary outcome will be compared between vamorolone and historical untreated controls using a mixed-effects linear model with treatment group. Age at study entry will be included as a covariate. The initial model will combine vamorolone doses and a subsequent secondary model will look at each dose in comparison to untreated natural history controls. This will allow the testing of whether vamorolone in general and vamorolone at individual doses have significant effects on the slope of the velocity. Additional hypotheses of efficacy will include similar linear modelling with the secondary outcomes. They will also include comparison groups including prednisone-treated or untreated natural history controls.</p> <p><b>Pharmacodynamics Analyses:</b></p> <p>Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover will be assessed. Longitudinal analysis of PD biomarkers will be studied as a function of treatment, with comparison to prednisone-treated and untreated historical controls, as appropriate.</p> <p><b>Safety Analyses:</b></p> <p>All evaluations of clinical safety will be listed with descriptive statistics by treatment group presented. The primary safety variable will be BMI z-score and will be assessed using the same type of statistical models used for efficacy. Additional secondary safety data will include height z-score, blood pressure, and ECG results. As no change in blood pressure or cardiac results is expected, these data will be analyzed using an analysis of covariance (ANCOVA) approach which includes the baseline value for each measurement as a covariate. Changes in height z-scores, for which an observed change is expected, will be modelled using a linear mixed effects model. Continuous, quantitative laboratory values will be analyzed similar to BMI z-scores. Categorized laboratory values and presence or absence of AEs will be compared using an exact chi-square test. Adverse events will be summarized overall and by dose level, system organ class (SOC) and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]); by dose level and relationship to study medication; and by dose level and intensity (CTCAE grade). Additional hypotheses of safety will include similar linear modelling with the secondary and exploratory outcomes.</p>
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## TABLE OF CONTENTS

<b>PROTOCOL AMENDMENT TRACKING</b> .....	<b>5</b>
<b>STUDY SYNOPSIS</b> .....	<b>6</b>
<b>LIST OF TABLES</b> .....	<b>18</b>
<b>LIST OF FIGURES</b> .....	<b>19</b>
<b>LIST OF ABBREVIATIONS</b> .....	<b>20</b>
<b>1 INTRODUCTION</b> .....	<b>24</b>
<b>1.1 BACKGROUND AND UNMET NEED</b> .....	<b>24</b>
<b>1.2 NONCLINICAL EXPERIENCE</b> .....	<b>26</b>
<b>1.2.1 Safety Pharmacology</b> .....	<b>26</b>
<b>1.2.2 Pharmacokinetics and Metabolism</b> .....	<b>28</b>
<b>1.2.3 Toxicology</b> .....	<b>32</b>
<b>1.3 CLINICAL EXPERIENCE</b> .....	<b>42</b>
<b>1.3.1 Phase I Study in Healthy Adult Volunteers</b> .....	<b>42</b>
<b>1.4 RATIONALE FOR STUDY DESIGN</b> .....	<b>55</b>
<b>1.5 OVERALL BENEFIT/RISK</b> .....	<b>57</b>
<b>2 STUDY OBJECTIVES AND ENDPOINTS</b> .....	<b>58</b>
<b>2.1 STUDY OBJECTIVES</b> .....	<b>58</b>
<b>2.1.1 Primary Objectives</b> .....	<b>58</b>
<b>2.1.2 Secondary Objectives</b> .....	<b>59</b>
<b>2.1.3 Exploratory Objective</b> .....	<b>59</b>
<b>2.1.4 Ancillary Study</b> .....	<b>59</b>
<b>2.2 STUDY ENDPOINTS</b> .....	<b>60</b>
<b>2.2.1 Safety Endpoints</b> .....	<b>60</b>
<b>2.2.2 Clinical Efficacy Endpoints</b> .....	<b>61</b>
<b>2.2.3 Pharmacodynamic Endpoints</b> .....	<b>62</b>
<b>2.2.4 Exploratory Endpoints</b> .....	<b>62</b>
<b>2.2.5 Endpoints for Subject Reported Outcomes</b> .....	<b>62</b>
<b>3 STUDY DESIGN</b> .....	<b>62</b>
<b>3.1 OVERALL STUDY DESIGN</b> .....	<b>62</b>
<b>3.2 STUDY SUMMARY</b> .....	<b>65</b>
<b>4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS</b> .....	<b>66</b>
<b>4.1 SUBJECT SCREENING, ENROLLMENT, AND IDENTIFICATION LOG</b> .....	<b>66</b>
<b>4.2 INCLUSION CRITERIA</b> .....	<b>66</b>

4.3	EXCLUSION CRITERIA.....	67
4.4	WITHDRAWAL OF SUBJECTS FROM STUDY .....	68
4.5	REPLACEMENT OF WITHDRAWN SUBJECTS.....	69
4.6	TERMINATION OF STUDY .....	69
5	TREATMENT OF STUDY SUBJECTS .....	70
5.1	STUDY MEDICATION ADMINISTERED.....	70
5.2	IDENTITY OF INVESTIGATIONAL PRODUCT .....	70
5.3	DOSAGE SCHEDULE AND ADMINISTRATION OF STUDY MEDICATION.....	70
5.4	RATIONALE FOR DOSE SELECTION .....	72
5.5	TREATMENT COMPLIANCE .....	73
5.6	STUDY DRUG DOSE INTERRUPTION, DE-ESCALATION, OR DISCONTINUATION .....	73
5.7	PRIOR AND CONCOMITANT MEDICATIONS AND THERAPIES.....	74
5.7.1	<i>Prior Therapy</i> .....	74
5.7.2	<i>Concomitant Therapy</i> .....	74
5.7.3	<i>Prohibited Therapies</i> .....	75
5.7.4	<i>Permitted Therapies</i> .....	75
5.8	STUDY MEDICATION MANAGEMENT.....	76
5.8.1	<i>Packaging and Labeling of Study Medication</i> .....	76
5.8.2	<i>Storage of Study Medication</i> .....	77
5.8.3	<i>Study Medication Shipping and Handling</i> .....	77
5.8.4	<i>Study Medication Accountability</i> .....	78
5.9	PROCEDURES FOR ASSIGNING SUBJECT STUDY NUMBERS.....	78
6	STUDY SCHEDULE.....	79
6.1	TIME AND EVENTS SCHEDULE .....	79
6.2	INFORMED CONSENT/HIPAA AUTHORIZATION.....	83
6.3	VISIT SCHEDULE AND PROCEDURES.....	84
6.3.1	<i>Baseline Period (Day -1)</i> .....	84
6.3.2	<i>Treatment Period Day 1</i> .....	87
6.3.3	<i>Treatment Period Weeks 2-24</i> .....	87
6.3.4	<i>Dose Tapering Period (Weeks 25-29)</i> .....	89
6.4	SUBJECT DISCONTINUATION.....	90
6.5	STUDY COMPLETION.....	90
7	STUDY ASSESSMENTS AND MEASUREMENTS .....	90
7.1	DEMOGRAPHIC ASSESSMENTS.....	90
7.2	SAFETY AND TOLERABILITY ASSESSMENTS.....	91
7.2.1	<i>Interim Medical History</i> .....	91
7.2.2	<i>Physical Examination, Weight, and Height</i> .....	91

7.2.3	<i>Vital Signs</i> .....	92
7.2.4	<i>Clinical Laboratory Tests</i> .....	92
7.2.5	<i>12-Lead ECG</i> .....	95
7.2.6	<i>Adverse Events and Serious Adverse Events</i> .....	96
7.2.7	<i>Study Medication Acceptability Assessment</i> .....	103
7.3	<b>CLINICAL EFFICACY AND PHARMACODYNAMIC ASSESSMENTS</b> .....	104
7.3.1	<i>Quantitative Muscle Testing (QMT)</i> .....	104
7.3.2	<i>Time to Stand Test (TTSTAND)</i> .....	104
7.3.3	<i>Time to Climb Test (TTCLIMB)</i> .....	104
7.3.4	<i>Time to Run/Walk Test (TTRW)</i> .....	105
7.3.5	<i>North Star Ambulatory Assessment (NSAA)</i> .....	105
7.3.6	<i>Six-minute Walk Test (6MWT)</i> .....	106
7.3.7	<i>Pharmacodynamic Biomarker Panel</i> .....	106
7.3.8	<i>Pediatric Outcomes Data Collection Instrument</i> .....	107
7.4	<b>TOTAL BLOOD VOLUME REQUIRED</b> .....	108
8	<b>DATA COLLECTION</b> .....	108
8.1	<b>SOURCE DOCUMENTS</b> .....	108
8.2	<b>ELECTRONIC CASE REPORT FORM COMPLETION</b> .....	109
8.3	<b>DATA PROCESSING</b> .....	110
8.4	<b>SUBJECT DIARIES</b> .....	110
9	<b>STATISTICAL METHODS AND PLANNED ANALYSES</b> .....	110
9.1	<b>SAMPLE SIZE DETERMINATION</b> .....	110
9.2	<b>STATISTICAL AND ANALYTICAL PLAN (SAP)</b> .....	112
9.2.1	<i>Deviations from the Statistical Analysis Plan</i> .....	112
9.3	<b>ANALYSIS POPULATIONS</b> .....	113
9.3.1	<i>Safety Population</i> .....	113
9.3.2	<i>Full Analysis Set (FAS)</i> .....	113
9.3.3	<i>Control Population DNHS Study</i> .....	113
9.3.4	<i>Control Population Prednisone Study</i> .....	114
9.4	<b>MEASURES TAKEN TO AVOID/MINIMIZE BIAS</b> .....	114
9.5	<b>INTERIM ANALYSIS</b> .....	114
9.6	<b>MISSING, UNUSED, AND SPURIOUS DATA</b> .....	114
9.7	<b>STATISTICAL ANALYSIS</b> .....	114
9.7.1	<i>General Considerations</i> .....	114
9.7.2	<i>Subject Disposition, Demographics, and Baseline Characteristics</i> .....	115
9.7.3	<i>Safety Analyses</i> .....	115
9.7.4	<i>Clinical Efficacy and Pharmacodynamic Analyses</i> .....	116



<b>9.7.5</b>	<b>Concurrent Medications</b> .....	<b>117</b>
<b>10</b>	<b>STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS</b> .....	<b>117</b>
<b>10.1</b>	<b>REGULATORY APPROVAL AND GOOD CLINICAL PRACTICE</b> .....	<b>117</b>
<b>10.2</b>	<b>INVESTIGATOR RESPONSIBILITIES</b> .....	<b>118</b>
<b>10.2.1</b>	<b>Subject Information and Informed Consent</b> .....	<b>118</b>
<b>10.2.2</b>	<b>Institutional Review Board/Independent Ethics Committee Approval and Other Institutional Requirements</b> .....	<b>119</b>
<b>10.2.3</b>	<b>Study Documentation</b> .....	<b>120</b>
<b>10.2.4</b>	<b>Delegation of Investigator Responsibilities</b> .....	<b>121</b>
<b>10.3</b>	<b>PROTOCOL DEVIATIONS AND VIOLATIONS</b> .....	<b>122</b>
<b>10.3.1</b>	<b>Protocol Deviation and Violation Definitions</b> .....	<b>122</b>
<b>10.3.2</b>	<b>Reporting Deviations/Violations</b> .....	<b>122</b>
<b>10.4</b>	<b>STUDY RECORDS RETENTION AND DIRECT ACCESS TO SOURCE DOCUMENTS</b>	<b>122</b>
<b>10.5</b>	<b>STUDY MONITORING</b> .....	<b>124</b>
<b>10.6</b>	<b>QUALITY ASSURANCE</b> .....	<b>125</b>
<b>10.7</b>	<b>STUDY TERMINATION AND SITE CLOSURE</b> .....	<b>125</b>
<b>10.8</b>	<b>SITE TERMINATION</b> .....	<b>126</b>
<b>10.9</b>	<b>DISCONTINUATION OF STUDY</b> .....	<b>127</b>
<b>11</b>	<b>DISCLOSURE OF DATA</b> .....	<b>127</b>
<b>11.1</b>	<b>CONFIDENTIALITY</b> .....	<b>127</b>
<b>11.2</b>	<b>PUBLICATION</b> .....	<b>128</b>
<b>12</b>	<b>INVESTIGATOR’S PROTOCOL AGREEMENT</b> .....	<b>129</b>
<b>13</b>	<b>REFERENCES</b> .....	<b>130</b>
<b>14</b>	<b>APPENDICES</b> .....	<b>134</b>
<b>APPENDIX 14.1</b>	<b>VAMOROLONE DOSE CALCULATION WORKSHEET AND BULK DISPENSING GUIDE</b> .....	<b>135</b>

**LIST OF TABLES**

<b>Table 1</b>	<b>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 .....</b>	<b>45</b>
<b>Table 2</b>	<b>Summary of pharmacokinetic parameters for vamorolone after single dose oral administration of 8 mg/kg to healthy subjects under fed and fasted conditions .....</b>	<b>47</b>
<b>Table 3</b>	<b>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 .....</b>	<b>48</b>
<b>Table 4</b>	<b>Biomarkers previously defined to be responsive to chronic doses of glucocorticoids in DMD boys .....</b>	<b>56</b>
<b>Table 5</b>	<b>Planned Dose Level Composition.....</b>	<b>64</b>
<b>Table 6</b>	<b>Schedule of Study Activities .....</b>	<b>81</b>
<b>Table 7</b>	<b>Vamorolone Dose Tapering.....</b>	<b>89</b>
<b>Table 8</b>	<b>Hematology, Chemistry, and Lipids Clinical Laboratory Tests.....</b>	<b>94</b>
<b>Table 9</b>	<b>Urinalysis Clinical Laboratory Tests.....</b>	<b>94</b>
<b>Table 10</b>	<b>Pharmacodynamic Biomarkers .....</b>	<b>107</b>
<b>Table 11</b>	<b>Blood Sample Number and Volume .....</b>	<b>108</b>
<b>Table 12</b>	<b>6-month and 12-month Changes in Outcomes in 4-&lt;8 year-old DMD Boys.....</b>	<b>112</b>

## LIST OF FIGURES

<b>Figure 1</b>	<b>Arithmetic mean <math>\pm</math> standard error 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 - linear plot (top); semi-logarithmic plot (bottom) .....</b>	<b>44</b>
<b>Figure 2</b>	<b>Relationship between individual subject vamorolone <math>AUC_{(inf)}</math> 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 .....</b>	<b>45</b>
<b>Figure 3</b>	<b>Arithmetic mean <math>\pm</math> standard error plasma concentrations of vamorolone (VBP15) after single dose oral administration of 8 mg/kg to healthy subjects under fed and fasted conditions - linear (top panel) and semi-logarithmic (bottom panel) axes .....</b>	<b>46</b>
<b>Figure 4</b>	<b>Arithmetic mean <math>\pm</math> standard error 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 (linear axes) .....</b>	<b>49</b>
<b>Figure 5</b>	<b>Morning cortisol measures in the vamorolone Phase I MAD volunteers.* .....</b>	<b>51</b>
<b>Figure 6</b>	<b>Fasting serum glucose during the Phase I MAD period (two weeks daily treatment).....</b>	<b>53</b>

## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition/Term</b>
ACTH	adrenocorticotrophic hormone
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC <sub>0-24hr</sub>	area under the concentration-time curve from time 0 to 24 hours
AUC <sub>0-t</sub>	area under the concentration-time curve from time 0 to time t
AUC <sub>inf</sub>	area under the concentration-time curve from time 0 to infinity
AUC <sub>last</sub>	area under the plasma concentration-time curve from time 0 to the last observed measurable concentration
BMI	body mass index
BUN	blood urea nitrogen
C	Celsius
CD23	cluster designation 23
CFR	Code of Federal Regulations
CINRG	Cooperative International Neuromuscular Research Group
CK	creatine kinase
CL	clearance
ConA	concanavalin A
cm	centimeter
C <sub>max</sub>	maximum observed plasma concentration
CQMS	CINRG Quantitative Measurement System
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Material
CTX	carboxy-terminal telopeptide
CYP	cytochrome P450
dL	deciliter
DMD	Duchenne muscular dystrophy
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form

<b>Abbreviation</b>	<b>Definition/Term</b>
EDC	electronic data capture
F	Fahrenheit
F, F%	bioavailability, percent bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
hr	hour
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGFBP-2	insulin-like growth factor-binding protein 2
IGFBP-5	insulin-like growth factor-binding protein 5
IL-22BP	interleukin-22 binding protein
IND	Investigational New Drug
IRB	Institutional Review Board
K <sub>2</sub> -EDTA	dipotassium ethylenediaminetetraacetic acid
kg	kilogram
$\lambda_z$	elimination rate constant
L	liter
LLC	Limited Liability Company
LC-MS	Liquid Chromatography – Mass Spectrometry
LDH	lactate dehydrogenase
LDL	low density lipoprotein
m	meter
MAD	multiple ascending dose (study)
<i>mdx</i>	mouse model lacking dystrophin
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
MIST	Metabolites in Safety Testing

<b>Abbreviation</b>	<b>Definition/Term</b>
mITT	modified Intention to Treat
mL	milliliter
MMP-3	matrix metalloproteinase-3
MMP-12	matrix metalloproteinase-12
MS Band	Microsoft Band
NADPH	nicotinamide adenine dinucleotide phosphate
NF- $\kappa$ B	nuclear factor kappa-light-chain-enhancer of activated B cells
ng	nanogram
No., n	number
NOAEL	no observed adverse effect level
NSAA	North Star Ambulatory Assessment
OTC	over-the-counter (non-prescription medication)
%CV	percentage coefficient of variation
P1NP	serum aminoterminal propeptide of type I collagen
PBL	peripheral blood leukocytes
PD	pharmacodynamics
PHI	Protected Health Information
PK	pharmacokinetics
PR [PQ]	interval from onset of P wave to start of the QRS complex
Q	quarter
QMT	Quantitative Muscle Testing
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 interval between the start of the Q wave and end of the T wave
QT <sub>c</sub>	corrected QT interval
RBC	Red Blood Cell
RR	in electrocardiography, the interval between successive R waves (peaks of QRS complexes)
6MWT	Six-minute Walk Test
SAD	single ascending dose (study)
SAE	Serious Adverse Event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class

<b>Abbreviation</b>	<b>Definition/Term</b>
SOP	standard operating procedures
SSL	secure socket layers
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
$T_{max}$	time to maximum observed plasma concentration
TTCLIMB	Time to Climb (Test)
TTSTAND	Time to Stand (Test)
TTRW	Time to Run/Walk (Test)
US	United States
vs.	versus
$V_{ss}$	volume of distribution at steady state
$V_z$	terminal phase volume of distribution
WBC	White Blood Cell
WHO	World Health Organization

## 1 INTRODUCTION

### 1.1 Background and Unmet Need

Duchenne muscular dystrophy (DMD) is a rapidly progressive form of muscular dystrophy that occurs primarily in males and manifests prior to the age of six years. Duchenne muscular dystrophy affects approximately 1 in 3,600 to 9,300 male births worldwide.<sup>1</sup> Duchenne muscular dystrophy is caused by mutations in the dystrophin gene which codes for a protein that provides structural stability to the dystroglycan complex on muscle cell membranes.<sup>2</sup> The lack of dystrophin reduces plasma membrane stability. Membrane destabilization results in altered mechanical properties and aberrant signaling, which contribute to membrane fragility, necrosis, inflammation, and progressive muscle wasting.<sup>3</sup>

In addition to the significant contribution of membrane destabilization and mechanical injury in DMD, aberrant intracellular signaling cascades that regulate inflammatory and immune processes also contribute to DMD pathophysiology. Up-regulated inflammatory gene expression and activated immune cell infiltrates, at least partially mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) activation, are evident during early disease stages and play a significant role in muscle wasting.<sup>3</sup> NF- $\kappa$ B has been shown to regulate the expression of numerous inflammatory genes in immune cells and muscle fibers,<sup>4,5,6,7</sup> and the infiltration and activation of these cells can trigger muscle fiber death.<sup>8,9</sup>

Although significant advances have been made in understanding the etiology of DMD, a cure has not been found, and current treatment options are all medications used “off-label” to alleviate the symptoms of DMD. Despite scientific advances, only glucocorticoids, such as prednisone, have consistently demonstrated efficacy in clinical trials.<sup>10</sup> Further, many disease modifying technologies that are currently in development focus on subsets of dystrophin mutations and therefore do not address the unmet need in all persons with DMD. However, it is likely that glucocorticoids will need to be co-administered with many of these compounds for maximum effect and glucocorticoids have extensive side effect profiles, often limiting long-term administration. The current



goal of DMD research is to find a mutation-independent treatment that matches or exceeds the efficacy of glucocorticoids with a significantly lower side effect profile.

Vamorolone is a first generation delta-9, 11 chemical compound belonging to the structural class of synthetic steroidal drugs, which includes the glucocorticoids prednisone, methylprednisone, and dexamethasone.<sup>11</sup> The chemical structure of vamorolone has optimized four subactivities of traditional glucocorticoid drugs, namely transactivation, transrepression, physiochemical membrane properties, and mineralocorticoid receptor antagonism.<sup>11</sup> By reducing transactivation subproperties, retaining transrepression, imparting membrane stabilizing properties, and inhibiting the mineralocorticoid receptor pathway, vamorolone has favorable efficacy and side effect profiles relative to classic glucocorticoids in nonclinical models and is anticipated to be an attractive candidate for the treatment of DMD in pediatric patients.

*In vitro* and nonclinical data to date suggest that vamorolone may offer a much needed alternative to the current glucocorticoids which are standard of care for DMD,<sup>12</sup> with administration beginning around the age of 5 years in most developed countries, or even earlier in some cases.

The significant effects of glucocorticoids on growth and development, however, prevent their routine administration in infancy or ‘toddler’ years, despite evidence that the earlier the administration, the better the overall functional outcome.<sup>13</sup> The cumulative side effects of glucocorticoids, including excess weight, delayed puberty, fragile skin, loss of bone mineral density, bruising, and Cushingoid appearance continue to negatively impact on the quality of life of the individual, leading to significant variations in clinical practice.<sup>14</sup> Glucocorticoids also contribute to further muscle damage with long-term administration. Vamorolone has shown few if any of the side effects of traditional glucocorticoids in mouse models of DMD.<sup>11,15,16</sup>

This study is targeted to explore whether vamorolone will show at least equal efficacy to glucocorticoids with a more favorable side effect profile, thereby improving the quality of life for DMD patients. This profile would enable use of vamorolone in DMD boys who are at a younger age than when glucocorticoid treatment is currently initiated. In

addition, vamorolone could be prescribed in later stage non-ambulant young men with DMD and for a longer period of time, where the risk:benefit balance of glucocorticoids is often less favorable.

Efficacy may also be improved over classic glucocorticoids in the longer term. In addition to the anti-inflammatory properties of vamorolone as a result of NF- $\kappa$ B 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.<sup>17</sup> Further, vamorolone has been recently demonstrated to improve asynchronous remodeling, believed to be a component of progressive muscle weakness and wasting in DMD<sup>18</sup> and may also prevent muscle membrane damage, thereby delaying progression of the disease further. Vamorolone is an antagonist to the mineralocorticoid receptor, whereas glucocorticoids are typically agonists. An antagonist for the mineralocorticoid receptor, epleronone, was recently shown to significantly improve DMD heart function.<sup>19</sup> Finally, vamorolone imparts physical stability to myofiber plasma membranes, whereas prednisone destabilizes membranes. This property addresses the primary defect of membrane instability in dystrophin deficient myofibers in DMD.<sup>15</sup>

Potentially, the administration of vamorolone to a DMD patient may begin soon after birth to slow the dystrophic process of muscle, retaining regenerative capacity and substantially improving patient quality of life.

## **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*.

### **1.2.1 Safety Pharmacology**

Stunted growth is a significant side effect of chronic glucocorticoid use in children.<sup>20,21</sup> Chronic treatment with glucocorticoids negatively affects bone growth and development and can cause osteoporosis.<sup>22,23</sup>

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.<sup>15</sup>

In normal, male CD-1<sup>®</sup> mice, these effects were reproduced. Unlike CD-1 mice treated with prednisolone, CD-1 mice receiving vamorolone did not experience tibia length shortening.<sup>16</sup> 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 prednisone treatment in heart muscle of the *mdx* mouse has been reported.<sup>24</sup> Histologically, clear 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.<sup>15</sup> 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).<sup>15</sup>

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 ( $t_{1/2}$ ) 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  $t_{1/2}$  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  $t_{1/2}$  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**

CrI:CD1(ICR) mice were administered vamorolone or vehicle once daily for 28 consecutive days. Vamorolone exposure (as assessed by the  $C_{max}$  and area under the concentration-time curve [AUC]) 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 once daily 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).

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 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. There was a slight decrease in body weight attributed to vamorolone in both 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. No other abnormalities were observed in experimental mice (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 abnormalities observed (ReveraGen Report No. 1998-001).

#### **1.2.3.2 Multiple Dose**

Vamorolone or vehicle was administered to Crl:CD1(ICR) mice once daily 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 in food consumption, ophthalmic examination, or urinalysis during the study. 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 of the adrenal gland. 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).

A GLP-compliant study was carried out to evaluate the toxicity of the test article, vamorolone, in Crl:CD1<sup>®</sup> (ICR) mice after administration for 26 weeks, including evaluation of the reversibility, progression, or delayed appearance of any observed changes following a 4-week post-dose observation period. 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 the 5 mg/kg/day dose 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 the 45 mg/kg/day dose. 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 as 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 doses  $\geq 5$  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  $\geq 15$  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. However, 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 doses  $\geq 5$  mg/kg/day and females at doses  $\geq 15$  mg/kg/day that lacked correlative findings among other study endpoints; resolution for this observation could not be determined.

A mild vamorolone -related increase in albumin was observed in males at doses  $\geq 5$  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 the 45 mg/kg/day dose and females at the 15 mg/kg/day dose 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 the 45 mg/kg/day dose. Tan discoloration occurred in one female and four males at this dose in the dosing phase. This correlated with microvesicular/macrovacular 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; 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 the 45 mg/kg/day dose. Decreased anagen hair follicles were documented for individual animals when there were no anagen hair follicles in the section of skin. Incidence in controls and mice at the 5 and 15 mg/kg/day doses 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 no meaningful differences between treated animals 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 ( $AUC_{0-24hr}$ ) 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/day, did not appear to change following repeated administration of vamorolone at 15 mg/kg/day, and appeared to decrease following repeated administration of vamorolone at 45 mg/kg/day. Systemic exposure to vamorolone in males appeared to decrease following repeated administration of vamorolone.

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 NOAEL is considered to be 45 mg/kg/day under the conditions of this study.

Vamorolone or vehicle was administered to beagle dogs once daily 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 gross visual inspection, body weight, body temperature, food consumption, ophthalmology, electrocardiography or urinalysis parameters at necropsy. A dose-dependent decrease in the expected normal body weight gain was observed at all doses but weights generally increased to a normal level during the recovery period.

Adrenal gland weights decreased with vamorolone treatment, 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 determination 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).

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, relative to controls, over the course of the 39-week dose phase were observed 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 effects 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  $\geq 2$  mg/kg/day (microscopic correlate of bilateral cortical atrophy); increases in liver weights in both sexes at  $\geq 10$  mg/kg/day (microscopic correlates of panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation); increases in kidney weights in females at  $\geq 10$  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  $\geq 10$  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  $\geq 10$  mg/kg/day and cytoplasmic vacuolation of the mucosal epithelium in males at  $\geq 10$  mg/kg/day and females at  $\geq 2$  mg/kg/day); liver (hepatocellular vacuolation in males at  $\geq 10$  mg/kg/day and females at  $\geq 2$  mg/kg/day, panlobular hypertrophy in males at 50 mg/kg/day and females at  $\geq 10$  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  $\geq 10$  mg/kg/day, and cytoplasmic vacuolation of the bile duct epithelium in both sexes at  $\geq 10$  mg/kg/day); kidneys (bilateral tubular vacuolation in males at 50 mg/kg/day and females at  $\geq 10$  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  $\geq 2$  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  $\geq 2$  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  $\geq 10$  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  $\geq 10$  mg/kg/day); prostate gland (decreased secretory product in males at 50 mg/kg/day); thyroid glands (bilateral increased colloid in males at  $\geq 10$  mg/kg/day).

Many of the findings were felt 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).

Non-naive cynomolgus monkeys were administered vamorolone or vehicle once daily 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. They had resolved by the recovery interval in both sexes.

In both sexes receiving  $\geq 300$  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 has not generated a mutagenic signal based on these simulations.

### **1.3 Clinical Experience**

#### ***1.3.1 Phase I Study in Healthy Adult Volunteers***

Clinical experience is limited to a single Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001). This study evaluated the safety, tolerability, and PK of vamorolone in a Phase I randomized, 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 (6 drug, 2 placebo in each) receiving 14 daily doses of vamorolone (1.0, 3.0, 9.0 and 20.0 mg/kg/day). The clinical conduct for all seven SAD cohorts, and all four MAD cohorts has been completed; data analysis is ongoing.

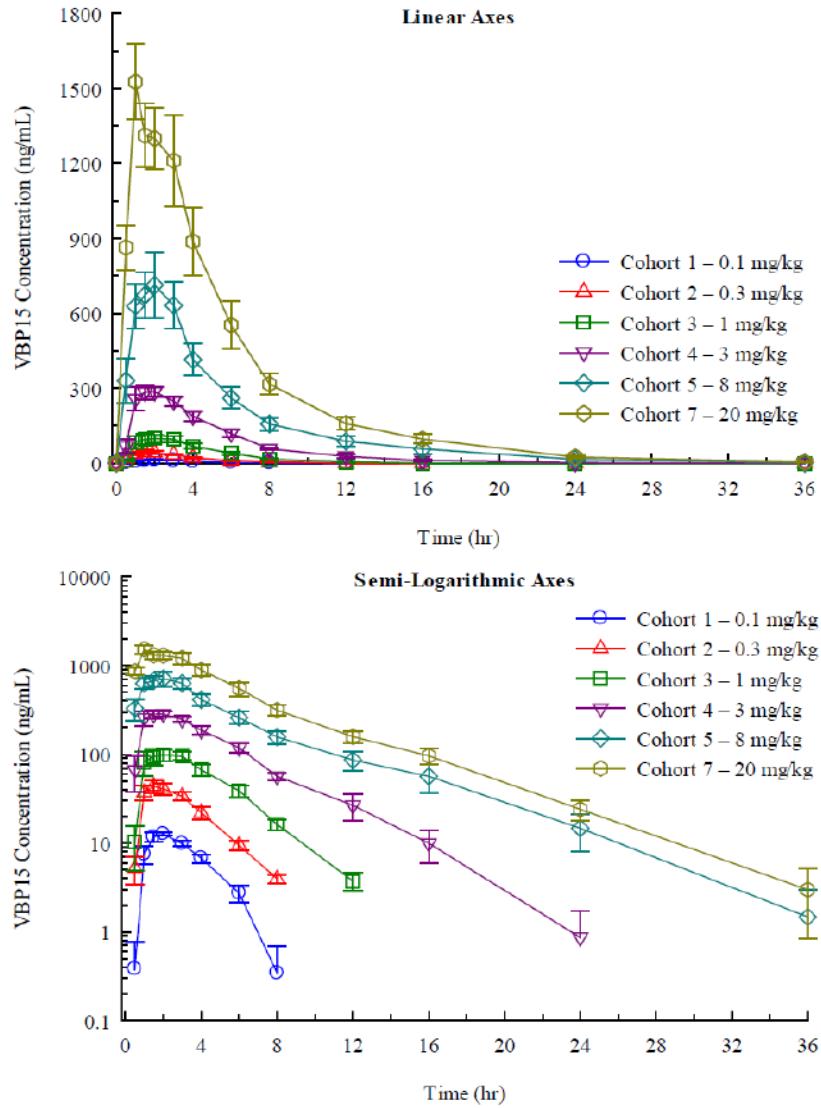
The primary objectives of the Phase I study were to evaluate the safety and tolerability of single and multiple oral doses of vamorolone, and to evaluate the PK of single doses and multiple doses of vamorolone. A secondary objective was to evaluate the effect of food on the absorption and PK of vamorolone. 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.

### ***1.3.1.1 SAD Cohorts***

#### ***1.3.1.1.1 SAD Cohorts – Pharmacokinetics Fasted***

Vamorolone PK data shows strong adherence to dose linearity and dose proportionality, with relatively little subject-subject variation (**Figure 1, Table 1, Figure 2**). 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, 3.8 and 3.8 hours, respectively (**Figure 1**).

**Figure 1** Arithmetic mean  $\pm$  standard error 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 - linear plot (top); semi-logarithmic plot (bottom)

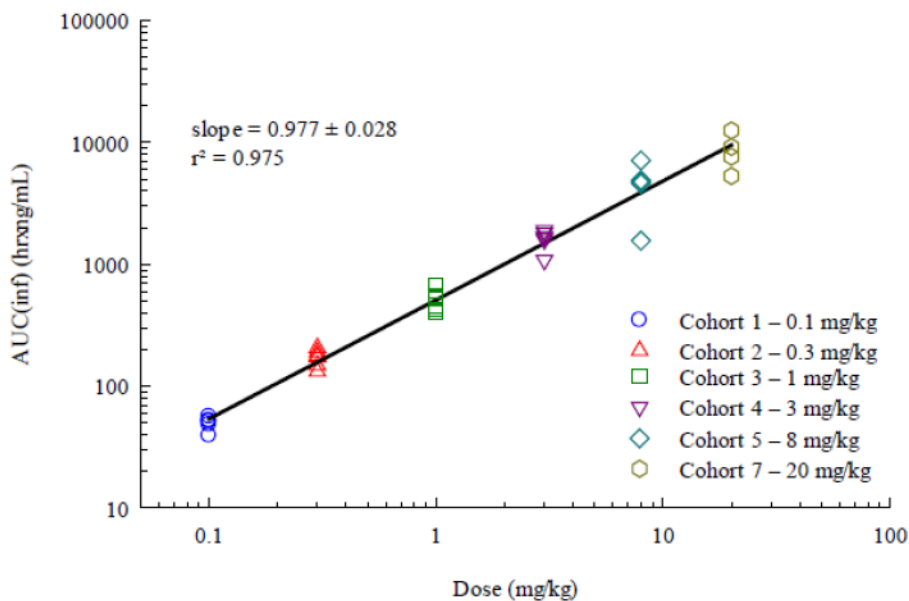


**Table 1 Summary of pharmacokinetic parameters for vamorolone after oral administration of single doses of 0.1, 0.3, 1.0, 3.0, 8.0, and 20.0 mg/kg to healthy subjects under fasted conditions**

Parameter*	Dose					
	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	8 mg/kg	20 mg/kg
C <sub>max</sub> (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)
T <sub>max</sub> (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 <sub>(0-t)</sub> (hr×ng/mL)	41.9 (16.8) (6)	161 (15.9) (6)	486 (19.7) (6)	1,578 (20.7) (6)	3,997 (35.0) (6)	8,545 (29.5) (6)
AUC <sub>(inf)</sub> (hr×ng/mL)	49.5 (12.5) (6)	170 (16.5) (6)	500 (19.2) (6)	1,600 (20.3) (6)	4,137 (62.1) (5)	8,277 (37.2) (4)
λ <sub>z</sub> (1/hr)	0.4064 (12.4) (6)	0.4376 (16.5) (6)	0.3829 (18.0) (6)	0.2792 (18.5) (6)	0.1823 (52.3) (5)	0.1827 (11.9) (4)
t <sub>1/2</sub> (hr)	1.71 (12.4) (6)	1.58 (16.5) (6)	1.81 (18.0) (6)	2.48 (18.5) (6)	3.80 (52.3) (5)	3.79 (11.9) (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)	1.93 (62.1) (5)	2.42 (37.2) (4)
V <sub>z</sub> /F (L/kg)	4.97 (6.06) (6)	4.03 (19.5) (6)	5.22 (19.1) (6)	6.72 (30.5) (6)	10.6 (57.8) (5)	13.2 (32.4) (4)

C<sub>max</sub> = maximum observed plasma concentration; T<sub>max</sub> = time to maximum observed plasma concentration; AUC<sub>(0-t)</sub> = area under concentration-time curve from time 0 to time t; AUC<sub>(inf)</sub> = area under concentration-time curve from time 0 to infinity; λ<sub>z</sub> = elimination rate constant; t<sub>1/2</sub> = terminal half-life; CL/F = apparent total clearance from plasma; V<sub>z</sub>/F = apparent volume of distribution during terminal phase.

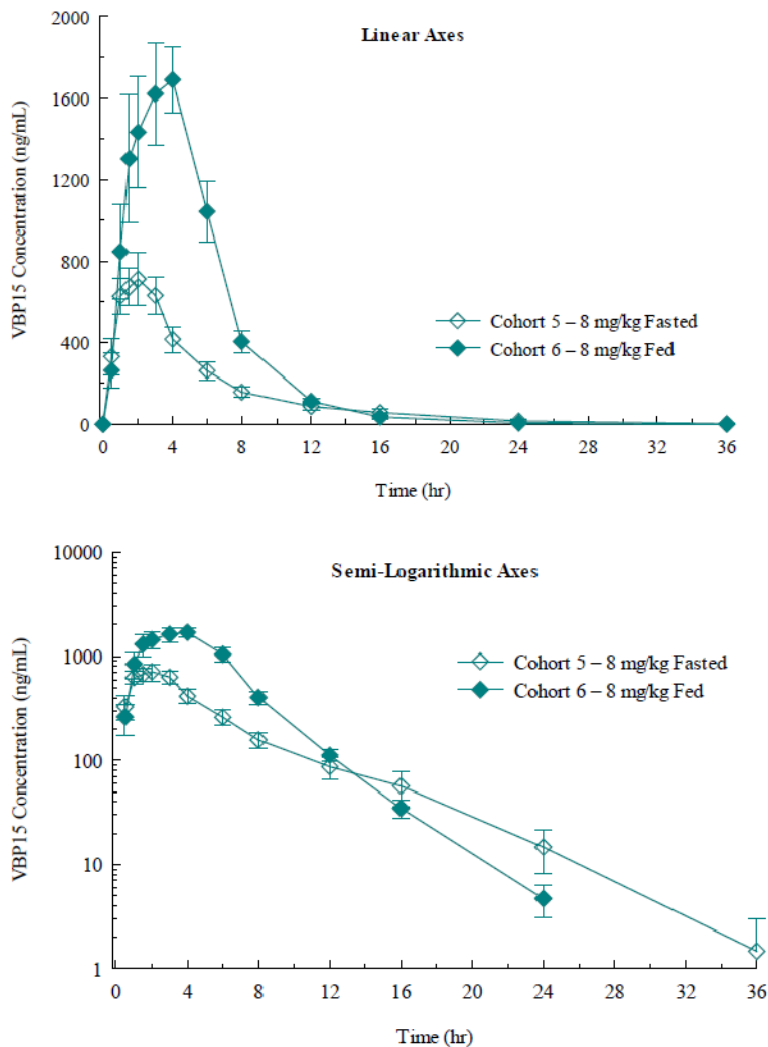
**Figure 2 Relationship between individual subject vamorolone AUC<sub>(inf)</sub> and dose after oral administration of single doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to healthy subjects under fasted conditions**



1.3.1.1.2 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) (Figure 3, Table 2).

**Figure 3 Arithmetic mean  $\pm$  standard error plasma concentrations of vamorolone (VBP15) after single dose oral administration of 8 mg/kg to healthy subjects under fed and fasted conditions - linear (top panel) and semi-logarithmic (bottom panel) axes**



**Table 2 Summary of pharmacokinetic parameters for vamorolone after single dose oral administration of 8 mg/kg to healthy subjects under fed and fasted conditions**

Parameter*	8 mg/kg		Ratio†
	Fasted	Fed	
C <sub>max</sub> (ng/mL)	718 (42.5) (6)	1,817 (31.4) (6)	2.53
T <sub>max</sub> (hr)	1.78 (6) [1.00 – 2.00]	4.00 (6) [2.00 – 6.00]	
AUC(0-t) (hr×ng/mL)	3,997 (55.0) (6)	10,139 (25.1) (6)	2.54
AUC(∞) (hr×ng/mL)	4,137 (62.1) (5)	10,170 (24.9) (6)	2.46
λ <sub>z</sub> (1/hr)	0.1823 (52.3) (5)	0.2950 (18.9) (6)	
t <sub>1/2</sub> (hr)	3.80 (52.3) (5)	2.35 (18.9) (6)	
CL/F (L/hr/kg)	1.93 (62.1) (5)	0.79 (24.9) (6)	
V <sub>z</sub> /F (L/kg)	10.6 (57.8) (5)	2.67 (23.4) (6)	

\*Geometric mean (%CV) (N) except T<sub>max</sub> for which the median (N) is reported.

†Ratio of the geometric means.

C<sub>max</sub> = maximum observed plasma concentration; T<sub>max</sub> = time to maximum observed plasma concentration; AUC<sub>(0-t)</sub> = area under concentration-time curve from time 0 to time t; AUC<sub>(∞)</sub> = area under concentration-time curve from time 0 to infinity; λ<sub>z</sub> = elimination rate constant; t<sub>1/2</sub> = terminal half-life; CL/F = apparent total clearance from plasma; V<sub>z</sub>/F = apparent volume of distribution during terminal phase.

#### 1.3.1.1.3 SAD Cohorts – Adverse Events

One subject in the SAD 8.0 mg/kg showed a delayed mild elevation of liver enzymes. This was not felt to be drug-related due to timing of the elevations, and it is not known if this was a drug-treated or placebo subject (study remains blinded). There were no other adverse events (AEs) seen in any dose group.

#### 1.3.1.2 MAD Cohorts

The Phase I MAD treatment plan was discussed in light of the initial PK data. The relatively short half-life of vamorolone (2-4 hours), coupled with the planned daily dose schedule, would be expected to give PK data on each single dose, not cumulative dose, as the dosing interval was  $> 5 \times t_{1/2}$ . Thus, the MAD component would be a study of individual daily doses, rather than dose-related accumulation and pharmacodistribution related to cumulative drug exposure. In other words, a typical goal of a MAD study is to determine steady state drug levels after multiple doses; yet with the short half-life of vamorolone, useful information would not be expected to be gained with the current daily

dosing schedule. Safety and tolerability are additional goals of the MAD study, and these remain important endpoints independent of the PK studies.

*1.3.1.2.1 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. The clinical conduct of all four cohorts has been 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**

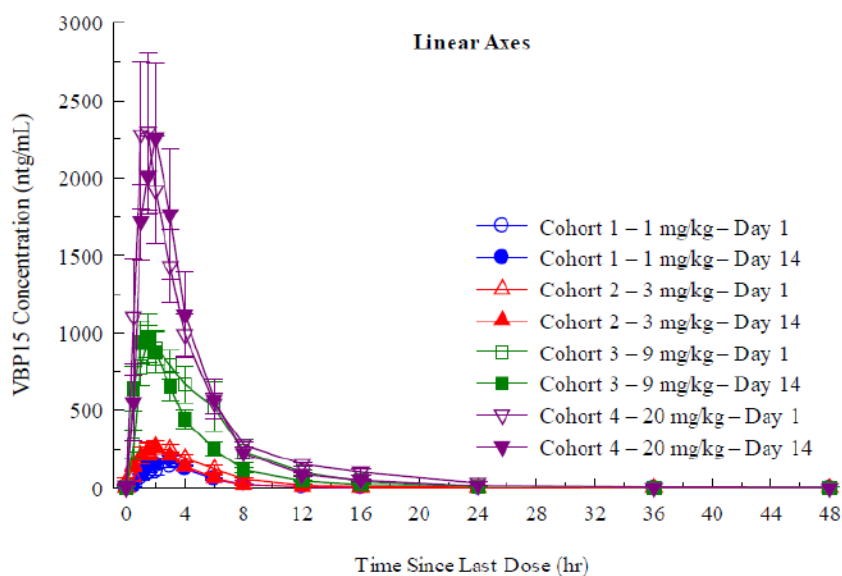
	Vamorolone Dose			
	1 mg/kg	3 mg/kg	9 mg/kg	20 mg/kg
Day 1 C <sub>max</sub> (ng/mL)	153 (15.9)	281 (36.9)	1,082 (23.3)	2,416 (51.1)
T <sub>max</sub> (hr)	3.04 [1.50 – 4.00]	2.01 [1.00 – 3.00]	1.75 [1.00 – 6.00]	1.00 [0.50 – 3.00]
AUC <sub>(0-t)</sub> (hr <sub>y</sub> ng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)
AUC <sub>(0-24)</sub> (hr <sub>x</sub> ng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)
AUC <sub>(inf)</sub> (hr <sub>x</sub> ng/mL)	695 (22.1)	1,487 (23.7)	5,745 (29.5)	10,190 (27.0)
λ <sub>z</sub> (1/hr)	0.3848 (10.9)	0.2918 (18.1)	0.2317 (22.6)	0.1747 (44.3)
t <sub>1/2</sub> (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 <sub>z</sub> /F (L/kg)	3.74 (16.9)	6.91 (34.8)	6.76 (46.9)	11.2 (77.6)
Day 14 C <sub>max</sub> (ng/mL)	203 (30.1)	276 (35.6)	935 (48.3)	2,491 (27.9)
T <sub>max</sub> (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 <sub>(0-24)</sub> (hr <sub>x</sub> ng/mL)	794 (22.3)	1,494 (18.6)	4,366 (20.2)	9,309 (38.8)
λ <sub>z</sub> (1/hr)	0.3993 (20.4)	0.3273 (25.2)	0.1629 (63.5)	0.1879 (31.6)
t <sub>1/2</sub> (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 <sub>z</sub> /F (L/kg)	3.15 (20.6)	6.14 (39.7)	12.7 (79.9)	11.4 (49.1)

C<sub>max</sub> = maximum observed plasma concentration; T<sub>max</sub> = time to maximum observed plasma concentration; AUC<sub>(0-t)</sub> = area under concentration-time curve from time 0 to time t; AUC<sub>(0-24)</sub> = area under concentration-time curve from time 0 to 24 hours; AUC<sub>(inf)</sub> = area under concentration-time curve from time 0 to infinity; λ<sub>z</sub> = elimination rate constant; t<sub>1/2</sub> = terminal half-life; CL/F = apparent total clearance from plasma; V<sub>z</sub>/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  $t_{1/2}$  (~2 hour) and dosing interval (24 hours) (**Figure 4**; **Table 3**).

**Figure 4** Arithmetic mean  $\pm$  standard error 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 (linear axes)



#### 1.3.1.2.2 MAD Cohorts – Adverse Events

Three subjects have discontinued dosing; one subject (1.0 mg/kg/day group) withdrew consent on Day 10 so that he could receive care for an exacerbation of a previously existing dental condition. Dosing was discontinued in a second subject on Day 9 (on placebo in the 1.0 mg/kg/day cohort after completing 8 days of dosing) due to an increase in alanine aminotransferase (ALT). The subject's baseline value was 40 (normal  $\leq 50$ ); on Days 7, 8, and 9, it was 70, 86, and 106, respectively. Following cessation of dosing, the ALT has slowly declined and is continuing to be followed. Aspartate

aminotransferase (AST) was within normal limits with the exception of a value of 47 on Day 9 (normal  $\leq 45$ ), which was again normal the following day. Alkaline phosphatase, bilirubin, and coagulation parameters have remained within normal limits and the subject has remained asymptomatic. A third subject who was on active drug in the 20 mg/kg dose group was discontinued after 9 days of dosing due to an increase in ALT. The subject's baseline value was 43 (normal  $\leq 50$ ) at screening; on Days 7, 8, and 9, it was 56, 60, and 73, respectively. Following cessation of dosing, the ALT increased to 96 and 104 on Days 10 and 12; on Day 17, it had declined to 85. The subject continues to be followed and has remained asymptomatic. Aspartate aminotransferase was within normal limits with the exception of a value of 47 on Day 12 (normal  $\leq 45$ ); total bilirubin was 0.7 at screening (normal 0.2-1.2); it was increased at 1.4, 1.9, and 1.4 on Days 1, 2, and 3, respectively, and within normal limits for the remainder of dosing and follow-up. No subject in the 3.0 or 9.0 mg/kg/day cohorts had to discontinue dosing for an AE.

#### 1.3.1.2.3 *Pharmacodynamic Safety Biomarkers*

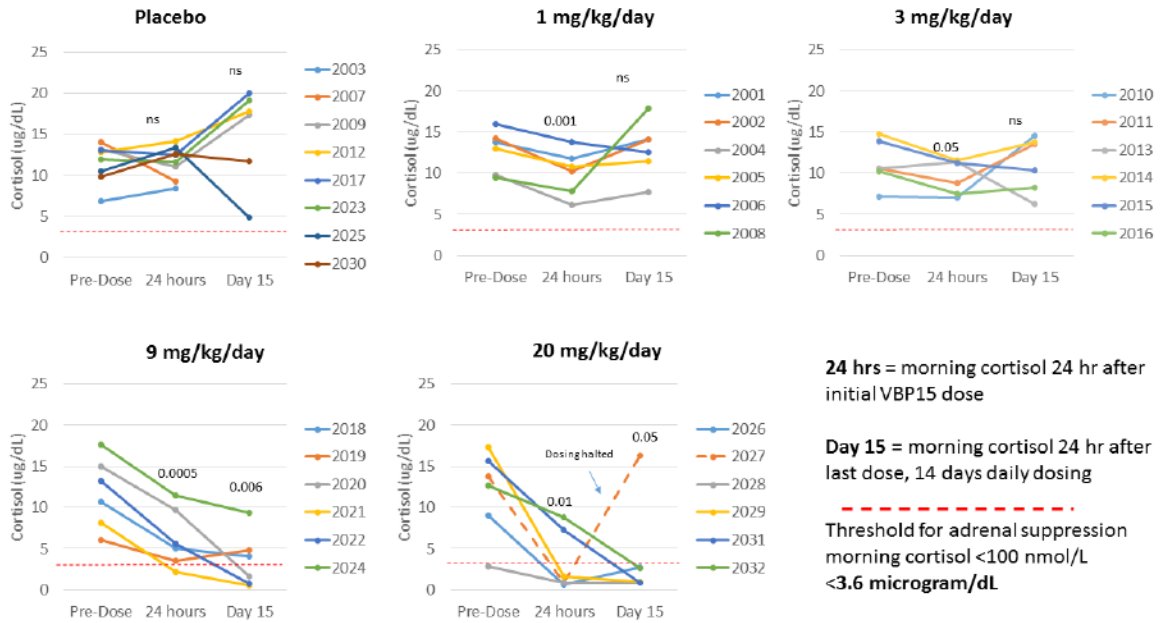
Vamorolone has shown improved safety profiles relative to prednisone in nonclinical testing, both *in vitro* and *in vivo*.<sup>15,17</sup> Safety concerns with glucocorticoids include suppression of the adrenal axis and insulin resistance. Pharmacodynamic biomarker assays of suppression of the adrenal 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 adrenocorticotrophic hormone (ACTH) levels in normal volunteers.<sup>25</sup> More chronic suppression of the adrenal axis, characterized as severe, is typically diagnosed when morning cortisol is  $< 100$  nmol/L ( $< 3.6$  microgram/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**). Active substance volunteers 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 measures in the vamorolone Phase I MAD volunteers.\***



\* 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,<sup>25</sup> suggesting that vamorolone has an improved safety window regarding adrenal axis suppression.

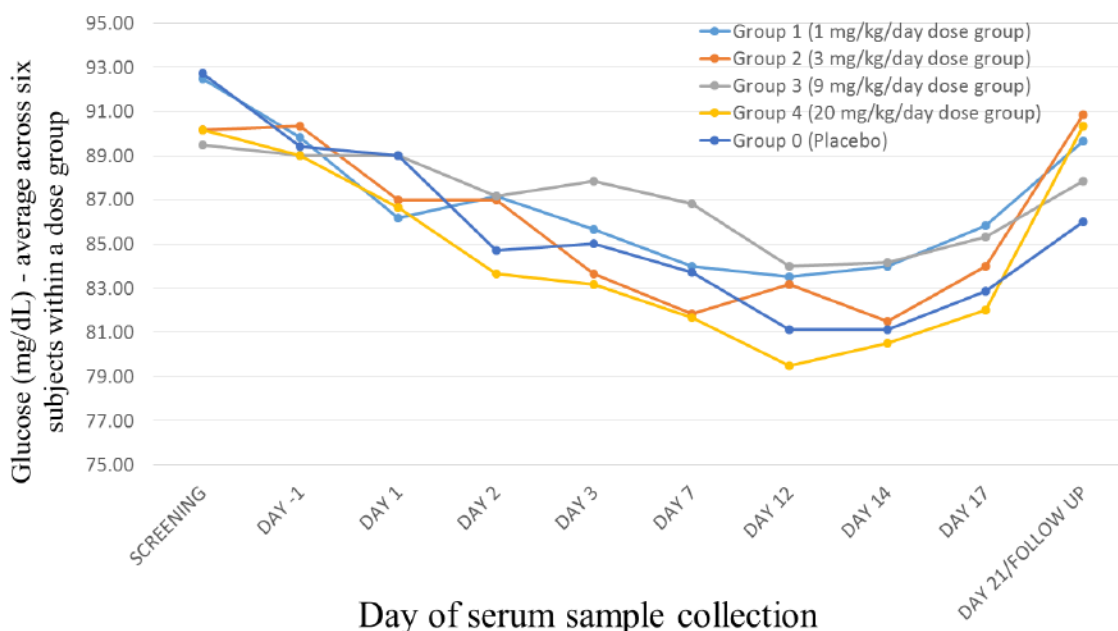
Vamorolone thus shows approximately a 100-fold improvement in safety window compared to prednisone on a mg/kg comparative basis. These data are consistent with *in vitro* and *ex vivo* nonclinical mouse data comparing VBP15/vamorolone to prednisone for adrenal suppression.<sup>15</sup>

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.<sup>25</sup> Insulin resistance may be an important safety signal for dystrophic muscle, where the dysfunctional myofibers have been shown to have inadequate energy stores,<sup>18,26</sup> 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).<sup>27,28</sup>

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.<sup>29</sup>

### 1.3.1.3 Summary of Phase I data

In summary:

- 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 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, 3.8, 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.

- 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. These data were then compared to the fasted 8.0 mg/kg cohort data. The comparison showed that absorption was increased by 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone (steroidal compound).
- For the MAD cohorts, there were no AEs precluding further escalations in dosing.
- Regarding the primary target organ, liver, one subject on placebo in the 1.0 mg/kg/day cohort and one subject on vamorolone in the 20 mg/kg/day cohort showed mild elevations of liver enzymes, and drug dosing was halted. No subjects in the 3.0 or 9.0 mg/kg/day MAD cohorts showed elevations of liver enzymes.
- Safety PD biomarker studies showed that vamorolone had an improved safety window for adrenal axis suppression (100-fold increase in therapeutic window), and no evidence of insulin resistance, compared to prednisone studies reported in the literature.

The results show that the half-life of vamorolone is very similar to glucocorticoids, such as prednisone. Despite the short half-life, prednisone is typically given once per day for most indications (including DMD), and once daily dosing is also proposed for vamorolone. Previous studies of increasing the frequency of drug administration of glucocorticoids have shown that this has increased side effect profiles without a significant gain in efficacy. Thus, the mechanism of action of glucocorticoids may be related to the short-term (pulsed) daily drug exposure. As vamorolone is thought to share a similar anti-inflammatory mechanism of action as glucocorticoids (NF- $\kappa$ B inhibition), it is felt that the daily pulsed exposure in the Phase I MAD is most relevant to the planned clinical trials in DMD including the Phase II MAD and Phase II efficacy/safety studies, where daily dosing schedules will be followed. The option of increasing the dosing regimen in the Phase I MAD to better study drug accumulation and steady state PD was

considered, but this was felt to be unrelated to planned Phase II trials, and drug mechanism of action.

#### **1.4 Rationale for Study Design**

Vamorolone is under development for the treatment of DMD. The first-in-human clinical assessment of vamorolone is ongoing in the SAD/MAD study (VBP15-001) and is providing an initial clinical assessment and assessment of the PK characteristics of vamorolone following administration of an oral suspension of vamorolone in healthy adult subjects. While there are likely to be some differences between adults and children, and between healthy and DMD subjects, the data from VBP15-001 have established the 2-4 hour half-life of vamorolone, food effect, dose proportionality and variability among subjects.

A Phase IIa Multiple Ascending Dose study (VBP15-002) will determine the safe and tolerable dose(s) of vamorolone to enable future studies with chronic administration in DMD subjects, aged 4-7 years. The narrow age window for this study is driven by several factors: 1) the average age of diagnosis is still approximately 4.8 years due to lack of screening programs; 2) the current standards of clinical care in Western countries, where glucocorticoid therapy is typically initiated between 5 and 7 years of age for DMD patients; and 3) the observation that peak function for DMD patients occurs at around 7 years of age (after which time most affected males with DMD will begin to decline), all of which result in a narrow age window to identify steroid-naïve males with DMD.

Key safety parameters in conjunction with PK data are being evaluated during the course of the Phase IIa study to assess vamorolone safety and tolerability. Exploratory clinical efficacy parameters and PD biomarkers of tissue breakdown and repair are also being evaluated.

The vamorolone development program has made advances in biomarker discovery and development in DMD, with a subset of these studies recently published.<sup>30</sup> A panel of biomarkers in DMD patient sera that show response to chronic (~4 month) treatment with glucocorticoids has been identified. These chronic prednisone PD biomarkers were discovered through study of serum samples of DMD patients enrolled in the Cooperative

International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS). SomaScan aptamer panels testing 1,200 serum proteins were used to discover a candidate set of prednisone-responsive biomarkers, with a subset of these validating in a longitudinal sample set (individual DMD patients pre/post steroid treatment). These PD biomarkers were assigned to a safety panel or efficacy panel based on comparison to normal controls and information concerning the function of each protein (Table 4). All safety biomarkers were validated in a separate cohort of pediatric inflammatory disease patients (longitudinal pre/post steroids). The same SomaScan assay will be used on the chronic samples from the vamorolone Phase IIa trial (entry, 2 weeks treatment, 2 weeks washout), with initial data analyses limited to those validated biomarkers shown (Table 4).

**Table 4 Biomarkers previously defined to be responsive to chronic doses of glucocorticoids in DMD boys**

Chronic safety	Assay method	Chronic efficacy	Assay method
MMP-3	SomaScan	CD23	SomaScan
Leptin	SomaScan	MDC	SomaScan
Insulin	SomaScan	IL-22BP	SomaScan
IGFBP-5	SomaScan	Lymphotoxin a1/b2	SomaScan
Angiotensinogen	SomaScan	IGFBP-2	SomaScan
Afamin	SomaScan	Integrin a1b1; CD49a	SomaScan
17-hydroxyprogesterone	LC-MS	MMP-12	SomaScan
Corticosterone	LC-MS		
Testosterone	LC-MS		
11-deoxycortisol	LC-MS		

Adrenal axis suppression is a well-documented safety signal with chronic use of glucocorticoids. As noted above, nonclinical data suggest that vamorolone may not cause adrenal axis suppression. To test whether vamorolone treatment causes chronic adrenal axis suppression, four steroid hormones will be tested by LC-MS in the vamorolone-treated DMD boys (17-hydroxyprogesterone, corticosterone, testosterone, 11-deoxycortisol) (Table 4). All four steroid hormones showed significant reductions



after glucocorticoid treatment in DMD boys in the cross-sectional and longitudinal CINRG DNHS participants.

The current study is designed to provide long-term safety, efficacy, and PD data for the vamorolone dose(s) that are recognized as safe and well-tolerated in Phase IIa study VBP15-002 testing and which are anticipated to be tested in a future Phase IIb study. Enrollment in the Phase IIa extension study will be offered to subjects who complete the Phase IIa study, in order to extend the treatment duration and increase the potential for direct benefit of study treatment to these pediatric DMD patients. Each subject will receive vamorolone treatment in this Phase IIa extension study at the same dose level he received in the Phase IIa study. It is anticipated that subjects will enroll in this study on one of four dose levels (0.25, 0.75, 2.0, or 6.0 mg/kg/day) and continue on that dose level for the duration of the 24-week study. Evaluation of up to four dose levels in this long-term study will allow comparison of the dose levels for change from Baseline in safety parameters, muscle strength and function efficacy parameters, and PD biomarker levels over 24 weeks of treatment; in particular, for the PD biomarkers, evaluation of change from Baseline over a longer (24-week) period may aid in the clinical validation of biomarkers which exhibit small changes over time. Comparisons of efficacy and safety parameters with historical natural history (untreated)<sup>31,32,33,34</sup> and prednisone-treated control groups<sup>35</sup> will be performed as primary outcomes of this study.

This trial will be conducted in compliance with this protocol, Good Clinical Practice (GCP), applicable Food and Drug Administration (FDA) requirements, and the recently issued FDA guidance on developing drugs for treatment for Duchenne muscular dystrophy and related dystrophinopathies.<sup>36</sup>

It is obligatory that the Investigator become familiar with all sections of the Vamorolone Investigator's Brochure.<sup>29</sup>

## **1.5 Overall Benefit/Risk**

The current study is a long-term safety and efficacy study in young boys with DMD. 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. The adverse effects of

vamorolone over a 24-week treatment period are not currently known. In the Phase I SAD/MAD study in healthy adults, no serious adverse events were observed in any cohort. Cohorts tested in the Phase I MAD study were 1.0, 3.0, 9.0 and 20.0 mg/kg/day for 14 days. In the Phase I MAD clinical trial in adult volunteers, vamorolone showed suppression of the adrenal axis at higher doses (9.0 mg/kg/day and 20.0 mg/kg/day in the fasted state).<sup>29</sup> 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).

Subjects may or may not receive direct health benefit from participating in the study. Subjects will receive vamorolone at one of four planned dose levels (0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, or 6.0 mg/kg/day) over the course of the 24-week trial. While it is anticipated from nonclinical studies that these dose levels may be efficacious in the treatment of DMD, there are no clinical efficacy data yet available to validate this hypothesis. In view of the initial clinical evidence of safety and the monitorable nature of key nonclinical toxicological findings, data support an acceptable risk profile for vamorolone.

## **2 STUDY OBJECTIVES AND ENDPOINTS**

### **2.1 Study Objectives**

#### **2.1.1 Primary Objectives**

The primary objectives of this study are:

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

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

### **2.1.2 Secondary Objectives**

The secondary objectives of this study are:

1. To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. prednisone-treated historical controls, on serum pharmacodynamic (PD) biomarkers of safety (insulin resistance, adrenal axis suppression, and bone turnover);
2. To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period vs. untreated historical controls, on serum PD biomarkers of efficacy (inflammatory protein suppression); and
3. To investigate the effects of vamorolone, administered orally at daily doses up to 6.0 mg/kg over a 24-week Treatment Period, on muscle strength, mobility and functional exercise capacity vs. historical controls as measured by Quantitative Muscle Testing (QMT), Time to Run/Walk Test (TTRW), North Star Ambulatory Assessment (NSAA), Time to Climb Test (TTCLIMB), and 6-minute Walk Test (6MWT) in boys ages 4-7 years with DMD.

### **2.1.3 Exploratory Objective**

The exploratory objective of this study is:

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

### **2.1.4 Ancillary Study**

An optional ancillary study titled “Use of Microsoft Bands as an Outcome Measure in Boys with DMD - Parallel study to Clinical Study Protocol VBP15-003” will be undertaken in parallel to this VBP15-003 study, and enrolling participants from

VBP15-003. The objectives of the ancillary study are to demonstrate that community-based activity monitoring through the use of a Microsoft Band (MS Band) is feasible and reliable; to determine the relationship of data collected through the MS Band and clinical assessment measures of function; and to determine the ability of the MS Band to measure daily activity patterns and explore changes in patterns that occur over time. Data collected as part of VBP15-003 will be shared with this study for data analysis purposes if the subject's parent/legal guardian consents for his participation in both studies.

## **2.2 Study Endpoints**

### ***2.2.1 Safety Endpoints***

#### ***2.2.1.1 Primary Safety Endpoint***

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

#### ***2.2.1.2 Additional Safety Endpoints***

1. BMI z-score: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points.
2. Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC): Overall by treatment, by treatment and relationship, and by treatment and intensity (see [Section 7.2.6](#));
3. Vital signs [blood pressure, heart rate, respiratory rate, body temperature]: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
4. Body weight: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
5. Clinical laboratory values (hematology and biochemistry): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;

6. Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL]): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
7. Urinalysis by dipstick and microscopic analysis: Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
8. 12-lead electrocardiogram (ECG): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;

Data for the following additional safety outcomes will be listed only:

1. Physical examination findings at Pretreatment and Week 24.

### ***2.2.2 Clinical Efficacy Endpoints***

#### ***2.2.2.1 Primary Clinical Efficacy Endpoint***

1. Time to Stand Test (TTSTAND) velocity (rise/second): Comparison with a historical natural history (untreated) control group for change from Baseline to Week 24.

#### ***2.2.2.2 Secondary Efficacy Endpoints***

1. Time to Stand Test (TTSTAND) velocity (rise/second): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
2. Time to Climb (4 Steps) Test (TTCLIMB): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
3. North Star Ambulatory Assessment (NSAA): Change in timed assessments and total score from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
4. Quantitative Muscle Testing (QMT): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points;
5. Total distance traveled, in meters, in completing the Six-minute Walk Test (6MWT): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points; and

6. Time to Run/Walk Test (TTRW): Change from Baseline to each of the scheduled on-treatment and post-treatment assessment time points.

### **2.2.3 Pharmacodynamic Endpoints**

1. Concentrations of serum PD biomarkers: osteocalcin, ACTH, insulin, glucose, 17-hydroxyprogesterone, carboxy-terminal telopeptide (CTX), serum aminoterminal propeptide of type I collagen (PINP), cortisol, testosterone, corticosterone, 11-deoxycortisol, and hemoglobin A1c (HbA1c).

### **2.2.4 Exploratory Endpoints**

1. Levels of an extended panel of PD biomarkers using SomaScan aptamer arrays and proteomic profiling.

### **2.2.5 Endpoints for Subject Reported Outcomes**

Safety endpoints based on subject reports of AEs are listed in [Section 2.2.1.2](#). Subjects will be asked to assess acceptability of vamorolone by a 5-point hedonic scale (see [Section 7.2.7](#)). Additionally, subjects' parents/legal guardians will be asked to complete the Pediatric Outcomes Data Collection Instrument (see [Section 7.3.8](#)). No other subject-reported outcomes are planned.

## **3 STUDY DESIGN**

### **3.1 Overall Study Design**

This Phase IIa extension study is an open-label, multiple-dose study to evaluate the long-term safety, tolerability, efficacy and PD of vamorolone administered once daily by liquid oral suspension over a Treatment Period of 24 weeks to boys ages 4-7 years with DMD.

Only subjects who have completed Phase IIa core study VBP15-002 Week 4 Follow-up Visit assessments will be eligible for participation in this open-label extension study. Participation in this extension study will be discussed with the subject's parent or guardian prior to the VBP15-002 Week 4 Visit. Standard of care treatment (glucocorticoids) for DMD may be offered to the subject following completion of the Phase IIa VBP15-002 study, if the subject's parent or guardian does not wish to enroll the

subject in the extension study and/or the Investigator feels it to be in the best interest of the subject. A total of up to approximately 48 subjects will be enrolled into this extension study.

The parents or legal guardians of subjects who choose to enroll in this extension study will give written informed consent for the extension study at the VBP15-003 Baseline Day -1 Visit. The Baseline Day -1 Visit, including signing of the ICF, may occur at the conclusion of the VBP15-002 Week 4 Visit following completion of all Week 4 assessments; alternatively, the Baseline Day -1 Visit and VBP15-003-specific ICF signing may occur up to 8 weeks after the final VBP15-002 Week 4 Visit, at the convenience of the subject's parent or legal guardian and discretion of the Investigator. Subjects are considered to be enrolled in the VBP15-003 extension study after the parent or guardian has signed the VBP15-003-specific ICF at the Baseline Day -1 Visit. Each subject will retain the study identification number assigned to him at the start of the Phase IIa core study.

For subjects who enroll in the VBP15-003 extension study within 28 days after completion of all final VBP15-002 Week 4 assessments, many of the safety, efficacy, and PD assessments performed for the VBP15-002 study at the final Week 4 Visit will be used to determine extension study eligibility or to provide baseline study data for the extension study and do not need to be repeated at the VBP15-003 Baseline Day -1 Visit (see [Table 6](#)). For these subjects, additional extension study procedures will still be performed at the Baseline Day -1 Visit, within 24 hours prior to administration of the first dose of study drug in the extension study. Subjects who enroll in the VBP15-003 extension study > 28 days after the date of the final VBP15-002 Week 4 Visit must have all Baseline Day -1 assessments performed, according to the schedule in [Table 6](#).

Subjects will begin dosing in this study on Study Day 1 at the same vamorolone dose level they received in the Phase IIa core study. Subjects will continue to receive vamorolone at the dose received in the Phase IIa core study for the duration of the 24-week Treatment Period, unless new safety data indicate the dose level should be de-escalated.

The planned dose levels are 0.25 mg/kg (Dose Level Group 1), 0.75 mg/kg (Dose Level Group 2), 2.0 mg/kg (Dose Level Group 3), and 6.0 mg/kg (Dose Level Group 4) (see [Table 5](#)). Approximately 12 subjects may be eligible for extension study dosing at each of the dose levels tolerated in the Phase IIa study.

**Table 5**      **Planned Dose Level Composition**

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

If dose limiting toxicities are identified in the Phase IIa core study which preclude confirmation of safety of all four planned dose levels, the dose levels in this extension study will be modified, as needed.

In the event any clinical observation suggests an intolerability for an individual subject to the study medication, in the opinion of the Investigator, the subject's dose level may be decreased to the next lower dose level (e.g., a subject taking 6.0 mg/kg/day decreased to 2.0 mg/kg/day) and maintained at that lower dose level throughout the duration of the Treatment Period. In the event the next lower dose level is also not tolerated and is considered a safety risk to the subject, in the opinion of the Investigator, Study Chair, and Medical Monitor, the subject should be withdrawn from the study. Details of dose interruption, de-escalation, and discontinuation are presented in [Section 5.6](#).

Subjects will be assessed for safety and tolerability, clinical efficacy, and PD at scheduled visits throughout the 24-week Treatment Period (see [Section 6](#) for a schedule of study assessments). Treatment Period study visits will occur at Week 2, Week 4, and every 4 weeks thereafter through Week 24 ([Table 6](#)). Adverse events, including SAEs, and concomitant medications will be recorded throughout the study.

Once daily Treatment Period study drug dosing will occur from Day 1 until the Week 24 Visit ([Section 5.3](#)). Study drug dosing will occur at home on all days except the days of the Week 12 and Week 24 Visits, when dosing will occur at the study site.



Subject diaries will be dispensed at Baseline Day -1 and at each monthly study visit to record AEs and concomitant medications taken during the study.

All subjects will return to the clinical site for Week 24 assessments. Following completion of the 24-week Treatment Period, subjects may be offered further extended treatment with vamorolone in a separate extension study, or switch to standard of care treatment (e.g., glucocorticoids) for DMD, as deemed appropriate for each subject. Alternatively, subjects may choose to discontinue vamorolone and not begin glucocorticoid treatment for DMD. Subjects who switch to standard of care glucocorticoids for DMD or who discontinue treatment will participate in a Dose-tapering Period of 2-5 weeks in duration, following the end of the Treatment Period and prior to discharge from the study (see [Section 6.3.4](#)); subjects who elect to receive further vamorolone treatment will be discharged from the VBP-003 study after completion of final VBP-003 study assessments at the Week 24 Visit, prior to enrollment in a subsequent extension study. Subjects will be discharged from the study following completion of all final Week 24 or Dose-tapering Period assessments, as appropriate.

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 final Week 24 safety and efficacy assessments at the time of early discontinuation.

In view of the time schedule for international, national and local approvals, this Phase IIa extension study protocol and related documentation will be submitted for regulatory approval concurrent with Phase IIa core study VBP15-002.

### **3.2 Study Summary**

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

The study is comprised of a Pretreatment Baseline Period of up to 24 hours in duration, which begins at the signing of the extension study-specific informed consent, a 24-week Treatment Period, and a 2- to 5-week Dose-tapering Period for subjects who elect to transition off vamorolone treatment at the end of the study.

## **4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS**

### **4.1 Subject Screening, Enrollment, and Identification Log**

All subjects who complete the Week 4 Follow-up assessments in the VBP15-002 core study will be eligible for enrollment in this VBP15-003 extension study, provided they meet all VBP15-003 study entry criteria. Limited data will be collected for subjects who do not qualify for enrollment into the extension study, or who are not interested in participating in the study, including date of birth and reason for exclusion from the study. Subjects are considered to be enrolled in the VBP15-003 extension study after the parent or guardian has signed the VBP15-003-specific ICF at the Baseline Day -1 Visit. The Baseline Day -1 Visit, including signing of the ICF, may occur at the conclusion of the VBP15-002 Week 4 Visit following completion of all Week 4 assessments; alternatively, the Baseline Day -1 Visit and VBP15-003-specific ICF signing may occur up to 8 weeks after the final VBP15-002 Week 4 Visit, at the convenience of the subject's parent or legal guardian and discretion of the Investigator.

Subject enrollment and identification logs will be maintained for all subjects enrolled in the study. These logs will be reviewed during routine monitoring calls and/or visits.

### **4.2 Inclusion Criteria**

To qualify for enrollment in this extension study, the subject must satisfy the following inclusion criteria:

1. Subject's parent or legal guardian has provided written informed consent/HIPAA authorization prior to any extension study-specific procedures;
2. Subject has previously completed study VBP15-002 up to and including the Week 4 Follow-up assessments within 8 weeks prior to enrollment; and

3. Subject and parent/guardian are willing and able to comply with scheduled visits, study drug administration plan, and study procedures.

#### **4.3 Exclusion Criteria**

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

1. Subject had a serious or severe adverse event in study VBP15-002 that, in the opinion of the Investigator, was probably or definitely related to vamorolone use and precludes safe use of vamorolone for the subject in this study;
2. Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression;
3. Subject has current or history of chronic systemic fungal or viral infections;
4. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication;
5. Subject has evidence of symptomatic cardiomyopathy. [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary];
6. Subject is currently being treated or has received previous treatment with oral glucocorticoids or other immunosuppressive agents. [Notes: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 3 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 DMD are permitted but must be administered at stable dose for at least 3 months prior to study drug administration];
7. Subject has used idebenone within 4 weeks prior to the first dose of study medication;

8. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;
9. Subject has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the Investigator;
10. 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; or
11. Subject is currently taking any investigational drug, or has taken any investigational drug other than vamorolone within 3 months prior to the start of study treatment.

**Note:** Subjects may be re-evaluated if ineligible due to a transient condition which would prevent the subject from participating.

#### **4.4 Withdrawal of Subjects from Study**

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 Investigator has the right to terminate participation of a subject in the study for any of the following reasons:

- The subject's parent/legal guardian is uncooperative/noncompliant and does not adhere to study responsibilities, including failure to appear at 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;
- The Sponsor 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, the Sponsor or designee (e.g., Coordinating Center) 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.

All subjects who withdraw from the study prior to the Week 24 Visit should return to the study site for Week 24 assessments at the time of early withdrawal, assuming the subject has not withdrawn consent. 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 the Sponsor.

#### **4.5 Replacement of Withdrawn Subjects**

Only subjects who have completed the Phase IIa study are eligible to enroll in this extension study. Subjects prematurely discontinued from the VBP15-003 extension study will not be replaced.

#### **4.6 Termination of Study**

This study may be prematurely terminated if, in the opinion of the Sponsor, 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, the Sponsor 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 the Sponsor and provided the reason(s) for the termination or suspension.

Subject enrollment at a given site may be terminated by the Sponsor. 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.

## **5 TREATMENT OF STUDY SUBJECTS**

### **5.1 Study Medication Administered**

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

Planned vamorolone dose levels: 0.25 mg/kg, 0.75 mg/kg/day, 2.0 mg/kg, and 6.0 mg/kg.

Vamorolone 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 2- to 5-week Dose-tapering Period, prior to discharge from the study (see [Section 6.3.4](#)).

### **5.2 Identity of Investigational Product**

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

Name:	Vamorolone
Active Substance:	VBP15
Strength:	4% by weight
Dosage Form:	Oral suspension
Manufacturer:	Velesco Pharma

### **5.3 Dosage Schedule and Administration of Study Medication**

Subjects who have completed the Phase IIa VBP15-002 core study and who meet all other eligibility criteria (see [Section 4.2](#) and [Section 4.3](#)) will be enrolled into this extension study on Baseline Day -1, following signing of the extension-study-specific ICF. Subjects will retain the enrollment numbers assigned to them for the Phase IIa VBP15-002 core study.

Subjects will receive vamorolone 0.25 mg/kg, 0.75 mg/kg/day, 2.0 mg/kg, or 6.0 mg/kg, administered orally once daily from Study Day 1 to Week 24. A subset of subjects may also receive vamorolone for an additional 1-4 weeks according to a dose-tapering protocol following the end of the Treatment Period (see [Section 6.3.4](#)).

The site pharmacist or designated site study staff will dispense study medication in 100 mL bottles to each subject enrolled in the study (see [Section 5.8.1](#) and [Appendix 14.1](#)). All subjects will receive vamorolone 4% oral suspension. Bottles will be fitted with adaptors by the site pharmacist or designated site study staff prior to dispensing.

Study medication sufficient for 12 weeks of dosing (plus overage) will be dispensed by trained study staff on Study Day -1 and at the Week 12 Visit. Subjects who participate in the Dose-tapering Period will be dispensed study medication at the Week 24 Visit sufficient for the 4-week Dose-tapering Period. Each subject's dose (in mg) will be calculated based on the weight of the subject (in kg) recorded at the dispensing visit (see [Appendix 14.1](#) for a dose calculation worksheet).

Enrolled subjects will receive all doses of vamorolone under the supervision of parent or legal guardian or trained study staff. The doses administered on the dates of the Week 12 and Week 24 Visits will be administered at the study site; all other doses, including the first dose administered on Study Day 1, will be administered at home. Study drug will be administered by mouth using a volumetric syringe supplied by the site. Following administration of the dose of study drug, 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 of water to ensure the full dose has been ingested. Subjects should receive each dose of study medication at approximately the same time of day.

The daily dose of study medication should be taken with 8 ounces of whole milk (or equivalent high fat food portion). At the Week 12 and Week 24 Visits, the subject will be asked to consume an 8-ounce glass of whole milk (or equivalent high fat food portion) and 1 cup of cereal at the study site within approximately 30 minutes prior to administration of the dose of study medication. There are no other food or drink restrictions before or after dosing during the study.

The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled monthly visit. Study medication returned at the Weeks 4, 8, 16, and 20 Visits will be redispensed to subjects at the end of each visit, after interim

compliance monitoring, for continued dosing through the remainder of the 12-week dispensing interval. Drug product returned at the Weeks 12 and 24 Visits, and end of the Dose-Tapering Period, if applicable, will be retained at the clinical study site for investigational drug accountability monitoring.

#### **5.4 Rationale for Dose Selection**

Dose levels were chosen for this study to ensure the safety of subjects enrolled in the study, to allow demonstration of efficacy and PD effects, and to ensure adequate safety in future clinical studies and in the patient population after FDA regulatory approval. All dosing will be done in the morning with a glass of whole milk (8 ounces or 230 mL) or similar fat equivalent meal (approximately 8 grams fat).

Each subject will enroll in this extension study to receive the same dose that he received during the VBP15-002 core study. The planned dose levels in this study are 0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg. If dose-limiting toxicities are observed in the Phase 2a core study at doses being used in this study, dose level(s) will be de-escalated, as appropriate.

The rationale for the lowest dose of 0.25 mg/kg/day, administered with a glass of whole milk is as follows: As Phase II dosing in 4-7 year old DMD children will be done at home in the morning, challenges were considered with subject and parent compliance with either fasting in the morning (prior to school or other activities), or a rigid prescribed diet of known fat content. To balance compliance with appropriate assessments of bioavailability and monitoring of safety, it was decided to administer morning doses at home with a glass of whole milk (~8 grams of fat) or similar fat content meal.

From the Phase I study in adult volunteers, a high fat diet (40 grams) increased bioavailability of vamorolone (8.0 mg/kg/day) by 250% compared to the fasted cohort at this dose. As a formal food effect study has not been done, we must assume that any fat intake with drug delivery has the potential to have a 250% increase in bioavailability vs. the fasted state. Thus, a conservative approximation of vamorolone drug exposure in DMD children when taken with a glass of whole milk is 250% of the fasted bioavailability. A starting dose of 0.25 mg/kg/day with a glass of milk would be



equivalent to 0.625 mg/kg/day fasted, and this starting dose is 3.1% of the highest safe dose tested in adults (20.0 mg/kg/day fasted).

The highest dose to be administered, 6.0 mg/kg/day, will similarly be administered with a glass of milk, with an expected increased bioavailability of 250%, or equivalent to 15.0 mg/kg/day fasted. As 20.0 mg/kg/day fasted in adult volunteers was shown to be safe in the Phase I adult volunteer study, the proposed highest dose in 4-7 year old children is approximately 75% of the safe highest adult dose. Based on the Phase I PD biomarker safety data presented in [Section 1.3](#), safety signals reflective of insulin resistance are not anticipated at any of the planned Phase 2a extension dose levels. Also based on the Phase I data, regarding the safety signal of suppression of the adrenal axis, no evidence of adrenal suppression is anticipated at the planned 0.25 mg/kg/day, 0.75 mg/kg/day and 2.0 mg/kg/day dose levels in the Phase IIa extension study; suppression of the adrenal axis may be observed at 6.0 mg/kg/day.

## **5.5 Treatment Compliance**

Subject compliance with the dosing schedule will be assessed by site maintenance of accurate study drug dispensing and return records. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. The Investigator or designee will instruct the subject's parent or guardian with regard to proper dosing of study medication, and will reinforce the importance of taking all study medication per protocol instructions. The volume of unused study medication remaining in each bottle returned will be documented in the source documents and on the appropriate electronic case report form (eCRF).

## **5.6 Study Drug Dose Interruption, De-escalation, or Discontinuation**

Administration of study drug to individual subjects should be interrupted, and the case discussed with the Study Chair and Medical Monitor within 24 hours, in the event any clinical observation suggests an intolerability of an individual subject to the study medication, in the opinion of the Investigator. In such an event, the subject's dose level may be decreased to the next lower dose level (e.g., a subject taking 6.0 mg/kg/day decreased to 2.0 mg/kg/day) and maintained at that lower dose level throughout the

duration of the study. In the event the next lower dose level is also not tolerated and is considered a safety risk to the subject, in the opinion of the Investigator, Study Chair and Medical Monitor, the subject should be withdrawn from the study.

In the event that dose-limiting toxicities are observed in the VBP15-002 Phase IIa study that require de-escalation of dose in the extension study, subjects will be de-escalated as dictated by safety results in the VBP15-002 study.

## **5.7 Prior and Concomitant Medications and Therapies**

### **5.7.1 Prior Therapy**

Any changes in non-study medication/therapy, including administration of new medication(s), change of dose, or discontinuation of medication, that occur after completion of the VBP15-002 core study Week 4 assessments and prior to administration of the first dose of study medication in the extension study will be captured as prior medications (Medication History) in the extension study eCRF.

### **5.7.2 Concomitant Therapy**

Any medications that are started after administration of the first dose of study medication in the extension study will be recorded as concomitant medications on the appropriate eCRF. Subject diaries will be provided to subjects to record any concomitant medication changes during the study (see [Section 8.4](#)).

All medications (prescription and over-the-counter [OTC]) taken during the study must be recorded in the source documents and in the eCRF, including the name of the medication (or device or procedure), 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 and/or his parent or guardian, if applicable, 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), mexrenone (mexrenoate potassium); use must be discontinued at least 4 weeks prior to the first dose of study medication;
- Oral glucocorticoids or other oral immunosuppressive agents. Subjects who have received more than 3 months cumulative treatment with oral immunosuppressive agents or last treatment within 3 months prior to first dose of study medication are ineligible for study entry. [Note: Inhaled and/or topical corticosteroids prescribed for an indication other than DMD are permitted but must be administered at stable dose for at least 3 months prior to study drug administration];
- Idebenone (use must be discontinued at least 4 weeks prior to first dose of study medication);
- Live attenuated vaccines (use must be avoided for the duration of participation in the study);
- Any investigational medications other than vamorolone (use must be discontinued at least 3 months prior to the first dose of study medication).

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

### **5.7.4 Permitted Therapies**

Every effort should be made NOT to take 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.

## **5.8 Study Medication Management**

### ***5.8.1 Packaging and Labeling of Study Medication***

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. ReveraGen BioPharma, Inc. or designee will provide CTM in bulk quantities sufficient to satisfy the protocol requirement. Clinical trial material 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 100 mL glass bottles; each bottle will contain 4 grams of vamorolone as a 4% suspension in sterile water. Bulk drug supplies will be labeled with the name of Sponsor, protocol number, lot number, expiration or retest date, and other appropriate study information. Bottle labels will include the following statement: "Caution: New Drug – Limited by Federal Law to Investigational Use" or comparable statement, as required by ex-US regulatory authorities.

100 mL bottles of 4% vamorolone oral suspension will be dispensed to the subject's parent or legal guardian at the Baseline Day -1 Visit and at 12-week intervals (see [Appendix 14.1](#) for instructions on calculating the number of vamorolone bottles to be dispensed at each visit); dispensed bottle(s) of study medication will be returned at each subsequent monthly visit for interim compliance monitoring (Weeks 4, 8, 16, and 20) or prior to dispensing bottle(s) for the next dosing interval (Weeks 12 and 24). Bottles will be fitted with adaptors by the site pharmacist or designated site study staff prior to dispensing. Each vamorolone study medication bottle may be used for a single subject only. The volume per dose to be administered to each subject depends on the subject weight calculated at the dispensing visit; see [Appendix 14.1](#) for complete instructions on calculating dose volume. Clinical supplies dispensed by the study site staff and ready for administration to subjects will be labeled with the dispense date, protocol number, vamorolone dose level, and volume to be administered per dose.

### ***5.8.2 Storage of Study Medication***

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. Bulk study medication should be stored at refrigerated temperature (2°C – 8°C; 36°F – 46°F). Excursions to ambient temperature are allowed. Access to study medication stored at the study site must be limited to authorized clinic personnel.

### ***5.8.3 Study Medication Shipping and Handling***

Clinical trial material will be shipped to the study sites only after receipt of required documents in accordance with applicable regulatory requirements and Sponsor procedures.

Clinical trial material will only be dispensed once a subject has (1) a signed ICF/HIPAA authorization on file, and has been enrolled in the extension study; (2) met all eligibility criteria for entry into the extension study, (3) completed all Pretreatment requirements.

It is essential to this study that all CTM be accounted for during the study period. All unused study medication will be retained at the study site for reconciliation and collection by the Sponsor's study monitors (or designees) during routine monitoring visits. Study site personnel should not dispose of any CTM. Final disposition of all unused CTM will be coordinated by the Sponsor's study monitors (or designees) 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), in accordance with all applicable regulatory requirements and the Site Signature Log/Delegation of Authority. Only authorized study personnel or the subject's parent or legal guardian 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 identification of the subject to whom the study drug was dispensed
- The date(s) and quantity of the study drug dispensed to the subject
- The date(s) and quantity of the study drug returned by the subject.

All records and drug supplies must be available for inspection by the Study Monitor at every monitoring visit. Unused medication will be returned to ReveraGen or its designee at the end of the study. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to ReveraGen 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 or its designee.

#### **5.9 Procedures for Assigning Subject Study Numbers**

This is an open-label study. Subjects enrolled in this extension study will retain the enrollment numbers assigned to them at the start of the VBP15-002 core study. All data for all subjects whose parent or guardian signs the ICF for the extension study will be identified using the unique subject identification number. Subjects are considered to be enrolled in this extension study when the parent or guardian signs the extension study-specific ICF at the Baseline Day -1 Visit. 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. This record will also 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:

- **Pretreatment Baseline Period:** The 24-hour period immediately prior to administration of the first dose of study medication (Study Day -1), which includes signing of the extension study-specific ICF and enrollment into the extension study. The Baseline Day -1 Visit may coincide with the final Week 4 Follow-up Visit in the VBP15-002 core study. Alternatively, subjects may return to the study site up to 8 weeks after completion of the VBP15-002 Week 4 assessments for Baseline Day -1 ICF signing and completion of Baseline assessments.
- **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 the Week 24 Visit and administration of the final dose of Treatment Period study medication. Subjects electing to continue vamorolone therapy under a subsequent extension protocol will be discharged from the VBP15-003 study following completion of all Week 24 safety, efficacy, and PD assessments.
- **Dose-tapering Period:** The 2- to 5-week interval following the end of the 24-week Treatment Period during which subjects who elect to either switch to standard of care glucocorticoids for DMD, or discontinue vamorolone and not begin standard of care glucocorticoid treatment, at the end of the study will have their vamorolone dose tapered to 0 mg/kg/day. The length of time required for this tapering will depend upon the dose received during the Treatment Period (see [Section 6.3.4](#)). Subjects whose dose is tapered during the Dose-tapering Period will be discharged from the study following completion of all final Dose-tapering Period assessments.

The procedures to be completed during each study period are presented in the Schedule of Study Assessments in **Table 6** and in the sections that follow. Detailed descriptions of the assessments and the definitions of study endpoints are provided in **Section 7** and **Section 2.2**. Any deviation from study procedures should be noted in the source documents and in the eCRF, and significant deviations should be reported immediately to the Sponsor.

Overall, approximately 24-29 weeks are allocated for each subject to complete the study, including a 1-day Pretreatment Baseline Period and a 24-week Treatment Period for all subjects. For subjects who elect to either switch to standard of care glucocorticoids for DMD, or discontinue vamorolone and not begin glucocorticoid treatment at the end of the study, an additional 2-5 weeks are allocated for vamorolone dose tapering.



**Table 6 Schedule of Study Activities**

	Pretreatment Period	Treatment Period									Dose-tapering Period
	Baseline	Day		Week							
Study Day or Week/Visit	-1 <sup>a</sup>	1 <sup>b</sup>	2 (±1d)	4 (±2d)	8 (±5d)	12 (±1w)	16 (±1w)	20 (±1w)	24 <sup>c</sup> (±1w)	26-29 <sup>d</sup> (±1w)	
Inclusion/Exclusion Criteria	X										
Informed Consent	X <sup>e</sup>										
Enrollment	X										
Interim Medical History	X <sup>f</sup>										
Medication History	X <sup>g</sup>										
Physical Examination	X <sup>h</sup>								X		
Height	X					X			X		
Weight	X			X	X	X	X	X	X		
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	
Blood for Clinical Labs <sup>j</sup>	X <sup>h</sup>		X	X	X	X	X	X	X	X	
Urinalysis <sup>k</sup>	X <sup>h</sup>			X	X		X		X		
Blood for Serum PD Biomarker Panel <sup>l</sup>	X <sup>h</sup>				X		X		X	X	
Fasting blood for insulin, glucose <sup>m</sup>						X			X		
12-lead ECG <sup>n</sup>	X <sup>h</sup>					X			X		
Dispense Study Medication	X					X			X <sup>o</sup>		
Return Study Medication/ Compliance Monitoring				X	X	X	X	X	X	X	
Study Medication Dosing <sup>p</sup>		X	—————→							X	
Vamorolone dose tapering <sup>q</sup>										X	
Time to Stand Test (TTSTAND)	X <sup>h</sup>					X			X		
Time to Climb Test (TTCLIMB)	X <sup>h</sup>					X			X		
Time to Run/Walk Test (TTRW)	X <sup>h</sup>					X			X		
NSAA <sup>r</sup>	X <sup>h</sup>					X			X		
Quantitative Muscle Testing (QMT)	X <sup>h</sup>					X			X		
Six-minute Walk Test (6MWT)	X <sup>h</sup>					X			X		
Pediatric Outcomes Data Collection Instrument	X					X			X		
Study Medication Acceptability Assessment <sup>s</sup>						X			X		
Dispense Subject Diaries <sup>t</sup>	X			X	X	X	X	X	X <sup>p</sup>		
Return Subject Diaries			X	X	X	X	X	X	X	X	
AE/SAE Recording <sup>u</sup>	X	—————→									
Concomitant Medications		X	—————→							X	X
Discharge from Study									X <sup>v</sup>	X <sup>w</sup>	

d = day(s); w = week.

- a. Baseline Day -1, within 24 hours prior to administration of the first dose of study drug. The Baseline Visit for Study VBP15-003 can coincide with the final Week 4 Follow-up Visit for Study VBP15-002 or occur up to 8 weeks after the date of the VBP15-002 Week 4 Visit.
- b. Treatment Day 1 begins at the time of administration of the first dose of VBP15-003 study medication at home. No scheduled study visit will occur on Day 1.
- c. Subjects who prematurely discontinue from the study prior to Week 24 should complete the Week 24 assessments at the time of early discontinuation.
- d. All subjects EXCEPT those who elect to continue vamorolone therapy in a further extension study must continue in the Dose-tapering Period and have their vamorolone dose tapered at weekly intervals over a 1-4 week period prior to discharge from this study. Subjects participating in the Dose-tapering Period will have one study site visit during this period, at the end of dose tapering (Weeks 25-29) (see [Section 6.3.4](#)).
- e. Informed Consent for this extension study may be obtained at the Study VBP15-002 Week 4 Follow-up Visit, after completion of all final VBP15-002 study assessments and prior to any extension study-specific procedures.
- f. Interim Medical History will be collected on Baseline Day -1 for all subjects, and will include any AEs that occurred during the VBP15-002 core study and are ongoing at the time of entry into VBP15-003 (see [Section 7.2.1](#)).
- g. Any changes in medication/therapy including administration of new medication(s), change of dose, or discontinuation of medication after completion of the VBP15-002 core study and prior to administration of the first dose of study medication in VBP15-003 will be captured as Prior Medications.
- h. If the Baseline Day -1 Visit occurs  $\leq$  28 days after the date of the final VBP15-002 core study Week 4 Visit, these assessments do not need to be repeated for the VBP15-003 study. Clinical laboratory and urinalysis test results from the VBP15-002 Week 2 or Week 4 Visit (whichever is available and later) may be used and should be reviewed by the Site Investigator to determine eligibility for Baseline Day -1 enrollment into the extension study.
- i. Supine blood pressure, oral temperature, respiratory rate, and heart rate.
- j. Blood for hematology, chemistry, and lipids.
- k. Urinalysis by dipstick and microscopic analysis.
- l. Blood collected for cortisol, P1NP, osteocalcin, 17-hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, CTX, ACTH, HbA1c (not collected at Baseline), SomaScan, and proteomic testing.
- m. Blood will be collected for insulin and glucose determination in the morning after subjects have fasted for  $\geq$  6 hours, prior to the daily dose of study medication.
- n. ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.
- o. Only for subjects who will participate in the Dose-tapering Period.
- p. The dose of study medication on the days of the Week 12 and Week 24 Visits will be administered after 1) a fasting blood draw for insulin and glucose; and 2) breakfast provided by the study site. All other doses will be taken at home.
- q. Subjects who elect to switch to standard of care glucocorticoids, or discontinue vamorolone and not begin glucocorticoid treatment for DMD at the end of the study will have their vamorolone dose tapered at weekly intervals to a dose of 0 mg/kg/day prior to final study assessments (see [Section 6.3.4](#)).
- r. North Star Ambulatory Assessment; includes the Time to Stand Test (TTSTAND).
- s. Study medication acceptability assessed immediately before (smell) and after (taste) dosing at the Week 12 and Week 24 Visits.
- t. Subject diaries used to record any concomitant medications taken and any AEs experienced during the study.
- u. All AEs and SAEs must be collected in the source documents and eCRF from the date of the subject's written informed consent until the Week 24 Visit or the subject's participation in the study is completed. Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator agrees follow-up is not necessary.
- v. Subjects who elect to continue vamorolone therapy in a subsequent extension study may be discharged from the study following completion of all final Week 24 procedures.
- w. Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments (see [Section 6.3.4](#)).

## **6.2 Informed Consent/HIPAA Authorization**

The parents or guardians of subjects who choose to enroll in this extension study will give written informed consent for this study at the Baseline Day -1 Visit. If the Baseline Day -1 Visit coincides with the VBP15-002 Week 4 Visit, the parents or guardians of subjects will give written informed consent for this study at the Phase IIa VBP15-002 Week 4 Visit, following completion of all VBP15-002 Week 4 assessments. The Investigator (or designated staff) will obtain the written informed consent and HIPAA authorization, if applicable, from the subject's parent or guardian prior to any extension study-specific procedures. Each subject's parent or guardian will receive an explanation of the nature and purposes of the study from the Investigator or designee. 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's parent or guardian will be asked if s/he understands that the study is for research purposes only and that it may not provide any therapeutic benefit to the subject. Each subject's parent or guardian will be asked if s/he understands that the subject is free to withdraw from the study at any time without prejudice. The Investigator or designee will review the elements of the HIPAA and Protected Health Information (PHI) with each subject's parent or guardian and each subject's parent or guardian will be asked if s/he understands HIPAA authorization and PHI. Each subject's parent or guardian will be required to sign a study ICF (and HIPAA authorization, if applicable) before any procedures are performed for the extension study. The written assent of children will be obtained per individual site guidelines.

The Investigator or designee will obtain written informed consent from each subject's parent or guardian prior to subject's participation in the extension study on Informed Consent Forms 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's legal representative 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 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's legal representative. The study subject's legal representative will receive a copy of the signed consent form.

### **6.3 Visit Schedule and Procedures**

During the study, there will be a total of up to 9 study site visits: Pretreatment Baseline Visit (Day -1); Treatment Period Weeks 2, 4, 8, 12, 16, 20, and 24; and a final Dose-tapering Period Visit for subjects whose vamorolone dose is tapered at the end of the Treatment Period. Each subject will receive the investigational product at stable dose for a period of 24 weeks. Subjects who participate in the Dose-tapering Period will receive additional vamorolone at decreasing dose over a 1- to 4-week interval, and will return to the study site for final study assessments at the end of the 2- to 5-week Dose-tapering Period. The Baseline Day -1 Visit may take place on the same day as the final Phase IIa VBP15-002 Week 4 Visit. In this case, Baseline Day -1 procedures should be performed after completion of all final VBP15-002 Week 4 assessments. See [Section 7](#) for a detailed description of the safety, clinical efficacy, and PD assessments to be performed in this study.

#### **6.3.1 Baseline Period (Day -1)**

For all subjects, the Baseline Day -1 Visit will occur after completion of all VBP15-002 Week 4 procedures and within 24 hours prior to administration of the first dose of study medication in the VBP15-003 extension study.

Parents or guardians of subjects who have completed all VBP15-002 study assessments will sign the ICF for the VBP15-003 extension study at the Baseline Day -1 Visit. If the VBP15-002 Week 4 Visit will serve as the Baseline Visit for VBP15-003, the VBP15-003-specific ICF must be signed after completion of all final VBP15-002 Week 4 assessments and prior to the performance of any extension study-specific procedures ([Section 6.2](#)).

Subjects whose VBP15-003 Baseline Day -1 Visit occurs  $\leq 28$  days after the final VBP15-002 Week 4 Visit do not need to repeat, at the Baseline Day -1 Visit, the physical

examination, clinical laboratory tests, PD biomarker blood draw, 12-lead ECG, and clinical efficacy assessments performed at the VBP15-002 Week 4 Visit.

VBP15-002 Week 2 or Week 4 (whichever is available and later) clinical laboratory blood (hematology, chemistry, and lipids) and urinalysis test results should be received by the site and reviewed by the Investigator to determine eligibility for Baseline Day -1 enrollment into the extension study.

Subjects will retain the subject identification number assigned for the Phase IIa VBP15-002 core study.

Any new medications taken from the time of completion of the VBP15-002 study to administration of the first dose of study medication in the VBP15-003 study, or any changes to medications taken during the core study, will be recorded as Prior Medications on the appropriate eCRF. See [Section 7](#) for detailed descriptions and instructions for completion of each safety, efficacy, and PD assessment.

The following procedures will be performed at the Baseline Day -1 Visit (see [Table 6](#)):

- Review of Inclusion and Exclusion Criteria (see [Section 4.2](#) and [Section 4.3](#))
- Written informed consent for extension study (see [Section 6.2](#))
- Enrollment (see [Section 5.9](#))
- Recording of Interim Medical History (see [Section 7.2.1](#))
- Recording of Medication History (see [Section 5.7.1](#))
- Recording of AEs and SAEs beginning at the time written informed consent is obtained (see [Section 7.2.6](#))
- Complete physical examination (**not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date**) (see [Section 7.2.2](#)).
- Measurement of height and weight (see [Section 7.2.2](#))
- Recording of vital signs (supine blood pressure, heart rate, oral temperature, respiratory rate) (see [Section 7.2.3](#))

- Clinical laboratory evaluation including hematology, clinical chemistry, lipids, and urinalysis tests **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.2.4](#))
- Blood samples for PD biomarkers including ACTH, osteocalcin, 17-hydroxyprogesterone, CTX, P1NP, cortisol, testosterone, corticosterone, and 11-deoxycortisol. Blood will also be collected and stored for future proteomics profiling and SomaScan studies. **(Not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date.)** (see [Section 7.3.7](#))
- 12-lead ECG **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.2.5](#))
- Quantitative Muscle Testing (QMT) **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.3.1](#))
- Time to Run/Walk Test (TTRW) **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.3.4](#))
- Time to Stand Test (TTSTAND) **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.3.2](#))
- Time to Climb Test (TTCLIMB) **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.3.3](#))
- North Star Ambulatory Assessment (NSAA) **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.3.5](#))
- Six-minute Walk Test (6MWT) **(not to be repeated if Baseline Day -1 is  $\leq$  28 days after the VBP15-002 Week 4 Visit assessment date)** (see [Section 7.3.6](#))

- Pediatric Outcomes Data Collection Instrument completed by parent/legal guardian (see [Section 7.3.8](#)).
- Dispensing of study medication and subject diaries (see [Section 5.3](#) and [Section 8.4](#))

### ***6.3.2 Treatment Period Day 1***

Treatment Period Day 1 begins with administration of the first dose of study medication. There is no scheduled clinic visit on Day 1.

Subjects will take the first dose of study medication at home on the morning of the day after the Day -1 Visit, on Study Day 1, under the supervision of a parent or guardian ([Section 5.3](#)).

### ***6.3.3 Treatment Period Weeks 2-24***

Subjects will return to the study site for safety, efficacy, and PD assessments beginning at Week 2 and continuing through Week 24, according to the schedule of visits in [Table 6](#).

Subjects will continue to receive daily oral administration of vamorolone throughout the 24-week Treatment Period, taken following ingestion of 8 ounces of whole milk. If whole milk is not tolerable to the subject, a serving of another high fat food may be substituted.

Dosing is to occur at home throughout the 24-week Treatment Period, except at the Week 12 and Week 24 Visits when dosing will occur at the study site. Subjects must have fasted  $\geq 6$  hours prior to arrival at the study site for Week 12 and Week 24 procedures and assessments. The pre-dose blood draws for PD (insulin and glucose only) determination must be collected after subjects have fasted for  $\geq 6$  hours. Breakfast (an 8-ounce glass of whole milk [or equivalent high fat food portion] and 1 cup of cereal) will be served at the study site after the blood draw for insulin and glucose, and within approximately 30 minutes prior to administration of the dose of study medication. Study medication acceptability will be assessed by a 5-point hedonic scale immediately before (smell) and after (taste) administration of the daily dose of study medication at the

Week 12 and Week 24 Visits. All other Week 12 and Week 24 assessments should be performed after administration of the final dose of study medication.

Clinical efficacy assessments (QMT, TTSTAND, TTRW, TTCLIMB, NSAA, and 6MWT) and the Pediatric Outcomes Data Collection Instrument will be conducted at 12-week intervals (Weeks 12 and 24). Weight will be recorded every 4 weeks and height will be measured at 12-week intervals. Vital signs will be recorded at each study visit. A physical examination will be performed at Week 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 including Somascan and proteomics profiling will be collected at scheduled visits throughout the study (see [Table 6](#)). Adverse events, including SAEs, and concomitant medications will be assessed at each study visit and recorded throughout the study.

Study medication will be dispensed at 12-week intervals and returned for dosing compliance monitoring at 1-month intervals for all subjects. Study medication returned at the Week 4, 8, 16, and 20 Visits will be redispensed to the subject at the end of each visit, after interim compliance monitoring, for continued dosing through the end of the 12-week dispensing interval. Subjects will receive subject diaries at each 1-month interval visit and return the diaries at each subsequent visit. Diaries will be reviewed with the subject's parent or guardian by the study staff to assess AEs and changes to concomitant medications/therapies.

Limited safety assessments and review of the subject diary are conducted at the Week 2 Visit.

Subjects who will not participate in the Dose-tapering Period (see [Section 6.3.4](#)) will be discharged from the study following completion of all Week 24 assessments. Subjects who do participate in the Dose-tapering Period will be dispensed vamorolone (and standard of care glucocorticoid at the discretion of the Investigator for subjects who elect to transition to standard of care glucocorticoid treatment) at the Week 24 Visit, as well as instructions for tapering the dose of vamorolone during the Dose-tapering Period.



**6.3.4 Dose Tapering Period (Weeks 25-29)**

Subjects who elect to transition to standard of care glucocorticoid treatment for DMD, or discontinue vamorolone and not begin standard of care glucocorticoid treatment for DMD at the end of the study will have their vamorolone dose tapered prior to discharge from the study. Subjects who discontinue study medication prior to completion of Week 24 assessments will also participate in the Dose-tapering Period if possible and if, in the opinion of the Investigator, it is safe to do so. Dose tapering will be performed in a stepwise manner, according to the subject’s vamorolone dose during the 24-week Treatment Period, as outlined in [Table 7](#). Subjects who elect to transition to a standard of care glucocorticoid will have their vamorolone dose tapered as in [Table 7](#), and will begin treatment with a standard of care glucocorticoid on the day dose tapering begins. These subjects will continue to receive standard of care glucocorticoid treatment, with drug and dose at the discretion of the Investigator, throughout the duration of the Dose-tapering Period and after discharge from the study.

The subject’s weight recorded at the Week 24 Visit will be used to calculate dose volume for all dose de-escalations during the Dose-tapering Period (see [Appendix 14.1](#))

**Table 7 Vamorolone Dose Tapering**

Treatment Period Vamorolone Dose Level	Week 25 Dose Level	Week 26 Dose Level	Week 27 Dose Level	Week 28 Dose Level	Week 29 Dose Level
0.25 mg/kg/day	0.125 mg/kg/day	0 mg/kg/day			
0.75 mg/kg/day	0.375 mg/kg/day	0.125 mg/kg/day	0 mg/kg/day		
2.0 mg/kg/day	1 mg/kg/day	0.5 mg/kg/day	0.25 mg/kg/day	0 mg/kg/day	
6.0 mg/kg/day	3 mg/kg/day	1.5 mg/kg/day	0.75 mg/kg/day	0.25 mg/kg/day	0 mg/kg/day

All subjects participating in the Dose-tapering Period will return to the study site for final study assessments approximately one week after the final dose de-escalation (i.e., approximately one week after the subject has received his last dose of vamorolone). The duration of the Dose-tapering Period will therefore vary depending upon the vamorolone dose received by the subject during the Treatment Period, from a total duration of two weeks (for subjects receiving 0.25 mg/kg/day vamorolone; final study visit at Week 26)

to five weeks (for subjects receiving vamorolone 6.0 mg/kg/day; final study visit at Week 29).

At the final study visit, subjects participating in the Dose-tapering Period will have vital signs recorded, and blood collected for clinical laboratory tests and PD biomarker panel. 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 completion of all final Dose-tapering Period assessments.

#### **6.4 Subject Discontinuation**

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. For subjects who withdraw early, final Week 24 assessments should be performed at the time of early discontinuation (see [Section 6.3.3](#)). Site personnel will document all assessments, including any AEs, in the source documents and eCRF. Subjects who discontinue study medication should follow vamorolone dose tapering procedures described in [Section 6.3.4](#) and detailed in the Manual of Operations.

#### **6.5 Study Completion**

A completed subject is defined as a subject who has completed the 24-week Treatment Period and Dose-tapering Period, if applicable, and has not prematurely withdrawn from the study for any reason.

### **7 STUDY ASSESSMENTS AND MEASUREMENTS**

#### **7.1 Demographic Assessments**

Demographic information (birth date, race, and ethnicity) collected during the VBP15-002 study will be used for this study; collection of data will not be repeated during this study.

## **7.2 Safety and Tolerability Assessments**

### **7.2.1 Interim Medical History**

At the Baseline Day -1 Visit, interim medical history will be recorded for each subject, including medical history migrated from the VBP15-002 core study and any medical history that occurred in the period between completion of VBP15-002 and enrollment into the VBP15-003 extension study. Migrated medical history will include any condition that was recorded as medical history for the VBP15-002 core study. Medical history occurring between completion of VBP15-002 and VBP15-003 enrollment will include surgical history and concurrent diseases, including any changes from the core study. All AEs that are recorded during the VBP15-002 core study and are ongoing at the time of enrollment into the VBP15-003 study will be recorded as medical history in the VBP15-003 study.

Interim medical history will be recorded in the source documents and in the eCRF.

### **7.2.2 Physical Examination, Weight, and Height**

A complete physical examination will be performed at the Baseline Day -1 and Week 24 Visits, 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. If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 physical examination does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).

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

Height (in cm) will be recorded at Baseline Day -1, and Weeks 12 and 24. Weight (in kg) will be recorded at Baseline Day -1, Week 4, and each scheduled monthly visit thereafter through Week 24. Weight recorded at each monthly visit will be used to calculate the vamorolone dose volume for each subsequent month's dosing (see [Appendix 14.1](#)).

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

### **7.2.3 Vital Signs**

Vital signs (supine blood pressure, heart rate, respiration rate, and oral temperature) will be recorded at Baseline Day -1, Week 2, Week 4, and each scheduled monthly visit thereafter through Week 24, and at the final Week 26-29 study visit for subjects whose dose is tapered during the Dose-tapering Period. Vital signs should be recorded after the subject has been resting for at least 5 minutes.

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

If vital signs assessment is performed at the same study visit as blood sampling and ECG recording, the following sequence should be followed: 1) ECG recording; 2) vital signs assessment; and 3) blood sampling.

### **7.2.4 Clinical Laboratory Tests**

Each subject will have blood drawn and urine collected for the hematology, chemistry, lipids, and urinalysis clinical laboratory tests listed in [Table 8](#) and [Table 9](#), below, at the Baseline Day -1, and Week 4, 8, 16, and 24 Visits. Subjects whose dose is tapered will also have clinical laboratory tests performed at the final Week 26-29 Visit at the end of the Dose-tapering Period. If the Baseline Day -1 Visit occurs  $\leq$  28 days after the date of the final VBP15-002 core study Week 4 Visit, clinical laboratory tests do not need to be repeated on Baseline Day -1 for the VBP15-003 study (results from the VBP15-002 core study will be used as baseline measurements for the VBP15-003 study).

For all subjects, the clinical laboratory test results obtained at the VBP15-002 Week 2 Visit will be used to assess extension study eligibility, unless VBP15-002 Week 4 Visit clinical laboratory test results are available: if the VBP15-002 Week 4 Visit clinical laboratory test results are available prior to VBP15-003 enrollment, VBP15-002 Week 4 results will be used to assess extension study eligibility. Review of VBP15-002 Week 2 results (or VBP15-002 Week 4 results if available) is required prior to enrollment of the subject into this extension study.

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

For the hematology, chemistry, and lipids laboratory tests, blood will be collected by direct venipuncture of peripheral veins. Approximately 4.5 mL (7 mL at non-US sites) of blood will be obtained for clinical laboratory tests at each scheduled visit. A total of approximately 18-27 mL (28-42 mL at non-US sites) of blood will be collected over the course of this study for clinical laboratory evaluation (see [Section 7.4](#) for details of blood volumes to be collected).

If blood sampling is performed at the same study visit as vital signs assessment and ECG recording, the following sequence should be followed: 1) ECG recording; 2) vital signs assessment; and 3) blood sampling.

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, and Lipids Clinical Laboratory Tests**

<b>Hematology</b>	
Red Blood Cells (RBC)	Numerical platelet count (estimate not acceptable)
Hemoglobin	White Blood Cells (WBC) with differential (percent)
Hematocrit	
<b>Chemistry</b>	
Sodium	Total Bilirubin <sup>a</sup>
Potassium	Uric Acid
Chloride	Glucose
Calcium	Alkaline phosphatase (ALP)
Inorganic Phosphorus	Gamma Glutamyl Transferase (GGT)
Blood Urea Nitrogen (BUN)	Aspartate aminotransferase (AST)
Creatinine	Alanine aminotransferase (ALT)
Total Protein	Creatine kinase (CK)
Albumin	Lipase
Bicarbonate	Amylase
Lactate Dehydrogenase (LDH)	
<b>Lipids</b>	
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](#). Urine will be analyzed by dipstick and microscopic analysis by the central laboratory at all assessment time points.

**Table 9 Urinalysis Clinical Laboratory Tests**

<b>Urinalysis (including microscopic examination)</b>	
<b>Dipstick<sup>a</sup></b>	<b>Microscopic Analysis</b>
Protein	WBC/hpf
Glucose	RBC/hpf
Ketones	Casts
pH	Bacteria
Leukocyte esterase	
Blood	

<sup>a</sup>A midstream clean-catch urine specimen will be collected for dipstick analysis.

Clinical laboratory tests will be performed by a central laboratory; results will be reported to the study site and transferred electronically into the clinical study database.

The procedures for the collection, handling, and shipping of laboratory samples will be specified in the Laboratory Manual(s) provided to the clinical center.

#### **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 to determine if the abnormality represents an AE, and followed-up until the results have returned to the normal range, stabilized, and/or an adequate explanation for the abnormality is found. If a clear explanation is established, it should be recorded in the source documents and eCRF. 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 indicated (see [Section 7.2.6](#)).

#### **7.2.5 12-Lead ECG**

12-lead ECGs will be collected at the Baseline Day -1, Week 12, and Week 24 Visits. If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 12-lead ECG does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used). 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 sampling, vital signs assessment, and ECG recordings are scheduled at the same study visits, the following sequence should be followed: 1) ECG recording; 2) vital signs assessment; and 3) blood sampling.

ECG results will be read locally. Results must be interpreted and recorded on the appropriate eCRF.

#### **7.2.6 Adverse Events and Serious Adverse Events**

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 which 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 product. Pre-existing conditions that worsen during a study are to be reported as AEs.

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. Subjects who enroll in the VBP15-003 extension study will have any AEs which initiated during VBP15-002 participation and which are ongoing at the time of enrollment into VBP15-003 recorded in the VBP15-003 eCRF and followed during VBP15-003 participation. In addition, subjects (and their parent or legal guardian) 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 participant's physical appearance will be recorded in the source documents and in the subject's eCRF. The date and time 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. 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). All AEs will be graded by CTCAE, Version 4.03. Details of any medications given to the subject to abate the AE should be recorded in the appropriate eCRF.

### **Intensity**

All clinical 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 Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, 5-point scale, and reported in detail as indicated on 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; incapacitating with inability to work or perform normal daily activity.

Life-Threatening (Grade 4): Urgent intervention indicated.

Death (Grade 5): Death related to AE.

### **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.

### **Clinical Laboratory Test Abnormalities**

Clinical laboratory test results will be recorded in the designated eCRF. 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, 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.

### **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 Sponsor agree that follow-up is no

longer needed. If a clear explanation of cause is established, it should be recorded in the source documents 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 follow-up of AEs will be documented in the source documents and will be described in the final report only if considered relevant by the Investigator, the Study Chair, the Medical Monitor and/or the Sponsor.

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 the Study Sponsor.

### **Dosing Error**

For the purposes of this study, a dosing error is defined as a dose exceeding or less than the scheduled dose of 0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, or 6.0 mg/kg specified for each dose level group. Such occurrences should 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 should not be recorded as an AE unless there are associated signs or symptoms.
- A dosing error with associated non-serious AEs should be recorded as AEs on the relevant AE forms in the eCRF.
- A dosing error with an associated SAE should be recorded as an SAE.
- Details of all dosing errors, including actual dose administered, should be documented in the source documents and recorded on the Protocol Deviations eCRF.

### **7.2.6.1    *Serious Adverse Events***

For treatment-eligible subjects, SAEs 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.

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. Serious adverse events that begin after the subject's participation in the study is complete but that the Investigator considers to be related to study drug will be reported to the Sponsor within 24 hours of discovery by the Investigator.

During the SAE collection period, the Investigator or clinical site personnel should notify the PRA safety management team of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event; notification to the PRA safety management team will trigger alerts to the Coordinating Center, Study Chair, the Sponsor, and the Medical Monitor. The Investigator will provide the initial notification by completing the SAE eCRF in the electronic data capture (EDC), which must include the Investigator's assessment of the relationship of the event to investigational drug. In the unlikely event that the electronic study database is inaccessible and the Investigator is unable to complete the SAE eCRF within 24 hours, the SAE Notification Form (pdf) should be completed and emailed or printed/faxed to the PRA safety management team.

In addition, notification is sent by the Investigator to the IRB and the subject's Primary Care Physician.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the PRA safety management team within 24 hours of knowledge of the new or follow-up information, which will forward the information to the Coordinating Center, Study Chair, the Sponsor, and the Medical Monitor.

All SAE reports should be completed within the EDC.

The Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study.

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, 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 term “sudden death” should only be used when the cause is of a cardiac origin as per standard definition.

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

Any AE or clinically significant abnormal laboratory test value, 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 PRA safety management team, who will notify the Coordinating Center, 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 PRA safety management team, who will notify the Coordinating Center, Study Chair, the Sponsor, and the Medical Monitor within 24 hours of the Investigator becoming aware of the new information.

Related SAEs MUST be collected and reported regardless of the time elapsed from the last administration of study drug, even if the study has been closed. Unrelated 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.

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 eCRF 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 eCRF 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:**

**Email CHOSafety@prahs.com  
Drug Safety Fax: 1-888-772-6919 or 1-434-951-3482**

**SAE Questions: Drug Safety Hotline: 1-800-772-2215 or 1-434-951-3489**

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 the Study Sponsor 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.

#### ***7.2.7 Study Medication Acceptability Assessment***

Acceptability of the study medication will be assessed using a 5-point hedonic scale immediately before (smell) and after (taste) dosing at the Week 12 and Week 24 Visits. The assessments will be administered by trained study staff. Results will be recorded in the source documents and eCRF.

### **7.3 Clinical Efficacy and Pharmacodynamic Assessments**

#### **7.3.1 Quantitative Muscle Testing (QMT)**

Quantitative Muscle Testing (QMT) will be administered to subjects at the Baseline Day -1, Week 12, and Week 24 Visits using the CINRG Quantitative Measurement System (CQMS).<sup>37</sup> If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 QMT does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).

The QMT measures unilateral strength of four muscle groups: elbow flexion/extension, and knee flexion/extension.<sup>37</sup> Complete instructions for administering the QMT are given in the study manual to be supplied to the sites prior to study start.

Results will be collected using the CQMS3 software and transferred into the eCRF.

#### **7.3.2 Time to Stand Test (TTSTAND)**

The Time to Stand Test (TTSTAND) will be administered to subjects at the Baseline Day -1, Week 12, and Week 24 Visits. If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 TTSTAND does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).

The TTSTAND measures the speed (m/s; velocity) with which the child can stand to an erect position from supine (floor), and is administered as part of the NSAA (see [Section 7.3.5](#)). Complete instructions for administering and scoring the TTSTAND are given in the study manual to be supplied to the sites prior to study start.

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

#### **7.3.3 Time to Climb Test (TTCLIMB)**

The Time to Climb Test (TTCLIMB) will be administered to subjects at the Baseline Day -1, Week 12, and Week 24 Visits. If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 TTCLIMB does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).



The TTCLIMB measures the time (in seconds) required for the subject to climb 4 standard stairs, beginning and ending in a standing position with arms at the sides.<sup>38</sup> Complete instructions for administering the TTCLIMB are given in the study manual to be supplied to the sites prior to study start.

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

#### **7.3.4 Time to Run/Walk Test (TTRW)**

The TTRW will be administered to subjects at the Baseline Day -1, Week 12, and Week 24 Visits. If the Baseline Day -1 Visit occurs  $\leq$  28 days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 TTRW does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).

The Time to Run/Walk Test (TTRW) measures the time (in seconds) that it takes a subject to run or walk 10 meters and is administered as part of the NSAA (see [Section 7.3.5](#)). Complete instructions for administering and scoring the TTRW are given in the study manual to be supplied to sites prior to study start.

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

#### **7.3.5 North Star Ambulatory Assessment (NSAA)**

The North Star Ambulatory Assessment (NSAA) is a clinical assessment scale specifically designed to measure functional ability in ambulant boys with DMD.<sup>39</sup> The NSAA consists of 17 scored items and 2 timed tests, including the TTRW and the TTSTAND (see [Section 7.3.2](#)). The NSAA will be conducted at the Baseline Day -1, Week 12, and Week 24 Visits. If the Baseline Day -1 Visit occurs  $\leq$  28 days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 NSAA does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).

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

The NSAA should be administered BEFORE the 6MWT at study visits where both tests are administered.

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

### **7.3.6 Six-minute Walk Test (6MWT)**

Functional exercise capacity and mobility will be assessed in all subjects by means of the Six-minute Walk Test (6MWT) at the Baseline Day -1, Week 12, and Week 24 Visits. If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 6MWT does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used).

This evaluation is a modified version of the 6MWT, adapted for use in DMD patients.<sup>40</sup>

The total distance traveled, in meters, should be recorded along with the validity of the test as assessed by the test administrator in the source documents and in the eCRF. If a subject cannot complete 6 minutes of walking, the total meters and the time until discontinuation of the test should be recorded. Complete instructions for administering the 6MWT are given in the study manual to be supplied to the sites prior to study start.

The 6MWT should be administered AFTER the NSAA at study visits where both tests are administered.

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

### **7.3.7 Pharmacodynamic Biomarker Panel**

Blood samples will be collected to explore the effect of vamorolone on biomarkers of muscle cellular pathology, biomarkers associated with chronic glucocorticoid treatment, and biomarkers associated with insulin resistance, adrenal suppression, and bone turnover, as listed in **Table 10**. Blood samples will be collected at the Baseline Day -1 and Weeks 8, 16, and 24 Visits, and at the final Dose-tapering Period Visit for subjects whose vamorolone dose is tapered at the end of the study. If the Baseline Day -1 Visit occurs  $\leq 28$  days after the date of the final VBP15-002 core study Week 4 Visit, the Baseline Day -1 blood draw for the PD biomarker panel does not need to be repeated (results from the VBP15-002 Week 4 Visit will be used). The biomarker analysis includes ACTH, osteocalcin, 17-hydroxyprogesterone, CTX, P1NP, cortisol, HbA1c (except Baseline), testosterone, corticosterone, and 11-deoxycortisol. Blood will also be

collected at each of these time points and stored for future proteomics profiling and SomaScan studies.

Blood samples will be collected at the Weeks 12 and 24 Visits for measurement of glucose and insulin, after the subject has fasted for  $\geq 6$  hours and prior to administration of the daily dose of study medication.

A total of 61-93 mL (58-89 mL at non-US sites) of blood will be collected for PD biomarkers, including blood collected for fasting glucose and insulin, over the course of the 24-week to 29-week study (see [Section 7.4](#)).

**Table 10 Pharmacodynamic Biomarkers**

<b>Adrenal Suppression</b>
Cortisol
17- hydroxyprogesterone
ACTH
Testosterone
Corticosterone
11- Deoxycortisol
<b>Insulin Resistance</b>
Glucose
Insulin
HbA1c
<b>Bone Turnover</b>
Osteocalcin
P1NP
CTX
<b>Exploratory Biomarkers</b>
SomaScan and Proteomics Profiling

**7.3.8 Pediatric Outcomes Data Collection Instrument**

Quality of life will be assessed by completion of the Pediatric Outcomes Data Collection Instrument. The subject parent/legal guardians will be asked to complete this instrument at the Baseline Day -1, Week 12, and Week 24 Visits.

Results will be recorded in the eCRF.

## 7.4 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 24-week to 29-week study are summarized in **Table 11**. A total of 79-120 mL (86-131 mL at non-US sites) of blood will be collected from each subject over the course of the up to 29-week study.

**Table 11 Blood Sample Number and Volume**

Test	Total mL of Blood							
	Day -1 <sup>a</sup>	Week 4	Week 8	Week 12	Week 16	Week 24	Week 26-29 (End of Dose-taper) <sup>b</sup>	Total Volume
Clinical Safety Labs <sup>c</sup>	4.5 (7.0) <sup>d</sup>	4.5 (7.0) <sup>d</sup>	4.5 (7.0) <sup>d</sup>		4.5 (7.0) <sup>d</sup>	4.5 (7.0) <sup>d</sup>	4.5 (7.0) <sup>d</sup>	18-27 (28-42) <sup>d</sup>
PD Biomarker Panel	15 <sup>e</sup>		17 <sup>f</sup> (16) <sup>f,d</sup>		17 <sup>f</sup> (16) <sup>f,d</sup>	17 <sup>f</sup> (16) <sup>f,d</sup>	17 <sup>f</sup> (16) <sup>f,d</sup>	51-83 (48-79) <sup>d</sup>
PD Insulin/Glucose				5 <sup>g</sup>		5 <sup>g</sup>		10
Total Volume by Visit (mL)	19.5 (22) <sup>d</sup>	4.5 (7.0) <sup>d</sup>	21.5 (23) <sup>d</sup>	5	21.5 (23) <sup>d</sup>	26.5 (28) <sup>d</sup>	21.5 (23) <sup>d</sup>	79-120 (86-131) <sup>d</sup>
<b>Total Volume: 79-120 mL (86-131 mL)<sup>d</sup></b>								

<sup>a</sup> Day -1 blood draws for clinical labs and PD biomarkers will not be repeated for subjects whose Day -1 Visit coincides with the final VBP15-002 Week 4 Visit and who had blood drawn for clinical labs and PD biomarkers for the VBP15-002 Week 4 Visit.

<sup>b</sup> Only subjects who participate in the Dose-tapering Period will have bloods drawn.

<sup>c</sup> Hematology, Chemistry, Lipids.

<sup>d</sup> Blood volume to be collected at non-US sites.

<sup>e</sup> cortisol, P1NP, osteocalcin, 17- hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, CTX, ACTH, SomaScan, and proteomics testing.

<sup>f</sup> cortisol, P1NP, osteocalcin, 17- hydroxyprogesterone, testosterone, corticosterone, 11-deoxycortisol, CTX, ACTH, HbA1c, SomaScan, and proteomics testing.

<sup>g</sup> Subjects must have fasted  $\geq 6$  hours prior to blood draws. Blood will be drawn prior to administration of the dose of study medication.

## 8 DATA COLLECTION

### 8.1 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 on the appropriate source documents.

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 date of enrollment, and the reason the subject was not entered (if applicable). All subjects initially considered for enrollment are to be recorded in this log.

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.

## **8.2 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 Code of Federal Regulations (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 user name and password should never be shared and their electronic signature constitutes the legally binding equivalent of a hand-written signature. Only trained personnel certified by the Coordinating Center will receive a user name 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, quantitative muscle testing).

The Coordinating Center 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 access to all source documents in order to verify eCRF entries.

### **8.3 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 9.7** and the Statistical Analysis Plan (SAP).

### **8.4 Subject Diaries**

The parent or legal guardian of each subject will be given a subject diary at the Baseline Day -1 Visit in which to record any new concomitant medications and any changes to existing concomitant medications taken during the study, as well as any AEs experienced by the subject during the study. Parents/legal guardians 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 monthly visit for use through the time of the next scheduled monthly visit. Collection of final diaries will occur at the Week 24 Visit, or at the end of the Dose-tapering Period for subjects whose vamorolone dose is tapered at the end of the study. The information recorded in the diary will be considered source documentation, and any information recorded in the diary should be transcribed by study staff to the appropriate eCRF.

## **9 STATISTICAL METHODS AND PLANNED ANALYSES**

### **9.1 Sample Size Determination**

Eligible subjects are those who enrolled in the VBP15-002 study and have completed up to and including the Follow-up Week 4 study assessments, up to approximately 48 subjects (n=12 per vamorolone dose group).

This is an open-label extension study with no placebo control. Historical control data are available for the same age range (4-7 years), at largely the same study sites, with the same outcome measures. Untreated natural history control population data is from the ongoing CINRG DNHS study of ~400 DMD boys.<sup>31,32,33,34</sup> Prednisone-treated historical control data is from a clinical trial of prednisone carried out by the CINRG group.<sup>35</sup> The vamorolone Phase IIa extension trial is carried out with daily dosing. To more accurately determine sample size numbers to detect a glucocorticoid effect on efficacy, sample size calculations were limited to the daily prednisone treatment arm of the CINRG glucocorticoid clinical trial (n=11-13), at 6 or 12 months, for three gross motor milestone outcomes (TTSTAND, TTRW, TTCLIMB) (**Table 12**). Sample size was also calculated assuming the observed effect of vamorolone was 100%, 80% or 60% of that observed with daily glucocorticoids (**Table 12**).

The primary pharmacological safety outcome proposed in the Phase IIa extension trial is change in BMI z-score. Daily glucocorticoids show a relatively rapid increase in BMI z-score (6 month change in non-treated = -0.14; 6 month change in prednisone-treated = +0.54) (**Table 12**). Vamorolone is not anticipated to show an increase in BMI.

**Table 12 6-month and 12-month Changes in Outcomes in 4-<8 year-old DMD Boys**

Outcome	Time (months)	Untreated – Natural history study		Treated – Prednisone trial		N needed per group to detect a significant difference – Using observed changes	N needed per group to detect a significant difference – Using conservative change estimates <sup>^</sup>	N needed per group to detect a significant difference – Using conservative change estimates <sup>^^</sup>
		N	Mean ± SD	N	Mean ± SD			
BMI (Z-score)	6	40	-0.14 ± 0.78	13	0.54 ± 0.66	12	15	
	12	26	-0.25 ± 0.83	13	0.63 ± 0.45	7	6	
Time to run/walk 10 m velocity (m/s)	6	39	0.02 ± 0.31	13	0.35 ± 0.32	12	19	28
	12	26	0.01 ± 0.25	12	0.42 ± 0.23	5	7	11
Time to climb 4 stairs velocity (climb/s)	6	40	0.01 ± 0.07	13	0.11 ± 0.08	7	11	17
	12	26	0.01 ± 0.06	12	0.16 ± 0.10	5	7	10
Time to stand from supine velocity (rise/s)	6	38	0.004 ± 0.07	12	0.10 ± 0.10	10	16	23
	12	26	-0.01 ± 0.06	11	0.11 ± 0.09	5	8	9

Notes: a) All patients are 4-<8 years of age at study start.  
 b) Data from untreated subjects in the CINRG DMD Natural history study;<sup>31,32,33,34</sup> data from treated subjects in the CINRG Prednisone trial.<sup>35</sup>  
 c) Compares all only daily dose prednisone-treated patients to untreated patients.  
 d) All calculations assume a repeated measures ANOVA model with one pre- and one post-measurement. Correlation between repeated measures used as follows: 0.75 for height changes, 0.70 for 6 month BMI changes, and 0.65 for 12 month BMI changes, and 0.575 for 6 and 12 month velocity changes. Power = 0.80 and alpha = 0.025 for all calculations to account for multiple group comparisons (i.e. two vamorolone doses, each compared to prednisone for safety and placebo for efficacy).  
<sup>^</sup> Conservative change estimates were defined as follows: For BMI, the expected change in vamorolone was set to 0.0 rather than the observed decrease. For timed tests, the expected change in vamorolone was set to 80% of the observed change in the prednisone group.  
<sup>^^</sup> Conservative change estimates were defined as follows: For timed tests, the expected change in vamorolone was set to 60% of the observed change in the prednisone group (with SD at 80%).

**9.2 Statistical and Analytical Plan (SAP)**

The sections below summarize the intended statistical methods and analyses for the extension study. A more detailed SAP will be written and finalized prior to finalization of the clinical study database. 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. Any changes to the planned methods and analyses will be described and justified in the SAP and/or in the final clinical study report, as appropriate.

**9.2.1 Deviations from the Statistical Analysis Plan**

An SAP will be written and finalized prior to any lock of the study database. 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. Any deviation(s) from the original SAP will be described and justified in the clinical study report.

### **9.3 Analysis Populations**

All analyses will be based on the actual treatment each subject received. Four populations will be defined for data analysis.

#### ***9.3.1 Safety Population***

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

#### ***9.3.2 Full Analysis Set (FAS)***

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

#### ***9.3.3 Control Population DNHS Study***

The control population from the DNHS study will include all study subjects who were observed as part of the study in ages  $\geq 4$  years and  $<7$  years of age at a start of an interval of observation and observed for at least one year. Further, the subjects need to have had at least two visits in a time interval of no more than 15 months (e.g., Month 24 and Month 36 of observation for a subject who entered at age 2 or 3). The subject should have been able to walk independently without assistive devices at the start of the interval and should have been able to complete the TTSTAND. The subject should not have had any history of disease or impairment or medications that would have made him ineligible to receive the vamorolone intervention as defined by the Phase IIa study exclusion criteria. The subject should have been glucocorticoid-naïve for the entire interval

considered in the control population for this study and should not have begun any investigational treatment for the interval considered for the control comparison. Finally, the control intervals to be considered should have the study outcomes of TTSTAND, TTCLIMB, TTRW, NSAA, 6MWT and QMT measured. It is acceptable if the participant had progressive disease and could not perform a measurement at a later point in the interval; this will be a velocity zero.

#### ***9.3.4 Control Population Prednisone Study***

The control population from the prednisone study will include all subjects who were younger than 7 years old at entry and who were randomized to the daily prednisone arm.

#### **9.4 Measures Taken to Avoid/Minimize Bias**

Not applicable.

#### **9.5 Interim Analysis**

No interim statistical analyses are planned.

#### **9.6 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; while those for efficacy measurements will be imputed using methodology as described in the SAP.

#### **9.7 Statistical Analysis**

##### ***9.7.1 General Considerations***

Statistical analyses will be performed using SAS<sup>®</sup>.

All measurements will be analyzed based upon the type of distribution, and descriptive statistics will be presented by treatment group and 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.

Baseline measurement is defined as the last non-missing value prior to the first dose of study drug in the extension study.

### ***9.7.2 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.

Subject demographics (e.g., age, race, and ethnicity) and baseline characteristics (e.g., height, weight, and months/years since DMD diagnosis) will be summarized descriptively by analysis population. Listings of individual subject data sorted by dose group will be reviewed for any differences among the dose groups.

### ***9.7.3 Safety Analyses***

All subjects who received at least one dose of vamorolone (Safety Population) will be included in the safety analyses. In general, descriptive statistics for each safety endpoint will be presented by dose level, while individual subject listings of safety endpoints, sorted by dose group, will be reviewed for any evidence of dose-related differences or trends in the safety profile of vamorolone.

All safety data will be listed.

Baseline measurement is defined as the non-missing value of the core study VBP15-002 Follow-up Week 4 or last non-missing value prior to first administration of study drug in the extension study.

All evaluations of clinical safety will be listed with descriptive statistics presented by treatment group. The primary safety variable will be BMI z-score and will be assessed using the same type of statistical models used for efficacy. Additional secondary safety data will include height z-score, blood pressure, and ECG results. As no change in blood pressure or cardiac results is expected, these data will be analyzed using an analysis of covariance (ANCOVA) approach which includes the baseline value for each measurement as a covariate. Changes in height z-scores, for which an observed change is expected, will be modelled using a linear mixed effects model. Continuous, quantitative

laboratory values will be analyzed similar to BMI z-scores. Categorized laboratory values and presence or absence of AEs will be compared using an exact chi-square test.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs will be summarized overall and by dose level, SOC and preferred term; dose level, SOC, preferred term, and intensity (CTCAE grade); and dose level, SOC, preferred term, and relationship to study drug. Additional AE analyses will be at the subject level: the number of subjects who had any AE, the distribution of number of AEs per subject within a dose level, worst intensity in a subject within a dose level, highest level of relationship to study treatment for each subject within a dose level.

Additional hypotheses of safety will include similar linear modelling with the secondary and exploratory outcomes.

Physical examination results will be listed only.

#### ***9.7.4 Clinical Efficacy and Pharmacodynamic Analyses***

The evaluations of clinical efficacy and PD will be performed using the FAS Population.

The primary efficacy outcome is the time to stand from supine velocity (TTSTAND).

Secondary efficacy outcomes are the NSAA assessment, time to climb four stairs (TTCLIMB), time to run/walk 10 meters (TTRW), Quantitative Muscle Testing (QMT), and the distance walked in 6 minutes (6MWT). The primary outcome will be compared between vamorolone and historical untreated controls using a mixed-effects linear model with treatment group. Age at study entry will be included as a covariate. The initial model will combine vamorolone doses and a subsequent secondary model will look at each dose in comparison to untreated natural history controls. This will allow the testing of whether vamorolone in general and vamorolone at individual doses have significant effects on the slope of the velocity. Additional hypotheses of efficacy will include similar linear modelling with the secondary outcomes. They will also include differing comparison groups including untreated natural history controls.

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover will be assessed. Longitudinal analysis of PD biomarkers will be studied as a function of

treatment, with comparison to prednisone-treated and untreated historical controls, as appropriate.

Individual clinical efficacy and PD data will be listed.

#### **9.7.5 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 4.3). All concomitant medications will be detailed in the subject data listings.

## **10 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS**

### **10.1 Regulatory Approval and Good Clinical Practice**

This study will be conducted in accordance with the principles of the 18<sup>th</sup> World Medical Assembly (Helsinki, June 1964), and amendments of the 29<sup>th</sup> (Tokyo, 1975), 35<sup>th</sup> (Venice, 1983), 41<sup>st</sup> (Hong Kong, 1989), 48<sup>th</sup> (Somerset West, 1996), 52<sup>nd</sup> (Edinburgh, 2000), 53<sup>rd</sup> (Washington, 2002), 55<sup>th</sup> (Tokyo, 2004), 59<sup>th</sup> (Seoul, 2008), and 64<sup>th</sup> (Fortaleza, 2013) World Medical Assemblies.

Further, the trial will be conducted in accordance with:

- International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP)
- The United States (US) FDA Code of Federal Regulations, Title 21 CFR Part 312 – Investigational New Drug Application, Part 50 – Protection of Human Patients with particular focus in SubPart D, and/or Part 56 – Institutional Review Boards
- US Health Insurance Portability and Accountability Act of 1996 (HIPAA).

## **10.2 Investigator Responsibilities**

### ***10.2.1 Subject Information and Informed Consent***

Before being admitted to the extension study, a parent/guardian must consent in writing for the subject to participate. Written or verbal assent will also be obtained from each subject as required per regulations. An approved ICF will be given to each parent/guardian which will contain all US federally required elements, all ICH-required elements, and HIPAA authorization information, if applicable, in language that is understandable to the parent/guardian. The consent should note that the Investigator is receiving compensation for the expenses of conducting the study.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator or designee will review the study with the parent/guardian of each 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 parent/guardian of the subject. The Investigator or designee and the parent/guardian of the subject must both sign and date the ICF after review and before the subject can participate in the study. The parent/guardian of 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 parent/guardian of 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.

### ***10.2.2 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 scientific committees for approval.

The Investigator will forward to the Sponsor, or designee (Coordinating Center), a copy of the IRB/IEC's approval of this protocol, amendments, ICF and any changes to the ICF, based on the FDA regulations set forth in Part 56 of Title 21 of the CFR. The Investigator will also keep documentation of study approval by internal scientific committees per institutional requirements.

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 Sponsor or designee (Coordinating Center). 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 IRB Assurance Number may be accepted as a substitute for the IRB membership list. 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.

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

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.

### ***10.2.3 Study Documentation***

#### ***10.2.3.1 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<sup>29</sup>
- Protocol Acceptance 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.

#### ***10.2.3.2 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 in [Section 10.2.3.1](#)



- 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.

#### ***10.2.3.3 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
- Substantive correspondence with the Sponsor and IRB/IEC
- Notification of the end of the trial to the IRB/IEC.

#### ***10.2.4 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.

### **10.3 Protocol Deviations and Violations**

#### ***10.3.1 Protocol Deviation and Violation Definitions***

##### ***10.3.1.1 Protocol Deviation***

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and 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.

##### ***10.3.1.2 Protocol Violation***

A protocol violation is a deviation from the IRB/IEC-approved protocol that may 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.

#### ***10.3.2 Reporting Deviations/Violations***

Upon discovery of a major protocol deviation or violation, the Investigator is responsible for reporting protocol deviations or violations to the IRB/IEC and Sponsor or designee (Coordinating Center) within 24 hours of discovery.

All other deviations must be reported in writing within 7 days of the event or its discovery.

### **10.4 Study Records Retention and Direct Access to Source Documents**

Federal regulations require that, following completion of a clinical study, a copy of all records of that study be maintained by the Investigator for at least the shorter of the following two time periods:

- Two years after FDA approval of the drug for the indication for which it was investigated, or

- In situations where no application is to be submitted or an application is not approved for such indication, 2 years after the Investigational New Drug (IND) Application is discontinued and the FDA is notified.

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 the Sponsor, or designee, as well as representatives of the FDA or other 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.

The Sponsor 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 enrollment log
3. Record of all relevant communications between the Investigator and the IRB/IEC
4. Composition of the IRB/IEC
5. Record of all relevant communications between the Investigator and the Sponsor (or designee)
6. 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
7. Drug accountability records (see [Section 5.8.4](#))
8. Record of any body fluids or tissue samples retained
9. All other source documents (subject records, hospital records, laboratory records, etc.)

10. All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

### **10.5 Study Monitoring**

In accordance with applicable regulations, GCP, and the procedures of the Sponsor 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 10.7](#).

#### **10.6 Quality Assurance**

At its discretion, the Sponsor or its designee may conduct a quality assurance audit of this study. Auditing procedures of the Sponsor 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.

#### **10.7 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 the Sponsor
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, the Sponsor 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), the Sponsor 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 the Sponsor. In addition, the site must conduct final disposition of all unused study medications in accordance with the Sponsor procedures for the study.

#### **10.8 Site Termination**

The Sponsor 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 at a reasonable rate
2. Failure of the Investigator to comply with applicable laws and/or pertinent FDA regulations
3. Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, FDA, or other regulatory authorities
4. Insufficient adherence to protocol requirements.

If participation of a study site is terminated, the Sponsor 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 the Sponsor.

Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

## **10.9 Discontinuation of Study**

The Sponsor 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 the Sponsor and Medical Monitor, safety data suggest that the medical safety of subjects is being or may become compromised.

## **11 DISCLOSURE OF DATA**

### **11.1 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 and handling of personal data will be in compliance with HIPAA. 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 birth date 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 obliterated before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects' parents or guardians will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB/IEC to inspect the subjects' medical records to verify the information collected. The subjects' parents or guardians will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA, as applicable.

The parents or guardians of all participants in the United States will provide written 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, and will contain a waiver of subject access to study-related private health information until the conclusion of the clinical study. 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.

Study data will be shared with the study 'Use of Microsoft Bands as an Outcome Measure in Boys with DMD - Parallel study to Clinical Study Protocol VBP15-003' if the subject's parent/legal guardian consents for his participation in both studies.

## **11.2 Publication**

ReveraGen BioPharma, Inc. retains the ownership of all data and results collected during this study. Therefore, the Sponsor 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 the US FDA or the 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 the Sponsor or designee, and are unpublished, are confidential and must remain the sole property of the Sponsor. 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 the Sponsor is obtained. The Sponsor 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 the Sponsor. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor 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 the Sponsor. Additionally, the Sponsor, may, for any reason, withhold approval for publication or presentation.

## **12 INVESTIGATOR'S PROTOCOL AGREEMENT**

The Investigator's Protocol Agreement at the front of this document must be signed by the study site Principal Investigator. The original *or a copy* must be kept on file by the Sponsor and the Investigator must retain the original *or a copy*. The Protocol Agreement signifies review and acceptance of the protocol by the Principal Investigator prior to initiation of the study.

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## 14 APPENDICES

## **Appendix 14.1 Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide**

Vamorolone is administered once daily as a 4% 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:

$$\text{Equation 1} \quad \frac{\text{Subject Weight (kg)} \times \text{Dose Level (mg/kg)}}{40 \text{ mg/mL}} = \text{Subject Dose (in mL)}$$

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), or 0.2 mL (5 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 0.25 mg/kg/day with a body weight of 27 kg:

$$\frac{\text{Subject Weight (27 kg)} \times \text{Dose Level (0.25 mg/kg)}}{40 \text{ mg/mL}} = 0.169 \text{ mL}$$

The subject will receive a dose volume of 0.169 mL per dose throughout the following 12 weeks. Dose will be administered using a 1 mL volumetric syringe rounded to the nearest 0.01 mL, or 0.17 mL daily.

**Example 2:** Dose volume calculation for a subject receiving 6.0 mg/kg/day with a body weight of 23 kg:

$$\frac{\text{Subject Weight (23 kg)} \times \text{Dose Level (6.0 mg/kg)}}{40 \text{ mg/mL}} = 3.45 \text{ mL}$$

The subject will receive a dose volume of 3.45 mL per dose throughout the following 12 weeks. Dose will be administered using a 5 mL volumetric syringe rounded to the nearest 0.2 mL, or 3.4 mL daily.

### **Vamorolone 4% Suspension Dispensing Guide**

Each subject enrolled in the study will be dispensed 100 ml bottle(s) of vamorolone 4% suspension at the Baseline Day -1 Visit, sufficient for dosing through the time of the

Week 12 Visit. Additional supplies will be dispensed at Week 12, sufficient for dosing through Week 24. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4% suspension at the Week 24 Visit, sufficient for dose tapering to 0 mg/kg/day (see [Section 6.3.4](#)).

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 by 100 mL, the number of mL per bottle, as shown in Equation 2, below:

$$\text{Equation 2} \quad \frac{\text{Daily Dose (mL/day)} \times 91 \text{ Days}}{100 \text{ mL}} = \text{\#Bottles to be Dispensed}$$

**Example 3:** Calculation of number of bottles to be dispensed for a subject taking a daily dose of 0.17 mL (from Example 1 above):

$$\frac{\text{Daily Dose (0.17 mL/day)} \times 91 \text{ Days}}{100 \text{ mL}} = 0.15 \text{ Bottles}$$

The number of bottles dispensed is rounded to the nearest whole integer, or 1 bottle to be dispensed.

**Example 4:** Calculation of number of bottles to be dispensed for a subject taking a daily dose of 3.4 mL (from Example 2 above):

$$\frac{\text{Daily Dose (3.4 mL/day)} \times 91 \text{ Days}}{100 \text{ mL}} = 3.09 \text{ Bottles}$$

The number of bottles dispensed is rounded to the nearest whole integer, or 4 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 each monthly visit through Week 24 and at the end of the Dose-tapering Period, if applicable. Drug product returned at the Weeks 4, 8, 16, and 20 Visits will be redispensed to subjects at the end of the visit, after interim compliance monitoring; drug product returned at the Weeks 12 and



24 Visits, and end of the Dose-Tapering Period, if applicable, will be retained at the clinical study site for investigational drug accountability monitoring.