CLINICAL STUDY PROTOCOL

Protocol Title:	**Amendment #3 for a Phase II Open-Label, Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with Duchenne Muscular Dystrophy (DMD)**
Protocol Number:	VBP15-006
Document Number:	VBP15-006-A3 (Version 1.0)
FDA IND No.:	118,942
Investigational Product:	Vamorolone
Sponsor:	Santhera Pharmaceuticals (Switzerland) Ltd Hohenrainstrasse 24 4133 Pratteln Switzerland
Prinicipal Investigator	Jean Mah, M.D Email: PI
Medical Monitor:	PI Email: PI
Document Date:	**11 April 2023**

SIGNATURES OF AGREEMENT FOR VBP15-006

Amendment #3 for a Phase II Open-Label, Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with Duchenne Muscular Dystrophy (DMD)

Reviewed and Approved by:

PI

PI

PPD

Santhera Pharmaceuticals (Switzerland) Ltd

Date

INVESTIGATOR PROTOCOL AGREEMENT

Amendment #3 for a Phase II Open-Label, Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with Duchenne Muscular Dystrophy (DMD)

PROTOCOL NUMBER:	VBP15-006
SPONSOR:	Santhera Pharmaceuticals (Switzerland) Ltd
DOCUMENT DATE:	11 April 2023

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 Santhera Pharmaceuticals (Switzerland) Ltd.

I agree to conduct the study according to this protocol and the obligations and requirements of clinical Investigators and all other requirements set out in the Declaration of Helsinki listed in 21 CFR part 312, and ICH principles of Good Clinical Practice (GCP) and in accordance with all applicable laws, guidances and directives of the jurisdiction where the study is being conducted. I will not initiate this study without the approval of an Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

I understand that, should the decision be made by Santhera Pharmaceuticals (Switzerland) Ltd 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 Santhera Pharmaceuticals (Switzerland) Ltd.

For protocol amendments, I agree not to implement the amendment without agreement from Santhera Pharmaceuticals (Switzerland) Ltd and prior submission to and written approval (where required) from the IRB/IEC, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

Investigator's Signature

Date

Investigator's Name (Please print)

Address (Please print):

RETAIN THE ORIGINAL (WET-INK OR VALIDATED E-SIGNATURE) SIGNED AGREEMENT AT YOUR SITE AND SEND A SCANNED COPY OF THE SIGNED ORIGINAL TO SANTHERA PHARMACEUTICALS (SWITZERLAND) LTD, OR DESIGNEE

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of a serious adverse event (SAE) (see Section 7.6.6), the Investigator will complete the SAE 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 ICON safety management team within 24 hours, using the contact information below:

In United States and Canada:

Email: CHOSafety@iconplc.com

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

SAE Questions: Drug Safety Helpline: 1 800 772 2215

In Europe, Asia, Pacific, Africa and Australia:

Email: MHGSafety@iconplc.com

Drug Safety Fax: +44 1792 525720

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

PROTOCOL AMENDMENT TRACKING

Document	Document Number	Approval Date
Original Protocol	VBP15-006	14 October 2021
Amendment #1	VB15-006-A1 (Version 1.1)	14 April 2022
Amendment #2	VB15-006-A2 (Version 1.0)	09 February 2023
Amendment #3	VB15-006-A3 (Version 1.0)	11 April 2023

Reasons for Protocol Amendment #3:

PPD, the central laboratory was providing an EDTA-1ML K2 (Plastic) tube for collection of specific samples. However the manufacturer of this item has informed PPD that they are discontinuing the manufacture of this item globally, effective immediately. As such and since there is no equivalent tube with 1 mL volume, PPD needs to replace it with an alternate tube EDTA-1.2 mL S-Monovette K2 (Plastic). As a consequence, the volumes of blood collected at the study visits need to be revised.

The following changes have been included in this amendment and will be implemented following the standard approval process:

- Replace the 1 mL EDTA blood sampling tube by the 1.2 mL and revise the sampling plan (HbA1c is analyzed from the hematology sample).

Reasons for Protocol Amendment #2:

The following changes have been included in this amendment and will be implemented following the standard approval process:

- To make editorial modifications regarding transfer of Sponsor from ReveraGen BioPharma, Inc. to Santhera Pharmaceutical (Switzerland) Ltd.
- To update section 1 following Investigator's Brochure revision (version 12)
- To update the reference list
- To update Dosing Recommendation for children weighing 50 kg or more

- To describe the procedure of the dose tapering after discontinuation of vamorolone
- To include ambulatory status recording as part of physical examination at Baseline
- To define a new age subgroup (12 to <18 years) in which 10 additional glucocorticoid-treated subjects will be recruited, to the vamorolone daily dose of 6 mg/kg and to add exploration of the gonadal and thyroid axis biomarkers in this subgroup. To update the total number of participating subjects accordingly.
- To clarify that date of birth may be collected where local regulations allow.

Reasons for Protocol Amendment #1

- To clarify vamorolone is a 4.0% wt/vol suspension and provide details of vamorolone packaging
- To clarify that age of enrollment will be collected and date of birth will not
- To clarify standing height will be measured in all participants who can stand independently
- To remove glutamate dehydrogenase (GLDH) from laboratory evaluations
- To clarify vamorolone administration will take place at the study site during the Week 6 visit
- To specify subjects should be fasted ≥6 hours prior to all study visits when blood will be drawn

STUDY SYNOPSIS

Protocol Title	A Phase II Open-label, Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2-<4 Years and 7-<18 Years with Duchenne Muscular Dystrophy (DMD)
Name of Sponsor	Santhera Pharmaceuticals (Switzerland) Ltd
Protocol Number	VBP15-006
Drug Substance	17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione
Investigational Drug Product	Vamorolone, 4.0% weight per volume (wt/vol) suspension for oral dosing
Phase of Development	Phase II
Indication	Treatment of Duchenne muscular dystrophy (DMD)
Primary Objective	To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD.
Secondary Objectives	1. To evaluate the pharmacokinetics (PK) of vamorolone administered orally in boys ages 2 to <4 and 7 to <18 years with DMD. 2. To confirm the vamorolone exposure in boys ages 2 to < 4 and 7 to <18 years with DMD at 2.0 and 6.0 mg/kg and to adjust the doses if appropriate to achieve similar vamorolone areas under the concentration-time curve (AUCs) across the entire pediatric age range.
Exploratory Objectives	1. To compare the efficacy, as measured by the effect on muscle function, of vamorolone administered orally at daily doses of 2.0 mg/kg versus 6.0 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD; 2. To evaluate the effect of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period on behavior and neuropsychology in boys ages 2 to <4 and 7 to <18 years with DMD; 3. To evaluate the effect of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period on physical functioning in boys ages 2 to <4 and 7 to <18 years with DMD; 4. To evaluate the ease of administration of vamorolone in boys ages 2 to <4 years with DMD and study medication acceptability of vamorolone in boys ages 7 to <18 years with DMD at daily oral doses of 2.0 mg/kg and 6.0 mg/kg; 5. To investigate the effects of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period on pharmacodynamic (PD) biomarkers of safety and efficacy in boys ages 2 to <4 and 7 to <18 years with DMD.
Study Design	This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, pharmacokinetic (PK), PD, clinical efficacy, behavior and neuropsychology, and physical functioning of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a treatment period of 3 months in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

	The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month open-label Treatment Period (Weeks 1-12); and a -week Dose-tapering Period for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study. Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent and assent, as required, is obtained. • **Within the 2 to <4 years age group,** the initial 10 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 10 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit. • **Within the 7 to <18 years age group** (including an additional 12 to <18 years age group), both corticosteroid-treated and untreated, the initial 12 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 22 eligible subjects (including 10 subjects from an additional 12 to <18 years age group) will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The first 6 subjects in each age group at 2.0 mg/kg will serve as the PK/safety run-in cohorts. PK assessments will be performed at week 2, and together with the safety assessment during the first 4 weeks of treatment, will be the basis to confirm whether 2.0 and 6.0 mg/kg/day will be used in the subsequent patients or if a dose adjustment is needed to avoid over or under-exposure of vamorolone in patients for any of the two age groups. Glucocorticoid-treated subjects in the 7 to <18 years age group will take their final dose of SoC glucocorticoid therapy for DMD on Baseline Day -1, within 24 hours prior to administration of the first dose of vamorolone study medication. All subjects will begin their assigned vamorolone treatment on Treatment Period Day 1 and will continue to receive their assigned vamorolone treatment throughout the duration of the 3-month Treatment Period (Weeks 1-12). At the end of the 3-month Treatment Period (Week 12), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible, or to transition to SoC treatment for DMD (may include glucocorticoids). Subjects completing VBP15-006 and enrolling directly into the expanded access or compassionate use program or transitioning directly to SoC glucocorticoid treatment will not need to taper their vamorolone dose prior to participation in the expanded access or compassionate use program or initiation of SoC glucocorticoid treatment. All subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin the dose tapering period during which the dose of study medication will be progressively reduced and discontinued.
Planned Sample Size	A total of approximately 20 subjects will enrolled within the 2 to <4 years age group, as follows: • Vamorolone 2.0 mg/kg/day (n=10); enrolled first • Vamorolone 6.0 mg/kg/day (n=10); enrolled after previous dose group A total of approximately 34 subjects will be enrolled to treatment within the 7 to <18 years age group, with 2.0 mg/kg/day groups enrolled first, as follows: • Vamorolone 2.0 mg/kg/day, steroid untreated at entry (n=6)

	• Vamorolone 2.0 mg/kg/day, steroid treated at entry (n=6) • Vamorolone 6.0 mg/kg/day, steroid untreated at entry (n=6) • Vamorolone 6.0 mg/kg/day, steroid treated at entry (n=6) • Vamorolone 6.0 mg/kg/day, 12 to <18 years and steroid treated at entry (n=10; additional group)
Inclusion Criteria	1. Subject's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements; 2. Subject has a centrally confirmed (by TRiNDS central genetic counselor[s]) diagnosis of DMD, defined as: a. Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency, and clinical picture consistent with typical DMD, OR b. Identifiable mutation within the DMD gene (deletion/duplication of one or more exons), where reading frame can be predicted as 'out-of-frame,' and clinical picture consistent with typical DMD, OR c. Complete dystrophin gene sequencing showing an alteration (point mutation, duplication, other) that is expected to preclude production of the dystrophin protein (i.e., nonsense mutation, deletion/duplication leading to a downstream stop codon), with a clinical picture consistent with typical DMD; 3. Subject is male, 2 to <4 years or 7 to <18 years of age at time of enrollment in the study; 4. If 7 to <18 years of age and currently taking standard of care glucocorticoids for treatment of DMD, subject has been taking standard of care glucocorticoids at stable dose for at least 3 months prior to enrollment in the study and will continue the same stable dose regimen through the date of the Baseline Day -1 Visit. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study]; 5. If 7 to <18 years of age, and not currently glucocorticoid-treated, subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to enrollment. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study]; 6. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. [Notes: Serum gamma glutamyl transferase (GGT), creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit. An abnormal vitamin D level that is considered clinically significant will not exclude a subject from participating]; 7. Subject has evidence of chicken pox immunity as determined by: • Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period; OR

	• Documentation, provided at the Screening Visit, that the subject has had 2 doses of varicella vaccine, with or without serologic evidence of immunity; the second of the 2 immunizations must have been given at least 14 days prior to assignment to a dose group; 8. Subject and parent(s)/guardian(s) are willing and able to comply with scheduled visits, study drug administration plan, and study procedures.
Exclusion Criteria	1. Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression; 2. Subject has current or history of chronic systemic fungal or viral infections; 3. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to enrollment; 4. Subject has a history of primary hyperaldosteronism; 5. Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary]; 6. If 2 to <4 years of age, 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 1 month cumulative, with last use at least 3 months prior to enrollment, will be considered for eligibility on a case-by-case basis, unless discontinued for intolerance. Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study]; 7. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents; 8. Subject has used idebenone within 4 weeks prior to enrollment; 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; 11. Subject is taking (or has taken within 4 weeks prior to enrollment) herbal remedies and supplements which can impact muscle strength and function (e.g., Co-enzyme Q10, creatine, etc); 12. Subject is taking (or has taken within 3 months prior to enrollment) any medication indicated for DMD, including Exondys51, Exondys53, Exondys45, Viltepso and Translarna; 13. Subject has been administered a live attenuated vaccine within 14 days prior to the first dose of study medication; 14. Subject is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to enrollment; 15. Subject has previously been enrolled in the VBP15-006 study or any other vamorolone study.

	Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result.
Number of Centers	The study will be conducted at approximately 6 Canadian study sites.
Study Period	First subject screened: 4Q 2021 Last subject last visit: 1Q 2024
Study Duration	Approximately 24 months total duration
Individual Subject Study Duration	Up to approximately 21 weeks: • Screening Period: up to 5 weeks • Baseline Period: 1 day • Treatment Period: 12 weeks (Weeks 1-12) • Dose-tapering Period: 4 up to 8 weeks, only for subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the study. Subjects who complete the Treatment Period Week 12 assessments will be given the option of continuing vamorolone treatment by expanded access or compassionate use, if possible, under separate protocol. Subjects who continue directly with vamorolone treatment by expanded access or compassionate use or who transition directly to SoC glucocorticoid treatment for DMD will be discharged from the VBP15--006 study following completion of all Week 12 assessments and will not participate in the Dose--tapering Period.
Study Drug Formulation, Dosage & Administration	**Treatment Period and Dose-tapering Period** Subjects will be administered 4.0% wt/vol oral suspension (Formulation route of synthesis 2 [ROS2]). The planned vamorolone doses are 2 mg/kg and 6 mg/kg daily. The initial patients enrolled in each age group will receive 2 mg/kg/day to confirm the PK and safety of vamorolone in both age groups at this dose level. After review of the PK and safety data from at least 6 patients in each age cohort, subsequent patients can be enrolled at the 6 mg/kg /day dose level. If the intended dose of vamorolone is 6 mg/kg/day, AND patients weigh 50 kg or more, the daily dose should be capped at 300mg. Considering the linearity of vamorolone pharmacokinetics, if the intended patient dose is 2mg/kg/day, the dose is capped at 100mg per day for patients weighing 50kg or more.. All subjects: vamorolone 4.0% wt/vol oral suspension (investigational medicine) will be administered once daily over the 12-week Treatment Period (Weeks 1-12) and during the Dose-tapering Period, if applicable. The oral suspension study medication will be administered in the study unit at the Day 1, Week 2, and Week 12 study visits; all other doses will be administered at home. Study drug oral suspensions 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. Participants must fast ≥6 hours prior to the Day1, Week 2, Week 6 and Week 12 study visits, when dosing will occur at the study site. The daily dose of study medication administered at home should be taken in the morning with breakfast. There are no other food or drink restrictions before or after dosing.

Study Summary	This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, physical functioning, and sleep-wake activity of vamorolone over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD. Subjects will be assessed for safety and tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning at scheduled visits throughout the study. Screening assessments will be performed prior to assignment to a study group. All subjects will be assigned to treatment at the Baseline Day -1 Visit. After completion of Screening and Baseline assessments and assignment to treatment, subjects will return to the study clinic on Day 1 for safety, PK, and PD assessments prior to administration of the first dose of study medication. Additional study visits will occur at Week 2, Week 6, and Week 12. Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor regarding study conduct. Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day (for participants weighing 50kg and over, the dose is capped at 100mg/day) or 6.0 mg/kg/day (for participants weighing 50kg and over, the dose is capped at 300mg/day), beginning the next day on Treatment Period Day 1. For all subjects, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit. Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site. Subject diaries will be dispensed at the Day 1, Week 2, Week 6, and Week 12 (for subjects participating in the Dose-tapering Period) Visits to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication. The scheduled Week 12 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling. The scheduled 12-lead electrocardiogram (ECG), eye examination, Pediatric Outcome Data Collection Instrument (PODCI), and Personal Adjustment and Role Skills Scale III (PARS III) may be completed on the day prior to the final Week 12 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 12 dose of study medication. The scheduled physical examination, weight, height, vital signs, clinical laboratory tests, blood draws for PD biomarker analysis, Ease of Study Medication Administration Assessment (2 to <4 years only)/Study Medication Acceptability Assessment (7 to <18 years only), functional assessments (Bayley-III Gross Motor scale [ages 2 to <4 years] and Performance of Upper Limb (PUL) Test [7 to <18 years]), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 12 dose of study medication.

	Subjects who complete the VBP15-006 study assessments through the Week 12 Visit may be given the opportunity to continue to receive vamorolone as part of an expanded access or compassionate use program under separate protocol, or alternatively transition to SoC treatment (including glucocorticoids) for DMD. Standard of care treatment for DMD may be offered to the subject following completion of the VBP15-006 study if the subject's parent(s) or guardian(s) does not wish to enroll the subject in the expanded access or compassionate use program and/or the Investigator feels it to be in the best interest of the subject. Subjects who complete the VBP15-006 study and will enroll directly into the expanded access or compassionate use program to continue vamorolone treatment or will transition directly onto SoC glucocorticoid treatment for DMD will be discharged from the VBP15-006 study following completion of all Week 12 assessments. Subjects who will not continue vamorolone treatment in the expanded access or compassionate use program, and who will not transition directly to SoC glucocorticoid treatment for DMD, will have their vamorolone dose tapered during Dose-tapering Period prior to discharge from the study. . Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the dose tapering is proceeding according to protocol to assess potential signs or symptoms of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have. 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 12 Visit should return to the study unit for scheduled Week 12 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun and will not transition directly to SoC glucocorticoids should undergo dose-tapering following early completion of the Week 12 assessments.

Safety Measures	• Body Mass Index (BMI)
	• Body Mass Index z-score
	• Weight and Height (standing height collected for subjects in 2 to <4 years age group and all participants who can stand independently; height calculated from ulnar length in subjects in 7 to <18 years age group)
	• Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature [modality for determining temperature should be consistent for each subject at all assessment time points throughout the study])
	• Physical examination, including examination for infections
	• Cushingoid features
	• Clinical laboratory tests:
	  • Hematology and clinical chemistry
	  • Urinalysis
	  • Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])
	  • Vitamin D level
	• 12-lead electrocardiogram (ECG)
	• Eye examination
	• Clinical signs and symptoms (AEs and SAEs)

	• Grading of clinical and clinical laboratory AEs will be according to the Common Terminology Criteria for Adverse Events (CTCAE, v.5.0)
Pharmacodynamic Measures	Blood will be collected for serum PD biomarker analysis to evaluate effects of vamorolone on biomarkers of safety (i.e., biomarkers associated with insulin resistance [fasting glucose and insulin, and hemoglobin A1c {HbA1c}], adrenal suppression [morning cortisol], and bone turnover [osteocalcin, C-terminal peptide fragment of collagen 1 {CTX}, and aminoterminal propeptide of type I collagen {P1NP}]), and additional exploratory biomarkers. Blood samples for analysis of PD biomarkers will be collected prior to the first dose of study medication at the Day 1 Visit, and prior to the final dose of study medication at the Week 12 Visit. Blood samples for PD biomarkers will be collected after subjects have fasted for ≥ 6 hours, and prior to the daily dose of study medication.
Pharmacokinetic Measures	• Blood will be collected for vamorolone PK analysis on Day 1 and Week 2 visits. • For ages 2 to <4 years, blood sampling is within 30 minutes prior to and 1-, 2-, and 6-hours following the first dose of study medication at the Day 1 Visit, and within 30 minutes prior to and 1-, 2- and 6- hours following the daily dose of study medication at the Week 2 Visit . • For ages 7 to <18 years, blood sampling is within 30 minutes prior to and 1-, 2-, 4-, 6- and 8-hours following the first dose of study medication at the Day 1 Visit, and within 30 minutes prior to and 1-, 2-, 4-, 6- and 8-hours following the first dose of study medication at the Week 2 Visit .
Clinical Efficacy Measures	• Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale (ages 2 to <4 years only) • Performance of Upper Limb (PUL) test (ages 7 to <18 years only)
Patient-reported Outcome Measures	• Pediatric Outcome Data Collection Instrument (PODCI) • Personal Adjustment and Role Skills Scale, ed. 3 (PARS III) questionnaire • Ease of Study Medication Administration Assessment (ages 2 to <4 years only) • Study Medication Acceptability Assessment (ages 7 to <18 years only)
Statistical Methods	**Sample Size:** This is an open-label, multiple dose study. Study medication is administered daily in this Phase II trial.

	For this Phase II study in DMD boys ages 2 to <4 years and 7 to <18 years, a total of approximately 20 subjects in the 2 to <4 years age group will be enrolled with approximately 10 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day). A total of approximately 34 subjects in the 7 to <18 years age group will be enrolled with approximately 12 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day) and each dose level group stratified 1:1 by glucocorticoid treatment status at study entry to include approximately 6 subjects glucocorticoid-untreated and 6 subjects glucocorticoid-treated at study entry, to which 10 subjects 12 to <18 years are added to the 6 mg/kg dose level. This sample size is considered sufficient to detect drug safety concerns in a pediatric population ages 2 to <4 and 7 to <18 years with DMD based on clinical judgment and prior study of vamorolone at these doses. In addition, this sample size is sufficiently large to determine PK parameters. A drop-out rate is not considered; subjects who withdraw early from the study may be replaced. **Analysis Populations:** Three populations will be defined for data analysis: Safety Population, modified Intent-to-Treat Population, and Pharmacokinetic Population. Safety Population All subjects who receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety and PD assessments. Results will be presented "as treated." Modified Intent-to-Treat (mITT) Population All subjects who receive at least one dose of study medication and have at least one post-baseline efficacy assessment will be included in the mITT Population. The mITT Population is the primary analysis population for clinical efficacy. Subjects who receive at least one dose of study medication but never have post-baseline assessments will be excluded. Results will be presented "as assigned." Pharmacokinetic (PK) Population All subjects who receive at least one dose of vamorolone study medication and have sufficient data for PK analysis will be included in the PK Population. **General Statistical Considerations:** All measurements will be analyzed based upon the type of distribution and descriptive statistics presented by age group, vamorolone dose level, glucocorticoid treatment status at entry (ages 7 to <18 years only), and time point, as appropriate. No formal interim statistical analyses are planned, apart from the interim safety data views and presentations to be created for the DSMB. Missing values for safety outcomes will be treated as missing, unless stated otherwise. Individual subject listings of endpoints, sorted by age group, vamorolone dose level, and glucocorticoid treatment at entry (ages 7 to <18 years only) will be reviewed for any evidence of dose-related differences or trends. Baseline measurement is defined as the last non-missing value prior to the first dose of study drug. **Safety and Tolerability Analyses:** All evaluations of clinical safety will be listed and presented using descriptive statistics by age group, dose level, and time point. Additional summaries will be provided by glucocorticoid use (users versus non-users).

	Safety data will include BMI, weight, height, vital signs, eye examination results, and ECG results, and these will be presented using descriptive statistics. The BMI and height values will be evaluated both on the original scale and as z-scores. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed. Furthermore, continuous safety endpoints will be evaluated using a Mixed Model for Repeated Measures (MMRM), when appropriate. The models will include the baseline value as a covariate and visit, dose level, glucocorticoid use (when appropriate) and the relevant interaction terms as fixed effects. Separate models will be used for each age group. In case of no repeated measures (endpoint is assessed at one post-baseline visit only), Analysis of Covariance (ANCOVA) models will be used instead of MMRM. Adverse events will be summarized overall and by age group, dose level, glucocorticoid treatment at entry (ages 7 to <18 years only), system organ class (SOC) and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]). Further analyses will be conducted by seriousness, severity and relationship to study medication. Adverse events leading to premature discontinuation of the study will be evaluated separately. **Pharmacokinetic Analyses:** For the age 2 to <4 years groups, the pre-dose and 1-, 2-, and 6-hour post-dose plasma concentration measurements of vamorolone at Day 1 and Week 2 will be assessed. For the age 7 to <18 years groups, the pre-dose and 1-, 2-, 4-, 6, and 8-hour post-dose plasma concentration measurements of vamorolone at Day 1 and Week 2 will be assessed Comparison of drug exposures by age group, dose level, and glucocorticoid treatment at entry (ages 7 to <18 years only) will be aggregated with PK data from previous studies in DMD boys for comparison across the entire pediatric age range and with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to age group, dose level, and glucocorticoid treatment at entry (7-<18 years only), as applicable. **Pharmacodynamic Analyses:** Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of safety and efficacy, including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4), will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers by dose level within age group. Change from baseline will be presented. For subjects 7 to <18 years of age, descriptive statistics will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment to a dose group. The changes in serum PD biomarkers will be compared to the data collected in a previously conducted vamorolone study VBP15-004. The changes from baseline to week 12 in the present study (by dose level and age group) will be compared to the changes from baseline to week 12 in the four treatment groups of study VBP15-004 (vamorolone 2.0 mg/kg, vamorolone 6.0 mg/kg, placebo and prednisone 0.75 mg/kg). Furthermore, the differences between the groups will be evaluated with ANCOVA models including baseline value as a covariate and the treatment/age group as a fixed factor. Additional analyses will be conducted by glucocorticoid use group, when appropriate. **Clinical Efficacy Analyses:**

	The exploratory efficacy outcomes are the Bayley-III Gross Motor scale (2 to <4 years age group) and PUL Test (7 to <18 years age group). Standard descriptive statistics will be used to summarize the clinical efficacy endpoints by dose level within age group. Change from baseline will be presented. Within each age group, pairwise comparisons will be made to compare change from baseline for the vamorolone 6 mg/kg/day dose level group vs. the vamorolone 2 mg/kg/day dose level group. For subjects 7 to <18 years of age, descriptive statistics will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment. Furthermore, the changes from baseline to week 12 will be compared using ANCOVA models, including baseline value as a covariate and dose level and glucocorticoid use status (when appropriate) and the relevant interaction terms as fixed factors. Separate models will be used for each age group. **Patient-reported Outcome Analyses:** Patient-reported Outcomes including the PODCI, PARS III, Ease of Study Medication Administration Assessment, and the Study Medication Acceptability Assessment will be listed and presented using descriptive statistics by age group, dose level, and time point. For subjects 7 to <18 years of age, descriptive statistics for change from baseline assessments (PODCI and PARS III) will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of participation and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment to a dose group.

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LIST OF ABBREVIATIONS

Abbreviation	Definition/Term
%CV	percent coefficient of variation
ACTH	adrenocorticotropic hormone
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-24hr	area under the concentration-time curve from time 0 to 24 hours
AUC(0-t)	area under the concentration-time curve from time 0 to time t
AUC(inf)	area under the concentration-time curve from time 0 to infinity
AUClast	area under the plasma concentration-time curve from time 0 to the last observed measurable concentration
Bayley-III	Bayley Scales of Infant and Toddler Development-III
BMI	body mass index
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
ConA	Concanavalin A
cm	centimeter
Cmax	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Material
CTMS	Clinical Trial Management Software
CTX	C-terminal peptide fragment of collagen 1
CYP	cytochrome P450
DILI	drug-induced liver injury
dL	deciliter
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency

Abbreviation	Definition/Term
F%	percent bioavailability
FDA	Food and Drug Administration
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
hr	hour
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IXRS	Interactive Voice/Web Response System
kg	kilogram
L	liter
LLC	Limited Liability Company
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LS	least squares
µg	microgram
m	meter
m2	square meter
MAD	multiple ascending dose (study)
MD	Medical Doctor (physician)
Mdx	mouse model lacking dystrophin
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	modified Intent-to-Treat
mL	milliliter
MTD	maximum tolerated dose
N, No.	number
NADPH	nicotinamide adenine dinucleotide phosphate

Abbreviation	Definition/Term
NCA	noncompartmental analytical (methods)
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
ng	nanogram
nM	nanomolar
nmol	nanomole
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Cooperation and Development
OTC	over-the-counter (non-prescription medication)
oz	ounce
P1NP	aminoterminal propeptide of type I collagen
PARS III	Personal Adjustment and Role Skills Scale III
PBL	peripheral blood leukocytes
PD	pharmacodynamics
PHI	Protected Health Information
PK	pharmacokinetics
PODCI	Pediatric Outcomes Data Collection Instrument
PR [PQ]	time from onset of P wave to start of the QRS complex
PUL	Performance of Upper Limb (Test)
QD	once daily (dosing)
QRS	in electrocardiography, the complex consisting of Q, R, and S waves, corresponding to depolarization of ventricles [complex]
QSAR	quantitative structure-activity relationship
QT	in cardiology, the time between the start of the Q wave and end of the T wave
QTc	corrected QT interval
RBC	Red Blood Cell
ROS	route of synthesis
RR	in electrocardiography, the interval between successive Rs (peaks of QRS complexes)
SAD	single ascending dose (study)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedures
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	terminal half-life
TEAE	treatment-emergent adverse event

Abbreviation	Definition/Term
Tmax	time to maximum observed plasma concentration
TRiNDS	Therapeutic Research in Neuromuscular Disorders Solutions
US	United States
vs.	versus
Vss	volume of distribution at steady state
WBC	White Blood Cell
WHO	World Health Organization
wt	weight

1. INTRODUCTION

1.1. Background and Unmet Need

DMD is the most common childhood muscular dystrophy with a birth incidence worldwide of 1 in 3,600 to 9,300 males [Mah et al, 2014]. Clinical characteristics of DMD are proximal muscle weakness presenting in childhood and progressive involvement of most muscle groups, leading to loss of ambulation late in the first decade or early in the second decade of life. Weakness progresses, with the patient requiring assistance with the activities of daily living by the late teens or in their early twenties. Patients with DMD often succumb from respiratory failure and/or cardiac failure.

DMD is an X-linked recessive disorder caused by mutations in the *DMD* gene [Koenig 1987] which codes for the dystrophin protein that provides structural stability to the dystrophin-associated glycoprotein complex on muscle cell membranes [Hoffman et al, 1987]. The lack of dystrophin reduces plasma membrane stability, resulting in membrane fragility and necrosis [Evans et al, 2009].

Upregulated inflammatory gene expression and activated immune cell infiltrates are present during early disease stages and play a significant role in muscle wasting [Chen et al, 2005]. The transcription factor NF-κB has been shown to regulate the expression of numerous inflammatory genes in immune cells and muscle fibers [Pahl, 1999; Dogra et al, 2006; Acharyya et al, 2007; Kumar et al, 2003] and the infiltration and activation of these cells can trigger muscle fiber death [Acharyya et al, 2007].

GR agonists, such as prednisone and deflazacort [Malik et al, 2012] are currently the cornerstone for the treatment of patients with DMD according to American Academy of Neurology practice guidelines [Gloss et al, 2016] and the DMD Care Considerations Working Group [Birnkrant et al, 2018]. The benefits of long-term glucocorticoid therapy have been shown to include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery [Birnkrant et al, 2018].

The adverse effects of glucocorticoids include weight gain, cushingoid appearance, growth delay, behavior changes, an increased frequency of vertebral fractures, skin fragility, cataract, increased intra ocular pressure, adrenal suppression, insulin resistance

[Kauh et al, 2012] and muscle atrophy [Schakman et al, 2013]. These adverse drug reactions (ADRs) negatively impact quality of life and cause considerable variation in clinical practice including suboptimal dosing [Griggs et al, 2013; Bello et al, 2015].

The significant adverse effects of glucocorticoids on growth also prevent their routine administration in infants or toddlers, despite evidence that better outcomes are achieved with earlier administration [Merlini et al, 2012; Pane et al, 2014; Ciafaloni et al, 2016; Connolly et al, 2019; McMillan 2019; Buckon et al, 2022].

There is therefore an ongoing need to develop glucocorticoids with a better safety profile.

Rationale to develop vamorolone for DMD

Preclinical and clinical studies have shown that vamorolone addresses the anti-inflammatory activity of the GR and avoids some of its unwanted effects such as growth stunting, inhibition of bone metabolism, and induction of neutrophilia.

The anti-mineralocorticoid activity of vamorolone, as shown in the preclinical studies may be beneficial since the renin-angiotensin-aldosterone axis is thought to be involved in the pathogenesis of skeletal muscle fibrosis and cardiomyopathy in DMD [Rodriguez-Gonzalez et al, 2021; Howard et al, 2022].

In addition, the lack of activation/inactivation of vamorolone by 11-β-HSD 1 and 2 may be an advantage since the pharmacological activity of prednisone, including some of its adverse effects such as osteoporosis, is linked to its local activation to prednisolone by 11- β-HSD 1 [Fenton et al, 2019; Morgan et al, 2014; Fenton et al, 2021; Webster et al, 2021; Cooper et al, 2003].

Lastly, the observed effect of cell membrane repair after injury in mice may be particularly relevant for dystrophin-deficient cells in DMD where plasma membranes are inherently unstable.

Based on this differentiated profile, vamorolone has the potential to combine the known efficacy of glucocorticoids in DMD with a better safety profile.

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*. Refer to the current IB for updated information on the nonclinical experience of vamorolone.

1.3. Clinical Experience

Clinical experience with vamorolone is comprised of a completed Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001), completed Phase IIa (VBP15-002) and Phase II extension (VBP15-003) trials in DMD boys, completed Phase II long-term extension (VBP15-LTE) trial in DMD boys, and a completed Phase IIb active- and placebo-controlled trial in DMD boys (VBP15-004). Vamorolone is extensively metabolized in the liver hence the impact of an impaired hepatic function on vamorolone PK was assessed in a clinical study in adult volunteers with moderate impaired hepatic function [VBP15-HI]. [VBP15-DDI] study investigated the effect of itraconazole on the PK of on a single dose of vamorolone in healthy subjects. Furthermore, two relative bioavailability (BA) and food effect (FE) studies have been conducted (VBP15-PKFORM and VBP15-PKFORM-002) comparing the formulation used in clinical studies (ROS1) with the to-be-marketed formulation (ROS2).

Refer to the current IB version for updated and detailed information on the development program for vamorolone.

1.4. Pharmacokinetics of Vamorolone

The PK of vamorolone in subjects with DMD aged 4 to 7 years was thoroughly evaluated with intense PK sampling on Days 1 and 14 of daily vamorolone administration in Study VBK15-002. Vamorolone peak plasma concentrations occurred on average 2 to 4 hours after dosing, exposure increased linearly with dose and the exposure after 6.0 mg/kg/day in terms of mean (SD) Cmax and AUC0-inf was 970 (270) ng/mL and 3606 (897) ng.hr/mL, respectively on Day 14). The mean (SD) t½ of vamorolone at

6.0 mg/kg/day was 1.4 (0.35) hours and no accumulation is observed with daily administration.

The Population PK (PPK) evaluation based on PK data from studies VBP15-002 and VBP15-004 estimated the CL/F and V/F values for a typical DMD patient weighing 20 kg and taking vamorolone with a meal as 58 L/hr and 162 L, respectively The PPK estimate vamorolone Tmax is 2.4 hours, the estimated elimination half-life in DMD boys is 1.9 hours and the calculated exposure at steady state after 6.0 mg/kg/day in terms of Cmax and AUC0-inf was 555 ng/mL and 2944 ng.hr/mL, respectively, in a typical DMD patient weighing 20 kg and taking vamorolone with a meal.

The results of the two bioavailability/food effect studies (VBP15-PK-FORM and VBP15-PK-FORM-002) support the change from the Clinical Formulation (ROS1) to the To-be-marketed Formulation (ROS2). The To-be marketed Formulation (ROS2) demonstrates a lower food effect than the Clinical Formulation (ROS1) and offers more reliable dosing (i.e., more consistent exposure) when taken with different types of food.

Hepatic impairment increases the exposure to vamorolone. Subjects with moderate HI had 1.7 and 2.6-fold higher Cmax and AUC0inf values compared to age, weight and sex matched healthy adults

The PK evaluation based on all 18 subjects showed no relevant increase in peak concentrations of vamorolone in the presence of the potent CYP3A4 inhibitor itraconazole, but AUC0-inf increased by 33.7%. Median Tmax of vamorolone was 2 hours when administered alone and was delayed when combined with itraconazole (4 hours). Thus, itraconazole has a weak effect on vamorolone PK.

Refer to the current IB version for full and updated clinical pharmacology information.

1.5. Safety and Efficacy of Vamorolone in DMD (Study VBP-004)

The results of study VBP15-004, a randomized, double-blind, placebo controlled and prednisone referenced study showed that vamorolone produced clinically meaningful, statistically significant, and robust improvements in multiple measurements of lower limb motor function compared to placebo after 24 weeks of treatment. The improvements in

motor function with vamorolone were similar to those seen with prednisone, a standard of care for children with DMD. The positive effects achieved at 24 weeks with vamorolone 6 mg/kg remained stable over the course of the second period of the pivotal trial up to 48 weeks, both for patients who remained on vamorolone 6 mg/kg in both periods and for those who switched from prednisone 0.75 mg/kg to vamorolone 6 mg/kg. Although the magnitude of effects on motor function in vamorolone 2 mg/kg was less well maintained over time, an improvement compared to baseline was still observed after 12 months.

In study VBP15-004, a higher proportion of subjects presented with a least one TEAE in the vamorolone 2 and 6 mg/kg groups (83.3% and 89.3%, respectively) compared to placebo (79.3%) but in line with the prednisone 0.75 mg/kg group (83.9%). Clinically-relevant TEAEs, pre-defined as moderate to severe events, SAEs, or events leading to discontinuation, were reported at similar rates in the placebo (31.0%) and vamorolone 2 mg/kg groups (26.7%), less in the vamorolone 6 mg/kg group (14.3%), and more frequent in the prednisone 0.75 mg/kg group (41.9%). These results indicate that the increased proportion of subjects presenting with at least one TEAE in both of the vamorolone groups compared to placebo was driven by an excess in mild TEAEs, while prednisone was also associated with an increase in moderate to severe events.

Adverse Events of Special Interest, pre-defined as groupings of events typically associated with glucocorticosteroid therapy, were reported in a similar percentage of subjects in the placebo (69.0%) and vamorolone 2 mg/kg (66.7%) groups and higher percentages in the prednisone 0.75 mg/kg (77.4%) and vamorolone 6 mg/kg (78.6%) groups.

The safety profile of vamorolone shares some risks with those described with glucocorticoids, such as:

- Vamorolone causes dose-dependent adrenal suppression. The level of adrenal suppression was slightly larger in vamorolone 6 mg/kg than prednisone 0.75 mg/kg based on mean morning cortisol values, while the vamorolone 2 mg/kg had a partial effect.

- Cushingoid features were frequently reported dose-dependent AEs with vamorolone. The incidence of cushingoid features were similar in vamorolone 6 mg/kg and prednisone 0.75 mg/kg. Most of the events were reported as non-clinically significant and did not lead to discontinuation of vamorolone.
- Vamorolone 6 mg/kg was associated with an increase in BMI compared to placebo and comparable to the effect seen in prednisone 0.75 mg/kg. Vamorolone 2 mg/kg showed a less pronounced effect of limited clinical relevance.
- Vamorolone 6 mg/kg was associated with an increased risk for behavioural problems, mainly mild irritability, which were more frequently reported in the first 6 months of treatment.
- Gastrointestinal symptoms were reported at similar frequency than placebo over the first 6 months of treatment but showed evidence for dose-dependency over the long-term treatment suggestive of a drug effect.

While the safety profile of vamorolone shares some risks with those described with glucocorticoids, it shows clinically relevant differences for a clinically improved safety profile in long-term therapy:

- Absence of a deleterious effect on biomarkers of bone metabolism
- Normal growth with any dose of vamorolone, supported by the absence of a change in height z-scores similar to placebo at 6 months, 12 months and in the long term in study VBP15-LTE, while evidence of growth stunting was already seen at Month 6 for the prednisone group.
- A reduced frequency and severity of behavior related events on 6 mg/kg vamorolone compared with prednisone, while 2 mg/kg vamorolone was similar to placebo.

In addition, the findings of the vamorolone development programs suggests the potential for other differential effect in the long-term safety profile of vamorolone, such as:

- Absence of a clinically relevant effect on glucose metabolism in study VBP15-004 and over up to 30 months of treatment in study VBP15-002/002/LTE
- Absence of an effect on neutrophil counts while neutrophilia was observed early after starting treatment with prednisone.
- Absence of cases of cataracts or increase in intraocular pressure in studies VBP15-004 and VBP15-002/003/LTE

Additional long-term data would be required to further characterize the risks.

These data support a positive benefit-risk profile for vamorolone at the 2 mg/kg and 6 mg/kg doses. The efficacy at the vamorolone 6 mg/kg dose is similar to current standard of care, prednisone, with an improved safety and tolerability profile compared to prednisone. The vamorolone 2 mg/kg shows robust efficacy compared to placebo at 24 weeks and a further improved safety and tolerability profile compared to vamorolone 6 mg/kg and prednisone 0.75 mg/kg.

Refer to the current IB version for the most updated clinical information.

1.6. Rationale for Study Design

The current Phase II study is designed to confirm the safe and tolerable dose(s) of vamorolone to be used to treat DMD in boys aged 2 to <4 years and 7 to <18 years, based upon safety and PK data, and to perform an exploratory evaluation of PD, clinical efficacy, behavior and neuropsychology, and physical functioning over a treatment period of 12 weeks. Steroid-naïve subjects in the 2 to <4 years age group will be recruited for study, dictated by 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. Enrollment of boys in the 7 to <18 years age group will be stratified to accommodate both glucocorticoid-treated and glucocorticoid-untreated subjects at time of study entry, to reflect real-world clinical experience with glucocorticoid treatment for DMD in older boys; analyses will be conducted separately for subjects in each glucocorticoid treatment group. A group of 10 subjects is added to ensure a sufficient number of glucocorticoid-treated subjects 12 to <18 years of age are exposed to the

higher dose (6 mg/kg). This change is introduced through protocol amendment #2 because the 7 to <18 years of age group is recruiting a very limited number of these older subjects. This imbalanced recruitment could potentially prevent objectives of the study to be met by not sufficiently exploring the 12 to <18 years age range.

The vamorolone dose levels of 2.0 mg/kg/day and 6.0 mg/kg/day chosen for study have been shown to be safe and well-tolerated, and associated with improvements in muscle and strength assessments, in previous and ongoing vamorolone Phase II studies in boys 4 to <7 years of age. As a new route of synthesis of vamorolone, ROS2, will be used, boys will enroll into the 2.0 mg/kg/day group first, and drug exposure compared to previous ROS1 experience prior to enrolling into the higher 6.0 mg/kg/day dose group. Based on pharmacokinetics of vamorolone, the daily dose will be capped for the patients weighing 50 kg and above at 300mg in the 6mg/kg/day dose groups and 100mg in the 2mg/kg/day dose groups.

Subjects who meet all eligibility criteria in this study (VBP15-006) will be assigned to one of seven treatment groups as shown in **Table 1.** Groups 1, 3, and 4 will be fully enrolled at 2.0 mg/kg/day prior to assignment of subsequent participants to Groups 2, 5, 6 and 7 at 6.0 mg/kg/day.

Table 1. Study Assignment Schedule

Group	Planned Number of Subjects	Glucocorticoid Status	Ages 2 to <4 Years	Ages 7 to <18 Years
1	10	Naïve*	Vamorolone, 2.0 mg/kg/day	
2	10	Naïve*	Vamorolone, 6.0 mg/kg/day	
3	6	Untreated at entry		Vamorolone, 2.0 mg/kg/day/
4	6	Treated at entry		Vamorolone, 2.0 mg/kg/day/
5	6	Untreated at entry		Vamorolone, 6.0 mg/kg/day/
6	6	Treated at entry		Vamorolone, 6.0 mg/kg/day/
7	10	Treated at entry		Vamorolone, 6.0 mg/kg/day/

*Naïve is defined as having had no prior glucocorticoid treatment for DMD, and past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to enrollment, to be considered for enrollment on a case-by-case basis.

Group 1 (age 2 to <4 years, vamorolone 2.0 mg/kg/day), Group 3 (age 7 to <18 years untreated at entry, vamorolone 2.0 mg/kg/day), and Group 4 (age 7 to <18 years treated at entry, vamorolone 2.0 mg/kg/day) will be fully enrolled prior to Groups 2, 5, 6 and 7 (6.0 mg/kg/day).

Evaluation of the two dose levels of vamorolone during the 12-week Treatment Period in this study will allow comparison of change from baseline in safety parameters, muscle strength and functional efficacy parameters, and PD biomarker levels over 12 weeks of treatment within each age group.

Key safety parameters in conjunction with PK data will be evaluated during the course of the study to assess vamorolone safety and tolerability.

To evaluate clinical efficacy, effect of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day on muscle strength will be assessed using the Bayley-III Gross Motor scale (2 to <4 years age group) and the Performance of Upper Limb (PUL) Test (7 to <18 years age group). These functional assessments were chosen as accurate reflections of muscle strength for subjects with DMD within each of the two age groups studied [Connolly et al. 2014]; Pane at al. 2014].

Moreover, behavior and neuropsychology, physical functioning, and sleep-wake activity will be measured as exploratory outcomes using the Personal Adjustment and Role Skills Scale III (PARS III), and Pediatric Outcomes Data Collection Instrument (PODCI). Acceptability of the vamorolone suspension will be assessed using the parent-reported Ease of Study Medication Administration Assessment (ages 2 to <4 years) and the subject-reported Study Medication Acceptability Assessment (ages 7 to <18 years).

Pharmacodynamic safety biomarker findings in DMD patients receiving vamorolone 2.0 mg/kg/day or 6.0 mg/kg/day over 12 weeks will be compared within each age group. Serum PD biomarkers bridged to later clinical safety concerns will be assessed over time as exploratory safety measures. These PD biomarkers include:

1. Adrenal suppression. Pharmacological doses of glucocorticoids cause suppression of the hypothalamo-pituitary-adrenal axis, leading to low concentration of endogenous cortisol and other steroidal hormones in serum.

Adrenal suppression is directly associated with risk of adrenal crisis,. Measurement of morning cortisol concentrations, 24 hr after the last dose, will reflect the degree of adrenal suppression. Plasma cortisol secretion typically follows a circadian pattern with the highest concentrations early in the morning; a morning serum cortisol concentration less than 3.6 µg/dL (or 100 nM) is highly suggestive of adrenal suppression.

2. Bone turnover. Pharmacological doses of glucocorticoids suppress bone formation and bone resorption, leading to later osteopenia and bone fragility [van Staa et al. 2000]. Bone fragility is a significant adverse effect of chronic pharmacologic glucocorticoids in DMD as this can lead to fracture, especially vertebral fractures, which increases the likelihood of premature loss of ambulation. Serum biomarkers that have been bridged to later clinical outcomes of osteopenia in adults are osteocalcin (bone formation; glucocorticoids decrease serum levels), aminoterminal propeptide of type I collagen (P1NP) (bone formation; glucocorticoids decrease serum levels), and CTX (bone resorption; glucocorticoids increase serum levels in adults
3. Insulin resistance. Insulin resistance has been bridged to later clinical outcomes, including heart disease, type 2 diabetes, and vascular disease. Serum biomarkers that are accepted as measures of insulin resistance are increased serum glucose and insulin. This can be measured after acute (hours after first dose) or chronic (after weeks or months of dosing) glucocorticoid treatment.

Exploratory safety outcomes will be assessed by additional serum safety biomarkers that have been defined in glucocorticoid-treated DMD and inflammatory bowel disease patients. Additional exploratory measures of efficacy include PD biomarkers that have previously been shown to be glucocorticoid-responsive in DMD boys, pediatric inflammatory bowel disease, adult vasculitis, and pediatric myositis.

This trial will be conducted in compliance with this protocol, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable Health Canada

regulatory requirements , and the issued FDA guidance on developing drugs for treatment for DMD and related dystrophinopathies [FDA, 2015].

1.7. Overall Benefit/Risk

Vamorolone has shown positive benefit-risk profile for both doses. The dose of 2mg/kg shows an even more favorable safety and tolerability profile as most of the vamorolone-related risks were dose-dependent, still with evidence of efficacy, thus providing an alternative dose with a positive benefit-risk profile that could be considered for patients having tolerability concerns. At 6mg/kg dose , the efficacy is similar to current standard of care, prednisone, with an improved safety and tolerability profile supporting its use as the recommended starting dose for the long-term treatment of DMD. Please refer to the current Investigator Brochure for more information.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is:

To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

1. To evaluate the pharmacokinetics of vamorolone administered orally in boys ages 2 to <4 and 7 to <18 years with DMD;
2. To confirm the vamorolone exposure in boys ages 2 to <4 and 7 to18 years with DMD at 2.0 and 6.0 mg/kg and to adjust the doses if appropriate to achieve similar vamorolone AUCs across the entire pediatric age range.

2.1.3. Exploratory Objectives

The exploratory objectives of this study are:

1. To compare the efficacy, as measured by the effect on muscle function, of vamorolone administered orally at daily doses of 2.0 mg/kg versus 6.0 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD;
2. To evaluate the effect of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period on behavior and neuropsychology in boys ages 2 to <4 and 7 to <18 years with DMD;
3. To evaluate the effect of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period on physical functioning in boys ages 2 to <4 and 7 to <18 years with DMD;

4. To evaluate the ease of administration of vamorolone in boys ages 2 to <4 years with DMD and study medication acceptability of vamorolone in boys ages 7 to <18 years with DMD at daily oral doses of 2.0 mg/kg and 6.0 mg/kg;
5. To investigate the effects of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period on pharmacodynamic biomarkers of safety and efficacy in boys ages 2 to <4 and 7 to <18 years with DMD.

2.2. Study Endpoints

2.2.1. Safety Endpoints

For each vamorolone dose level and age group, the following endpoints will be evaluated. Additionally, for selected endpoints, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment to a dose group:

1. BMI z-score: Change from baseline to Week 12;
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 7.6**);
3. Vital signs (sitting blood pressure, heart rate, respiratory rate, and body temperature): Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points;
4. Body weight and height: Change from baseline to each of the scheduled on--treatment and post-treatment assessment time points;
5. Cushingoid features: Change from baseline to each of the scheduled on-treatment and post-treatment assessment time points (changes from baseline will be recorded as AEs);

6. Clinical laboratory values: Change from baseline to each of the scheduled on--treatment and post-treatment assessment time points in:
    - Hematology and clinical chemistry
    - Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])
    - Vitamin D level
    - Urinalysis;
7. 12-lead ECG: Change from baseline to Week 12;
8. Eye examination for detection of clinically significant abnormalities (cataracts and/or glaucoma): Change from baseline to Week 12.

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

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

2.2.2. Pharmacokinetic Endpoints

Blood will be collected for vamorolone population PK analysis on Day 1 and Week 2 visits

- For ages 2 to <4 years, blood sampling is within 30 minutes prior to and 1-, 2-, and 6-hours following the first dose of study medication at the Day 1 Visit, and within 30 minutes prior to and 1-, 2- and 6- hours following the daily dose of study medication at the Week 2 Visit.
- For ages 7 to <18 years, blood sampling is within 30 minutes prior to and 1-, 2-, 4-, 6- and 8-hours following the first dose of study medication at the Day 1 Visit, and within 30 minutes prior to and 1-, 2-, 4-, 6- and 8-hours following the first dose of study medication at the Week 2 Visit.

2.2.3. Exploratory Endpoints

For each vamorolone dose level and age group, the following endpoints will be evaluated. Additionally, for selected endpoints, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment to a dose group and also between subjects <12 years and subjects ≥ 12 years:

1. Clinical efficacy assessments: Change from baseline to Week 12 in the Bayley-III Gross Motor scale (ages 2 to <4 years) and PUL Test (ages 7 to <18 years);
2. Behavioral changes (PARS III): Change from baseline to Week 12;
3. Physical functioning (PODCI): Change from baseline to Week 12;
4. Ease of study medication administration (ages 2 to <4 years) and study medication acceptability (ages 7 to <18 years) assessed at each of the scheduled study assessment time points

2.2.4. Pharmacodynamic Endpoints

For each vamorolone dose level and age group, the following pharmacodynamic biomarkers reflective of safety concerns of glucocorticoids will be evaluated. Additionally, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment:

1. Adrenal suppression. First-in-morning serum cortisol levels will be measured 24 hours after the last dose of vamorolone. Cortisol measures falling below 2.4 µg/dL (66nM) for boys below 12 years or 3.6 µg/dL (100 nM) for boys 12 years or older will be considered to be indicative of adrenal suppression;
2. Bone turnover. Measures of serum osteocalcin and serum P1NP are reflective of bone formation, and measures of serum CTX are reflective of bone resorption. Serum osteocalcin, serum CTX, and serum P1NP will be measured;

3. Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance with serum elevations of both insulin and sometimes glucose and HbA1c. Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose and insulin, and hemoglobin A1c (HbA1c) will be measured
4. Exploratory biomarkers for aspects of safety and efficacy, including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4)

2.2.5. Endpoints for Patient-Reported Outcomes

Safety endpoints based on subject reports of AEs are listed in Section 2.2.1.

Additionally, subjects' parent(s)/legal guardian(s) will be asked to complete the PODCI physical function assessment (see **Section 7.4.1**), and the PARS III behavioral assessment (see **Section 7.4.2**).

The parent(s)/legal guardian(s) of each subject in the 2 to <4 years age group will be asked to complete the Ease of Study Medication Administration Assessment (see **Section 7.4.3**); subjects in the 7 to <18 years age group will complete the Study Medication Acceptability Assessment (see **Section 7.4.4**).

No other patient-reported outcomes are planned.

3. STUDY DESIGN

3.1. Overall Study Design

This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning of vamorolone (the investigational medication) 2.0 mg/kg, and 6.0 mg/kg administered daily by liquid oral suspension over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month Treatment Period (Weeks 1 to 12); and up to8 weeks for the Dose-tapering Period (for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study

Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained. Within the 2 to <4 years age group, the initial 10 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 10 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

Within the 7 to <18 years age group (which is including an additional 12 to <18 years age group), both corticosteroid-treated and untreated, the initial 12 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 22 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

The first 6 subjects in each age group at 2.0 mg/kg will serve as the PK/safety run-in cohorts. PK assessments will be performed at Week 2 and, together with the safety assessment during the first 4 weeks of treatment, will be the basis to confirm whether 2.0 and 6.0 mg/kg/day will be used in the subsequent patients or if a dose adjustment is needed to avoid over or under-exposure in patients for any of the two age groups.

The 7 to <18 years age group will be further stratified by glucocorticoid treatment status at study entry, with assignment of subjects 1:1:1:1 to groups: 1. Glucocorticoid-treated subjects, 2.0 mg/kg/day treatment group; 2. Glucocorticoid-treated subjects, 6.0 mg/kg/day treatment group; 3. Glucocorticoid-untreated subjects 2.0 mg/kg/day treatment group; 4. Glucocorticoid-untreated subjects 6.0 mg/kg/day treatment group. An additional group of 10 glucocorticoid-treated 12 to <18 years subjects will be assigned to the 6 mg/kg/day treatment. Glucocorticoid-treated subjects in the 7 to <18 years age group will take their final dose of SoC glucocorticoid therapy for DMD on Baseline Day -1, within 24 hours prior to administration of the first dose of vamorolone study medication.

All subjects will begin their assigned vamorolone treatment on Treatment Period Day 1 and will continue to receive their assigned vamorolone treatment throughout the duration of the 3month- Treatment Period (Weeks 1-12).

At the end of the 3-month Treatment Period (Week 12), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible, or to transition to SoC treatment for DMD (may include glucocorticoids). Subjects completing VBP15-006 and enrolling directly into the expanded access or compassionate use program or transitioning directly to SoC glucocorticoid treatment will not need to taper their vamorolone dose prior to participation in the expanded access or compassionate use program or initiation of SoC glucocorticoid treatment. All subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin the Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.

3.2. Study Summary

This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning vamorolone (the investigational medication) over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

A total of approximately 10 subjects ages 2 to <4 years will be assigned to receive vamorolone 2.0 mg/kg/day. After the first 6 subjects have enrolled at this dose level, the pharmacokinetics of vamorolone after 2 weeks of treatment and the safety of vamorolone during the first week of administration will be assessed. If the vamorolone exposure in terms of AUC is close to the expected target exposure of approximately 1200 ng.h/mL (reference value from 2.0 mg/kg given to 4 to 7-year-old boys in VBP15-004) dosing will proceed as planned with 2.0 mg/kg/day for the remainder of this group and enrollment of the subsequent 10 subjects ages 2 to <4 years assigned to receive 6.0 mg/kg/day can proceed. If the vamorolone exposure at 2.0 mg/kg/day in the initial 6 patients of this age group deviates substantially from the target or if unexpected safety signals are observed, the doses for vamorolone for the subsequent subjects can be adjusted to avoid over- or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range.After the planned DSMB review of the PK and safety data from the safety and PK run-in, subjects receiving 2 mg/kg/day can increase the vamorolone dose up to the confirmed high dose level if deemed appropriate by the investigator.

A total of approximately 34 subjects ages 7 to <18 years will be assigned to receive vamorolone 2.0 mg/kg/day (glucocorticoid-untreated at study entry), 2.0 mg/kg/day (glucocorticoid-treated at study entry), 6.0 mg/kg/day (glucocorticoid-untreated at study entry), or 6.0 mg/kg/day (glucocorticoid-treated at study entry) (n=6 per dose level and glucocorticoid treatment status group plus n=10 for the additional 12 to <18 years age group [6.0 mg/kg/day - glucocorticoid-treated]). The dose cohort of 2.0 mg/kg/day will be enrolled first and the PK and safety assessment from the first 6 subjects in this age group will be used to confirm the doses for the subsequent subjects following the same process as described for the younger age range.Subjects will be assessed for safety and tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning at scheduled visits throughout the study (see **Section 6** for a schedule of study assessments). Screening assessments will be performed prior to assignment to a dose group. All subjects will be assigned to treatment at the Baseline Day -1 Visit.

After completion of Screening and Baseline assessments, and assignment to a dose group for treatment, subjects will return to the study clinic on Day 1 for safety, PK, and PD

assessments prior to administration of the first dose of study medication. Additional study visits will occur at Week 2, Week 6, and Week 12.

The dose cohort of 2.0 mg/kg/ will be enrolled first and the PK of vamorolone after 2 weeks of treatment and the safety of vamorolone during the first week of administration from the first 6 subjects in this age group will be used to confirm the doses for the subsequent subjects following the same process as described for the younger age range.

If the vamorolone exposure at 2.0 mg/kg in the initial 6 patients of this age group deviates substantially from the target or if unexpected safety signals are observed, the high doses level for vamorolone for the subsequent subjects may be adjusted.

Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor regarding study conduct.

If the intended dose of vamorolone is 6mg/kg, but patients weigh 50 kg or more, the daily dose should be capped at 300mg/day. Considering the linearity of vamorolone pharmacokinetics, if the patient is dosed at 2mg/kg, the dose is capped at 100mg daily for patients weighing 50 kg and above.

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit (see **Section 5.3**). Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site.

Subject diaries will be dispensed at the Day 1, Week 2, Week 6, and Week 12 Visits (for subjects participating in the Dose-tapering Period) to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication.

The scheduled Week 12 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling. The scheduled 12-lead ECG, eye examination, PODCI, and PARS III may be completed on the day prior to the final Week 12 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 12 dose of study medication. The scheduled physical examination, weight, height, vital signs, clinical laboratory tests, blood draws for PD biomarker analysis, Ease of Study Medication Administration Assessment (ages 2 to <4 years only)/Study Medication Acceptability Assessment (ages 7 to <18 years only), functional assessments (Bayley-III Gross Motor scale [ages 2 to <4 years] and PUL Test [ages 7 to <18 years]), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 12 dose of study medication.

Subjects who complete the VBP15-006 study assessments through the Week 12 Visit may be given the opportunity to continue to receive vamorolone as part of an expanded access or compassionate use program under separate protocol, or alternatively transition to SoC treatment (including glucocorticoids) for DMD. Standard of care treatment for DMD may be offered to the subject following completion of the VBP15-006 study if the subject, or subject's parent(s) or guardian(s) does not wish to enroll the subject in the expanded access or compassionate use program and/or the Investigator feels it to be in the best interest of the subject.

Subjects who complete the VBP15-006 study and will enroll directly into the expanded access or compassionate use program to continue vamorolone treatment or will transition directly onto SoC glucocorticoid treatment for DMD will be discharged from the VBP15-006 study following completion of all Week 12 assessments. Subjects who will not continue vamorolone treatment in the expanded access or compassionate use program, and who will not transition directly to SoC glucocorticoid treatment for DMD , will have their vamorolone dose tapered during the Dose-tapering Period- prior to discharge from the study.. Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the dose tapering is proceeding according to protocol (see **Section 6.3.5**), to assess potential signs or symptoms of adrenal insufficiency, and to address any questions the parent(s)/guardian(s) may have.. 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 VBP15-006 study prior to the Week 12 Visit should return to the study unit for scheduled Week 12 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun and will not transition directly to SoC glucocorticoids should undergo dose-tapering (see **Section 6.3.5**) following early completion of the Week 12 assessments.

3.3. Dose Group Assignment

Following consent, completion of all Screening assessments, and review of study entry criteria to confirm subject eligibility for the study, the subject may be assigned to treatment at the Baseline Day -1 Visit.

Subjects in the 2 to <4 years age group will be initially assigned to the 2.0 mg/kg/day treatment group. After this treatment group is fully enrolled (n=10) and after pharmacokinetics and safety in the initial 6 children is evaluated and the doses are confirmed, then enrollment into the 2 to <4 years age group assigned to the planned 6.0 mg/kg/day treatment group will take place.

Similarly, subjects in the 7 to <18 years age group will be assigned to the 2.0 mg/kg/day treatment groups first, then subsequently assigned to the planned 6.0 mg/kg/day treatment groups. A total of approximately 34 subjects ages 7 to <18 years will be assigned 1:1:1:1 to receive vamorolone 2.0 mg/kg/day (glucocorticoid-untreated at study entry), 2.0 mg/kg/day (glucocorticoid-treated at study entry), 6.0 mg/kg/day (glucocorticoid-untreated at study entry), or 6.0 mg/kg/day (glucocorticoid-treated at study entry) (n=6 per dose level and glucocorticoid treatment status group plus n=10 for the additional 12 to <18 years age group [6.0 mg/kg/day - glucocorticoid-treated]).

Assignment to dose group will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study. The following information will be sent to the TRiNDS Study Coordinator:

- Participant's Study Subject Identification Number
- Participant's Age at Enrollment
- Participant's glucocorticoid status at entry (7 to <18 years only)

The Study Coordinator will send an email report with the dose level group assignment, and a report generated and sent to the site pharmacy or designated site study staff confirming dose and entering the treatment period.

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1. Subject Enrollment and Identification Log

Subjects will be recruited through the clinics of participating site investigators and other mechanisms including patient registries, national and international networks, and patient foundations. After identification of a possible subject, the site investigator will discuss the study with the subject's parent(s) or legal guardian(s). The subject's parent(s) or guardian(s) will be provided with a copy of the study subject information sheet document and allowed time to consider participation prior to signing. Individuals interested in participating will be asked to come to one of the participating study sites to complete the informed consent process with a site investigator or designee prior to initiation of screening procedures. Subjects will not be excluded on the basis of race, ethnicity, or age, except that the target population for the trial is 2 to <4 years and 7 to <18 years of age.

A subject enrollment log will be maintained at each investigational site for all subjects who are screened for the study, including those not assigned to treatment. Limited data will be collected for these subjects, including age at enrollment and reason for exclusion from the study. Subject enrollment logs will be maintained for all subjects enrolled in the study. This record will also include the dates of subject enrollment and completion/termination.

The Site Investigator will keep a record relating the names of the subjects to their enrollment numbers (subject identification log) to permit efficient verification of data subject files, when required. These logs will be reviewed during routine monitoring calls and/or visits.

4.2. Inclusion Criteria

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

1. Subject's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA)

authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements;

2. Subject has a centrally confirmed (by TRiNDS central genetic counselor[s]) diagnosis of DMD, as defined as:

   - Dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency, and clinical picture consistent with typical DMD, OR
   - Identifiable mutation within the DMD gene (deletion/duplication of one or more exons), where reading frame can be predicted as 'out-of-frame,' and clinical picture consistent with typical DMD, OR
   - Complete dystrophin gene sequencing showing an alteration (point mutation, duplication, other) that is expected to preclude production of the dystrophin protein (i.e., nonsense mutation, deletion/duplication leading to a downstream stop codon), with a clinical picture consistent with typical DMD;

3. Subject is male, 2 to <4 years or 7 to <18 years of age at time of enrollment in the study;

4. If 7 to <18 years of age and currently taking standard of care glucocorticoids for treatment of DMD, subject has been taking standard of care glucocorticoids at stable dose for at least 3 months prior to enrollment in the study and will continue the same stable dose regimen through the date of the Baseline Day -1 Visit. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study];

5. If 7 to <18 years of age, and not currently glucocorticoid-treated, subject has not received oral glucocorticoids or other oral immunosuppressive agents for at least 3 months prior to enrollment. [Note: Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to enrollment or if administered at

stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study];

6. Clinical laboratory test results are within the normal range at the Screening Visit, or if abnormal, are not clinically significant, in the opinion of the Investigator. [Notes: Serum gamma glutamyl transferase (GGT), creatinine, and total bilirubin all must be ≤ upper limit of the normal range at the Screening Visit. An abnormal vitamin D level that is considered clinically significant will not exclude a subject from participation];
7. Subject has evidence of chicken pox immunity as determined by:
    - Presence of IgG antibodies to varicella, as documented by a positive test result from the local laboratory from blood collected during the Screening Period, OR
    - Documentation, provided at the Screening Visit, that the subject has had 2 doses of varicella vaccine, with or without serologic evidence of immunity; the second of the 2 immunizations must have been given at least 14 days prior to assignment to dose group; and
8. Subject and parent(s)/guardian(s) 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 participation in this study if he meets any of the following exclusion criteria:

1. Subject has current or history of major renal or hepatic impairment, diabetes mellitus or immunosuppression;
2. Subject has current or history of chronic systemic fungal or viral infections;
3. Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), or mexrenone (mexrenoate potassium) within 4 weeks prior to enrollment;

4. Subject has a history of primary hyperaldosteronism;
5. Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary];
6. If 2 to <4 years of age, 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 1 month cumulative, with last use at least 3 months prior to enrollment will be considered for eligibility on a case-by-case basis, unless discontinued for intolerance. Inhaled and/or topical glucocorticoids are permitted if last use is at least 4 weeks prior to enrollment or if administered at stable dose beginning at least 4 weeks prior to enrollment and anticipated to be used at the stable dose regimen for the duration of the study];
7. Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;
8. Subject has used idebenone within 4 weeks prior to enrollment;
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;
11. Subject is taking (or has taken within 4 weeks prior to enrollment) herbal remedies and supplements which can impact muscle strength and function (e.g., Co-enzyme Q10, creatine, etc);
12. Subject is taking (or has taken within 3 months prior to enrollment) any medication indicated for DMD, including Exondys51 and Translarna;
13. Subject has been administered a live attenuated vaccine within 14 days prior to the first dose of study medication;

14. Subject is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to enrollment; or
15. Subject has previously been enrolled in the VBP15-006 study or any other vamorolone study.

Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result after vaccination has been completed Subjects may be rescreened in case of ongoing medical condition developing during the screening period, e.g. acute viral infection, or laboratory abnormality that could affect safety if the subject would start vamorolone. In this case, the subject can be rescreened after resolution of the medical condition.

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 attend study visits;
- Difficulty in obtaining blood samples from the subject for safety monitoring;
- The subject experiences an unmanageable or non-tolerable AE/SAE which is considered to be possibly, probably, or definitely related to study drug, in the opinion of the Investigator, and may jeopardize the subject's health;
- 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.

Any subject who discontinues the study prior to the Week 12 Visit should return to the study unit for scheduled Week 12 assessments at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study after study medication dosing has begun and will not transition directly to SoC glucocorticoids should undergo dose-tapering following early completion of the Week 12 assessments. Subjects will also be asked to return to the study unit at the end of the tapering period for a final study visit. In the event a subject withdraws informed consent, no further study procedures should be performed and no additional data should be collected. Any data collected up to the point of withdrawal of informed consent may be used by the Sponsor.

4.5. 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.

Subjects who are participating at a given site at the time it is terminated by the Sponsor will be offered the opportunity to continue to participate in the study at an alternative active site. Subjects who decline the offer to participate at an alternative active site and who will not transition directly to SoC glucocorticoid treatment will need to undergo dose tapering at the time the original site is terminated according to the dose-tapering schedule (see **Section 6.3.5**).

5. TREATMENT OF STUDY SUBJECTS

5.1. Study Medication Administered

Planned vamorolone dose levels:2.0 mg/kg/day and 6.0 mg/kg/day. Doses can be adjusted based on PK and safety data from the first 6 patients per age group to avoid over- or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range.The recommended dose of vamorolone is 6 mg/kg once daily in patients weighing less than 50 kg. In patients weighing 50 kg and above, the high dose level (6 mg/kg/day) must be capped at 300 mg once daily and the low dose level (2mg/kg/day) must be capped at 100 mg once daily.

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

A total of approximately 10 subjects in the 2 to <4 years age group will be enrolled into the 2.0 mg/kg/day treatment group. After the pharmacokinetics and safety is determined in the initial 6 subjects and the doses are confirmed, enrollment will continue for 10 subjects in the 2 to <4 years age group into the planned 6.0 mg/kg/day treatment group.

A total of approximately 12 subjects in the 7 to <18 years age group will be enrolled into the 2.0 mg/kg/day treatment groups (6 untreated at entry, 6 corticosteroid-treated at entry). After the pharmacokinetics and safety is determined in the initial 6 subjects and the doses are confirmed, enrollment will continue for 22 subjects in the 7 to <18 years age group into the planned 6.0 mg/kg/day treatment group (6 untreated at entry, 6 corticosteroid-treated at entry plus 10 for the additional 12 to <18 years age group (glucocorticoid-treated).

Vamorolone 4.0% weight per volume (wt/vol) oral suspension (investigational medicine) will be administered to all subjects once daily for 12 weeks, from Study Day 1 until the Week 12 Visit. At the end of the 12-week Treatment Period, a subset of subjects may receive additional vamorolone treatment in a Dose-tapering Period prior to discharge from the study (see **Section 6.3.5**).

5.2. Identity of Investigational Product

Santhera will supply the following investigational study medication:

Active Substance:	Vamorolone
Strength:	4.0% wt/vol
Dosage Form:	Oral suspension
Formulation:	ROS2
Manufacturer:	Purna Pharmaceuticals NV/SA

5.3. Dosage Schedule and Administration of Study Medication

Subjects in the 2 to <4 years age group and subjects in the 7 to <18 years age group will be administered vamorolone 4.0% wt/vol oral suspension (Formulation ROS2).

All subjects will receive study medication, administered orally once daily for 12 weeks, from Study Day 1 to the Week 12 Visit. At the end of the 12-week Treatment Period, subjects who will not continue directly with further vamorolone or SoC glucocorticoid treatment at the end of the study will be tapered off suspension study medication (Dose-tapering Period,) prior to discharge from the study (see **Section 6.3.5**).

The site pharmacist or designated site study staff will dispense study medication to each subject in 125 mL bottles sufficient for 6 weeks of dosing (as needed for Dose-tapering Period) plus overage at the Day 1 Visit, just prior to dosing, and at the Week 6 Visit (and Week 12 Visit to subjects participating in the Dose-tapering Period), according to the subject's dose assignment and subject body weight (in kg) recorded at the dispensing visit (Day -1 weight for Day 1 dispensing) (see Appendix 15.1 for a dose calculation worksheet).

Each subject's dose (in mL) will be calculated and written on the labels of the bottles to be dispensed at a given visit by trained site staff based on the weight of the subject (in kg) recorded at the dispensing visit. The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled study visit. Study medication suspension dispensed at the Day 1 Visit should be brought in with the subject to the Week 2 Visit, for Week 2 dosing in -clinic and compliance monitoring; this study medication will be returned to the subject at the end of the Week 2 Visit for continued

dosing through the Week 6 Visit; new study medication will not be dispensed at the Week 2 Visit.

All subjects will receive all doses under the supervision of parents or legal guardians or trained study staff. Dosing is to occur at home throughout the 12-week Treatment Period, except at the Day 1, Week 2, Week 6, and Week 12 Visits when dosing will occur at the study site. Subjects should receive each dose of study medication in the morning together with breakfast and at approximately the same time of day. On days where vamorolone is administered in clinic, subjects should arrive fasted for ≥6 hours and should eat breakfast with their dose of study drug.

Vamorolone suspension will be administered orally using a volumetric syringe supplied by the site. Following administration of the dose of study drug suspension, the syringe will be filled once with water, and the water will be administered by mouth using the volumetric syringe. The subject will then drink approximately 50 mL (approximately 2 ounces) of water to ensure the full dose has been ingested. The daily dose of study medication should be taken with breakfast. There are no other food or drink restrictions before or after dosing.

At the Day 1, Week 2, Week 6, and Week 12 study visits, subjects will arrive at the study clinic and will eat breakfast at the study site after collection of fasting lab samples and within 30 minutes prior to administration of the dose of study medication.

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

5.4. Rationale for Dose Selection

Dose levels of the investigational medication were chosen for this study to ensure the safety of subjects participating in the study, to allow suitable population PK assessment and demonstration of PD effects, and to evaluate clinical efficacy. Vamorolone at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day has been demonstrated to be safe and well-tolerated in 48 DMD boys ages 4 to <7 years (12 subjects at each dose level) in a 2-week Phase IIa study (VBP15-002), and a 24-week

Phase II extension study (VBP15-003). The safety of these doses were also evaluated in the same subjects in the ongoing VBP15-LTE 24-month extension study. The safety of the 2.0 mg/kg/day and 6.0 mg/kg/day doses is also being studied in a recently completed 52-week double-blind, comparator- and placebo-controlled study (VBP15-004) in 120 subjects receiving vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo for the first 24 weeks of the study, and then vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for the final 24 weeks of the study.

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

One subject receiving vamorolone 6.0 mg/kg in the Phase II extension study (VBP15-003) who had an incidental early morning cortisol drawn following an AE of presyncope had evidence of adrenal suppression. In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 µg/dL [100 nM]) consistent with chronic adrenal suppression.

Thus, based on the available data in the VBP15-003 study regarding the safety signal of suppression of the adrenal axis, the possibility of adrenal suppression is present in subjects at the 2.0 and 6.0 mg/kg/day dose levels.

The results of the VBP15-003 24-week extension study and the interim results of the ongoing 24-month VBP15-LTE study suggest that doses of vamorolone of 2.0 mg/kg/day

and 6.0 mg/kg/day produced significant enhancement of muscle strength, mobility, and functional exercise capacity.

The results of the VBP15-004 24-week double-blind, placebo- and prednisone-controlled study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day showed significant enhancement of muscle strength, mobility, and functional exercise capacity vs. placebo. This study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day did not cause the stunting of growth and deleterious changes in bone biomarkers seen with prednisone in this head-to-head comparison. Additional efficacy and safety results can be found in the current IB.

Based on the safety and efficacy results observed in these earlier studies in DMD boys aged 4 to 7 years, doses of vamorolone at 2.0 mg/kg/day and 6.0 mg/kg/day were chosen for evaluation in the current study enrolling younger and older subjects. For the 6 mg/kg, a cap dose of 300 mg once daily has been established for children weighing more than 50 kg based on pharmacokinetic modeling to account for the expected high pharmacokinetic exposures due to growth and maturation of the pediatric population. Since the effect of age on the pharmacokinetics of vamorolone is not yet established and since this is the first time that the to-be-marketed formulation of ROS2 will be administered to DMD boys, a PK/safety run-in at 2.0 mg/kg/day is included into the study to evaluate the PK and safety in subjects 2 to <4 and 7 to <18 years of age and to adjust the doses if needed to avoid over- and underexposure of vamorolone in these age groups and to ensure a consistent vamorolone AUC across the entire pediatric age range. All doses of vamorolone will be administered in the morning with breakfast.

5.5. Treatment Compliance

Subject compliance with the dosing schedule will be assessed by site maintenance of accurate study drug dispensing and return records, and accurate recording of incomplete or missed doses by completion of a diary by the subject's parent or guardian. 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(s) or guardian(s) with regard to proper dosing of study medication and completion of subject diaries and

will reinforce the importance of taking all study medication per protocol instructions. Doses of study drug on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered at the participating study site by a trained investigational staff member. All incomplete or missed doses are to be documented in the source document and on the appropriate eCRF page. The volume of unused study medication remaining in each bottle returned, as measured by the weight of returned bottles, will be documented in the source documents and on the appropriate eCRF page.

5.6. Study Drug Dose Interruption or Discontinuation

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

In the event any clinical observation suggests an intolerability of an individual subject to the study medication, in the opinion of the Investigator, the case should be discussed with the Medical Monitor within 24 hours and study drug discontinuation should be considered. In view of the potential effect of the study drugs on adrenal glands, the study drugs cannot be discontinued suddenly. In case study drug needs to be discontinued, for whatever reason, the dose tapering process described for the end of the treatment period should be followed. If a subject discontinues study drug due to intolerability, the subject will be withdrawn from the study. The subject should return to the study site for completion of Week 12 assessments at the time of early withdrawal, prior to participation in the Dose -tapering Period, as appropriate. Any AE still ongoing at the time of study drug discontinuation will be monitored until it has returned to baseline status, stabilized, or the Investigator and Sponsor agree that follow-up is no longer needed.

5.7. Prior and Concomitant Medications and Therapies

5.7.1. Prior Therapy

All medications (prescription and over-the-counter [OTC]) taken within 3 months prior to the Screening Visit through Baseline Day -1 (until just prior to administration of the first

dose of study medication) will be captured as prior medications (Medication History) in the source document and the eCRF, including the name of the medication (or device or procedure), the dosage and regimen, the indication, and the treatment start and stop dates. All past (lifetime) steroid use will be recorded.

5.7.2. Concomitant Therapies

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

All medications (prescription and OTC) taken during the study must be recorded in the source documents and in the eCRF, including the name of the medication, dosage and regimen, reason for therapy, and treatment start and stop dates. Furthermore, each change in concomitant medication (e.g., new treatment, discontinuation of treatment, or change in dosage/regimen) during the study must be documented in the same manner. Details of any non-pharmacological therapies (e.g., devices, procedures), including name, reason for therapy (i.e., DMD or non-DMD), 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), and mexrenone (mexrenoate potassium): use must be discontinued at least 4 weeks prior to enrollment;
- Oral glucocorticoids or other immunosuppressive agents. Subjects in the 2 to <4 years age group who have received prior treatment with oral immunosuppressive

agents are ineligible for study entry. [Note: Past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to enrollment, will be considered for eligibility on a case-by-case basis, unless discontinued for intolerance.] Subjects in the 7 to <18 years age group who have been receiving SoC glucocorticoids for treatment of DMD for at least 3 months prior to enrollment in the study will continue the same stable dose regimen through the date of the Baseline Day-1 Visit; the SoC glucocorticoids must be discontinued on Day 1. Subjects in the 7 to <18 years age group who are not currently receiving oral glucocorticoids or other oral immunosuppressive agents must have discontinued all such agents at least 3 months prior to enrollment. [Note: Inhaled and/or topical glucocorticoids are permitted but must be administered at stable dose beginning at least 4 weeks prior to enrollment, and anticipated to be used at the stable dose regimen for the duration of the study.]

- Idebenone: use must be discontinued at least 4 weeks prior to enrollment;
- Live attenuated vaccines: use must be avoided within 14 days prior to first dose of study medication and for the duration of participation in the study;
- Any investigational medications other than vamorolone: use must be discontinued at least 3 months prior to enrollment;
- Other medications indicated for the treatment of DMD, including Exondys 51 and Translarna: use must be discontinued at least 3 months prior to enrollment;
- Any approved medications or herbal remedies which can impact strength and function (including, but not limited to, Co-enzyme Q10 and creatine): use must be discontinued at least 4 weeks prior to enrollment.

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

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

5.7.4. Permitted Therapies

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

5.7.5. Hydrocortisone

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

5.7.6. Vitamin D

Serum Vitamin D levels will be measured at Screening and at the Week 12 Visit. Vitamin D insufficiency and deficiency (i.e., serum 25[OH] D concentration less than 20 ng/mL [50 nmol/L]) will be treated with high doses of Vitamin D supplement according to local site guidelines. Vitamin D supplements will be recorded in the source document and in the eCRF.

5.8. Study Medication Management

5.8.1. Packaging and Labeling of Study Medication

The site pharmacist or designated study staff will receive clinical trial material (CTM) when all regulatory requirements have been completed by the site. Additional CTM will be available upon request. The Study Sponsor through the designated central pharmacy will provide CTM in bulk quantities sufficient to satisfy the protocol requirement. Vamorolone will be shipped in bulk to the study site's registered pharmacist or designated study staff in suitably labeled study cartons. Cartons will contain study medication packaged in sterile 125 mL (4 oz) amber bottles with a 100 mL fill volume with child-resistant cap with a 28 mm bottle press-in adapter.

Bottles of investigational medication suspension will contain 4.0 grams of vamorolone/100 mL (4.0% orange-flavored suspension).

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

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

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

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

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 CTM should be stored at refrigerated temperature (2ºC - 8ºC; 36ºF - 46ºF). Excursions to ambient temperature are allowed (see Pharmacy Manual for details).

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

5.8.3. Study Medication Shipping and Handling

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. Study sites will receive CTM in bulk in sufficient quantity to satisfy the protocol requirements.

Clinical trial material will only be dispensed to the subject once the subject's parent/guardian has (1) a signed informed consent form (ICF) and HIPAA (as applicable) authorization on file, (2) met all eligibility criteria for entry into the study, (3) completed all Pretreatment requirements, and (4) been assigned to treatment.

It is essential to this study that all CTM be accounted for during the study period. All unused (i.e., undispensed; dispensed and returned) study medication will be retained at the study site for reconciliation by the Sponsor's study monitors (or designees) during routine monitoring visits. Final disposition of all unused CTM will be coordinated by the Sponsor's study monitors (or designees) throughout and at the end of the study (see **Section 5.8.4**).

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

At the Baseline (Day -1) Visit, subjects will be assigned to treatment by communication with the TRiNDS Study Coordinator. At the Day 1 Visit, the trained site staff will record the dose level, volume in mL per suspension dose, and dispense date on the bottle label(s). Labeled study drug supplies sufficient to last until the Week 6 Visit will be dispensed to each subject. The first dose of study medication will be administered in clinic on Study Day 1. The initial drug supply will be sufficient to allow for the Week 6 Visit to occur on the latest date permissible within the protocol -specified visit window (6 weeks ± 3 days). No additional study drug supplies will be dispensed at the Week 2 Visit.

Additional bulk CTM supply will be packaged, labeled (as described above) and couriered to the site as needed to satisfy enrollment.

5.8.4. Study Medication Accountability

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

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

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

5.9. Procedures for Assigning Subject Identification Numbers

This is a non-randomized, open-label study. Following the signing of the written Informed Consent Form (ICF), subjects will be assigned, by age group (and by glucocorticoid treatment status at entry for subjects in the 7 to <18 years age group), a unique site-specific 6-digit subject ID number in sequential order of screening into the study. The site will notify the TRiNDS Coordinating Center of the newly assigned subject number.

All data for all subjects whose parent(s) or guardian(s) signs the ICF for the study will be identified using the unique 6-digit subject ID number. Subjects are considered to be enrolled in the study when the parent(s) or guardian(s) signs the study specific ICF at Screening.

These subject ID numbers assigned upon signing of the written ICF will be retained through enrollment and throughout participation in the study. Subject ID numbers assigned to subjects who fail screening may not be used again.

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

6. STUDY SCHEDULE

6.1. Time and Events Schedule

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

- **Pretreatment Screening Period:** The up-to-32-day interval, from subject's parent(s) or guardian(s) signing of the Informed Consent/HIPAA authorization until completion of all designated screening procedures, at least 24 hours prior to the first dose of study medication. All screening procedures must be completed by Day -1.
- **Pretreatment Baseline Period:** The 24-hour period immediately prior to administration of the first dose of study medication (Day -1). Subjects meeting all eligibility criteria will be assigned to a treatment group on Baseline Day -1, within 24 hours prior to administration of the first dose of study medication.
- **Treatment Period:** The 12-week interval starting with administration of the first dose of study medication on Study Day 1 and continuing through the time of completion of all scheduled Week 12 Visit assessments. Subjects who will continue directly with further vamorolone or SoC glucocorticoid treatment will be discharged from the study following completion of all scheduled Week 12 assessments.
- **Dose-tapering Period:** The interval following the end of the 12-week Treatment Period during which subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin a Dose tapering-period during which the dose of study medication will be progressively reduced and discontinued (see **Section 6.3.5**). Subjects will be discharged from the study following completion of all final Dose-tapering Period assessments.
- The procedures to be completed at each visit during each study period are presented in the Schedule of Study Activities (**Table 2**) and in the sections that follow. (Note: For each visit the acceptable time window around the planned visit

date, where applicable, is provided.) Detailed descriptions of the assessments and the definitions of study endpoints are provided in Section 7 and Section 2, respectively. Any deviation from study procedures should be noted in the source documents and in the Clinical Trial Management Software (CTMS), and significant deviations should be reported immediately to the Sponsor.

- Overall, up to approximately 21 weeks are allocated for each subject to complete the study, including a 32-day Pretreatment Screening Period, a one-day Pretreatment Baseline Period, a 12-week Treatment Period, plus a Dose -Tapering Period, as applicable. Upon the completion of the study, subjects may have the option to receive additional vamorolone treatment by enrolling in an expanded access or compassionate use program.
- Subjects who continue directly with vamorolone treatment by expanded access or compassionate use or who transition directly to SoC glucocorticoid treatment for DMD will be discharged from the VBP15006 study following completion of all Week 12 assessments and will not participate in the Dose tapering Period.
- Subjects who do not enroll directly into an expanded access or compassionate use program and who do not transition directly to SoC glucocorticoid treatment for DMD will participate in the Dose-tapering Period and will be discharged from the VBP15006 study following completion of all Dose tapering Period assessments.

Table 2. Schedule of Study Activities

	Pretreatment Period		**Treatment Period**				**Dose-tapering Period[a]**	
	SCR	**BL**						
	Day			**Week**				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Informed consent	X							
Enrollment[f]	X							
Inclusion/exclusion criteria	X							
Assignment[g]		X						
Demographics	X							
Medical history	X							

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	-33 to -2	-1[b]	Day 1[b]	2[c] (±1d)	6[c] (±3d)	12[c,d] (±5d)	14	16[c,d,e] (±1d)
Medication history	X	X						
Physical examination	X	X[ee]			X	X		X
Cushingoid features	X	X			X	X		X
Height[h]	X					X		
Weight	X	X		X	X	X		X
Vital signs[i]	X	X	X[j]	X	X	X		X
Blood for clinical labs[k]	X		X[l]		X[l]	X[l]		X
Blood for vitamin D	X					X[l]		
Confirmation of varicella immunity	X							
Urinalysis[m]	X		X		X	X		X
Blood for serum PD biomarker panel[n]			X[l]			X[l]		
Fasting blood for insulin, glucose			X[l]	X[l]	X[l]	X[l]		
Blood for HbA1c	X					X[l]		
Blood for morning cortisol[o]			X[l]			X[l]		
Blood for Plasma PK			X[p]	X[p]				
12-lead ECG[q]	X					X		
Eye examination	X					X		
Dispense study medication			X		X	X[r]		
Return study medication/ compliance monitoring				X[s]	X	X		X
Study medication dosing[t]			X →			X		
Study medication dose tapering						X[r] →		X
Telephone call to subject							X[u]	
Bayley-III Gross Motor[v]	X	X				X		
PUL Test[w]	X	X				X		
Pediatric Outcomes Data Collection Instrument (PODCI)	X					X		
PARS III	X					X		

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	-33 to -2	-1[b]	Day 1[b]	2[c] (±1d)	6[c] (±3d)	12[c,d] (±5d)	14	16[c,d,e] (±1d)
Ease of Study Medication Administration Assessment[x]					X	X		
Study Medication Acceptability Assessment[y]					X	X		
Dispense subject diaries[z]			X	X	X	X[q]		
Return subject diaries				X	X	X		X
AE/SAE recording[aa]	X	→	→	→	→	→	→	X[bb]
Prior/Concomitant medications	X	→	→	→	→	→	→	X
Discharge from study						X[cc]		X[dd]

BL = Baseline; d = day(s); SCR = Screening.

a. Only subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the 12-week Treatment Period will begin a Dose tapering Period during which the dose of study medication will be progressively reduced and discontinued.

b. All Day -1 assessments must be completed within 24 hours prior to administration of the first dose of study medication on Day 1.

c. Time windows around the Week 2, Week 6, and Week 12 Visits are allowances from date of Day 1 Visit; time window around Week 16 Visit is allowance from date of Week 12 Visit.

d. Subjects who prematurely discontinue from the study prior to Week 12 should complete the Week 12 assessments at the time of early withdrawal and undergo Dose-tapering, where appropriate.

e. Subjects will have one study site visit during the Dose-tapering Period, at one week after the dose of study medication has been discontinued (Week 16).

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

g. Assignment to a treatment group is done by the TRiNDS Study Coordinator at the Baseline Day -1 Visit.

h. Standing height will be measured for subjects in the 2 to <4 years age group and participants ages 7 to <18 years who can stand independently; ulnar length will be measured and used to calculate height for subjects in the 7 to <18 years age group.

i. Sitting blood pressure, body temperature, respiratory rate, and heart rate.

j. Vital signs recorded prior to administration of the first dose of study drug at the Day 1 Visit.

k. Blood for hematology, chemistry, and lipids. All samples should be collected after subject has fasted for >6 hours.

l. Blood samples collected after subjects have fasted for ≥ 6 hours, and prior to daily dose of study drug.

m. Urinalysis by dipstick and microscopic analysis.

n. Blood collected for PD biomarkers at Day 1 pre-dose and Week 12 predose includes exploratory safety outcomes of bone turnover (osteocalcin, CTX, P1NP), as well as in the additional 12 to <18 years age group, suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4). Blood remaining from collected blood samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies for aspects of safety and efficacy. All pre-dose samples should be collected after subject has fasted for ≥ 6 hours.

o. Blood collected for morning cortisol should be collected before 10 AM local time.

p. Blood samples for population PK analysis will be collected within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), and within 30 minutes pre-dose, and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years).

q. 12-lead ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.

r. Only for subjects participating in the Dose-tapering Period.

s. Study medication brought by subjects to the Week 2 Visit for dosing and compliance assessment will be redispensed to subjects at the end of the visit.

t. During the Treatment Period, the dose of study medication on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered with breakfast in the study clinic. All other doses will be taken with breakfast at home.

u. Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the study drug tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have.

v. Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale will be completed for subjects in the 2 to <4 years age group only.

w. Performance of Upper Limb (PUL) test will be performed by subjects in the 7 to <18 years age group only.

x. Ease of Study Medication Administration Assessment will be completed for subjects in the 2 to <4 years age group only.

y. Study Medication Acceptability Assessment will be completed by subjects in the 7 to <18 years age group only.

z. Subject diaries used to record any changes in concomitant medications taken, any AEs experienced during the study, and any incomplete or missed doses of study medication.

aa. All AEs and SAEs must be recorded in the source documents and eCRF from the date of the subject's written informed consent until the final Week 16 Visit or the subject's participation in the study is completed (SAEs through 30 days after final dose study drug). Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator believes follow-up is not necessary.

bb. For subjects who do not continue into an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in VBP15-006 Dose-tapering Period to confirm the final SAE status of the subject.

cc. Subjects who elect to continue vamorolone therapy by enrolling directly into an expanded access or compassionate use program or who will transition directly to SoC glucocorticoid therapy may be discharged from the study following completion of all final Week 12 assessments.

dd. Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments (Week 16).

ee. Including Ambulatory status.

6.2. Informed Consent and Assent Procedures

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

The parent(s) or guardian(s) of all subjects are to give informed consent in accordance with the Declaration of Helsinki, US 21 Code of Federal Regulations (CFR) Part 50, International Conference on Harmonisation (ICH) guidelines on GCP and all applicable laws, guidances, and directives of the jurisdiction where the study is being conducted.

The parent(s) or guardian(s) of subjects who choose to enroll in this study will give written informed consent during the Screening Period. The Investigator (or designated staff) will obtain the written informed consent from the subject's parent(s) or guardian(s) prior to performing any study-related procedures. Each subject's parent(s) or guardian(s) will receive an explanation of the nature and purposes of the study from the Investigator or designee. Time will be given to the parent(s)/guardian(s) to ask questions and make their decision as to whether they would like for their child to participate. The Investigator or designee will ensure the study is appropriate for the subject. Reasons for exclusion will be documented for subjects found ineligible during the Pretreatment Period. The subject's parent(s) or guardian(s) 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(s) or guardian(s) will be asked if s/he understands that the subject is free to withdraw from the study at any time without prejudice. Each subject's parent(s) or guardian(s) will be required to sign a study ICF (and HIPAA authorization, if applicable) before any procedures are performed for the study; both parents or guardians will sign the ICF in jurisdictions where this is required.

If applicable, the assent of the child himself will also be obtained, if possible, in writing per individual where a child is intellectually capable of assenting (and in accordance with local regulations), and with the permission of the parent(s)/guardian(s).

The Investigator or designee will obtain written informed consent from each subject's parent(s) or guardian(s) prior to the subject's participation in the study using ICFs approved by the appropriate IRB/IEC at each site. Consent must be obtained in

accordance with the principles outlined in the current version of the Declaration of Helsinki. Informed Consent Forms must be dated and signed by the Investigator or designee and the subject's legal representative(s), and the original signed consent form must be kept by the Investigator in the study subject's file. "Legal representative" means an individual whom a judicial or other body has authorized under applicable law to consent on behalf of a prospective study subject to the subject's participation in the procedure(s) involved in the research. The Study Monitor will ensure that the ICF has been signed by the subject's legal representative(s). The study subject's legal representative(s) will receive a copy of the signed consent form.

6.2.1. HIPAA and Protected Health Information

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

6.3. Visit Schedule and Procedures

During the study, there will be a total of up to seven study site visits: Pretreatment Screening Visit (screening procedures can be performed on more than one day if necessary); Pretreatment Baseline Day -1 Visit; Treatment Period Day 1 and Weeks 2, 6, and 12 Visits, and final Dose-tapering Period Week 16 Visit. In addition, to facilitate completion of all required Week 12 assessments, some of the assessments scheduled for the Week 12 Visit may be completed on the day prior to the Week 12 dose of study medication, if needed (see **Section 6.3.4**).

Each subject will receive the assigned, open-label study medication at stable daily dose for a period of 12 weeks. Following completion of the 12-week Treatment Period, all subjects who will not be continuing directly to receive vamorolone by expanded access or

compassionate use or transitioning directly to SoC glucocorticoid therapy will taper their study medication during the Dose-tapering Period (up to 8 weeks) and will return to the study site for study assessments at the end of the Dose-tapering Period, See **Section 7** for a detailed description of the safety, PK, clinical efficacy, PD, behavior and neuropsychology, physical functioning, and sleep-wake activity assessments to be performed during this study.

6.3.1. Screening Period (Day -33 to -2)

The Investigator or study staff will discuss with each subject and the subject's parent(s) or legal guardian(s) the nature and purpose of the study and the required study procedures. The subject's medical history and medication history will be reviewed to determine initial eligibility for participation in the study and the subject's de-identified dystrophin genetic test report and/or muscle biopsy report will be sent to the Central Genetic Counselor(s) for confirmation that the subject meets the DMD diagnostic inclusion criteria. Demographic information will be collected.

Following the signing of the written ICF, subjects will be considered to be enrolled in the study and will be assigned a unique site-specific 6-digit subject ID number that will be comprised of protocol, site, and subject numbers in sequential order of screening into the study. All data will be identified using the unique subject ID number. The site Investigator will keep a record relating the names of the subjects to their subject ID numbers (subject identification log) to permit efficient verification of data subject files, when required. This record will also include the dates of subject enrollment and completion/termination. The Coordinating Center will not collect names or other identifiers except dates (diagnosis, study visits), age at enrollment, and the subject ID number.

Subjects will undergo the procedures in the bulleted list below and in **Table 2** during the Screening Period. The procedures may be completed over the course of several visits, if necessary, but all scheduled Screening procedures must be completed within the timeframe of Day -33 to Day -2, and the actual date each procedure is performed must be recorded in the source document and eCRF. Any parameter/test may be repeated at the

Investigator's discretion during Pretreatment Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result.

Subjects meeting all Screening eligibility tests will be assigned to treatment at the Baseline Day -1 Visit.

- Enrollment (see **Section 5.9**)
- Review of the Inclusion and Exclusion Criteria (see **Sections 4.2** and **4.3)**
- Recording of the medical history, including any toxicities or allergy-related events to prior treatments (see **Section 7.2.1**)
- Recording of prior medications (Medication History) (see **Section 5.7.1**)
- Complete physical examination, including weight (in kilograms) and height (in cm) and assessment of cushingoid features (see **Section 7.2.2**)
- Recording of vital signs (sitting blood pressure, heart rate, body temperature, respiratory rate) (see **Section 7.2.3**)
- Collection of blood for clinical laboratory testing (hematology, clinical chemistry, lipids, and vitamin D) and collection of urine for urinalysis (see **Section 7.2.4**)
- Collection of blood for HbA1c (see **Section 7.2.6**)
- Confirmation of chicken pox immunity (see **Section 7.2.5**)
- 12-lead ECG (see **Section 7.2.9**)
- Eye exam (see **Section 7.2.10**)
- Bayley-III Gross Motor scale (ages 2 to <4 years only) (see **Section 7.3.1**)
- PUL Test (ages 7 to <18 years only) (see **Section 7.3.2**)
- Pediatric Outcomes Data Collection Instrument questionnaire (PODCI) (see **Section 7.4.1**)
- PARS III questionnaire (see **Section 7.4.2**)

- Recording of AEs and SAEs beginning at the time written informed consent is obtained (see **Section 7.6**)

6.3.2. Baseline Period (Day -1) Visit

Subjects who have met all study eligibility criteria will return to the study site during the Pretreatment Baseline Period (Day -1, the 24-hour interval immediately preceding administration of the first dose of study medication) for baseline assessments and will be assigned to treatment group by the TRiNDS Study Coordinator at the Baseline Day -1 Visit. Subjects will retain their 6-digit study identification number which was assigned during the Screening Period.

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

- Physical examination including weight (in kilograms) and assessment of cushingoid features and ambulatory status (see **Section 7.2.2**)
- Recording of vital signs (sitting blood pressure, heart rate, body temperature, respiratory rate) (see **Section 7.2.3**)
- Bayley-III Gross Motor scale **(ages 2 to <4 years only)** (see **Section 7.3.1**)
- PUL Test **(ages 7 to <18 years only)** (see **Section 7.3.2**)
- Recording of AEs and SAEs; review of all AEs for resolution status and date (see **Section 7.6**)
- Recording of prior medications (Medication History) (see **Section 5.7.1**)
- Assignment (see **Section 3.3**)

6.3.3. Treatment Period Day 1 Visit

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

Subjects will take the first dose of study medication in clinic on the day after the Pretreatment Baseline (Day -1) Visit. Breakfast will be served at the study site after the blood and urine collections for clinical laboratory tests and the blood draws for PD biomarkers, and within 30 minutes prior to administration of the dose of study medication.

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

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

- Recording of vital signs (sitting blood pressure, heart rate, body temperature, respiratory rate) prior to administration of first dose of study drug (see **Section 7.2.3**)
- Clinical laboratory evaluation including hematology, clinical chemistry, lipids, and urinalysis tests, prior to administration of first dose of study drug (see **Section 7.2.4**)
- Blood samples for PD biomarkers including fasting glucose and insulin, osteocalcin, CTX, serum P1NP, and morning cortisol, prior to administration of first dose of study drug (see **Section 7.2.6**). Blood remaining from collected samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies , including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4).
- Blood samples for plasma PK, collected within 30 minutes prior to administration of first dose of study medication and at various time points post-dose (see **Section 7.2.7**)

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

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

6.3.4. Treatment Period (Weeks 1-12)

Subjects will return to the study site for safety, PK, clinical efficacy, PD, behavior and neuropsychology, and physical functioning assessments beginning at Week 2 and continuing through the Week 12 Visit, according to the schedule of assessments in **Table 2**.

Subjects will continue to receive daily oral administration of vamorolone suspension according to their assigned treatment throughout the 12-week Treatment Period. The daily dose of study medication should be taken with breakfast.Dosing is to occur at home throughout the 12-week Treatment Period, except at the Week 2, 6, and 12 study visits, when dosing will occur at the study site. Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the Weeks 2, 6, and 12 study visits. Breakfast will be served at the study site after the blood collections for clinical laboratory tests (all visits) and Vitamin D (Week 12 only); pre-dose blood draw for plasma PK analysis (Week 2 only); and blood draws for PD biomarkers, including insulin, glucose, HbA1c, morning cortisol, osteocalcin, CTX, P1NP (Week 12 only); and within 30 minutes prior to administration of the dose of study medication. Blood samples for plasma PK analysis will also be collected pre-dose and at several time points post-dose at the Week 2 Visit (see **Section 7.2.7**). Ease of Administration of Study Medication Administration (ages 2 to <4 years) and Study Medication Acceptability (7 to <18 years) will be assessed at the Weeks 6 and 12 Visits. Apart from blood and urine sample collections, all other

scheduled assessments should be performed after administration of the study medication in clinic.

Study medication will be dispensed at Weeks 6 and 12 (for subjects participating in the Dose-tapering Period) Visits, and returned at Weeks 2 (compliance monitoring only; will be re-dispensed at end of visit), 6 and 12 for all subjects. Subjects will receive subject diaries at each study visit beginning at Day 1 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, changes to concomitant medications/therapies, and any missed or incomplete doses of study medication.

Safety assessments will be conducted at the Week 2 Visit.

Clinical efficacy assessments (Bayley-III Gross Motor scale [ages 2 to <4 years] and PUL Test [ages 7 to <18 years]) and the subject reported outcomes (PARS III, PODCI, Ease of Study Medication Administration Assessment (ages 2 to <4 years), and Study Medication Acceptability Assessment (7 to <18 years) will be conducted as specified in the schedule of study activities.

Weight will be recorded at every visit and height will be measured at the Week 12 Visit. Vital signs will be recorded at each study visit. A physical examination including assessment of cushingoid features will be performed at Weeks 6 and 12. A 12-lead ECG will be recorded at Week 12. Blood and urine samples for clinical laboratory tests and blood for the serum PD biomarker panel will be collected at scheduled visits throughout the study (**Table 2**). An eye examination to exclude cataracts and glaucoma will be performed at Week 12. Adverse events, including SAEs, and concomitant medications will be assessed at each study visit and recorded throughout the study.

The scheduled Week 12 assessments may be performed over a 2-day period, if necessary, to facilitate scheduling. The scheduled 12-lead ECG, eye examination, PODCI, and PARS III may be completed on the day prior to the final Week 12 dose of study medication; alternatively, these assessments may be performed on the date of the final Week 12 dose of study medication. The scheduled physical examination, weight, height, vital signs, clinical laboratory tests, blood draws for PD biomarker analysis, Ease of

Study Medication Administration Assessment (ages 2 to <4 years only)/Study Medication Acceptability Assessment (ages 7 to <18 years only), functional assessments (Bayley-III Gross Motor scale [ages 2 to <4 years] and PUL Test [ages 7 to <18 years]), recording of AEs/SAEs and concomitant medications, and return of subject diaries should be performed on the date of the final Week 12 dose of study medication.

Subjects who complete the VBP15-006 study and will enroll directly into the expanded access or compassionate use program to continue vamorolone treatment or will transition directly onto SoC glucocorticoid treatment for DMD will be discharged from the VBP15-006 study following completion of all Week 12 assessments. Subjects who will not continue vamorolone treatment in the expanded access or compassionate use program, and who will not transition directly to SoC glucocorticoid treatment for DMD, will have their vamorolone dose tapered prior to discharge from the study (see **Section 6.3.5**). Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have.

6.3.5. Dose-tapering Period (Weeks 13-16)

All subjects who complete the study and opt not to continue directly with vamorolone treatment in an expanded access or compassionate use program, and who will not transition directly to SoC glucocorticoid treatment for DMD, will participate in a Dose tapering Period during which the dose of study medication will be progressively reduced. In addition, subjects who discontinue study medication after the first dose and prior to Week 12 will also participate in the Dose-tapering Period if possible and if, in the opinion of the Investigator, it is safe to do so.

The purpose of dose-tapering is to aid in re-establishment of adrenal function if adrenal suppression has occurred during vamorolone treatment. Dose tapering will be performed in a stepwise manner, according to the subject's most recent calculated liquid formulation dose during the 12-week Treatment Period.

Dose tapering for vamorolone will be performed as outlined in **Table 3**. For subjects who have completed the Treatment Period, the subject's weight recorded at the Week 12 Visit will be used to calculate dose volume for all dose de-escalations during the Dose-tapering Period.

Table 3. Study medication dose tapering recommendation

Week 12 Dose Level	Decreased by 50% for 1 week	Decreased by 50% for 1 week	Decreased by 60% for 1 week
2 mg/kg/day	1 mg/kg/day	0.5 mg/kg/day	0.2 mg/kg/day Then stop vamorolone
6 mg/kg/day	3 mg/kg/day	1.5 mg/kg/day	0.6 mg/kg/day Then stop vamorolone

For the steroid-treated 7 to <18 years age group on 6 mg/kg/day

Week 12 Dose Level	Decreased by 25% for 2 weeks	Decreased by 33% for 2 weeks	Decreased by 33% for 2 weeks
6 mg/kg/day	4.5 mg/kg/day	3 mg/kg/day	2 mg/kg/day Then start hydrocortisone

From [Bowden at al. 2019]

Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have. In addition, subjects will be assessed promptly for adrenal suppression if unwell at any time during the Dose-Tapering Period.

For subjects in the steroid-treated 7 to <18 years age group on 6 mg/kg/day, the tapering period could be extended for 2 additional 2 weeks to a maximum of 8 weeks, if medically warranted. Further progressive glucocorticoid-tapering should then be done on hydrocortisone, as indicated above. There will be a low threshold for recommending commencement of daily oral prednisone or hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these circumstances.

The end-of-study visit (Week 16) will be scheduled approximately one week after the final de-escalation to 0 mg but 1 to 3 days after the last dose of vamorolone, i.e. after

starting hydrocortisone, in the steroid-treated 7 to <18 years age group on 6 mg/kg/day at Week 12.

Subjects will have non-fasting but morning blood and urine samples collected for clinical laboratory tests at the Week 16 Visit. Subjects will also have a physical examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including SAEs, and concomitant medications will be assessed. Subject diaries will be returned and reviewed with site staff.

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

6.4. Subject Discontinuation

Any subject who chooses to withdraw from the study after Day 1 and prior to the Week 12 Visit should return to the study site for Week 12 assessments at the time of early withdrawal, whenever possible (see **Section 6.3.4**), assuming the subject has not withdrawn consent, and will participate in the Dose-tapering Period,. Site personnel will document and evaluate all assessments, including any AEs and lab results, in the source documents and eCRF.

In the event that a subject withdraws early from the study prior to the Week 12 Visit, the reason for discontinuation must be fully documented in the source documents and the eCRF.

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

Subjects who discontinue study medication should follow the procedures for dose tapering, as outlined in **Section 6.3.5** and **Table 3**.

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

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

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

The final end-of-study visit will be scheduled approximately one week after the final dose tapering to 0 mg/kg subjects if it is more than 4 weeks after last treatment dose (i.e., Week 12 dose, if treatment was not discontinued)..

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

Subjects will be discharged from the study following final Early Termination/Week 16 assessments.

6.5. Subject and Study Completion

A completed subject is defined as a subject who has completed the Treatment Period, through the Week 12 Visit assessments, and Dose-tapering Period, if applicable, and has not prematurely withdrawn from the study for any reason. The study will be completed when the final subject has completed his final study visit (“last subject, last visit”).

7. STUDY ASSESSMENTS AND MEASUREMENTS

7.1. Demographic Assessments

Demographic information (age at enrollment, race and ethnicity; date of birth may also be collected where allowed) will be collected during the Pretreatment Screening Period and will be recorded on the appropriate eCRF page.

7.2. Safety and Tolerability Assessments

7.2.1. Medical History

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

7.2.2. Physical Examination, Cushingoid Features, Ambulatory status, Weight, and Height

A complete physical examination will be performed at Screening, Baseline Day -1, Week 6, and Week 12, and at the final Dose-tapering Period Visit, and will include examination of the following: head, eyes, ears, nose, and throat, neck *(including an examination of the thyroid),* heart, lungs, abdomen *(including an examination of the liver and spleen),* lymph nodes, extremities, nervous system, and skin. Particular attention will be paid to any sign or symptom of infection. Clinically significant changes from baseline should be recorded as AEs. Particular attention will be paid in identifying any sign of cushingoid features, which should also be recorded as AEs if they first appear or worsen

during the study. Ambulatory status as assessed by the investigator will be recorded at Baseline.

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

Height (in cm) will be recorded at Screening and Week 12. Standing height will be recorded for subjects in the 2 to <4 years age group and all participants in the 7 to <18 years age group who can stand independently.

Weight (in kg) will be recorded at Screening, Baseline, Day -1, Week 2, Week 6, and Week 12, and at the final Week 16 Dose-tapering Visit. Weight recorded at the dispensing visit will be used to calculate the study medication dose for the subsequent dispensing interval (see **Section 5.3**).

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

7.2.3. Vital Signs

Vital signs (sitting blood pressure, heart rate, respiration rate, and body temperature) will be recorded at Screening, Baseline Day -1, Day 1 pre-dose, Week 2, Week 6, and Week 12, and at the final Dose-tapering Visit. Vital signs should be recorded after the subject has been resting for at least 5 minutes. Body temperature may be measured using oral, tympanic, or temporal recording devices; however, the same methodology must be used for all assessments of a given subject.

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

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

7.2.4. Clinical Laboratory Tests

Each subject will have blood drawn and urine collected for the hematology, chemistry, lipids, and urinalysis clinical laboratory tests listed in **Table 4** and **Table 5** below, during the Screening Period, at the Day 1, Week 6, Week 12, and Week 16 Visits. Blood for

vitamin D is collected at the Screening and Week 12 Visits only. Fasted blood samples for clinical laboratory tests will be collected pre-dose at the Day 1, Week 2, Week 6, Week 12, and Week 16 Visits. Urine samples may be collected non-fasting at all scheduled visits. Details of blood and urine collections can be found in the Laboratory Manual.

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. A total of approximately 21 mL of blood will be collected over the course of this study for clinical safety laboratory evaluation, including measurement of vitamin D (see **Section 7.2.8** for details of blood volumes to be collected).

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

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

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

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

Any clinically significant test abnormality as defined above should be recorded as an AE (unless it was considered spurious), and repeat analysis performed until resolution or

until the Investigator or medically qualified sub-investigator determines that resolution of the abnormality is not expected.

Table 4. Hematology, Chemistry, and Lipids Clinical Laboratory Tests

Hematology	
Red Blood Cells (RBC)	Numerical platelet count (estimate not acceptable)
Hemoglobin	White Blood Cells (WBC) with differential (percent)
Hematocrit	
Chemistry	
Sodium	Total Bilirubin[a]
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)	Vitamin D[b]
Cystatin C	
Lipids	
Triglycerides	Low Density Lipoprotein (LDL)
Total cholesterol	High density Lipoprotein (HDL)
a. If outside normal range, direct bilirubin will be measured and reported. b. Vitamin D levels measured at Screening and Week 12 only.	

Urine will be collected for routine analysis, by dipstick and microscopic analysis, for the tests described in **Table 5**.

Table 5. Urinalysis Clinical Laboratory Tests

Urinalysis (including microscopic examination)	
Dipstick[a]	Microscopic Analysis

Protein	WBC/hpf
Glucose	RBC/hpf
Ketones	Casts
pH	Bacteria
Leukocyte esterase	
Blood	
a. A midstream clean-catch urine specimen will be collected for dipstick analysis.	

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

7.2.5. Chicken Pox Immunity

Subjects must provide evidence of immunity to varicella zoster virus to be eligible for assignment to treatment. Evidence of immunity may be determined by either a positive anti-varicella IgG antibody test result obtained during the Screening Period, or documentation, provided at the Screening Visit, that the subject has had 2 doses of varicella vaccine, with or without serologic immunity, with the second of the 2 doses given at least 14 days prior to assignment to a dose group. For subjects whose anti-

varicella antibody titer will be measured at Screening, a 2 mL blood sample will be collected for antibodies (IgG) to Varicella Zoster virus to confirm immunity. The blood sample will be sent to the local laboratory for testing.

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

7.2.6. Pharmacodynamic Biomarker Panel

Blood samples will be collected to explore the effect of vamorolone on biomarkers associated with glucocorticoid safety concerns (exploratory outcomes for adrenal suppression, insulin resistance, and bone turnover, as well as, in the additional 12 to <18 years age group, suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4)), as listed in **Table 6**.

Blood samples will be collected pre-dose at the Day 1 and Week 12 Visits for analysis of biomarkers for exploratory outcome measures of adrenal suppression, bone turnover, and insulin resistance (HbA1c will be analyzed at Screening and Week 12). Approximately 6 mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin [insulin resistance], morning cortisol [adrenal suppression], and osteocalcin, P1NP, and CTX [bone turnover] biomarkers) at each scheduled collection time point; HbA1c will be analyzed from the hematology sample . Samples collected at the Day 1 and Week 12 Visits will be collected after the subject has fasted for ≥ 6 hours and prior to administration of the daily dose of study medication; the sample collected at the Screening Visit for HbA1c measurement may be collected non-fasting. Blood for morning cortisol measurement should be collected before 10 AM local time.

Blood remaining from collected samples not needed for protocol-specified analyses at each of the blood collection time points may be stored for future exploratory biomarker studies for aspects of safety and efficacy. These remaining blood samples may be

released for research purposes, including research on biomarkers in DMD. Any released samples will have no identifying subject information.

Additional HbA1c determination should be performed if urine glucose is positive and/or fasted glucose levels are above normal limits at any of the scheduled assessment time points (see Laboratory Manual).

A total of approximately 19 mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin, morning cortisol, osteocalcin, CTX, and P1NP, as well as, in the additional 12 to <18 years age group, LH, FSH, TSH, FT4) over the course of the 21-week study (see **Section 7.2.8**).

Table 6. Pharmacodynamic Biomarkers – Exploratory Safety Outcomes

Adrenal Suppression
Cortisol – morning
Insulin Resistance
Glucose – fasting
Insulin – fasting
HbA1c
Bone Turnover
Osteocalcin
CTX
P1NP
Suppression of the gonadal axis
LH
FSH
Suppression of the thyroid axis
TSH
FT4

7.2.7. Pharmacokinetic Assessment

At the Day 1 and Week 2 Visits, all subjects will have blood collected for PK assessments within 30 minutes prior to and at 1, 2, and 6 hours (ages 2 to <4 years), or within 30 minutes prior to and at 1, 2, 4, 6 and 8 hours (ages 7 to <18 years) following

administration of the daily dose of study medication. Approximately 1.2 mL of blood will be collected into K_2-EDTA tubes at each assessment time point (total of approximately 10 mL blood collected for PK assessment in 2 to < 4-year-old subjects and total of approximately 15 mL blood collected for PK assessments in ages 7 to <18 years).

Plasma concentrations of vamorolone will be measured using a specific and validated liquid chromatography tandem mass spectrometry assay. PK assessments will be performed by a central laboratory. The procedures for the collection, handling, and shipping of laboratory samples will be specified in the Laboratory Manual(s) provided to the study sites.

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

If PK and PD or clinical laboratory blood samples are to be collected at the same time point, the PK blood sample should be collected in the order specified in the laboratory collection flow chart.

7.2.8. Total Blood Volume Required

The number and volume of blood samples and total volume of blood to be collected from each subject throughout the duration of the up-to-21-week study are summarized in **Table 7**. A total of approximately 51 mL of blood will be collected from each 2 to <4-year-old subject, and appoximately 56 mL of blood will be collected from each 7 to <18-year-old subject over the course of the up-to-21-week study.

Table 7. Blood Sample Number and Volume by Study Visit

Test	Blood Volume (mL)						
	SCR	Day 1	Week 2	Week 6	Week 12	Week 16	Total Volume
Clinical Safety Labs[a]	3.7[b]	3.7[b]		3.7[b]	3.7[b]	3.7[b]	18.5
Varicella Zoster IgG	2						2
Vitamin D	1.2				1.2[b]		2.4
PD Biomarker Panel[c]		9.2[b]			9.2[b]		18.4
PK[d]							
Ages 2 to <4 years		4.8	4.8				9.6
Ages 7 to <18 years		7.2	7.2				14.4
Total Volume by Visit (mL)	6.9			3.7	14.1	3.7	
Ages 2 to <4 years		17.7	4.8				50.9
Ages 7 to <18 years		20.1	7.2				55.7
Total Volume: 50.9 mL (ages 2 to <4 year); 55.7 mL (ages 7 to <18 year)							

SCR = Screening

[a] Hematology, Chemistry, Lipids, HbA1c

[b] Subjects must have fasted ≥ 6 hours prior to blood draws.

[c] Fasting glucose, insulin, morning cortisol, CTX, P1NP, osteocalcin; pre-dose on Day 1 and Week 12.

[d] Blood drawn for population PK within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), or 30 minutes pre-dose and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years). Subjects must be fasting at the time of collection of the Day 1 and Week 2 pre-dose samples.

7.2.9. 12-Lead ECG

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

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

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

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

7.2.10. Eye Examination

An eye examination will be performed by a certified and appropriately trained optometrist or ophthalmologist at Screening and Week 12 to assess for presence and degree of cataracts and glaucoma. Number and severity of cataracts, if present, will be recorded. Ocular pressure and presence/absence of glaucoma will be recorded.

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

7.3. Assessment of Muscle Function

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

7.3.1. Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor Scale

The Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale will be assessed for subjects in the 2 to <4 years age group at the Screening, Baseline Day -1, and Week 12 Visits.

The Bayley-III Gross Motor scale is comprised of 72 items that assess developmental functioning and include movement of the limbs and torso, static positioning (e.g., sitting, standing), dynamic movement including locomotion and coordination, balance, and motor planning [Connolly et al, 2019]. Complete instructions for administering and scoring the Bayley-III Gross Motor scale are given in the Clinical Evaluator Manual to be supplied to the sites prior to study start.

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

7.3.2. Performance of Upper Limb (PUL) Test

The Performance of Upper Limb (PUL) Test will be assessed at the Screening, Baseline Day -1, and Week 12 Visits.

The PUL was developed specifically for DMD and is capable of assessing a wide-spectrum of upper extremity function in both ambulant and non-ambulant individuals with DMD. The PUL provides a total upper extremity functional score capable of characterizing overall progression and severity of disease, while its component subscores, which assess the 3 major level dimensions (shoulder-, middle-, and distal-levels), can track the stereotypical proximal-to-distal progressive loss of upper limb function in DMD [Pane et al, 2014]. Complete instructions for administering the PUL are given in the Clinical Evaluator Manual to be supplied to the sites prior to study start.

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

7.4. Patient-Reported Outcome Measures

7.4.1. Pediatric Outcomes Data Collection Instrument (PODCI)

Physical functioning will be assessed by completion of the Pediatric Outcomes Data Collection Instrument (PODCI). The subject's parent(s)/legal guardian(s) will be asked to complete this instrument at the Screening and Week 12 Visits.

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

7.4.2. Behavioral Assessment

One instrument, for completion by the parent(s)/guardian(s), will be used for behavior assessment screening and evaluation of behavior change. This is the PARS III, a scale designed to measure psychosocial adjustment of children with chronic physical illnesses. The PARS III will be completed by the parent(s)/guardian(s) at the Screening and Week 12 Visits. The PARS III is available in all primary languages spoken at sites for this study.

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

7.4.3. Ease of Study Medication Administration Assessment

Ease of administration of the study medication will be assessed by the parent(s)/guardian(s) for subjects in the 2 to <4 years age group at the Weeks 6 and 12 Visits. Results will be recorded in the source document and eCRF.

7.4.4. Study Medication Acceptability Assessment

Acceptability of the study medication will be assessed by subjects in the 7 to <18 years age group using a 5-point hedonic scale immediately before (smell) and after (taste) dosing at the Week 6 and Week 12 Visits. The assessments will be administered by trained study staff. Results will be recorded in the source document and eCRF.

7.5. Subject Diary

The parent(s) or legal guardian(s) of each subject will be given a subject diary at the Day 1 Visit in which to record any new concomitant medications and any changes to existing concomitant medications taken during the study, any AEs experienced by the subject during the study, and any missed or incomplete doses of study medication. Parent(s)/legal guardian(s) 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 visit for use through the time of the next scheduled visit. Collection of final diaries will occur at the end of the Dose-tapering Period, or at discharge from the study.

7.6. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a subject and does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational

product, whether or not considered related to the drug. Pre-existing conditions that worsen during a study are to be reported as AEs.

Signs and symptoms of DMD should not be recorded as AEs, unless their nature or severity is unexpected for the course of the disease.

The Investigator is responsible for reporting AEs and SAEs to the Sponsor or designee. For reported death of a participant, the Investigator shall supply the Sponsor and the IRB/IEC with any additional information requested.

Adverse events will be recorded from the date of informed consent and through the time of the subject's last study visit (study completion or early discontinuation). Serious adverse events will be recorded from the date of informed consent, throughout the clinical trial, and for up to 30 days after the final administration of study drug. In addition, subjects (and their parent[s] or legal guardian ([s]) 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 document and in the subject's eCRF. The date of onset will be recorded. Any laboratory abnormality that is outside the normal range and is considered an AE (see **Section 7.2.4**) should be recorded as an AE on the appropriate eCRF page. The details recorded shall include the nature, date of onset, final outcome and its date, seriousness,intensity assessment (Common Terminology Criteria for Adverse Events [CTCAE] grade), and a determination of the relationship of the event to administration of the study drug (i.e., causality). The intensity of all AEs will be graded by CTCAE, Version 5.0. Details of any medications given to the subject to abate the AE should be recorded on the appropriate eCRF page.

7.6.1. Intensity

All AEs encountered during the clinical study will be recorded in the eCRF. Intensity of AEs will be graded using the most current version of the CTCAE, version 5.0, 5-point

scale, and reported in detail as indicated in the eCRF. A description of the intensity scales can be found below:

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

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

Severe (Grade 3): Severe or medically significant but not immediately life -threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL; incapacitating with inability to work or perform normal daily activity.

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

Death (Grade 5): Death related to AE.

7.6.2. Relationship

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

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

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

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases after dosing is complete. (There are important exceptions when an AE does not disappear upon discontinuation of study

drug, yet drug relatedness clearly exists, e.g., [1] bone marrow depression and [2] tardive dyskinesia.)

4. It follows a known pattern of response to the suspected study drug.

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

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

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

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

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

7.6.3. Clinical Laboratory Test Abnormalities

Clinical laboratory test results will be recorded on the designated eCRF page. The intensity of abnormal clinical laboratory test results that are AEs will also be graded

using current FDA and the Council for International Organizations of Medical Sciences (CIOMS) drug-induced liver injury (DILI) guidance and the most current version of the CTCAE, version 5.0, 5-point scale and reported in detail as indicated in the eCRF. A description of the intensity scale can be found above.

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

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

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

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

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

7.6.4. Follow-Up of Adverse Events

Adverse events will be followed until they have returned to baseline status, stabilized, or the Investigator 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 document and

eCRF. In the event of unexplained abnormal laboratory test values, the tests may be repeated as soon as possible and followed up until they have returned to the normal range or baseline value and/or an adequate explanation of the abnormality is found. In case of ongoing AEs at the time of database closure, the data obtained at the time of database closure will be used in the statistical analysis. The further follow-up of AEs will be documented in the source document and CRF.

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.

7.6.5. Dosing Error

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

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

7.6.6. Serious Adverse Events

Serious adverse events (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. For subjects who do not continue to receive vamorolone in an expanded access or compassionate use program,

site staff will make a phone call to the home 31-35 days after the final dose of study medication in the VBP15-006 study to confirm the final SAE status of the subject.

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

During the SAE collection period, the Investigator or clinical site personnel should notify the Coordinating Center of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event; notification to the Coordinating Center will trigger alerts to the Sponsor. The Investigator will provide the initial notification by completing the SAE Report Form in the electronic data capture (EDC) system, which must include the Investigator's assessment of the relationship of the event to investigational drug, and must be signed by the Investigator.

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

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the Coordinating Center within 24 hours of knowledge of the new or follow-up information, which will forward the information to , the Sponsor.

All SAE reports should be completed within the EDC.

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

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

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

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

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

In United States and Canada:

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

In Europe, Asia, Pacific, Africa and Australia:

Email: MHGSafety@iconplc.com

Drug Safety Fax: +44 1792 525720

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

Serious Adverse Events will be recorded from the time the subject's written informed consent is obtained. Serious adverse events that occur within 30 days of study drug dosing must continue to be recorded and reported to 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.

Suspected Unexpected Serious Adverse Reaction (SUSAR) Identification and Reporting

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected (not identified in the Investigator's Brochure). Sponsor will inform Investigators of SUSARs in a manner and timeframe consistent with applicable national regulatory requirements.

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

8. STUDY COMMITTEES

Data and Safety Monitoring Board

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

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

The DSMB will be responsible for:

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

9. DATA COLLECTION

9.1. Source Documents

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

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

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

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

9.2. Electronic Case Report Form Completion

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

The Coordinating Center will design an electronic database in OpenClinica for this study. Access rights to the EDC system for the study site team members will need to be requested. Every user of the system will be made aware of the fact that usernames and

passwords should never be shared and their electronic signature constitutes the legally binding equivalent of a handwritten signature. Only trained personnel certified by the Coordinating Center will receive a username and password.

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

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

9.3. Data Processing

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

9.4. Subject Diaries

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

10. STATISTICAL METHODS AND PLANNED ANALYSES

10.1. Sample Size Determination

This is an open-label, parallel group, multiple dose study. Study medication is administered daily in this Phase II trial.

For this Phase II study in DMD boys ages 2 to <4 years and 7 to <18 years, a total of approximately 20 subjects in the 2 to <4 years age group will be enrolled with approximately 10 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day). A total of approximately 34 subjects in the 7 to <18 years age group will be enrolled with approximately 12 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day) and each dose level group stratified 1:1 by glucocorticoid treatment status at study entry to include approximately 6 glucocorticoid-untreated subjects and 6 glucocorticoid-treated subjects at study entry, plus 10 subjects for the additional 12 to <18 years age group [6.0 mg/kg/day - glucocorticoid-treated]. This sample size is considered sufficient to detect drug safety concerns in a pediatric population ages 2 to <4 and 7 to <18 years with DMD based on clinical judgment and prior study of vamorolone at these doses. The 10 additional 12 to <18 years subjects will further ensure that the full age range is included. In addition, this sample size is sufficiently large to determine PK parameters.

A drop-out rate is not considered; subjects who withdraw early from the study may be replaced.

10.2. Statistical and Analytical Plan (SAP)

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

10.2.1. Deviations from the Statistical Analysis Plan

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

10.3. Analysis Populations

Three populations will be defined for data analysis: Safety Population, modified Intent-to-Treat (mITT) Population, and the Pharmacokinetic Population.

10.3.1. Safety Population

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

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

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

10.3.3. Pharmacokinetic (PK) Population

All subjects who receive at least one dose of vamorolone study medication and have sufficient data for PK analysis will be included in the PK Population.

10.4. Measures Taken to Avoid/Minimize Bias

Not applicable.

10.5. Interim Analysis

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

10.6. Missing, Unused, and Spurious Data

The possibility of bias from missing data of subjects who prematurely discontinue will be addressed in the clinical study report. Missing values for safety and exploratory

outcomes will be treated as missing, unless stated otherwise. Full details are presented in the SAP.

10.7. Statistical Analysis

10.7.1. General Considerations

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

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

All statistical tests will be performed at the 0.05 level. Paired t-tests will be utilized for select variables. Baseline measurement is defined as the last non-missing value prior to the first dose of study drug in the study.

10.7.2. Subject Disposition, Demographics, and Baseline Characteristics

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

Subject demographics (e.g., age, race, and ethnicity) and baseline characteristics (e.g., height, weight, and months/years since DMD diagnosis) will be summarized descriptively by dose level within age group, and overall. In addition, tables will be presented according to glucocorticoid status at study entry (ages 7 to <18 years only). Baseline characteristics presented in these summary tables will be reviewed for any clinically relevant differences among the treatment groups or age stratification groups, and may be accounted for in the statistical models for the endpoints.

10.7.3. Safety and Tolerability Analyses

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

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

Safety data will include BMI, weight, height, vital signs, eye examination results, and ECG results, and these will be presented using descriptive statistics. The BMI and height values will be evaluated both on the original scale and as z-scores. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed.

Furthermore, continuous safety endpoints will be evaluated using a Mixed Model for Repeated Measures (MMRM), when appropriate. The models will include the baseline value as a covariate and visit, dose level, glucocorticoid use (when appropriate) and the relevant interaction terms as fixed effects. Separate models will be used for each age group. In case of no repeated measures (endpoint is assessed at one post-baseline visit only), Analysis of Covariance (ANCOVA) models will be used instead of MMRM.

Adverse events will be summarized overall and by age group, dose level, glucocorticoid treatment at entry (7 to <18 years only), SOC, and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]. Further analyses will be conducted by seriousness, severity and relationship to study medication. Adverse events leading to premature discontinuation of the study will be evaluated separately.

Physical examination results will be listed only.

10.7.4. Pharmacokinetic Analyses

The pre-dose and post-dose plasma concentration measurements of vamorolone at Day 1 and Week 2 will be used for comparison of drug exposures by age group, dose level, and glucocorticoid treatment at entry (ages 7 to <18 years only). They will be aggregated with PK data from previous studies in DMD boys for comparison across the entire pediatric age range and with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation

to age group, dose level, and glucocorticoid treatment at entry (ages 7 to <18 years only), as applicable.

A separate population PK Analysis Plan will be created to further describe these analyses.

10.7.5. Pharmacodynamic Analyses

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

All PD biomarker results will be summarized and listed.

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of safety and efficacy (including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4)) will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers by dose level within age group. Change from baseline will be presented. For subjects 7 to <18 years of age, descriptive statistics will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment.

The changes in serum PD biomarkers will be compared to the corresponding data if available collected in a previously conducted vamorolone study VBP15-004. The changes from baseline to week 12 in the present study (by dose level and age group) will be compared to the changes from baseline to week 12 in the four treatment groups of study VBP15-004 (vamorolone 2.0 mg/kg, vamorolone 6.0 mg/kg, placebo and prednisone 0.75 mg/kg). Furthermore, the differences between the groups will be evaluated with ANCOVA models including baseline value as a covariate and the treatment/age group as a fixed factor. Additional analyses will be conducted by glucocorticoid use group, when appropriate.

Full details will be provided in the SAP.

10.7.6. Clinical Efficacy Analyses

The evaluations of clinical efficacy will be performed using the mITT Population. Analyses will be performed as per treatment.

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

The exploratory efficacy outcomes are the Bayley-III Gross Motor scale (2 to <4 years age group) and PUL Test (7 to <18 years age group). Standard descriptive statistics will be used to summarize the clinical efficacy endpoints by dose level within age group. Change from baseline will be presented. Within each age group, pairwise comparisons will be made to compare change from baseline for the vamorolone 6.0 mg/kg/day dose level group vs. the vamorolone 2.0 mg/kg/day dose level group. For subjects 7 to <18 years of age, descriptive statistics will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment.

Furthermore, the changes from baseline to week 12 in the efficacy outcomes will be compared using ANCOVA models, including baseline value as a covariate and dose level and glucocorticoid use status (when appropriate) and the relevant interaction terms as fixed factors. Separate models will be used for each age group.

Full details will be provided in the SAP

10.7.7. Patient-Reported Outcome Analyses

Patient-reported Outcomes including the PODCI, PARS III, Ease of Study Medication Administration Assessment, and the Study Medication Acceptability Assessment will be listed and presented using descriptive statistics by age group, dose level, and time point. For subjects 7 to <18 years of age, descriptive statistics for change from baseline assessments (PODCI and PARS III) will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those

subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment.

Full details will be provided in the SAP.

10.7.8. Concurrent Medications

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

11. STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

11.1. Regulatory Approval and Good Clinical Practice

This study will be conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, June 1964), and amendments of the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), 59th (Seoul, 2008), and 64th (Fortaleza, 2013) World Medical Assemblies and ICH E6 Guideline for Good Clinical Practice (GCP).

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

11.2. Investigator Responsibilities

11.2.1. Subject Information and Informed Consent

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

If applicable, 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 written in a language they understand.

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

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

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

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

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

Study medication can only be supplied to the Investigator after documentation of all ethical and legal requirements for starting the study has been received by the 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 Investigator will keep the IRB/IEC informed regarding the progress of the study, per institutional requirements. No changes will be made in the study without IRB/IEC

approval, except when required to eliminate apparent immediate hazards to the subjects. In cases where any implemented deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants is implemented without prior IRB/IEC approval, the implemented deviation should be notified as soon as possible not only to the IRB/IEC for review and approval/favorable opinion but also to the regulatory authority(ies).

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

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

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

11.2.3. Study Documentation

11.2.3.1. Before the Start of the Study

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

- Fully signed protocol and protocol-supporting manuals
- Investigator's Brochure
- Investigator Protocol Agreement form signed by the Investigator
- IRB/IEC-approved copy of the ICF

- Curriculum vitae of the Investigator and all sub-investigators
- A letter of IRB/IEC approval for protocol
- A list of members of the IRB/IEC and their affiliations
- A copy of the Investigator-signed FDA 1572 form
- An Investigator-signed financial disclosure form
- Investigator/site study contract.

11.2.3.2. During the Study

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

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

11.2.3.3. After the Study

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

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

- Subject enrollment log
- Subject identification log
- Substantive correspondence with the Sponsor and IRB/IEC
- Notification of the end of the trial to the IRB/IEC.

11.2.4. Delegation of Investigator Responsibilities

The Investigator must (a) ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and licensure, if relevant) to perform the task; and (b) provide adequate supervision. The Investigator should maintain a list of sub investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.3. Protocol Deviations

11.3.1. Protocol Deviation Definitions

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

11.3.1.1. Protocol Deviation

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

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

11.3.1.2. Important Protocol Deviation

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

11.3.2. Reporting Important Protocol Deviations

Upon discovery of an important protocol deviation, the Investigator is responsible for reporting the important protocol deviation to the IRB/IEC and Sponsor or designee (Coordinating Center) within 24 hours of discovery, or according to local site requirements.

All deviations must be recorded in the CTMS.

11.4. Study Records Retention and Direct Access to Source Documents

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

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

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 identification log
3. Subject enrollment log
4. Record of all relevant communications between the Investigator and the IRB/IEC
5. Composition of the IRB/IEC

6. Record of all relevant communications between the Investigator and the Sponsor (or designee)
7. List of sub investigators and other appropriately qualified persons to whom the Investigator has delegated significant study related duties, together with their roles in the study and their signatures
8. Drug accountability records (See **Section 5.8.4**)
9. Record of any body fluids or tissue samples retained
10. All other source documents (subject records, hospital records, laboratory records, etc.)
11. All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

11.5. Study Monitoring

In accordance with applicable regulations, GCP, and the procedures of 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 11.7.**

11.6. 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.

11.7. Study Termination and Site Closure

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

1. Provision of all study data to 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.

11.8. 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
2. Failure of the Investigator to comply with applicable laws and/or pertinent regulations
3. Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities

4. Insufficient adherence to protocol requirements.

If participation of a study site is terminated, the Sponsor 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 relevant regulations where the study is being conducted.

11.9. 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.

12. DISCLOSURE OF DATA

12.1. Confidentiality

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

Subject names will remain confidential and will not be included in the database. Only enrollment number, age at enrolment and birth date (may be collected where allowed by local regulations) will be recorded on the eCRF. If the subject's name appears on any other document collected (e.g., hospital discharge summary), the name must be redacted before the document is transmitted to 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 applicable data protection / privacy laws in the relevant countries.

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.

12.2. Publication

Santhera Pharmaceuticals (Switzerland) Ltd 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 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 Santhera Pharmaceuticals (Switzerland) Ltd or another entity delegated by Santhera Pharmaceuticals (Switzerland) Ltd

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.

13. INVESTIGATOR PROTOCOL AGREEMENT

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

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15. APPENDICES

15.1. Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide

15.1.1. Dose Calculation Worksheet

Vamorolone is administered once daily as a 4.0% oral suspension. The volume per dose is determined by the subject's dosing level and body weight (in kg) at each study medication dispensing visit, as shown by *Equation 1*:

Equation 1

$$\frac{\textbf{Subject Weight (kg) x Dose Level (mg/kg)}}{\textbf{40 mg/mL}} = \textbf{Subject Dose (in mL)}$$

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),** 0.2 mL **(5 mL syringe)**, or 0.2 mL **(10 mL syringe)** depending upon the total dose volume and calibration of the volumetric syringe to be used for administration of dose, as shown in the examples below:

Example 1: Dose volume calculation for a subject receiving **2.0** mg/kg/day with a body weight of **23** kg:

$$\frac{\textit{Subject Weight (23 kg) x Dose Level (2.0 mg/kg)}}{\textit{40 mg/mL}} = \textit{1.15 mL}$$

The subject will receive a daily dose volume of **1.15** mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a **5** mL volumetric syringe rounded to the nearest 0.2 mL; i.e., **1.2** mL daily.

Example 2: Dose volume calculation for a subject receiving **6.0 mg/kg/day** with a body weight of **15** kg:

$$\frac{\textit{Subject Weight (15 kg) x Dose Level (6.0 mg/kg)}}{\textit{40 mg/mL}} = \textit{2.25 mL}$$

The subject will receive a daily dose volume of **2.25** mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a **10** mL volumetric syringe rounded to the nearest 0.2 mL; i.e., 2.2 mL daily.

15.1.2. Vamorolone 4.0% Suspension Dispensing Guide

Each subject enrolled in the study will be dispensed 125 ml bottle(s) of vamorolone 4.0% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the

scheduled Week 6 Visit. Additional supplies will be dispensed at the Week 6 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4.0% suspension at the Week 12 Visit, sufficient for dose tapering to 0.0 mg/kg/day (see **Section 6.3.5**).

The number of bottles to be dispensed at each dispensing visit for the following 6-week dosing period is calculated by multiplying the subject's daily dose (in mL/day) (as calculated by *Equation 1*) by 49 days (42 days in the dosing period + 7 days overage) and dividing that number by 100 mL, the number of mL per bottle, as shown in *Equation 2*, below:

Equation 2

$$\frac{\text{Daily Dose (mL/day)} \times 49 \text{ Days}}{100 \text{ mL}} = \text{\#Bottles to be Dispensed for 6 weeks dosing}$$

Example 3: Calculation of number of bottles to be dispensed for 6-week dosing for a subject taking a daily dose of **1.2** mL (from Example 1 above):

$$\frac{\text{Daily Dose (1.2 mL/day)} \times 49 \text{ Days}}{100 \text{ mL}} = 0.59 \text{ Bottles}$$

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 6-week dosing for a subject taking a daily dose of **2.2** mL (from Example 2 above):

$$\frac{\text{Daily Dose (2.2 mL/day)} \times 49 \text{ Days}}{100 \text{ mL}} = 1.1 \text{ Bottles}$$

The number of bottles dispensed is rounded to the nearest whole integer, or **2** bottles to be dispensed.

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

Any unused or partially used drug product should be returned at the Week 6 and Week 12 Visits, respectively, and at the end of the Dose-tapering Period, if applicable, and retained at the clinical study site for investigational drug accountability monitoring.

15.2. Protocol Amendment #1 Complete List of Changes

The following changes have been incorporated into the protocol under this protocol amendment, as summarized in the Protocol Amendment Tracking, Reasons for Protocol Amendment #1. Protocol sections that have been changed are itemized below with the original and revised text. Changes that were strictly editorial (e.g., punctuation, correction of spelling errors) are not included.

Study Synopsis, Investigational Drug Product

Original Text:

Vamorolone, 4.0% wt/wt suspension for oral dosing

Revised Text:

Vamorolone, 4.0% wt/vol suspension for oral dosing

Study Synopsis, Study Drug Formulation, Dosage & Administration

Original Text:

Treatment Period and Dose-tapering Period

Subjects will be administered 4.0% wt/wt oral suspension (Formulation ROS2).

All subjects in both age groups: vamorolone 4.0% wt/wt oral suspension (investigational medicine) will be administered once daily over the 12-week Treatment Period (Weeks 1-12) and during the 4-week Dose-tapering Period, as applicable. The site pharmacist will dispense study medication in 110 mL bottles sufficient for 6 weeks of dosing (4 weeks for Dose-tapering Period) plus overage to subjects at the Day 1 and Week 6 Visits (and Week 12 Visit to subjects participating in the Dose-tapering Period), according to the subject's assignment to a dose group and subject body weight recorded at the dispensing visit (Day -1 weight for Day 1 dispensing).

Revised Text:

Treatment Period and Dose-tapering Period

Subjects will be administered 4.0% wt/vol oral suspension (Formulation route of synthesis 2 [ROS2]).

All subjects in both age groups: vamorolone 4.0% wt/vol oral suspension (investigational medicine) will be administered once daily over the 12-week Treatment Period (Weeks 1-12) and during the 4-week Dose-tapering Period, as applicable. The site pharmacist will dispense study medication in 125 mL bottles sufficient for 6 weeks of dosing (4 weeks for Dose-tapering Period) plus overage to subjects at the Day 1 and Week 6 Visits (and Week 12 Visit to subjects participating in the Dose-tapering

Period), according to the subject's assignment to a dose group and subject body weight recorded at the dispensing visit (Day -1 weight for Day 1 dispensing).

Study Synopsis, Study Drug Formulation, Dosage & Administration

Original Text:

The daily dose of study medication should be taken in the morning with breakfast. There are no other food or drink restrictions before or after dosing.

Revised Text:

Participants must fast ≥6 hours prior to the Day1, Week 2, Week 6, and Week 12 study visits, when dosing will occur at the study site. The daily dose of study medication administered at home should be taken in the morning with breakfast. There are no other food or drink restrictions before or after dosing.

Study Synopsis, Study Summary

Original Text:

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects in both age groups, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit. Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, and Week 12 Visits, when dosing will occur at the study site.

Revised Text:

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects in both age groups, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit. Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site.

Study Synopsis, Safety Measures

Original Text:

Weight and Height (standing height collected for subjects in 2-<4 years age group; height calculated from ulnar length in subjects in 7-<18 years age group)

Revised Text:

Weight and Height (standing height collected for subjects in 2 to <4 years age group and all participants who can stand independently; height calculated from ulnar length in subjects in 7 to <18 years age group)

3.2 Study Summary, Paragraph 7

Original Text:

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects in both age groups, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit (see **Section 5.3**). Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, and Week 12 Visits, when dosing will occur at the study site.

Revised Text:

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects in both age groups, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit (see **Section 5.3**). Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site.

3.3 Dose group assignment, Paragraph 4

Original Text:

Assignment to dose group will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study. The following information will be sent to the TRiNDS Study Coordinator:

- Participant's Study Subject Identification Number
- Participant's Date of Birth

- Participant's glucocorticoid status at entry (7 to <18 years only)

Revised Text:

Assignment to dose group will require the site investigator, or designee, to verify that the subject meets the inclusion/exclusion criteria of the study. The following information will be sent to the TRiNDS Study Coordinator:

- Participant's Study Subject Identification Number
- Participant's Age at Enrollment
- Participant's glucocorticoid status at entry (7 to <18 years only)

4.1 Subject Enrollment and Identification Log, Paragraph 2

Original Text:

A subject enrollment log will be maintained at each investigational site for all subjects who are screened for the study, including those not assigned to treatment. Limited data will be collected for these subjects, including date of birth and reason for exclusion from the study. Subject enrollment logs will be maintained for all subjects enrolled in the study. This record will also include the dates of subject enrollment and completion/termination.

Revised Text:

A subject enrollment log will be maintained at each investigational site for all subjects who are screened for the study, including those not assigned to treatment. Limited data will be collected for these subjects, including age at enrollment and reason for exclusion from the study. Subject enrollment logs will be maintained for all subjects enrolled in the study. This record will also include the dates of subject enrollment and completion/termination.

5.1 Study Medication Administered, Paragraph 1

Original Text:

Planned vamorolone dose levels: 2.0 mg/kg and 6.0 mg/kg. Doses can be adjusted based on PK and safety data from the first 6 patients per age group to avoid over- or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range

Revised Text:

Planned vamorolone dose levels: 2.0 mg/kg/day and 6.0 mg/kg/day. Doses can be adjusted based on PK and safety data from the first 6 patients per age group to avoid over- or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range.

5.1 Study Medication Administered, Paragraph 5

Original Text:

Vamorolone 4.0% wt/wt oral suspension (investigational medicine) will be administered to all subjects once daily for 12 weeks, from Study Day 1 until the Week 12 Visit. At the end of the 12-week Treatment Period, a subset of subjects may receive additional vamorolone treatment in a dose-tapering manner during a 4-week Dose-tapering Period prior to discharge from the study (see **Section 6.3.5**).

Revised Text:

Vamorolone 4.0% wt/vol oral suspension (investigational medicine) will be administered to all subjects once daily for 12 weeks, from Study Day 1 until the Week 12 Visit. At the end of the 12-week Treatment Period, a subset of subjects may receive additional vamorolone treatment in a dose-tapering manner during a 4-week Dose-tapering Period prior to discharge from the study (see **Section 6.3.5**).

5.2 Identity of Investigational Product

Original Text:

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

Active Substance:	Vamorolone
Strength:	4.0% wt/wt
Dosage Form:	Oral suspension
Formulation:	ROS2
Manufacturer:	Purna Pharmaceuticals NV/SA

Revised Text:

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

Active Substance:	Vamorolone
Strength:	4.0% wt/vol
Dosage Form:	Oral suspension
Formulation:	ROS2
Manufacturer:	Purna Pharmaceuticals NV/SA

5.3 Dosage Schedule and Administration of Study Medication

Original Text:

Subjects in the 2 to <4 years age group and subjects in the 7 to <18 years age group will be administered vamorolone 4.0% wt/wt oral suspension (Formulation ROS2).

All subjects in both age groups will receive study medication, administered orally once daily for 12 weeks, from Study Day 1 to the Week 12 Visit. At the end of the 12-week Treatment Period, subjects who will not continue directly with further vamorolone or SoC glucocorticoid treatment at the end of the study will be tapered off suspension study medication over a 4-week Dose-tapering Period, prior to discharge from the study (see **Section 6.3.5**).

The site pharmacist or designated site study staff will dispense study medication to each subject in 110 mL bottles sufficient for 6 weeks of dosing (4 weeks for Dose-tapering Period) plus overage at the Day 1 Visit, just prior to dosing, and at the Week 6 Visit (and Week 12 Visit to subjects participating in the Dose-tapering Period), according to the subject's dose assignment and subject body weight (in kg) recorded at the dispensing visit (Day -1 weight for Day 1 dispensing) (see **Appendix 15.1** for a dose calculation worksheet).

Each subject's dose (in mL) will be calculated and written on the labels of the bottles to be dispensed at a given visit by trained site staff based on the weight of the subject (in kg) recorded at the dispensing visit. The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled study visit. Study medication suspension dispensed at the Day 1 Visit should be brought in with the subject to the Week 2 Visit, for Week 2 dosing in-clinic and compliance monitoring; this study medication will be returned to the subject at the end of the Week 2 Visit for continued dosing through the Week 6 Visit; new study medication will not be dispensed at the Week 2 Visit.

All subjects will receive all doses under the supervision of parents or legal guardians or trained study staff. Dosing is to occur at home throughout the 12-week Treatment Period, except at the Day 1, Week 2, and Week 12 Visits when dosing will occur at the study site. Subjects should receive each dose of study medication in the morning together with breakfast and at approximately the same time of day.

Vamorolone suspension will be administered orally using a volumetric syringe supplied by the site. Following administration of the dose of study drug suspension, the syringe will be filled once with water and the water will be administered by mouth using the volumetric syringe. The subject will then drink approximately 50 mL (approximately 2 ounces) of water to ensure the full dose has been ingested. The daily dose of study medication should be taken with breakfast. There are no other food or drink restrictions before or after dosing.

At the Day 1, Week 2, and Week 12 study visits, subjects will arrive at the study clinic and will eat breakfast at the study site within 30 minutes prior to administration of the dose of study medication.

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

Revised Text:

Subjects in the 2 to <4 years age group and subjects in the 7 to <18 years age group will be administered vamorolone 4.0% wt/vol oral suspension (Formulation ROS2).

All subjects in both age groups will receive study medication, administered orally once daily for 12 weeks, from Study Day 1 to the Week 12 Visit. At the end of the 12-week Treatment Period, subjects who will not continue directly with further vamorolone or SoC glucocorticoid treatment at the end of the study will be tapered off suspension study medication over a 4-week Dose-tapering Period, prior to discharge from the study (see **Section 6.3.5**).

The site pharmacist or designated site study staff will dispense study medication to each subject in 125 mL bottles sufficient for 6 weeks of dosing (4 weeks for Dose-tapering Period) plus overage at the Day 1 Visit, just prior to dosing, and at the Week 6 Visit (and Week 12 Visit to subjects participating in the Dose-tapering Period), according to the subject's dose assignment and subject body weight (in kg) recorded at the dispensing visit (Day -1 weight for Day 1 dispensing) (see **Appendix 15.1** for a dose calculation worksheet).

Each subject's dose (in mL) will be calculated and written on the labels of the bottles to be dispensed at a given visit by trained site staff based on the weight of the subject (in kg) recorded at the dispensing visit. The dispensed study medication bottle(s) will be returned to the study site at each subsequent scheduled study visit. Study medication suspension dispensed at the Day 1 Visit should be brought in with the subject to the Week 2 Visit, for Week 2 dosing in-clinic and compliance monitoring; this study medication will be returned to the subject at the end of the Week 2 Visit for continued dosing through the Week 6 Visit; new study medication will not be dispensed at the Week 2 Visit.

All subjects will receive all doses under the supervision of parents or legal guardians or trained study staff. Dosing is to occur at home throughout the 12-week Treatment Period, except at the Day 1, Week 2, Week 6, and Week 12 Visits when dosing will occur at the study site. Subjects should receive each dose of study medication in the morning together with breakfast and at approximately the same time of day. On days where vamorolone is administered in clinic, subjects should arrive fasted for >6 hours and should eat breakfast with their dose of study drug.

Vamorolone suspension will be administered orally using a volumetric syringe supplied by the site. Following administration of the dose of study drug suspension, the syringe will be filled once with water, and the water will be administered by mouth using the volumetric syringe. The subject will then drink approximately 50 mL (approximately 2 ounces) of water to ensure the full dose has been ingested. The daily dose of study medication should be taken with breakfast. There are no other food or drink restrictions before or after dosing.

At the Day 1, Week 2, Week 6, and Week 12 study visits, subjects will arrive at the study clinic and will eat breakfast at the study site after collection of fasting lab samples and within 30 minutes prior to administration of the dose of study medication.

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

5.5 Treatment Compliance

Original Text:

Subject compliance with the dosing schedule will be assessed by site maintenance of accurate study drug dispensing and return records, and accurate recording of incomplete or missed doses by completion of a diary by the subject's parent or guardian. 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(s) or guardian(s) with regard to proper dosing of study medication and completion of subject diaries, and will reinforce the importance of taking all study medication per protocol instructions. Doses of study drug on the days of the Day 1, Week 2, and Week 12 Visits will be administered at the participating study site by a trained investigational staff member. All incomplete or missed doses are to be documented in the source document and on the appropriate eCRF page. The volume of unused study medication remaining in each bottle returned, as measured by the weight of returned bottles, will be documented in the source documents and on the appropriate eCRF page.

Revised Text:

Subject compliance with the dosing schedule will be assessed by site maintenance of accurate study drug dispensing and return records, and accurate recording of incomplete or missed doses by completion of a diary by the subject's parent or guardian. 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(s) or guardian(s) with regard to proper dosing of study medication and completion of subject diaries and will reinforce the importance of taking all study medication per protocol instructions. Doses of study drug on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered at the participating study site by a trained investigational staff member. All incomplete or missed doses are to be documented in the source document and on the appropriate eCRF page. The volume of unused study medication remaining in each bottle returned, as measured by the weight of returned bottles, will be documented in the source documents and on the appropriate eCRF page.

5.8.1 Packaging and Labeling of Study Medication, Paragraph 1

Original Text:

The site pharmacist or designated study staff will receive clinical trial material (CTM) when all regulatory requirements have been completed by the site. Additional CTM will be available upon request. The Study Sponsor through the designated central pharmacy will provide CTM in bulk quantities sufficient to satisfy the protocol requirement. Vamorolone will be shipped in bulk to the study site's registered pharmacist or designated study staff in suitably labeled study cartons. Cartons will contain study medication packaged in sterile 120 mL (4 oz) amber bottles with a 110 mL fill volume with child-resistant cap with a 24 mm bottle press in adapter. Bottles are filled with 110 mL of suspension in order to guarantee a delivery of 100 mL.

Revised Text:

The site pharmacist or designated study staff will receive clinical trial material (CTM) when all regulatory requirements have been completed by the site. Additional CTM will be available upon request. The Study Sponsor through the designated central pharmacy will provide CTM in bulk quantities sufficient to satisfy the protocol requirement. Vamorolone will be shipped in bulk to the study site's registered pharmacist or designated study staff in suitably labeled study cartons. Cartons will contain study medication packaged in sterile 125 mL (4 oz) amber bottles with a 100 mL fill volume with child-resistant cap with a 28 mm bottle press in adapter.

Table 7. Schedule of Study Activities

Original Text: Table 7. Schedule of Study Activities

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Informed consent	X							
Enrollment[f]	X							
Inclusion/exclusion criteria	X							
Assignment[g]		X						
Demographics	X							
Medical history	X							
Medication history	X	X						
Physical examination	X	X			X	X		X
Cushingoid features	X	X			X	X		X
Height[h]	X					X		
Weight	X	X		X	X	X		X
Vital signs[i]	X	X	X[j]	X	X	X		X

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Blood for clinical labs[k]	X		X[l]			X[l]		X
Blood for vitamin D	X					X[l]		
Confirmation of varicella immunity	X							
Urinalysis[m]	X		X		X	X		X
Blood for serum PD biomarker panel[n]			X[l]			X[l]		
Fasting blood for insulin, glucose			X[l]			X[l]		
Blood for HbA1c	X					X[l]		
Blood for morning cortisol[o]			X[l]			X[l]		
Blood for Plasma PK			X[p]	X[p]				
12-lead ECG[q]	X					X		
Eye examination	X					X		
Dispense study medication			X		X	X[r]		
Return study medication/ compliance monitoring				X[s]	X	X		X
Study medication dosing[t]			X →	→	→	X		
Study medication dose tapering						X[r] →	→	X
Telephone call to subject							X[u]	
Bayley-III Gross Motor[v]	X	X				X		
PUL Test[w]	X	X				X		
Pediatric Outcomes Data Collection Instrument (PODCI)	X					X		
PARS III	X					X		
Ease of Study Medication Administration Assessment[x]					X	X		
Study Medication Acceptability Assessment[y]					X	X		
Dispense subject diaries[z]			X	X	X	X[q]		
Return subject diaries				X	X	X		X

	Pretreatment Period		Treatment Period					Dose-tapering Period[a]
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
AE/SAE recording[aa]	X	→	→	→	→	→	→	X[bb]
Prior/Concomitant medications	X	→	→	→	→	→	→	X
Discharge from study						X[cc]		X[dd]

BL = Baseline; d = day(s); SCR = Screening.

a. Only subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the 12-week Treatment Period will begin a 4week open-label Dosetapering Period during which the dose of study medication will be progressively reduced and discontinued.

b. All Day -1 assessments must be completed within 24 hours prior to administration of the first dose of study medication on Day 1.

c. Time windows around the Week 2, Week 6, and Week 12 Visits are allowances from date of Day 1 Visit; time window around Week 16 Visit is allowance from date of Week 12 Visit.

d. Subjects who prematurely discontinue from the study prior to Week 12 should complete the Week 12 assessments at the time of early withdrawal and undergo Dose-tapering, where appropriate.

e. Subjects will have one study site visit during the Dose-tapering Period, at one week after the dose of study medication has been discontinued (Week 16).

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

g. Assignment to a treatment group is done by the TRiNDS Study Coordinator at the Baseline Day -1 Visit.

h. Standing height will be measured for subjects in the 2- <4 years age group; ulnar length will be measured and used to calculate height for subjects in the 7 to <18 years age group.

i. Sitting blood pressure, body temperature, respiratory rate, and heart rate.

j. Vital signs recorded prior to administration of the first dose of study drug at the Day 1 Visit.

k. Blood for hematology, chemistry, and lipids.

l. Blood samples collected after subjects have fasted for ≥ 6 hours, and prior to daily dose of study drug.

m. Urinalysis by dipstick and microscopic analysis.

n. Blood collected for PD biomarkers includes exploratory safety outcomes (osteocalcin, CTX, P1NP) at Day 1 pre-dose and Week 12 predose. Blood remaining from collected blood samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies for aspects of safety and efficacy. All pre-dose samples should be collected after subject has fasted for ≥ 6 hours.

o. Blood collected for morning cortisol should be collected before 10 AM local time.

p. Blood samples for population PK analysis will be collected within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (2 to <4 years), and within 30 minutes pre-dose, and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (7 to <18 years).

q. 12-lead ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.

r. Only for subjects participating in the Dose-tapering Period.

s. Study medication brought by subjects to the Week 2 Visit for dosing and compliance assessment will be redispensed to subjects at the end of the visit.

t. During the Treatment Period, the dose of study medication on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered with breakfast in the study clinic. All other doses will be taken with breakfast at home.

u. Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the study drug tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have.

v. Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale will be completed for subjects in the 2 to <4 years age group only.

w. Performance of Upper Limb (PUL) test will be performed by subjects in the 7 to <18 years age group only.

x. Ease of Study Medication Administration Assessment will be completed for subjects in the 2 to <4 years age group only.

y. Study Medication Acceptability Assessment will be completed by subjects in the 7 to <18 years age group only.

z. Subject diaries used to record any changes in concomitant medications taken, any AEs experienced during the study, and any incomplete or missed doses of study medication.

aa. All AEs and SAEs must be recorded in the source documents and eCRF from the date of the subject's written informed consent until the final Week 16 Visit or the subject's participation in the study is completed (SAEs through 30 days after final dose study drug). Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator believes follow-up is not necessary.

bb. For subjects who do not continue into an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in VBP15-006 Dose-tapering Period to confirm the final SAE status of the subject.

cc. Subjects who elect to continue vamorolone therapy by enrolling directly into an expanded access or compassionate use program or who will transition directly to SoC glucocorticoid therapy may be discharged from the study following completion of all final Week 12 assessments.

dd. Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments (Week 16).

Revised Text:

	Pretreatment Period		**Treatment Period**				**Dose-tapering Period[a]**	
	SCR	**BL**						
	Day			**Week**				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Informed consent	X							
Enrollment[f]	X							
Inclusion/exclusion criteria	X							
Assignment[g]		X						
Demographics	X							
Medical history	X							
Medication history	X	X						
Physical examination	X	X			X	X		X
Cushingoid features	X	X			X	X		X
Height[h]	X					X		
Weight	X	X		X	X	X		X

	Pretreatment Period		Treatment Period					Dose-tapering Period[a]
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Vital signs[i]	X	X	X[j]	X	X	X		X
Blood for clinical labs[k]	X		X[l]		X[l]	X[l]		X
Blood for vitamin D	X					X[l]		
Confirmation of varicella immunity	X							
Urinalysis[m]	X		X		X	X		X
Blood for serum PD biomarker panel[n]			X[l]			X[l]		
Fasting blood for insulin, glucose			X[l]	X[l]	X[l]	X[l]		
Blood for HbA1c	X					X[l]		
Blood for morning cortisol[o]			X[l]			X[l]		
Blood for Plasma PK			X[p]	X[p]				
12-lead ECG[q]	X					X		
Eye examination	X					X		
Dispense study medication			X		X	X[r]		
Return study medication/ compliance monitoring				X[s]	X	X		X
Study medication dosing[t]			X →			X		
Study medication dose tapering						X[r] →		X
Telephone call to subject							X[u]	
Bayley-III Gross Motor[v]	X	X				X		
PUL Test[w]	X	X				X		
Pediatric Outcomes Data Collection Instrument (PODCI)	X					X		
PARS III	X					X		
Ease of Study Medication Administration Assessment[x]					X	X		
Study Medication Acceptability Assessment[y]					X	X		
Dispense subject diaries[z]			X	X	X	X[q]		

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Return subject diaries				X	X	X		X
AE/SAE recording[aa]	X	→	→	→	→	→	→	X[bb]
Prior/Concomitant medications	X	→	→	→	→	→	→	X
Discharge from study						X[cc]		X[dd]

BL = Baseline; d = day(s); SCR = Screening.

a. Only subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the 12-week Treatment Period will begin a 4-week open-label Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.

b. All Day -1 assessments must be completed within 24 hours prior to administration of the first dose of study medication on Day 1.

c. Time windows around the Week 2, Week 6, and Week 12 Visits are allowances from date of Day 1 Visit; time window around Week 16 Visit is allowance from date of Week 12 Visit.

d. Subjects who prematurely discontinue from the study prior to Week 12 should complete the Week 12 assessments at the time of early withdrawal and undergo Dose-tapering, where appropriate.

e. Subjects will have one study site visit during the Dose-tapering Period, at one week after the dose of study medication has been discontinued (Week 16).

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

g. Assignment to a treatment group is done by the TRiNDS Study Coordinator at the Baseline Day -1 Visit.

h. Standing height will be measured for subjects in the 2 to <4 years age group and participants ages 7 to <18 years who can stand independently; ulnar length will be measured and used to calculate height for subjects in the 7 to <18 years age group.

i. Sitting blood pressure, body temperature, respiratory rate, and heart rate.

j. Vital signs recorded prior to administration of the first dose of study drug at the Day 1 Visit.

k. Blood for hematology, chemistry, and lipids. All samples should be collected after subject has fasted for >6 hours.

l. Blood samples collected after subjects have fasted for ≥ 6 hours, and prior to daily dose of study drug.

m. Urinalysis by dipstick and microscopic analysis.

n. Blood collected for PD biomarkers includes exploratory safety outcomes of bone turnover (osteocalcin, CTX, P1NP) at Day 1 pre-dose and Week 12 pre-dose. Blood remaining from collected blood samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies for aspects of safety and efficacy. All pre-dose samples should be collected after subject has fasted for ≥ 6 hours.

o. Blood collected for morning cortisol should be collected before 10 AM local time.

p. Blood samples for population PK analysis will be collected within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), and within 30 minutes

pre-dose, and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years).

q. 12-lead ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.

r. Only for subjects participating in the Dose-tapering Period.

s. Study medication brought by subjects to the Week 2 Visit for dosing and compliance assessment will be redispensed to subjects at the end of the visit.

t. During the Treatment Period, the dose of study medication on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered with breakfast in the study clinic. All other doses will be taken with breakfast at home.

u. Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the study drug tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have.

v. Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale will be completed for subjects in the 2 to <4 years age group only.

w. Performance of Upper Limb (PUL) test will be performed by subjects in the 7 to <18 years age group only.

x. Ease of Study Medication Administration Assessment will be completed for subjects in the 2 to <4 years age group only.

y. Study Medication Acceptability Assessment will be completed by subjects in the 7 to <18 years age group only.

z. Subject diaries used to record any changes in concomitant medications taken, any AEs experienced during the study, and any incomplete or missed doses of study medication.

aa. All AEs and SAEs must be recorded in the source documents and eCRF from the date of the subject's written informed consent until the final Week 16 Visit or the subject's participation in the study is completed (SAEs through 30 days after final dose study drug). Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator believes follow-up is not necessary.

bb. For subjects who do not continue into an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in VBP15-006 Dose-tapering Period to confirm the final SAE status of the subject.

cc. Subjects who elect to continue vamorolone therapy by enrolling directly into an expanded access or compassionate use program or who will transition directly to SoC glucocorticoid therapy may be discharged from the study following completion of all final Week 12 assessments.

dd. Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments (Week 16).

6.3.1 Screening Period (Day -33 to -2), Paragraph 2

Original Text:

Following the signing of the written ICF, subjects will be considered to be enrolled in the study, and will be assigned a unique site-specific 6-digit subject ID number that will be comprised of protocol, site, and subject numbers in sequential order of screening into the study. All data will be identified using the unique subject ID number. The site Investigator will keep a record relating the names of the subjects to their subject ID numbers (subject identification log) to permit efficient verification of data subject files, when required. This record will also include the dates of subject enrollment and completion/termination. The Coordinating Center will not collect

names or other identifiers except dates (diagnosis, study visits), date of birth, and the subject ID number.

Revised Text:

Following the signing of the written ICF, subjects will be considered to be enrolled in the study and will be assigned a unique site-specific 6-digit subject ID number that will be comprised of protocol, site, and subject numbers in sequential order of screening into the study. All data will be identified using the unique subject ID number. The site Investigator will keep a record relating the names of the subjects to their subject ID numbers (subject identification log) to permit efficient verification of data subject files, when required. This record will also include the dates of subject enrollment and completion/termination. The Coordinating Center will not collect names or other identifiers except dates (diagnosis, study visits), age at enrollment, and the subject ID number.

6.3.4 Treatment Period (Weeks 1-12), Paragraphs 1-3

Original Text:

Subjects will return to the study site for safety, PK, clinical efficacy, PD, behavior and neuropsychology, and physical functioning beginning at Week 2 and continuing through the Week 12 Visit, according to the schedule of assessments in **Table 7**.

Subjects will continue to receive daily oral administration of vamorolone suspension according to their assigned treatment throughout the 12-week Treatment Period. The daily dose of study medication should be taken with breakfast.

Dosing is to occur at home throughout the 12-week Treatment Period, except at the Weeks 2 and 12 study visits, when dosing will occur at the study site. Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the Weeks 2 and 12 study visits. Breakfast will be served at the study site after the blood collections for clinical laboratory tests and Vitamin D (Week 12 only); pre-dose blood draw for plasma PK analysis (Week 2 only); and blood draws for PD biomarkers, including insulin, glucose, HbA1c, morning cortisol, osteocalcin, CTX, P1NP (Week 12 only); and within 30 minutes prior to administration of the dose of study medication. Blood samples for plasma PK analysis will also be collected pre-dose and at several time points post-dose at the Week 2 Visit (see **Section 7.2.7**). Ease of Administration of Study Medication Administration (ages 2 to <4 years) and Study medication Acceptability (7 to <18 years) will be assessed at the Weeks 6 and 12 Visits. Apart from blood and urine sample collections, all other scheduled assessments should be performed after administration of the study medication in clinic.

Revised Text:

Subjects will return to the study site for safety, PK, clinical efficacy, PD, behavior and neuropsychology, and physical functioning assessments beginning at Week 2 and

continuing through the Week 12 Visit, according to the schedule of assessments in **Table 7**.

Subjects will continue to receive daily oral administration of vamorolone suspension according to their assigned treatment throughout the 12 week Treatment Period. The daily dose of study medication should be taken with breakfast.

Dosing is to occur at home throughout the 12-week Treatment Period, except at the Week 2, 6, and 12 study visits, when dosing will occur at the study site. Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the Weeks 2, 6, and 12 study visits. Breakfast will be served at the study site after the blood collections for clinical laboratory tests (all visits) and Vitamin D (Week 12 only); pre-dose blood draw for plasma PK analysis (Week 2 only); and blood draws for PD biomarkers, including insulin, glucose, HbA1c, morning cortisol, osteocalcin, CTX, P1NP (Week 12 only); and within 30 minutes prior to administration of the dose of study medication. Blood samples for plasma PK analysis will also be collected pre-dose and at several time points post-dose at the Week 2 Visit (see **Section 7.2.7**). Ease of Administration of Study Medication Administration (ages 2 to <4 years) and Study Medication Acceptability (7 to <18 years) will be assessed at the Weeks 6 and 12 Visits. Apart from blood and urine sample collections, all other scheduled assessments should be performed after administration of the study medication in clinic.

6.4 Subject Discontinuation, Paragraph 1

Original Text:

Any subject who chooses to withdraw from the study after Day 1 and prior to the Week 12 Visit should return to the study site for Week 12 assessments at the time of early withdrawal, whenever possible (see **Section 6.3.4**), assuming the subject has not withdrawn consent, and will participate in the 4-week Dose-tapering Period. Site personnel will document all assessments, including any AEs, in the source documents and eCRF.

Revised Text:

Any subject who chooses to withdraw from the study after Day 1 and prior to the Week 12 Visit should return to the study site for Week 12 assessments at the time of early withdrawal, whenever possible (see **Section 6.3.4**), assuming the subject has not withdrawn consent, and will participate in the 4-week Dose-tapering Period. Site personnel will document and evaluate all assessments, including any AEs and lab results, in the source documents and eCRF.

6.4 Subject Discontinuation, Paragraph 9

Original Text:

Subjects will have non-fasting blood and urine samples collected for clinical laboratory tests at the final Early Termination/Week 16 Visit. Subjects will also have a physical examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including SAEs, and concomitant medications will be assessed. Subject diaries will be returned and reviewed with site staff.

Revised Text:

Subjects will have non-fasting blood and urine samples collected for clinical laboratory tests at the final Early Termination/Week 16 Visit. Subjects will also have a physical examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including SAEs, lab results, and concomitant medications will be assessed and documented. Subject diaries will be returned and reviewed with site staff.

7.1 Demographic Assessments

Original Text:

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

Revised Text:

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

7.2.2 Physical Examination, Cushingoid Features, Weight, and Height, Paragraph 3

Original Text:

Height (in cm) will be recorded at Screening and Week 12. Standing height will be recorded for subjects in the 2 to <4 years age group. Ulnar length of the non-dominant arm, measured from the olecranon (point of elbow) to the styloid process (prominent bone of the wrist), will be used to calculate height for subjects in the 7 to <18 years age group (see Manual of Operations for a detailed description of methodology).

Revised Text:

Height (in cm) will be recorded at Screening and Week 12. Standing height will be recorded for subjects in the 2 to <4 years age group and all participants in the 7 to <18 years age group who can stand independently. Ulnar length of the non-dominant arm,

measured from the olecranon (point of elbow) to the styloid process (prominent bone of the wrist), will be used to calculate height for subjects in the 7 to <18 years age group (see Manual of Operations for a detailed description of methodology).

7.2.4 Clinical Laboratory Tests, Paragraph 1

Original Text:

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, during the Screening Period, at the Day 1, Week 6, Week 12, and Week 16 Visits. Blood for vitamin D is collected at the Screening and Week 12 Visits only. Fasted blood samples for clinical laboratory tests will be collected pre-dose at the Day 1 and Week 12 Visits. Non-fasted blood samples for clinical laboratory tests will be collected at the Screening, and Weeks 6 and 16 Visis. Urine samples may be collected non-fasting at all scheduled visits. Details of blood and urine collections can be found in the Laboratory Manual.

Revised Text:

Each subject will have blood drawn and urine collected for the hematology, chemistry, lipids, and urinalysis clinical laboratory tests listed in **Table 9** and **Table 10** below, during the Screening Period, at the Day 1, Week 6, Week 12, and Week 16 Visits. Blood for vitamin D is collected at the Screening and Week 12 Visits only. Fasted blood samples for clinical laboratory tests will be collected pre-dose at the Day 1, Week 2, Week 6, Week 12, and Week 16 Visits. Urine samples may be collected non-fasting at all scheduled visits. Details of blood and urine collections can be found in the Laboratory Manual.

7.2.4 Clinical Laboratory Tests, Table 9, Chemistry

Original Text:

Chemistry	
Sodium	Total Bilirubin[a]
Potassium	Uric Acid
Chloride	Glucose
Calcium	Glutamate dehydrogenase (GLDH)
Inorganic Phosphorus	Alkaline phosphatase (ALP)
Blood Urea Nitrogen (BUN)	Gamma Glutamyl Transferase (GGT)
Creatinine	Aspartate aminotransferase (AST)
Total Protein	Alanine aminotransferase (ALT)
Albumin	Creatine kinase (CK)

Bicarbonate	Lipase
Lactate Dehydrogenase (LDH)	Amylase
Cystatin C	Vitamin D[b]

Revised Text: Table 4.

Chemistry	
Sodium	Total Bilirubin[a]
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)	Vitamin D[b]
Cystatin C	

7.2.7 Pharmacokinetic Assessment, Paragraph 4

Original Text:

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

Revised Text:

If PK and PD or clinical laboratory blood samples are to be collected at the same time point, the PK blood sample should be collected in the order specified in the laboratory collection flow chart.

7.2.8 Total Blood Volume Required

Original Text:

The number and volume of blood samples and total volume of blood to be collected from each subject throughout the duration of the up-to-21-week study are summarized in **Table 11**. A total of 49 mL of blood will be collected from each 2 to <4 year

subject, and 57 mL of blood will be collected from each 7 to <18 year subject over the course of the up to-21-week study.

Revised Text:

The number and volume of blood samples and total volume of blood to be collected from each subject throughout the duration of the up-to-21-week study are summarized in **Table 12** A total of 48.3 mL of blood will be collected from each 2 to <4-year-old subject, and 52.3 mL of blood will be collected from each 7 to <18-year-old subject over the course of the up to-21-week study.

7.2.8 Total Blood Volume Required, Table 12

Original Text: Table 12

Test	Blood Volume (mL)						
	SCR	Day 1	Week 2	Week 6	Week 12	Week 16	Total Volume
Clinical Safety Labs[a]	3	3[b]		3	3[b]	3	15
Varicella Zoster IgG	2						2
Vitamin D	2				2[b]		4
PD Biomarker Panel[c]		5[b]			5[b]		10
HbA1c	1				1[b]		2
PK[d]							
Ages 2 to <4 years		8	8				16
Ages 7 to <18 years		12	12				24
Total Volume by Visit (mL)	8			3	11	3	
Ages 2 to <4 years		16	8				49
Ages 7 to <18 years		20	12				57
Total Volume: 49 mL (2 to <4 year); 57 mL (7 to <18 year)							

SCR = Screening

[a] Hematology, Chemistry, Lipids; volume includes blood for exploratory PD biomarkers.

[b] Subjects must have fasted ≥ 6 hours prior to blood draws.

[c] Fasting glucose, insulin, morning cortisol, CTX, P1NP, osteocalcin; pre-dose on Day 1 and Week 12.

[d] Blood drawn for population PK within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (2 to <4 year), or 30 minutes pre-dose and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (7 to <18 year). Subjects must be fasting at the time of collection of the Day 1 and Week 2 pre-dose samples.

Revised Text: Table 7

Test	Blood Volume (mL)						
	SCR	**Day 1**	**Week 2**	**Week 6**	**Week 12**	**Week 16**	**Total Volume**
Clinical Safety Labs[a]	3.5[b]	3.5[b]		3.5[b]	3.5[b]	3.5[b]	17.5
Varicella Zoster IgG	2						2
Vitamin D	1.2				1.2[b]		2.4
PD Biomarker Panel[c]		8.2[b]			8.2[b]		16.4
HbA1c	1				1[b]		2
PK[d]							
Ages 2 to <4 years		4	4				8
Ages 7 to <18 years		6	6				12
Total Volume by Visit (mL)	7.7			3.5	13.9	3.5	
Ages 2 to <4 years		15.7	4				48.3
Ages 7 to <18 years		17.7	6				52.3
Total Volume: 48.3 mL (ages 2 to <4 year); 52.3 mL (ages 7 to <18 year)							

SCR = Screening

[a] Hematology, Chemistry, Lipids

[b] Subjects must have fasted ≥ 6 hours prior to blood draws.

[c] Fasting glucose, insulin, morning cortisol, CTX, P1NP, osteocalcin; pre-dose on Day 1 and Week 12.

[d] Blood drawn for population PK within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), or 30 minutes pre-dose and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years). Subjects must be fasting at the time of collection of the Day 1 and Week 2 pre-dose samples.

7.6 Adverse Events and Serious Adverse Events

Original Text:

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.

Revised Text:

The condition of the subjects, inclusive of lab values, will be monitored throughout the duration of the study by the clinical site study team and by recording of AEs in subject diaries.

7.6.3 Clinical Laboratory Test Abnormalities, Paragraph 1

Original Text:

Clinical laboratory test results will be recorded on the designated eCRF page. The intensity of abnormal clinical laboratory test results that are AEs will also be graded using the most current version of the CTCAE, version 4.03, 5-point scale and reported

in detail as indicated in the eCRF. A description of the intensity scale can be found above.

Revised Text:

Clinical laboratory test results will be recorded on the designated eCRF page. The intensity of abnormal clinical laboratory test results that are AEs will also be graded using current FDA and the Council for International Organizations of Medical Sciences (CIOMS) drug-induced liver injury (DILI) guidance and 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.

10.3.2 Modified Intent-to-Treat (mITT) Population

Original Text:

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

Revised Text:

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

15.1 Vamorolone Dose Calculation Worksheet and Bulk Dispensing Guide, Paragraph 3 and First Example

Original Text:

Calculated dose volume will be rounded to the nearest 0.01 mL (**1 mL syringe**), 0.1 mL (**3 mL syringe**), 0.2 mL (**5 mL syringe**), or 0.2 mL (**10 mL syringe**) depending upon the total dose volume and calibration of the volumetric syringe to be used for administration of dose, as shown in the examples below:

Example 5: Dose volume calculation for a subject receiving **2.0** mg/kg/day with a body weight of **23** kg:

$$\frac{\textit{Subject Weight (23 kg)} \times \textit{Dose Level (2.0 mg/kg)}}{\textit{40 mg/mL}} = \textit{1.15 mL}$$

The subject will receive a daily dose volume of 1.15 mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a 3 mL volumetric syringe rounded to the nearest 0.2 mL, or 1.2 mL daily.

Revised Text:

Calculated dose volume will be rounded to the nearest 0.01 mL (**1 mL syringe**), 0.2 mL (**5 mL syringe**), or 0.2 mL (**10 mL syringe**) depending upon the total dose volume and calibration of the volumetric syringe to be used for administration of dose, as shown in the examples below:

Example 1: Dose volume calculation for a subject receiving **2.0** mg/kg/day with a body weight of **23** kg:

$$\frac{\textit{Subject Weight (23 kg) x Dose Level (2.0 mg/kg)}}{\textit{40 mg/mL}} = \textit{1.15 mL}$$

The subject will receive a daily dose volume of **1.15** mL per dose throughout the period until the next scheduled study medication dispensing visit. Dose will be administered using a **5** mL volumetric syringe rounded to the nearest 0.2 mL; i.e., **1.2** mL daily.

15.1.2 Vamorolone 4.0% Suspension Dispensing Guide, Paragraph 1

Original Text:

Each subject enrolled in the study will be dispensed 100 ml bottle(s) of vamorolone 4.0% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 6 Visit. Additional supplies will be dispensed at the Week 6 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4.0% suspension at the Week 12 Visit, sufficient for dose tapering to 0.0 mg/kg/day (see **Section 6.3.5**).

Revised Text:

Each subject enrolled in the study will be dispensed 125 ml bottle(s) of vamorolone 4.0% suspension at the Baseline Day 1 Visit, sufficient for dosing through the time of the scheduled Week 6 Visit. Additional supplies will be dispensed at the Week 6 Visit, sufficient for dosing through the time of the scheduled Week 12 Visit. Subjects whose vamorolone dose is tapered during the Dose-tapering Period will be dispensed additional vamorolone 4.0% suspension at the Week 12 Visit, sufficient for dose tapering to 0.0 mg/kg/day (see **Section 6.3.5**).

15.3. Protocol Amendment #2 Complete List of Changes

A Protocol version tracking changes between Edition A1 version 1.1 and A2 version 1.0 will be provided.

The following changes have been incorporated into the protocol under this protocol amendment, as summarized in the Protocol Amendment Tracking, Reasons for Protocol Amendment #2. Protocol sections that have been changed are itemized below with the original and revised text. Changes that were strictly editorial (e.g., punctuation, correction of spelling errors) are not included.

Protocol cover page

Original Text:

Sponsor: ReveraGen BioPharma, Inc.
155 Gibbs St.
Suite 433
Rockville, MD 20850

Study Chair: PPD
Phone:
Email: PI

Medical Monitor: PI
Phone:
Email: PI

Revised Text:

Sponsor: Santhera Pharmaceuticals (Switzerland) Ltd
Hohenrainstrasse 24
4133 Pratteln
SwitzerlandSanthera Pharmaceuticals Ltd

Principal Investigator: Jean Mah, M.D.

Email: PI

Medical Monitor: PI

Email: PI

SIGNATURES OF AGREEMENT FOR VBP15-006

Original Text:

Reviewed and Approved by:

_____ _____

PI
PPD
ReveraGen BioPharma, Inc.

Date

_____ _____

PPD
Study Chair
Alberta Children's Hospital Research Institute
University of Calgary

Date

_____ _____

PI
Medical Monitor
PPD
ReveraGen BioPharma, Inc.

Date

Revised Text:

Reviewed and Approved by:

_____ _____

PI
PPD
Santhera Pharmaceuticals Ltd

Date

Investigator Protocol Agreement

Original Text:

PROTOCOL NUMBER: VBP15-006

SPONSOR: ReveraGen BioPharma, Inc.

DOCUMENT DATE: 14 April 2022

By my signature, I confirm that my staff and I have carefully read and understand this protocol, protocol amendment, amended protocol, or revised protocol and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by ReveraGen BioPharma, Inc.
I agree to conduct the study according to this protocol and the obligations and requirements of clinical Investigators and all other requirements set out in the Declaration of Helsinki listed in 21 CFR part 312, and ICH principles of Good Clinical Practice (GCP) and in accordance with all applicable laws, guidances and directives of the jurisdiction where the study is being conducted. I will not initiate this study without the approval of an Institutional 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, I agree not to implement the amendment without agreement from ReveraGen BioPharma, Inc. and prior submission to and written approval (where required) from the IRB/IEC, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

_____ _____
Investigator's Signature Date

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

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

Revised Text:

PROTOCOL NUMBER: VBP15-006

SPONSOR: Santhera Pharmaceuticals Ltd

DOCUMENT DATE: 09 February 2023

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 Santhera Pharmaceuticals (Switzerland) Ltd.

I agree to conduct the study according to this protocol and the obligations and requirements of clinical Investigators and all other requirements set out in the Declaration of Helsinki listed in 21 CFR part 312, and ICH principles of Good Clinical Practice (GCP) and in accordance with all applicable laws, guidances and directives of the jurisdiction where the study is being conducted. I will not initiate this study without the approval of an Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

I understand that, should the decision be made by Santhera Pharmaceuticals (Switzerland) Ltd 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 Santhera Pharmaceuticals (Switzerland) Ltd.

For protocol amendments, I agree not to implement the amendment without agreement from Santhera Pharmaceuticals (Switzerland) Ltd and prior submission to and written approval (where required) from the IRB/IEC, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

_____ _____

Investigator's Signature Date

_____

Investigator's Name (Please print)

Address (Please print):

RETAIN THE ORIGINAL (WET-INK OR VALIDATED E-SIGNATURE) SIGNED AGREEMENT AT YOUR SITE AND SEND A SCANNED COPY OF THE SIGNED

ORIGINAL TO SANTHERA PHARMACEUTICALS (SWITZERLAND) LTD, OR DESIGNEE

Study Synopsis, Name of the Sponsor

Original Text:

ReveraGen Bio Pharma, Inc

Revised Text:

Santhera Pharmaceuticals (Switzerland) Ltd

Study Synopsis, Investigational Drug Product

Original Text:

Vamorolone, 4.0% wt/vol suspension for oral dosing

Revised Text:

Vamorolone, 4.0% weight per volume (wt/vol) suspension for oral dosing

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Study Synopsis, Drug substance

Original Text:

delta-1,4,9(11)-pregnatriene-17-alpha,21-dihydroxy-16-alpha-methyl-3,20-dione

Revised Text:

17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione

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Study Synopsis, Study Design

Original Text:

The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month open-label Treatment Period (Weeks 1-12); and a 4-week open-label Dose-tapering Period (Week 13-16) for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study.

Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent, is obtained.

- **Within the 2 to <4 years age group,** the initial 10 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 10 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.
- **Within the 7 to <18 years age group**, both corticosteroid-treated and untreated, the initial 12 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 12 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

Revised Text:

The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month open-label Treatment Period (Weeks 1-12); and a 4-week Dose-tapering Period for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study.

Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent and assent, as required, is obtained.

- **Within the 2 to <4 years age group,** the initial 10 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 10 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.
- **Within the 7 to <18 years age group** (including an additional 12 to <18 years age group), both corticosteroid-treated and untreated, the initial 12 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 22 eligible subjects (including 10 subjects from the additional 12 to <18 years age group) will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

Study Synopsis, Planned Sample Size

Original Text:

A total of approximately 24 subjects will be enrolled to treatment within the 7 to <18 years age group, with 2.0 mg/kg/day groups enrolled first, as follows:

- Vamorolone 2.0 mg/kg/day, steroid untreated at entry (n=6)
- Vamorolone 2.0 mg/kg/day, steroid treated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, steroid untreated at entry (n=6)

- Vamorolone 6.0 mg/kg/day, steroid treated at entry (n=6)

Revised Text:

A total of approximately 34 subjects will be enrolled to treatment within the 7 to <18 years age group, with 2.0 mg/kg/day groups enrolled first, as follows:

- Vamorolone 2.0 mg/kg/day, steroid untreated at entry (n=6)
- Vamorolone 2.0 mg/kg/day, steroid treated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, steroid untreated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, steroid treated at entry (n=6)
- Vamorolone 6.0 mg/kg/day, 12 to <18 years and steroid treated at entry (n=10, additional group)

Study Synopsis, Individual Subject, Study Duration

Original Text:

Up to approximately 21 weeks:

- Screening Period: up to 5 weeks
- Baseline Period: 1 day
- Treatment Period: 12 weeks (Weeks 1-12)
- Dose-tapering Period: 4 weeks (only for subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the study) (Weeks 13-16)

Revised Text:

Up to approximately 21 weeks:

- Screening Period: up to 5 weeks
- Baseline Period: 1 day
- Treatment Period: 12 weeks (Weeks 1-12)
- Dose-tapering Period: 4 up to 8 weeks, only for subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the study.

Study Synopsis, Study Drug Formulation, Dosage & Administration

Original Text:

Treatment Period and Dose-tapering Period

Subjects will be administered 4.0% wt/vol oral suspension (Formulation route of synthesis 2 [ROS2]). and individual patients receiving 2 mg/kg can increase their dose to the high dose level if deemed appropriate by the investigatorAll subjects in both age groups: vamorolone 4.0% wt/vol oral suspension (investigational medicine) will be administered once daily over the 12-week Treatment Period (Weeks 1-12) and during the 4-week Dose-tapering Period, as applicable. The site pharmacist will dispense study medication in 125 mL bottles sufficient for 6 weeks of dosing (4 weeks for Dose-tapering Period) plus overage to subjects at the Day 1 and Week 6 Visits (and Week 12 Visit to subjects participating in the Dose-tapering Period), according to the subject's assignment to a dose group and subject body weight recorded at the dispensing visit (Day -1 weight for Day 1 dispensing).

Revised Text:

Treatment Period and Dose-tapering Period

Subjects will be administered 4.0% wt/vol oral suspension (Formulation route of synthesis 2 [ROS2]).

The planned vamorolone doses are 2 mg/kg and 6 mg/kg daily. The initial patients enrolled in each age group will receive 2 mg/kg/day to confirm the PK and safety of vamorolone in both age groups at this dose level. After review of the PK and safety data from at least 6 patients in each age cohort, subsequent patients can be enrolled at the 6 mg/kg /day dose level. If the intended dose of vamorolone is 6 mg/kg/day, AND patients weigh 50 kg or more, the daily dose should be capped at 300mg. Considering the linearity of vamorolone pharmacokinetics, if the intended patient dose is 2mg/kg/day, the dose is capped at 100mg per day for patients weighing 50kg or more.. All subjects: vamorolone 4.0% wt/vol oral suspension (investigational medicine) will be administered once daily over the 12-week Treatment Period (Weeks 1-12) and during the Dose-tapering Period, if applicable.

Study Synopsis, Study Summary

Original Text:

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects in both age groups, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit. Study drug dosing will occur at home on all days except

dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site

Revised Text:

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day (for participants weighing 50kg and over, the dose is capped at 100mg/day) or 6.0 mg/kg/day (for participants weighing 50kg and over, the dose is capped at 300mg/day), beginning the next day on Treatment Period Day 1. For all subjects, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit. Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site.

Study Synopsis, Safety Measures

Original Text:

Grading of clinical and clinical laboratory AEs will be according to the Common Terminology Criteria for Adverse Events (CTCAE), v.4.03

Revised Text:

Grading of clinical and clinical laboratory AEs will be according to the Common Terminology Criteria for Adverse Events (CTCAE), v5.0

Study Synopsis, Statistical methods

Original Text:

Sample Size:

For this Phase II study in DMD boys ages 2 to <4 years and 7 to <18 years, a total of approximately 20 subjects in the 2 to <4 years age group will be enrolled with approximately 10 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day). A total of approximately 24 subjects in the 7 to <18 years age group will be enrolled with approximately 12 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day) and each dose level group stratified 1:1 by glucocorticoid treatment status at study entry to include approximately 6 subjects glucocorticoid-untreated and 6 subjects glucocorticoid-treated at study entry. This sample size is considered sufficient to detect drug safety concerns in a pediatric population ages 2 to <4 and 7 to <18 years with DMD based on clinical judgment and prior study of vamorolone at these doses. In addition, this sample size is sufficiently large to determine PK parameters.

(…)

Pharmacodynamic Analyses:

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of safety and efficacywill be assessed.

Revised Text:

Sample Size:

This is an open-label, multiple dose study. Study medication is administered daily in this Phase II trial.

For this Phase II study in DMD boys ages 2 to <4 years and 7 to <18 years, a total of approximately 20 subjects in the 2 to <4 years age group will be enrolled with approximately 10 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day). A total of approximately 34 subjects in the 7 to <18 years age group will be enrolled with approximately 12 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day) and each dose level group stratified 1:1 by glucocorticoid treatment status at study entry to include approximately 6 subjects glucocorticoid-untreated and 6 subjects glucocorticoid-treated at study entry, to which 10 subjects 12 to <18 years are added to the 6 mg/kg dose level. This sample size is considered sufficient to detect drug safety concerns in a pediatric population ages 2 to <4 and 7 to <18 years with DMD based on clinical judgment and prior study of vamorolone at these doses. In addition, this sample size is sufficiently large to determine PK parameters.

(…)

Pharmacodynamic Analyses:

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of safety and efficacy, including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4), will be assessed.

1.1 Background and Unmet Need

Original Text:

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. 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. 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.

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-κB) activation, are evident during early disease stages and play a significant role in muscle wasting. NF-κB has been shown to regulate the expression of numerous inflammatory genes in immune cells and muscle fibers, and the infiltration and activation of these cells can trigger muscle fiber death.

Although significant advances have been made in understanding the etiology of DMD, a cure has not been found, and until recently treatment options were medications used "off- label" to alleviate the symptoms of DMD. Despite scientific advances, only glucocorticoids, such as prednisone or deflazacort, have consistently demonstrated efficacy in clinical trials. Indeed, the United States Food and Drug Administration (US FDA) recently approved deflazacort as a treatment for DMD. 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 adverse effect profiles, often limiting long-term administration. A current goal of DMD research is to find a mutation-independent treatment that matches or exceeds the efficacy of glucocorticoids with a significantly lower adverse 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, prednisolone, methylprednisolone, and dexamethasone. The chemical structure of vamorolone has optimized five subactivities of traditional glucocorticoid drugs, namely transactivation, transrepression, physiochemical membrane properties, is not a substrate for the corticosteroid modulatory 11β-hydroxysteroid dehydrogenase enzymes (11BHSD1, 11BHSD2), and is a potent mineralocorticoid receptor antagonist. Comparative structure/activity relationship studies using the active metabolites of prednisone, deflazacort, and vamorolone have demonstrated differential binding of vamorolone to the target glucocorticoid receptor, and downstream changes in pharmacodynamics. By reducing transactivation subproperties, retaining transrepression, imparting membrane stabilizing properties, and inhibiting the mineralocorticoid receptor pathway, and lack of inactivation by 11β-hydroxysteroid dehydrogenase enzymes, vamorolone has favorable efficacy and adverse effect profiles relative to classic glucocorticoids in nonclinical models and is anticipated to be an attractive candidate for the treatment of DMD in pediatric patients.

In vitro, nonclinical, and clinical data to date suggest that vamorolone may offer a much needed alternative to the current glucocorticoids which are standard of care for DMD 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. The cumulative adverse 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. Glucocorticoids also contribute to further muscle damage with long-term administration. Vamorolone has shown few if any of the adverse effects of traditional glucocorticoids in mouse models of DMD.

This study is designed to explore, in DMD boys ages 2 to <4 years and 7 to <18 years, whether vamorolone will show similar efficacy to glucocorticoids with a more favorable adverse effect profile, thereby improving the quality of life for these DMD patients. This profile would enable use of vamorolone in DMD boys 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-□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. Further, vamorolone has been recently demonstrated to improve asynchronous remodeling, believed to be a component of progressive muscle weakness and wasting in DMD 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. Finally, vamorolone imparts physical stability to myofiber plasma membranes, whereas prednisolone destabilizes membranes. This property addresses the primary defect of membrane instability in dystrophin deficient myofibers in DMD.

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.

Revised Text:

DMD is the most common childhood muscular dystrophy with a birth incidence worldwide of 1 in 3,600 to 9,300 males [Mah et al, 2014]. Clinical characteristics of DMD are proximal muscle weakness presenting in childhood and progressive involvement of most muscle groups, leading to loss of ambulation late in the first decade or early in the second decade of life. Weakness progresses, with the patient requiring assistance with the activities of daily living by the late teens or in their early

twenties. Patients with DMD often succumb from respiratory failure and/or cardiac failure.

DMD is an X-linked recessive disorder caused by mutations in the *DMD* gene [Koenig 1987] which codes for the dystrophin protein that provides structural stability to the dystrophin-associated glycoprotein complex on muscle cell membranes [Hoffman et al, 1987]. The lack of dystrophin reduces plasma membrane stability, resulting in membrane fragility and necrosis [Evans et al, 2009].

Upregulated inflammatory gene expression and activated immune cell infiltrates are present during early disease stages and play a significant role in muscle wasting [Chen et al, 2005]. The transcription factor NF-κB has been shown to regulate the expression of numerous inflammatory genes in immune cells and muscle fibers [Pahl, 1999; Dogra et al, 2006; Acharyya et al, 2007; Kumar et al, 2003] and the infiltration and activation of these cells can trigger muscle fiber death [Acharyya et al, 2007].

GR agonists, such as prednisone and deflazacort [Malik et al, 2012] are currently the cornerstone for the treatment of patients with DMD according to American Academy of Neurology practice guidelines [Gloss et al, 2016] and the DMD Care Considerations Working Group [Birnkrant et al, 2018]. The benefits of long-term glucocorticoid therapy have been shown to include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery [Birnkrant et al, 2018].

The adverse effects of glucocorticoids include weight gain, cushingoid appearance, growth delay, behavior changes, an increased frequency of vertebral fractures, skin fragility, cataract, increased intra ocular pressure, adrenal suppression, insulin resistance [Kauh et al, 2012] and muscle atrophy [Schakman et al, 2013]. These adverse drug reactions (ADRs) negatively impact quality of life and cause considerable variation in clinical practice including suboptimal dosing [Griggs et al, 2013; Bello et al, 2015].

The significant adverse effects of glucocorticoids on growth also prevent their routine administration in infants or toddlers, despite evidence that better outcomes are achieved with earlier administration [Merlini et al, 2012; Pane et al, 2014; Ciafaloni et al, 2016; Connolly et al, 2019; McMillan 2019; Buckon et al, 2022].

There is therefore an ongoing need to develop glucocorticoids with a better safety profile.

Rationale to develop vamorolone for DMD

Preclinical and clinical studies have shown that vamorolone addresses the anti-inflammatory activity of the GR and avoids some of its unwanted effects such as growth stunting, inhibition of bone metabolism, and induction of neutrophilia.

The anti-mineralocorticoid activity of vamorolone, as shown in the preclinical studies may be beneficial since the renin-angiotensin-aldosterone axis is thought to be involved in the pathogenesis of skeletal muscle fibrosis and cardiomyopathy in DMD [Rodriguez-Gonzalez et al, 2021; Howard et al, 2022].

In addition, the lack of activation/inactivation of vamorolone by 11-β-HSD 1 and 2 may be an advantage since the pharmacological activity of prednisone, including some of its adverse effects such as osteoporosis, is linked to its local activation to prednisolone by 11- β-HSD 1 [Fenton et al, 2019; Morgan et al, 2014; Fenton et al, 2021; Webster et al, 2021; Cooper et al, 2003].

Lastly, the observed effect of cell membrane repair after injury in mice may be particularly relevant for dystrophin-deficient cells in DMD where plasma membranes are inherently unstable.

Based on this differentiated profile, vamorolone has the potential to combine the known efficacy of glucocorticoids in DMD with a better safety profile.

1.2 Nonclinical Experience Section

Original Text:

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

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

Revised Text:

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*. Refer to the current IB for updated information on the nonclinical experience of vamorolone.

Sections 1.2.1. Safety Pharmacology, 1.2.2. Pharmacokinetics and metabolism, 1.2.3 Toxicology

Revised text:

These sections are deleted and reference is made to the current IB version

1.3 Clinical experience

Original Text:

Clinical experience with vamorolone is comprised of a completed Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001), completed Phase IIa (VBP15-002) and Phase II extension (VBP15-003) trials in DMD boys, completed Phase II long-term extension (VBP15-LTE) trial in DMD boys, and a completed Phase IIb active- and placebo-controlled trial in DMD boys (VBP15-004). Furthermore, two

relative bioavailability and food effect studies have been conducted (VBP15-PKFORM and VBP15-PKFORM-002) comparing the formulation used in clinical studies (ROS1) with the to-be-marketed formulation (ROS2).

Revised Text:

Clinical experience with vamorolone is comprised of a completed Phase I clinical trial of vamorolone in healthy adult volunteers (VBP15-001), completed Phase IIa (VBP15-002) and Phase II extension (VBP15-003) trials in DMD boys, completed Phase II long-term extension (VBP15-LTE) trial in DMD boys, and a completed Phase IIb active- and placebo-controlled trial in DMD boys (VBP15-004). Vamorolone is extensively metabolized in the liver hence the impact of an impaired hepatic function on vamorolone PK was assessed in a clinical study in adult volunteers with moderate impaired hepatic function [VBP15-HI]. [VBP15-DDI] study investigated the effect of itraconazole on the PK of on a single dose of vamorolone in healthy subjects. Furthermore, two relative bioavailability and food effect studies have been conducted (VBP15-PKFORM and VBP15-PKFORM-002) comparing the formulation used in clinical studies (ROS1) with the to-be-marketed formulation (ROS2).

Section 1.3. All subsections (1.3.1. to 1.3.4.)

Revised text:

These sub-sections of 1.3. are deleted and reference is made to the current IB version

1.4 Pharmacokinetics of Vamorolone

New section. Rationale for study design, former Section 1.4., is moved to Section 1.6..

Revised text:

The PK of vamorolone in subjects with DMD aged 4 to 7 years was thoroughly evaluated with intense PK sampling on Days 1 and 14 of daily vamorolone administration in Study VBK15-002. Vamorolone peak plasma concentrations occurred on average 2 to 4 hours after dosing, exposure increased linearly with dose and the exposure after 6.0 mg/kg/day in terms of mean (SD) Cmax and AUC0-inf was 970 (270) ng/mL and 3606 (897) ng.hr/mL, respectively on Day 14). The mean (SD) t½ of vamorolone at 6.0 mg/kg/day was 1.4 (0.35) hours and no accumulation is observed with daily administration.

The Population PK (PPK) evaluation based on PK data from studies VBP15-002 and VBP15-004 estimated the CL/F and V/F values for a typical DMD patient weighing 20 kg and taking vamorolone with a meal as 58 L/hr and 162 L, respectively The PPK estimate vamorolone Tmax is 2.4 hours, the estimated elimination half-life in DMD boys is 1.9 hours and the calculated exposure at steady state after 6.0 mg/kg/day in terms of Cmax and AUC0-inf was 555 ng/mL and 2944 ng.hr/mL, respectively, in a typical DMD patient weighing 20 kg and taking vamorolone with a meal.

The results of the two bioavailability/food effect studies (VBP15-PK-FORM and VBP15-PK-FORM-002) support the change from the Clinical Formulation (ROS1) to the To-be-marketed Formulation (ROS2/fine). The To-be marketed Formulation (ROS2/fine) demonstrates a lower food effect than the Clinical Formulation (ROS1) and offers more reliable dosing (i.e., more consistent exposure) when taken with different types of food.

Hepatic impairment increases the exposure to vamorolone. Subjects with moderate HI had 1.7 and 2.6-fold higher Cmax and AUC0inf values compared to age, weight and sex matched healthy adults

The PK evaluation based on all 18 subjects showed no relevant increase in peak concentrations of vamorolone in the presence of the potent CYP3A4 inhibitor itraconazole, but AUC0-inf increased by 33.7%. Median Tmax of vamorolone was 2 hours when administered alone and was delayed when combined with itraconazole (4 hours). Thus, itraconazole has a weak effect on vamorolone PK.

Refer to the current IB version for full and updated clinical pharmacology information

1.5 Safety and Efficacy of Vamorolone in DMD (Study VBP-004)

New section. Overall Benefit/Risk, former Section 1.5., is moved to Section 1.7..

Revised Text:

The results of study VBP15-004, a randomized, double-blind, placebo controlled and prednisone referenced study showed that vamorolone produced clinically meaningful, statistically significant, and robust improvements in multiple measurements of lower limb motor function compared to placebo after 24 weeks of treatment. The improvements in motor function with vamorolone were similar to those seen with prednisone, a standard of care for children with DMD. The positive effects achieved at 24 weeks with vamorolone 6 mg/kg remained stable over the course of the second period of the pivotal trial up to 48 weeks, both for patients who remained on vamorolone 6 mg/kg in both periods and for those who switched from prednisone 0.75 mg/kg to vamorolone 6 mg/kg. Although the magnitude of effects on motor function in vamorolone 2 mg/kg was less well maintained over time, an improvement compared to baseline was still observed after 12 months.

In study VBP15-004, a higher proportion of subjects presented with a least one TEAE in the vamorolone 2 and 6 mg/kg groups (83.3% and 89.3%, respectively) compared to placebo (79.3%) but in line with the prednisone 0.75 mg/kg group (83.9%). Clinically-relevant TEAEs, pre-defined as moderate to severe events, SAEs, or events leading to discontinuation, were reported at similar rates in the placebo (31.0%) and vamorolone 2 mg/kg groups (26.7%), less in the vamorolone 6 mg/kg group (14.3%), and more frequent in the prednisone 0.75 mg/kg group (41.9%). These results indicate that the increased proportion of subjects presenting with at least one TEAE in both of the

vamorolone groups compared to placebo was driven by an excess in mild TEAEs, while prednisone was also associated with an increase in moderate to severe events.

Adverse Events of Special Interest, pre-defined as groupings of events typically associated with glucocorticosteroid therapy, were reported in a similar percentage of subjects in the placebo (69.0%) and vamorolone 2 mg/kg (66.7%) groups and higher percentages in the prednisone 0.75 mg/kg (77.4%) and vamorolone 6 mg/kg (78.6%) groups.

The safety profile of vamorolone shares some risks with those described with glucocorticoids, such as

- Vamorolone causes dose-dependent adrenal suppression. The level of adrenal suppression was slightly larger in vamorolone 6 mg/kg than prednisone 0.75 mg/kg based on mean morning cortisol values, while the vamorolone 2 mg/kg had a partial effect.
- Cushingoid features were frequently reported dose-dependent AEs with vamorolone. The incidence of cushingoid features were similar in vamorolone 6 mg/kg and prednisone 0.75 mg/kg. Most of the events were reported as non-clinically significant and did not lead to discontinuation of vamorolone.
- Vamorolone 6 mg/kg was associated with an increase in BMI compared to placebo and comparable to the effect seen in prednisone 0.75 mg/kg. Vamorolone 2 mg/kg showed a less pronounced effect of limited clinical relevance.
- Vamorolone 6 mg/kg was associated with an increased risk for behavioural problems, mainly mild irritability, which were more frequently reported in the first 6 months of treatment.
- Gastrointestinal symptoms were reported at similar frequency than placebo over the first 6 months of treatment but showed evidence for dose-dependency over the long-term treatment suggestive of a drug effect.

While the safety profile of vamorolone shares some risks with those described with glucocorticoids, it shows clinically relevant differences for a clinically improved safety profile in long-term therapy:

- Absence of a deleterious effect on biomarkers of bone metabolism
- Normal growth with any dose of vamorolone, supported by height z-scores similar to placebo at 6 months, remaining within the normal CDC growth curves at 12 months and in the long term in study VBP15-LTE, while evidence of growth stunting was already seen at Month 6 for the prednisone group.
- A reduced frequency and severity of behavior related events on 6 mg/kg vamorolone compared with prednisone, while 2 mg/kg vamorolone was similar to placebo.

In addition, the findings of the vamorolone development programs suggests the potential for other differential effect in the long-term safety profile of vamorolone, such as:

- Absence of a clinically relevant effect on glucose metabolism in study VBP15-004 and over up to 30 months of treatment in study VBP15-002/002/LTE
- Absence of an effect on neutrophil counts while neutrophilia was observed early after starting treatment with prednisone.
- Absence of cases of cataracts or increase in intraocular pressure in studies VBP15-004 and VBP15-002/003/LTE

Additional long-term data would be required to further characterize the risks.

These data support a positive benefit-risk profile for vamorolone at the 2 mg/kg and 6 mg/kg doses. The efficacy at the vamorolone 6 mg/kg dose is similar to current standard of care, prednisone, with an improved safety and tolerability profile compared to prednisone. The vamorolone 2 mg/kg shows robust efficacy compared to placebo at 24 weeks and a further improved safety and tolerability profile compared to vamorolone 6 mg/kg and prednisone 0.75 mg/kg.

Refer to the current IB version for full and updated clinical information.

1.6 Rationale for study

Original text

1.4 Rationale for study

The current Phase II study is designed to confirm the safe and tolerable dose(s) of vamorolone to be used to treat DMD in boys aged 2 to <4 years and 7 to <18 years, based upon safety and PK data, and to perform an exploratory evaluation of PD, clinical efficacy, behavior and neuropsychology, and physical functioning over a treatment period of 12 weeks. Steroid-naïve subjects in the 2 to <4 years age group will be recruited for study, dictated by 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. Enrollment of boys in the 7 to <18 years age group will be stratified to accommodate both glucocorticoid-treated and glucocorticoid-untreated subjects at time of study entry, to reflect real-world clinical experience with glucocorticoid treatment for DMD in older boys; analyses will be conducted separately for subjects in each glucocorticoid treatment group.

The vamorolone dose levels of 2.0 mg/kg/day and 6.0 mg/kg/day chosen for study have been shown to be safe and well-tolerated, and associated with improvements in muscle and strength assessments, in previous and ongoing vamorolone Phase II studies in boys 4 to <7 years of age. As a new route of synthesis of vamorolone, ROS2, will be used, boys will enroll into the 2.0 mg/kg/day group first, and drug exposure compared to previous ROS1 experience prior to enrolling into the higher 6.0 mg/kg/day dose group.

Subjects who meet all eligibility criteria in this study (VBP15-006) will be assigned to one of six treatment groups as shown in **Table 5.** Groups 1, 3, and 4 will be fully enrolled at 2.0 mg/kg/day prior to assignment of subsequent participants to Groups 2, 5, and 6 at 6.0 mg/kg/day.

Table 5. Study Assignment Schedule

Group	Planned Number of Subjects	Glucocorticoid Status	Ages 2 to <4 Years	Ages 7 to <18 Years
1	10	Naïve*	Vamorolone, 2.0 mg/kg/day	
2	10	Naïve*	Vamorolone, 6.0 mg/kg/day	
3	6	Untreated at entry		Vamorolone, 2.0 mg/kg/day/
4	6	Treated at entry		Vamorolone, 2.0 mg/kg/day/
5	6	Untreated at entry		Vamorolone, 6.0 mg/kg/day/
6	6	Treated at entry		Vamorolone, 6.0 mg/kg/day/

*Naïve is defined as having had no prior glucocorticoid treatment for DMD, and past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to enrollment, to be considered for enrollment on a case-by-case basis.

Group 1 (age 2 to <4 years, vamorolone 2.0 mg/kg/day), Group 3 (age 7 to <18 years untreated at entry, vamorolone 2.0 mg/kg/day), and Group 4 (age 7 to <18 years treated at entry, vamorolone 2.0 mg/kg/day) will be fully enrolled prior to Groups 2, 5 and 6 (6.0 mg/kg/day).

(…)

Pharmacodynamic safety biomarker findings in DMD patients receiving vamorolone 2.0 mg/kg/day or 6.0 mg/kg/day over 12 weeks will be compared within each age group. Serum PD biomarkers bridged to later clinical safety concerns will be assessed over time as exploratory safety measures. These PD biomarkers include:

1. **Adrenal suppression.** Pharmacological doses of glucocorticoids cause suppression of the hypothalamo-pituitary-adrenal axis, leading to low

concentration of endogenous cortisol and other steroidal hormones in serum. Adrenal suppression is directly associated with risk of adrenal crisis, delay of puberty and stunting of growth. Measurement of morning cortisol concentrations will reflect the degree of adrenal suppression. Plasma cortisol secretion typically follows a circadian pattern with the highest concentrations early in the morning; a morning serum cortisol concentration less than 3.6 µg/dL (or 100 nM) is highly suggestive of adrenal suppression.

2. **Bone turnover.** Pharmacological doses of glucocorticoids cause an imbalance of bone formation and bone resorption, leading to later osteopenia and bone fragility. Bone fragility is a significant adverse effect of chronic pharmacologic glucocorticoids in DMD as this can lead to fracture, which increases the likelihood of premature loss of ambulation. Serum biomarkers that have been bridged to later clinical outcomes of osteopenia are osteocalcin (bone formation; glucocorticoids decrease serum levels), aminoterminal propeptide of type I collagen (P1NP) (bone formation; glucocorticoids decrease serum levels), and CTX (bone resorption; glucocorticoids increase serum levels). Decreases of osteocalcin and P1NP and increases of CTX are reflective of abnormal bone turnover, a risk factor bridged to later bone fragility.

3. **Insulin resistance.** Insulin resistance is the term where increased blood glucose triggers increased insulin secretion from the pancreatic islet cells, but the elevated serum insulin fails to sufficiently trigger glucose uptake by muscle and/or liver. Thus, peripheral tissues are resistant to insulin signaling (insulin resistance). Insulin resistance has been bridged to later clinical outcomes, including heart disease, type 2 diabetes, and vascular disease. Serum biomarkers that are accepted as measures of insulin resistance are increased serum glucose and insulin. This can be measured after acute (hours after first dose) or chronic (after weeks or months of dosing) glucocorticoid treatment.

Additional exploratory safety outcomes are measures of additional serum safety biomarkers that have been defined in glucocorticoid-treated DMD and inflammatory

bowel disease patients. Additional exploratory measures of efficacy include PD biomarkers that have previously been shown to be glucocorticoid-responsive in DMD boys, pediatric inflammatory bowel disease, adult vasculitis, and pediatric myositis.

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

It is obligatory that the Investigator become familiar with all sections of the vamorolone Investigator's Brochure.

Revised Text

1.6 Rationale for study

The current Phase II study is designed to confirm the safe and tolerable dose(s) of vamorolone to be used to treat DMD in boys aged 2 to <4 years and 7 to <18 years, based upon safety and PK data, and to perform an exploratory evaluation of PD, clinical efficacy, behavior and neuropsychology, and physical functioning aover a treatment period of 12 weeks. Steroid-naïve subjects in the 2 to <4 years age group will be recruited for study, dictated by 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. Enrollment of boys in the 7 to <18 years age group will be stratified to accommodate both glucocorticoid-treated and glucocorticoid-untreated subjects at time of study entry, to reflect real-world clinical experience with glucocorticoid treatment for DMD in older boys; analyses will be conducted separately for subjects in each glucocorticoid treatment group. A group of 10 subjects is added to ensure a sufficient number of glucocorticoid-treated subjects 12 to <18 years of age are exposed to the higher dose (6 mg/kg). This change is introduced through protocol amendment #2 because the 7 to <18 years of age group is recruiting a very limited number of these older

subjects. This imbalanced recruitment could potentially prevent objectives of the study to be met by not sufficiently exploring the 12 to <18 years age range.

The vamorolone dose levels of 2.0 mg/kg/day and 6.0 mg/kg/day chosen for study have been shown to be safe and well-tolerated, and associated with improvements in muscle and strength assessments, in previous and ongoing vamorolone Phase II studies in boys 4 to <7 years of age. As a new route of synthesis of vamorolone, ROS2, will be used, boys will enroll into the 2.0 mg/kg/day group first, and drug exposure compared to previous ROS1 experience prior to enrolling into the higher 6.0 mg/kg/day dose group. Based on pharmacokinetics of vamorolone, the daily dose will be capped for the patients weighing 50 kg and above at 300mg in the 6mg/kg/day dose groups and 100mg in the 2mg/kg/day dose groups.

Subjects who meet all eligibility criteria in this study (VBP15-006) will be assigned to one of seven treatment groups as shown in **Table 1.** Groups 1, 3, and 4 will be fully enrolled at 2.0 mg/kg/day prior to assignment of subsequent participants to Groups 2, 5, 6 and 7 at 6.0 mg/kg/day.

Table 6. Study Assignment Schedule

Group	Planned Number of Subjects	Glucocorticoid Status	Ages 2 to <4 Years	Ages 7 to <18 Years
1	10	Naïve*	Vamorolone, 2.0 mg/kg/day	
2	10	Naïve*	Vamorolone, 6.0 mg/kg/day	
3	6	Untreated at entry		Vamorolone, 2.0 mg/kg/day/
4	6	Treated at entry		Vamorolone, 2.0 mg/kg/day/
5	6	Untreated at entry		Vamorolone, 6.0 mg/kg/day/
6	6	Treated at entry		Vamorolone, 6.0 mg/kg/day/
7	10	Treated at entry		Vamorolone, 6.0 mg/kg/day/

*Naïve is defined as having had no prior glucocorticoid treatment for DMD, and past transient use of oral glucocorticoids or other oral immunosuppressive agents for no longer than 1 month cumulative, with last use at least 3 months prior to enrollment, to be considered for enrollment on a case-by-case basis.

Group 1 (age 2 to <4 years, vamorolone 2.0 mg/kg/day), Group 3 (age 7 to <18 years untreated at entry, vamorolone 2.0 mg/kg/day), and Group 4 (age 7 to <18 years treated at entry, vamorolone 2.0 mg/kg/day) will be fully enrolled prior to Groups 2, 5, 6 and 7 (6.0 mg/kg/day).

(…)

Pharmacodynamic safety biomarker findings in DMD patients receiving vamorolone 2.0 mg/kg/day or 6.0 mg/kg/day over 12 weeks will be compared within each age group. Serum PD biomarkers bridged to later clinical safety concerns will be assessed over time as exploratory safety measures. These PD biomarkers include:

1. Adrenal suppression. Pharmacological doses of glucocorticoids cause suppression of the hypothalamo-pituitary-adrenal axis, leading to low concentration of endogenous cortisol and other steroidal hormones in serum. Adrenal suppression is directly associated with risk of adrenal crisis,. Measurement of morning cortisol concentrations, 24 hr after the last dose, will reflect the degree of adrenal suppression. Plasma cortisol secretion typically follows a circadian pattern with the highest concentrations early in the morning; a morning serum cortisol concentration less than 3.6 µg/dL (or 100 nM) is highly suggestive of adrenal suppression.
2. Bone turnover. Pharmacological doses of glucocorticoids suppress bone formation and bone resorption, leading to later osteopenia and bone fragility [van Staa et al. 2000]. Bone fragility is a significant adverse effect of chronic pharmacologic glucocorticoids in DMD as this can lead to fracture, especially vertebral fractures, which increases the likelihood of premature loss of ambulation. Serum biomarkers that have been bridged to later clinical outcomes of osteopenia in adults are osteocalcin (bone formation; glucocorticoids decrease serum levels), aminoterminal propeptide of type I collagen (P1NP) (bone formation; glucocorticoids decrease serum levels), and CTX (bone resorption; glucocorticoids increase serum levels in adults
3. Insulin resistance. Insulin resistance has been bridged to later clinical outcomes, including heart disease, type 2 diabetes, and vascular disease. Serum biomarkers that are accepted as measures of insulin resistance are increased serum glucose and insulin. This can be measured after acute (hours after first dose) or chronic (after weeks or months of dosing) glucocorticoid treatment.

Exploratory safety outcomes will be assessed by additional serum safety biomarkers that have been defined in glucocorticoid-treated DMD and inflammatory bowel disease patients. Additional exploratory measures of efficacy include PD biomarkers that have previously been shown to be glucocorticoid-responsive in DMD boys, pediatric inflammatory bowel disease, adult vasculitis, and pediatric myositis.

This trial will be conducted in compliance with this protocol, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable Health Canada

regulatory requirements , and the issued FDA guidance on developing drugs for treatment for DMD and related dystrophinopathies [FDA 2015].

1.7 Overall Benefit/Risk

Original Text:

1.5 Overall Benefit/Risk

It is anticipated that the adverse effect profile of the investigational product will be more favorable than standard of care glucocorticoids in the long term. There were no serious adverse events (SAEs) reported over the 14-day treatment in the Phase I clinical trial in healthy adult volunteers, nor in the four cohorts (0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg) of the Phase IIa study (VBP15-002; 14-day treatment) in boys ages 4 to <7 years with DMD. There were a total of 4 SAEs in the Phase II VBP15-003 study, three SAEs to date in the VBP15-LTE extension study, and one SAE to date in the VBP15-004 study: two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, one SAE of influenza- associated dehydration in a subject receiving 6.0 mg/kg/day, two SAEs of acute myoglobinuria in a subject receiving 6.0 mg/kg/day, and one SAE of viral gastroenteritis in a subject receiving blinded study drug, who was admitted to the hospital for dehydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study. In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the fasted state. On the basis of mean GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day did not appear to induce liver toxicity over a 24-week treatment period in the VBP15-003 study. In the VBP15-002 study, after 2 weeks of treatment, 0 of 11 tested participants who received vamorolone 0.25 mg/kg/day, 0 of 11 tested participants who received vamorolone 0.75 mg/kg/day, 2 of 11 (18.2%) tested participants who received vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested participants who received vamorolone 6 mg/kg/day had a depressed morning cortisol (<3.6 µg/dL [100 nmol/L]) consistent with chronic adrenal suppression. In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 µg/dL [100 nM]) consistent with chronic adrenal suppression. Instructions for detecting adrenal crisis and the circumstances in which stress dose steroids should be provided will be included in the Informed Consent Form (ICF) and Manual of Operations, and Investigators should monitor clinical study participants closely to identify elevations in liver-specific enzymes. In the VBP15-004 double-blind, placebo- and prednisone-controlled study, a lower proportion of subjects in the Safety Population who experienced at least one TEAE during Treatment Period #1 was observed for subjects in the placebo group (79.3%) compared to subjects in the prednisone 0.75

mg/kg/day (83.9%), vamorolone 2.0 mg/kg/day (83.3%), and vamorolone 6.0 mg/kg/day (89.3%) groups: 23 subjects (79.3%) in the placebo group experienced a total of 77 TEAEs; 26 subjects (83.9%) in the prednisone 0.75 mg/kg/day group experienced a total of 121 TEAEs; 25 subjects (83.3%) in the vamorolone 2.0 mg/kg/day group experienced a total of 97 TEAEs; and 25 subjects (89.3%) in the vamorolone 6.0 mg/kg/day group experienced a total of 91 TEAEs; a greater total number of TEAEs was experienced by subjects in the prednisone group (121), with fewer TEAEs experienced by subjects in the placebo (77), vamorolone 2.0 mg/kg/day (97), and vamorolone 6.0 mg/kg/day (91) groups (Table 6). A total of 51 subjects (43.2%) in the Safety Population experienced at least one treatment-related TEAE: eight subjects (27.6%) in the placebo group; 14 subjects (45.2%) in the prednisone 0.75 mg/kg/day group; 10 subjects (33.3%) in the vamorolone 2.0 mg/kg/day group; and 19 subjects (67.9%) in the vamorolone 6.0 mg/kg/day group. None of the treatment-related TEAEs was serious. One subject (3.2%) in the prednisone 0.75 mg/kg/day group reported a TEAE with CTCAE grade ≥ 3.

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

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

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

Table 6. Overall Summary of Adverse Events (Safety Population)

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

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

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

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

Potential Health Benefits: Subjects may or may not receive direct health benefit from participating in the study. Subjects will be assigned to vamorolone at one of two planned dose levels (2.0 mg/kg/day and 6.0 mg/kg/day) over the course of the 12-week trial. In the VBP15-003 study, clinical efficacy was assessed by Timed Function Tests. Improvement in Time to Stand, Time to Climb, Time to Run/Walk 10 Meters, and 6-Minute Walk Test were seen predominantly for the 2.0 and 6.0 mg/kg/day dose level groups, with many of the improvements showing statistical significance compared to an untreated Duchenne Natural History Group. In the VBP15-004 double-blind study, both 2.0 and 6.0 mg/kg/day vamorolone groups showed significant improvement vs. placebo on motor outcomes, and improvements were comparable to the prednisone group. In view of the initial clinical evidence of safety, the improvements observed in the assessments of efficacy, and the nature of potential adverse effects that can be monitored, the data support an acceptable benefit/risk profile for vamorolone.

Revised Text:

1.7 Overall Benefit/Risk

Vamorolone has shown positive benefit-risk profile for both doses. The dose of 2mg/kg shows an even more favorable safety and tolerability profile as most of the vamorolone-related risks were dose-dependent, still with evidence of efficacy, thus providing an alternative dose with a positive benefit-risk profile that could be considered for patients having tolerability concerns. At 6mg/kg dose , the efficacy is similar to current standard

of care, prednisone, with an improved safety and tolerability profile supporting its use as the recommended starting dose for the long-term treatment of DMD. Please refer to the current Investigator Brochure for more information.

2.2.3 Exploratory Endpoints

Original Text

For each vamorolone dose level and age group, the following endpoints will be evaluated. Additionally, for selected endpoints, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment to a dose group:

Revised Text

For each vamorolone dose level and age group, the following endpoints will be evaluated. Additionally, for selected endpoints, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment to a dose group and also between subjects <12 years and subjects ≥ 12 years:

2.2.4 Pharmacodynamic Endpoints

Original Text

For each vamorolone dose level and age group, the following pharmacodynamic biomarkers reflective of safety concerns of glucocorticoids will be evaluated. Additionally, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment:

1. Adrenal suppression. First-in-morning serum cortisol levels will be measured. Cortisol measures falling below 3.6 µg/dL (100 nM) will be considered to be indicative of the development of adrenal suppression;
2. Bone turnover. Measures of serum osteocalcin and serum P1NP are reflective of bone formation, and measures of serum CTX are reflective of bone reabsorption. Ratios of osteocalcin and CTX predict later clinical safety concerns of osteopenia and bone fragility. Serum osteocalcin, serum CTX, and serum P1NP will be measured;
3. Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance resistance, with serum elevations of both insulin and glucose.

Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose and insulin, and hemoglobin A1c (HbA1c) will be measured;

4. Exploratory biomarkers for aspects of safety and efficacy.

Revised Text:

For each vamorolone dose level and age group, the following pharmacodynamic biomarkers reflective of safety concerns of glucocorticoids will be evaluated. Additionally, subjects within the 7 to <18 years age group who were on glucocorticoid therapy at the time of assignment to a dose group may be evaluated separately from those who were off glucocorticoid therapy for at least 3 months prior to assignment:

1. Adrenal suppression. First-in-morning serum cortisol levels will be measured 24 hours after the last dose of vamorolone. Cortisol measures falling below 2.4 µg/dL (66nM) for boys below 12 years or 3.6 µg/dL (100 nM) for boys 12 years or older will be considered to be indicative of adrenal suppression
2. Bone turnover. Measures of serum osteocalcin and serum P1NP are reflective of bone formation, and measures of serum CTX are reflective of bone resorption. Serum osteocalcin, serum CTX, and serum P1NP will be measured;
3. Insulin resistance. Glucocorticoids cause both acute and chronic insulin resistance with serum elevations of both insulin and sometimes glucose and HbA1c. Measures of hyperinsulinemia and hyperglycemia are accepted measures of insulin resistance. Fasting glucose and insulin, and hemoglobin A1c (HbA1c) will be measured; you can have insulin resistance with normal glucose values
4. Exploratory biomarkers for aspects of safety and efficacy, including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4).

3.1 Overall Study Design

Original Text

This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning of vamorolone (the investigational medication) 2.0 mg/kg, and 6.0 mg/kg administered daily by liquid oral suspension over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month open label Treatment Period (Weeks 112);

and a 4 week open label Dose-tapering Period (Week 13-16) for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study

Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained.

Within the 2 to <4 years age group, the initial 10 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 10 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

Within the 7 to <18 years age group, both corticosteroid-treated and untreated, the initial 12 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 12 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

The first 6 subjects in each age group at 2.0 mg/kg will serve as the PK/safety run-in cohorts. PK assessments will be performed at Week 2 and, together with the safety assessment during the first 4 weeks of treatment, will be the basis to confirm whether 2.0 and 6.0 mg/kg/day will be used in the subsequent patients or if a dose adjustment is needed to avoid over or under-exposure in patients for any of the two age groups.

The 7 to <18 years age group will be further stratified by glucocorticoid treatment status at study entry, with assignment of subjects 1:1:1:1 to groups: 1. Glucocorticoid-treated subjects, 2.0 mg/kg/day treatment group; 2. Glucocorticoid-treated subjects, 6.0 mg/kg/day treatment group; 3. Glucocorticoid-untreated subjects 2.0 mg/kg/day treatment group; 4. Glucocorticoid-untreated subjects 6.0 mg/kg/day treatment group. Glucocorticoid-treated subjects in the 7 to <18 years age group will take their final dose of SoC glucocorticoid therapy for DMD on Baseline Day -1, within 24 hours prior to administration of the first dose of vamorolone study medication.

All subjects in both age group will begin their assigned vamorolone treatment on Treatment Period Day 1 and will continue to receive their assigned vamorolone treatment throughout the duration of the 3month- Treatment Period (Weeks 1-12).

At the end of the 3-month Treatment Period (Week 12), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if possible, or to transition to SoC treatment for DMD (may include glucocorticoids). Subjects completing VBP15-006 and enrolling directly into the expanded access or compassionate use program or transitioning directly to SoC glucocorticoid treatment will not need to taper their vamorolone dose prior to participation in the expanded access or compassionate use program or initiation of SoC glucocorticoid treatment. All subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin a 4-week open label Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.

Revised text

This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning of vamorolone (the investigational medication) 2.0 mg/kg, and 6.0 mg/kg administered daily by liquid oral suspension over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month Treatment Period (Weeks 1 to 12); and up to 8 weeks for the Dose-tapering Period (for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study

Subjects will be enrolled into the study at the Screening Visit, at the time written informed consent is obtained.

Within the 2 to <4 years age group, the initial 10 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 10 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

Within the 7 to <18 years age group (which is including an additional 12 to <18 years age group), both corticosteroid-treated and untreated, the initial 12 eligible subjects will be assigned to the 2.0 mg/kg/day treatment group at the Baseline Day -1 Visit. The subsequent 22 eligible subjects will be assigned to the 6.0 mg/kg/day treatment group at the Baseline Day -1 Visit.

The first 6 subjects in each age group at 2.0 mg/kg will serve as the PK/safety run-in cohorts. PK assessments will be performed at Week 2 and, together with the safety assessment during the first 4 weeks of treatment, will be the basis to confirm whether 2.0 and 6.0 mg/kg/day will be used in the subsequent patients or if a dose adjustment is needed to avoid over or under-exposure in patients for any of the two age groups.

The 7 to <18 years age group will be further stratified by glucocorticoid treatment status at study entry, with assignment of subjects 1:1:1:1 to groups: 1. Glucocorticoid-treated subjects, 2.0 mg/kg/day treatment group; 2. Glucocorticoid-treated subjects, 6.0 mg/kg/day treatment group; 3. Glucocorticoid-untreated subjects 2.0 mg/kg/day treatment group; 4. Glucocorticoid-untreated subjects 6.0 mg/kg/day treatment group. An additional group of 10 glucocorticoid-treated 12 to <18 years subjects will be assigned to the 6 mg/kg/day treatment. Glucocorticoid-treated subjects in the 7 to <18 years age group will take their final dose of SoC glucocorticoid therapy for DMD on Baseline Day -1, within 24 hours prior to administration of the first dose of vamorolone study medication.

All subjects will begin their assigned vamorolone treatment on Treatment Period Day 1 and will continue to receive their assigned vamorolone treatment throughout the duration of the 3month- Treatment Period (Weeks 1-12).

At the end of the 3-month Treatment Period (Week 12), subjects will be given the option to receive vamorolone in an expanded access or compassionate use program, if

possible, or to transition to SoC treatment for DMD (may include glucocorticoids). Subjects completing VBP15-006 and enrolling directly into the expanded access or compassionate use program or transitioning directly to SoC glucocorticoid treatment will not need to taper their vamorolone dose prior to participation in the expanded access or compassionate use program or initiation of SoC glucocorticoid treatment. All subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin the Dose- Period during which the dose of study medication will be progressively reduced and discontinued.

3.2 Study Summary

Original Text

(…)

A total of approximately 24 subjects ages 7 to <18 years will be assigned to receive vamorolone 2.0 mg/kg/day (glucocorticoid-untreated at study entry), 2.0 mg/kg/day (glucocorticoid-treated at study entry), 6.0 mg/kg/day (glucocorticoid-untreated at study entry), or 6.0 mg/kg/day (glucocorticoid-treated at study entry) (n=6 per dose level and glucocorticoid treatment status group). The dose cohort of 2.0 mg/kg/day will be enrolled first and the PK and safety assessment from the first 6 subjects in this age group will be used to confirm the doses for the subsequent subjects following the same process as described for the younger age range. A total of approximately 44 subjects will be enrolled into the study as shown in Table 5.

The study is comprised of a Pretreatment Screening Period of up to 32 days duration, a 1 day Pretreatment Baseline Period, a 12 week Treatment Period, and a 4 week Dose tapering Period (for subjects not continuing directly with further Vamorolone treatement or transitioning directly to SoC glucocorticoid treatment) Subject will be enrolled into this study at the time written informed consent is given, and assigned to treatment only after completion of all Pretreatment Screening assessments.

Subjects will be assessed for safety and tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning at scheduled visits throughout the study (see **Section 6** for a schedule of study assessments). Screening assessments will be performed prior to assignment to a dose group. All subjects will be assigned to treatment at the Baseline Day -1 Visit.

After completion of Screening and Baseline assessments, and assignment to a dose group for treatment, subjects in both age group will return to the study clinic on Day 1 for safety, PK, and PD assessments prior to administration of the first dose of study medication. Additional study visits will occur at Week 2, Week 6, and Week 12.

Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor regarding study conduct.

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects in both age groups, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit (see **Section 5.3**). Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site.

Revised text

(…)

A total of approximately 34 subjects ages 7 to <18 years will be assigned to receive vamorolone 2.0 mg/kg/day (glucocorticoid-untreated at study entry), 2.0 mg/kg/day (glucocorticoid-treated at study entry), 6.0 mg/kg/day (glucocorticoid-untreated at study entry), or 6.0 mg/kg/day (glucocorticoid-treated at study entry) (n=6 per dose level and glucocorticoid treatment status group plus n=10 for the additional 12 to <18 years age group [6.0 mg/kg/day - glucocorticoid-treated]). The dose cohort of 2.0 mg/kg/day will be enrolled first and the PK and safety assessment from the first 6 subjects in this age group will be used to confirm the doses for the subsequent subjects following the same process as described for the younger age range.Subjects will be assessed for safety and tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, and physical functioning at scheduled visits throughout the study (see **Section 6** for a schedule of study assessments). Screening assessments will be performed prior to assignment to a dose group. All subjects will be assigned to treatment at the Baseline Day -1 Visit.

After completion of Screening and Baseline assessments, and assignment to a dose group for treatment, subjects will return to the study clinic on Day 1 for safety, PK, and PD assessments prior to administration of the first dose of study medication. Additional study visits will occur at Week 2, Week 6, and Week 12.

The dose cohort of 2.0 mg/kg/ will be enrolled first and the PK of vamorolone after 2 weeks of treatment and the safety of vamorolone during the first week of administration from the first 6 subjects in this age group will be used to confirm the doses for the subsequent subjects following the same process as described for the younger age range.

If the vamorolone exposure at 2.0 mg/kg in the initial 6 patients of this age group deviates substantially from the target or if unexpected safety signals are observed, the high doses level for vamorolone for the subsequent subjects may be adjusted.

Adverse events, including serious adverse events (SAEs), and concomitant medications will be recorded throughout the study. A Data and Safety Monitoring Board (DSMB) will review SAEs and other pertinent safety data at regular intervals during the study and make recommendations to the Sponsor regarding study conduct.

If the intended dose of vamorolone is 6mg/kg, but patients weigh 50 kg or more, the daily dose should be capped at 300mg/day. Considering the linearity of vamorolone

pharmacokinetics, if the patient is dosed at 2mg/kg, the dose is capped at 100mg daily for patients weighing 50 kg and above.

Glucocorticoid-treated subjects in the 7 to <18 years age group will receive their final dose of SoC glucocorticoid treatment for DMD on Baseline Day -1 and switch to their assigned vamorolone treatment, 2.0 mg/kg/day or 6.0 mg/kg/day, beginning the next day on Treatment Period Day 1. For all subjects, daily study drug dosing during the Treatment Period will occur from the date of the Day 1 Visit through the date of the Week 12 Visit (see **Section 5.3**). Study drug dosing will occur at home on all days except dates of the Day 1, Week 2, Week 6, and Week 12 Visits, when dosing will occur at the study site.

3.3 Dose group assignment

Original Text

(…)

Similarly, subjects in the 7 to <18 years age group will be assigned to the 2.0 mg/kg/day treatment groups first, then subsequently assigned to the planned 6.0 mg/kg/day treatment groups. A total of approximately 24 subjects ages 7 to <18 years will be assigned 1:1:1:1 to receive vamorolone 2.0 mg/kg/day (glucocorticoid-untreated at study entry), 2.0 mg/kg/day (glucocorticoid-treated at study entry), 6.0 mg/kg/day (glucocorticoid-untreated at study entry), or 6.0 mg/kg/day (glucocorticoid-treated at study entry) (n=6 per dose level and glucocorticoid treatment status group).

Revised Text

(…)

Similarly, subjects in the 7 to <18 years age group will be assigned to the 2.0 mg/kg/day treatment groups first, then subsequently assigned to the planned 6.0 mg/kg/day treatment groups. A total of approximately 34 subjects ages 7 to <18 years will be assigned 1:1:1:1 to receive vamorolone 2.0 mg/kg/day (glucocorticoid-untreated at study entry), 2.0 mg/kg/day (glucocorticoid-treated at study entry), 6.0 mg/kg/day (glucocorticoid-untreated at study entry), or 6.0 mg/kg/day (glucocorticoid-treated at study entry) (n=6 per dose level and glucocorticoid treatment status group plus n=10 for the additional 12 to <18 years age group [6.0 mg/kg/day - glucocorticoid-treated]).

4.3 Exclusion Criteria

Original Text

[….]

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

Revised Text

[….]

Note: Any parameter/test may be repeated at the Investigator's discretion during Screening to determine reproducibility. In addition, subjects may be rescreened if ineligible due to negative anti-varicella IgG antibody test result after vaccination has been completed Subjects may be rescreened in case of ongoing medical condition developing during the screening period, e.g. acute viral infection, or laboratory abnormality that could affect safety if the subject would start vamorolone. In this case, the subject can be rescreened after resolution of the medical condition.

5.1 Study Medication Administered

Original Text

Planned vamorolone dose levels:2.0 mg/kg/day and 6.0 mg/kg/day. Doses can be adjusted based on PK and safety data from the first 6 patients per age group to avoid over- or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range.

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

A total of approximately 10 subjects in the 2 to <4 years age group will be enrolled into the 2.0 mg/kg/day treatment group. After the pharmacokinetics and safety is determined in the initial 6 subjects and the doses are confirmed, enrollment will continue for 10 subjects in the 2 to <4 years age group into the planned 6.0 mg/kg/day treatment group.

A total of approximately 12 subjects in the 7 to <18 years age group will be enrolled into the 2.0 mg/kg/day treatment groups (6 untreated at entry, 6 corticosteroid-treated at entry). After the pharmacokinetics and safety is determined in the initial 6 subjects and the doses are confirmed, enrollment will continue for 12 subjects in the 7 to <18 years age group into the planned 6.0 mg/kg/day treatment group.

Revised Text

Planned vamorolone dose levels:2.0 mg/kg/day and 6.0 mg/kg/day. Doses can be adjusted based on PK and safety data from the first 6 patients per age group to avoid over- or under exposure and to achieve a consistent vamorolone AUC across the entire pediatric age range. The recommended dose of vamorolone is 6 mg/kg once daily in patients weighing less than 50 kg. In patients weighing 50 kg and above, the high dose level (6 mg/kg once daily) must be capped at 300 mg once daily and the low dose level (2mg/kg/day) must be capped at 100 mg once daily.

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

A total of approximately 10 subjects in the 2 to <4 years age group will be enrolled into the 2.0 mg/kg/day treatment group. After the pharmacokinetics and safety is determined in the initial 6 subjects and the doses are confirmed, enrollment will continue for 10 subjects in the 2 to <4 years age group into the planned 6.0 mg/kg/day treatment group.

A total of approximately 12 subjects in the 7 to <18 years age group will be enrolled into the 2.0 mg/kg/day treatment groups (6 untreated at entry, 6 corticosteroid-treated at entry). After the pharmacokinetics and safety is determined in the initial 6 subjects and the doses are confirmed, enrollment will continue for 22 subjects in the 7 to <18 years age group into the planned 6.0 mg/kg/day treatment group (6 untreated at entry, 6 corticosteroid-treated at entry plus 10 for the additional 12 to <18 years age group (glucocorticoid-treated).

5.4 Rationale for Dose Selection

Original text

(…)

The results of the VBP15-004 24-week double-blind, placebo- and prednisone-controlled study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day showed significant enhancement of muscle strength, mobility, and functional exercise capacity vs. placebo. This study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day did not cause the stunting of growth and deleterious changes in bone biomarkers seen with prednisone in this head-to-head comparison.

Based on the safety and efficacy results observed in these earlier studies in DMD boys aged 4 to 7 years, doses of vamorolone at 2.0 mg/kg/day and 6.0 mg/kg/day were chosen for evaluation in the current study enrolling younger and older subjects. Since the effect of age on the pharmacokinetics of vamorolone is not yet established and since this is the first time that the to-be-marketed formulation of ROS2 will be administered to DMD boys, a PK/safety run-in at 2.0 mg/kg/day is included into the study to evaluate the PK and safety in subjects 2 to <4 and 7 to <18 years of age and to adjust the doses if needed to avoid over- and underexposure of vamorolone in these age groups and to ensure a consistent vamorolone AUC across the entire pediatric age range. All doses of vamorolone will be administered in the morning with breakfast.

Revised Text

(…)

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

capacity vs. placebo. This study showed that doses of vamorolone 2.0 mg/kg/day and 6.0 mg/kg/day did not cause the stunting of growth and deleterious changes in bone biomarkers seen with prednisone in this head-to-head comparison. Additional efficacy and safety results can be found in the current IB.

Based on the safety and efficacy results observed in these earlier studies in DMD boys aged 4 to 7 years, doses of vamorolone at 2.0 mg/kg/day and 6.0 mg/kg/day were chosen for evaluation in the current study enrolling younger and older subjects. For the 6 mg/kg, a cap dose of 300 mg once daily has been established for children weighing more than 50 kg based on pharmacokinetic modeling to account for the expected high pharmacokinetic exposures due to growth and maturation of the pediatric population. Since the effect of age on the pharmacokinetics of vamorolone is not yet established and since this is the first time that the to-be-marketed formulation of ROS2 will be administered to DMD boys, a PK/safety run-in at 2.0 mg/kg/day is included into the study to evaluate the PK and safety in subjects 2 to <4 and 7 to <18 years of age and to adjust the doses if needed to avoid over- and underexposure of vamorolone in these age groups and to ensure a consistent vamorolone AUC across the entire pediatric age range. All doses of vamorolone will be administered in the morning with breakfast.

5.6 Study Drug Dose Interruption or Discontinuation

Original text

(…)

In the event any clinical observation suggests an intolerability of an individual subject to the study medication, in the opinion of the Investigator, the case should be discussed with the Study Chair and Medical Monitor within 24 hours and study drug discontinuation should be considered. In view of the potential effect of the study drugs on adrenal glands, the study drugs cannot be discontinued suddenly. In case study drug needs to be discontinued, for whatever reason, the dose tapering process described for the end of the treatment period should be followed. If a subject discontinues study drug due to intolerability, the subject will be withdrawn from the study. The subject should return to the study site for completion of Week 12 assessments at the time of early withdrawal, prior to participation in the Dose-tapering Period, as appropriate. Any AE still ongoing at the time of study drug discontinuation will be monitored until it has returned to baseline status, stabilized, or the Investigator, Study Chair, Medical Monitor and Sponsor agree that follow-up is no longer needed.

Revised Text

(…)

In the event any clinical observation suggests an intolerability of an individual subject to the study medication, in the opinion of the Investigator, the case should be discussed

with the Medical Monitor within 24 hours and study drug discontinuation should be considered. In view of the potential effect of the study drugs on adrenal glands, the study drugs cannot be discontinued suddenly. In case study drug needs to be discontinued, for whatever reason, the dose tapering process described for the end of the treatment period should be followed. If a subject discontinues study drug due to intolerability, the subject will be withdrawn from the study. The subject should return to the study site for completion of Week 12 assessments at the time of early withdrawal, prior to participation in the Dose -tapering Period, as appropriate. Any AE still ongoing at the time of study drug discontinuation will be monitored until it has returned to baseline status, stabilized, or the Investigator and Sponsor agree that follow-up is no longer needed.

6.1 Time and Events Schedule

Original Text

(…)

- **Dose-tapering Period**: The 4-week interval following the end of the 12-week Treatment Period during which subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin a 4week open label Dose tapering- Period during which the dose of study medication will be progressively reduced and discontinued (see **Section 6.3.5**). Subjects will be discharged from the study following completion of all final Dose-tapering Period assessments

(…)

Table 7. Schedule of Study Activities

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day			Week				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Informed consent	X							
Enrollment[f]	X							
Inclusion/exclusion criteria	X							
Assignment[g]		X						
Demographics	X							
Medical history	X							
Medication history	X	X						
Physical examination	X	X			X	X		X
Cushingoid features	X	X			X	X		X
Height[h]	X					X		
Weight	X	X		X	X	X		X
Vital signs[i]	X	X	X[j]	X	X	X		X
Blood for clinical labs[k]	X		X[l]		X[l]	X[l]		X
Blood for vitamin D	X					X[l]		
Confirmation of varicella immunity	X							
Urinalysis[m]	X		X		X	X		X
Blood for serum PD biomarker panel[n]			X[l]			X[l]		
Fasting blood for insulin, glucose			X[l]	X[l]	X[l]	X[l]		
Blood for HbA1c	X					X[l]		
Blood for morning cortisol[o]			X[l]			X[l]		
Blood for Plasma PK			X[p]	X[p]				
12-lead ECG[q]	X					X		
Eye examination	X					X		
Dispense study medication			X		X	X[r]		

	Pretreatment Period		Treatment Period				Dose-tapering Period[a]	
	SCR	BL						
	Day		Week					
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Return study medication/ compliance monitoring				X[s]	X	X		X
Study medication dosing[t]			X	→	→	X		
Study medication dose tapering						X[r]	→	X
Telephone call to subject							X[u]	
Bayley-III Gross Motor[v]	X	X				X		
PUL Test[w]	X	X				X		
Pediatric Outcomes Data Collection Instrument (PODCI)	X					X		
PARS III	X					X		
Ease of Study Medication Administration Assessment[x]					X	X		
Study Medication Acceptability Assessment[y]					X	X		
Dispense subject diaries[z]			X	X	X	X[q]		
Return subject diaries				X	X	X		X
AE/SAE recording[aa]	X	→	→	→	→	→	→	X[bb]
Prior/Concomitant medications	X	→	→	→	→	→	→	X
Discharge from study						X[cc]		X[dd]

BL = Baseline; d = day(s); SCR = Screening.

a) Only subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the 12-week Treatment Period will begin a 4-week open-label Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.

b) All Day -1 assessments must be completed within 24 hours prior to administration of the first dose of study medication on Day 1.

c) Time windows around the Week 2, Week 6, and Week 12 Visits are allowances from date of Day 1 Visit; time window around Week 16 Visit is allowance from date of Week 12 Visit.

d) Subjects who prematurely discontinue from the study prior to Week 12 should complete the Week 12 assessments at the time of early withdrawal and undergo Dose-tapering, where appropriate.

e) Subjects will have one study site visit during the Dose-tapering Period, at one week after the dose of study medication has been discontinued (Week 16).

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

g) Assignment to a treatment group is done by the TRiNDS Study Coordinator at the Baseline Day -1 Visit.

h) Standing height will be measured for subjects in the 2 to <4 years age group and participants ages 7 to <18 years who can stand independently; ulnar length will be measured and used to calculate height for subjects in the 7 to <18 years age group.

i) Sitting blood pressure, body temperature, respiratory rate, and heart rate.

j) Vital signs recorded prior to administration of the first dose of study drug at the Day 1 Visit.

k) Blood for hematology, chemistry, and lipids. All samples should be collected after subject has fasted for >6 hours.

l) Blood samples collected after subjects have fasted for ≥ 6 hours, and prior to daily dose of study drug.

m) Urinalysis by dipstick and microscopic analysis.

n) Blood collected for PD biomarkers includes exploratory safety outcomes of bone turnover (osteocalcin, CTX, P1NP) at Day 1 pre-dose and Week 12 pre-dose. Blood remaining from collected blood samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies for aspects of safety and efficacy. All pre-dose samples should be collected after subject has fasted for ≥ 6 hours.

o) Blood collected for morning cortisol should be collected before 10 AM local time.

p) Blood samples for population PK analysis will be collected within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), and within 30 minutes pre-dose, and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years).

q) 12-lead ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.

r) Only for subjects participating in the Dose-tapering Period.

s) Study medication brought by subjects to the Week 2 Visit for dosing and compliance assessment will be redispensed to subjects at the end of the visit.

t) During the Treatment Period, the dose of study medication on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered with breakfast in the study clinic. All other doses will be taken with breakfast at home.

u) Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the study drug tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have.

v) Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale will be completed for subjects in the 2 to <4 years age group only.

w) Performance of Upper Limb (PUL) test will be performed by subjects in the 7 to <18 years age group only.

x) Ease of Study Medication Administration Assessment will be completed for subjects in the 2 to <4 years age group only.

y) Study Medication Acceptability Assessment will be completed by subjects in the 7 to <18 years age group only.

z) Subject diaries used to record any changes in concomitant medications taken, any AEs experienced during the study, and any incomplete or missed doses of study medication.

aa) All AEs and SAEs must be recorded in the source documents and eCRF from the date of the subject's written informed consent until the final Week 16 Visit or the subject's participation in the study is completed (SAEs through 30 days after final dose study drug). Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator believes follow-up is not necessary.

bb) For subjects who do not continue into an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in VBP15 006 Dose-tapering Period to confirm the final SAE status of the subject.

cc) Subjects who elect to continue vamorolone therapy by enrolling directly into an expanded access or compassionate use program or who will transition directly to SoC glucocorticoid therapy may be discharged from the study following completion of all final Week 12 assessments.

dd)Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments (Week 16).

Revised Text

(…)

- **Dose-tapering Period**: The interval following the end of the 12-week Treatment Period during which subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment will begin a Dose tapering- Period during which the dose of study medication will be progressively reduced and discontinued (see Section 6.3.5). Subjects will be discharged from the study following completion of all final Dose-tapering Period assessments

(…)

Table 2. Schedule of Study Activities

	Pretreatment Period		**Treatment Period**				**Dose-tapering Period[a]**	
	SCR	**BL**						
	Day			**Week**				
Study Day or Week/Visit	**-33 to -2**	**-1[b]**	**Day 1[b]**	**2[c] (±1d)**	**6[c] (±3d)**	**12[c,d] (±5d)**	**14**	**16[c,d,e] (±1d)**
Informed consent	X							
Enrollment[f]	X							
Inclusion/exclusion criteria	X							
Assignment[g]		X						
Demographics	X							
Medical history	X							
Medication history	X	X						
Physical examination	X	X[ee]			X	X		X
Cushingoid features	X	X			X	X		X
Height[h]	X					X		
Weight	X	X		X	X	X		X
Vital signs[i]	X	X	X[j]	X	X	X		X
Blood for clinical labs[k]	X		X[l]		X[l]	X[l]		X
Blood for vitamin D	X					X[l]		
Confirmation of varicella immunity	X							
Urinalysis[m]	X		X		X	X		X
Blood for serum PD biomarker panel[n]			X[l]			X[l]		
Fasting blood for insulin, glucose			X[l]	X[l]	X[l]	X[l]		
Blood for HbA1c	X					X[l]		

Blood for morning cortisol[o]			X[l]			X[l]		
Blood for Plasma PK			X[p]	X[p]				
12-lead ECG[q]	X					X		
Eye examination	X					X		
Dispense study medication			X		X	X[r]		
Return study medication/ compliance monitoring				X[s]	X	X		X
Study medication dosing[t]			X →			X		
Study medication dose tapering						X[r] →		X
Telephone call to subject							X[u]	
Bayley-III Gross Motor[v]	X	X				X		
PUL Test[w]	X	X				X		
Pediatric Outcomes Data Collection Instrument (PODCI)	X					X		
PARS III	X					X		
Ease of Study Medication Administration Assessment[x]					X	X		
Study Medication Acceptability Assessment[y]					X	X		
Dispense subject diaries[z]			X	X	X	X[q]		
Return subject diaries				X	X	X		X
AE/SAE recording[aa]	X →						→	X[bb]
Prior/Concomitant medications	X →						→	X
Discharge from study						X[cc]		X[dd]

BL = Baseline; d = day(s); SCR = Screening.

a) Only subjects who will not transition directly to further vamorolone or SoC glucocorticoid treatment at the end of the 12-week Treatment Period will begin a Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.

b) All Day -1 assessments must be completed within 24 hours prior to administration of the first dose of study medication on Day 1.

c) Time windows around the Week 2, Week 6, and Week 12 Visits are allowances from date of Day 1 Visit; time window around Week 16 Visit is allowance from date of Week 12 Visit.

d) Subjects who prematurely discontinue from the study prior to Week 12 should complete the Week 12 assessments at the time of early withdrawal and undergo Dose-tapering, where appropriate.

e) Subjects will have one study site visit during the Dose-tapering Period, at one week after the dose of study medication has been discontinued (Week 16).

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

g) Assignment to a treatment group is done by the TRiNDS Study Coordinator at the Baseline Day -1 Visit.

h) Standing height will be measured for subjects in the 2 to <4 years age group and participants ages 7 to <18 years who can stand independently; ulnar length will be measured and used to calculate height for subjects in the 7 to <18 years age group.

i) Sitting blood pressure, body temperature, respiratory rate, and heart rate.

j) Vital signs recorded prior to administration of the first dose of study drug at the Day 1 Visit.

k) Blood for hematology, chemistry, and lipids. All samples should be collected after subject has fasted for >6 hours.

l) Blood samples collected after subjects have fasted for ≥ 6 hours, and prior to daily dose of study drug.

m) Urinalysis by dipstick and microscopic analysis.

n) Blood collected for PD biomarkers at Day 1 pre-dose and Week 12 predose includes exploratory safety outcomes of bone turnover (osteocalcin, CTX, P1NP, as well as in the additional 12 to <18 years age group, suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4). Blood remaining from collected blood samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies for aspects of safety and efficacy. All pre-dose samples should be collected after subject has fasted for ≥ 6 hours.

o) Blood collected for morning cortisol should be collected before 10 AM local time.

p) Blood samples for population PK analysis will be collected within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), and within 30 minutes pre-dose, and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years).

q) 12-lead ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.

r) Only for subjects participating in the Dose-tapering Period.

s) Study medication brought by subjects to the Week 2 Visit for dosing and compliance assessment will be redispensed to subjects at the end of the visit.

t) During the Treatment Period, the dose of study medication on the days of the Day 1, Week 2, Week 6, and Week 12 Visits will be administered with breakfast in the study clinic. All other doses will be taken with breakfast at home.

u) Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the study drug tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have.

v) Bayley Scales of Infant and Toddler Development-III (Bayley-III) Gross Motor scale will be completed for subjects in the 2 to <4 years age group only.

w) Performance of Upper Limb (PUL) test will be performed by subjects in the 7 to <18 years age group only.

x) Ease of Study Medication Administration Assessment will be completed for subjects in the 2 to <4 years age group only.

y) Study Medication Acceptability Assessment will be completed by subjects in the 7 to <18 years age group only.

z) Subject diaries used to record any changes in concomitant medications taken, any AEs experienced during the study, and any incomplete or missed doses of study medication.

aa) All AEs and SAEs must be recorded in the source documents and eCRF from the date of the subject's written informed consent until the final Week 16 Visit or the subject's participation in the study is completed (SAEs through 30 days after final dose study drug). Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator believes follow-up is not necessary.

bb) For subjects who do not continue into an expanded access or compassionate use program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in VBP15 006 Dose-tapering Period to confirm the final SAE status of the subject.

cc) Subjects who elect to continue vamorolone therapy by enrolling directly into an expanded access or compassionate use program or who will transition directly to SoC glucocorticoid therapy may be discharged from the study following completion of all final Week 12 assessments.

dd) Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-tapering Visit assessments (Week 16).

ee) Including Ambulatory Status

6.3 Visit Schedule and Procedures

Original Text

(…)

Each subject will receive the assigned, open-label study medication at stable daily dose for a period of 12 weeks. Following completion of the 12-week Treatment Period, all subjects who will not be continuing directly to receive vamorolone by expanded access or compassionate use or transitioning directly to SoC glucocorticoid therapy will taper their study medication during the 4-week Dose-tapering Period and will return to the study site for study assessments at the end of the Dose-tapering Period (Week 16) ‘’See **Section 7** for a detailed description of the safety, PK, clinical efficacy, PD, behavior and neuropsychology, physical functioning, and sleep-wake activity assessments to be performed during this study.

Revised Text

(…)

Each subject will receive the assigned, open-label study medication at stable daily dose for a period of 12 weeks. Following completion of the 12-week Treatment Period, all subjects who will not be continuing directly to receive vamorolone by expanded access or compassionate use or transitioning directly to SoC glucocorticoid therapy will taper their study medication during the Dose-tapering Period (up to 8 weeks) and will return to the study site for study assessments at the end of the Dose-tapering Period, ’See **Section 7** for a detailed description of the safety, PK, clinical efficacy, PD, behavior and neuropsychology, physical functioning, and sleep-wake activity assessments to be performed during this study.

6.3.2 Baseline Period (Day -1) Visit

Original Text

(…)

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

- Physical examination including weight (in kilograms) and assessment of cushingoid features (see Section 7.2.2)

(…)

Revised Text

(…)

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

- Physical examination including weight (in kilograms) and assessment of cushingoid features and ambulatory status (see Section 7.2.2)

(…)

6.3.3 Treatment Period Day 1 Visit

Original Text

(…)

- Blood samples for PD biomarkers including fasting glucose and insulin, osteocalcin, CTX, serum P1NP, and morning cortisol, prior to administration of first dose of study drug (see **Section 7.2.6**). Blood remaining from collected samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies.

(…)

Revised Text

(…)

- Blood samples for PD biomarkers including fasting glucose and insulin, osteocalcin, CTX, serum P1NP, and morning cortisol, prior to administration of first dose of study drug (see **Section 7.2.6**). Blood remaining from collected samples not needed for protocol-specified analyses may be stored for future exploratory biomarker studies, including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4).

(…)

6.3.5 Dose-tapering Period (Weeks 13-16)

Original Text

All subjects who complete the study and opt not to continue directly with vamorolone treatment in an expanded access or compassionate use program, and who will not transition directly to SoC glucocorticoid treatment for DMD, will participate in a 4-week doubleblind Dosetapering Period during which the dose of study medication will be progressively reduced and discontinued prior to discharge from the study. In addition, subjects who discontinue study medication after the first dose and prior to Week 12 will also participate in the Dose-tapering Period if possible and if, in the opinion of the Investigator, it is safe to do so.

The purpose of dose-tapering is to aid in re-establishment of adrenal function if adrenal suppression has occurred during vamorolone treatment. Dose tapering will be performed in a stepwise manner, according to the subject's most recent calculated liquid formulation dose during the 12-week Treatment Period.

Dose tapering for vamorolone will be performed as outlined in **Table 8**. For subjects who have completed the Treatment Period, the subject's weight recorded at the Week 12 Visit will be used to calculate dose volume for all dose de-escalations during the Dose-tapering Period.

Table 8. Study Medication Dose Tapering

Treatment Period Dose Level	Week 13 Dose Level	Week 14 Dose Level	Week 15 Dose Level	Week 16 Dose Level
Formulation: 100%	50%	25%	10%	0%

Subjects will take the first dose of study medication in the Dose-tapering Period (Week 13 dose level) with a meal on the day following the Week 12 dose of study medication.in the glucocorticoid-treated cohorts, mainly those who have been on GC treatment for many months or yearon

Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the

parent(s)/guardian(s) may have. In addition, subjects will be assessed promptly for adrenal suppression if unwell at any time during the Dose-Tapering Period. There will be a low threshold for recommending commencement of daily oral prednisone or hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these circumstances.

The final end-of-study visit will be scheduled approximately one week after the final dose de-escalation to 0 mg/kg. Each subject will return to the study site for final study assessments when he has received no study medication for one week (Study Week 16).

Subjects will have non-fastingblood and urine samples collected for clinical laboratory tests at the final Week 16 Visit. Subjects will also have a physical examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including SAEs, and concomitant medications will be assessed. Subject diaries will be returned and reviewed with site staff.

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

Revised Text

All subjects who complete the study and opt not to continue directly with vamorolone treatment in an expanded access or compassionate use program, and who will not transition directly to SoC glucocorticoid treatment for DMD, will participate in a Dose tapering Period during which the dose of study medication will be progressively reduced. In addition, subjects who discontinue study medication after the first dose and prior to Week 12 will also participate in the Dose-tapering Period if possible and if, in the opinion of the Investigator, it is safe to do so.

The purpose of dose-tapering is to aid in re-establishment of adrenal function if adrenal suppression has occurred during vamorolone treatment. Dose tapering will be

performed in a stepwise manner, according to the subject's most recent calculated liquid formulation dose during the 12-week Treatment Period.

Dose tapering for vamorolone will be performed as outlined in Table 3 For subjects who have completed the Treatment Period, the subject's weight recorded at the Week 12 Visit will be used to calculate dose volume for all dose de-escalations during the Dose-tapering Period.

Table 3. Study medication dose tapering recommendation

Week 12 Dose Level	Decreased by 50% for 1 week	Decreased by 50% for 1 week	Decreased by 60% for 1 week
2 mg/kg/day	1 mg/kg/day	0.5 mg/kg/day	0.2 mg/kg/day Then stop vamorolone
6 mg/kg/day	3 mg/kg/day	1.5 mg/kg/day	0.6 mg/kg/day Then stop vamorolone

For the steroid-treated 7 to <18 years age group on 6 mg/kg/day

Week 12 Dose Level	Decreased by 25% for 2 weeks	Decreased by 33% for 2 weeks	Decreased by 33% for 2 weeks
6 mg/kg/day	4.5 mg/kg/day	3 mg/kg/day	2 mg/kg/day Then start hydrocortisone

From [Bowden at al. 2019]

Site study staff will contact the parent(s)/guardian(s) by telephone at Week 14 to ensure that the dose tapering is proceeding according to protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to address any questions the parent(s)/guardian(s) may have. In addition, subjects will be assessed promptly for adrenal suppression if unwell at any time during the Dose-Tapering Period.

For subjects in the steroid-treated 7 to <18 years age group on 6 mg/kg/day, the tapering period could be extended for 2 additional 2 weeks to a maximum of 8 weeks, if medically warranted. Further progressive glucocorticoid-tapering should then be done on hydrocortisone, as indicated above. There will be a low threshold for

recommending commencement of daily oral prednisone or hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these circumstances.

The end-of-study visit (Week 16) will be scheduled approximately one week after the final de-escalation to 0 mg but 1 to 3 days after the last dose of vamorolone, i.e. after starting hydrocortisone, in the steroid-treated 7 to <18 years age group on 6 mg/kg/day at Week 12.

Subjects will have non-fasting but morning blood and urine samples collected for clinical laboratory tests at the Week 16 Visit. Subjects will also have a physical examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including SAEs, and concomitant medications will be assessed. Subject diaries will be returned and reviewed with site staff.

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

7.1 Demographic Assessments

Original Text

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

Revised Text

Demographic information (age at enrollment, race and ethnicity, and date of birth may also be collected where allowed) will be collected during the Pretreatment Screening Period and will be recorded on the appropriate eCRF page.

7.2.2. Physical Examination, Cushingoid Features, Ambulatory status, Weight, and Height

Original text

7.2.2 Physical Examination, Cushingoid Features, Weight, and Height

A complete physical examination will be performed at Screening, Baseline Day -1, Week 6, and Week 12, and at the final Week 16 Dose-tapering Period Visit, and will include examination of the following: head, eyes, ears, nose, and throat, neck *(including an examination of the thyroid),* heart, lungs, abdomen *(including an examination of the liver and spleen),* lymph nodes, extremities, nervous system, and skin. Particular attention will be paid to any sign or symptom of infection. Clinically significant changes from baseline should be recorded as AEs. Particular attention will be paid in identifying any sign of cushingoid features, which should also be recorded as AEs if they first appear or worsen during the study.

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

Height (in cm) will be recorded at Screening and Week 12. Standing height will be recorded for subjects in the 2 to <4 years age group and all participants in the 7 to <18 years age group who can stand independently. Ulnar length of the non-dominant arm, measured from the olecranon (point of elbow) to the styloid process (prominent bone of the wrist), will be used to calculate height for subjects in the 7 to <18 years age group (see Manual of Operations for a detailed description of methodology).

Weight (in kg) will be recorded at Screening, Baseline, Day -1, Week 2, Week 6, and Week 12, and at the final Week 16 Dose-tapering Visit. Weight recorded at the dispensing visit will be used to calculate the study medication dose for the subsequent dispensing interval (see **Section 5.3**).

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

Revised text

7.2.2 Physical Examination, Cushingoid Features, Ambulatory status, Weight, and Height

A complete physical examination will be performed at Screening, Baseline Day -1, Week 6, and Week 12, and at the final Dose-tapering Period Visit, and will include examination of the following: head, eyes, ears, nose, and throat, neck *(including an examination of the thyroid),* heart, lungs, abdomen *(including an examination of the liver and spleen),* lymph nodes, extremities, nervous system, and skin. Particular attention will be paid to any sign or symptom of infection. Clinically significant changes from baseline should be recorded as AEs. Particular attention will be paid in identifying any sign of cushingoid features, which should also be recorded as AEs if they first appear or worsen during the study. Ambulatory status as assessed by the investigator will be recorded at Baseline.

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

Height (in cm) will be recorded at Screening and Week 12. Standing height will be recorded for subjects in the 2 to <4 years age group and all participants in the 7 to <18 years age group who can stand independently.

Weight (in kg) will be recorded at Screening, Baseline, Day -1, Week 2, Week 6, and Week 12, and at the final Week 16 Dose-tapering Visit. Weight recorded at the dispensing visit will be used to calculate the study medication dose for the subsequent dispensing interval (see **Section 5.3**).

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

7.2.6 Pharmacodynamic Biomarker Panel

Original text

Blood samples will be collected to explore the effect of vamorolone on biomarkers associated with glucocorticoid safety concerns (exploratory outcomes for adrenal suppression, insulin resistance, and bone turnover), as listed in **Table 11**.

(…)

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

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

A total of approximately 12 mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin, morning cortisol, osteocalcin, CTX, and P1NP) and measurement of HbA1c over the course of the 21-week study (see **Section 7.2.8**).

Table 11. Pharmacodynamic Biomarkers – Exploratory Safety Outcomes

Adrenal Suppression
Cortisol – morning
Insulin Resistance
Glucose – fasting
Insulin – fasting
HbA1c
Bone Turnover
Osteocalcin
CTX
P1NP

Revised text

Blood samples will be collected to explore the effect of vamorolone on biomarkers associated with glucocorticoid safety concerns (exploratory outcomes for adrenal suppression, insulin resistance, and bone turnover, as well as, in the additional 12 to <18 years age group, suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4)), as listed in Table 6.

(…)

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

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

A total of approximately 12 mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin, morning cortisol, osteocalcin, CTX, and P1NP, as well as, in the additional 12 to <18 years age group, LH, FSH, TSH, FT4)) and measurement of HbA1c over the course of the 21-week study (see **Section 7.2.8**).

Table 6. Pharmacodynamic Biomarkers – Exploratory Safety Outcomes

Adrenal Suppression
Cortisol – morning
Insulin Resistance
Glucose – fasting
Insulin – fasting
HbA1c
Bone Turnover
Osteocalcin
CTX
P1NP
Suppression of the gonadal axis
LH
FSH
Suppression of the thyroid axis
TSH
FT4

7.6 Adverse Events and Serious Adverse Events

Original text

The condition of the subjects, inclusive of lab value, will be monitored throughout the duration of the study by the clinical site study team and by recording of AEs in subject

An AE is any untoward medical occurrence in a subject and does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the drug. Pre-existing conditions that worsen during a study are to be reported as AEs.

Revised text

An AE is any untoward medical occurrence in a subject and does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the drug. Pre-existing conditions that worsen during a study are to be reported as AEs.

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7.6.4 Follow-Up of Adverse Events

Original Text

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 document and eCRF. In the event of unexplained abnormal laboratory test values, the tests may be repeated as soon as possible and followed up until they have returned to the normal range or baseline value and/or an adequate explanation of the abnormality is found. In case of ongoing AEs at the time of database closure, the data obtained at the time of database closure will be used in the statistical analysis. The further follow-up of AEs will be documented in the source document and will be described in the final report only if considered relevant by the Investigator, the Study Chair, The Medical Monitor and/or Sponsor and CRF.

Revised Text

Adverse events will be followed until they have returned to baseline status, stabilized, or the Investigator 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 document and eCRF. In the event of unexplained abnormal laboratory test values, the tests may be repeated as soon as possible and followed up until they have returned to the normal range or baseline value and/or an adequate explanation of the abnormality is found. In case of ongoing AEs at the time of database closure, the data obtained at the time of database closure will be used in the statistical analysis. The further follow-up of AEs will be documented in the source document and CRF.

7.6.6 Serious Adverse Events

Original Text

(…)

During the SAE collection period, the Investigator or clinical site personnel should notify the Coordinating Center of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event; notification to the Coordinating Center will trigger alerts to the Study Chair, the

Sponsor, and the Medical Monitor. The Investigator will provide the initial notification by completing the SAE Report Form in the electronic data capture (EDC) system, which must include the Investigator's assessment of the relationship of the event to investigational drug, and must be signed by the Investigator.

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

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

(…)

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

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

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

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

In United States and Canada:

Email: CHOSafety@prahs.com

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

SAE Questions: Drug Safety Helpline: 1 800 772 2215

In Europe, Asia, Pacific, Africa and Australia:

Email: MHGSafety@prahs.com

Drug Safety Fax: +44 1792 525720

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

Revised Text

(…)

During the SAE collection period, the Investigator or clinical site personnel should notify the Coordinating Center of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical staff becoming aware of the event; notification to the Coordinating Center will trigger alerts to the Sponsor. The Investigator will provide the initial notification by completing the SAE Report Form in the electronic data capture (EDC) system, which must include the Investigator's assessment of the relationship of the event to investigational drug, and must be signed by the Investigator.

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

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the Coordinating Center within 24 hours of knowledge of the new or follow-up information, which will forward the information to , the Sponsor.
(…)

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

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

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

In the event of an SAE, the Investigator will complete the SAE electronic case report form within 24 hours of first awareness of the event. In the unlikely event that the electronic study database is inaccessible and the Investigator is unable to

complete the SAE electronic case report form within 24 hours, the SAE Notification Form (pdf) should be completed and emailed or printed/faxed to the ICON safety management team within 24 hours, using the contact information below:

In United States and Canada:

Email: CHOSafety@iconplc.com

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

SAE Questions: Drug Safety Helpline: 1 800 772 2215

In Europe, Asia, Pacific, Africa and Australia:

Email: MHGSafety@iconplc.com

Drug Safety Fax: +44 1792 525720

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

8.1 Study Steering Committee

Revised Text

This section is deleted

10.1 Sample Size Determination

Original Text

(…)

For this Phase II study in DMD boys ages 2 to <4 years and 7 to <18 years, a total of approximately 20 subjects in the 2 to <4 years age group will be enrolled with approximately 10 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day). A total of approximately 24 subjects in the 7 to <18 years age group will be enrolled with approximately 12 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day) and each dose level group stratified 1:1 by glucocorticoid treatment status at study entry to include approximately 6 glucocorticoid-untreated subjects and 6 glucocorticoid-treated subjects at study entry. This sample size is considered sufficient to detect drug safety concerns in a pediatric population ages 2 to <4 and 7 to <18 years with DMD based on

clinical judgment and prior study of vamorolone at these doses. In addition, this sample size is sufficiently large to determine PK parameters.

Revised Text

(…)

For this Phase II study in DMD boys ages 2 to <4 years and 7 to <18 years, a total of approximately 20 subjects in the 2 to <4 years age group will be enrolled with approximately 10 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day). A total of approximately 34 subjects in the 7 to <18 years age group will be enrolled with approximately 12 subjects per dose level group (2.0 mg/kg/day and 6.0 mg/kg/day) and each dose level group stratified 1:1 by glucocorticoid treatment status at study entry to include approximately 6 glucocorticoid-untreated subjects and 6 glucocorticoid-treated subjects at study entry, plus 10 subjects for the additional 12 to <18 years age group [6.0 mg/kg/day - glucocorticoid-treated]. This sample size is considered sufficient to detect drug safety concerns in a pediatric population ages 2 to <4 and 7 to <18 years with DMD based on clinical judgment and prior study of vamorolone at these doses. The 10 additional 12 to <18 years subjects will further ensure that the full age range is included. In addition, this sample size is sufficiently large to determine PK parameters.

10.7.5 *Pharmacodynamic analyses*

Original Text

(…)

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of safety and efficacy will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers by dose level within age group. Change from baseline will be presented. For subjects 7 to <18 years of age, descriptive statistics will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment.

The changes in serum PD biomarkers will be compared to the data collected in a previously conducted vamorolone study VBP15-004. The changes from baseline to week 12 in the present study (by dose level and age group) will be compared to the

changes from baseline to week 12 in the four treatment groups of study VBP15-004 (vamorolone 2.0 mg/kg, vamorolone 6.0 mg/kg, placebo and prednisone 0.75 mg/kg). Furthermore, the differences between the groups will be evaluated with ANCOVA models including baseline value as a covariate and the treatment/age group as a fixed factor. Additional analyses will be conducted by glucocorticoid use group, when appropriate.

Revised Text

(…)

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover, as well as exploratory biomarkers of safety and efficacy (including in the additional 12 to <18 years age group: suppression of the gonadal axis (LH, FSH) and suppression of the thyroid axis (TSH, FT4)) will be assessed. Standard descriptive statistics will be used to summarize PD biomarkers by dose level within age group. Change from baseline will be presented. For subjects 7 to <18 years of age, descriptive statistics will be presented separately for those subjects who were on SoC glucocorticoid therapy at the time of assignment to a dose group and those subjects who had been off SoC glucocorticoid therapy for at least 3 months at the time of assignment.

The changes in serum PD biomarkers will be compared to the corresponding data if available collected in a previously conducted vamorolone study VBP15-004. The changes from baseline to week 12 in the present study (by dose level and age group) will be compared to the changes from baseline to week 12 in the four treatment groups of study VBP15-004 (vamorolone 2.0 mg/kg, vamorolone 6.0 mg/kg, placebo and prednisone 0.75 mg/kg). Furthermore, the differences between the groups will be evaluated with ANCOVA models including baseline value as a covariate and the treatment/age group as a fixed factor. Additional analyses will be conducted by glucocorticoid use group, when appropriate.

12.1 Confidentiality

Original Text

(…)

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 redacted 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 applicable data protection / privacy laws in the relevant countries.

Revised Text

(…)

Subject names will remain confidential and will not be included in the database. Only enrollment number, age at enrolment and birth date (may be collected where allowed by local regulations) will be recorded on the eCRF. If the subject's name appears on any other document collected (e.g., hospital discharge summary), the name must be redacted before the document is transmitted to 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 applicable data protection / privacy laws in the relevant countries.

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15.4. Protocol Amendment #3 Complete List of Changes

A Protocol version tracking changes between Edition A3 version 1.0 and A2 version 1.0 will be provided.

7.2.4 Clinical Laboratory Tests

Original Text:

For the hematology, chemistry, and lipids laboratory tests, blood will be collected by direct venipuncture of peripheral veins. A total of approximately **19** mL of blood will be collected over the course of this study for clinical safety laboratory evaluation, including measurement of vitamin D (see Section 7.2.8 for details of blood volumes to be collected).

Revised Text:

For the hematology, chemistry, and lipids laboratory tests, blood will be collected by direct venipuncture of peripheral veins. A total of approximately **21** mL of blood will be collected over the course of this study for clinical safety laboratory evaluation,

including measurement of vitamin D (see Section 7.2.8 for details of blood volumes to be collected).

7.2.6 Pharmacodynamic Biomarker Panels

Original Text:

Blood samples will be collected pre-dose at the Day 1 and Week 12 Visits for analysis of biomarkers for exploratory outcome measures of adrenal suppression, bone turnover, and insulin resistance (**blood for** HbA1c will be **collected** at Screening and Week 12). Approximately **5** mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin [insulin resistance], morning cortisol [adrenal suppression], and osteocalcin, P1NP, and CTX [bone turnover] biomarkers) at each scheduled collection time point; **an additional 1 mL of blood will be collected for measurement of HbA1c at each of the scheduled collection time points**. Samples collected at the Day 1 and Week 12 Visits will be collected after the subject has fasted for ≥ 6 hours and prior to administration of the daily dose of study medication; the sample collected at the Screening Visit for HbA1c measurement may be collected non-fasting. Blood for morning cortisol measurement should be collected before 10 AM local time.

[…]

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

A total of approximately **12** mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin, morning cortisol, osteocalcin, CTX, and P1NP, as well as, in the additional 12 to <18 years age group, LH, FSH, TSH, FT4) **and measurement of** HbA1c over the course of the 21-week study (see Section 7.2.8).

Revised Text:

Blood samples will be collected pre-dose at the Day 1 and Week 12 Visits for analysis of biomarkers for exploratory outcome measures of adrenal suppression, bone turnover, and insulin resistance (HbA1c will be **analyzed** at Screening and Week 12). Approximately **6** mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin [insulin resistance], morning cortisol [adrenal suppression], and osteocalcin, P1NP, and CTX [bone turnover] biomarkers) at each scheduled collection time point; **HbA1c will be analyzed from the hematology sample** . Samples collected at the Day 1 and Week 12 Visits will be collected after the subject has fasted for ≥ 6 hours and prior to administration of the daily dose of study medication; the sample collected at the Screening Visit for HbA1c measurement may be collected non-fasting. Blood for morning cortisol measurement should be collected before 10 AM local time.

[…]

Additional HbA1c determination should be **performed** if urine glucose is positive and/or fasted glucose levels are above normal limits at any of the scheduled assessment time points (see Laboratory Manual).

A total of approximately **19** mL of blood will be collected for the PD biomarker panel (fasting glucose and insulin, morning cortisol, osteocalcin, CTX, and P1NP, as well as, in the additional 12 to <18 years age group, LH, FSH, TSH, FT4) over the course of the 21-week study (see Section 7.2.8).

7.2.7 Pharmacokinetic Assessment

Original Text:

At the Day 1 and Week 2 Visits, all subjects will have blood collected for PK assessments within 30 minutes prior to and at 1, 2, and 6 hours (ages 2 to <4 years), or within 30 minutes prior to and at 1, 2, 4, 6 and 8 hours (ages 7 to <18 years) following administration of the daily dose of study medication. Approximately **2** mL of blood will be collected into K_2-EDTA tubes at each assessment time point (total of **16** mL blood collected for PK assessment in 2 to < 4-year-old subjects and total of **24** mL blood collected for PK assessments in ages 7 to <18 years).

Revised Text:

At the Day 1 and Week 2 Visits, all subjects will have blood collected for PK assessments within 30 minutes prior to and at 1, 2, and 6 hours (ages 2 to <4 years), or within 30 minutes prior to and at 1, 2, 4, 6 and 8 hours (ages 7 to <18 years) following administration of the daily dose of study medication. Approximately **1.2** mL of blood will be collected into K_2-EDTA tubes at each assessment time point (total of **approximately 10** mL blood collected for PK assessment in 2 to < 4-year-old subjects and total of **approximately 15** mL blood collected for PK assessments in ages 7 to <18 years).

7.2.8 Total Blood Volume Required

Original Text:

The number and volume of blood samples and total volume of blood to be collected from each subject throughout the duration of the up-to-21-week study are summarized in Table 7. A total of **48.3** mL of blood will be collected from each 2 to <4-year-old subject, and **52.3** mL of blood will be collected from each 7 to <18-year-old subject over the course of the up-to-21-week study.

Table 7. Blood Sample Number and Volume by Study Visit

Test	Blood Volume (mL)						
	SCR	Day 1	Week 2	Week 6	Week 12	Week 16	Total Volume
Clinical Safety Labs[a]	**3.5**[b]	**3.5**[b]		**3.5**[b]	**3.5**[b]	**3.5**[b]	**17.5**

Varicella Zoster IgG	2						2
Vitamin D	1.2				1.2[b]		2.4
PD Biomarker Panel[c]		**8.2[b]**			**8.2[b]**		**16.4**
HbA1c	**1**				**1[b]**		**2**
PK[d] Ages 2 to <4 years Ages 7 to <18 years		 **4** **6**	 **4** **6**				 **8** **12**
Total Volume by Visit (mL) Ages 2 to <4 years Ages 7 to <18 years	**7.7**	 **15.7** **17.7**	 **4** **6**	**3.5**	**13.9**	**3.5**	 **48.3** **52.3**
Total Volume: **48.3** mL (ages 2 to <4 year); **52.3** mL (ages 7 to <18 year)							
SCR = Screening [a] Hematology, Chemistry, Lipids [b] Subjects must have fasted ≥ 6 hours prior to blood draws. [c] Fasting glucose, insulin, morning cortisol, CTX, P1NP, osteocalcin; pre-dose on Day 1 and Week 12. [d] Blood drawn for population PK within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), or 30 minutes pre-dose and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years). Subjects must be fasting at the time of collection of the Day 1 and Week 2 pre-dose samples.							

Revised Text:

The number and volume of blood samples and total volume of blood to be collected from each subject throughout the duration of the up-to-21-week study are summarized in Table 7. A total of **approximately 51** mL of blood will be collected from each 2 to <4-year-old subject, and **appoximately 56** mL of blood will be collected from each 7 to <18-year-old subject over the course of the up-to-21-week study.

Table 7. Blood Sample Number and Volume by Study Visit

Test	Blood Volume (mL)						
	SCR	Day 1	Week 2	Week 6	Week 12	Week 16	Total Volume
Clinical Safety Labs[a]	**3.7[b]**	**3.7[b]**		**3.7[b]**	**3.7[b]**	**3.7[b]**	**18.5**
Varicella Zoster IgG	2						2
Vitamin D	1.2				1.2[b]		2.4
PD Biomarker Panel[c]		**9.2[b]**			**9.2[b]**		**18.4**
PK[d] Ages 2 to <4 years Ages 7 to <18 years		 **4.8** **7.2**	 **4.8** **7.2**				 **9.6** **14.4**

Total Volume by Visit (mL)	**6.9**			**3.7**	**14.1**	**3.7**	
Ages 2 to <4 years		**17.7**	**4.8**				**50.9**
Ages 7 to <18 years		**20.1**	**7.2**				**55.7**
Total Volume: **50.9** mL (ages 2 to <4 year); **55.7** mL (ages 7 to <18 year)							
SCR = Screening [a] Hematology, Chemistry, Lipids, **HbA1c** [b] Subjects must have fasted ≥ 6 hours prior to blood draws. [c] Fasting glucose, insulin, morning cortisol, CTX, P1NP, osteocalcin; pre-dose on Day 1 and Week 12. [d] Blood drawn for population PK within 30 minutes pre-dose and at 1, 2, and 6 hours post-dose at the Day 1 and Week 2 Visits (ages 2 to <4 years), or 30 minutes pre-dose and at 1, 2, 4, 6 and 8 hours post-dose at the Day 1 and Week 2 Visits (ages 7 to <18 years). Subjects must be fasting at the time of collection of the Day 1 and Week 2 pre-dose samples.							