



CLINICAL STUDY PROTOCOL				
Amendment #4				
Document Title: Amendment #4 for a Phase IIb Randomized, Dou Parallel Group, Placebo- and Active-controlled S Double-Blind Extension to Assess the Efficacy an Vamorolone in Ambulant Boys with Duchenne M Dystrophy (DMD)		ndment #4 for a Phase IIb Randomized, Double-blind, llel Group, Placebo- and Active-controlled Study with le-Blind Extension to Assess the Efficacy and Safety of prolone in Ambulant Boys with Duchenne Muscular ophy (DMD)		
Protocol Number:		VBP15-004		
Document Number	:	VBP15-004-A4 (Version 1.4)		
FDA IND No.:		118,942		
Investigational Pro	duct:	Vamorolone		
Sponsor:		ReveraGen BioPharma, Inc. 155 Gibbs St. Suite 433 Rockville, MD 20850		
Medical Monitors:				
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Document Date:		28 August 2020		
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48 49	SIGNATURES OF AGREEME	NT FOR VBP15-004-A4 (Version	1.4)
50 51 52 53	Amendment #4 for a Phase IIb Randon and Active-controlled Study with Doub Safety of Vamorolone in Ambulant 1 (nized, Double-blind, Parallel Grou le-Blind Extension to Assess the E Boys with Duchenne Muscular Dy DMD)	p, Placebo- fficacy and strophy
35	Reviewed and Approved by: Electronically signed by: Eric Hoffman Reason: approved Date: Aug 28, 2020 10:03 EDT		
57 58 59 60 82 63	Eric Hoffman, Ph.D. Chief Executive Officer ReveraGen BioPharma, Inc. Electronically signed by: Michela Guglieri Michela Guglieri Date: Sep 2, 2020 06:30 GMT+1	Date	
64 65 66	Michela Guglieri, M.D. Study Chair John Walton Muscular Dystrophy Research Cen	Date	
67 7468	Paula R. Clemens Reason: 1 aprive the document Date: Aug 31, 2020 09:42 EDT		
75 76 77 78 82	Paula R. Clemens, M.D. Study Vice Chair University of Pittsburgh School of Medicine <i>Electronically signed by: Johannes van den</i> <i>Anker</i> <i>Beason: approval</i> <i>Date: Sep 2, 2020 08:09 EDT</i>	Date	
83 84 85 86 87 88 90 91	John van den Anker, M.D., Ph.D. Medical Monitor Chief Medical Officer ReveraGen BioPharma, Inc. Electronically signed by: Benjamin D. Schwartz Benjamin D. Schwartz Date: Aug 28, 2020 11:26 CDT	Date	
92 93 94 95 97 98	Benjamin D. Schwartz, M.D., Ph.D. Consulting Medical Monitor The Camden Group, LLC <i>Electronically signed by: Laurel J. Mengle-Gaw</i> <i>Laurel J. Mengle-Gaw</i> ^{<i>Electronically signed by: Laurel J. Mengle-Gaw</i> <i>Laurel J. Mengle-Gaw</i>^{<i>Beason: author</i>}}	Date	
99 100 101 102 103 10 5 04	Laurel J. Mengle-Gaw, Ph.D. Consulting Clinical Monitor The Camden Group, LLC Mark Jaros 105 Electronically signed by: Mark Jaros Reason: 1 approve this document. Date: Sep 2, 2020 09:28 CDT	Date	
109 110 111	Mark J. Jaros, Ph.D. Consulting Statistician Summit Analytical, LLC	Date	

Amendment #4 for a Phase and Active-controlled Stuc Safety of Vamorolone i	e IIb Randomized, Double-blind, Parallel Group, Placebo ly with Double-Blind Extension to Assess the Efficacy and n Ambulant Boys with Duchenne Muscular Dystrophy (DMD)
PROTOCOL NUMBER:	VBP15-004
DOCUMENT NUMBER:	VBP15-004-A4 (Version 1.4)
SPONSOR:	ReveraGen BioPharma, Inc.
DOCUMENT DATE:	28 August 2020
By my signature, I confine this protocol, protocol an to comply with the conduct study conduct procedures	rm that my staff and I have carefully read and understand tendment, amended protocol, or revised protocol and agree of and terms of the study specified herein and with any othe provided by ReveraGen BioPharma, Inc.
I agree to conduct the requirements of clinical	study according to this protocol and the obligations and Investigators and all other requirements set out in the
Clinical Practice (GCP) d directives of the jurisdict	usted in 21 CFR part 312, and ICH principles of Good and in accordance with all applicable laws, guidances and ion where the study is being conducted. I will not initiate
this study without the Independent Ethics Comm	approval of an Institutional Review Board (IRB) on nittee (IEC).
I understand that, should terminate prematurely or decision will be commun withdraw from execution in writing to ReveraGen H	d the decision be made by ReveraGen BioPharma, Inc. to suspend the study at any time for whatever reason, such nicated to me in writing. Conversely, should I decide to of the study, I will communicate immediately such decision BioPharma, Inc.
For protocol amendmen agreement from Revera approval (where required immediate hazard to the permitted by all applicable	not harma, inc. hts, I agree not to implement the amendment without Sen BioPharma, Inc. and prior submission to and written) from the IRB/IEC, except when necessary to eliminate and subjects, or for administrative aspects of the study (where e regulatory requirements).
Investigator's Signature	Date
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156	SERIOUS ADVERSE EVENT CONTACT INFORMATION
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158	In the event of a serious adverse event (SAE) (see Section 7.5), the Investigator will
159	complete the SAE electronic case report form within 24 hours of first awareness of
160	the event. In the unlikely event that the electronic study database is inaccessible and
161	the Investigator is unable to complete the SAE electronic case report form within
162	24 hours, the SAE Notification Form (pdf) should be completed and emailed or
163	printed/faxed to the PRA safety management team within 24 hours, using the
164	contact information below:
165	In United States and Canada:
166	Email: CHOSafety@prahs.com
167	Drug Safety Fax: 1 888 772 6919 or 1 434 951 3482
168	SAE Questions: Drug Safety Helpline: 1 800 772 2215
169	In Europe, Asia, Pacific, Africa and Australia:
170	Email: MHGSafety@prahs.com
171	Drug Safety Fax: +44 1792 525720
172	SAE Questions: Drug Safety Helpline: +49 621 878 2154

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PROTOCOL AMENDMENT TRACKING

Document	Document Number	Approval Date
Original Protocol	VBP15-004	15 December 2017
Amendment #1	VBP15-004-A1 (Version 1.1)	04 May 2018
Amendment #2	VBP15-004-A2 (Version 1.2)	05 March 2019
Amendment #3	VBP15-004-A3 (Version 1.3)	21 May 2019
Amendment #4	VBP15-004-A4 (Version 1.4)	28 August 2020

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Reasons for Protocol Amendment #4:

- To revise one of the primary objectives of the study to compare the efficacy of vamorolone administered orally at a dose of 6.0 mg/kg/day vs. placebo over a 24week treatment period;
- 181
 2. To revise the primary efficacy endpoint to TTSTAND velocity, comparison of vamorolone 6.0 mg/kg/day vs. placebo in change from baseline to Week 24, to align with the primary objective;
- 184
 3. To add an additional secondary objective of the study to compare the efficacy of vamorolone administered orally at a dose of 2.0 mg/kg/day vs. placebo over a 24-week treatment period;
- 187
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 4. To delete a secondary objective of the study comparing the efficacy of vamorolone 2.0 mg/kg/day vs. 6.0 mg/kg/day over 24 weeks;
- 189
 189 5. To revise the list of safety endpoints to include linear growth velocity, and to clarify
 190 the endpoints for BMI z-score and ACTH Stimulation Test;
- 191 6. To revise the secondary efficacy endpoints for Treatment Period #1;
- 192 7. To add exploratory efficacy endpoints for Treatment Period #1;
- 193 8. To add comparison of each vamorolone group to the placebo group for PARS III;
- 9. To clarify Ease of Study Drug Administration exploratory endpoint;
- 10. To revise the methodology for sample size calculation, in consideration of the
 revised primary efficacy endpoint;
- 197 11. To add a Per Protocol Population for statistical analyses;
- 198 12. To revise the multiple testing procedures for the efficacy endpoints;
- 199 13. To revise the statistical methodology for efficacy and safety analyses;
- 14. To clarify the circumstances under which hospitalizations should be considered
 serious adverse events;

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203 204	15. To add assessment of suicidality and abuse potential associated with treatment from examination of adverse event data;
205 206	16. To clarify that demographic and baseline characteristics summary tables will not be presented by age stratification;
207 208 209	17. To update the safety information presented in Section 1.5 Overall Benefit/Risk and the serious adverse event information presented in Section 5.4 Rationale for Dose Selection to include current data from the vamorolone program;
210	18. To remove analysis of biomarkers of immune suppression;
211	19. To clarify that levels, not ratios, of serum osteocalcin and CTX1 will be reported;
212 213	20. To clarify that analyses of candidate genetic modifiers of DMD will be presented in an addendum report;
214	21. To clarify that spine x-ray data will be analyzed in an addendum report;
215	22. To remove BMD z-score from the list of parameters assessed by DXA scan;
216	23. To add an endpoint for the assessment of tolerability; and
217	24. To correct typographical errors.
218 219 220	The Sections changed by Amendment #4 are listed in was/is format in Appendix 15.1.
221 222 223	Additionally, a protocol clarification letter (Protocol Clarification Letter #2.1, 27 March 2020) was issued to outline modifications that could be made to study conduct due to COVID-19. The main reasons for the Protocol Clarification Letter were as follows:
224 225 226 227 228 229 230 231 232	1. To detail the modifications to study conduct and site monitoring to be implemented during the global COVID-19 pandemic. Modifications are allowed to informed consent process; visit schedule and on-site study visits; collection of clinical laboratory assessments, weight, vital signs, efficacy assessments, adverse events and concomitant medications; dispense, return, and review of subject diaries; investigational product dispensing, administration, and compliance measurement; recording of COVID-19-related protocol deviations; transition to vamorolone general access program; and site monitoring. The key modifications to be made on a visit-, site-, or subject-specific basis are:
233 234 235	a. to allow for scheduled assessments to be performed remotely, with the exception of Screening assessments, which must be performed at the study site;
236 237 238	 b. for critical safety assessments (i.e., clinical laboratory tests, collection of adverse events and concomitant medications), intervals between assessments should be no longer than 12 weeks;
239 240	c. in cases where on-site study visits are not possible for the completion of scheduled efficacy assessments, the Time to Stand Test (TTSTAND) will

	Vamorolone	28 August 2020
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242		be conducted remotely by a trained clinical evaluator by
243		videoconferencing interface; assessment of TTSTAND must be completed
244		at the Baseline, Week 24, and Week 48 assessment time points;
245	d.	to allow for investigational product sufficient for 12 weeks of dosing to be
246		shipped directly from the site to subjects' homes.

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STUDY SYNOPSIS

Protocol Title	A Phase IIb Randomized, Double-blind, Parallel Group, Placebo- and Active- controlled Study with Double-Blind Extension to Assess the Efficacy and Safety of Vamorolone in Ambulant Boys with Duchenne Muscular Dystrophy (DMD)			
Name of Sponsor	ReveraGen BioPharma, Inc.			
Protocol Number	VBP15-004			
Drug Substance	delta-1,4,9(11)-pregnatriene-17-alpha,21-dihydroxy-16-alpha-methyl-3,20-dione			
Investigational Drug Product	Vamorolone, 1.33% and 4.0% wt/wt suspension for oral dosing			
Phase of Development	Phase IIb			
Indication	Treatment of Duchenne muscular dystrophy (DMD)			
Primary Objectives	 To compare the efficacy of vamorolone administered orally at daily doses of 6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD; and 			
	2. To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD.			
Secondary Objectives	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD; 			
	 To compare the safety of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD; 			
	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD; 			
	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 48-week treatment period in ambulant boys ages 4 to <7 years with DMD vs. untreated DMD historical controls; 			
	5. To compare the safety of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 48-week treatment period in ambulant boys ages 4 to <7 years with DMD vs. prednisone-treated DMD historical controls; and			
	6. To evaluate the population pharmacokinetics (PK) of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD.			
Exploratory Objectives	1. To evaluate the satisfaction with treatment of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 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 24-week treatment period vs. daily			

	$ \begin{array}{c} \textbf{(vamorol} \\ \textbf{(vamorol} \\ \textbf{0.75 mg/} \\ \textbf{Study R:} \\ \hline \textbf{Group} \\ \hline 1 \\ \hline 2 \\ \hline 3 \\ \hline 4 \\ \hline 5 \\ \hline 6 \\ \# = \text{number} \\ \textbf{Subjects} \end{array} $	lone 2.0 kg/day andomi # 30 30 15 15 15 15 15 25 r of pl	mg/kg/day : vamorolone 6.0 mg/k : placebo) for Treatment Period #1 ization Schedule Treatment Period #1 Vamorolone, 2.0 mg/kg/day \rightarrow Vamorolone, 6.0 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow Placebo \rightarrow Placebo \rightarrow lanned randomized subjects in eac	<pre>sg/day : prednisone : Treatment Period #2 Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day h group </pre>		
	6) will (vamorol 0.75 mg/ Study Ra Group 1 2 3 4 5 6	lone 2.0 kg/day andomi # 30 30 15 15 15 15	mg/kg/day : vamorolone 6.0 mg/h: placebo) for Treatment Period #1ization ScheduleTreatment Period #1Vamorolone, 2.0 mg/kg/day \rightarrow Vamorolone, 6.0 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow Placebo \rightarrow Placebo \rightarrow	xg/day : prednisone Treatment Period #2 Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day		
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	6) will (vamorol 0.75 mg/ Study Ra Group 1 2 3 4	lone 2.0 kg/day andomi # 30 30 15 15	mg/kg/day : vamorolone 6.0 mg/k : placebo) for Treatment Period #1 ization Schedule Treatment Period #1 Vamorolone, 2.0 mg/kg/day \rightarrow Vamorolone, 6.0 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow	xg/day : prednisone : Treatment Period #2 Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day		
	6) will (vamorol 0.75 mg/ Study R: Group 1 2 3	lone 2.0 kg/day andomi # 30 30 15	mg/kg/day : vamorolone 6.0 mg/l : placebo) for Treatment Period #1 ization Schedule Treatment Period #1 Vamorolone, 2.0 mg/kg/day \rightarrow Vamorolone, 6.0 mg/kg/day \rightarrow Prednisone, 0.75 mg/kg/day \rightarrow	xg/day : prednisone : Treatment Period #2 Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day Vamorolone, 2.0 mg/kg/day		
	6) will (vamorol 0.75 mg/ Study R: 0 1 2	lone 2.0 kg/day andomi $\frac{\#}{30}$ 30	mg/kg/day : vamorolone 6.0 mg/k : placebo) for Treatment Period #1 ization Schedule Treatment Period #1 Vamorolone, 2.0 mg/kg/day \rightarrow Vamorolone, 6.0 mg/kg/day \rightarrow	<pre>sg/day : prednisone : Treatment Period #2 Vamorolone, 2.0 mg/kg/day Vamorolone, 6.0 mg/kg/day</pre>		
	(vamorol 0.75 mg/ Study Ra Group 1	lone 2.0 kg/day andomi $\frac{\#}{30}$	mg/kg/day : vamorolone 6.0 mg/l : placebo) for Treatment Period #1 ization Schedule Treatment Period #1 Vamorolone, 2.0 mg/kg/day \rightarrow	cg/day : prednisone : Treatment Period #2 Vamorolone, 2.0 mg/kg/day		
	(vamorol 0.75 mg/ Study Ra	lone 2.0 kg/day andomi #	mg/kg/day : vamorolone 6.0 mg/k : placebo) for Treatment Period #1 ization Schedule Treatment Period #1	(g/day : prednisone : Treatment Period #2		
	(vamorol 0.75 mg/	lone 2.0 kg/day andomi	mg/kg/day : vamorolone 6.0 mg/l : placebo) for Treatment Period #1 ization Schedule	cg/day : prednisone :		
	(vamorol	lone 2.0 kg/day	mg/kg/day : vamorolone 6.0 mg/l : placebo) for Treatment Period #1	kg/day : prednisone		
	0) will					
	6) will be combined, effectively resulting in a 1:1:1:1 randomization					
	where the two prednisone groups in Treatment Period #1 (Groups 3 and 4) will be combined and the two placebo groups in Treatment Period #1 (Groups 5 and					
	Subjects	Subjects will be randomized to one of six treatment groups in a 2:2:1:1:1:1 ratio,				
	28 + 1 da	iy to 48), and a 4-week Dose-tapering Per	iod (Weeks 49-52).		
	week Tra	ansition	Period (Weeks 25-28), a 20-weel	Treatment Period #2 (Weeks		
	The stud	ly is co	omprised of a 5-week Pretreatme	ent Screening Period, a 1-day		
	48 weeks	s in amb	bulant boys ages 4 to <7 years with	n DMD.		
	24 weeks	ednisor	ne 0.75 mg/kg/day and placebo o evaluate persistence of effect	over a Treatment Period o		
	vamorolo	one adn	ninistered orally at daily doses (of 2.0 mg/kg and 6.0 mg/kg		
Study Design	active-co	ontrollec	study is a randomized, double-bind study to evaluate the efficacy, sa	fety, PD, and population PK o		
	asso simi dise	larly a ase seve	ssociated with vamorolone-treaterity, or response to vamorolone or trudy, or response to vamorolone or trudy, is a rendemized, dayle blick	ted DMD subjects (baseling r prednisone treatment).		
	7. To de	termine	e if candidate genetic modifiers of with disease severity or responses	of DMD (gene polymorphisms		
	pred effic	lnisone acy in a	0.75 mg/kg on potential serum ambulant boys ages 4 to <7 years v	PD biomarkers of safety and with DMD; and		
	6. To c	ompare	the effects of vamorolone admini and 6.0 mg/kg over a 24 wee	stered orally at daily doses of k treatment period vs. daily		
	5. To c 2.0 ± pote	compare mg/kg a ntial se mbulant	e the effects of vamorolone admin and 6.0 mg/kg over a 24-week tr rum pharmacodynamics (PD) bio boys ages 4 to <7 years with DM	istered orally at daily doses of eatment period vs. placebo of markers of safety and efficacy D;		
	4. To a amb	ussess thus ulant bo	he ease of administration of the s bys ages 4 to <7 years with DMD;	tudy medication suspension t		
	3. To e 2.0 ± phys	valuate mg/kg a sical fur	the effect of vamorolone administ and 6.0 mg/kg over a 24-week tr actioning;	stered orally at daily doses of eatment period vs. placebo o		
		msone	0.75 mg/kg on behavior and neuro	psychology;		

	subjects randomized to receive vamorolone during Treatment Period #1 (Groups 1 and 2) will continue to receive vamorolone at the same dose, while subjects randomized to receive prednisone will have their dose tapered to zero, and subjects randomized to placebo will continue to receive placebo. The prednisone group will be used as an active control comparison for safety and efficacy endpoints as requested by the European Medicines Agency (EMA). The placebo group will be used as comparator for efficacy endpoints (superiority model) as requested by the EMA and Food and Drug Administration (FDA) protocol advisory board. Although glucocorticoids are part of the care recommendations for DMD, their adverse effect profile has limited their use. The age at which glucocorticoids should be started in DMD boys is uncertain, ranging from 4 to 7 years, based on a balance between benefits and side effects. In view of the age inclusion criteria and duration of the placebo-controlled study period (6 months), the use of a placebo group has been considered acceptable as in clinical practice it will not cause a real delay in prescription of an accepted treatment for this condition. Any exposure of placebo longer than 6 months was considered unethical. At the end of the Treatment Period #2, subjects may be given access to vamorolone through an additional study or general access program, or given the option to transition to standard of care treatment for DMD (may include glucocorticoids). Subjects completing VBP15-004 and enrolling directly into an additional vamorolone study or general access program to receive vamorolone will not need to taper their vamorolone dose prior to enrollment. All other subjects will begin a 4-week double-blind Dose-tapering Period during which the dose of study medication will be progressively reduced and discontinued.
Planned Sample Size	A total of approximately 120 subjects will be randomized (2:2:1:1:1:1) to treatment as follows (treatment assignment in Treatment Period #1 \rightarrow treatment assignment in Treatment Period #2):
	Vamorolone 2.0 mg/kg/day \rightarrow Vamorolone 2.0 mg/kg/day (n=30); Vamorolone 6.0 mg/kg/day \rightarrow Vamorolone 6.0 mg/kg/day (n=30); Prednisone 0.75 mg/kg/day \rightarrow Vamorolone 2.0 mg/kg/day (n=15); Prednisone 0.75 mg/kg/day \rightarrow Vamorolone 6.0 mg/kg/day (n=15); Placebo \rightarrow Vamorolone 2.0 mg/kg/day (n=15); or Placebo \rightarrow Vamorolone 6.0 mg/kg/day (n=15).
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 \geq 4 years and <7 years of age at time of enrollment in the study;
	4.	Subject weighs >13.0 kg and ≤ 39.9 kg at the Screening Visit;
	5.	Subject is able to walk independently without assistive devices;
	6.	Subject is able to complete the Time to Stand Test (TTSTAND) without assistance in <10 seconds, as assessed at the Screening Visit;
	7.	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 \leq 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 randomization];
	8.	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 randomization.
	9.	Subject is able to swallow tablets, as confirmed by successful test swallowing of placebo tablets during the Screening Period; and
	10.	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 had an acute illness within 4 weeks prior to the first dose of study medication;
	4.	Subject has used mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone (canrenoate potassium), prorenone (prorenoate potassium), mexrenone (mexrenoate potassium) within 4 weeks prior to the first dose of study medication;
	5.	Subject has a history of primary hyperaldosteronism;
	6.	Subject has evidence of symptomatic cardiomyopathy [Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary];
	7.	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 first dose of study medication, 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 first dose of study medication or if administered at stable dose beginning at least 4 weeks prior to first dose of study medication and anticipated to be used at the stable dose regimen for the duration of the study];
	8.	Subject has an allergy or hypersensitivity to the study medication or to any of its constituents;
	9.	Subject has used idebenone within 4 weeks prior to the first dose of study

medication; 10. Subject has severe behavioral or cognitive problems that preparticipation in the study, in the opinion of the Investigator; 11. Subject has previous or ongoing medical condition, medical his physical findings or laboratory abnormalities that could affect safety, i trait unlikely that retartment and follow-up will be correctly complete impair the assessment of study results, in the opinion of the Investigator 12. Subject is taking (or has taken within 4 weeks prior to the first does of medication) herbal remedies and supplements which can impact m strength and function (e.g., Co-enzyme Q10, creatine, etc.); 13. Subject is taking (or has taken within 3 months prior to the first does of study medication indicated for DMD, including Exond and Translarma; 14. Subject has been administered a live attenuated vaccine within 14 days to the first dose of study medication; 15. Subject is currently taking any other investigational drug or has taker other investigational drug or thas a sibling who is currently enrolled in any vamorolone study or Expanded Access Program, or who intends to enroll in any vamoror study or Expanded Access Program, or who intends to enroll in any vamoror study or Expanded Access Program during the subject's may be rescere if ineligible due to a transient condition which would prevent the subject participating, such as an upper respiratory tract infection or injury, or ineligible due to negative anti-varicella IgG antibody test result. Number of Centers The study will be conducted at approximately 30 study sites in approximat 15 countries, predominantly in the European Union (EU). Study Duration Up to approximately 36 months total duration		
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Subjects who complete the Treatment Period Week 48 assessments may be g the option of continuing vamorolone treatment in an additional vamoro		• Dose-tapering Period: 4 weeks (only for subjects who will transition off vamorolone at the end of the study)
directly with vamorolone treatment in the additional vamorolone study general access program will be discharged from the VBP15-004 study follo completion of all Week 48 assessments and the Week 48 Follow-up Visit A		Subjects who complete the Treatment Period Week 48 assessments may be given the option of continuing vamorolone treatment in an additional vamorolone study or general access program under separate protocol. Subjects who continue directly with vamorolone treatment in the additional vamorolone study or general access program will be discharged from the VBP15-004 study following completion of all Week 48 assessments and the Week 48 Follow-up Visit ACTH

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Treatment Period #1

Vamorolone 1.33% and vamorolone 4.0% wt/wt oral suspensions (investigational medicine), prednisone (active-control) or placebo will be administered once daily over the 24-week Treatment Period #1. Subjects receiving 2.0 mg/kg/day will be administered the vamorolone 1.33% wt/wt oral suspension, and subjects receiving 6.0 mg/kg/day will be administered the vamorolone 4.0% wt/wt oral suspension. To maintain the blind, matched suspension (vamorolone or placebo) and matched tablets (prednisone or placebo) will be administered. Each subject will receive a dose of suspension (vamorolone or placebo) and tablets (prednisone or placebo) each day. The number of tablets of prednisone 5 mg or matching placebo to be administered, based on subject weight and a prednisone dose of 0.75 mg/kg, is shown in the table below:

	Prednisone an	d Placebo	Tablet	Dosing
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Band	Weight range in kg	Weight used for calculation of dose per kg	Dose in mg based on 0.75 mg/kg prednisone	Number tablets of prednisone (5 mg) or matching placebo for given weight range
А	13-19.9	13.33 kg	10 mg	2
В	20-25.9	20.00 kg	15 mg	3
С	26-32.9	26.67 kg	20 mg	4
D	33-39.9	33.33 kg	25 mg	5

Study drugs will be administered in the study unit on Day 1, and at the Week 2, Week 12 and Week 24 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 suspension, the syringe will be filled once with water and the water will be administered by mouth using the volumetric syringe. Prednisone or matching placebo tablets will be taken either immediately before or immediately after the dose of suspension. 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 including at least 8 g of fat (approximately 8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion). There are no other food or drink restrictions before or after dosing.

Transition Period

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Vamorolone 1.33% wt/wt or 4.0% wt/wt (investigational medicine) or placebo oral suspension will continue to be administered once daily over the 4-week Transition Period. Prednisone (active control) and placebo tablets will be tapered over the 4-week Transition Period. All study medication will be administered once daily, in the same manner as during Treatment Period #1.

Treatment Period #2 and Dose-tapering Period

Vamorolone 1.33% wt/wt or 4.0% wt/wt oral suspension (investigational medicine) will be administered once daily over the 20-week Treatment Period #2, and during the 4-week Dose-tapering Period, as applicable. No study drug tablets are administered during Treatment Period #2 or the Dose-tapering Period. The oral suspension study medication will be administered once daily, in the same manner as during Treatment Period #1.

Study Summary	This Phase IIb study is a randomized, double-blind, parallel group, placebo- and active-controlled study with double-blind extension to evaluate the long-term efficacy, safety, tolerability, PD, and population PK of vamorolone (the investigational medicine) compared to prednisone (active control) and placebo over a Treatment Period of 24 weeks in boys ages 4 to <7 years with DMD, and determine the persistence of effect over a total Treatment Period of 48 weeks.
	Study drug dosing will occur from Day 1 until the Week 48 Visit. Study drug dosing will occur at home on all days except the Day 1, Week 2, Week 12, Week 24, Week 28, Week 30, Week 40, and Week 48 study visits, when dosing will occur at the study site.
	Subjects will be assessed for safety and tolerability, clinical efficacy, PD, and population PK at scheduled visits throughout the study. Treatment Period #1, Transition Period, and Treatment Period #2 study visits will occur at Day 1, Week 2, Week 6, Week 12, Week 18, Week 24, Week 28, Week 30, Week 34, Week 40 and Week 48; all subjects will return to the clinical site for a Week 24 Follow-up Visit and for a Week 48 Follow-up Visit, 48 ± 3 hours after administration of the final dose of Treatment Period #1 and Treatment Period #2 study medication, respectively, for ACTH Stimulation testing. Adverse events, including SAEs, and concomitant medications will be recorded throughout the study.
	Subject diaries will be dispensed at the Day 1 Visit and at each study visit thereafter through Week 48 to record AEs, changes to concomitant medications taken during the study, and any missed or incomplete doses of study medication.
	taken during the study, and any missed or incomplete doses of study medication. There is flexibility in the timing of completion of some of the scheduled Week 24 and Week 48 assessments. The scheduled physical examination, weight, vital signs, clinical laboratory tests, blood draws for PD biomarker analysis, blood draw for DNA testing (Week 24 only), Ease of Study Medication Administration Assessment, PODCI, PARS III, and functional assessments (TTSTAND, TTCLIMB, TTRW, NSAA, 6MWT, hand-held myometry, ROM) must all be performed on the date of the Week 24 or Week 48 dose of study medication. The 12-lead ECG may be performed on the date of the Week 24 or Week 48 dose of study medication, the day following the Week 24 or Week 48 dose of study medication, or the day of the Week 24 or Week 48 dose of study medication, or the day of the Week 24 or Week 48 Follow-up Visit. For the Week 24 assessments, completion of the DXA scan, spine X-rays, Fracture Questionnaire, 2-D echocardiography, eye examination, TSQM, and Blindedness Assessment may be performed up to 7 days following the date of the Week 24 dose of study medication to accommodate need for additional scheduling flexibility. For the Week 48 assessments, completion of the DXA scan, Fracture Questionnaire, 2-D echocardiography, eye examination, and TSQM may be performed on the date of the final Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, the day following the Week 48 dose of study medication, or the day of the Week 48 Follow-up Visit for subjects who will receive additional vamorolone therapy by enrolling directly into an additional vamorolone study or
	general access program, or up to 7 days following the date of the final Week 48 dose of study medication for subjects participating in the Dose-tapering Period. A Transition Period of 4 weeks in duration follows the end of Treatment Period #1 for all subjects. During this Transition Period, all subjects will continue to receive the liquid formulation (vamorolone 2.0 mg/kg or 6.0 mg/kg, or matching placebo) they received during Treatment Period #1 and will be tapered off their study medication tablets (prednisone or matching placebo). Site study staff will contact the parent(s)/guardian(s) by telephone at Week 26 to ensure that the tablet tapering is proceeding according to protocol, to assess potential signs or

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	parent(s)/guardian(s) may have. All subjects will return to the clinical site for the Week 28 assessments, prior to receiving their first dose of Treatment Period #2 study medication on the day after the Week 28 Visit (Week 28 + 1 day).
	Subjects who complete the VBP15-004 study assessments through the Week 48 Visit and Week 48 Follow-up Visit may be given access to vamorolone through an additional study or general access program, or given the option to transition to standard of care treatment (including glucocorticoids) for DMD. Standard of care treatment for DMD may be offered to the subject following completion of the Phase IIb VBP15-004 study, if the subject's parent or guardian does not wish to enroll the subject in the additional vamorolone study or general access program and/or the Investigator feels it to be in the best interest of the subject.
	Subjects who complete the VBP15-004 study and will enroll directly into an additional vamorolone study or general access program to continue vamorolone treatment will be discharged from the VBP15-004 study following completion of all Week 48 assessments and the Week 48 Follow-up Visit ACTH Stimulation Test. Subjects who will not continue vamorolone treatment in an additional vamorolone study or general access program, including those subjects who will transition to standard of care treatment for DMD, will have their vamorolone dose tapered during a 4-week Dose-tapering Period, prior to discharge from the study. Site study staff will contact the parent(s)/guardian(s) by telephone at Week 50 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 24 Visit should return to the study unit for scheduled Week 24 assessments and the Week 24 Follow-up Visit ACTH Stimulation Test at the time of early withdrawal, whenever possible; any subject who prematurely discontinues the study after Week 24 but prior to Week 28 should complete the scheduled Week 28 assessments at the time of early withdrawal, whenever possible; and any subject who prematurely discontinues the study after Week 28 but prior to Week 48 should complete the scheduled Week 48 assessments and the Week 48 Follow-up Visit ACTH Stimulation Test at the time of early withdrawal, whenever possible, assuming the subject has not withdrawn consent. Any subject who withdraws early from the study should undergo Early Discontinuation Dose-tapering.
Safety Measures	Body Mass Index (BMI)
	 Weight and Height 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
	Cushingoid features
	Clinical laboratory tests:
	 Hematology and clinical chemistry Urinalysis Linid and file (triplet i be to to be to b
	• Lipid profile (trigiverides, total cholesterol, low density

- lipoprotein [LDL], high density lipoprotein [HDL])
- Vitamin D level

	ACTH Stimulation Test
	• 12-lead electrocardiogram (ECG)
	• 2-D echocardiography
	• Eye examination
	• Dual-energy x-ray absorptiometry (DXA) scan
	• Spine X-ray
	Fracture Questionnaire
	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.4.03
Pharmacodynamic Measures	 Blood will be collected for serum PD biomarker testing to explore effects of vamorolone on biomarkers of muscle cellular pathology, and biomarkers associated with acute and chronic glucocorticoid treatment (aspects of both safety and efficacy). Secondary outcomes are serum biomarkers bridged to clinical outcomes of safety, including adrenal suppression, insulin resistance, and bone turnover. Exploratory outcomes are serum biomarkers that have been shown to be glucocorticoid-responsive in DMD patients, but not yet bridged to clinical outcomes (safety and efficacy). Samples for analysis of acute and chronic PD biomarker response will be collected at Day 1, Week 12, and Week 24, Week 28, Week 40, and Week 48 (predose), and final Dose-tapering Period Visit. Blood remaining from collected samples may be stored for future exploratory biomarker studies. Blood samples for PD biomarkers, including insulin and glucose, will be collected after subjects have fasted for ≥ 6 hours, and prior to the daily dose of study medication where applicable.
Pharmacokinetic Measures	• Blood will be collected from all subjects at the Week 30 Visit, at 2 hours post-dose, for vamorolone population PK analysis.
Clinical Efficacy Measures	 Time to Stand Test (TTSTAND) Time to Climb 4 steps (TTCLIMB) Time to Run/Walk 10 meters Test (TTRW) North Star Ambulatory Assessment (NSAA) Six-minute Walk Test (6MWT) Hand-held Myometry (elbow flexors/knee extensors) Range of Motion (ROM) in the ankles
Exploratory Measures	 Treatment satisfaction questionnaire (TSQM) Pediatric Outcome Data Collection Instrument (PODCI) PARS III questionnaire Ease of Study Medication Administration Assessment Blindedness Assessment DNA testing for candidate genetic modifiers of DMD
Statistical Methods	Sample Size: This is a randomized, double-blind, parallel group, placebo- and active- controlled study. Study medication is administered daily in this Phase IIb trial. Data for untreated subjects from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study and data for prednisone-treated subjects from the CINRG Prednisone study were used to help

314	estimate sample	sizes for this	s study.			
315 316 317 318 319	In the vamorolone VBP15-003 study and the interim analysis of the VBP15-LTE study, doses of 0.25 and 0.75 mg/kg/day showed little evidence of clinical benefit, whereas doses of 2.0 and 6.0 mg/kg/day both showed clear evidence of clinical benefit comparable to that seen with glucocorticoids (prednisone and deflazacort).					
320 321 322 323 324 325 326	In consideration of the primary efficacy endpoint in the current study, comparison of 6.0 mg/kg/day vamorolone versus placebo, sample size calculations were performed using data from vamorolone-treated subjects from the VBP15-002/VBP15-003 24-week treatment period. The analysis compared TTSTAND velocity from the combined 2.0 and 6.0 mg/kg/day groups (Treatment Group) to the combined 0.25 and 0.75 mg/kg/day groups (Pseudo-Placebo Group).					
327 328 329 330 331 332 333 334 335	Least squares (MMRM) mode parameter estim the comparison Placebo Group Week 24. For group, simple d data were used. variance, with all	(LS) means eling of VE ates of the p of the Treat (0.25 + 0.75) the estimate lescriptive st Power was pha =0.05.	from the m BP15-002/VB population me ment Group 5 mg/kg/day) es of standa tatistics from estimated us	mixed mode P15-003 24 eans in the s (2.0 + 6.0 r) on the mean rd deviation the VBP15 ing two-side	el for repeat -week data ample size cang/kg/day) van change fro s within eac 5-002/VBP15 ed t-tests assu	ted measures were used as alculations for s. the Pseudo- om baseline at h comparison -003 24-week uning unequal
336 337 338 339 340 341 342 343	The following table shows the resultant estimated power for various sample sizes per comparison group for comparing the Treatment Group $(2.0 + 6.0 \text{ mg/kg/day})$ vs. the Pseudo-Placebo Group $(0.25 + 0.75 \text{ mg/kg/day})$ on the mean change from baseline at Week 24 for the alternative hypothesis that H1: $\mu 1 \neq \mu 2$ assuming an alpha level of 0.05 and parameter estimates from the analyses described above for TTSTAND velocity:					
	Sample Size per Comparison Group	µ1 (Pseudo- Placebo)	μ2 (Treatment Group)	σ1 (Pseudo- Placebo)	σ2 (Treatment Group)	Estimated Power
	25	-0.0052	0.0450	0.0628	0.0530	84.89%
	28	-0.0052	0.0450	0.0628	0.0530	88.76%
	30	-0.0052	0.0450	0.0628	0.0530	90.81%
344 345 346 347 348 349 350 351 352	The sample size prednisone, and will provide app significant diffe velocity at Wea treatment group detect a statistic on TTSTAND v	e of 25 per placebo wil roximately 8 erence betw ek 24. Simi) will provid cally signific elocity at W	treatment gro l result in a 35% power at een 6.0 mg larly, a tota le approxima eant difference eek 24.	bup for 2.0 total enrollm alpha level /kg/day and l enrollmen itely 91% po the between (mg/kg/day, 6 nent of 100 s 0.05 to detec 1 placebo or t of 120 sub ower at alpha 5.0 mg/kg/day	.0 mg/kg/day, ubjects which t a statistically TTSTAND ojects (30 per level 0.05 to y and placebo
352	Note that subjects in the prednisone and placebo groups will actually be randomized into two groups each:					
354 355 356 357	 Prednisone 0.75 mg/kg/day → Vamorolone 2.0 mg/kg/day (n=15); Prednisone 0.75 mg/kg/day → Vamorolone 6.0 mg/kg/day (n=15); Placebo → Vamorolone 2.0 mg/kg/day (n=15); or Placebo → Vamorolone 6.0 mg/kg/day (n=15). 					

These groups will be pooled by initial treatment (prednisone or placebo) for the Treatment Period #1 analyses.

If the number of subjects who withdraw early from the study is high, additional subjects may be enrolled to achieve approximately 120 subjects completing the Week 24 Visit assessments.

Analysis Populations:

Four populations will be defined for data analysis: the Safety Population, the modified Intent-to-Treat Population, the Per Protocol Population (PPP), and the Pharmacokinetic (PK) Population.

Safety Population

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

Modified Intent-to-Treat (mITT) Population

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

Per Protocol Population

The PPP will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data. The PPP will also exclude some subjects because of missed assessments due to the COVID-19 pandemic. Exclusion of subjects from the PPP will be made on a subject-by-subject basis prior to database hard lock.

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 treatment group and time point, as appropriate. No formal interim statistical analyses are planned, apart from the interim unblinded safety data views and presentations to be created for the Data and Safety Monitoring Board (DSMB). The Week 24 analyses are the primary analyses for this study and will be performed after all subjects have completed Week 24 of Treatment Period #1. The Week 48 analyses (vamorolone versus untreated historical controls and vamorolone versus prednisone-treated historical controls) will be performed after all subjects have completed Treatment Period #2. Missing values for safety outcomes will be treated as missing, unless stated otherwise.

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

Treatment Period #1 analyses will be summarized by four treatment groups:

- Vamorolone 2.0 mg/kg/day (n=30);
- Vamorolone 6.0 mg/kg/day (n=30);
- Prednisone 0.75 mg/kg/day (n=30); and

• Placebo (n=30).
Treatment Period #2 analyses (besides historical control comparison data) will be summarized by six treatment groups:
 Vamorolone 2.0 mg/kg/day → Vamorolone 2.0 mg/kg/day (n=30); Vamorolone 6.0 mg/kg/day → Vamorolone 6.0 mg/kg/day (n=30); Prednisone 0.75 mg/kg/day → Vamorolone 2.0 mg/kg/day (n=15); Prednisone 0.75 mg/kg/day → Vamorolone 6.0 mg/kg/day (n=15); Placebo → Vamorolone 2.0 mg/kg/day (n=15); and
• Placebo \rightarrow Vamorolone 6.0 mg/kg/day (n=15).
Adjustment for Multiple Comparisons:
The primary efficacy endpoint tests vamorolone 6.0 mg/kg/day vs. placebo using TTSTAND velocity at Week 24 and occurs during Treatment Period #1 of the study. The primary efficacy endpoint supports the primary objective of this study. The study is thus powered for the efficacy comparison using an alpha level of 0.05 for success.
The secondary efficacy endpoints will be tested at Week 24 along with the primary efficacy endpoint using a fixed sequential testing process where the fixed sequence of testing will be done in the following order:
1. TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo
2. 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs. placebo
 6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs. placebo
 Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day vs. placebo
 Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day vs. placebo
6. 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone
7. 6MWT meters walked, vamorolone 2.0 mg/kg/day vs. prednisone
Each test in the sequence will be carried out using a two-sided alpha level of 0.05. Statistical testing of the primary/secondary efficacy endpoints will stop if a p-value >0.05 occurs or if a p-value ≤ 0.05 occurs in the wrong direction. In case the fixed sequential testing process stops, the results of the subsequent tests will be reported with nominal p-values, but p-values ≤ 0.05 in the right direction will not be considered proof of statistical testing success in these subsequent tests.
All other analyses will not be corrected for multiple comparisons (tests will be performed at the 0.05 alpha level), as they will be viewed and handled in the perspective of not testing a formal hypothesis.
Efficacy Analyses:
All evaluations of clinical efficacy will be listed and presented using descriptive statistics per treatment group and time point. The primary efficacy outcome is TTSTAND (velocity), comparison of vamorolone 6.0 mg/kg/day vs placebo. Secondary and exploratory efficacy outcomes are TTSTAND (velocity), comparison of vamorolone 2.0 mg/kg/day vs placebo; the NSAA assessment; TTCLIMB (velocity); TTRW (velocity); 6MWT; hand-held myometry (elbow
flexors and knee extensors); and ROM.
The primary efficacy outcome TTSTAND (velocity) change from baseline to Week 24 will be compared between the 6.0 mg/kg/day vamorolone dose group

and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed effects for treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline TTSTAND, age group (per stratification), and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, pairwise comparisons (using least squares [LS] mean contrasts) will be made to compare TTSTAND velocity at 24 weeks for the vamorolone 6.0 mg/kg/day dose level with placebo (primary efficacy outcome).

For secondary outcomes, the same models will be used as for the primary outcome (REML-based MMRM including fixed effects for treatment [vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo], age group [<6 years; \geq 6 years], week, baseline, and treatment-by-week interaction).

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

Sensitivity analyses will be performed to assess the impact of COVID-19 on the primary endpoint. Additional sensitivity and supportive analyses will be performed on the primary and secondary outcomes. Full details will be provided in the SAP.

Subjects who are randomized to receive vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for both treatment periods will have TTSTAND velocity change from baseline data captured over 48 weeks compared with untreated DMD historical control data. Full details will be provided in the Statistical Analysis Plan (SAP).

Patient Reported Outcome Analyses:

Patient Reported Outcomes including the TSQM, PODCI, PARS III, Ease of Study Medication Administration Assessment, and the Blindedness Assessment will be listed and presented using descriptive statistics by treatment and time point. In addition, comparison will be made for each vamorolone dose group with placebo for the PODCI and for each vamorolone dose group with prednisone and placebo for the PARS III, with p values computed for the comparisons. Full details will be provided in the SAP.

Safety Analyses:

All evaluations of clinical safety will be listed and presented using descriptive statistics per treatment group and time point. For the safety analyses during Treatment Period #1, the vamorolone dose levels will be compared to prednisone, as specified in the SAP.

Safety data will include BMI, weight, vital signs, 2D-echocardiogram, DXA scan, spine x-ray, eye examination results, ACTH Stimulation Test results, and ECG results, and these will be presented using descriptive statistics. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed. Adverse events will be summarized overall and by treatment group, system organ class (SOC) and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]); by treatment group and relationship to study medication; and by treatment group and intensity (CTCAE grade). Suicidality and abuse potential associated with treatment will

be assessed by examination of adverse event data. Full details will be provided in the SAP. In Treatment Period #1, BMI z-score change from baseline results will be compared between treatment groups using an REML-based MMRM analysis with treatment group, week of the visit, and the treatment-by-week interaction as factors, and baseline BMI z-score and age group as a covariate. Week will be included in the model as a categorical variable (Week 12 and 24) along with the treatment-by-week interaction. An unstructured within-subject covariance matrix will be used. If this analysis fails to converge, Akaike's information criterion will be used to select the best covariance structure from compound symmetry and autoregressive-1 (AR(1)). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Change from baseline in all continuous clinical laboratory test results will be tested using one sample t-tests with p-values presented along with the descriptive statistics at each assessment visit within each treatment group. **Pharmacodynamics Analyses:** Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover will be assessed. PD biomarkers will be analyzed using MMRMs similar to the primary efficacy model. Plots will be created. Additional exploratory PD biomarkers of both safety and efficacy may be assessed. Vamorolone-treated groups will be compared to both prednisone-treated and placebo groups. **Pharmacokinetic Analyses:** The 2-hr post-dose plasma concentration measurements of vamorolone at Week 30 will be used for comparison of drug exposures between the two dosing groups. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects.

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Abbreviation

610 LIS

611

LIST OF ABBREVIATIONS

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
AUC _{0-24hr}	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
AUC _{last}	area under the plasma concentration-time curve from time 0 to the last observed measurable concentration
BMI	body mass index
BUN	blood urea nitrogen
С	Celsius
CFR	Code of Federal Regulations
CINRG	Cooperative International Neuromuscular Research Group
CK	creatine kinase
CL	clearance
ConA	Concanavalin A
cm	centimeter
C _{max}	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Material
CTMS	Clinical Trial Management Software
CTX1	C-terminal peptide fragment of collagen 1
СҮР	cytochrome P450
dL	deciliter
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DXA	dual-energy x-ray absorptiometry

Abbreviation Definition/Term

ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
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
m ²	square meter
MAD	multiple ascending dose (study)
MCMC	Markov Chain Monte Carlo

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
MMRM	mixed model for repeated measures
MTD	maximum tolerated dose
N, No.	number
NADPH	nicotinamide adenine dinucleotide phosphate
NCA	non-compartmental analysis
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
ng	nanogram
nM	nanomolar
nmol	nanomole
NOAEL	no observed adverse effect level
NSAA	North Star Ambulatory Assessment
OTC	over-the-counter (non-prescription medication)
OZ	ounce
P1NP	serum 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
PPP	Per Protocol Population
PR [PQ]	time from onset of P wave to start of the QRS complex
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

Abbreviation Definition/Term

of the T wave

corrected QT interval

 QT_{c}

Abbreviation	Definition/Term
RBC	Red Blood Cell
REML	restricted maximum likelihood
ROM	Range of Motion
RR	in electrocardiography, the interval between successive Rs (peaks of QRS complexes)
6MWT	Six-minute Walk Test
SAD	single ascending dose (study)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedures
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T _{max}	time to maximum observed plasma concentration
TRINDS	Therapeutic Research in Neuromuscular Disorders Solutions
TSQM	Treatment Satisfaction Questionnaire for Medication
TTCLIMB	Time to Climb (Test)
TTSTAND	Time to Stand (Test)
TTRW	Time to Run/Walk (Test)
ULN	upper limit of normal
US	United States
vol	volume
VS.	versus
V_{ss}	volume of distribution at steady state
WBC	White Blood Cell
WHO	World Health Organization
wt	weight

1 INTRODUCTION

620 621

1.1 Background and Unmet Need

622 623 Duchenne muscular dystrophy (DMD) is a rapidly progressive form of muscular 624 dystrophy that occurs primarily in males and manifests prior to the age of six years. 625 Duchenne muscular dystrophy affects approximately 1 in 3,600 to 9,300 male births worldwide.¹ Duchenne muscular dystrophy is caused by mutations in the dystrophin 626 627 gene which codes for a protein that provides structural stability to the dystroglycan 628 complex on muscle cell membranes.² The lack of dystrophin reduces plasma membrane 629 stability. Membrane destabilization results in altered mechanical properties and aberrant signaling, which contribute to membrane fragility, necrosis, inflammation, and 630 progressive muscle wasting.³ 631

632 In addition to the significant contribution of membrane destabilization and mechanical 633 injury in DMD, aberrant intracellular signaling cascades that regulate inflammatory and immune processes also contribute to DMD pathophysiology. Up-regulated inflammatory 634 gene expression and activated immune cell infiltrates, at least partially mediated by 635 636 nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation, are 637 evident during early disease stages and play a significant role in muscle wasting.³ NF-κB has been shown to regulate the expression of numerous inflammatory genes in immune 638 cells and muscle fibers,^{4,5,6,7} and the infiltration and activation of these cells can trigger 639 muscle fiber death.^{8,9} 640

641 Although significant advances have been made in understanding the etiology of DMD, a 642 cure has not been found, and until recently treatment options were medications used "off-643 label" to alleviate the symptoms of DMD. Despite scientific advances, only 644 glucocorticoids, such as prednisone or deflazacort, have consistently demonstrated efficacy in clinical trials.¹⁰ Indeed, the United States Food and Drug Administration (US 645 646 FDA) recently approved deflazacort as a treatment for DMD. Further, many disease modifying technologies that are currently in development focus on subsets of dystrophin 647 648 mutations and therefore do not address the unmet need in all persons with DMD. 649 However, it is likely that glucocorticoids will need to be co-administered with many of
- 650 651 these compounds for maximum effect and glucocorticoids have extensive side effect profiles, often limiting long-term administration. The current goal of DMD research is to 652 653 find a mutation-independent treatment that matches or exceeds the efficacy of 654 glucocorticoids with a significantly lower side effect profile. 655 Vamorolone is a first generation delta-9, 11 chemical compound belonging to the 656 structural class of synthetic steroidal drugs, which includes the glucocorticoids prednisone, prednisolone, methylprednisolone, and dexamethasone.¹¹ The chemical 657 658 structure of vamorolone has optimized four subactivities of traditional glucocorticoid drugs, namely transactivation, transrepression, physiochemical membrane properties, and 659 660 mineralocorticoid receptor antagonism.¹¹ By reducing transactivation subproperties, retaining transrepression, imparting membrane stabilizing properties, and inhibiting the 661 662 mineralocorticoid receptor pathway, vamorolone has favorable efficacy and side effect 663 profiles relative to classic glucocorticoids in nonclinical models and is anticipated to be 664 an attractive candidate for the treatment of DMD in pediatric patients. 665 In vitro and nonclinical data to date suggest that vamorolone may offer a much needed alternative to the current glucocorticoids which are standard of care for DMD¹² with 666 administration beginning around the age of 5 years in most developed countries, or even 667 668 earlier in some cases. 669 The significant effects of glucocorticoids on growth and development, however, prevent 670 their routine administration in infancy or 'toddler' years, despite evidence that the earlier the administration, the better the overall functional outcome.¹³ The cumulative adverse 671 effects of glucocorticoids, including excess weight, delayed puberty, fragile skin, loss of 672 bone mineral density, bruising, and cushingoid appearance continue to negatively impact 673 674 on the quality of life of the individual, leading to significant variations in clinical practice.¹⁴ Glucocorticoids also contribute to further muscle damage with long-term 675 administration. Vamorolone has shown few if any of the adverse effects of traditional 676 glucocorticoids in mouse models of DMD.^{11,15,16} 677 678 This study is targeted to explore whether vamorolone will show at least equal efficacy to
- 679 glucocorticoids with a more favorable adverse effect profile, thereby improving the

- 681quality of life for DMD patients. This profile would enable use of vamorolone in DMD682boys at a younger age than when glucocorticoid treatment is currently initiated. In683addition, vamorolone could be prescribed in later stage non-ambulant young men with684DMD and for a longer period of time, where the risk:benefit balance of glucocorticoids is685often less favorable.
- 686 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-kB pathway 687 inhibition, vamorolone may also improve efficacy over conventional glucocorticoids due 688 689 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.¹⁷ Further, 690 691 vamorolone has been recently demonstrated to improve asynchronous remodeling, 692 believed to be a component of progressive muscle weakness and wasting in DMD¹⁸ and 693 may also prevent muscle membrane damage, thereby delaying progression of the disease 694 further. Vamorolone is an antagonist to the mineralocorticoid receptor, whereas 695 glucocorticoids are typically agonists. An antagonist for the mineralocorticoid receptor, 696 epleronone, was recently shown to significantly improve DMD heart function.¹⁹ Finally, 697 vamorolone imparts physical stability to myofiber plasma membranes, whereas 698 prednisolone destabilizes membranes. This property addresses the primary defect of membrane instability in dystrophin deficient myofibers in DMD.¹⁵ 699 700 Potentially, the administration of vamorolone to a DMD patient may begin soon after
- 701birth to slow the dystrophic process of muscle, retaining regenerative capacity and702substantially improving patient quality of life.
- 703 704

1.2 Nonclinical Experience

- The safety pharmacology, pharmacokinetics (PK) and metabolism, and toxicology of
 vamorolone have been evaluated in multiple nonclinical studies *in vitro* and in mice, rats,
 beagle dogs, and cynomolgus monkeys *in vivo*.
- All Good Clinical Laboratory (GLP) studies were conducted in, or inspected by, a
- country that has implemented the Organisation for Economic Cooperation and
- 710 Development (OECD) Mutual Acceptance of Data (MAD) system.

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711

1.2.1 Safety Pharmacology

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

717 The effect of vamorolone as compared to prednisolone on bone growth and development 718 was evaluated in the *mdx* mouse model of DMD that lacks dystrophin due to a premature 719 chain-terminating mutation in the mouse homologue of the dystrophin gene. In the pre-720 symptomatic *mdx* study, tibia length was measured to determine if vamorolone inhibited 721 bone growth. Prednisolone significantly decreased tibia length whereas vamorolone did 722 not affect tibia length at any concentration tested. Micro-computed tomography was 723 performed on femurs to examine bone density and structure. Comparison of vehicle, 724 prednisolone, and the highest vamorolone dose showed prednisolone to significantly 725 reduce trabecular thickness compared to vehicle, while vamorolone did not.¹⁵

In normal, male CD-1[®] mice, these effects were reproduced. Unlike CD-1 mice treated
 with prednisolone, CD-1 mice receiving vamorolone did not experience tibia length

shortening.¹⁶ However, at the highest vamorolone dose tested, mice did have

significantly reduced body length, though to a lesser extent as compared to prednisolone.

730 Duchenne muscular dystrophy is associated with cardiomyopathy that can become life 731 threatening, and increased fibrosis with prednisolone treatment in heart muscle of the 732 mdx mouse has been reported.²⁴ Histologically, clear fibrosis was evident in 50% of

young (8-week) prednisolone-treated mouse hearts compared to no incidence of fibrosis

identified in the other groups (wild type; *mdx* vehicle, and vamorolone-treated).

735 Pharmacologically, glucocorticoids show immunosuppressive and immunotoxic

properties that limit therapeutic windows and long-term use. Vamorolone (5, 15,

73730 mg/kg/day) was benchmarked against prednisolone (5 mg/kg/day) to determine if

 738 similar properties were observed.¹⁵ Untreated *mdx* mice showed increased numbers of

peripheral blood leukocytes (PBL) and enlarged spleens resulting from ongoing muscle

- 740 damage compared to wild type mice. Vamorolone treatment reduced spleen mass and
- 741 PBL counts in a dose-dependent manner. This finding is attributed to a reduction in

742	
743	muscle damage by vamorolone that decreases spleen size to levels resembling those in
744	wild type mice. Prednisolone reduced these measures below wild type, suggesting
745	immunosuppressive and/or immunotoxic properties. Further, prednisolone significantly
746	decreased viable splenocytes per gram of tissue (p< 0.005), whereas this decrease was not
747	observed for any vamorolone dose tested (ReveraGen Report No.
748	MDX-RBP-VBP15-02). ¹⁵
749 750	To further query the potential immune modulation, the effects of vamorolone and
751	prednisolone on counts of splenic B and T-lymphocytes isolated from treated <i>mdx</i> mice
752	were examined. CD4+ T-cell activation was assayed by stimulation of splenocytes with
753	the T-cell mitogen, concanavalin A (ConA). Splenocytes obtained from prednisolone-
754	treated mice displayed a significant reduction of the percentage of splenic activated
755	CD4+CD25+ T-cells upon ConA stimulation while splenocytes derived from
756	vamorolone-treated mice did not (ReveraGen Report No. MDX-RBP-VBP15-02).
757	Taken together, these findings suggest that while prednisolone treatment leads to a
758	reduction in T-cell number and activation status, vamorolone modulates inflamed mdx
759	immune systems towards a wild type state without compromising T-cell activation status.
760	1.2.2 Pharmacokinetics and Metabolism
761	Single Dose
762	Vamorolone PK profiles were determined in male CD-1 mice, Sprague Dawley rats and
763	beagle dogs after a single intravenous injection of 10 mg/kg and after a single oral dose
764	of 50 mg/kg in mice and rats and 30 mg/kg in dogs.
765	Pharmacokinetic results for vamorolone following a single intravenous administration of
766	10 mg/kg in Crl:CD1(ICR) mice demonstrated a clearance (CL) of 18.8 mL/min/kg. The
767	terminal half-life (t_{1/2}) was 0.35 hours. Volume of distribution at steady state (V_{ss}) was
768	0.76 L/kg. Following oral administration of 50 mg/kg in mice, the maximum observed
769	plasma concentration (C_{max}) of 6787 ng/mL was observed at 2 hours (time to maximum
770	observed plasma concentration $[T_{max}]$) after drug administration, and percent

bioavailability (F%) was 74.5%. Following oral administration of 15 mg/kg via cherry

772	
773	syrup, the C_{max} of 1527 ng/mL was observed at 2 hours after drug administration and
774	bioavailability was 47.7% (ReveraGen Report No. PH-DPMK-VBP-10-004).
775	Pharmacokinetic results for vamorolone following a single intravenous administration of
776	50 mg/kg in Sprague Dawley rats indicated a CL of 20.2 mL/min/kg. The $t_{\ensuremath{\nu_2}}$ was
777	0.58 hours. V_{ss} was 0.77 L/kg, which was similar to that observed in mice. After oral
778	administration of 50 mg/kg in rats, a C_{max} of 2543 ng/mL was observed at 4 hours after
779	dose administration, and bioavailability was 47.8% (ReveraGen Report No. PH-DPMK-
780	VBP-10-007).
781	In beagle dogs, vamorolone had a CL of 24.7 mL/min/kg. The $t_{\mbox{\tiny V2}}$ was 5.42 hours and V_{ss}
782	was 1.93 L/kg. After oral administration of 30 mg/kg in dogs, a C_{max} of 814 ng/mL was
783	observed at 6 hours after dose administration and bioavailability was 53.2% (ReveraGen
784	Report No. 48504-10-464).
785	Vamorolone clearance was therefore comparable in all 3 species studied
786	(19-25 mL/min/kg). Bioavailability ranged from approximately 50% in mouse (cherry
787	syrup), rat, and dog to 75% in the mouse (30% Labrafil) (ReveraGen Report Nos.
788	PH-DPMK-VBP-10-004, PH-DPMK-VBP-10-007, 48504-10-464).
789 790	Multiple Dose
791 792	Crl:CD1(ICR) mice were administered vamorolone or vehicle once daily (QD) for
793	28 consecutive days. Vamorolone exposure (as assessed by the C_{max} and area under the
794	plasma concentration-time curve from time 0 to the last observed measurable
795	concentration [AUC _{last}]) increased with increasing dose on Study Days 1 and 28.
796	Repeated dosing of vamorolone over a 28-day duration was associated with decreases in
797	mean vamorolone AUC _{last} values in the 30 and 100 mg/kg dose groups compared to
798	Day 1, indicating possible enzyme induction. On Study Day 28, mean AUC_{last} values
799	were 1.81-fold and 5.02-fold lower compared to Study Day 1 for the 30 and 100 mg/kg
800	dose groups, respectively. The observed difference in exposure relative to Day 1
801	increased with the increase in administered dose of vamorolone (ReveraGen Report No.
802	1998-009).

804	Beagle dogs were either administered vamorolone or vehicle QD for 28 consecutive days.
805	Vamorolone exposure in dogs (as assessed by C_{max} and AUC_{last}) generally increased with
806	increasing dose on Study Days 1 and 28. For the 2 and 10 mg/kg dose groups, exposure
807	on Day 28 was generally higher than on Day 1, indicating possible inhibition of
808	metabolism of vamorolone at these dose levels. On Day 28, mean AUC_{last} values were
809	2.35-fold and 2.43-fold (males) and 3.03-fold and 3.23-fold (females) higher compared to
810	Study Day 1 for the 2 and 10 mg/kg/day dose groups, respectively. For the 50 mg/kg
811	dose group, exposure on Day 28 was similar to that on Day 1. At the 50 mg/kg dose,
812	AUC _{last} values in males were 1.71-fold lower whereas females were 1.22 higher on
813	Day 28 compared to Day 1 (ReveraGen Report No. 031302).
814 815	Beagle dogs were administered vehicle or vamorolone at doses of 2 mg/kg/day,
816	10 mg/kg/day, or 50 mg/kg/day for 39 weeks. Systemic exposure (area under the plasma
817	concentration-time curve from time 0 to 24 hours $[AUC_{0-24hr}]$) to vamorolone appeared to
818	be independent of sex. Mean AUC_{0-24hr} and C_{max} values for vamorolone increased with
819	increasing dose in an approximately dose proportional manner on Days 1 and 270. Mean
820	systemic exposure (AUC _{0-24hr}) to vamorolone appeared to increase following repeated
821	administration of vamorolone. Due to the alterations in the feeding regimen, changes in
822	systemic exposure following repeated administration should be viewed with caution due
823	the influence of feeding on exposure. For the 2 and 10 mg/kg/day dose groups, exposure
824	on Day 270 was generally higher than on Day 1, indicating possible inhibition of
825	metabolism of vamorolone at these dose levels. On Day 270, mean AUC_{0-24hr} values
826	were 2.34-fold and 2.98-fold higher compared to Study Day 1 for the 2 and 10 mg/kg/day
827	dose groups, respectively. For the 50 mg/kg dose group, exposure on Day 270 was
828	2.07-fold higher compared to that on Day 1 (ReveraGen Report No. 1998-014).
829 830	Non neïve expendeus menkeys were administered vemeralene (200 and
03U 021	Non-naive cynomologus monkeys were administered vanioroione (soo and $600 \text{ mg/kg/day})$ or vahiala area daily for 7 consequities days. Non-relate supersure (as
831	ooo mg/kg/day) of venicle once dany for / consecutive days. Vanioroione exposure (as
832 822	assessed by C _{max} and AUC _{last}) generally increased with increasing dose on Study Days 1
833	and / with the exception of male monkeys on Day /, which showed no clear increase in
834	exposure between the 300 and 600 mg/kg/day dose levels. Repeated dosing over the

- 7-day study duration was associated with decreases in mean plasma vamorolone AUC_{last}
 values for female and male monkeys indicating possible metabolic induction. On Day 7,
 mean AUC_{last} values were 1.60-fold, 2.19-fold, and 2.02-fold lower in females and
 1.20-fold, 2.09-fold, and 2.88-fold lower in males compared to Study Day 1 for the 100,
 300 and 600 mg/kg/day dose groups, respectively (ReveraGen Report Nos. 1998-001,
 SW11-0418).
- 842 **Distribution**

843

855

In the plasma protein binding studies, percent bound was similar in human and mouse 844 845 cells in culture (88.06% and 86.71%, respectively). In the blood partition experiment done ex vivo, the blood to plasma ratio was similar between human and mouse (0.87 and 846 847 0.68, respectively), but the red blood cell to plasma ratio for the mouse (0.33) was less than half that of the human (0.74). Human *in vivo* data are presented in Section 1.3 848 849 (VBP15-001). In the blood/brain concentration mouse experiment in vivo, the plasma concentrations of vamorolone were higher than brain concentrations with the area under 850 the plasma concentration-time curve (AUC) and C_{max} approximately 2-fold higher in 851 plasma than in brain (ReveraGen Report Nos. ADME-NCG-PPB-NC135, ADME-VBP-852 853 PPB-V002, ADME-NCG-BP-NC134, NCATS 2013-38).

854 Metabolism

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

- The metabolic stability of vamorolone was assessed in non-Good Laboratory Practice
- 863 (GLP) studies. Based on the data generated, vamorolone was highly stable for up to
- 60 minutes in human, monkey, dog, and mouse liver microsomes in the presence or
- absence of nicotinamide adenine dinucleotide phosphate (NADPH) and stable for up to
- 60 minutes in rat liver in the absence of NADPH. Moderate metabolism was apparent in

868	rat liver microsomes in the presence of NADPH stimulation (35% remaining), suggesting
869	that rat was a high metabolizer of vamorolone relative to other species (mouse, dog,
870	human) (ReveraGen Report Nos. NIH-R2526, and ADME-VBP-LM-V003).
871	Vamorolone did not significantly inhibit any of the cytochrome P450 (CYP) enzyme
872	isoforms tested (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). Vamorolone
873	moderately induced CYP3A4 (24% to 42%), indicating that vamorolone is a potential
874	inducer of CYP3A4 (ReveraGen Report Nos. ADME-VBP-Inhibition-V005, ADME-
875	VBP-Induction-V006, ADME-VBP-Induction-V009).

876 *Excretion*

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877

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

883 **1.2.3 Toxicology**

884 Single Dose

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

Beagle dogs received single 60, 180, 360, and 750 mg/kg doses of vamorolone using an escalation study design with a 4-day washout period between doses. All animals survived dose escalation. Clinical signs attributed to vamorolone (750 mg/kg) included red discoloration of the ears and face. This effect occurred within a few hours of dosing and was transient. The highest dose also resulted in increased white blood cell count

- 898 (increased neutrophils and monocytes [female only] and decreased lymphocytes and 899 eosinophils [male and female]). At the 360 and 750 mg/kg dose levels, slight elevations 900 in albumin were observed. A mild elevation in cholesterol at the 750 mg/kg (and 901 possibly 360 mg/kg) dose level was also observed (ReveraGen Report No. 13788.01.01). In cynomolgus monkeys, single oral doses of up to 500 mg/kg were well tolerated with 902 903 no significant clinical observations (ReveraGen Report No. 1998-001). 904 Multiple Dose 905 Acute Toxicity Studies 906 907 Vamorolone or vehicle was administered to Crl:CD1(ICR) mice QD for 28 consecutive 908 days at doses of 10, 30 and 100 mg/kg/day. All animals survived to their scheduled 909 necropsy with the exception of a female mouse (100 mg/kg/day dose group) that was 910 found dead on Day 16. The cause of death was considered incidental and attributed to a 911 dosing injury based on the amount of red fluid in the thoracic cavity. 912 No effects attributable to vamorolone were observed on clinical observations, food 913 consumption, ophthalmic examination, or urinalysis during the study. A dose-dependent decrease in body weight gain was observed at all doses; however, weight was fully 914 915 regained during the recovery period. Adrenal gland weights were variable between 916 groups and generally decreased, but without a dose response relationship, and correlated 917 microscopically with minimal to moderate vacuolar degeneration and cortical atrophy. 918 After the 2-week recovery period there was evidence of vacuolar degeneration. Liver 919 weights were significantly increased at the 100 mg/kg/day dose level. Hepatocellular 920 hypertrophy, increased vacuolation, and necrosis (single cell) were seen in a few male 921 mice at 30 mg/kg/day. There was evidence of lipid and glycogen accumulation. Serum 922 alanine aminotransferase and aspartate aminotransferase levels were higher with 923 associated microscopic hypertrophy/vacuolation/necrosis at 100 mg/kg/day. Spleen 924 weights decreased in a dose-dependent manner and correlated with a decreased number 925 of lymphocytes in spleen. Thymus weights decreased in a dose dependent manner and 926 were associated microscopically with lymphoid atrophy. Mice had dose-dependent 927 reductions in serum lymphocytes which were significant in the 100 mg/kg dose group.
 - Page 45 of 232

After the recovery period, all parameters returned to normal (untreated) except forthymus weights, which were increased.

Based on the liver-related findings in this study, the no observed adverse effect level

932 (NOAEL) for vamorolone in mice is 30 mg/kg/day (ReveraGen Report No. 1998-009).

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

Adrenal gland weights decreased which correlated with mild or moderate diffuse bilateral
atrophy of the adrenal cortex, mild multifocal bilateral vacuolation of the adrenal cortex,
increased white blood cell and neutrophil counts, and decreased eosinophil counts. Liver
weights increased in the 50 mg/kg/day dose group, which correlated with diffuse

943 hypertrophy and vacuolation and increased levels of alkaline phosphatase and gamma

944 glutamyltransferase. Spleen weights decreased, which correlated with lymphoid

945 depletion. Thymus weights decreased, which corresponded to diffuse lymphoid

946 depletion. With the exception of diffuse depletion of lymphocytes in thymus in the

50 mg/kg group, all abnormal parameters returned to normal during the recovery period.

The NOAEL was considered by the study director to be 10 mg/kg/day. Although

reversible, the liver changes were considered adverse at 50 mg/kg/day because the

severity score was moderate and the changes were diffuse in nature in all animals treated

at the high dose. This is in contrast to the conclusion drawn by the study pathologist,

953 who considered the NOAEL to be 50 mg/kg/day due to reversibility following cessation

954 of dosing (ReveraGen Report No. 31302).

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

959	
960	There was a dose proportional decrease in body weight gain observed in males and
961	females at each dose (up to 11% and 9% respectively) related to vamorolone. A
962	cessation of the body weight loss in treatment was observed during the recovery phase
963	but no recovery of body weight lost during the 7 days of dosing was observed.
964	At termination there were non-significant increases in red cell mass and decreases in
965	lymphocytes (up to 56%) in the 600 mg/kg/day dose group. However, most individual
966	animals, including controls, had decreases in lymphocytes (up to 81%) at termination
967	relative to their respective pretest. They had resolved by the recovery interval in both
968	sexes.
969	In both sexes receiving \geq 300 mg/kg/day, there was increased urea nitrogen (up to 141%),
970	creatinine (up to 58%), total protein (up to 15%), albumin (up to 11%), globulin (up to
971	25%), and/or potassium (up to 39%) with concurrent decreases in sodium (up to 10%)
972	and chloride (up to 10%) relative to controls. At the recovery interval, the majority of
973	these effects had resolved (ReveraGen Report No. 1998-001).
974 975	Chronic toxicity studies
976 977	<u>26-week chronic toxicity study in mice</u>
976 977 978	<u>26-week chronic toxicity study in mice</u> A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the
976 977 978 979	<u>26-week chronic toxicity study in mice</u> A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a
976 977 978 979 980	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and
976 977 978 979 980 981	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations,
976 977 978 979 980 981 982	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and
976 977 978 979 980 981 982 983	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article.
976 977 978 979 980 981 982 983 984	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article. There were no vamorolone-related effects on mortality, detailed clinical observations,
976 977 978 979 980 981 982 983 984 985	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article. There were no vamorolone-related effects on mortality, detailed clinical observations, food consumption, ophthalmology, sperm evaluations, or bone lengths (femur or tibia).
976 977 978 979 980 981 982 983 984 985 986	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article. There were no vamorolone-related effects on mortality, detailed clinical observations, food consumption, ophthalmology, sperm evaluations, or bone lengths (femur or tibia). Five test article-treated mice were unscheduled deaths (euthanized <i>in extremis</i> or found
976 977 978 979 980 981 982 983 984 985 986 987	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article. There were no vamorolone-related effects on mortality, detailed clinical observations, food consumption, ophthalmology, sperm evaluations, or bone lengths (femur or tibia). Five test article-treated mice were unscheduled deaths (euthanized <i>in extremis</i> or found dead) during the dosing phase. Three of these were considered to be potentially due to
976 977 978 979 980 981 982 983 984 985 986 986 987 988	26-week chronic toxicity study in mice A 26-week chronic toxicity study was carried out in Crl:CD1®(ICR) mice to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week postdose observation period. Doses of vamorolone tested were 5, 15, and 45 mg/kg/day. Assessment of toxicity was based on mortality, clinical observations, body weight, and food consumption; ophthalmoscopic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for the test article. There were no vamorolone-related effects on mortality, detailed clinical observations, food consumption, ophthalmology, sperm evaluations, or bone lengths (femur or tibia). Five test article-treated mice were unscheduled deaths (euthanized <i>in extremis</i> or found dead) during the dosing phase. Three of these were considered to be potentially due to dosing injury based on microscopic findings in mediastinum, epicardium, or lung. One

spontaneous background finding. The death of one male at 5 mg/kg/day was
undetermined since there were no major pathologic findings to explain the unscheduled
death of this animal; there was no target organ toxicity in the mouse. Target organ
toxicity was not considered a contributor to the death of these animals and there was no
dose-relationship in incidence.

996A vamorolone-related increase in body weight gain was observed relative to controls in997males (+14%) and females (+23%) at 45 mg/kg/day. Increases in body weights at99845 mg/kg/day were not considered to be adverse due to the general health of the animals999overall. During the recovery phase, bodyweights in males returned to comparable levels1000with controls, however female body weights remained increased compared to female1001controls.

Evidence of a minimal to mild vamorolone-related hepatic effects were observed in males 1002 at $\geq 5 \text{ mg/kg/day}$ and females at 45 mg/kg/day, indicated by mild to moderate increases 1003 in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase activities, 1004 and/or total bilirubin, as related to microscopic hepatocellular vacuolation, inflammation, 1005 and/or necrosis in males at $\geq 15 \text{ mg/kg/day}$ and females at 45 mg/kg/day; these changes 1006 1007 had generally resolved at recovery collections with the exception of minimal increases in alanine aminotransferase activity in females at 45 mg/kg/day, which may have correlated 1008 1009 to microscopic liver pathology.

1010 A mild vamorolone-related increase in neutrophil counts was observed in both sexes at

1011 45 mg/kg/day with concurrent decreases in lymphocyte counts in females at

1012 45 mg/kg/day consistent with a glucocorticoid-like effect, as related to microscopic

1013 lymphoid depletion, although an inflammatory stimulus may have contributed to

- 1014 increases in neutrophil counts, as related to microscopic liver inflammation; these
- 1015 changes had generally resolved at recovery collections.
- 1016A mild vamorolone-related decrease in chloride was observed in males at \geq 5 mg/kg/day1017and females at \geq 15 mg/kg/day that lacked correlative findings among other study1018endpoints; resolution for this endpoint could not be determined.

- 1019
 1020 A mild vamorolone-related increase in albumin was observed in males at ≥ 5 mg/kg/day
 1021 and females at 45 mg/kg/day with concurrent mild increases in globulin in females at
 1022 45 mg/kg/day; these changes had resolved at recovery collections.
- 1023 A minor vamorolone-related alteration in lipid metabolism was observed in both sexes at
- 45 mg/kg/day and females at 15 mg/kg/day indicated by increases in triglyceride and/or
 cholesterol; these changes had resolved at recovery collections.
- 1026 Vamorolone-related macroscopic findings occurred in the liver of mice at 45 mg/kg/day.
- 1027 Tan discoloration occurred in one female and four males at this dose in the dosing phase.
- 1028 This correlated with microvesicular/macrovesicular hepatocyte vacuolation. There were
- 1029 no test article-related macroscopic findings in recovery animals.
- 1030 Test article-related microscopic findings occurred in adrenal gland (cortical atrophy- with
- 1031 correlating decreases in adrenal weights in females), liver (increased severity of
- 1032 centrilobular hypertrophy; hepatocyte vacuolation; hepatocyte vacuolation; and
- 1033 inflammation/necrosis), lymphoid tissues (thymus, spleen, mandibular lymph node,
- 1034 mesenteric lymph node, and gut-associated lymphoid tissue [GALT]) skin, and pancreatic
- 1035 islets (minimal to mild hypertrophy). Observed changes in these tissues are considered
- 1036 pharmacologically-mediated and not adverse.
- 1037 An increased incidence of decreased anagen hair follicles occurred in mice at
- 1038 45 mg/kg/day. Decreased anagen hair follicles was documented for individual animals
- 1039 when there were no anagen hair follicles in the section of skin. Incidence in controls and
- 1040 mice at 5 and 15 mg/kg/day were similar. A severity score was not given to the decrease
- 1041as this may have been somewhat dependent on size of skin sample. This change is not1042considered adverse.
- 1043There was full reversibility of lymphoid changes in thymus, spleen, mesenteric lymph1044node, mandibular lymph node, and GALT. There were no meaningful differences1045between treated and controls at the end of the recovery tissues for these lymphoid tissues.1046There was recovery of adrenal gland findings in females and partial recovery of adrenal
- 1047 gland findings in males. In addition, there was partial reversibility of liver findings for
- 1048 males and females. Minor changes persisted in the pancreas and skin.

1050	Systemic exposure to vamorolone appeared to be sex-dependent on Day 1
1051	(males > females) and appeared to be independent of sex on Day 179. Following daily
1052	administration of vamorolone in females and males, systemic exposure (AUC_{0-24hr}) and
1053	C_{max} values of vamorolone increased with increasing dose in a greater than dose
1054	proportional manner on Day 1 and in an approximately dose proportional manner on
1055	Day 179. Systemic exposure to vamorolone in females appeared to increase following
1056	repeated administration of vamorolone at 5 mg/kg, did not appear to change following
1057	repeated administration of vamorolone at 15 mg/kg, and appeared to decrease following
1058	repeated administration of vamorolone at 45 mg/kg. Systemic exposure to vamorolone in
1059	males appeared to decrease following repeated administration of vamorolone (Table 1).

$\frac{1060}{1082}$

Table 1.AUC0-24hr in Mice after 179 Days Treatment with 3 Dose Levels (5, 15
and 45 mg/kg/day)

Average AUC0-24hr (hr*ng/mL)					
Dose	Male		Female		
(mg/kg/day)	Day 1	Day 179	Day 1	Day 179	
5	5700	1150	159	991	
15	11600	3710	3450	4240	
45	50700	10200	27000	12700	

- 1063 1064
- 1065 The once daily administration of vamorolone via oral gavage to mice for 26 weeks at 5,
- 1066 15, and 45 mg/kg/day did not produce any adverse effects. Therefore, the No-
- 1067 Observable-Adverse-Effect Level (NOAEL) is considered to be 45 mg/kg/day under the
- 1068 conditions of this study.
- 1069 As liver is considered a primary target organ, the liver enzymes (aspartate
- 1070 aminotransferase [AST], alanine aminotransferase [ALT]) of mice in this study were
- 1071 studied at study termination (Figure 1).

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

AST levels for 26 weeks mice (terminal) ALT levels for 26 weeks mice (terminal)

10761077There were no differences between male and female mice regarding liver function1078enzymes. There were no drug-related elevations of AST at any dose. The highest dose1079tested (45 mg/kg/day) showed mild elevations of ALT with about half of values above1080the upper limit of normal range. The mild elevations of ALT were reversible, returning1081to within normal range after cessation of drug.

1082The Study Director concluded that the once daily administration of vamorolone via oral1083gavage to mice for 26 weeks at 5, 15, and 45 mg/kg/day did not produce any adverse1084effects. Therefore, the No-Observable-Adverse-Effect Level (NOAEL) is considered to1085be 45 mg/kg/day under the conditions of this study.

108639-week chronic toxicity study in beagle dogs1087

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

1095	
1096	Detailed clinical observations considered test article-related at 50 mg/kg/day, and
1097	reversible, included decreased activity (considered adverse), struggling during dosing,
1098	feces soft, limb function impaired, interdigital cysts, and unkempt appearance
1099	(considered adverse). Test article-related, dose-dependent increases in body weight gains
1100	correlating with increases in food consumption were observed relative to controls in
1101	males at all dose levels and in females at 10 and 50 mg/kg/day. Test article-related,
1102	reversible increases in average mean food consumption were observed relative to controls
1103	over the course of the 39-week dose phase in both sexes at 10 and 50 mg/kg/day.
1104	No test article-related ophthalmological effects were noted. No test-article-related
1105	changes were noted in respiratory rates or rectal temperatures. There may have been a
1106	mild dose-related reversible increase in the heart rate at the terminal post-dose interval
1107	that was significantly different from vehicle in both sexes following the 50 mg/kg/day
1108	dose. Semen analysis/evaluation for test article affects could not be conducted as there
1109	were not enough viable samples collected.
1110	Test article-related effects on clinical pathology endpoints with microscopic correlates
1111	included the following:
1112	• A hepatocellular and hepatobiliary effect in males at 10 mg/kg/day and both sexes
1113	at 50 mg/kg/day, which included increased alkaline phosphatase, gamma
1114	glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase
1115	activity. These changes correlated with microscopic changes in the liver, bile
1116	duct, and gall bladder. This spectrum of changes was considered adverse in both
1117	sexes at 50 mg/kg/day.
1118	• There was also evidence of an inflammatory response in both sexes at
1119	50 mg/kg/day, which included increased total leukocyte, neutrophil, and
1120	monocyte counts, and increased fibrinogen and/or globulin concentrations. The
1121	inflammatory response was likely secondary to inflammation in the liver
1122	associated with hepatocellular necrosis. Platelet counts were also increased in
1123	both sexes at 50 mg/kg/day and may have been secondary to the inflammatory
1124	response.

- Following a 4-week recovery period, all noted clinical pathological changes resolved, with the exceptions of increased alanine aminotransferase activity in both sexes at 50 mg/kg/day, and increased globulin in males at 50 mg/kg/day.
- Reversible, test article-related macroscopic findings included mildly to moderately 1130 enlarged livers in males and females at 50 mg/kg/day, which correlated microscopically 1131 1132 with panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation; hemorrhage in the gall bladder of one 50 mg/kg/day female, that was associated with 1133 moderate acute inflammation and mild vascular necrosis, and considered to be adverse; 1134 red focus/foci within the pylorus of the stomach of one 50 mg/kg/day female and one 1135 1136 male at 10 mg/kg/day, which correlated microscopically with mild acute inflammation in the female. 1137
- Test article-related organ weight changes at the terminal necropsy included decreases in 1138 1139 adrenal gland weights in both sexes at $\geq 2 \text{ mg/kg/day}$ (microscopic correlate of bilateral cortical atrophy); increases in liver weights in both sexes at $\geq 10 \text{ mg/kg/day}$ (microscopic 1140 correlates of panlobular hepatocellular hypertrophy and/or hepatocellular vacuolation); 1141 increases in kidney weights in females at $\geq 10 \text{ mg/kg/day}$ and males at 50 mg/kg/day 1142 (microscopic correlate of bilateral tubular vacuolation); decreases in prostate gland 1143 weights in males at 50 mg/kg/day (microscopic correlate of decreased secretory product). 1144 1145 These organ weight changes were all reversible, except for the decreases in the prostate gland. Microscopic evaluation revealed the following test article-related changes: 1146 adrenal glands (atrophy of the zona fasciculata and zona reticularis and 1147 1148 hypertrophy/hyperplasia of the zona glomerulosa in both sexes at $\geq 10 \text{ mg/kg/day}$ and atrophy was considered adverse); esophagus and pylorus of the stomach 1149 (erosion/ulceration in a few animals of both sexes at 50 mg/kg/day); gallbladder 1150 (hypertrophy/hyperplasia of the mucosal epithelium in both sexes at $\geq 10 \text{ mg/kg/day}$ and 1151 1152 cytoplasmic vacuolation of the mucosal epithelium in males at $\geq 10 \text{ mg/kg/day}$ and females at $\geq 2 \text{ mg/kg/day}$; liver (hepatocellular vacuolation in males at $\geq 10 \text{ mg/kg/day}$ 1153 and females at $\geq 2 \text{ mg/kg/day}$, panlobular hypertrophy in males at 50 mg/kg/day and 1154 females at $\geq 10 \text{ mg/kg/day}$, and inflammation/necrosis in both sexes at 50 mg/kg/day and 1155 1156 considered adverse, bile duct hyperplasia in both sexes at 50 mg/kg/day, bile duct

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1150	hyperturn hyperbolic at 50 mg/lag/day and famalag at > 10 mg/lag/day, and avtanlagmia
1158	hypertrophy in males at 50 mg/kg/day and remains at \geq 10 mg/kg/day, and cytoplasmic
1159	vacuolation of the bile duct epithelium in both sexes at ≥ 10 mg/kg/day); kidneys
1160	(bilateral tubular vacuolation in males at 50 mg/kg/day and females at \geq 10 mg/kg/day
1161	and an increased incidence of bilateral basophilic tubules in males and females at
1162	50 mg/kg/day); lymphoid depletion in both sexes at 50 mg/kg/day in mandibular and
1163	mesenteric lymph nodes, thymus and spleen (with extramedullary hematopoiesis in
1164	50 mg/kg/day females); bone marrow in the sternum (increased adipocytes in males at
1165	\geq 2 mg/kg/day and females at 50 mg/kg/day); testes (spermatocyte/spermatid
1166	degeneration in males at 50 mg/kg/day); epididymides (oligospermia/germ cell debris in
1167	males at 50 mg/kg/day); ovaries (absent corpora lutea in females at \geq 2 mg/kg/day and
1168	considered adverse); the mammary gland and other tissues in the female reproductive
1169	tract (uterus, cervix, and vagina) of these animals were consistent with animals that have
1170	not ovulated; vacuolation in the epithelium of the mammary gland duct in females at
1171	50 mg/kg/day; parotid salivary gland (cytoplasmic alteration in both sexes at
1172	\geq 10 mg/kg/day); biceps femoris (atrophy of the skeletal muscle in both sexes at
1173	50 mg/kg/day); skin (atrophy and alopecia/hypotrichosis in males at 50 mg/kg/day and
1174	females at ≥ 10 mg/kg/day); prostate gland (decreased secretory product in males at
1175 1176	50 mg/kg/day); thyroid glands (bilateral increased colloid in males at \geq 10 mg/kg/day).
1177	Many of the findings were considered by the Study Director to be consistent with the
1178	pharmacology of the test article including cortical atrophy of the adrenal glands (affecting
1179	the zona fasciculata and reticularis), generalized lymphoid depletion in lymphoid tissues
1180	(thymus, spleen, and lymph nodes), increased adipocytes in the bone marrow, atrophy of
1181	the skeletal muscle, alopecia/hypotrichosis and atrophy of the skin (thinning of the
1182	dermal collagen and atrophy of hair follicles and adnexa), an absence of corpora lutea in
1183	the ovary (likely indicative of delayed puberty), decreased secretory product in the
1184	prostate gland, and multiple changes in the liver. The liver had panlobular hypertrophy
1185	and vacuolation of hepatocytes consistent with glycogen accumulation. Due to the
1186	magnitude of hypertrophy and vacuolation, there were (likely secondary) foci of
1187	hepatocellular necrosis and inflammation.

- 1188 Test article-related microscopic findings at the recovery necropsy were present in the 1189 adrenal glands, liver, gallbladder, kidneys, stomach (pylorus), female reproductive tract 1190 1191 (ovaries), male reproductive tract (testes, epididymides, prostate gland), mesenteric 1192 lymph node, skeletal muscle (biceps femoris), and parotid salivary gland. 1193 The No Observed Adverse Effect Level was 2 mg/kg/day for males; a No Observed 1194 Adverse Effect Level was not observed for females (ReveraGen Report No. 1998-014). 1195 1196 7-day study in cynomolgus monkeys 1197 Non-naive cynomolgus monkeys were administered vamorolone or vehicle QD for 7 consecutive days at doses of 100, 300, and 600 mg/kg. All animals survived until the 1198 1199 end of the study period. There were effects on clinical observations, food consumption, and urinalysis attributable to vamorolone that are described below. 1200 1201 There was a dose proportional decrease in body weight gain observed in males and females at each dose (up to 11% and 9% respectively) related to vamorolone. A 1202 1203 cessation of the body weight loss in treatment was observed during the recovery phase but no recovery of body weight lost during the 7 days of dosing was observed. 1204 1205 At termination there were nonsignificant increases in red cell mass and decreases in 1206 lymphocytes (up to 56%) in the 600 mg/kg/day dose group. However, most individual 1207 animals, including controls, had decreases in lymphocytes (up to 81%) at termination relative to their respective pretest. These decreases had resolved by the recovery interval 1208 1209 in both sexes. In both sexes receiving $\geq 300 \text{ mg/kg/day}$, there was increased urea nitrogen (up to 141%), 1210 creatinine (up to 58%), total protein (up to 15%), albumin (up to 11%), globulin (up to 1211 1212 25%), and/or potassium (up to 39%) with concurrent decreases in sodium (up to 10%) and chloride (up to 10%) relative to controls. At the recovery interval, the majority of 1213 these effects had resolved (ReveraGen Report No. 1998-001). 1214 1215 **Genotoxicity** 1216 1217 The mutagenic and genotoxic potential of vamorolone was assessed in several assays. A
- 1218 non-GLP Ames screen was negative for bacterial mutations (ReveraGen Report No.

- BIO-VBP-001-AMES). In a GLP Ames test, no background lawn toxicity was observed;
 however, a reduction in revertant counts was observed (ReveraGen Report No.
 AD79DT.502ICH.BTL). Vamorolone was negative for inducing chromosomal
 aberrations in cultured mouse lymphocytes without and with metabolic activation
 (ReveraGen Report No. AD79DT.704.BTL).
- 1225 Femoral bone marrow was microscopically evaluated for the presence of polychromatic 1226 erythrocytes (PCEs) containing micronuclei. No significant reductions in the PCEs/EC 1227 (total erythrocytes) ratio were observed in the vamorolone groups compared to the 1228 vehicle control group. Although statistically significant increases in the incidence of 1229 micronucleated PCEs in the vamorolone treated groups were observed, no dose response 1230 was observed with respect to other groups and the values of micronuclei for the individual animals were within the historical range. Therefore, the statistically 1231 significant increase was considered as biologically insignificant (ReveraGen Report No. 1232 1233 AD76BK.123012ICH.BTL).
- 1234 A study was performed to evaluate the potential mutagenicity of two theoretical epoxide 1235 impurities related to the drug substance vamorolone (formerly VBP15), which is a 1236 steroid-like structure containing a delta 9,11 double bond. The delta 9,11 epoxide 1237 structures evaluated were VBP15-B-3, which is structurally similar to vamorolone except 1238 for the epoxide moiety, and VBP15-B-2, which has a 21-acetate substitution (vamorolone and VBP15-B-3 contain a 21-hydroxy moiety). Two validated and complementary 1239 in silico prediction methodologies were used for assessing mutagenic potential. The 1240 1241 statistics-based quantitative structure-activity relationship (QSAR) program MultiCASE 1242 CASE Ultra was used, employing four different modules (GT1 A7B, GT1 AT ECOLI, 1243 PHARM ECOLI, and PHARM SAL) designed to cover a wide range of molecular 1244 substructures collected from both proprietary and public compounds. In addition, the 1245 expert rule-based SAR program Derek Nexus was used to determine if the theoretical impurities contained structural alerts associated with known genotoxicants. CASE Ultra 1246 1247 predicted both VBP15-B-2 and VBP15-B-3 as negative for mutagenicity (ReveraGen Report "In Silico Mutagenicity Evaluation of Delta 9,11 Epoxide Structures of VBP15: 1248 1249 VBP15-B-2 [21-Acetate] and VBP15-B-3 [21-Hydroxy]").

Taken together, these data indicate vamorolone is negative for any mutagenic signal.
 1252
 1.3 Clinical Experience
 1254
 1255 Clinical experience with vamorolone is comprised of a completed Phase I clinical triateries

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, and an ongoing long-term extension (VBP15-LTE) trial in DMD boys.

- 1259 1.3.1 Phase I Study in Healthy Adult Male Volunteers (VBP15-001)
- 1260 Study Design and Objectives

1261 The safety, tolerability, and PK of vamorolone were initially evaluated in a Phase I randomized, placebo-controlled, double-blind, single ascending dose (SAD) and multiple 1262 1263 ascending dose (MAD) study. In the SAD portion of the study, Cohorts 1 through 5 and 1264 Cohort 7 were comprised of eight subjects each; six subjects in each cohort received a 1265 single oral dose of vamorolone (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 8.0 mg/kg, and 20 mg/kg, respectively) and two subjects in each cohort received placebo under 1266 1267 fasted conditions. In Cohort 6, six subjects received a single oral dose of 8.0 mg/kg vamorolone within 30 minutes of beginning a high fat/high calorie meal. The MAD 1268 1269 portion of the study had four cohorts of 8 subjects each; six subjects in each cohort 1270 received 14 daily doses of vamorolone (1.0, 3.0, 9.0 and 20.0 mg/kg/day) and two 1271 subjects in each cohort received placebo.

1272 The primary objectives of the Phase I study were to evaluate the safety and tolerability of 1273 single and multiple oral doses of vamorolone, and to evaluate the PK of single doses and 1274 multiple doses of vamorolone. A secondary objective was to evaluate the effect of food 1275 on the absorption and PK of vamorolone. Other objectives were to obtain samples from 1276 subjects on Day 1 (pre-dose) and Day 14 of the MAD cohorts for use in Metabolites in 1277 Safety Testing (MIST) assessments, and to test back-up PK samples from a subset of 1278 MAD subjects for pharmacodynamic (PD) biomarkers.

1279 *Pharmacokinetics*

1280

1281 <u>SAD Cohorts – Pharmacokinetics (Fasted)</u>

1283	Vamorolone PK data shows strong adherence to dose linearity and dose proportionality,
1284	with relatively little subject-subject variation (Figure 2, Table 2, Figure 3). The half-life
1285	was about 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0 and 20.0 mg/kg showed an
1286	extended tail, increasing half-life to 2.5, 3.3 and 4.3 hours, respectively (Figure 2,
1287	Table 2).
1288	

1289Figure 2.Plasma Concentrations of Vamorolone (VBP15) after Oral1290Administration of Single Doses of 0.1, 0.3, 1, 3, 8, and 20 mg/kg to1291Healthy Subjects Under Fasted Conditions



Data presented as arithmetic mean \pm standard error

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

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

*Geometric mean (%CV) (N) except T_{max} for which the median (N) [Range] is reported.

 C_{max} = maximum observed plasma concentration; T_{max} = time to maximum observed plasma concentration; $AUC_{(0-t)}$ = area under concentration-time curve from time 0 to time t; $AUC_{(inf)}$ = area under concentration-time curve from time 0

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to infinity; λ_z = elimination rate constant; $t_{1/2}$ = terminal half-life; CL/F = apparent total clearance from plasma; V_z/F = apparent volume of distribution during terminal phase.

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



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1312 <u>SAD Cohorts – Pharmacokinetics (Fed)</u>

1313 For the food effect group, a high fat meal (45 grams fat) was given to a cohort of Phase I

1314 SAD volunteers with the 8.0 mg/kg dose of vamorolone. These data were then compared

to the fasted 8.0 mg/kg cohort data. This showed that absorption was increased by

1316 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone

1317 (steroidal compound) (Figure 4, Table 3).



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Figure 4. Plasma Concentrations of Vamorolone (VBP15) After Single Dose Oral Administration of 8 mg/kg to Healthy Subjects Under Fed and Fasted Conditions



1323 Data presented as arithmetic mean ± standard error

Table 3.Summary of Pharmacokinetic Parameters for Vamorolone After Single
Dose Oral Administration of 8 mg/kg to Healthy Subjects Under Fed
and Fasted Conditions

	8 m		
Parameter*	Fasted	Fed	Ratio†
Cmax(ng/mL)	718 (42.5) (6)	1,817 (31.4) (6)	2.53
Tmax(hr)	1.78 (6)	4.00 (6)	
	[1.00 - 2.00]	[2.00 - 6.00]	
AUC(0-t) (hr×ng/mL)	3,997 (55.0) (6)	10,139 (25.1) (6)	2.54
AUC(inf) (hr×ng/mL)	3,602 (60.2) (4)	10,170 (24.9) (6)	2.82
$\lambda z (1/hr)$	0.2136 (40.9) (4)	0.2950 (18.9) (6)	
t½ (hr)	3.25 (40.9) (4)	2.35 (18.9) (6)	
CL/F			
(L/hr/kg)	2.22 (60.2) (4)	0.79 (24.9) (6)	
(L/hr)	196 (57.6) (4)	66.7 (28.4) (6)	
Vz/F			
(L/kg)	10.4 (61.8) (4)	2.67 (23.4) (6)	
(L)	919 (63.1) (4)	226 (29.2) (6)	

1328 *Geometric mean (%CV) (N) except T_{max} for which the median (N) is reported.

1329 *****Ratio of the geometric means.

1335 <u>MAD Cohorts</u>

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1336	The Phase I MAD treatment plan was discussed in light of the initial PK data. The
1337	relatively short half-life of vamorolone (2-4 hours), coupled with the planned daily dose
1338	schedule, would be expected to give PK data on each single dose, not cumulative dose, as
1339	the dosing interval was $> 5 \times t_{2}$. Thus, the MAD component would be a study of
1340	individual daily doses, rather than dose-related accumulation and pharmacodistribution
1341	related to cumulative drug exposure. In other words, a typical goal of a MAD study is to
1342	determine steady state drug levels after multiple doses; yet with the short half-life of
1343	vamorolone, useful information would not be expected to be gained with the current daily
1344	dosing schedule. Safety and tolerability are additional goals of the MAD study, and these
1345	remain important endpoints independent of the PK studies.
1346	MAD Cohorts – Pharmacokinetics Fasted
1347	The original design for the Phase I MAD was modified to remove the two lowest doses
1348	(0.1, 0.3 mg/kg/day), and to begin dosing at 1.0 mg/kg/day. The clinical conduct of all
1349	four cohorts has been completed (1.0 mg/kg/day, 3.0 mg/kg/day, 9.0 mg/kg/day,

1350 20.0 mg/kg/day) for the MAD study (Table 4).

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Table 4. Summary of Pharmacokinetic Parameters for Vamorolone During OralAdministration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days toHealthy Subjects Under Fasted Conditions

	Vamorolone Dose				
	1 mg/kg	3 mg/kg	9 mg/kg	20 mg/kg	
Day 1 C _{max} (ng/mL)	153 (15.9)	281 (36.9)	1,082 (23.3)	2,416 (51.1)	
T (hr)	3.04	2.01	1.75	1.00	
I_{max} (III)	[1.50 - 4.00]	[1.00 - 3.00]	[1.00 - 6.00]	[0.50 - 3.00]	
AUC _(0-t) (hr _x ng/mL)	686 (22.4)	6 (22.4) 1,471 (23.6)		10,182 (28.1)	
$AUC_{(0-24)}$ (hr×ng/mL)	686 (22.4)	1,471 (23.6)	5,709 (29.9)	10,182 (28.1)	
AUC(inf) (hrxng/mL)	695 (22.1)	1,487 (23.7)	5,745 (29.5)	10,190 (27.0)	
$\lambda_z (1/hr)$	0.3848 (10.9)	0.2918 (18.1)	0.2317 (22.6)	0.1747 (44.3)	
t _{1/2} (hr)	1.80 (10.9)	2.38 (18.1)	2.99 (22.6)	3.97 (44.3)	
CL/F (L/hr/kg)	1.44 (22.1)	2.02 (23.7)	1.57 (29.5)	1.96 (27.0)	
V _z /F (L/kg)	3.74 (16.9)	6.91 (34.8)	6.76 (46.9)	11.2 (77.6)	
Day 14 C _{max} (ng/mL)	203 (30.1)	276 (35.6)	935 (48.3)	2,491 (27.9)	
T (hr)	2.96	2.50	1.25	2.00	
I_{max} (IIF)	[1.50 - 3.00]	[1.00 - 4.00]	[0.55 - 3.00]	[1.00 - 2.00]	
AUC ₍₀₋₂₄₎ (hr×ng/mL)	794 (22.3)	1,494 (18.6)	4,366 (20.2)	9,309 (38.8)	
$\lambda_{z} (1/hr)$	0.3993 (20.4)	0.3273 (25.2)	0.1629 (63.5)	0.1879 (31.6)	
$t_{\frac{1}{2}}(hr)$	1.74 (20.4)	2.12 (25.2)	4.25 (63.5)	3.69 (31.6)	
CL/F (L/hr/kg)	1.26 (22.3)	2.01 (18.6)	2.06 (20.2)	2.15 (38.8)	
V _z /F (L/kg)	3.15 (20.6)	6.14 (39.7)	12.7 (79.9)	11.4 (49.1)	

1356 C_{max} = maximum observed plasma concentration; T_{max} = time to maximum observed plasma concentration; $AUC_{(0-t)}$ =1357area under concentration-time curve from time 0 to time t; $AUC_{(0-24)}$ = area under concentration-time curve from time 01358to 24 hours; $AUC_{(inf)}$ = area under concentration-time curve from time 0 to infinity; λ_z = elimination rate constant; $t_{z/2}$ =1359terminal half-life; CL/F = apparent total clearance from plasma; V_z/F = apparent volume of distribution during terminal1361

- 1362 Taking into account the small numbers and different subjects, the geometric mean values
- 1363 for C_{max} , AUC(0-t), and AUC(inf) are not different for the SAD and MAD cohorts. Within
- the MAD, there is good agreement between Days 1 and 14 at all dose groups. There is no
- 1365 accumulation the geometric mean C_{max} and $AUC_{(0-24)}$ on Days 1 and 14 are not
- 1366 different, consistent with the $t_{\frac{1}{2}}$ (~2-4 hours) and dosing interval (24 hours) (**Figure 5**;
- 1367 **Table 4**).

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Figure 5. Plasma Concentrations of Vamorolone (VBP15) on Days 1 and 14 During Oral Administration of 1, 3, 9, and 20 mg/kg Doses Once Daily for 14 Days to Healthy Subjects Under Fasted Conditions





Data presented as arithmetic mean \pm standard error

1375 *Safety*

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1377 <u>SAD Cohorts</u>

In the SAD part, overall, 6 subjects (11%) administered vamorolone experienced a total 1378 of 10 treatment-emergent adverse events (TEAEs); no subject in the placebo group 1379 experienced any TEAEs. There was no dose-related trend in the incidence or severity of 1380 TEAEs; the dose group with the highest number of subjects reporting TEAEs was the 1381 0.1 mg/kg dose group (2 subjects, 33%), and the highest number of TEAEs (3 events) 1382 was reported by 1 subject in the 1.0 mg/kg vamorolone dose group. In the 0.3 and 1383 1384 3.0 mg/kg vamorolone fasted and the 8.0 mg/kg fed dose groups, 1 subject per group 1385 (17%) experienced TEAEs, and no subjects in the 8.0 mg/kg and 20 mg/kg, fasted, dose groups experienced any TEAEs. The most common TEAEs were dizziness and 1386 headache, each reported by 2 subjects overall (4%); all other TEAEs were reported by 1387 only 1 subject (2%) and included ear pain, nausea, non-cardiac chest pain, and blood 1388 1389 bilirubin increased. Three subjects (6%) had TEAEs that were considered possibly related to treatment. Possibly related TEAEs included nausea (1 subject, 2%), dizziness 1390 (2 subjects, 4%), and headache (2 subjects, 4%). One subject (2%) had a moderate 1391

TEAE of blood bilirubin increased, which was considered unrelated to study drug. Allother TEAEs were mild in severity.

1395 <u>MAD Cohorts</u>

1396 In the MAD part, overall, a total of 6 subjects (19%) administered vamorolone or placebo experienced a total of 10 TEAEs: 2 subjects each in the 1.0 mg/kg vamorolone, 20 mg/kg 1397 vamorolone, and placebo groups, and none in the 3.0 mg/kg and 9.0 mg/kg dose groups. 1398 1399 There was no dose-related trend in the incidence or severity of TEAEs. The most 1400 common TEAE was headache (2 subjects, 6%); all other TEAEs occurred in only 1401 1 subject (3%) per group, and included nausea, toothache, vomiting, ALT increased, hepatic enzyme increased, arthralgia, dizziness, and syncope. TEAEs were considered 1402 possibly related in 2 subjects (6%) and remotely related in 1 subject (3%). Possibly 1403 1404 related AEs were ALT increased and hepatic enzyme increased, occurring in 1 subject in the 20 mg/kg vamorolone and placebo groups, respectively. The remotely related TEAEs 1405 were dizziness and syncope, both occurring in the same subject (1.0 mg/kg vamorolone). 1406 1407 All TEAEs were mild in severity.

1408With the exception of the AEs related to hepatic enzymes, there were no other1409meaningful changes in clinical laboratory parameters. Of note, glucose levels remained1410stable at all doses of vamorolone in both the SAD and MAD parts, suggesting that1411vamorolone does not induce insulin resistance at the doses and dosing duration studied;1412in addition, no changes in the white blood cell count differential were observed,1413suggesting that vamorolone did not induce immunosuppressive effects in this study

- 1414 population.
- 1415 1416

Pharmacodynamic Safety Biomarkers

Vamorolone has shown improved safety profiles relative to prednisone in nonclinical
testing, both *in vitro* and *in vivo*.^{15,17} Safety concerns with glucocorticoids include
suppression of the adrenal axis and insulin resistance. Pharmacodynamic biomarker
assays of suppression of the adrenal axis (serum cortisol) and insulin resistance (serum
glucose) were measured in the Phase I MAD studies of vamorolone.

1423	Suppression of the adrenal axis. Prednisone directly impinges on cortisol regulatory
1424	pathways (adrenal axis) both acutely and chronically. Acute suppression of adrenal
1425	function is seen within hours of doses of a single 0.1 mg/kg/day (approximate) dose of
1426	prednisone, as evidenced by reductions in adrenocorticotropic hormone (ACTH) levels in
1427	normal volunteers. ²⁵ More chronic suppression of the adrenal axis, characterized as
1428	severe, is typically diagnosed when morning cortisol is <100 nmol/L ($<3.6~\mu g/dL)$ when
1429	drawn > 24 hrs after the last dose of pharmacological steroids.
1430	Morning serum cortisol levels were measured in the vamorolone Phase I MAD cohorts, at
1431	baseline (prior to drug administration), 24 hours after the first dose (Day 1), and 24 hours
1432	after the 14-day dose (Day 15) (Figure 6). Active substance volunteers at four MAD
1433	dose levels are shown (1.0 mg/kg/day; 3.0 mg/kg/day; 9.0 mg/kg/day; 20.0 mg/kg/day);
1434	all subjects were treated for 14 days with daily dosing. The red hatched line on each
1435	graph shows a typical threshold for adrenal axis suppression (< 100 nmol/L, or
1436	$< 3.6 \mu g/dL$). P values shown are for paired T test, indicating significance of the
1437	consistency of longitudinal changes of subjects relative to their own individual baseline
1438	values. Acute adrenal axis suppression is measured at 24 hours (after first dose), whereas
1439	chronic adrenal axis suppression is measured after 14 days of daily dosing (24 hours after
1440	last dose).

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Figure 6. Morning Cortisol Measurements in the Vamorolone Phase I Healthy Subjects



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

Vamorolone showed little evidence of either acute (24 hour data), or chronic (Day 15 1447 data) suppression of the adrenal axis at doses of either 1.0 mg/kg/day or 3.0 mg/kg/day. 1448 1449 The data suggest that vamorolone induces variable, mild, acute and chronic suppression of the adrenal axis at 9.0 mg/kg/day, and stronger evidence of both acute and chronic 1450 adrenal axis suppression at 20.0 mg/kg/day. Prednisone typically shows both acute and 1451 chronic adrenal axis suppression approximately at 0.1 mg/kg/day,²⁵ suggesting that 1452 vamorolone has an improved safety window regarding adrenal axis suppression. 1453 Vamorolone thus shows approximately a 10-fold improvement in safety window 1454 1455 compared to prednisone on a mg/kg comparative basis. These data are consistent with

- *in vitro* and *ex vivo* nonclinical mouse data comparing vamorolone to prednisone for
- adrenal suppression.¹⁵

1458Insulin resistance. Prednisone induces the safety signal of insulin resistance, where1459glucose is not efficiently taken up from the blood by target tissues, such as muscle and1460liver, leading to hyperglycemia.²⁵ Insulin resistance may be an important safety signal1461for dystrophic muscle, where the dysfunctional myofibers have been shown to have

of vamorolone (Figure 7).

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1402	
1463	inadequate energy stores, ^{18,26} and insulin resistance likely limits availability of glycogen
1464	substrates for glycolysis. The hyperglycemia, in turn, leads to chronic increases in
1465	insulin levels (hyperinsulinemia).
1466	Levels of fasting glucose and insulin are reasonably sensitive and reliable measures of
1467	insulin resistance in non-diabetic individuals. Glucose is acutely (single dose) and
1468	chronically (multiple doses) elevated after treatment with pharmacological
1469	glucocorticoids. Glucose is elevated 24 hours after a single administration of
1470	glucocorticoids (2.0 mg/kg). ^{27,28}
1471	In the Phase I MAD of vamorolone, fasting serum glucose was measured at 10 time
1472	points during the 2-week study; each sample was taken 24 hours after the previous dose

Fasting Serum Glucose During the Phase I MAD Period (Two Weeks 1474 Figure 7. 1475 **Daily Treatment**)



Day of serum sample collection

1476 Glucose levels for all vamorolone dose groups were similar to those of the placebo group. 1477 1478 There was no evidence of elevations of glucose levels at any time point or any dose of vamorolone, suggesting that the side effect of insulin resistance was not seen with 1479 1480 vamorolone. These data are consistent with a nonclinical study in a dystrophin-deficient 1481 mouse model, where chronic treatment of prednisolone (5 mg/kg/day) versus vamorolone

1482						
1483	(15 mg/kg/day; 30 mg/kg/day) showed development of insulin resistance with					
1484	dnisolone, but not vamorolone. ²⁹					
1485	Summary of Phase I Data					
1486 1487	Pharmacokinetics					
1488						
1489	• Vamorolone PK data show strong adherence to dose linearity and dose					
1490	proportionality, with relatively little subject-subject variation (both SAD and					
1491	MAD).					
1492	• The half-life was about 2 hours for doses 0.1-1.0 mg/kg. Doses at 3.0, 8.0, and					
1493	20.0 mg/kg showed an extended tail, increasing half-life to 2.5, 3.8, and 3.8 hours,					
1494	respectively. The PK for the MAD cohorts was very similar to the SAD cohorts,					
1495	showing little if any drug accumulation, consistent with the short half-life and daily					
1496	dosing schedule					
1190						
1497	• There were no apparent relationships between CL/F and body size, either in terms					
1498	of body weight or BMI.					
1499	• For the food effect group, a high fat meal was given to a cohort of Phase I SAD					
1500	volunteers with the 8.0 mg/kg dose of vamorolone. Comparison of the data from					
1501	the high fat meal with the fasted 8.0 mg/kg cohort data showed that absorption was					
1502	increased by 2.5-fold by the high fat meal, consistent with the lipophilic character					
1503	of vamorolone (steroidal compound).					
1504	Safeta					
1504 1505	Salety					
1506	• Single and multiple daily doses of vamorolone up to 20 mg/kg were well tolerated					
1507	by healthy subjects, and a maximum tolerated dose (MTD) was not identified.					
1508	• Regarding the primary target organ, liver, one subject in the 20 mg/kg vamorolone					
1509	MAD dose group who had an elevation of serum bilirubin at baseline (pre-dose)					
1510	experienced an AE of ALT increased after 9 days of dosing; this AE was judged to					
1511	be possibly related to vamorolone and drug dosing was halted. No other subjects in					
1512	the vamorolone dose groups experienced AEs related to liver function					
1012	the valioroione dose groups experienced AES related to fiver function.					

1513						
1514	• Results of post-dose morning cortisol levels suggest that vamorolone causes acute					
1515	adrenal suppression after single dosing and chronic adrenal suppression after					
1516	multiple dosing, but only at the higher ($\geq 8.0 \text{ mg/kg}$) single and multiple doses					
1517	studied.					
1518	• Safety PD biomarker studies showed that vamorolone had an improved safety					
1519	window for adrenal axis suppression (100-fold increase in therapeutic window), no					
1520	evidence of insulin resistance, no changes in bone turnover markers (osteocalcin,					
1521	C-terminal peptide fragment of collagen 1[CTX1]), compared to prednisone studies					
1522	reported in the literature ^{25,30}					
1523	• There were no clinically significant changes in vital signs, ECGs, or physical					
1524	examinations.					
1525	1.3.2 Pharmacokinetics in Phase IIa Study in 4 to 7 years Duchenne Muscular					
1526	Dystrophy Boys (VBP15-002)					
1527	Forty-eight boys with DMD received oral doses of vamorolone once daily for 14 days at					
1528	doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day, 12 subjects					
1529	receiving vamorolone at each dose level. The drug was administered with a glass of					
1530	whole milk or other high-fat food. Six blood samples were collected on Day 1 and Day					
1531	14 at 0, 1, 2, 4, 6, and 8 hours post-dose and plasma was analyzed for vamorolone. The					
1532	time-course of plasma drug concentrations was assessed using noncompartmental					
1533	analytical (NCA) methods using the WinNonlin software (Certara).					
1534 1535	Of the 48 DMD subjects enrolled in the study (12 at each dosing level), 47 had evaluable					
1536	PK data. The average Day 1 and Day 14 vamorolone concentration versus time profiles					
1537	are shown in Figure 8 for the four dose levels. Overall, as expected, higher doses					
1538	resulted in higher plasma concentrations of vamorolone. In particular, plasma					
1539	vamorolone concentrations versus time showed a rapid to moderate rate of absorption, a					
1540	maximum concentration (C_{max}) at a T_{max} of 2 to 4 hours, and a decline phase with a					
1541	typical half-life $(t_{1/2})$ of 2 hours. For all 4 doses, the mean PK profiles on Day 1 and					
1542	Day14 appear similar. Many individual subjects had closely matching Day 1 and Day 14					

1544 profiles, but several did not. There was no accumulation of drug owing to the relatively

1545 short half-life and once-daily (morning) dosing.

1546Figure 8Mean Plasma Concentrations of Vamorolone after Once Daily Oral1547Administration of 0.25, 0.75, 2.0, and 6.0 mg/kg Doses

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

1552A summary of the observed (C_{max} and T_{max}) and calculated (AUC, $t_{1/2}$, and CL) PK1553parameters for all doses on Day 1 and Day 14 is provided in Table 5. Even with only 61554blood samples collected from each subject, the PK profiles adequately capture the overall1555exposures, but must be considered approximate. This particularly applies to the peak1556values and the half-lives. Nevertheless, there is good consistency in the data with1557moderate variability as SD values are reasonable and the coefficient of variation values1558are typically less than 50%.

1560The drug is absorbed at a moderate rate with peak concentrations typically occurring at 21561to 4 hours on both Days 1 and 14. The median T_{max} across all doses is typically 2 or 41562hours. The half-lives were similar on both days, averaging about 2 hours, although some1563subjects had irregular profiles without a clear decline phase. The apparent clearance (CL

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1565and CL/F) values were consistent across the dose levels for Day 1 as well as for Day 14,1566but the latter tended to average slightly lower (about 2400 mL/hr/kg on Day 1 and15671900 mL/hr/kg on Day 14).15681900 mL/hr/kg on Day 14).

1569Table 5.Summary of Pharmacokinetic Parameters for Vamorolone after Once1570Daily Oral Administration of 0.25, 0.75, 2.0 and 6.0 mg/kg Doses to DMD1571Boys

Day 1

Day 14

	Dose, mg/kg/day				Dose, mg/kg/day			
Parameters	0.25	0.75	2.0	6.0	0.25	0.75	2.0	6.0
Cmax [ng/ml]	22.9 (13.4)	75.9 (25.9)	199 (111)	855.6 (471)	32.2 (15.2)	124.7 (42.5)	252.5 (96)	970 (270)
T _{max} [h]	3.6 [4] (1.2)	4.6 [4] (2.1)	2.5 [2] (1.3)	2.7 [2] (1.3)	3.8 [4] (1.8)	3.8 [4] (2.2)	2.8 [2] (1)	2.3 [2] (0.86)
AUC _{inf} [hr·ng/ml]	118 (48)	379 (117)	761 (352)	3279 (1693)	164 (61)	544 (155)	1138 (467)	3606 (897)
$t_{1/2}[h]$	2.1 (0.85)	1.8 (0.43)	1.9 (0.79)	1.9 (0.95)	1.9 (0.96)	2.1 (0.8)	1.9 (1.02)	1.4 (0.35)
CL [ml/hr/kg]	2459 (897)	2285 (1103)	2697 (1285)	2320 (1375)	1828 (919)	1509 (482)	2047 (771)	1777 (476)
Values are mean (star	ndard deviation	on) and for T	max, which ar	e shown as n	nean [mediai	n] (standard o	leviation).	
An assessment of the linearity of the PK with dose using C _{max} and AUC is shown in								
Figure 9. Data for all individual subjects were used which also depict the variability for								
each dose level. While larger doses appear to present greater variability, this is a visual								
size distortion as the standard deviation is similar at each dose level (Table 5). Fitting								
the power equation of the form (C_{max} , $AUC_{inf} = a \times Dose^{b}$) resulted in 95% confidence								
intervals for b values that include 1.0 for C_{max} and AUC_{inf} for both Days 1 and 14								
indicative of linear relationships across this range of dose levels.								



Figure 9 Regression Analysis of C_{max} and AUC_{inf} versus Dose





(VBP15-002 and VBP15-003)

1598Adverse events: There were no serious adverse events (SAEs) reported over the 14-day1599treatment in the Phase I clinical trial in healthy adult volunteers, nor in the four cohorts1600(0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and 6.0 mg/kg) of the Phase IIa study (VBP15-002;160114-day treatment) in boys ages 4 to <7 years with DMD. There were a total of 4 SAEs in</td>
1603 the Phase II VBP15-003 study and three SAEs to date in the VBP15-LTE extension 1604 study: two SAEs of pneumonia in two different subjects (both subjects receiving 1605 vamorolone 0.75 mg/kg/day), one SAE of bilateral testicular torsion and one SAE of 1606 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, and two SAEs of acute myoglobinuria 1607 in the same subject receiving 6.0 mg/kg/day. Each of these SAEs was considered 1608 unrelated to study drug, and none of them resulted in discontinuation from the study. In 1609 1610 the VBP15-003 study, there were a total of 218 TEAEs among 42 of the 48 subjects 1611 (87.5%). In VBP15-003 study, the TEAEs with the highest incidence were viral upper respiratory tract infection (41.7%); pyrexia (35.4%); cough (18.8%); vomiting (14.6%); 1612 1613 and diarrhea (10.4%). 1614 1615 Body Mass Index (BMI): Body Mass Index was measured throughout the VBP15-003 1616 study. The mean change from baseline to Week 24 for BMI was 0.03, 0.20, 0.23, and 1617 1.15 for the 0.25, 0.75, 2.0, and 6.0 mg/kg/day dose level groups, respectively. Body Mass Index increases generally reflect an increase in weight. Body Mass Index z-score 1618 1619 was monitored in the VBP15-003 study. The mean change from baseline to Week 24 for 1620 BMI z-score for the 6.0 mg/kg/day group showed a statistically significant increase compared to the mean change from baseline to Week 24 for the 0.25 mg/kg/day and 1621 1622 0.75 mg/kg/day dose level groups. In contrast, the mean change from baseline to Week 24 for the 2.0 mg/kg/day dose level group in BMI z-score was minimal and 1623 1624 comparisons with the other vamorolone dose level groups lacked statistical significance. The mean increase from baseline to Week 24 for BMI z-score was similar for the 1625 1626 6.0 mg/kg/day group and a daily prednisone-treated historical control group. 1627 Potential liver toxicity: In the Phase I clinical trial in adult volunteers, vamorolone 1628 showed mild elevations of liver enzymes in one subject receiving 20.0 mg/kg in the 1629 1630 fasted state, and dosing was halted. All DMD subjects have elevated serum ALT and 1631 AST enzymes because of the muscle condition. For that reason, two enzymes, glutamate 1632 dehydrogenase (GLDH) and gamma glutamyl transferase (GTT), that are preferentially 1633 expressed in liver were evaluated in the VBP15-003 study. None of the mean changes in 1634 GLDH from baseline to any of the VBP15-003 on-treatment assessment time points were

1635	
1636	statistically significant for any dose level group. Although the mean changes from
1637	baseline to Week 8, Week 16, and Week 24 in GLDH levels did not show a dose
1638	response, shift analysis of GLDH levels did suggest a possible dose-related shift to higher
1639	GLDH levels at 2.0 mg/kg/day and 6.0 mg/kg/day at Weeks 16 and 24. Mean GGT
1640	levels and individual subject values at each VBP15-003 assessment time point across the
1641	four dose level groups remained at or below the normal range. On the basis of these mean
1642	GLDH and GGT data, vamorolone at dose levels up to 6.0 mg/kg/day does not appear to
1643	induce liver toxicity over a 24-week treatment period.
1644	Adrenal suppression: In the VBP15-003 study, after 24 weeks of treatment, 0 of 8 tested
1645	participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants (0.75 mg/kg/day), 5 of
1646	12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants
1647	(6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μ g/dL [100 nM]) consistent with
1648	chronic adrenal suppression. ²⁹
1649	Insulin resistance: In the VBP15-003 study, mean changes from baseline for fasting
1650	insulin showed dose-and time-related changes for all dose level groups at Week 12 and
1651	Week 24. Statistical significance was observed for mean increase from baseline for the
1652 1653	6.0 mg/kg/day dose level group at Week 12 and Week 24.

1654Bone Turnover: In the VBP15-003 study, pharmacodynamic biomarker testing for bone1655turnover markers suggested that vamorolone does not have the detrimental bone effects1656observed with prednisone and deflazacort.

1657 1658

1.4 Rationale for Study Design

The proposed Phase IIb clinical trial (VBP15-004) is designed as a pivotal study to show 1659 that vamorolone treatment over a Treatment Period of 24 weeks leads to superior 1660 improvements in strength and mobility versus placebo (efficacy), with a reduced adverse 1661 effect profile versus prednisone treatment (safety), and to demonstrate persistence of 1662 effect over a Treatment Period of 48 weeks. To determine efficacy, functional outcomes 1663 1664 in DMD patient groups receiving one of two doses of vamorolone over 24 weeks will be compared to functional outcomes of DMD patients receiving placebo. To determine 1665 safety, body mass index (BMI) and PD safety biomarker findings in DMD patients 1666

- receiving one of two dose levels of vamorolone over 24 weeks will be compared to DMD
 patients receiving prednisone. The two dose levels of vamorolone to be studied have
 been chosen based upon data obtained in the Phase IIa and Phase II extension studies
 (VBP15-002; VBP15-003).
 This Phase IIb study is a double-blind study of two dose levels of vamorolone, with
 placebo and prednisone-treated control arms.
- 1674 Subjects who meet all eligibility criteria in this study (VBP15-004) will be randomized to 1675 one of six treatment groups as shown in **Table 6**.

Group	Planned Number of Subjects	Treatment Period #1 (24 Weeks)	Treatment Period #2 (20 Weeks)
1	30	Vamorolone, 2.0 mg/kg/day \rightarrow	Vamorolone, 2.0 mg/kg/day
2	30	Vamorolone, 6.0 mg/kg/day \rightarrow	Vamorolone, 6.0 mg/kg/day
3	15	Prednisone, 0.75 mg/kg/day \rightarrow	Vamorolone, 2.0 mg/kg/day
4	15	Prednisone, 0.75 mg/kg/day \rightarrow	Vamorolone, 6.0 mg/kg/day
5	15	Placebo \rightarrow	Vamorolone, 2.0 mg/kg/day
6	15	Placebo \rightarrow	Vamorolone, 6.0 mg/kg/day

Table 6.Study Randomization Schedule

1679

1678 Evaluation of the two dose levels of vamorolone, prednisone, and placebo during the 24-1679 week Treatment Period #1 in this study will allow comparison of change from baseline in safety parameters, muscle strength and functional efficacy parameters, and PD biomarker 1680 1681 levels over 24 weeks of treatment as compared to no treatment (placebo) or standard of care treatment (prednisone). In particular, evaluation of change of the PD biomarkers 1682 1683 from baseline over a longer (24-week) period may aid in the clinical validation of 1684 biomarkers which exhibit small changes over time. In addition, evaluation of the two dose levels of vamorolone over the total 48-week period of the study will allow 1685 assessment of the persistence of effect. 1686

- 1687The primary efficacy outcome is the Time to Stand (TTSTAND) from the floor1688(velocity), and comparison will be made between the 6.0 mg/kg/day dose level of1689vamorolone and the placebo group at Week 24. Multiple secondary and exploratory1690efficacy outcomes will be measured, including TTSTAND, Time to Run/Walk 10 meters
- 1691 (TTRW), Time to Climb four stairs (TTCLIMB), North Star Ambulatory Assessment

1692	
1693	(NSAA), 6-Minute Walk Test (6MWT), Range of Motion test (ROM), and hand-held
1694	myometry (elbow flexors and knee extensors). Additional exploratory measures of
1695	efficacy include PD biomarkers that have previously been shown to be glucocorticoid-
1696	responsive in DMD boys and inflammatory bowel disease in children. ³¹ Moreover,
1697	physical functioning, behavior, neuropsychology, and satisfaction with treatment will be
1698	measured as exploratory outcomes using the parent proxy-report of Pediatric Outcomes
1699	Data Collection Instrument (PODCI), PARS III, Treatment Satisfaction Questionnaire
1700	(TSQM), and Ease of Study Medication Administration Assessment for the study
1701	medication suspension, respectively.
1702	For the safety measure of body mass index (BMI) z-score, comparisons will be made
1703	between each dose level of vamorolone and the prednisone-treated group. Additional
1704	secondary safety measures are serum biomarkers bridged to later clinical safety concerns.
1705	These include:
1706	1. Adrenal suppression. Pharmacological doses of glucocorticoids cause
1707	suppression of the hypothalamo-pituitary-adrenal axis, leading to low
1708	concentration of endogenous cortisol and other steroidal hormones in serum.
1709	Adrenal suppression is directly associated with risk of adrenal crisis, delay of
1710	puberty and stunting of growth. Measurement of morning cortisol concentrations
1711	will reflect the degree of adrenal suppression. Plasma cortisol secretion typically
1712	follows a circadian pattern with the highest concentrations early in the morning; a
1713	morning serum cortisol concentration less than 3.6 μ g/dL (or 100 nM) is highly
1714	suggestive of adrenal suppression. A single cortisol measurement at other times
1715	of the day is of limited value and dynamic testing with Cosyntropin (a synthetic
1716	peptide of ACTH, also known as tetracosactide) is a standard approach to the
1717	assessment of endogenous cortisol production. ³² Serum cortisol levels less than
1718	18 μ g/dL (500 nM) 30 or 60 minutes after stimulation with Cosyntropin (250 μ g)
1719	are considered diagnostic of adrenal suppression.
1720	2. Bone turnover. Pharmacological doses of glucocorticoids cause an imbalance of
1721	bone formation and bone resorption, leading to later osteopenia and bone

1722	
1723	fragility. ³³ Bone fragility is a significant adverse effect of chronic pharmacologic
1724	glucocorticoids in DMD as this can lead to fracture, which increases the
1725	likelihood of premature loss of ambulation. Serum biomarkers that have been
1726	bridged to later clinical outcomes of osteopenia are osteocalcin (bone formation;
1727	glucocorticoids decrease serum levels), and CTX1 (bone resorption;
1728	glucocorticoids increase serum levels). Decreases of osteocalcin and increases of
1729	CTX1 are reflective of abnormal bone turnover, a risk factor bridged to later
1730	bone fragility.
1731	3. Insulin resistance. Insulin resistance is the term where increased blood glucose
1732	triggers increased insulin secretion from the pancreatic islet cells, but the
1733	elevated serum insulin fails to sufficiently trigger glucose uptake by muscle
1734	and/or liver. Thus, peripheral tissues are resistant to insulin signaling (insulin
1735	resistance). Insulin resistance has been bridged to later clinical outcomes,
1736	including heart disease, type 2 diabetes, and vascular disease. Serum biomarkers
1737	that are accepted as measures of insulin resistance are increased serum glucose
1738	and insulin. This can be measured after acute (hours after first dose) or chronic
1739	(after weeks or months of dosing) glucocorticoid treatment.
1740	Additional exploratory safety outcomes are measures of additional serum safety
1741	biomarkers that have been defined in glucocorticoid-treated DMD and inflammatory
1742	bowel disease patients.
1743	This trial will be conducted in compliance with this protocol, and in accordance with the
1744	ethical principles that have their origin in the Declaration of Helsinki, and that are
1745	consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements,
1746	and the recently issued FDA guidance on developing drugs for treatment for DMD and
1747	related dystrophinopathies. ³⁴
1748	It is obligatory that the Investigator become familiar with all sections of the vamorolone
1749	Investigator's Brochure. ²⁹

1.5 Overall Benefit/Risk

1752 It is anticipated that the adverse effect profile of the investigational product will be more 1753 1754 favorable than standard of care glucocorticoids in the long term. There has been a total 1755 of 11 SAEs in the vamorolone program to date: a total of 4 SAEs in the VBP15-003 study, a total of 3 SAEs in the VBP15-LTE study, a total of 3 SAEs in the VBP15-004 1756 1757 study, and 1 SAE in the VBP15-EAP program. There have been two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day); one SAE 1758 of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 1759 mg/kg/day; one SAE of influenza associated dehydration in a subject receiving 6.0 1760 1761 mg/kg/day; two SAEs of acute myoglobulinemia in the same subject receiving 6.0 1762 mg/kg/day; one SAE of viral gastroenteritis with secondary dehydration in a subject 1763 receiving blinded study drug; one SAE of asthma exacerbation in the setting of 1764 respiratory syncytial virus and bronchiolitis in a subject receiving vamorolone at either 1765 2.0 mg/kg/day or 6.0 mg/kg/day; one SAE of perforated appendicitis occurring with 30 days after the subject completed the VBP15-004 study, and one SAE of viral 1766 1767 gastroenteritis requiring hospitalization for hydration. Each of these SAEs was 1768 considered unrelated to study drug, and none of them resulted in discontinuation from the study. 1769

In the Phase I clinical trial in adult volunteers, vamorolone showed mild elevations of 1770 1771 liver enzymes in one subject receiving 20.0 mg/kg in the fasted state. One subject participating in VBP15-004 developed an AE of acute cholestatic hepatitis manifested by 1772 elevated transaminases, direct bilirubin, ALP and GGT during Treatment Period #1 and 1773 1774 after study drug interruption and restart, redeveloped acute cholestatic hepatitis in Treatment Period #2. Unblinding of the treatment assignment for this subject, to 1775 1776 facilitate decisions regarding subsequent standard of care corticosteroid therapy, 1777 indicated that the subject had been on vamorolone 6.0 mg/kg/day in both Treatment 1778 Period #1 and Treatment Period #2. In the VBP15-002 study, after 2 weeks of treatment, 0 of 11 tested participants who 1779

1780 received vamorolone 0.25 mg/kg/day, 0 of 11 tested participants who received

1781	
1782	vamorolone 0.75 mg/kg/day, 2 of 11 (18.2%) tested participants who received
1783	vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested participants who received
1784	vamorolone 6 mg/kg/day had a depressed morning cortisol (<3.6 µg/dL [100 nmol/L])
1785	consistent with chronic adrenal suppression. In the VBP15-003 study, after 24 weeks of
1786	treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants
1787	(0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%)
1788	tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μ g/dL
1789	[100 nM]) consistent with chronic adrenal suppression. Instructions for detecting adrenal
1790	crisis and the circumstances in which stress dose steroids should be provided will be
1791	included in the Informed Consent Form (ICF) and Manual of Operations, and
1792	Investigators should monitor clinical study participants closely to identify elevations in
1793	liver-specific enzymes.
1794	Potential Health Benefits: Subjects may or may not receive direct health benefit from
1795	participating in the study. Some subjects will be randomly assigned to vamorolone at one
1796	of two planned dose levels (2.0 mg/kg/day and 6.0 mg/kg/day) over the course of the
1797	48-week trial. In the VBP15-003 study, clinical efficacy was assessed by Timed
1798	Function Tests. Improvement in Time to Stand, Time to Climb, Time to Run/Walk
1799	10 Meters, and 6-Minute Walk Test were seen predominantly for the 2.0 and
1800	6.0 mg/kg/day dose level groups, with many of the improvements showing statistical
1801	significance compared to an untreated Duchenne Natural History Group. In view of the
1802	initial clinical evidence of safety, the improvements observed in the assessments of
1803	efficacy, and the nature of potential adverse effects that can be monitored, the data
1804	support an acceptable benefit/risk profile for vamorolone.
1805 1806	2 STUDY OBJECTIVES AND ENDPOINTS

- 1807
 2.1
 Study Objectives

 1808
 1808
 1808
 1808
- 18092.1.1 Primary Objectives1810
- 1811 The primary objectives of this study are:

	Vamoro Amenda Protoco	blone 28 August 2020 ment #4 Document No. VBP15-004-A4 (Version 1.4) l No.: VBP15-004 IND 118,942
1812		
1813	1.	To compare the efficacy of vamorolone administered orally at daily doses of
1814		6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to
1815		<7 years with DMD; and
1816		
1817	2.	To evaluate the safety and tolerability of vamorolone administered orally at daily
1818		doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with
1819		DMD.
1820	2.1.2	Secondary Objectives
1821	These	and any chieves of this stady and
1822	The se	condary objectives of this study are:
1823	1.	To compare the efficacy of vamorolone administered orally at daily doses of
1825		2.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to
1826		<7 years with DMD;
1827	2.	To compare the safety of vamorolone administered orally at daily doses of
1828		2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone
1829		0.75 mg/kg in ambulant boys ages 4 to $<$ 7 years with DMD;
1830 1831	3.	To compare the efficacy of vamorolone administered orally at daily doses of
1832		2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone
1833		0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD:
1834		or to highly highly highly agos the straight with Divid,
1835	4.	To compare the efficacy of vamorolone administered orally at daily doses of
1836		2.0 mg/kg and $6.0 mg/kg$ over a 48-week treatment period in ambulant boys ages
1837		4 to <7 years with DMD vs. untreated DMD historical controls;
1838	5.	To compare the safety of vamorolone administered orally at daily doses of
1839		2.0 mg/kg and 6.0 mg/kg over a 48-week treatment period in ambulant boys ages
1840		4 to <7 years with DMD vs. prednisone-treated DMD historical controls; and
1841	6.	To evaluate the population pharmacokinetics of vamorolone administered orally
1842		at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years
1843		with DMD.

1844		
1845 1846	2.1.3	Exploratory Objectives
1847 1848	The ex	xploratory objectives of this study are:
1849	1.	To evaluate the satisfaction with treatment of vamorolone administered orally at
1850		daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily
1851		prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
1852	2.	To evaluate the effect of vamorolone administered orally at daily doses of
1853		2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone
1854 1855		0.75 mg/kg on behavior and neuropsychology;
1856	3.	To evaluate the effect of vamorolone administered orally at daily doses of 2.0
1857		mg/kg and 6.0 mg/kg over a 24-week treatment period vs. placebo on physical
1858		functioning;
1859	4.	To assess the ease of administration of the study medication suspension to
1860		ambulant boys ages 4 to <7 years with DMD;
1861	5.	To compare the effects of vamorolone administered orally at daily doses of
1862		2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. placebo on
1863		potential serum PD biomarkers of safety and efficacy in ambulant boys ages 4 to
1864 1865		<7 years with DMD;
1866	6.	To compare the effects of vamorolone administered orally at daily doses of
1867		2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone
1868		0.75 mg/kg on potential serum PD biomarkers of safety and efficacy in ambulant
1869		boys ages 4 to <7 years with DMD; and
1870	7.	To determine if candidate genetic modifiers of DMD (gene polymorphisms
1871		associated with disease severity, or response to glucocorticoid treatment) are
1872		similarly associated with vamorolone-treated DMD subjects (baseline disease
1873		severity, or response to vamorolone or prednisone treatment).

1874		
1875 1876	2.2	Study Endpoints
1877 1878	2.2.1	Safety Endpoints
1879	1.	BMI z-score: Change from baseline to each of the scheduled on-treatment and
1880		post-treatment assessment time points;
1881	2.	Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
1882		by system organ class (SOC): Overall by treatment, by treatment and relationship,
1883		and by treatment and intensity (see Section 7.5);
1884	3.	Vital signs (sitting blood pressure, heart rate, respiratory rate, and body
1885		temperature): Change from baseline to each of the scheduled on-treatment and
1886		post-treatment assessment time points;
1887	4.	Body weight and height: Change from baseline to each of the scheduled
1888		on-treatment and post-treatment assessment time points;
1889	5.	Cushingoid features: Change from baseline to each of the scheduled on-treatment
1890		and post-treatment assessment time points (changes from baseline will be
1891		recorded as AEs);
1892	6.	Clinical laboratory values: Change from baseline to each of the scheduled
1893		on-treatment and post-treatment assessment time points in:
1894		Hematology and clinical chemistry
1895		• Lipid profile (triglycerides, total cholesterol, low density lipoprotein [LDL]
1070		
1897		high density lipoprotein [HDL])
1898		Vitamin D level
1899		
1900		• Urinalysis;
1901	7	12 los delastro condicerror (ECC). Change from baseline to each of the scheduled
1902	/.	an treatment and post treatment accessment time points:
1903		on-ucaunem and post-ucaunem assessment time points;
1904	8.	2D-echocardiogram: Change from baseline to Week 24 and Week 48;

1905	
1906	9. Dual-energy x-ray absorptiometry (DXA) scan: Change from baseline to Week 24
1907	and Week 48 in spine BMD, total body BMD, spine and total body bone mass,
1908	and total body composition (lean mass, fat mass, fat-free mass, Lean Mass Index,
1909	and Fat Mass Index);
1910	10. Spine x-rays: Change from baseline to Week 24 assessment;
1911	
1912	11. Eye examination for detection of clinically significant abnormalities (cataracts
1913	and/or glaucoma) at Week 24 and Week 48 assessments compared to baseline;
1914	12. ACTH Stimulation Test: measure of adrenal suppression at Week 24 and
1915	Week 48. Percentage of subjects in each treatment group with cortisol levels <18
1916	μ g/dL (or 500 nM) 30 or 60 minutes after stimulation with Cosyntropin;
1917	13. Linear growth velocity: Change from baseline to each of the scheduled
1918	on-treatment and post-treatment assessment time points in height percentile for
1919	age.
1920	Data for the following additional safety outcomes will be listed only:
1921	
1922	1. Physical examination findings at each of the pretreatment, on-treatment, and
1923	post-treatment assessment time points.
1924	2. Fracture Questionnaire results at pretreatment, Week 24, and Week 48.
1925	
1926	Tolerability Endpoint
1927	1 Premature discontinuations of study treatment due to adverse events
1929	1. Tremature discontinuations of study aroument due to adverse events.
1930	2.2.2 Clinical Efficacy Endpoints
1931	Primary Clinical Efficacy Endpoint
1932	1. Time to Stand Test (TTSTAND) velocity (rise/second): Comparison of the
1933	vamorolone 6.0 mg/kg/day dose level group versus the placebo group in change
1934	from baseline to the Week 24 assessment.
1935	Secondary Efficacy Endpoints
1936	
1937	1. Change from baseline to Week 24 for the following comparisons:

1938	
1939	• TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo
1940	
1941	• 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs.
1942	placebo
1943	• 6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs.
1944	placebo
1945	• Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day
1946	vs. placebo
1947	• Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day
1948	vs. placebo
1949	• 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone
1950	
1951	 6MWT meters walked, vamorolone 2.0 mg/kg/day vs. prednisone
1952	
1953	2. Change from baseline to each of the scheduled study assessment time points for
1954	each treatment group up to Week 48 for:
1955	• Time to Stand Test (TTSTAND) velocity (rise/second);
1956	
1957	• Time to Climb (4 Steps) Test (TTCLIMB) velocity (tasks/second);
1958	
1959	• Time to Run/Walk Test (TTRW) velocity (meters/second) to complete
1960	10 meters of a 14 meter course;
1961	• Total distance traveled, in meters, in completing the Six-minute Walk Test
1962	(6MWT);
1963	• North Star Ambulatory Assessment (NSAA);
1964	
1965	• Hand-held myometry (elbow flexors and knee extensors); and
1966	
1967	• Range of motion in the ankles (ROM).
1968	
1969	Exploratory Efficacy Enapoints
1970 1071	1 Change from baseline to each of the scheduled study assessment time points up to
17/1	1. Change from baseline to each of the seneutricu study assessment time points up to
1972	and including Week 24 for the following comparisons:

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1973			
1974	•	TTSTAND velocit	y, vamorolone 6.0 mg/kg/day vs placebo (Week 6 and 12
1975		only)	
1976	•	TTSTAND velocit	y, vamorolone 2.0 mg/kg/day vs placebo (Week 6 and 12
1977		only)	
1978	•	6 Minute Walk Tes	st (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs.
1979		placebo (Week 12	only)
1980	•	6 Minute Walk Tes	st (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs.
1981		placebo (Week 12	only)
1982	•	Time to Run/Walk	(TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day
1983		vs. placebo (Week)	12 only)
1984	•	Time to Run/Walk	(TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day
1985		vs. placebo (Week)	12 only)
1986	•	6MWT meters wal	ked, vamorolone 6.0 mg/kg/day vs. prednisone (Week 12
1987		only)	
1988	•	6MWT meters wal	ked, vamorolone 2.0 mg/kg/day vs. prednisone (Week 12
1989		only)	
1990	•	NSAA total score,	vamorolone 6.0 mg/kg/day vs. placebo
1991	•	NSAA total score,	vamorolone 2.0 mg/kg/day vs. placebo
1992	•	Hand-held Myome	try knee extensors, vamorolone 6.0 mg/kg/day vs. placebo
1993	•	Hand-held Myome	try knee extensors, vamorolone 2.0 mg/kg/day vs. placebo
1994	•	Hand-held Myome	try elbow extensors, vamorolone 6.0 mg/kg/day vs. placebo

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Hand-held Myometry elbow extensors, vamorolone 2.0 mg/kg/day vs. placebo

TTCLIMB velocity, vamorolone 6.0 mg/kg/day vs. placebo

TTCLIMB velocity, vamorolone 2.0 mg/kg/day vs. placebo

ROM in the ankles, vamorolone 6.0 mg/kg/day vs. placebo

ROM in the ankles, vamorolone 2.0 mg/kg/day vs. placebo

2000		
2001	2.2.3	Additional Exploratory Endpoints
2002 2003	1.	Treatment satisfaction questionnaire (TSQM): Comparison of each vamorolone
2004		dose level group to the prednisone group at the Week 24 visit; comparison of each
2005		treatment group at the Week 48 visit;
2006	2.	Pediatric Outcomes Data Collection Instrument (PODCI): Comparison of each
2007		vamorolone dose level group to the placebo group for change from baseline to the
2008		Week 24 assessment; comparison of each treatment group for change from
2009		baseline to the Week 48 assessment;
2010	3.	Behavioral changes (PARS III): Comparison of each vamorolone dose level group
2011		to the prednisone group and to the placebo group for change from baseline to each
2012		of the scheduled study assessment time points up to the Week 24 assessment;
2013		comparison of each treatment group for change from baseline to the Week 48
2014		assessment;
2015	4.	Ease of study medication administration (Question 1 only: tablet vs liquid)
2016		assessed at each of the scheduled study assessment time points;
2017	5.	Blindedness Assessment at each of the scheduled study assessment time points;
2018		and
2019	6.	DNA testing for candidate genetic modifiers of DMD.
2021	2.2.4	Pharmacodynamic Endpoints
2022 2023	1.	The following pharmacodynamic biomarkers are considered secondary outcome
2024		measures focusing on safety outcomes. In each case, the biomarkers studied
2025		reflect safety concerns of glucocorticoids:
2026		a. Adrenal suppression. First-in-morning serum cortisol levels will be
2027		measured. Cortisol measures falling below 3.6 μ g/dL (or 100 nM) will be
2028		considered to be indicative of the development of adrenal suppression.
2029		ACTH Stimulation Test will be performed at the Screening Visit and at
2030		the Week 24 Follow-up Visit (48 ± 3 hours after the final dose of
2031		Treatment Period #1 study medication) and at the Week 48 Follow-up

2032	
2033	Visit (48 \pm 3 hours after the final dose of Treatment Period #2 study
2034	medication): cortisol levels $\leq 18 \ \mu g/dL$ (or 500 nM) 30 or 60 minutes after
2035	stimulation with Cosyntropin (250 μ g) will be considered to be indicative
2036	of adrenal suppression.
2037	b. Bone turnover. Measures of serum osteocalcin are reflective of bone
2038	formation, and measures of serum CTX1 are reflective of bone
2039	reabsorption. Levels of osteocalcin and CTX1 predict later clinical safety
2040	concerns of osteopenia and bone fragility.
2041	c. Insulin resistance. Glucocorticoids cause both acute and chronic insulin
2042	resistance, with serum elevations of both insulin and glucose. Measures of
2043	hyperinsulinemia and hyperglycemia are accepted measures of insulin
2044	resistance.
2045	2. Exploratory biomarkers for aspects of safety and efficacy ³¹
2046 2047	2.2.5 Endpoints for Patient-Reported Outcomes
2048 2049	Safety endpoints based on subject reports of AFs are listed in Section 2.2.1
2050	Surety enapoints bused on subject reports of TiLs are listed in Section 2.2.1.
2051	The parent/legal guardian of each subject will be asked to assess the ease of
2052	administration of the study medication suspension (see Section 7.4.4).
2053	Additionally, subjects' parents/legal guardians will be asked to complete the PODCI (see
2054	Section 7.4.1). Satisfaction with treatment will be measured using the Treatment
2055	Satisfaction Questionnaire (TSQM) which also will be completed by the parent/legal
2056	guardian (see Section 7.4.2). Additionally, the PARS III behavioral assessment will be
2057	completed by the parent/guardian (see Section 7.4.3). Finally, the subject's parent/legal
2058	guardian will complete a Blindedness Assessment at the Week 24 Visit (see Section
2059	7.4.5).
2060	No other patient-reported outcomes are planned.

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3 STUDY DESIGN

3.1 Overall Study Design

2065 This Phase IIb study is a randomized, double-blind, parallel group, placebo- and active-2066 controlled study with double-blind extension to evaluate the long-term efficacy, safety, 2067 2068 tolerability, PD, and population PK of vamorolone (the investigational medicine) compared to prednisone (active control) and placebo over a Treatment Period of 2069 2070 24 weeks in boys ages 4 to <7 years with DMD, and determine the persistence of effect over a total Treatment Period of 48 weeks. Six treatment groups will receive either 2071 2072 vamorolone at one of two doses (2.0 mg/kg or 6.0 mg/kg), prednisone (0.75 mg/kg), or placebo once daily for 24 weeks, and will receive vamorolone at one of two doses 2073 (2.0 mg/kg or 6.0 mg/kg) daily for an additional 20 weeks. A total of approximately 2074 120 subjects will be randomized into the study as shown in Table 6. 2075

- 2076To maintain the blind during Treatment Period #1, matched suspension (vamorolone or2077placebo) and matched tablets (prednisone or placebo) will be administered. Each subject2078will receive a dose of suspension (vamorolone or placebo) and tablets (prednisone and2079placebo) once daily during Treatment Period #1. The number of tablets and volume of2080suspension per dose will be determined by body weight.
- 2081The study is comprised of a Pretreatment Screening Period of up to 32 days duration, a20821-day Pretreatment Baseline Period, a 24-week Treatment Period #1, a 4-week Transition
- 2083 Period, a 20-week Treatment Period #2, and a 4-week Dose-tapering Period. Subjects
- 2083 reflow, a 20-week freatment reflow #2, and a 4-week Dose-tapering reflow. Subjects 2084 will be enrolled into this study at the time written informed consent is given, and
- 2085 randomized to treatment only after completion of all Pretreatment Screening assessments.
- 2086 Study drug dosing will occur from Day 1 until the Week 48 Visit (Section 5.3). Study
- drug dosing will occur at home on all days except the Day 1, Week 2, Week 12, Week
- 208824, Week 28, Week 30, Week 40, and Week 48 study visits, when dosing will occur at2089the study site.
- 2090 Subjects will be assessed for safety and tolerability, clinical efficacy, PD, and population 2091 PK at scheduled visits throughout the study (see Section 6 for a schedule of study 2092 assessments). Treatment Period #1, Transition Period, and Treatment Period #2 study

2093	
2094	visits will occur at Day 1, Week 2, Week 6, Week 12, Week 18, Week 24, Week 28,
2095	Week 30, Week 34, Week 40 and Week 48 (Table 11); all subjects will return to the
2096	clinical site for a Week 24 Follow-up Visit and for a Week 48 Follow-up Visit, 48 ± 3
2097	hours after administration of the final dose of Treatment Period #1 and Treatment Period
2098	#2 study medication, respectively, for ACTH Stimulation testing. Adverse events,
2099	including SAEs, and concomitant medications will be recorded throughout the study.
2100	Subject diaries will be dispensed at the Day 1 Visit and at each study visit thereafter
2101	through Week 48 to record AEs, changes to concomitant medications taken during the
2102	study, and any missed or incomplete doses of study medication.
2103	There is flexibility in the timing of completion of some of the scheduled Week 24 and
2104	Week 48 assessments. The scheduled physical examination, weight, vital signs, clinical
2105	laboratory tests, blood draws for PD biomarker analysis, blood draw for DNA testing
2106	(Week 24 only), Ease of Study Medication Administration Assessment, PODCI, PARS
2107	III, and functional assessments (TTSTAND, TTCLIMB, TTRW, NSAA, 6MWT, hand-
2108	held myometry, ROM) must all be performed on the date of the Week 24 or Week 48
2109	dose of study medication. The 12-lead ECG may be performed on the date of the Week
2110	24 or Week 48 dose of study medication, the day following the Week 24 or Week 48
2111	dose of study medication, or the day of the Week 24 or Week 48 Follow-up Visit. For
2112	the Week 24 assessments, completion of the DXA scan, spine X-rays, Fracture
2113	Questionnaire, 2-D echocardiography, eye examination, TSQM, and Blindedness
2114	Assessment may be performed up to 7 days following the date of the Week 24 dose of
2115	study medication to accommodate need for additional scheduling flexibility. For the
2116	Week 48 assessments, completion of the DXA scan, Fracture Questionnaire, 2-D
2117	echocardiography, eye examination, and TSQM may be performed on the date of the
2118	final Week 48 dose of study medication, the day following the Week 48 dose of study
2119	medication, or the day of the Week 48 Follow-up Visit for subjects who will receive
2120	additional vamorolone therapy by enrolling directly into an additional vamorolone study
2121	or general access program, or up to 7 days following the date of the final Week 48 dose
2122	of study medication for subjects participating in the Dose-tapering Period.

A Transition Period of 4 weeks in duration follows the end of Treatment Period #1 for all 2124 subjects. During this Transition Period, all subjects will continue to receive the liquid 2125 2126 formulation (vamorolone 2.0 mg/kg or 6.0 mg/kg, or matching placebo) they received 2127 during Treatment Period #1 and will be tapered off their study medication tablets 2128 (prednisone or matching placebo). Site study staff will contact the parent(s)/guardian(s) by telephone at Week 26 to ensure that the tablet tapering is proceeding according to 2129 protocol, to assess potential signs or symptoms indicative of adrenal suppression, and to 2130 2131 address any questions the parent(s)/guardian(s) may have. All subjects will return to the 2132 clinical site for the Week 28 assessments, prior to receiving their first dose of Treatment Period #2 study medication on the day after the Week 28 Visit (Week 28 + 1 day) (see 2133 2134 Section 6.3.6).

2135 Subjects who complete the VBP15-004 study assessments through the Week 48 Visit and Week 48 Follow-up Visit may be given access to vamorolone through an additional study 2136 or general access program, or given the option to transition to standard of care treatment 2137 (including glucocorticoids) for DMD. Standard of care treatment for DMD may be 2138 offered to the subject following completion of the Phase IIb VBP15-004 study, if the 2139 2140 subject's parent or guardian does not wish to enroll the subject in the additional vamorolone study or general access program and/or the Investigator feels it to be in the 2141 best interest of the subject. 2142

Subjects who will enroll directly into the additional vamorolone study or general access 2143 program to continue vamorolone treatment will be discharged from the VBP15-004 study 2144 2145 following completion of all Week 48 assessments and the Week 48 Follow-up Visit ACTH Stimulation Test. Subjects who will not continue vamorolone treatment in the 2146 2147 additional vamorolone study or general access program, including those subjects who will transition to standard of care treatment for DMD, will have their vamorolone dose 2148 2149 tapered during a 4-week Dose-tapering Period, prior to discharge from the study. Site study staff will contact the parent(s)/guardian(s) by telephone at Week 50 to ensure that 2150 2151 the dose tapering is proceeding according to protocol (see Section 6.3.7), to assess 2152 potential signs or symptoms of adrenal suppression, and to address any questions the 2153 parent(s)/guardian(s) may have.

In the event that any clinical or laboratory parameters remain abnormal at the time of 2155 discharge from the study, the subject will be followed medically, as clinically indicated. 2156 2157 Any subject who discontinues the study prior to the Week 24 Visit should return to the study unit for scheduled Week 24 assessments and the Week 24 Follow-up Visit ACTH 2158 2159 Stimulation Test at the time of early withdrawal, whenever possible; any subject who 2160 prematurely discontinues the study after Week 24 but prior to Week 28 should complete the scheduled Week 28 assessments at the time of early withdrawal, whenever possible; 2161 2162 and any subject who prematurely discontinues the study after Week 28 but prior to Week 2163 48 should complete the scheduled Week 48 assessments and the Week 48 Follow-up 2164 Visit ACTH Stimulation Test at the time of early withdrawal, whenever possible, 2165 assuming the subject has not withdrawn consent. Any subject who withdraws early from 2166 the study should undergo Early Discontinuation Dose-tapering (see Section 6.4).

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8.2 Randomization

Following consent and review of study entry criteria to confirm subject eligibility for the 2169 2170 study, the subject can be randomized to treatment. Randomization should be performed at least 10 days prior to the baseline visit and will be achieved via the Interactive 2171 Voice/Web Response System (IXRS) system with user name and password access. 2172 Randomization will be stratified by participant's age (< 6 vs. ≥ 6 years). Randomization 2173 will be stratified only by age; randomization will not be stratified by investigational site. 2174 Randomization will require the site investigator, or designee, to verify that the subject 2175 2176 meets the inclusion/exclusion criteria of the study, and to verify that the child has not 2177 previously been randomized. The following information will need to be entered into the IXRS system in order to assign the subject to a treatment group and the appropriate age 2178 2179 stratification group:

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- Participant's Date of Birth
- Participant's weight, as recorded at the Screening Visit.

Participant's Study Subject Identification Number

2185 When the site investigator/designee completes the randomization procedures via the 2186 IXRS system, an e-mail report with the randomization number and age stratification 2187 2188 group will be generated and sent to the clinical trials supply company confirming 2189 randomization into the trial. 2190 The randomization number will be assigned by the IXRS system and will only be used for study drug supply and shipment. Once the information has been received, the clinical 2191 2192 trials supply company will prepare a subject-specific kit of study medication and ship it 2193 to the pharmacy at the study site. 2194 Randomization procedures should be completed at least 10 days prior to the Baseline 2195 Visit in order to allow study drug supply to be shipped to the site in time to be dispensed to the participant by the site investigator for Day 1 dosing. 2196 3.3 2197 Blinding 2198 To achieve double-blinding, the supplies company will manufacture identical liquid 2199 2200 formulations for vamorolone and placebo, and identical tablet formulation for prednisone and placebo. Each dose of study medication will consist of doses of both a liquid 2201 2202 formulation (vamorolone or placebo) and tablets (prednisone or placebo) through Week 2203 28, and liquid formulation only following Week 28 through Week 48 (see Table 7). 2204 To blind the liquid formulation, the supplies company will manufacture 1.33% and 4.0% wt/wt vamorolone suspension formulations, and placebo suspension formulation, 2205 2206 identical in appearance. Subjects who are randomized to receive vamorolone 2.0 mg/kg will receive the 1.33% vamorolone suspension, and subjects who are randomized to 2207 receive vamorolone 6.0 mg/kg will receive the 4.0% vamorolone suspension. Study 2208 medication will be shipped to the sites in 100 mL bottles labeled with subject-specific 2209 2210 identifiers. Trained site study staff will calculate study medication dose volume based on 2211 subject body weight for all subjects as 0.15 mL/kg, regardless of treatment assignment. 2212 Subjects, parents/guardians, site investigators and all other site study staff will not know 2213 to which treatment group the subject has been assigned and will remain blinded to the 2214 identity of the treatment assignment until the end of the study (last subject last visit) and the database has been locked. 2215

3.4 Unblinding 2218

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

2226 Subjects who experience a medical emergency, whether their treatment remains blinded 2227 or is unblinded, should be covered with stress steroids, except for unblinded subjects who 2228 were receiving placebo.

All subjects who have study medication withdrawn without unblinding will need to undergo dose-tapering according to the schedule in Section 6.4.

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

2234 Unblinding will be performed and treatment assignment obtained through the IXRS 2235 system with username and password code. The expectation is that emergency unblinding 2236 will occur only very rarely; for example, when the subject needs emergency surgery and 2237 information about all treatment interventions is required. In the exceptional circumstance 2238 that knowledge of the study drug assignment appears essential for providing appropriate medical management, the site investigator should make every effort to contact the study 2239 2240 chair or the independent Medical Monitor to discuss the rationale for breaking the blind. 2241 If the site investigator still believes that unblinding is needed, or the study chair and independent Medical Monitor are not available for contact, the site investigator will 2242 follow the IXRS unblinding procedures for unblinding the subject in question (see the 2243 2244 Manual of Operations for details on how to unblind a subject using the IXRS system). 2245 After breaking the blind, the site staff should record details regarding the reasons for 2246 breaking the blind, including any AEs leading to the unblinding, in the source documents

2248	and electronic case report form (eCRF). Once the blind is broken for a given subject,
2249	study drug will be discontinued and the subject will be withdrawn from the study.
2250	Furthermore, as the subject might have received glucocorticoids (prednisone) as part of
2251	the study and as vamorolone appears to affect the adrenal axis, prednisone and
2252	vamorolone cannot be discontinued without a proper dose-tapering period.
2253	Any subject whose treatment is unblinded prior to the Week 24 Visit should return to the
2254	clinic for Week 24 assessments at the time of unblinding, whenever possible, assuming
2255	the subject has not withdrawn consent; any subject whose treatment is unblinded after
2256	Week 24 and prior to the Week 28 Visit should return to the clinic for Week 28
2257	assessments at the time of unblinding, whenever possible, assuming the subject has not
2258	withdrawn consent; any subject whose treatment is unblinded after Week 28 and prior to
2259	the Week 48 Visit should return to the clinic for Week 48 assessments at the time of
2260	unblinding, whenever possible, assuming the subject has not withdrawn consent. Since
2261	all subjects will receive vamorolone at one of two dose levels during Treatment Period #2
2262	(Weeks $28 - 48$), the identification, through unblinding, of the vamorolone dose level to
2263	which a given subject is assigned is unlikely to give additional useful information, and
2264	thus the need to unblind treatment assignment is remote during this study period. Any
2265	subject whose treatment, upon unblinding, is revealed to be either vamorolone or
2266	prednisone, will need to follow the dose-tapering protocol (Section 6.4 specific to the
2267	time of unblinding); these subjects will also be asked to return to the clinic at the end of
2268	the tapering period for final Dose-tapering Period assessments, whenever possible. If the
2269	subject was taking placebo prior to unblinding, study drug tapering will not be required;
2270	however, the subject should return for final Week 24 assessments at the time of
2271	unblinding and withdrawal from the study. After unblinding, a subject may be prescribed
2272	standard of care glucocorticoids, if clinically indicated.
2273	Subjects who discontinue the study for any reason other than a medical emergency
2274	will not be unblinded.

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4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Subject Enrollment and Identification Log

2279 Subjects will be recruited through the clinics of participating site investigators and other 2280 mechanisms including patient registries, national and international networks and patient 2281 2282 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 2283 2284 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 2285 2286 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 2287 screening procedures. Subjects will not be excluded on the basis of race, ethnicity, or 2288 age, except that the target population for the trial is 4 to <7 years of age. 2289

- A subject enrollment log will be maintained at each investigational site for all subjects who are screened for the study, including those not randomized 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.
- 2296The Site Investigator will keep a record relating the names of the subjects to their2297enrollment numbers (subject identification log) to permit efficient verification of data2298subject files, when required. These logs will be reviewed during routine monitoring calls2299and/or visits.
- 2300 2301

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4.2 Inclusion Criteria

2303To qualify for randomization in this study, the subject must satisfy the following2304inclusion criteria:

23051. Subject's parent(s) or legal guardian(s) has (have) provided written informed2306consent and Health Insurance Portability and Accountability Act (HIPAA)2307authorization, where applicable, prior to any study-related procedures;

2308		
2309		participants will be asked to give written or verbal assent according to local
2310		requirements;
2311	2.	Subject has a centrally confirmed (by TRiNDS central genetic counselor[s])
2312		diagnosis of DMD, as defined as:
2313		• Dystrophin immunofluorescence and/or immunoblot showing complete
2314		dystrophin deficiency, and clinical picture consistent with typical DMD, OR
2315		• Identifiable mutation within the DMD gene (deletion/duplication of one or
2316		more exons), where reading frame can be predicted as 'out-of-frame,' and
2317		clinical picture consistent with typical DMD, OR
2318		• Complete dystrophin gene sequencing showing an alteration (point mutation,
2319		duplication, other) that is expected to preclude production of the dystrophin
2320		protein (i.e., nonsense mutation, deletion/duplication leading to a downstream
2321		stop codon), with a clinical picture consistent with typical DMD;
2322	3.	Subject is \geq 4 years and <7 years of age at time of enrollment in the study;
2323	4.	Subject weighs >13.0 kg and \leq 39.9 kg at the Screening Visit;
2324	5.	Subject is able to walk independently without assistive devices;
2325	6.	Subject is able to complete the Time to Stand Test (TTSTAND) without
2326		assistance in <10 seconds, as assessed at the Screening Visit;
2327	7.	Clinical laboratory test results are within the normal range at the Screening Visit,
2328		or if abnormal, are not clinically significant, in the opinion of the Investigator.
2329		[Notes: Serum gamma glutamyl transferase (GGT), creatinine, and total bilirubin
2330		all must be \leq upper limit of the normal range at the Screening Visit. An abnormal
2331		vitamin D level that is considered clinically significant will not exclude a subject
2332		from randomization];
2333	8.	Subject has evidence of chicken pox immunity as determined by:
2334		• Presence of IgG antibodies to varicella, as documented by a positive test
2335		result from the local laboratory from blood collected during the Screening
2336		Period, OR

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2337		
2338	Documentation, provide	d at the Screening Visit, that the subject has had 2
2339	doses of varicella vaccir	e, with or without serologic evidence of immunity;
2340	the second of the 2 imm	unizations must have been given at least 14 days
2341	prior to randomization.	
2342	9. Subject is able to swallow tak	plets, as confirmed by successful test swallowing of
2343	placebo tablets during the Sc	reening Period; and
2344	10. Subject and parent(s)/guardia	n(s) are willing and able to comply with scheduled
2345	visits, study drug administrat	ion plan, and study procedures.
2346	4.3 Exclusion Criteria	
2347	A subject will be excluded from rand	lomization in this study if he meets any of the
2349	following exclusion criteria:	
2350	1. Subject has current or history	of major renal or hepatic impairment, diabetes
2351	mellitus or immunosuppressi	on;
2352	2. Subject has current or history	of chronic systemic fungal or viral infections;
2353	3. Subject has had an acute illne	ess within 4 weeks prior to the first dose of study
2354	medication;	
2355	4. Subject has used mineralocom	ticoid receptor agents, such as spironolactone,
2356	eplerenone, canrenone (canre	moate potassium), prorenone (prorenoate potassium),
2357	mexrenone (mexrenoate pota	ssium) within 4 weeks prior to the first dose of study
2358	medication;	
2359	5. Subject has a history of prim	ary hyperaldosteronism;
2360	6. Subject has evidence of symp	otomatic cardiomyopathy [Note: Asymptomatic
2361	cardiac abnormality on inves	tigation would not be exclusionary];
2362	7. Subject is currently being tre	ated or has received previous treatment with oral
2363	glucocorticoids or other imm	unosuppressive agents [Notes: Past transient use of
2364	oral glucocorticoids or other	oral immunosuppressive agents for no longer than 1
2365	month cumulative, with last	use at least 3 months prior to first dose of study
2366	medication, will be considered	d for eligibility on a case-by-case basis, unless

Vamorolone

2368	discontinued for intolerance. Inhaled and/or topical glucocorticoids are permitted
2369	if last use is at least 4 weeks prior to first dose of study medication or if
2370	administered at stable dose beginning at least 4 weeks prior to first dose of study
2371	medication and anticipated to be used at the stable dose regimen for the duration
2372	of the study];
2373	8. Subject has an allergy or hypersensitivity to the study medication or to any of its
2374	constituents;
2375	9. Subject has used idebenone within 4 weeks prior to the first dose of study
2376	medication;
2377	10. Subject has severe behavioral or cognitive problems that preclude participation in
2378	the study, in the opinion of the Investigator;
2379	11. Subject has previous or ongoing medical condition, medical history, physical
2380	findings or laboratory abnormalities that could affect safety, make it unlikely that
2381	treatment and follow-up will be correctly completed or impair the assessment of
2382	study results, in the opinion of the Investigator;
2383	12. Subject is taking (or has taken within 4 weeks prior to the first dose of study
2384	medication) herbal remedies and supplements which can impact muscle strength
2385	and function (e.g., Co-enzyme Q10, Creatine, etc);
2386	13. Subject is taking (or has taken within 3 months prior to the first dose of study
2387	medication) any medication indicated for DMD, including Exondys51 and
2388	Translarna;
2389	14. Subject has been administered a live attenuated vaccine within 14 days prior to
2390	the first dose of study medication;
2391	15. Subject is currently taking any other investigational drug or has taken any other
2392	investigational drug within 3 months prior to the first dose of study medication;
2393	16. Subject has a sibling who is currently enrolled in any vamorolone study or
2394	Expanded Access Program, or who intends to enroll in any vamorolone study or
2395	Expanded Access Program during the subject's participation in the VBP15-004
2396	study; or

2397	
2398	17. Subject has previously been enrolled in the study.
2399	Note: Any parameter/test may be repeated at the Investigator's discretion during
2400	Screening to determine reproducibility. In addition, subjects may be rescreened if
2401	ineligible due to a transient condition which would prevent the subject from participating,
2402	such as an upper respiratory tract infection or injury, or if ineligible due to negative
2403	anti-varicella IgG antibody test result.
2404	
2405	4.4 Withdrawal of Subjects from Study
2406 2407	A subject may withdraw from the study, or may be withdrawn by his parent or guardian
2408	at any time without the need to justify the decision.
2409	The Investigator has the right to terminate participation of a subject in the study for any
2410	of the following reasons:
2411	• The subject's parent/legal guardian is uncooperative/noncompliant and does not
2412	adhere to study responsibilities, including failure to attend study visits;
2413	• Difficulty in obtaining blood samples from the subject for safety monitoring;
2414	The scale of a second
2415	• The subject experiences an unmanageable or non-tolerable AE/SAE which is
2416	considered to be possibly, probably, or definitely related to study drug, in the
2417	opinion of the Investigator, and may jeopardize the subject's health;
2418	• The Sponsor terminates the study;
2419	
2420	• Any other reason relating to subject safety or integrity of the study data;
2421	The subject is uphlinded to study treatment
2422	• The subject is unblinded to study treatment.
2424	In the event a subject is withdrawn from the study, the Sponsor or designee (e.g.,
2425	Coordinating Center) will be informed within one business day. If there is a medical
2426	reason for withdrawal, the subject will remain under the supervision of the Investigator
2427	until resolution of the event.
2428	All subjects who withdraw from the study prior to the Week 24 Visit should return to
2429	the study site for Week 24 assessments and the Week 24 Follow-up Visit ACTH
2430	Stimulation Test at the time of early withdrawal and undergo Dose-tapering, where
27JU	summation rest at the time of early withdrawar and undergo Dose-tapering, where

possible (see Section 6.4.1 and Section 7.2.7), subjects who prematurely discontinue 2432 from the study after Week 24 but prior to Week 28 should complete the Week 28 2433 2434 assessments at the time of early withdrawal and undergo Dose-tapering, where 2435 possible (see Section 6.4.2), and subjects who prematurely discontinue from the study 2436 after Week 28 but prior to Week 48 should complete the Week 48 assessments and the Week 48 Follow-up Visit ACTH Stimulation Test at the time of early withdrawal 2437 and undergo Dose-tapering, where possible (see Section 6.3.7 and Section 7.2.7), 2438 2439 assuming the subject has not withdrawn consent. Subjects will also be asked to come 2440 back at the end of the tapering period for a follow up visit. In the event a subject withdraws informed consent, no further study procedures should be performed and no 2441 2442 additional data should be collected. Any data collected up to the point of withdrawal 2443 of informed consent may be used by the Sponsor. 2444 4.5 **Termination of Study** 2445 This study may be prematurely terminated if, in the opinion of the Sponsor, there is 2446 sufficient reasonable cause. An example of a circumstance that may warrant termination 2447 is determination of unexpected, significant, or unacceptable risks to participants. 2448 If the study is prematurely terminated or suspended, the Sponsor will promptly inform the 2449 2450 site Investigators and the regulatory authority(ies) of the termination or suspension and 2451 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 2452 2453 the Investigator/institution or the Sponsor and provided the reason(s) for the termination 2454 or suspension. Subject enrollment at a given site may be terminated by the Sponsor. Possible reasons 2455 for termination of the study at a given site include, but are not limited to: 2456 1. Unsatisfactory enrollment with respect to quantity or quality 2457 2458 2. Inaccurate or incomplete data collection 2459 2460 3. Falsification of records 2461 2462 4. Failure to adhere to the protocol. 2463

2464	
2465	Subjects who are participating at a given site at the time it is terminated by the Sponsor
2466	will be offered the opportunity to continue to participate in the study at an alternative
2467	active site. Subjects who decline the offer to participate at an alternative active site will
2468	need to undergo dose tapering at the time the original site is terminated according to the
2469	dose-tapering schedule (see Section 6.4).
2470	5 TREATMENT OF STUDY SUBJECTS
2471	5.1 Study Madiantians Administrand
2472	5.1 Study Medications Administered
2473	5.1.1 Study Medications Administered During Treatment Period #1
2475	
2476	Vamorolone 1.33% wt/wt or 4.0% wt/wt oral suspension (investigational medicine),
2477	prednisone (active control) or placebo will be administered once daily over the 24-week
2478	Treatment Period #1.
2479	There are six treatment groups in this study. The oral suspensions and tablets for
2480	Treatment Period #1 are shown in Table 7 for subjects who will be randomly assigned
2481	(2:2:1:1:1:1) to the following six treatment groups.

2482Table 7.Study Medications for the Six Treatment Groups During Treatment2483Period #1

Tuesta ant Casar	Study Medications		
i reatment Group	Oral Suspension	Tablets	
Treatment Group 1	2.0 mg/kg vamorolone	placebo	
Treatment Group 2	6.0 mg/kg vamorolone	placebo	
Treatment Group 3	placebo	0.75 mg/kg prednisone	
Treatment Group 4	placebo	0.75 mg/kg prednisone	
Treatment Group 5	placebo	placebo	
Treatment Group 6	placebo	placebo	

2485 2486

Vamorolone will be administered as a 1.33% wt/wt suspension for oral dosing at the planned dose level of 2.0 mg/kg and as a 4.0% wt/wt suspension for oral dosing at the planned dose level of 6.0 mg/kg. Prednisone will be administered as tablets for oral dosing at a dose of 0.75 mg/kg. Prednisone tablets will be dispensed at a dosage strength

2491	
2492	of 5 mg/tablet. To maintain the blind, matched suspension (vamorolone or placebo) and
2493	tablets (prednisone or placebo) have been produced. Each subject will receive a dose of
2494	suspension (0.15 mL/kg of vamorolone [1.33% oral suspension for the 2.0 mg/kg dose
2495	level or 4.0% oral suspension for the 6.0 mg/kg dose level] or placebo) and tablets
2496	(prednisone or placebo) each day (see Section 3.3). The number of tablets per dose will
2497	be determined by body weight (see Table 10).
2498	The clinical trials supplies companies will manufacture identical liquid formulation of
2499	vamorolone and placebo and identical tablets for prednisone and placebo to maintain the
2500	blind. Liquid solution of prednisone could not have been matched for color and flavor
2501	with vamorolone to maintain the blind. Therefore, a double-dummy design is being used
2502	in this study.
2503 2504	5.1.2 Study Medications Administered During Transition Period
2505	Vamorolone 1.33% wt/wt or 4.0% wt/wt oral suspension (investigational medicine),
2506	prednisone (active control) or placebo will be administered once daily over the 4-week
2507	Transition Period. Prednisone and placebo tablets will be tapered over the 4-week
2508	Transition Period (see Table 12).
2509	The oral suspensions and tablets for the Transition Period are shown in Table 8 for

- subjects in each of the six treatment groups.
- 2511Table 8.Study Medications for the Six Treatment Groups During the Transition2512Period

Treatment Crown	Study Medications		
I reatment Group	Oral Suspension	Tablets (Tapering Doses)	
Treatment Group 1	2.0 mg/kg vamorolone	placebo	
Treatment Group 2	6.0 mg/kg vamorolone	placebo	
Treatment Group 3	placebo	prednisone	
Treatment Group 4	placebo	prednisone	
Treatment Group 5	placebo	placebo	
Treatment Group 6	placebo	placebo	

2514	
2515	Vamorolone will continue to be administered as a 1.33% wt/wt suspension for oral
2516	dosing at the planned dose level of 2.0 mg/kg and as a 4.0% wt/wt suspension for oral
2517	dosing at the planned dose level of 6.0 mg/kg. Prednisone will be administered as tablets
2518	for oral dosing with decreasing number of tablets over the 4-week Transition Period
2519	(Table 12). Prednisone tablets will be dispensed at a dosage strength of 5 mg/tablet. To
2520	maintain the blind, each subject will receive a dose of suspension (0.15 mL/kg of
2521	vamorolone [1.33% oral suspension for the 2.0 mg/kg dose level or 4.0% oral suspension
2522	for the 6.0 mg/kg dose level] or placebo) and tablets (prednisone or placebo) each day
2523	(see Section 3.3). The number of tablets per dose will be tapered to zero (0) over the
2524	4-week Transition Period (see Table 12).
2525 2526	5.1.3 Study Medications Administered During Treatment Period #2 and the
2527	Dose-tapering Period
2528	Vamorolone 1.33% wt/wt or 4.0% wt/wt oral suspension (investigational medicine) will
2529	be administered once daily over the 20-week Treatment Period #2, and during the 4-week
2530	Dose-tapering Period, as applicable. No study drug tablets are administered during
2531	Treatment Period #2 or the Dose-tapering Period.
2532	The oral suspensions for Treatment Period #2 are shown in Table 9 for subjects in each
2533	of the six treatment groups.

Table 9.Study Medications for the Six Treatment Groups During TreatmentPeriod #2 and the Dose-tapering Period

Tucotmont Cucun	Study Medications		
I reatment Group	Oral Suspension		
Treatment Group 1	2.0 mg/kg vamorolone		
Treatment Group 2	6.0 mg/kg vamorolone		
Treatment Group 3	2.0 mg/kg vamorolone		
Treatment Group 4	Group 4 6.0 mg/kg vamorolone		
Treatment Group 5	2.0 mg/kg vamorolone		
Treatment Group 6	6.0 mg/kg vamorolone		

2537						
2538	Vamorolone will be administered as a 1.33% wt/wt suspension for oral dosing at the					
2539	planned dose level of 2.0 mg/kg and as a 4.0% wt/wt suspension for oral dosing at the					
2540	planned dose level of 6.0 mg/kg. During Treatment Period #2, each subject will receive a					
2541	dose of suspension (0.15 mL/kg of vamorolone [1.33% oral suspension for the 2.0 mg/kg					
2542	dose level or 4.0% oral suspension for the 6.0 mg/kg dose level] each day (see					
2543	Section 3.3). The dose of suspension study medication will be tapered according to the					
2544	schedule outlined in Section 6.3.7 during the Dose-tapering Period.					
2545	5.2 Identity of Investigational Product					
2546 2547	ReveraGen BioPharma, Inc. will supply the following investigational study medications:					
2548	Vamorolone					
2549	Active Substance:	Vamorolone				
2550	Strength:	1.33% wt/wt and 4.0% wt/wt				
2551	Dosage Form:	Oral suspension				
2552	Manufacturer:	Velesco Pharmaceutical Services				
2553	Prednisone					
2554	Active Substance:	Prednisone				
2555	Strength:	5 mg				
2556	Dosage Form:	Tablet				
2557	Manufacturer:	Piramal Healthcare UK Limited				
2558	Placebo to Match Vamorolone					
2559	Dosage Form:	Oral suspension				
2560	Manufacturer:	Velesco Pharmaceutical Services				
2561	Placebo to Match Prednison	<u>e</u>				
2562	Dosage Form:	Tablet				
2563	Manufacturer:	Piramal Healthcare UK Limited				

2564	
2565	5.3 Dosage Schedule and Administration of Study Medication
2567	The site pharmacist or designated site study staff will dispense blinded study medication
2568	to each subject randomized in the study (see Section 5.8). Subjects will receive one of
2569	six study medication combinations depending on their treatment group assignment
2570	(Table 7).
2571	To maintain the study blind, matched suspension (vamorolone or placebo) and tablets
2572	(prednisone or placebo) have been produced (see Section 3.3). Vamorolone will be
2573	administered as a suspension for oral dosing $(1.33\% \text{ wt/wt suspension for the } 2.0 \text{ mg/kg}$
2574	dose level or as a 4.0% wt/wt suspension for the 6.0 mg/kg dose level) (see Pharmacy
2575	Manual for instructions on calculation of suspension dose volume). Prednisone will be
2576	administered as 5 mg tablets for oral dosing.
2577	Each subject will receive a dose of suspension (vamorolone or placebo) and tablets
2578	(prednisone or placebo) each day during Treatment Period #1, and a dose of suspension
2579	(vamorolone or placebo) each day during Treatment Period #2. The number of
2580	prednisone or matching placebo tablets per dose will depend upon body weight, as
2581	indicated below (Table 10). All subjects will receive 0.15 mL/kg per dose of a
2582	vamorolone or placebo suspension (Table 7).

Weight Bands for Prednisone or Matching Tablet Dosing Table 10

Band	Weight range in kg	Weight used for calculation of dose per kg	Prednisone dose in mg based on 0.75 mg/kg	Number tablets of prednisone (5 mg) or matching placebo per dose for given weight range
А	13-19.9	13.33 kg	10 mg	2
В	20-25.9	20.00 kg	15 mg	3
С	26-32.9	26.67 kg	20 mg	4
D	33-39.9	33.33 kg	25 mg	5

2585 2586

Subjects will receive study medication, administered orally once daily for 48 weeks, from 2587

Study Day 1 to the Week 48 Visit. At the end of the 24-week Treatment Period #1, all 2588

subjects will be tapered off the tablet study medication over a 4-week Transition Period.
Those subjects randomized to receive placebo will also undergo tablet dose-tapering to
maintain the study blind. At the end of the 20-week Treatment Period #2, subjects who
will transition off vamorolone treatment at the end of the study will be tapered off
suspension study medication over a 4-week Dose-tapering Period, prior to discharge from
the study (see Section 6.3.7).

Study medication sufficient for 4, 6, or 8 weeks of dosing (plus overage), depending upon 2596 2597 the dispensing interval, will be dispensed by trained study staff at the Day 1 Visit, just prior to dosing, and at Week 6, Week 12, Week 18, Week 24 Follow-up, Week 28, 2598 2599 Week 34, Week 40, and Week 48 Follow-up. Each subject's dose (in mL for suspension 2600 formulation; in number of tablets for tablet formulation) will be calculated and written on 2601 the labels of the bottles and blisters to be dispensed at a given visit by trained site staff 2602 based on the weight of the subject (in kg) recorded at the previous visit: weight at 2603 Screening will be used to calculate dose of suspension and tablets for drug supply dispensed at Day 1; weight at the Week 2 Visit will be used to calculate dose of 2604 2605 suspension and tablets for drug supply dispensed at Week 6; weight at the Week 6 Visit 2606 will be used to calculate dose of suspension and tablets for drug supply dispensed at Week 12; weight at the Week 12 Visit will be used to calculate dose of suspension and 2607 2608 tablets for drug supply dispensed at Week 18; weight at the Week 18 Visit will be used to calculate dose of suspension and tablets for drug supply dispensed at Week 24 Follow-up 2609 2610 for the Transition Period; weight at the Week 24 Visit will be used to calculate dose of suspension for drug supply dispensed at Week 28; weight at the Week 30 Visit will be 2611 used to calculate dose of suspension for drug supply dispensed at Week 34; weight at the 2612 Week 34 Visit will be used to calculate dose of suspension for drug supply dispensed at 2613 Week 40; and weight at the Week 40 Visit will be used to calculate dose of suspension 2614 and tablets for drug supply dispensed at the Week 48 Follow-up Visit for the Dose-2615 tapering Period. The dispensed study medication bottle(s) and blister(s) will be returned 2616 2617 to the study site at each subsequent scheduled study visit. Study medication suspension and tablets dispensed at the Day 1 Visit should be brought in with the subject to the 2618 2619 Week 2 Visit, for Week 2 dosing in-clinic and compliance monitoring; this study

2621 medication will be returned to the subject at the end of the Week 2 Visit for continued 2622 dosing through the Week 6 Visit: new study medication will not be dispensed at the 2623 Week 2 Visit. In a similar manner, study medication dispensed at the Week 28 Visit 2624 should be brought in with the subject to the Week 30 Visit, for Week 30 dosing in-clinic 2625 and compliance monitoring; this study medication will be returned to the subject at the 2626 end of the Week 30 Visit for continued dosing through the Week 34 Visit: new study 2627 medication will not be dispensed at the Week 30 Visit.

2628 Randomized subjects will receive all doses under the supervision of parents or legal

2629 guardians or trained study staff. Study drugs will be administered in the study unit at the 2630 Day 1, Week 2, Week 12, Week 24, Week 28, Week 30, Week 40, and Week 48 study

visits; all other doses will be administered at home. Subjects should receive each dose ofstudy medication in the morning and at approximately the same time of day.

2633 Vamorolone or matching placebo suspension will be administered orally using a

volumetric syringe supplied by the site. Following administration of the dose of study

2635 drug suspension, the syringe will be filled once with water and the water will be

administered by mouth using the volumetric syringe. Prednisone or matching placebo

tablets will be taken either immediately before or immediately after the dose of

suspension. The subject will then drink approximately 50 mL (approximately 2 ounces)

of water to ensure the full dose has been ingested. The dose of study medication should

be taken with breakfast, including at least 8 g of fat (approximately 8 ounces [240 mL] of

2641full-fat milk or equivalent high-fat food portion). There are no other food or drink2642restrictions before or after dosing.

At the Day 1, Week 2, Week 12, Week 24, Week 28, Week 30, Week 40, and Week 48 study visits, subjects will arrive at the study clinic after having fasted for ≥ 6 hours, and will eat breakfast at the study site within 30 minutes prior to administration of the dose of study medication; breakfast at the site will include at least 8 g of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).

2648 Any missed or incomplete doses of study medication should be recorded in the Subject 2649 Diary and reported immediately to the site Investigator.

- 2651 5.4 **Rationale for Dose Selection** 2652 Dose levels of the investigational medication were chosen for this study to ensure the 2653 2654 safety of subjects participating in the study, and to allow demonstration of efficacy and PD effects. The prednisone (active control) dose was selected based on current standard 2655 of care practice in boys with DMD. 2656 All doses of study medication will be administered in the morning with breakfast, 2657 including at least 8 g of fat (approximately 8 ounces [240 mL] of full-fat milk or 2658 equivalent high-fat food portion). 2659 Based on the comparison between the PK parameters in DMD boys receiving 0.25 mg/kg 2660 2661 or 0.75 mg/kg vamorolone with a glass of full-fat milk or equivalent fat-containing food and the PK parameters in healthy adult males receiving similar doses of vamorolone 2662 fasted, it appears that the 2.5-fold increase in exposure observed between the fasted and 2663 fed conditions in the healthy adult males (Section 1.3.1) is not reproduced in the DMD 2664 boys (see Section 1.3.2). The rationale for the lowest vamorolone dose of 2.0 mg/kg/day, 2665 administered with a glass of full-fat milk or equivalent fat-containing food is as follows: 2666 A starting dose of 2.0 mg/kg/day with a glass of milk is approximately 10% of the 2667 highest safe dose tested in adults (20.0 mg/kg/day fasted). 2668 2669 The highest vamorolone dose to be administered, 6.0 mg/kg/day, will similarly be administered with a glass of full-fat milk or equivalent fat-containing food. As 2670 2671 20.0 mg/kg/day fasted in adult volunteers was shown to be safe in the Phase I adult volunteer study, the proposed highest dose in 4 to 7 year-old children is approximately 2672 2673 30% of the highest safe adult dose. Based on the Phase I PD biomarker safety data 2674 presented in Section 1.3, safety signals reflective of insulin resistance are not anticipated at either of the planned dose levels. Also based on the Phase I data, vamorolone showed 2675 little evidence of either acute (24-hour data) or chronic (Day 15 data) suppression of the 2676 adrenal axis at doses of either 1.0 mg/kg/day or 3.0 mg/kg/day. The data suggest that 2677 vamorolone induces variable, mild, acute and chronic suppression of the adrenal axis at 2678 9.0 mg/kg/day, and stronger evidence of both acute and chronic adrenal axis suppression 2679
- 2680 at 20.0 mg/kg/day.
Vamorolone at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 2682 6.0 mg/kg/day has been demonstrated to be safe and well-tolerated in a 2-week Phase IIa 2683 study (VBP15-002) in 4 to <7 years DMD boys. There has been a total of 11 SAEs in the 2684 2685 vamorolone program to date: a total of 4 SAEs in the VBP15-003 study, a total of 3 SAEs in the VBP15-LTE study, a total of 3 SAEs in the VBP15-004 study, and 1 SAE in the 2686 VBP15-EAP program. There have been two SAEs of pneumonia in two different 2687 subjects (both subjects receiving vamorolone 0.75 mg/kg/day); one SAE of bilateral 2688 2689 testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day; 2690 one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day; two SAEs of acute myoglobulinemia in the same subject receiving 6.0 mg/kg/day; one SAE 2691 of viral gastroenteritis with secondary dehydration in a subject receiving blinded study 2692 2693 drug; one SAE of asthma exacerbation in the setting of respiratory syncytial virus and 2694 bronchiolitis in a subject receiving vamorolone at either 2.0 mg/kg/day or 6.0 mg/kg/day; one SAE of perforated appendicitis occurring with 30 days after the subject completed 2695 2696 the VBP15-004 study, and one SAE of viral gastroenteritis requiring hospitalization for hydration. Each of these SAEs was considered unrelated to study drug, and none of them 2697 2698 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 2699 2700 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 2701 2702 (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 2703 (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 µg/dL [100 nM]) consistent with 2704 chronic adrenal suppression.²⁹ Thus, based on the available data in the Phase I and Phase 2705 II studies regarding the safety signal of suppression of the adrenal axis, the possibility of 2706 adrenal suppression is present in subjects at the 2.0 and 6.0 mg/kg/day dose levels. 2707 The dose of prednisone has been selected according to the Care Recommendation for 2708 DMD (daily prednisone 0.75 mg/kg/day). The weight-dose bands (Table 10) have been 2709 selected to ensure that subjects will not be overdosed in view of the potential side effects. 2710

2712 **5.5 Treatment Compliance**

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2713 Subject compliance with the dosing schedule will be assessed by site maintenance of 2714 accurate study drug dispensing and return records, and accurate recording of incomplete 2715 or missed doses by completion of a diary by the subject's parent or guardian. The 2716 2717 Investigator is responsible for ensuring that dosing is administered in compliance with the 2718 protocol. The Investigator or designee will instruct the subject's parent or guardian with 2719 regard to proper dosing of study medication and completion of subject diaries, and will 2720 reinforce the importance of taking all study medication per protocol instructions. Doses 2721 of study drug on the days of the Day 1, Week 2, Week 12, and Week 24 Visits 2722 (Treatment Period #1), Week 28 (Transition Period), and Week 30, Week 40, and 2723 Week 48 (Treatment Period #2) will be administered at the participating study site by a 2724 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 2725 2726 unused study medication remaining in each bottle returned, as well as the number of unused tablets, will be documented in the source documents and on the appropriate eCRF 2727 2728 page.

2729 **5.6 Study Drug Dose Interruption or Discontinuation**

2731 Subjects whose study medication is interrupted should continue to follow the original 2732 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 2733 2734 visit-specific assessments. If the study medication is interrupted during the scheduled 2735 Week 24 F/U or Week 48 F/U Visit, the scheduled ACTH Stimulation Test should be 2736 performed, but the site should contact the Study Chair or Medical Monitor prior to the Week 24 or Week 48 Visit to discuss whether the dose of hydrocortisone scheduled for 2737 2738 one day prior to the ACTH Stimulation Test should be given.

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 the Independent Medical Monitor within 24 hours and study drug discontinuation should be considered. In view of the potential effect of the study drugs

2744	on adrenal glands, the study drugs cannot be discontinued suddenly. In case study drug
2745	needs to be discontinued, for whatever reason, the dose tapering process described for the
2746	end of the treatment period should be followed. If a subject discontinues study drug due
2747	to intolerability, the subject will be withdrawn from the study. Study drug
2748	discontinuation due to intolerability will not usually require unblinding (see Section 3.4).
2749	The subject should return to the study site for completion of Week 24 assessments and
2750	the Week 24 Follow-up Visit ACTH Stimulation Test at the time of early withdrawal (if
2751	withdrawal is prior to the Week 24 Visit), or Week 48 assessments and the Week 48
2752	Follow-up Visit ACTH Stimulation Test (if withdrawal is after Week 24 and prior to the
2753	Week 48 Visit), prior to participation in the Dose-tapering Period. Any AE still ongoing
2754	at the time of study drug discontinuation will be monitored until it has returned to
2755	baseline status, stabilized, or the Investigator, Study Chair, Medical Monitor and Sponsor
2756	agree that follow-up is no longer needed.

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5.7 Prior and Concomitant Medications and Therapies

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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.

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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 7.4.6).

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 2777 change in dosage/regimen) during the study must be documented in the same manner. 2778 Details of any non-pharmacological therapies (e.g., devices, procedures), including name, 2779 2780 reason for therapy (i.e., DMD or non-DMD), and dates of therapy will also be recorded. 2781 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. 2782 5.7.3 Prohibited Therapies 2783 2784 Subjects must discontinue use of the following medications prior to participation in the 2785 study, as indicated, and refrain from using these medications throughout the duration of 2786 2787 the study: Mineralocorticoid receptor agents, such as spironolactone, eplerenone, canrenone 2788 ٠ (canrenoate potassium), prorenone (prorenoate potassium), mexrenone 2789 2790 (mexrenoate potassium): use must be discontinued at least 4 weeks prior to the 2791 first dose of study medication; Oral glucocorticoids or other immunosuppressive agents. Subjects who have 2792 2793 received prior treatment with immunosuppressive agents are ineligible for study entry. [Notes: Inhaled and/or topical glucocorticoids are permitted but must be 2794 2795 administered at stable dose beginning at least 4 weeks prior to first dose of study 2796 medication, and are anticipated to be used at the stable dose regimen for the 2797 duration of the study; past transient use of oral or inhaled glucocorticoids or other 2798 oral immunosuppressive agents for no longer than 1 month cumulative, with last 2799 use at least 3 months (or last use at least one month prior for inhaled 2800 glucocorticoids) prior to first dose of study medication, will be considered for eligibility on a case-by-case basis.] 2801 Idebenone: use must be discontinued at least 4 weeks prior to the first dose of 2802 study medication 2803 Live attenuated vaccines: use must be avoided within 14 days prior to first dose of 2804 • study medication and for the duration of participation in the study 2805

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2807	• Any investigational medications other than vamorolone: use must be discontinued
2808	at least 3 months prior to the first dose of study medication
2809	• Other medications indicated for the treatment of DMD, including Exondys 51 and
2810	Translarna: use must be discontinued at least 3 months prior to the first dose of
2811	study medication.
2812	• Any approved medications or herbal remedies which can impact strength and
2813	function (including, but not limited to, Co-enzyme Q10, creatine): use must be
2814	discontinued at least 4 weeks prior to the first dose of study medication.
2815	In addition, vamorolone should be used with caution with any drug metabolized by
2816	cytochrome P450 3A4 (CYP3A4).
2817	The Investigator should contact the Study Chair and Medical Monitor concerning
2818	individual medications or therapies not listed that may be of concern.
2819	5.7.4 Permitted Therapies
2820 2821	Every effort should be made NOT to start any prescription or OTC medications during
2822	the study. Concomitant medications should be maintained on the same dose and regimen
2823	throughout the study whenever possible. However, all other medications other than those
2824	specifically prohibited above may be taken during the study, if clinically indicated,
2825	provided they are recorded in the source documents and in the eCRF.
2826 2827	5.7.5 Hydrocortisone
2828	All subjects will be given a single dose of hydrocortisone (5 mg or 10 mg) 24 hours after
2829	the final dose of Treatment Period #1 study medication at the Week 24 Visit, and
2830	24 hours after the final dose of Treatment Period #2 study medication at the Week 48
2831	Visit. The hydrocortisone dose will be approximately 8 mg/m^2 , rounded up to either 5
2832	mg or 10 mg; subjects will be provided with either a single 5 mg or 10 mg hydrocortisone
2833	tablet which will be dispensed by the site staff at the Week 24 and Week 48 Visits.
2834	In addition, all subjects should be covered with "stress dosing" of hydrocortisone (or
2835	prednisone) during times of illness, injury, or surgery (see Section 7.2.7).

Vitamin D

5.7.6

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2838 Serum Vitamin D levels will be measured at Screening and at the Weeks 12, 24, 40, and 2839 48 Visits. Vitamin D insufficiency and deficiency (serum 25[OH] D concentration less 2840 than 20 ng/mL or less than 50 nmol/L) will be treated with high doses of Vitamin D 2841 supplement according to local site guidelines. Vitamin D supplements will be recorded 2842 2843 in the source document and in the eCRF. 2844 5.8 **Study Medication Management** 2845 Packaging and Labeling of Study Medication 2846 5.8.1 2847 When all entry criteria are met, and at least 10 days prior to the Baseline Day -1 Visit, 2848 2849 subjects will be randomized to treatment via the IXRS system. Subject-specific suspension and tablet study drug supplies sufficient for the first six weeks of Treatment 2850 2851 Period #1 will be packaged, labeled (with MED ID number and other protocol-specific information) and couriered to the pharmacy at the recruiting site prior to the Baseline 2852 2853 Visit for the subject. 2854 Investigational medication suspension and matching placebo suspension will be packaged in sterile 120 mL (4 oz) amber bottles with a 100 mL fill volume with child-resistant cap 2855 2856 with a 24 mm bottle press-in adapter. Bottles are filled with 110 mL of suspension in 2857 order to guarantee a delivery of 100 mL. 2858 Bottles of investigational medication suspension will contain either 1.33 grams of vamorolone/100 mL (1.33% orange-flavored suspension) or 4.0 grams of 2859 vamorolone/100 mL (4.0% orange-flavored suspension). The matching placebo 2860 suspension will be identical in appearance and taste to the vamorolone suspensions. The 2861 volume per dose to be administered to each subject depends on the subject's weight (in 2862 kg) recorded at the visit prior to each study drug dispensing visit. Each subject will 2863 receive a volume of 0.15 mL/kg of a vamorolone suspension or matching placebo 2864 suspension (Table 7). Instructions for the calculation of each dose of liquid formulation 2865

2866 are given in the Pharmacy Manual.

2867 Prednisone 5 mg tablets and matching placebo will be dispensed in blister packs, each 2868 containing 15 tablets. The number of tablets to be administered per dose to each subject 2869 2870 depends on the subject body weight calculated at the visit prior to each study drug 2871 dispensing visit (Table 10). 2872 Drug supplies will be labeled with the Sponsor name, protocol number, lot number, 2873 expiration or retest date, and other appropriate study information. Carton, bottle, and 2874 blister pack labels will be written in accordance with all applicable laws, guidance and directives of the jurisdiction where the study is being conducted. 2875 2876 Trained site staff will write the dose in mL (suspension) and number of tablets (tablets) on the bottle and blister pack labels, respectively, prior to bottle and blister pack 2877 2878 dispensing to subjects. 2879 At the Screening Visit, a test packet containing placebo tablets will be provided by the 2880 site investigator to confirm the subject's ability to swallow tablets. The test of 2881 swallowing ability will take place at the Screening Visit. At the beginning of the trial, the 2882 clinical trials supply company will provide each site with sufficient test packets for their anticipated recruitment numbers. These test packets will be stored in a locked cupboard, 2883 2884 at ambient room temperature. Study medication will be dispensed to the subject's parent or legal guardian for 2885 Treatment Period #1 dosing at the Day 1 Visit and at the Week 6, Week 12 and Week 18 2886 Visits. At the Week 24 Follow-up Visit, a 4-week supply of study medication for the 2887 2888 Week 25 to Week 28 Transition Period will be dispensed. Study medication will be 2889 dispensed to the subject's parent or legal guardian for Treatment Period #2 dosing at the 2890 Week 28, Week 34, and Week 40 Visits. At the Week 48 Follow-up Visit, study 2891 medication for the Dose-tapering Period will be dispensed. Dispensed bottles and unused 2892 tablets of study medication will be returned at each subsequent study visit, prior to 2893 dispensing bottle(s)/blister pack(s) for the next dispensing interval (see Section 5.3). 2894 Each study medication bottle and blister pack may be used for a single subject only.

Clinical supplies dispensed by the study site staff and ready for administration to subjects will be labeled with the dispense date, protocol number, MED ID number, and volume (suspension) or number of tablets to be administered per dose.

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5.8.2 Storage of Study Medication

2901All Clinical Trial Materials (CTM) for use in the trial must be stored in a locked2902container/cabinet free from environmental extremes, under the responsibility of the2903institutional pharmacist or Principal Investigator. Study medication suspensions should2904be stored at refrigerated temperature $(2^{\circ}C - 8^{\circ}C; 36^{\circ}F - 46^{\circ}F)$. Excursions to ambient2905temperature are allowed (see Pharmacy Manual for details). Study medication tablets2906will be stored in a locked cupboard, at ambient room temperature.

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

2909 5.8.3 Study Medication Shipping and Handling

2911 Clinical trial material will be shipped to the study sites only after receipt of required
2912 documents in accordance with applicable regulatory requirements and Sponsor
2913 procedures.

When all entry criteria are met, at least 10 days prior to the Baseline Visit, subjects will 2914 2915 be randomized to treatment via the IXRS system. Subject-specific suspension and tablet 2916 drug supplies will be packaged, labeled (with MED ID number and other protocol-specific information) and couriered to the pharmacy at the study site prior to the 2917 Baseline Visit for the subject. At the Day 1 Visit, the trained site staff will record the 2918 volume in mL per suspension dose (bottles) and number of tablets per dose (blister packs) 2919 on the bottle and blister pack labels, respectively. Labeled study drug supplies sufficient 2920 to last until the Week 6 Visit will be dispensed to each subject. The first dose of study 2921 medication will be administered in clinic on Study Day 1. The initial drug supply will be 2922 2923 sufficient to allow for the Week 6 Visit to occur on the latest date permissible within the protocol-specified visit window (6 weeks \pm 3 days). No additional study drug supplies 2924 2925 will be dispensed at the Week 2 Visit.

- Prior to the subsequent study drug dispensing visits (i.e., Week 6, Week 12, Week 18, 2927 Week 24 Follow-up, Week 28, Week 34, Week 40, Week 48 Follow-up), additional study 2928 2929 drug supplies will be ordered using the IXRS system. Study drug dispensed at the 2930 Week 28, Week 34, Week 40, and Week 48 Follow-up Visits for dosing during 2931 Treatment Period #2 and the Dose-tapering Period will consist of liquid suspension only (no tablets). The new subject-specific drug supply will be packaged, labeled (as 2932 described above) and couriered to the site. Study drug will be ordered at least 10 days 2933 2934 prior to the next scheduled study drug dispensing visit to allow time for the new supplies 2935 to be shipped to the site in time for the next scheduled dispensing visit. 2936 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).
- 2942 Clinical trial material must be dispensed and administered according to the procedures 2943 described in this protocol. Only subjects randomized in the study may receive study 2944 medication, in accordance with all applicable regulatory requirements. Only authorized 2945 study personnel may supply CTM. Authorized study personnel refers to the Investigator 2946 (or designee) and hospital pharmacists, in accordance with all applicable regulatory 2947 requirements and the Site Signature Log/Delegation of Authority. Only authorized study 2948 personnel or the subject's parent or legal guardian may administer CTM.
- 2949 2950

5.8.4 Study Medication Accountability

- 2951The Investigator is responsible for the control of drugs under investigation. Adequate2952records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing2953Log) of the study drug must be maintained. The Drug Dispensing Log must be kept2954current and should contain the following information:
- 2955
- 2956 2957
- The Subject ID number of the subject to whom the study drug was dispensed
 - The MED ID number of the dispensed kit

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- The date(s) and quantity of the study drug dispensed to the subject
- The date(s) and quantity of the study drug returned by the subject.

2962 2963 All records and drug supplies must be available for inspection by the Study Monitor at every monitoring visit. Unused medication will be returned to ReveraGen Inc. or its 2964 2965 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 ReveraGen or its designee. The 2966 2967 completed Drug Dispensing Log and Drug Return Record(s) will be returned to ReveraGen Inc or its designee. The Investigator's copy of the Drug Return Record(s) 2968 2969 must accurately document the return of all study drug supplies to ReveraGen Inc. or its designee. 2970

2971 **5.9 Procedures for Assigning Subject Study Numbers**

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

2980 **6**

STUDY SCHEDULE

2981 2982

6.1 Time and Events Schedule

2983298429852985study periods:

Pretreatment Screening Period: The up to 32-day interval, from subject's parent or guardian signing of the Informed Consent/HIPAA authorization until completion of all designated screening procedures, 24 hours prior to the first dose of study medication. All screening procedures must be completed by Day -11.
 Subjects meeting all eligibility criteria will be randomized by Day -11, at least 10 days prior to the Baseline Day -1 Visit.

2992	
2993	• Pretreatment Baseline Period: The 24-hour period immediately prior to
2994	administration of the first dose of study medication (Baseline Day -1).
2995	• Treatment Period #1: The 24-week interval starting with administration of the
2996	first dose of study medication on Study Day 1 and continuing through the time of
2997	the Week 24 Follow-up Visit. Treatment Period #1 includes administration of the
2998	final dose of Treatment Period #1 study medication at the Week 24 Visit, and
2999	ACTH Stimulation testing at the Week 24 Follow-up Visit, 48 ± 3 hours after the
3000	final dose of Treatment Period #1 study medication.
3001	• Transition Period: The 4-week interval following the end of the 24-week
3002	Treatment Period #1 during which subjects will continue on their suspension
3003	study medication at the same dose they received during the Treatment Period #1
3004	and have their tablet study medication dose tapered to zero (0) tablets/day (see
3005	Section 6.3.5). Once subjects have completed all study assessments for the
3006	Transition Period, they will enter Treatment Period #2.
3007	• Treatment Period #2: The 20-week interval starting with administration of the
3008	first dose of Treatment Period #2 study medication on the day after the Week 28
3009	Visit (Week 28 + 1 day) and continuing through the time of the Week 48
3010	Follow-up Visit. Treatment Period #2 includes administration of the final dose of
3011	Treatment Period #2 study medication at the Week 48 Visit, and ACTH
3012	Stimulation testing at the Week 48 Follow-up Visit, 48 ± 3 hours after the final
3013	dose of Treatment Period #2 study medication. Subjects who will not participate
3014	in the Dose-tapering Period will be discharged from the study following
3015	completion of the Week 48 assessments and the ACTH Stimulation Test at the
3016	Week 48 Follow-up Visit.
3017	• Dose-tapering Period: The 4-week interval following the end of the 20-week
3018	Treatment Period #2 during which subjects will have their suspension study
3019	medication dose tapered to 0 mg/kg/day (see Section 6.3.7). Once subjects have
3020	completed the Dose-tapering Period, they will be discharged from the study
3021	following completion of all final Dose-tapering Period assessments.

3022	
3023	The procedures to be completed at each visit during each study period are presented in
3024	the Schedule of Study Activities in Table 11 and in the sections that follow. (Note: In
3025	Table 11, each visit with the acceptable time window around the planned visit date,
3026	where applicable, is provided.) Detailed descriptions of the assessments and the
3027	definitions of study endpoints are provided in Section 7 and Section 2, respectively. Any
3028	deviation from study procedures should be noted in the source documents and in the
3029	Clinical Trial Management Software (CTMS), and significant deviations should be
3030	reported immediately to the Sponsor.
3031	Overall, up to approximately 57 weeks are allocated for each subject to complete the
3032	study, including a 32-day Pretreatment Screening Period, a one-day Pretreatment
3033	Baseline Period, a 24-week Treatment Period #1, a 4-week Transition Period, a 20-week
3034	Treatment Period #2, plus a 4-week Dose-Tapering Period, as applicable. Upon the
3035	completion of the study, subjects may have the option to enroll in an additional
3036	vamorolone study or general access program.
3037	Subjects electing to enroll directly into an additional vamorolone study or general access
3038	program to continue vamorolone therapy will be discharged from the VBP15-004 study
3039	following completion of all final Week 48 assessments and ACTH Stimulation testing at
3040	the Week 48 Follow-up Visit, and will be enrolled in the additional vamorolone study or
3041	general access program (separate written protocol and ICF).
3042	Subjects completing the VBP15-004 study and enrolling directly into the additional
3043	vamorolone study or general access program to continue vamorolone treatment do not
3044	need to dose taper in VBP15-004.

Table 11Schedule of Study Activities

	Pretreatment Period				Treat	nent Pe	riod #1			Tran	sition	Treatment Period #2						Dose-tapering		
	SCR	BL								re	rioa							re	rioa	
		Day									W	eek								
Study Day or Week/Visit	-33 to -2 ^a	-1 ^b	1°	$\begin{array}{c} 2 \\ (\pm 1d)^d \end{array}$	$6 (\pm 3d)^d$	$\frac{12}{(\pm 1w)^d}$	18 (±1w) ^d	$\frac{24^{\rm e}}{(\pm 1{\rm w})^{\rm d}}$	24 (F/U) ^e	26	$\begin{array}{c} 28^{\rm f} \\ (\pm 1 d)^{\rm d} \end{array}$	28+1d	$30 \\ (\pm 1d)^d$	34 (±3d) ^d	$\begin{array}{c} 40 \\ (\pm 1 \mathrm{w})^{\mathrm{d}} \end{array}$	$\frac{48^{\text{g}}}{(\pm 1 \text{w})^{\text{d}}}$	48 F/U ^g	50	$52^{h} (\pm 1d)^{d}$	
Informed consent	Х																			
Enrollment ¹	Х																			
Inclusion/exclusion criteria	Х	Xj																		
Randomization ^k	Х																			
Demographics	Х																			
Medical history	Х																			
Medication history	Х	Х																		
Physical examination	Х	Х			Х	Х	Х	Х			Х			Х	Х	Х			Х	
Cushingoid features		Х			Х	Х	Х	Х			Х			Х	Х	Х			Х	
Height	Х					Х		Х						Х		Х				
Weight	Х	Х		Х	Х	Х	X^{l}	Х			Х		Х	Х	Xl	Х			Х	
Vital signs ^m	Х	Х	X ⁿ	Х	Х	Х	Х	Х			Х		Х	Х	Х	Х			Х	
Blood for clinical labs ^o	Х		Xp	Xp	Х	Xp	Х	Xp			Xp		Xp	Х	Xp	Xp			Xp	
Blood for HbA1c ^o	Х							Х								Х				
Blood for vitamin D ^o	Х					Х		Х							Х	Х				
Confirmation of varicella immunity	Х																			
Urinalysis ^q	Х		Xp	Xp	Х	Xp	Х	Xp			Xp		Xp	Х	Xp	Xp			Xp	
Blood for serum PD biomarker panel ^{r,s}			Х			Х		Х			X				Х	Х			X	
Fasting blood for insulin, glucose ^s			Х			Х		Х			Х				Х	Х			X	
Blood for DNA Testing								Х												
ACTH Stimulation Test	Х								Xt								Xt			
Blood for Plasma PK													Xu							
12-lead ECG ^v	Х					Х		Х							Х	Х				
2D-echocardiogram	Х							Х								X				

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5	0
5	1
5	2

	Pretreatment Period			Treatment Period #1							sition	Treatment Period #2							Dose-tapering		
	SCR	BL								Pe	rioa							Pe	rioa		
		Day		Week																	
Study Day or Week/Visit	-33 to -2 ^a	-1 ^b	1°	$\frac{2}{(\pm 1d)^d}$	$\begin{array}{c} 6 \\ (\pm 3d)^d \end{array}$	$12 (\pm 1w)^d$	$\frac{18}{(\pm 1w)^d}$	$\begin{array}{c} 24^{\rm e} \\ (\pm 1 {\rm w})^{\rm d} \end{array}$	24 (F/U) ^e	26	$\begin{array}{c} 28^{\rm f} \\ (\pm 1d)^{\rm d} \end{array}$	28+1d	30 (±1d) ^d	34 (±3d) ^d	$\frac{40}{(\pm 1w)^d}$	$\frac{48^{\rm g}}{(\pm 1{\rm w})^{\rm d}}$	48 F/U ^g	50	$52^{h} (\pm 1d)^{d}$		
Eye examination	Х							X								Х					
DXA scan	Х							X								X					
Spine X-ray	Х							X													
Fracture Questionnaire	Х							X								Х					
Dispense study medication			Х		Х	X	Х		Х		Х			Х	Х		Х				
Return study medication/ compliance monitoring				Xw	X	Х	х	Х			Х		Xw	Х	Х	Х			Х		
Study medication dosing ^x			Х -					► X				X –				→X					
Study medication dose tapering									Xy -		►X						х -		►X		
Telephone call to subject ^z										Х								Х			
Time to Stand Test (TTSTAND)	Х	Х			X	X		X						Х	Х	X					
Time to Climb Test (TTCLIMB)	Х	Х				X		X							Х	X					
Time to Run/Walk Test (TTRW)	Х	Х				Х		Х							X	X					
NSAA ^{aa}	Х	Х				X		X							Х	Х					
Myometry (elbow flexors, knee extensors)	Х	Х				Х		Х							Х	X					
Six-minute Walk Test (6MWT)	Х	Х				Х		Х							Х	X					
Range of Motion (ROM) - ankles	Х	Х				Х		Х							Х	X					
Pediatric Outcomes Data Collection Instrument (PODCI)	X							Х								X					
Treatment Satisfaction Questionnaire (TSQM)								X								Х					

	Pretreatment Period SCR BL			Treatment Period #1						Tran Pe	isition riod	Treatment Period #2				#2		Dose-tapering Period	
		Day			Week														
Study Day or Week/Visit	-33 to -2 ^a	-1 ^b	1°	$\begin{array}{c} 2\\ (\pm 1d)^d \end{array}$	6 (±3d) ^d	$\frac{12}{(\pm 1w)^d}$	18 (±1w) ^d	$\begin{array}{c} 24^{\rm e} \\ (\pm 1 {\rm w})^{\rm d} \end{array}$	24 (F/U) ^e	26	$\begin{array}{c} 28^{\rm f} \\ (\pm 1d)^{\rm d} \end{array}$	28+1d	30 (±1d) ^d	34 (±3d) ^d	40 (±1w) ^d	$48^{\rm g} \\ (\pm 1 {\rm w})^{\rm d}$	48 F/U ^g	50	$52^{h} (\pm 1d)^{d}$
PARS III	Х					Х		Х								Х		1	
Ease of Study Medication Administration Assessment ^{bb}				X		Х		Х					Х		X	Х			
Blindedness Assessment								Х										ł	
Dispense subject diaries ^{cc}			Х	Х	Х	Х	Х	Х			Х		Х	Х	Х	Х		1	
Return subject diaries				Х	Х	Х	Х	Х	X ^{dd}		Х		Х	Х	Х	Х	Xee		Х
AE/SAE recording ^{ff}	X -																		► X ^{gg}
Concomitant medications			Х																► X
Discharge from study																	X ^{hh}		X ⁱⁱ

56 BL = Baseline; d = day(s); F/U = Follow-up; SCR = Screening; w = week.

- The Pretreatment Screening Period spans Day -33 through Day -2, but all screening procedures must be completed by Day -11. Subjects meeting all eligibility criteria will be randomized by Day -11, at least 10 days prior to the Baseline Day -1 Visit.
- b. Baseline Day -1, within 24 hours prior to administration of the first dose of study drug.
- 60 c. Treatment Day 1 begins at the time of administration of the first dose of study medication in the clinic.
- d. Time windows around the Week 2, Week 6, Week 12, Week 18, and Week 24 Visits are allowances from date of Day 1 Visit. Time window around the Week 28 Visit is allowance from date of Week 24 F/U Visit. Time windows around the Week 30, Week 34, Week 40, and Week 48 Visits are allowances from date of Week 28+1d Visit. Time window around the Week 52 Visit is allowance from date of Week 48 F/U Visit.
- 64 e. Subjects who prematurely discontinue from the study prior to Week 24 should complete the Week 24 assessments and the Week 24 Follow-up Visit ACTH Stimulation Test at the time of
 65 early withdrawal and undergo Early Discontinuation Dose-tapering, where possible (see Section 6.4.1 and Section 7.2.7). The Week 24 Follow-up Visit must occur to allow the ACTH
 66 Stimulation Test to be performed 48 ± 3 hours after the final dose of Treatment Period #1 study medication.
- f. Subjects who prematurely discontinue from the study after Week 24 but prior to Week 28 should complete the Week 28 assessments, and undergo Early Discontinuation Dose-tapering, where possible (see Section 6.4.2).
- g. Subjects who prematurely discontinue from the study after Week 28 but prior to Week 48 should complete the Week 48 assessments and the Week 48 Follow-up Visit ACTH Stimulation Test at the time of early withdrawal and undergo Dose-tapering, where possible (see Section 6.4.3 and Section 7.2.7). The Week 48 Follow-up Visit must occur to allow the ACTH Stimulation Test to be performed 48 ± 3 hours after the final dose of Treatment Period #2 study medication.
- h. Subjects will have one study site visit during the Dose-tapering Period, at one week after the dose of liquid formulation has been discontinued (Week 52) (see Section 6.3.7).
- i. Subjects are considered to be enrolled in the study at the time written informed consent is obtained.

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- j. Study eligibility should be rechecked and confirmed at Baseline Day -1 Visit.
- k. Randomization occurs by Interactive Voice/Web Response System (IXRS) after subjects are confirmed to have met all study entry criteria, at least 10 days prior to the Baseline Day -1 Visit.
- 1. Weight recorded at the Week 18 Visit and the Week 40 Visit will be used to calculate doses for study drug dispensed at the Week 24 Follow-up and Week 48 Follow-up Visits, respectively.
- 80 m. Sitting blood pressure, body temperature, respiratory rate, and heart rate.
- 81 n. Vital signs recorded prior to administration of the first dose of study drug at the Day 1 Visit.
- 82 o. Blood for hematology, chemistry, and lipids, including HbA1c and Vitamin D where applicable.
- 83 p. Blood samples (collected after subjects have fasted for ≥ 6 hours) and urine collected at scheduled visit, and prior to dose of study drug where applicable.
- q. Urinalysis by dipstick and microscopic analysis.
- r. Blood collected for PD biomarkers includes secondary safety outcomes (morning cortisol, osteocalcin, CTX1, P1NP), and exploratory safety and efficacy PD biomarkers.
- $\frac{86}{87}$ s. Blood samples for PD biomarkers and fasting glucose and insulin determination will be collected after subjects have fasted for ≥ 6 hours, prior to the daily dose of study medication where applicable.
- t. Subjects will return to the study site for the Week 24 Follow-up Visit for an ACTH Stimulation Test 48 hours ± 3 hours after administration of the final dose of Treatment Period #1 study medication, and for the Week 48 Follow-up Visit for an ACTH Stimulation Test 48 hours ± 3 hours after administration of the final dose of Treatment Period #2 study medication (see Section 7.2.7).
- 91 u. Blood sample for population PK analysis will be collected 2 hours after administration of the daily dose of study medication.
- 92 v. 12-lead ECG recorded after subject has rested quietly in a supine position for at least 5 minutes.
- 93 w. Study medication brought by subjects to the Week 2 Visit and Week 30 Visit for dosing and compliance assessment will be redispensed to subjects at the end of the visit.
- x. The dose of study medication on the days of the Day 1, Week 2, Week 12, Week 24, Week 28, Week 30, Week 40, and Week 48 Visits will be administered after 1) fasting blood draws; and 2) breakfast provided by the study site. All other doses will be taken at home. See Section 6.3.3 for other Day 1 pre-dose safety assessments.
- 96 y. Doses of tablet study drug will be tapered and suspension study drug will be continued, during Weeks 24-28.
- Site study staff will contact the parent(s)/guardian(s) by telephone at Weeks 26 and 50 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.
- aa. North Star Ambulatory Assessment; includes the Time to Stand Test (TTSTAND).
- bb. Ease of Study Medication Administration assessed at the Weeks 2, 12, and 24, 30, 40, and 48 Visits.
- 01 cc. 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.
- dd. Subject diaries dispensed at the Week 24 Visit will be returned and redispensed at the Week 24 F/U Visit; final return will occur at the Week 28 Visit.
- ee. Subject diaries dispensed at the Week 48 Visit will be returned at the Week 48 F/U Visit, and will be redispensed to subjects participating in the Dose-tapering Period for final return at the Week 52 Visit.
- 05ff. 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 52 Visit or the subject's participation in the
study is completed (SAEs through 30 days after final study drug dose). Ongoing AEs will be followed to resolution, stabilization, or until such time the Investigator agrees follow-up is not
necessary.
- gg. For subjects who do not continue to receive vamorolone through an additional vamorolone study or general access program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in VBP15-004 Dose-tapering Period to confirm the final SAE status of the subject.

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hh. Subjects who elect to continue vamorolone therapy by enrolling directly into an additional vamorolone study or general access program may be discharged from the study following completion of all final Week 48 assessments, including the Week 48 Follow-up Visit ACTH Stimulation Test.

ii. Subjects who participate in the Dose-tapering Period may be discharged from the study following completion of all final Dose-Tapering Visit assessments (Week 52) (see Section 6.3.7).

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- 6.2 Informed Consent and Assent Procedures
- 3119 Subjects are considered to be enrolled in the study at the time written informed consent is 3120 obtained.

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

- 3125 The parent(s) or guardian(s) of subjects who choose to enroll in this study will give
- 3126 written informed consent at the Screening Visit, Day -33 to Day -11. The Investigator (or
- 3127 designated staff) will obtain the written informed consent from the subject's parent(s) or
- 3128 guardian(s) prior to any study-specific procedures. Each subject's parent(s) or
- 3129 guardian(s) will receive an explanation of the nature and purposes of the study from the
- 3130 Investigator or designee. Time will be given to the parent(s)/guardian(s) to ask questions
- and make their decision on whether they would like for their child to participate. The
 Investigator or designee will ensure the study is appropriate for the subject. Reasons for
- anvestigator of designee will ensure the study is appropriate for the subject. Reasons for
 anvestigator of designee will ensure the study is appropriate for the subject. Reasons for
 anvestigator of designee will ensure the study is appropriate for the subject. Reasons for
 anvestigator of designee will ensure the study is appropriate for the subject. Reasons for
 anvestigator of designee will ensure the study is appropriate for the subject. Reasons for
 anvestigator of 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
- 3136 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
- 3138 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
- 3140 parents or guardians will sign the ICF in jurisdictions where this is required.
- 3141 If applicable, the assent of the child himself will also be obtained, if possible in writing 3142 per individual where a child is intellectually capable of assenting (and in accordance with 3143 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 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 3148 Consent Forms must be dated and signed by the Investigator or designee and the subject's 3149 3150 legal representative(s) and the original signed consent form must be kept by the 3151 Investigator in the study subject's file. "Legal representative" means an individual whom a judicial or other body authorized under applicable law to consent on behalf of a 3152 prospective study subject to the subject's participation in the procedure(s) involved in the 3153 research. The Study Monitor will ensure that the ICF has been signed by the subject's 3154 3155 legal representative(s). The study subject's legal representative(s) will receive a copy of 3156 the signed consent form.

3157 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.

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6.3 Visit Schedule and Procedures

3168 During the study, there will be a total of up to 16 study site visits: Pretreatment Screening 3169 3170 Visit (screening procedures can be performed on more than one day if necessary); Pretreatment Baseline Day -1 Visit; Treatment Period #1 Day 1 and Weeks 2, 6, 12, 18, 3171 3172 and 24 Visits, and Week 24 Follow-up Visit; Transition Period Week 28 Visit; Treatment Period #2 Weeks 30, 34, 40, 48 Visits, and Week 48 Follow-up Visit; and final Dose-3173 3174 tapering Period Week 52 Visit. In addition, to facilitate completion of all required 3175 Week 24 and Week 48 assessments, some of the assessments scheduled for the Week 24 3176 and Week 48 Visits may be completed on the day following the Week 24 (Week 48) dose 3177 of study medication, the day of the Week 24 (Week 48) Follow-up Visit, or in some cases up to 7 days following the date of the Week 24 (Week 48) dose of study medication, if 3178 3179 needed (see Section 6.3.4 and Section 6.3.6).

- 3180 Each subject will receive the double-blind study medication at stable daily dose for an 3181 initial period of 24 weeks (Treatment Period #1). Following completion of the 24-week 3182 Treatment Period #1, all subjects will continue to receive the suspension formulation 3183 3184 (vamorolone or matching placebo) at the same dose they received during the Treatment Period #1, while tapering the number of tablets (prednisone or matching placebo) during 3185 the 4-week double-blind Transition Period, and will return to the study site for study 3186 3187 assessments at the end of the Transition Period (Week 28), prior to receiving the first 3188 dose of study medication for Treatment Period #2 at home on Week 28 + 1 day. 3189 Each subject will receive double-blind study medication at stable daily dose for a period 3190 of 20 weeks (Treatment Period #2). Following completion of the 20-week Treatment 3191 Period #2, all subjects who will not be continuing to receive vamorolone in an additional 3192 vamorolone study or general access program (separate protocol) will taper their liquid formulation study medication during the 4-week double-blind Dose-Tapering Period, and 3193 3194 will return to the study site for study assessments at the end of the Dose-Tapering Period 3195 (Week 52). See Section 7 for a detailed description of the safety, clinical efficacy, PD, 3196 and PK assessments to be performed in this study.
- 3197 3198

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.

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 study 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 study number. The site Investigator will keep a record relating the names of the subjects to their subject study

3211	
3212	numbers (subject identification log) to permit efficient verification of data subject files,
3213	when required. This record will also include the dates of subject enrollment and
3214	completion/termination. The Coordinating Center will not collect names or other
3215	identifiers except dates (diagnosis, study visits), date of birth, and the subject study
3216	number.
3217	Subjects will undergo the procedures in the bulleted list below during the Screening
3218	Period. The procedures may be completed over the course of several visits, if necessary,
3219	but all scheduled Screening procedures must be completed within the timeframe of
3220	Day -33 to Day -11, and the actual date each procedure is performed must be recorded in
3221	the source document and eCRF. Any parameter/test may be repeated at the Investigator's
3222	discretion during Pretreatment Screening to determine reproducibility. In addition,
3223	subjects may be rescreened if ineligible due to a transient condition which would prevent
3224	the subject from participating, such as an upper respiratory tract infection.
3225	Subjects meeting all Screening eligibility tests will be randomized to treatment during the
3226	Screening Period.
3227	• Review of the Inclusion and Exclusion Criteria (see Sections 4.2 and 4.3)
3228	• Recording of the medical history, including any toxicities or allergy-related
3230	events to prior treatments (see Section 7.2.1)
3231	• Recording of prior medications (Medication History) (see Section 5.7.1)
3232	• Complete physical examination including weight (in kilograms) and height
3234	(in cm) (see Section 7.2.2)
3235	• Recording of vital signs (sitting blood pressure, heart rate, body temperature,
3236	respiratory rate) (see Section 7.2.3)
3237	• Collection of blood for clinical laboratory testing (hematology, clinical
3238	chemistry, lipids, HbA1c, and vitamin D) and collection of urine for urinalysis
3239	(see Section 7.2.4)
3240	• Testing for chicken pox immunity (see Section 7.2.5)

3241	
3242	• 12-lead ECG (see Section 7.2.10)
3243	
3244	 2D-echocardiogram (see Section 7.2.11)
3245	
3246	• Time to Stand Test (TTSTAND) (see Section 7.3.1)
3247	
3248	• Time to Climb Test (TTCLIMB) (see Section 7.3.2)
3249	
3250	• Time to Run/Walk Test (TTRW) (see Section 7.3.3)
3251	
3252	• North Star Ambulatory Assessment (NSAA) (see Section 7.3.4)
3253	
3254	• Six-minute Walk Test (6MIWT) (see Section 7.3.5)
3233 2256	• Hand hald myometry (alboyy flavors and know extensors) (see Section 7.3.6)
3250	• Hand-field myometry (eldow flexors and knee extensors) (see Section 7.5.0)
3258	• Range of Motion (ROM) in the ankles (see Section 7.3.7)
3259	• Range of Motion (ROM) in the ankles (see Section 7.5.7)
3260	• Eve exam (see Section 7 2 12)
3261	
3262	• DXA scan (see Section 7.2.13)
3263	
3264	• Spine X-rays (see Section 7.2.14)
3265	
3266	• ACTH Stimulation Test (see Section 7.2.7)
3267	
3268	• Pediatric Outcomes Data Collection Instrument questionnaire (PODCI) (see
3269	Section 7.4.1)
3270	
3271	• PARS III questionnaire (see Section 7.4.3)
3272	
3273	• Recording of AEs and SAEs beginning at the time written informed consent is
2274	abtained (see Section 7.5)
3274	obtained (see Section 7.5)
3275	• Randomization (see Section 3.2)
2076	
5270 2077	622 Papeling Pariod (Day 1) Visit
3278	0.3.2 Baseune Ferioa (Day -1) visu
3278	Subjects who have met all study eligibility criteria and been randomized to treatment via
5217	Subjects who have met an study englotinty enterna and been randomized to treatment via
3280	IXRS during the Screening Period, and for whom subject-specific blinded study
3281	medication has been shipped to and received by the study site will return to the study site
3282	during the Pretreatment Baseline Period (Day -1, the 24-hour interval immediately

3283	
3284	preceding administration of the first dose of study medication) for baseline assessments.
3285	Subjects will retain their 6-digit study identification number which was assigned during
3286	the Screening Period.
3287 3288 3289	The following procedures will be completed at the Baseline Day -1 Visit:
3290	• Physical examination including weight (in kilograms) and assessment of
3291	cushingoid features (see Section 7.2.2)
3292	• Recording of vital signs (sitting blood pressure, heart rate, body temperature,
3293	respiratory rate) (see Section 7.2.3)
3294 3295	• Time to Stand Test (TTSTAND) (see Section 7.3.1)
3296 3297	• Time to Climb Test (TTCLIMB) (see Section 7.3.2)
3298 3299	• Time to Run/Walk Test (TTRW) (see (see Section 7.3.3)
3300 3301	• North Star Ambulatory Assessment (NSAA) (see Section 7.3.4)
3302	• Six-minute Walk Test (6MWT) (see Section 7.3.5)
3304 3305	• Hand-held myometry (elbow flexors and knee extensors) (see Section 7.3.6)
3306 3307	• Range of Motion (ROM) in the ankles (see Section 7.3.7)
3308	• Recording of AEs and SAEs; review of all AEs for resolution status and date
3309	(see Section 7.5)
3310	• Recording of prior medications (Medication History) (see Section 5.7.1)
3311 3312 3313	6.3.3 Treatment Period #1 Day 1 Visit
3314	At the Treatment Period #1 Day 1 Visit, certain procedures will be performed prior to
3315	administration of the first dose of study drug and are listed in this section. Treatment
3316	Period #1 Day 1, for purposes of the study analyses, begins with administration of the
3317	first dose of study medication.
3318	Subjects will take the first dose of study medication in clinic on the day after the
3319	Pretreatment Baseline Visit. Subjects must have fasted ≥ 6 hours prior to arrival at the

3320	
3321 study site for the Day 1 Visit. Breakfast, including at least 8 g of fat (8 ounces [240 mL]
3322 of full-fat milk or equivalent high-fat food portion) will be served at t	he study site after
the blood and urine collections for clinical laboratory tests and the blo	ood draw for PD
biomarkers, including insulin and glucose, and within 30 minutes price	or to administration
3325 of the dose of study medication.	
3326 Subjects will receive a medical "alert" card stating that participation i	n the study may
3327 increase the subjects' risk of adrenal suppression. The card will inclu	de instructions for
3328 families and clinicians regarding management of possible adrenal sup	pression during
emergencies, including coverage with "stress doses" of hydrocortison	e (or prednisone)
during times of illness, injury, or surgery.	
3331 The following procedures will be completed at the Treatment Period #	#1 Day 1 Visit:
3332 Becording of vital signs (citting blood pressure heart rate boo	ly tomporatura
2224 respiratory rate) prior to administration of first does of study d	lma (soo
2225 Section 7.2.3)	nug (see
5555 Section 7.2.5)	
• Clinical laboratory evaluation including hematology, clinical of	chemistry, lipids,
and urinalysis tests, prior to administration of first dose of stud	dy drug (see
Section 7.2.4)	
• Blood samples for fasted glucose and insulin, prior to adminis	tration of first dose
3340of study drug (see Section 7.2.6)	
• Blood samples for PD biomarkers including osteocalcin, CTX	1, serum
aminoterminal propeptide of type I collagen (P1NP), and corti	isol, prior to
administration of first dose of study drug (see Section 7.2.6).	Blood remaining
3344 from collected samples not needed for protocol-specified analy	yses may be stored
3345 for future exploratory biomarker studies.	
• Dispensing of study medication and administration of first dos	se (see Section 5.8.1
and Section 5.3, respectively)	
• Dispensing of subject diary (see Section 7.4.6)	

at

3351	• Recording of AEs and SAEs; review of all AEs for resolution status and date
3352	(see Section 7.5)
3353	• Recording of concomitant medications (see Section 5.7)
3354 3355	On Day 1, the subject will be discharged from the clinic after completion of all scheduled
3356	assessments.
3357	6.3.4 Treatment Period #1 (Weeks 1-24)
3358 3359	Subjects will return to the study site for safety, efficacy, and PD assessments beginning at
3360	Week 2 and continuing through the Week 24 Follow-up Visit, according to the schedule
3361	of visits in Table 11 .
3362	Subjects will continue to receive daily oral administration of vamorolone/placebo
3363	suspension and prednisone/placebo tablets throughout the 24-week Treatment Period #1.
3364	The daily dose of study medication should be taken with breakfast, including at least 8 g
3365	of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).
3366	Dosing is to occur at home throughout the 24-week Treatment Period #1, except at the
3367	Weeks 2, 12 and 24 study visits when dosing will occur at the study site. Subjects must
3368	have fasted ≥ 6 hours prior to arrival at the study site for the Weeks 2, 12, and 24 study
3369	visits. Breakfast, including at least 8 g of fat (8 ounces [240 mL] of full-fat milk or
3370	equivalent high-fat food portion) will be served at the study site after the blood and urine
3371	collections for clinical laboratory tests and the blood draws for PD biomarkers, including
3372	insulin and glucose (Weeks 12 and 24 only), and within 30 minutes prior to
3373	administration of the dose of study medication. Ease of administration of the suspension
3374	study medication will be assessed at the Weeks 2, 12, and 24 Visits. Apart from blood
3375	and urine sample collections, all other scheduled assessments should be performed after
3376	administration of the study medication in clinic.
3377	Study medication will be dispensed at Weeks 6, 12, 18, and at the Week 24 Follow-up
3378	Visit, and returned at Weeks 2 (compliance monitoring only; will be redispensed at end
3379	of visit), 6, 12, 18, and 24 for all subjects. Subjects will receive subject diaries at each
3380	study visit and return the diaries at each subsequent visit. Diaries will be reviewed with

- 3381 the subject's parent or guardian by the study staff to assess AEs, changes to concomitant 3382 3383 medications/therapies, and any missed or incomplete doses of study medication. 3384 Limited safety assessments will be conducted at the Week 2 Visit. 3385 Clinical efficacy assessments (TTSTAND, TTRW, TTCLIMB, NSAA, 6MWT, 3386 3387 hand-held myometry, and ROM) and the subject reported outcomes (TSQM, PODCI, Ease of Study Medication Administration Assessment, and PARS III) will be conducted 3388 3389 as specified in the schedule of study activities (Table 11). Weight will be recorded at every visit and height will be measured at 12-week intervals. Vital signs will be recorded 3390 3391 at each study visit. A physical examination including assessment of cushingoid features will be performed every 6 weeks. A 12-lead ECG will be recorded at Weeks 12 and 24. 3392 3393 2D-echocardiography will be performed at Week 24. Blood and urine samples for 3394 clinical laboratory tests and blood for the serum PD biomarker panel will be collected at 3395 scheduled visits throughout the study (Table 11). Blood will be collected at Week 24 for DNA testing for candidate genetic modifiers of DMD. An eye examination to exclude 3396 cataracts and glaucoma will be performed at Week 24. A DXA scan and spine X-ray will 3397 be performed at Week 24. A Blindedness Assessment will be completed by the 3398 3399 parent(s)/guardian(s) at the Week 24 Visit. Adverse events, including SAEs, and concomitant medications will be assessed at each study visit and recorded throughout the 3400 3401 study. 3402 There is flexibility in the timing of completion of some of the scheduled Week 24 assessments. The scheduled physical examination, weight, vital signs, clinical laboratory 3403 3404 tests, blood draws for PD biomarker analysis and DNA testing, Ease of Study Medication Administration Assessment, PODCI, PARS III, and functional assessments (TTSTAND, 3405 TTCLIMB, TTRW, NSAA, 6MWT, hand-held myometry, ROM) must all be performed 3406 3407 on the date of the final Week 24 dose of Treatment Period #1 study medication. The
- 3408 12-lead ECG may be performed on the date of the final Week 24 dose of study
- 3409 medication, the day following the final Week 24 dose of study medication, or the day of
- 3410 the Week 24 Follow-up Visit. Completion of the DXA scan, spine X-ray, Fracture
- 3411 Questionnaire, 2-D echocardiography, eye examination, TSQM, and Blindedness

- Assessment may be performed on the date of the final Week 24 dose of study medication
 or up to 7 days following the date of the final Week 24 dose of study medication to
 accommodate need for additional scheduling flexibility.
- 3416 At the Week 24 Visit, all subjects will be dispensed a single dose of oral hydrocortisone
- 3417 (5 mg or 10 mg) to be administered 24 hours after administration of the final dose of
 3418 study medication at the Week 24 Visit. The hydrocortisone dose will be approximately
- 8 mg/m², rounded up to either 5 mg or 10 mg; subjects will be provided with either a
 single 5 mg or 10 mg hydrocortisone tablet which will be dispensed by the site staff at the
- 3421 Week 24 Visit (see Manual of Operations for details).
- 3422 Subjects will return to the study site approximately 48 hours after administration of the
- 3423 Week 24 dose of Treatment Period #1 study medication (and approximately 24 hours
- 3424 after the oral hydrocortisone) for ACTH Stimulation testing. The ACTH Stimulation
- 3425 Test will be performed in the morning, before 12 noon local time, 48 ± 3 hours after 3426 administration of the final dose of Treatment Period #1 study medication, and prior to 3427 administration of the first dose of study drug in the Transition Period (see Manual of
- 3428 Operations for details).
- 3429At the end of the 24-week Treatment Period, including the Week 24 Follow-up Visit for3430the ACTH Stimulation Test, all subjects will begin a 4-week double-blind Transition3431Period during which the doses of the tablet study medication will be progressively3432reduced and discontinued (see Section 6.3.5). Subjects will take the first doses of study3433medication in the Transition Period with a high-fat meal on the same day as the Week 243434Follow-up Visit ACTH Stimulation Test, as soon as possible after ACTH Stimulation3435testing has been completed.
- 3436 3437

6.3.5 Transition Period (Weeks 25-28)

All subjects will participate in the 4-week double-blind dose Transition Period. During this period, all subjects will continue on the same dose of their liquid formulation (either vamorolone or matching placebo) as they were administered during Treatment Period #1 and will have dose-tapering of their prednisone or matching placebo tablets as outlined in

3443 **Table 12.** This tapering is to aid in re-establishment of adrenal function if adrenal

3444 suppression has occurred in the prednisone-treated patients.

Treatment Period Dose (No. tabs)	Week 25 Dose (No. tabs)Week 26 Dose (No. tabs)		Week 27 Dose (No. tabs)	Week 28 Dose (No. tabs)	
2	1	0			
3	2	1	0		
4	3	2	1	0	
5	3	2	1	0	

3445 Table 12. Tablet Dose Tapering

3447	No. = number; tabs = tablets.
3448	

3449 Subjects will take the first doses of study medication in the Transition Period with a high-3450 fat meal on the same day as the Week 24 Follow-up Visit ACTH Stimulation Test, as

3451 soon as possible after ACTH Stimulation testing has been completed.

3452 Site study staff will contact the parent(s)/guardian(s) by telephone at Week 26 to ensure 3453 that the tablet tapering is proceeding according to protocol, to assess potential signs or

3454 symptoms indicative of adrenal suppression, and to address any questions the

3455 parent(s)/guardian(s) may have. In addition, subjects will be assessed promptly for

3456 adrenal suppression if unwell at any time during the Transition Period. There will be a

3457 low threshold for recommending commencement of daily oral prednisone or

3458 hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these3459 circumstances.

Each subject will return to the study site for Week 28 safety study assessments.

3462 Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the Week 28

3463 Visit. Breakfast will be served at the study site after the blood and urine collection for

3464 clinical laboratory tests and the blood draw for PD biomarkers, including fasting glucose

- 3465 and insulin. At the Week 28 Visit, subjects will also have a physical examination with
- 3466 weight, assessment of cushingoid features and vital signs recorded. Study medication
- 3467 will be returned for compliance monitoring. Adverse events, including SAEs, and
- 3468 concomitant medications will be assessed. Subject diaries will be returned and reviewed3469 with site staff.

3470	
3471	6.3.6 Treatment Period #2 (Week 28 + 1 Day through Week 48)
3472 3473	Subjects will take the first dose of study medication in Treatment Period #2 at home on
3474	the day after the Week 28 Visit (Week 28 + 1 day). There is no scheduled study visit at
3475	Week 28 + 1 day.
3476	Subjects will return to the study site for safety, efficacy, and PD assessments beginning at
3477	Week 30 and continuing through the Week 48 Follow-up Visit, according to the schedule
3478	of visits in Table 11. Population PK assessments will be performed on blood collected at
3479	the Week 30 Visit only.
3480	Subjects will receive daily oral administration of vamorolone suspension throughout the
3481	20-week Treatment Period #2, from Week 28+1 day through the day of the Week 48
3482	Visit. The daily dose of study medication should be taken with breakfast, including at
3483	least 8 g of fat (8 ounces [240 mL] of full-fat milk or equivalent high-fat food portion).
3484	Dosing is to occur at home throughout the 20-week Treatment Period #2 except at the
3485	Weeks 30, 40, and 48 study visits when dosing will occur at the study site. Subjects must
3486	have fasted \geq 6 hours prior to arrival at the study site for the Weeks 30, 40, and 48 study
3487	visits. Breakfast, including at least 8 g of fat (8 ounces [240 mL] of full-fat milk or
3488	equivalent high-fat food portion) will be served at the study site after the blood and urine
3489	collections for clinical laboratory tests and the blood draws for PD biomarkers, including
3490	insulin and glucose (Weeks 40 and 48 only), and within 30 minutes prior to
3491	administration of the dose of study medication. Ease of suspension study medication
3492	administration will be assessed at the Weeks 30, 40, and 48 Visits. Apart from blood and
3493	urine sample collections, all other scheduled assessments should be performed after
3494	administration of the study medication in clinic.
3495	Study medication will be dispensed at Weeks 34, 40, and at the Week 48 Follow-up Visit
3496	(for subjects participating in the Dose-tapering Period only), and returned at Weeks 30
3497	(compliance monitoring only; will be redispensed at end of visit), 34, 40, and 48 for all
3498	subjects. Subjects will receive subject diaries at each study visit and return the diaries at
3499	each subsequent visit. Diaries will be reviewed with the subject's parent or guardian by

3500 3501 the study staff to assess AEs, changes to concomitant medications/therapies, and any missed or incomplete doses of study medication. 3502 3503 Limited safety assessments and blood draw for population PK analysis will be conducted 3504 at the Week 30 Visit. 3505 Clinical efficacy assessments (TTSTAND, TTRW, TTCLIMB, NSAA, 6MWT, 3506 hand-held myometry, and ROM) and the subject reported outcomes (TSQM, PODCI, 3507 Ease of Study Medication Administration Assessment, and PARS III) will be conducted as specified in the schedule of study activities (Table 11). Weight will be recorded at 3508 3509 every visit and height will be measured at Weeks 34 and 48. Vital signs will be recorded at each study visit. A physical examination including assessment of cushingoid features 3510 3511 will be performed at Weeks 34, 40, and 48. A 12-lead ECG will be recorded at Weeks 40 3512 and 48. 2D-echocardiography will be performed at Week 48. Blood and urine samples 3513 for clinical laboratory tests and blood for the serum PD biomarker panel will be collected at scheduled visits throughout Treatment Period #2 (Table 11). A blood sample for 3514 plasma PK will be collected at Week 30, two hours following dosing. An eye 3515 3516 examination to exclude cataracts and glaucoma will be performed at Week 48. A DXA 3517 scan will be performed at Week 48. Adverse events, including SAEs, and concomitant medications will be assessed at each study visit and recorded throughout the study. 3518 3519 There is flexibility in the timing of completion of some of the scheduled Week 48 assessments. The scheduled physical examination, weight, vital signs, clinical laboratory 3520 3521 tests, blood draws for PD biomarker analysis, Ease of Study Medication Administration 3522 Assessment, PODCI, PARS III, and functional assessments (TTSTAND, TTCLIMB, 3523 TTRW, NSAA, 6MWT, hand-held myometry, ROM) must all be performed on the date of the final Week 48 dose of Treatment Period #2 study medication. The 12-lead ECG 3524 3525 may be performed on the date of the final Week 48 dose of study medication, the day 3526 following the final Week 48 dose of study medication, or the day of the Week 48 Follow-3527 up Visit. Completion of the DXA scan, Fracture Questionnaire, 2-D echocardiography, eye examination, and TSQM, may be performed on the date of the final Week 48 dose of 3528 3529 study medication, the day following the Week 48 dose of study medication, or the day of

3530 the Week 48 Follow-up Visit (for subjects receiving vamorolone therapy by enrolling 3531 directly into an additional vamorolone study or general access program), or up to 7 days 3532 3533 following the date of the final Week 48 dose of study medication (for subjects 3534 participating in the Dose-tapering Period) to accommodate need for additional scheduling flexibility. 3535 3536 At the Week 48 Visit, all subjects will be dispensed a single dose of oral hydrocortisone (5 mg or 10 mg) to be administered 24 hours after administration of the final dose of 3537 study medication at the Week 48 Visit. The hydrocortisone dose will be approximately 3538 8 mg/m^2 , rounded up to either 5 mg or 10 mg; subjects will be provided with either a 3539 single 5 mg or 10 mg hydrocortisone tablet which will be dispensed by the site staff at the 3540 3541 Week 48 Visit (see Manual of Operations for details). 3542 Subjects will return to the study site approximately 48 hours after administration of the 3543 final (Week 48) dose of Treatment Period #2 study medication (and approximately 24 hours after the oral hydrocortisone) for ACTH Stimulation testing. The ACTH 3544 Stimulation Test will be performed in the morning, before 12 noon local time, 48 ± 3 3545 hours after administration of the final Treatment Period #2 dose of study medication, and 3546 3547 prior to administration of the first dose of study drug in the Dose-tapering Period if the subject is to taper, or prior to the first dose of study medication in the additional 3548 vamorolone study or general access program for subjects transitioning directly to that 3549 protocol (see Manual of Operations for details). 3550 At the end of the 20-week Treatment Period #2, including the Week 48 Follow-up Visit 3551 3552 for the ACTH Stimulation Test, subjects may be given the option of continuing vamorolone therapy by enrolling into an additional vamorolone study or general access 3553 program. Subjects enrolling directly into an additional vamorolone study or general 3554 3555 access program will not need to taper their vamorolone dose prior to enrollment. All 3556 other subjects will begin a 4-week double-blind Dose-tapering Period during which the 3557 doses of suspension study medication will be progressively reduced and discontinued (see Section 6.3.7). 3558

Subjects who will not participate in the Dose-tapering Period (see Section 6.3.7) will be 3560 discharged from the study following completion of all Week 48 assessments, including 3561 the Week 48 Follow-up Visit ACTH Stimulation Test. Subjects who do participate in the 3562 3563 Dose-tapering Period will be dispensed vamorolone at the Week 48 Follow-up Visit, as well as instructions for tapering the dose of vamorolone during the Dose-tapering Period. 3564 Subjects will take the first dose of study medication in the Dose-tapering Period with a 3565 high-fat meal on the same day as the Week 48 Follow-up Visit ACTH Stimulation Test, 3566 3567 as soon as possible after ACTH Stimulation testing has been completed.

3568 3569

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6.3.7 Dose-tapering Period (Weeks 49-52)

3570 All subjects who complete the study and opt not to continue vamorolone therapy by enrolling into an additional vamorolone study or general access program will participate 3571 3572 in a 4-week double-blind Dose-tapering Period during which the doses of suspension 3573 study medication will be progressively reduced and discontinued. In addition, subjects who discontinue study medication after Week 28 and prior to Week 48 will also 3574 participate in the Dose-tapering Period if possible and if, in the opinion of the 3575 Investigator, it is safe to do so. The purpose of dose-tapering is to aid in re-establishment 3576 3577 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 3578 3579 recent calculated liquid formulation dose during the 20-week Treatment Period #2.

3580 Dose tapering for the liquid formulation (vamorolone) will be performed as outlined in
3581 Table 13. For subjects who have completed Treatment Period #2, the subject's weight
3582 recorded at the Week 40 Visit will be used to calculate dose volume for all dose
3583 de-escalations during the Dose-tapering Period.

3584 3585

Table 13. Suspension Dose Tapering

Treatment Period #2	Week 49	Week 50	Week 51	Week 52
Dose Level	Dose Level	Dose Level	Dose Level	Dose Level
Formulation: 100%	50%	25%	10%	0%

- 3587 Subjects will take the first dose of study medication in the Dose-tapering Period with a 3588 3589 high-fat meal on the same day as the Week 48 Follow-up Visit ACTH Stimulation Test, 3590 as soon as possible after ACTH Stimulation testing has been completed. 3591 Site study staff will contact the parent(s)/guardian(s) by telephone at Week 50 to ensure 3592 that the dose tapering is proceeding according to protocol, to assess potential signs or 3593 symptoms indicative of adrenal suppression, and to address any questions the 3594 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 3595 3596 a low threshold for recommending commencement of daily oral prednisone or 3597 hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these circumstances. 3598 3599 The final end-of-study visit will be scheduled approximately one week after the final 3600 dose de-escalation. Each subject will return to the study site for final study assessments when he has received no suspension study medication for one week (Study Week 52). 3601 Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the final Week 52 3602 3603 Dose-tapering Visit. Breakfast will be served at the study site after the blood and urine collection for clinical laboratory tests and the blood draw for PD biomarkers, including 3604 fasting glucose and insulin. At the final Week 52 Visit, subjects will also have a physical 3605 3606 examination with weight, assessment of cushingoid features and vital signs recorded. Study medication will be returned for compliance monitoring. Adverse events, including 3607 SAEs, and concomitant medications will be assessed. Subject diaries will be returned 3608 3609 and reviewed with site staff. 3610 Subjects participating in the Dose-tapering Period will be discharged from the study 3611 following completion of all Dose-tapering Period assessments. **Subject Discontinuation** 3612 6.4 3613 3614 In the event that a subject withdraws early from the study prior to the Week 48 Visit, the reason for discontinuation must be fully documented in the source documents and the 3615
- 3616 eCRF.

3617	
3618	Any subject who withdraws from the study prior to the Week 24 Visit should return to
3619	the study site for Week 24 assessments and the Week 24 Follow-up Visit ACTH
3620	Stimulation Test at the time of early withdrawal, whenever possible (see Section 6.3.4);
3621	any subject who prematurely discontinues from the study after Week 24 but prior to
3622	Week 28 should complete the Week 28 assessments at the time of early withdrawal,
3623	whenever possible (see Section 6.3.5); and any subject who prematurely discontinues
3624	from the study after Week 28 but prior to Week 48 should complete the Week 48
3625	assessments and the Week 48 Follow-up Visit ACTH Stimulation Test at the time of
3626	early withdrawal, whenever possible (see Section 6.3.6), assuming the subject has not
3627	withdrawn consent. Site personnel will document all assessments, including any AEs, in
3628	the source documents and eCRF.
3629	In the event a subject withdraws informed consent, no further study procedures should be
3630	performed and no additional data should be collected. Any data collected up to the point
3631	of withdrawal of informed consent may be used by the Sponsor. Every effort will be
3632	made to ensure that subjects who withdraw consent undergo dose-tapering, as
3633	appropriate, prior to the date of withdrawal of consent. Subjects who withdraw early
3634	from the study may be replaced, at the discretion of the Sponsor.
3635	Subjects who discontinue study medication should follow the procedures for the
3636	applicable Early Discontinuation Dose-tapering Period described below and detailed in
3637	the Manual of Operations, whenever possible. Dose tapering for subjects who
3638	discontinue the study early is to aid in re-establishment of adrenal function if adrenal
3639	suppression has occurred in the prednisone and/or vamorolone treated patients.
3640	Subjects will be assessed promptly if unwell during the tapering phase or in the weeks
3641	following study medication cessation due to the risk of adrenal suppression. There will
3642	be a low threshold for recommending commencement of daily oral prednisone or
3643	hydrocortisone, or intravenous hydrocortisone if hospitalization occurs in these
3644	circumstances.

3645 The final end-of-study visit will be scheduled approximately one week after the final 3646 3647 dose de-escalation. Each subject will return to the study site for final study assessments 3648 when he has received no suspension and/or tablet study medication for one week. 3649 Subjects must have fasted ≥ 6 hours prior to arrival at the study site for the final Early 3650 Discontinuation Dose-tapering Visit. Breakfast will be served at the study site after the 3651 blood and urine collection for clinical laboratory tests and the blood draw for PD biomarkers, including fasting glucose and insulin. At the final Study Visit, subjects will 3652 also have a physical examination with weight, assessment of cushingoid features and 3653 vital signs recorded. Study medication will be returned for compliance monitoring. 3654 3655 Adverse events, including SAEs, and concomitant medications will be assessed. Subject 3656 diaries will be returned and reviewed with site staff. 3657 6.4.1 Early Discontinuation Prior to Week 24 3658 Any subject who discontinues the study after Day 1 and prior to the Week 24 Visit should 3659 return to the study site for Week 24 assessments and the Week 24 Follow-up ACTH 3660 Stimulation Test at the time of early withdrawal, and will participate in a 4-week Early 3661 3662 Discontinuation Dose Tapering Period, whenever possible. Dose tapering will be performed in a stepwise manner, according to the subject's most recently calculated 3663 liquid and tablet formulation doses during the 24-week Treatment Period #1. 3664 Dose tapering for tablets (prednisone and matching placebo) will be performed as 3665

3666 outlined in Table 14.

3667

 Table 14.
 Tablet Dose Tapering for Subjects Discontinuing Prior to Week 24

Treatment Period Dose (No. tabs)	Week 25 Dose (No. tabs)	Week 26 Dose (No. tabs)	Week 27 Dose (No. tabs)	Week 28 Dose (No. tabs)
2	1	0		
3	2	1	0	
4	3	2	1	0
5	3	2	1	0

3669 3670

No. = number; tabs = tablets.

- 3671 Dose tapering for the liquid formulation (vamorolone and matching placebo) will be
- 3672 performed as outlined in Table 15.

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 Table 15.
 Suspension Dose Tapering for Subjects Discontinuing Prior to Week 24

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

As soon as possible after ACTH Stimulation testing has been completed at the Week 24 3677 3678 Follow-up/Early Termination Visit, subjects will take the first doses of study medication

3679 in the Early Discontinuation Dose Tapering Period with a high-fat meal on the same day.

6.4.2 Early Discontinuation After Week 24 and Prior to Week 28 3680

3681 Subjects who discontinue from the study after Week 24 and prior to Week 28 will 3682 continue on the same schedule for dose tapering of tablets they are already following for 3683 3684 Transition Period dosing, and will begin the 4-week suspension dose tapering schedule 3685 shown in Table 16.

3686 3688

 Table 16.
 Suspension Dose-Tapering for Subjects Discontinuing After Week 24
 and Prior to Week 28

	Formulation Dose Level (% of Volume Administered During Treatment Period #1) at Each Week Following Discontinuation				
Time of Early Discontinuation	100%	50%	25%	10%	0%
Week 25	Week 25	Week 26	Week 27	Week 28	Week 29
Week 26	Week 26	Week 27	Week 28	Week 29	Week 30
Week 27	Week 27	Week 28	Week 29	Week 30	Week 31
WCCK 27	WCCK 27	WCCK 20	WCCK 2)	WEEK JU	WEEK JI

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Each subject will return to the study site for final study assessments when he has received 3690 no suspension or tablet study medication for one week (Study Week 29, Week 30, or

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Week 31, depending on when the subject discontinued [see Table 16]). 3692

6.4.3 Early Discontinuation After Week 28 and Prior to Week 48 3693 3694

Subjects who discontinue from the study after Week 28 and before the Week 48 Visit 3695

3696 will follow the same schedule for dose tapering of suspension as described in

Section 6.3.7. 3697
3698							
3699	6.5 Subject and Study Completion						
3700 3701	A completed subject is defined as a subject who has completed Treatment Period #1 and						
3702	Treatment Period #2, through the Week 48 and Week 48 Follow-up Visit assessments,						
3703	and Dose-tapering Period, if applicable, and has not prematurely withdrawn from the						
3704	study for any reason. The study will be completed when the final subject has completed						
3705	his final study visit ("last subject, last visit").						
3706	7 STUDY ASSESSMENTS AND MEASUREMENTS						
3707 3708 3709	7.1 Demographic Assessments						
3709 3710	Demographic information (birth date, race, and ethnicity) will be collected during the						
3711	Pretreatment Screening Period and will be recorded on the appropriate eCRF page.						
3712 3713 3714	7.1.1 Genetic Modifiers of DMD						
3715	Approximately 6 mL of blood will be collected at the Week 24 Visit for DNA testing to						
3716	determine if candidate genetic modifiers of DMD (gene polymorphisms associated with						
3717	disease severity or response to glucocorticoid treatment) are similarly associated with						
3718	vamorolone-treated DMD patients (baseline disease severity or response to vamorolone						
3719	or prednisone treatment).						
3720 3721	DNA testing will be performed by a certified central laboratory.						
3722	The procedures for the collection, handling, and shipping of blood samples for DNA						
3723	testing will be specified in the Laboratory Manual(s) provided to the clinical center.						
3724 3725	Results will be presented in an addendum report.						
3726 3727 2728	7.2 Safety and Tolerability Assessments						
3728 3729 3730	7.2.1 Medical History						
3731	The medical history will be recorded at the Screening Visit and will include significant						
3732	past medical or surgical procedures as well as previous and current co-existent diseases.						
3733	It should include the date (month/year) the subject was diagnosed with DMD, initial						
3734	symptoms of DMD and the age at which they were first identified, and any toxicities						

3736or allergies to prior treatments. It should include relevant medical history for the3737following body systems: head, eyes, ears, nose and throat (HEENT), respiratory,3738cardiovascular, gastrointestinal, endocrine, hematological, dermatological, genital-3739urinary, neurological, musculoskeletal, psychological/psychiatric, and any other history3740of medical significance. The medical history will be recorded on the appropriate eCRF3741page.

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7.2.2 Physical Examination, Cushingoid Features, Weight, and Height

3745A complete physical examination will be performed at Screening, Baseline Day -1 and3746every 6 weeks thereafter through Treatment Period #1, at the Week 28 Transition Period3747Visit, at Weeks 34, 40, and 48 of Treatment Period #2, and at the final Week 523748Dose-tapering Period Visit, and will include examination of the following: head, eyes,3749ears, nose, and throat, neck (*including an examination of the thyroid*), heart, lungs,

- 3750 abdomen (including an examination of the liver and spleen), lymph nodes, extremities,
- 3751 nervous system, and skin. Clinically significant changes from baseline should be
- recorded as AEs. Particular attention will be paid in identifying any sign of cushingoid
- 3753 features, which should also be recorded as AEs if they first appear or worsen during the3754 study.
- 3755Additional unscheduled symptom-directed physical examinations may be conducted at3756any time at the Investigator's discretion.
- Height (in cm) will be recorded at Screening, and Weeks 12, 24, 34, and 48. Weight
- 3758 (in kg) will be recorded at Screening, Baseline Day -1, Week 2, Week 6, Week 12,
- 3759 Week 18, Week 24, Week 28, Week 30, Week 34, Week 40, and Week 48, and at the
- 3760 final Week 52 Dose-tapering Visit (Table 11). Weight recorded at the previous visit will
- 3761 be used to calculate the study medication (suspension and tablets) dose for the subsequent
- 3762 dispensing interval (see Section 5.3).
- 3763 Results will be recorded in the source documents and on the appropriate eCRF page.

7.2.3 *Vital Signs*

37663767Vital signs (sitting blood pressure, heart rate, respiration rate, and body temperature) will3768be recorded at Screening, Baseline Day -1, Day 1, Week 2, Week 6, Week 12, Week 18,3769Week 24, Week 28, Week 30, Week 34, Week 40, and Week 48, and at the final Week 523770Dose-tapering Visit. Vital signs should be recorded after the subject has been resting for3771at least 5 minutes. Body temperature may be measured using oral, tympanic, or temporal3772recording devices; however, the same methodology must be used for all assessments of a3773given subject.

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

3776 If vital signs are recorded at the same study visit as blood sampling and ECG recording,

at least 15 minutes should elapse after collection of blood samples and before performing
ECG and recording vital signs.

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7.2.4 Clinical Laboratory Tests

Each subject will have blood drawn and urine collected for the hematology, chemistry, 3781 3782 lipids, and urinalysis clinical laboratory tests listed in **Table 17** and **Table 18**, below, 3783 during the Screening Period, at the Day 1 Visit, and at each of the subsequent study visits 3784 specified in Table 11. Blood for vitamin D and HbA1c are collected at specific visits 3785 only (Table 17). Fasted blood and urine samples for clinical laboratory tests will be collected pre-dose at the Day 1 and Weeks 2, 12, 24, 28, 30, 40, and 48 Visits, and fasted 3786 samples will be collected at the final Week 52 Dose-tapering Period Visit. Non-fasted 3787 3788 blood and urine samples for clinical laboratory tests will be collected at the Screening, 3789 and Weeks 6, 18, and 34 Visits. Details of blood draws can be found in the Laboratory 3790 Manual.

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

- 3793 For the hematology, chemistry, and lipids laboratory tests, blood will be collected by
- direct venipuncture of peripheral veins. A total of approximately 140 mL of blood will
- be collected over the course of this study for clinical safety laboratory evaluation (see
- 3796 Section 7.2.9 for details of blood volumes to be collected).

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3798	If blood sampling is performed at the same study visit as vital signs assessment and ECG
3799	recording, at least 15 minutes should elapse after collection of blood samples and before
3800	performing ECG and recording vital signs.
3801	Any abnormal hematology, chemistry, lipid, or urinalysis test result deemed clinically
3802	significant by the Investigator or medically qualified sub-investigator may be repeated,
3803	including test results obtained on the final study day.
3804	Any treatment-emergent abnormal laboratory test result that is clinically significant, i.e.,
3805	meeting one or more of the following conditions, should be recorded as a single diagnosis
3806	on the AE section of the eCRF:
3807	Accompanied by clinical symptoms
3808 3809	• Requiring a change in concomitant therapy (e.g., addition of, interruption of,
3810	discontinuation of, or any other change in a concomitant medication, therapy, or
3811	treatment)
3812	• Is otherwise considered clinically significant by the Investigator
3813	
3814	Any clinically significant test abnormality as defined above should be recorded as an AE
3815	(unless it was considered spurious), and repeat analysis performed until resolution or
3816	until the Investigator or medically qualified sub-investigator determines that resolution of
3817	the abnormality is not expected.

Table 17. 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	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				
HbA1c ^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, Weeks 12, 24, 40, and 48 only.c. HbA1c levels measured at Screening, Week 24, and Week 48 only.					

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3822 Urine will be collected for routine analysis, by dipstick and microscopic analysis, for the

3823 tests described in Table 18.

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Table 18. 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 c	ollected for dipstick analysis.				
Blood for hemoglobin A1c (HbA1c) determination is collected at the scheduled					
Screening, Week 24 and Week 48 Visits, and should also be collected if urine glucose is					
positive and/or fasted glucose levels are above normal limits (see Section 7.2.6 and					

3831 Laboratory Manual).

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.

3835 The procedures for the collection, handling, and shipping of laboratory samples will be 3836 specified in the Laboratory Manual provided to the clinical center.

3837 Follow-up of Abnormal Laboratory Test Results

In the event of a medically significant, unexplained, or abnormal clinical laboratory test 3839 value, the test(s) may be repeated, evaluated by the Investigator for sustainability and 3840 reproducibility to determine if the abnormality represents an AE, and followed-up until 3841 the results have returned to the normal range, stabilized, and/or an adequate explanation 3842 for the abnormality is found. If a clear explanation is established, it should be recorded in 3843 3844 the source documents and eCRF. The clinical laboratory will clearly mark all laboratory 3845 test values that are outside the normal range and the Investigator will indicate which of these deviations are clinically significant. These clinically significant deviating 3846 laboratory results will then be further described as AEs, and the relationship to the 3847 3848 treatment, in the Investigator's opinion, will be indicated (see Section 7.5).

3849 3850 7.2.5 **Chicken Pox Immunity** 3851 Subjects must provide evidence of immunity to varicella zoster virus to be eligible for 3852 3853 randomization to treatment. Evidence of immunity may be determined by either a 3854 positive anti-varicella IgG antibody test result obtained during the Screening Period, or 3855 documentation, provided at the Screening Visit, that the subject has had 2 doses of 3856 varicella vaccine, with or without serologic immunity, with the second of the 2 doses given at least 14 days prior to randomization. For subjects whose anti-varicella antibody 3857 3858 titer will be measured at Screening, a 2 mL blood sample will be collected for antibodies 3859 (IgG) to Varicella Zoster virus to confirm immunity. The blood sample will be sent to 3860 the local laboratory for testing. 3861 If antibodies are not detected in the blood sample sent to the local laboratory, and 3862 documentation of two previous vaccinations against varicella cannot be provided, 3863 immunization before starting the trial will be advised and the immunization status must be re-checked prior to randomization (see Manual of Operations for details). Lack of 3864 willingness to immunize a child who is not already immune to chicken pox will be a 3865 reason for exclusion of the child from the trial. 3866 3867 7.2.6 Pharmacodynamic Biomarker Panel 3868 3869 Blood samples will be collected to explore the effect of vamorolone on biomarkers associated with glucocorticoid safety concerns (secondary outcomes for adrenal 3870 3871 suppression, insulin resistance, and bone turnover), as listed in Table 19. 3872 Blood samples will be collected pre-dose at the Day 1 and Weeks 12, 24, 28, 40, and 48 3873 Visits, and at the final Week 52 Dose-tapering Period Visit for analysis of biomarkers for secondary outcome measures of adrenal suppression, bone turnover, and insulin 3874 3875 resistance. Approximately 2 mL of blood will be collected for the PD biomarker panel (osteocalcin, P1NP, and CTX bone turnover markers) at each scheduled collection time 3876 3877 point; blood samples for analysis of morning cortisol levels (adrenal suppression 3878 biomarker) and fasting glucose and insulin (insulin resistance biomarkers) will be collected as part of the clinical laboratory tests and require no additional blood volume. 3879 3880 All samples will be collected after the subject has fasted for ≥ 6 hours and prior to

3881	
3882	administration of the daily dose of study medication at dosing visits. Blood remaining
3883	from collected samples not needed for protocol-specified analyses at each of these time
3884	points may be stored for future exploratory biomarker studies for aspects of safety and
3885	efficacy. These remaining blood samples may be released to scientists worldwide for
3886	research purposes, including research on biomarkers in DMD. Any released samples will
3887	have no identifying subject information.
3888	Blood 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 Section 7.2.4 and Laboratory Manual).
- 3891 A total of approximately 14 mL of blood will be collected for the PD biomarker panel
- 3892 (osteocalcin, P1NP, and CTX bone turnover markers) over the course of the 57-week
 3893 study (see Section 7.2.9).

3894 Table 19. Pharmacodynamic Biomarkers – Secondary Safety Outcomes

Adrenal Suppression			
Cortisol - morning			
Insulin Resistance			
Glucose – fasting			
nsulin - fasting			
Bone Turnover			
Dsteocalcin			
CTX1			
PINP			

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7.2.7 ACTH Stimulation Test

3899The ACTH Stimulation Test will be performed in the morning during the Screening Visit,

- 3900 in the morning of the Week 24 Follow-up Visit (48 ± 3 hours after the final dose of
- 3901 Treatment Period #1 study medication), and in the morning of the Week 48 Follow-up
- 3902 Visit (48 ± 3 hours after the final dose of Treatment Period #2 study medication) to assess
- 3903 the adrenal gland stress response.
- All subjects will be given a single dose of hydrocortisone (5 mg or 10 mg) 24 hours after
- the dose of study medication at the Week 24 Visit and 24 hours after the dose of study
- 3906 medication at the Week 48 Visit. The hydrocortisone dose will be approximately

3907 8 mg/m^2 , rounded up to either 5 mg or 10 mg; subjects will be provided with either a 3908 3909 single 5 mg or 10 mg hydrocortisone tablet which will be dispensed by the site staff at the Week 24 or Week 48 Visit (see Manual of Operations for details). 3910 3911 Subjects will return to the study site approximately 48 hours after administration of the 3912 final (Week 24) dose of Treatment Period #1 study medication (and approximately 3913 24 hours after the dose of oral hydrocortisone), and approximately 48 hours after 3914 administration of the final (Week 48) dose of Treatment Period #2 study medication (and approximately 24 hours after the dose of oral hydrocortisone) for ACTH Stimulation 3915 3916 testing. The ACTH Stimulation Test will be initiated as close to 8 AM local time as 3917 possible, but in any case completed in the morning, before 12 noon local time, 48 ± 3 hours after administration of the final Treatment Period #1 or Treatment Period #2 dose 3918 3919 of study medication, and prior to administration of the first dose of study drug in the Transition Period (Week 24) or Dose-Tapering Period (Week 48) (see Manual of 3920 3921 Operations for details). The ACTH Stimulation Test involves insertion of a saline lock and then administration of 3922 250 µg of Cosyntropin at time zero. Blood samples for cortisol measurement are 3923 3924 collected at time 0 immediately prior to Cosyntropin administration, and at 30 ± 5 3925 minutes and 60 ± 5 minutes after Cosyntropin administration. 3926 The potential side effects of ACTH Stimulation testing (nausea, sweating, dizziness, 3927 palpitations, facial flushing) will be discussed with the subject and the family before starting the test. Cortisol levels below 18 μ g/dL (equivalent to 500 nM) 30 or 60 minutes 3928 3929 after stimulation with Cosyntropin will be considered indicative of adrenal suppression. 3930 Approximately 2 mL of blood will be collected at each time point for cortisol 3931 measurement; a total of approximately 6 mL of blood will be collected during each of the 3932 Screening Visit, the Week 24 Follow-up Visit (48 ± 3 hours following the final dose of 3933 Treatment Period #1 study medication), and the Week 48 Follow-up Visit (48 ± 3 hours following the final dose of Treatment Period #2 study medication) for the ACTH 3934 3935 Stimulation Test (see Section 7.2.9).

3936	
3937	Blood samples will be sent to a central laboratory, and results centrally interpreted
3938	(Children's Hospital of Eastern Ontario). Results of the Week 24 analysis will not be
3939	reported to the study sites.
3940 3941	7.2.8 Population PK Assessment
3942	At the Week 30 Visit, all subjects will have blood collected for PK assessments at
3943	2 hours post-dose. Approximately 2 mL of blood will be collected into K_2 -EDTA tubes
3944	at the single assessment time point.
3945 3946	Plasma concentrations of vamorolone will be measured using a specific and validated
3947	liquid chromatography tandem mass spectrometry assay. PK assessments will be
3948	performed by a central laboratory. The procedures for the collection, handling, and
3949	shipping of laboratory samples will be specified in the Laboratory Manual(s) provided to
3950	the study sites.
3951 3952	The exact time of blood sampling will be recorded in the source document and eCRF.
3953	
3954	If PK and PD or clinical laboratory blood samples are to be collected at the same time
3955	point, the PK blood sample should be collected prior to the PD blood sample(s), which in
3956	turn should be collected prior to the clinical laboratory blood samples.
3957 3958	7.2.9 Total Blood Volume Required
3959	The number and volume of blood samples and total volume of blood to be collected from
3960	each subject throughout the duration of the 57-week study are summarized in Table 20.
3961	A total of 182 mL of blood will be collected from each subject over the course of the

3962 up-to-57-week study.

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Table 20. Blood Sample Number and Volume by Study Visit

	Total mL of Blood															
Test	SCR	Day 1	Week 2	Week 6	Week 12	Week 18	Week 24	Week 24 F/U	Week 28	Week 30	Week 34	Week 40	Week 48	Week 48 F/U	Week 52	Total Volume
Clinical Safety Labs ^a	12 ^b	10 ^c	10 ^c	10	12 ^c	10	12 ^{b,c}		10 ^c	10 ^c	10	12 ^c	12 ^{b,c}		10 ^c	140 ^b
Varicella Zoster IgG	2															2
PD Biomarker Panel ^d		2			2		2		2			2	2		2	14
PD Insulin/Glucose ^c		From Clinical Safety Lab Sample			From Clinical Safety Lab Sample		From Clinical Safety Lab Sample		From Clinical Safety Lab Sample			From Clinical Safety Lab Sample	From Clinical Safety Lab Sample		From Clinical Safety Lab Sample	
DNA Testing							6									6
ACTH Stimulation Test ^e	6							6						6		18
PK ^f										2						2
Total Volume by Visit (mL)	20	12	10	10	14	10	20	6	12	12	10	14	14	6	12	182
	Total Volume: 182 mL															

F/U = Follow-up; SCR = Screening

^a Hematology, Chemistry, Lipids; GLDH; volume includes blood for vitamin D testing, fasting insulin and glucose, cortisol, and exploratory PD biomarkers, where applicable.

^o Includes blood for HbA1c testing.

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

Osteocalcin, CTX1, P1NP, pre-dose on dosing days; subjects must have fasted ≥ 6 hours prior to pre-dose and Week 52 blood draws.

^e ACTH Stimulation Test performed at Screening, Week 24 Follow-up Visit, 48 ± 3 hours after the final dose of Treatment Period #1 study medication and prior to first dose of study medication in the Transition Period, and Week 48 Follow-up Visit, 48 ± 3 hours after the final dose of Treatment Period #2 study medication and prior to first dose of study medication in the Dose-Tapering Period.

Blood drawn for population PK at 2 hours post-dose at the Week 30 Visit.

7.2.10 12-Lead ECG

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12-lead ECGs will be recorded at the Screening, Week 12, Week 24, Week 40, and Week 48 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.

98712-lead ECGs will be obtained over a 3- to 5-minute period after the subject has been988resting quietly in a supine position for at least 5 minutes.

989If blood sampling, vital signs assessment, and ECG recordings are scheduled at the same990study visits, at least 15 minutes should elapse between collection of blood samples and991before performing ECG and recording vital signs.

- ECG results will be read locally. Results must be interpreted and recorded on the appropriate eCRF page.
- 7.2.11 2D-echocardiography

Standard trans-thoracic echocardiogram will be performed at Screening, Week 24, and Week 48 to assess cardiac status. The echocardiograms must be manually reviewed and interpreted locally by medically qualified personnel. No central reading of echocardiography results is planned. The findings will be categorized as: normal; abnormal but not clinically significant; abnormal and clinically significant. An echocardiogram result that is abnormal and clinically significant will be recorded in medical history if detected during the Screening Period and will be considered as an AE if detected after the first dose of study medication. Adequate management should be initiated if any abnormalities of clinical significance are detected.

D05Echocardiographic parameters to be recorded will be described in the Manual ofD06Operations. Results must be interpreted and recorded on the appropriate eCRF page.

008 7.2.12 Eye Examination

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An eye examination will be performed by a certified and appropriately trained optometrist or ophthalmologist at Screening, Week 24, and Week 48 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.

7.2.13 Bone Health and DXA Scan (total body and spine)

Data on bone mass, density, and total body composition (fat mass, fat-free mass, lean mass, Lean Mass Index, and Fat Mass Index) will be collected by DXA during the Screening Period (depending on local facilities, this may require an additional visit but should be completed prior to starting study medication), and at Week 24 and Week 48.

Antero-posterior spine (L1-L4) and total body (without head) bone mineral density (BMD) by DXA scan will be collected. DXA quality control will be performed as described in the Manual of Operations. DXA scans will be analyzed centrally by a certified medical radiation technologist at Children's Hospital of Ottawa in Ottawa, Canada. The Screening result will represent a baseline assessment for long-term follow up. Additional DXA scanning may be arranged if clinically indicated throughout the study.

Vitamin D deficiency and insufficiency will be treated with Vitamin D supplements (see Section 5.7.6).

Vertebral and non-vertebral fractures will be assessed and recorded at Screening, Week 24, and Week 48 using a Fracture Questionnaire. Fractures will be recorded as medical history if reported during the Screening Period and as AEs if detected following the first dose of study medication and confirmed by radiologic investigation. The Fracture Questionnaires completed at the Weeks 24 and 48 Visits will document all Vamorolone Amendment #4 Protocol No.: VBP15-004

radiographically confirmed fractures which occurred during the course of the study, following the first dose of study medication.

7.2.14 Spine X-rays

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Data on bone health will also be collected by lateral spine X-ray (T4-L5) during the)43)44 Screening Period (depending on local facilities, this may require an additional visit but should be completed prior to starting study medication) and at the Week 24 Visit. Lateral)45 spine X-ray will be analyzed centrally by two certified pediatric radiologists at Children's)46 Hospital of Ottawa in Ottawa, Canada, who are blinded to the results of one another; a)47 third radiologist will resolve any discrepancies arising from the first two readings.)48 Quantification of any vertebral fractures detected will be performed. The Screening)49 result will represent a baseline assessment for long-term follow up. Additional spine)50 X-rays may be arranged if clinically indicated throughout the study.)51

Spine x-ray data will be analyzed in an addendum report.

Fractures will be recorded as medical history if detected during the Screening Period and as AEs if detected following the first dose of study medication.

7.3 Assessment of Muscle Strength and Function

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

060 7.3.1 Time to Stand Test (TTSTAND)

The Time to Stand Test (TTSTAND) will be assessed at the Screening, Baseline Day -1, Week 6, Week 12, Week 24, Week 34, Week 40 and Week 48 Visits.

The TTSTAND measures the time (in seconds) required for the subject to stand to an erect position from a supine position (floor), and is assessed as part of the NSAA (see Section 7.3.4). Complete instructions for administering and scoring the TTSTAND are given in the Clinical Evaluator Manual to be supplied to the sites prior to study start.

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

)69 Time to Climb Test (TTCLIMB))70 7.3.2 071 The Time to Climb Test (TTCLIMB) will be assessed at Screening, Baseline Day -1,)72 Week 12, Week 24, Week 40, and Week 48 Visits.)73 The TTCLIMB measures the time (in seconds) required for the subject to climb)74)75 4 standard stairs, beginning and ending in a standing position with arms at the sides.³⁵ Complete instructions for administering the TTCLIMB are given in the Clinical)76 Evaluator Manual to be supplied to the sites prior to study start.)77 Results will be recorded in the source documents and in the eCRF. 078)79 7.3.3 Time to Run/Walk Test (TTRW) 080)81 The Time to Run/Walk Test (TTRW) will be assessed at Screening, Baseline Day -1,)82 Week 12, Week 24, Week 40, and Week 48 Visits.)83 The TTRW measures the time (in seconds) that it takes a subject to run or walk 10 meters)84 and is assessed as part of the NSAA (see Section 7.3.4). Complete instructions for)85 administering and scoring the TTRW are given in the Clinical Evaluator Manual to be)86 supplied to sites prior to study start.)87 Results will be recorded in the source documents and in the eCRF.)88)89 7.3.4 North Star Ambulatory Assessment (NSAA))90)91 The North Star Ambulatory Assessment (NSAA) is a clinical assessment scale)92 specifically designed to measure functional ability in ambulant boys with DMD.³⁶ The)93 NSAA consists of 17 scored items and 2 timed tests, including the TTRW and the)94 TTSTAND (see Section 7.3.1). The NSAA will be conducted at Screening, Baseline)95 Day -1, Week 12, Week 24, Week 40, and Week 48 Visits.)96 Subjects should be barefoot and wear comfortable clothing. Complete instructions for)97 administering and scoring the NSAA are given in the Clinical Evaluator Manual to be)98)99 supplied to the sites prior to study start. The NSAA should be assessed BEFORE the 6MWT at study visits where both tests are 100 performed. 101

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103	Results will be recorded in the source documents and in the eCRF.
104	7.2.5 Sim minute Wall Track (CMUT)
105 106	7.3.5 Six-minute walk lest (GMWI)
107	Functional exercise capacity and mobility will be assessed in all subjects by means of the
108	Six-minute Walk Test (6MWT) at Screening, Baseline Day -1, Week 12, Week 24,
109	Week 40, and Week 48 Visits. This evaluation is a modified version of the 6MWT,
110	adapted for use in DMD patients. ³⁷
111	The total distance traveled, in meters, should be recorded along with the validity of the
112	test as assessed by the test administrator in the source documents and in the eCRF. If a
113	subject cannot complete 6 minutes of walking, the total meters and the time until
114	discontinuation of the test should be recorded. Subjects should wear comfortable shoes
115	(trainers) and clothing. Complete instructions for administering the 6MWT are given in
116	the Clinical Evaluator Manual to be supplied to the sites prior to study start.
117	The 6MWT should be assessed AFTER the NSAA at study visits where both tests are
118	performed.
119	Results will be recorded in the source documents and in the eCRF.
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121	7.3.6 Hand-Held Myometry (eldow flexors and knee extensors)
122	Muscle strength will be measured with hand-held myometry. Elbow flexor muscles will
124	be measured in the upper limbs and quadriceps muscle will be used for the lower limbs.
125	Measurements will be performed unilaterally on the elbow and knee muscles, on the
126	same side as the dominant hand (see Clinical Evaluator Manual for details). Muscle
127	strength will be measured at Screening, Baseline Day -1, Week 12, Week 24, Week 40,
128	and Week 48 Visits.
129	Results will be recorded in the source documents and eCRF.
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131	7.3.7 Range of Motion (ROM)
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133	Range of motion (ROM) at the ankle joint will be measured using a standard goniometer

Range of motion (ROM) at the ankle joint will be measured using a standard goniometer at the Screening, Baseline Day -1, Week 12, Week 24, Week 40, and Week 48 Visits. Measurements will be performed on both the right and left ankle joints.

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137Training will be given to study staff and specific detailed instructions are included in the138Clinical Evaluator Manual.

Results will be recorded in the source documents and 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 parent/legal guardians will be asked to complete this instrument at the Screening, Week 24, and Week 48 Visits.

148The completed Instrument is considered the source documentation for this assessment.149Results will be recorded in the eCRF.

150 7.4.2 Treatment Satisfaction Questionnaire (TSQM)

Satisfaction with treatment will be measured at the Week 24 and Week 48 Visits using the Treatment Satisfaction Questionnaire for Medication (TSQM). The TSQM consists of 14 Likert-scale items that yield four subscale scores: Effectiveness, Side Effects, Convenience, and Global Satisfaction (the latter being a component of the primary outcome variable for the proposed trial). A child-report version of the TSQM is not available. Therefore, the parent (s)/guardian(s) will be asked to report from their perspective of the boy's treatment. TSQM is available in all primary languages spoken at sites for this study.

160The completed Questionnaire is considered the source documentation for this assessment.161Results will be recorded in the eCRF.

162 7.4.3 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 instrument will be completed by the parent(s)/guardian(s) at the Screening Visit and

169	at the Weeks 12, 24, and 48 Visits. The PARS III is available in all primary languages
170	spoken at sites for this study.
171	The completed assessment is considered the source documentation. Results will be
172	recorded in the eCRF.
173	7.4.4 Ease of Study Medication Administration Assessment
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1/5	Ease of administration of the suspension study medication will be assessed by the
176	parent(s)/guardian(s) at the Weeks 2, 12, 24, 30, 40, and 48 Visits. Results will be
177	recorded in the source documents and eCRF.
178	7.4.5 Blindedness Assessment
179	The subject's negative (a) the site Driver of Investigator and the Olivical
180	The subject's parent(s)/guardian(s), the site Principal Investigator, and the Clinical
181	Evaluator will each complete a Blindedness Assessment at the Week 24 Visit. This is a
182	brief questionnaire which asks each evaluator to predict the identity of the study
183	medication (vamorolone, prednisone, or placebo) the subject was taking during
184	Treatment Period #1, and to rate on a 4-point scale his/her level of certainty and the
185	reason for the chosen level of certainty.
186	Results will be recorded in the source documents and in the eCRF.
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188 189	7.4.6 Subject Diary
190	The parent or legal guardian of each subject will be given a subject diary at the Day 1
191	Visit in which to record any new concomitant medications and any changes to existing
192	concomitant medications taken during the study, any AEs experienced by the subject
193	during the study, and any missed or incomplete doses of study medication. Parents/legal
194	guardians will be instructed in how to record information in the diary and will be
195	instructed to bring the diary with them to each study visit for review by study staff for
196	completeness and accuracy. A new diary will be dispensed at each visit for use through
197	the time of the next scheduled visit. Collection of final diaries will occur at the Week 52
198	Visit, at the end of the Dose-tapering Period.

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7.5 Adverse Events and Serious Adverse Events

The condition of the subjects will be monitored throughout the duration of the study by the clinical site study team and by recording of AEs in subject diaries. An AE is any untoward medical occurrence in a subject which does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the 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 or legal guardian) will be questioned by study staff at each study visit for any new signs or symptoms or changes in existing signs or symptoms.

All AEs and SAEs that are spontaneously reported, identified during questioning, or are 220 apparent from a participant's physical appearance, will be recorded in the source 221 222 documents 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 223 224 Section 7.2.4) should be recorded as an AE on the appropriate eCRF page. The details recorded shall include the nature, date of onset, final outcome and its date, intensity 225 226 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., 227 causality). All AEs will be graded by CTCAE, Version 4.03. Details of any medications 228 given to the subject to abate the AE should be recorded on the appropriate eCRF page. 229

7.5.1 Intensity 231 232 All clinical AEs encountered during the clinical study will be recorded in the eCRF. 233 Intensity of AEs will be graded using the most current version of the CTCAE, 234 version 4.03, 5-point scale, and reported in detail as indicated in the eCRF. A description 235 of the intensity scales can be found below: 236 Mild (Grade 1): Asymptomatic or mild symptoms: clinical or diagnostic observations 237 238 only; intervention not indicated. Moderate (Grade 2): Minimal, local, or noninvasive intervention indicated; limiting 239 age-appropriate instrumental activities of daily living (ADL). 240 241 Severe (Grade 3): Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; 242 disabling; limiting self-care ADL; incapacitating with inability to work or perform 243 244 normal daily activity. 245 Life-Threatening (Grade 4): Urgent intervention indicated. 246 247 Death (Grade 5): Death related to AE. 248 Relationship 249 7.5.2 250 Relationship to study drug will be graded on a 5-point scale (definite, probable, possible, 251 252 remote, or unrelated). A description of the relationship scale can be found below: 253 Definite: This category applies to an AE that meets at least criteria 1, 2, and 4 of the 254 "Probable" category. Probable: This category applies to those AEs that are considered, with a high degree 255 of certainty, to be related to the study drug. An AE may be considered probable, if 256 (must include first 3): 257 258 1. It follows a reasonable temporal sequence from administration of the study 259 260 drug.

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262	2. It cannot be reasonably explained by the known characteristics of the
263	subject's clinical state, environmental or toxic factors, or other modes of
264	therapy administered to the subject.
265	3. It disappears or decreases after dosing is complete. (There are important
266	exceptions when an AE does not disappear upon discontinuation of study
267	drug, yet drug relatedness clearly exists, e.g., [1] bone marrow depression
268	and [2] tardive dyskinesia.)
269	4. It follows a known pattern of response to the suspected study drug.
270	Possible: This category applies to those AEs for which the connection with study
271	rossible. This category applies to mose AEs for which the connection with study
272	drug administration appears unlikely but cannot be ruled out with certainty. An AE
273	may be considered possibly related to study drug if or when (must include first 2):
274	1. It follows a reasonable temporal sequence from administration of the study
275	drug.
276	2. It may have been produced by the subject's clinical state, environmental or
277	toxic factors, or other modes of therapy administered to the subject.
278	3. It follows a known pattern of response to the suspected study drug.
279	
280	<u>Remote</u> : In general, this category is applicable to an AE that meets the following
281	criteria (must include the first 2):
282	1. It does not follow a reasonable temporal sequence from administration of
283	the study drug.
284	2. It may readily have been produced by the subject's clinical state,
285	environmental or toxic factors, or other modes of therapy administered to
286	the subject.
287	3. It does not follow a known pattern of response to the suspected study drug.
288	
289	Unrelated: This category is applicable to those AEs which are judged to be clearly
290	and incontrovertibly due only to extraneous causes (disease, environment, etc.) and

291 292 do not meet the criteria for study drug relationship listed under remote, possible, or probable. 293 294 295 7.5.3 **Clinical Laboratory Test Abnormalities** 296 Clinical laboratory test results will be recorded on the designated eCRF page. The 297 intensity of abnormal clinical laboratory test results that are AEs will also be graded 298 using the most current version of the CTCAE, version 4.03, 5-point scale and reported in 299 detail as indicated in the eCRF. A description of the intensity scale can be found above. 300 Any treatment-emergent abnormal clinical laboratory test result that is clinically 301 significant, i.e., meeting one or more of the following conditions, should be recorded as a 302 single diagnosis on the AE section of the eCRF: 303 Accompanied by clinical symptoms 304 305 Requiring a change in concomitant therapy (e.g., addition of, interruption of, 306 discontinuation of, or any other change in a concomitant medication, therapy, or 307 308 treatment) Is otherwise considered clinically significant by the Investigator 309 • 310 This applies to any protocol and non-protocol-specified safety laboratory result from 311 tests performed after the first dose of study drug, which falls outside the laboratory 312 reference range and meets the clinical significance criteria per Investigator standard 313 operating procedures (SOPs). 314 This does not apply to any abnormal laboratory result that falls outside the laboratory 315 reference range, but does not meet the clinical significance criteria (which will be 316 analyzed and reported as laboratory abnormalities); those that are considered AEs of the 317 type explicitly exempted by the protocol; or those that are the result of an AE which has 318 319 already been reported. Please Note: any clinical laboratory abnormality fulfilling the criteria for an SAE should 320 be reported as such, in addition to being recorded as an AE in the eCRF. 321

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7.5.4 Follow-Up of Adverse Events

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

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

7.5.5 *Dosing Error*

For the purposes of this study, a dosing error is defined as a dose exceeding or less than the scheduled dose of liquid formulation, tablet formulation, or both. 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 documents and recorded in the appropriate documentation.

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7.5.6 Serious Adverse Events

Serious adverse events will be collected and reported during the study from the time informed consent is obtained through 30 days after the final dose of study medication, according to the protocol and applicable regulations. For subjects who do not continue into an additional vamorolone study or general access program, site staff will make a phone call to the home 31-35 days after the final dose of study medication in the VBP15-004 Dose-tapering Period 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 367 the Coordinating Center of all SAEs, regardless of relationship to the investigational 368 drug, within 24 hours of clinical staff becoming aware of the event; notification to the 369 Coordinating Center will trigger alerts to the Study Chair, the Sponsor, and the Medical 370 Monitor. The Investigator will provide the initial notification by completing the SAE 371 Report Form in the electronic data capture (EDC) system, which must include the 372 Investigator's assessment of the relationship of the event to investigational drug, and 373 must be signed by the Investigator. 374
- 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.
- All SAE reports should be completed within the EDC.

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383	An AE or suspected adverse reaction is considered serious if, in the view of either the
384	Investigator or Sponsor, it results in any of the following outcomes:
385	• Is fatal (results in the outcome of death)
386	Is life threatening
387	• Is me-inreatening
389	• Requires in-patient hospitalization or prolongation of existing hospitalization
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391	• Results in persistent or significant incapacity or substantial disruption of the
392	ability to conduct normal life functions
393	• Is a congenital anomaly or birth defect
394 395	• Is an important medical event that may jeopardize the subject and may require
	• Is an important medical event that may jeopardize the subject and may require
396	medical or surgical intervention to prevent one of the outcomes listed above.
397	The terms death and sudden death are clearly distinct and must not be used
398	interchangeably.
399	Hospital admissions scheduled prior to the study are not considered SAEs unless the
400	hospitalization is prolonged due to an adverse event. Planned admissions as part of the
401	study, hospitalizations for scheduled treatment of a preexisting condition that has not
402	worsened, and hospitalization for an elective procedure are not considered SAEs.
403	Hospitalizations for fewer than 24 hours and emergency room/department visits are not
404	considered SAEs.
405	Any AE or clinically significant abnormal laboratory test value, as determined by the
406	Investigator, that is serious and which occurs during the course of the study (as defined
407	above) must be reported to the Coordinating Center, who will notify the Study Chair, the
408	Sponsor and the Medical Monitor within 24 hours of the Investigator becoming aware of
409	the event. Additional information that becomes available for an SAE after the initial
410	report is submitted will be reported to the Coordinating Center, who will notify the Study
411	Chair, the Sponsor and the Medical Monitor within 24 hours of the Investigator becoming
412	aware of the new information.

414	All SAEs must be collected and reported during the study from the time of informed
415	consent through 30 days after the final dose of study medication. All SAEs, related and
416	unrelated, must be reported to the Sponsor within 24 hours of first awareness.
417	If, at any time during the study, a subject experiences an SAE, appropriate care should be
418	instituted.
419	In the event of a serious adverse event (SAE), the Investigator will complete the SAE
420	electronic case report form within 24 hours of first awareness of the event. In the
421	unlikely event that the electronic study database is inaccessible and the Investigator
422	is unable to complete the SAE electronic case report form within 24 hours, the SAE
423	Notification Form (pdf) should be completed and emailed or printed/faxed to the
424	PRA safety management team within 24 hours, using the contact information below:
425	In United States and Canada:
426	Email: CHOSafety@prahs.com
427	Drug Safety Fax: 1 888 772 6919 or 1 434 951 3482
428	SAE Questions: Drug Safety Helpline: 1 800 772 2215
429	In Europe, Asia, Pacific, Africa and Australia:
430	Email: MHGSafety@prahs.com
431	Drug Safety Fax: +44 1792 525720
432	SAE Questions: Drug Safety Helpline: +49 621 878 2154
433 434	Serious Adverse Events will be recorded from the time the subject's written informed
435	consent is obtained. Serious adverse events that occur within 30 days of study drug
436	dosing must continue to be recorded and reported to the Study Sponsor or its designee.
437	Should there be an SAE that occurs that suggests an increased risk to the participants, the
438	following steps will be considered, depending on the number and severity of the SAE(s):
439	modification of the protocol, investigation of the relationship of the SAE(s) to study drug
440	suspension of the study, and/or discontinuation of the study.

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442 443	Suspected Unexpected Serious Adverse Reaction (SUSAR) Identification and Reporting
444	A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse
445	reaction that is both serious and unexpected (not identified in the Investigator's
446	Brochure ²⁹). Sponsor will inform Investigators of SUSARs in a manner and timeframe
447	consistent with applicable national regulatory requirements.
448	The study will comply with all local regulatory requirements. This study adheres to the
149	definition and reporting requirements of ICH Guideline for Clinical Safety Data
450	Management, Definitions and Standards for Expedited Reporting.
451	8 STUDY COMMITTEES
452	9.1 Study Steering Committee
+53 454	8.1 Study Steering Committee
455	A study steering committee (SSC – VISION-DMD) will be responsible for protocol
456	development, review of any study amendments, and coordination of study conduct and
457	interpretation of study results. The SSC comprises the Sponsor, study chairs and medical
458	monitors for the VBP15-003, VBP15-LTE, VBP15-004, and other studies, as applicable,
459	the project managers, and the patient representatives.
460	8.2 Data and Safety Monitoring Board
461 462	An unblinded Data and Safety Monitoring Board (DSMB) operating autonomously from
163	the SSC and the site investigators, will be responsible for providing independent
164	recommendations to the SSC about risk-benefit of the study and for any modification
165	affacting sofaty or data integrity required during the course of the study. The DSMP
+05	members must not be actively involved in study design, conduct or daily management of
+00	this study and must not have financial propriety professional or other interests that may
+07	this study and must not have infancial, propriety, professional, of other interests that may
468	affect impartial, independent decision-making.
469	Specialists may be invited to participate as non-voting members at any time if additional
470	expertise is desired. The DSMB will formally interact with the SSC through the sharing
471	of blinded DSMB meeting minutes.
472	The DSMB will be responsible for:

Examining accumulating safety and other relevant data at pre-specified points 474 during the course of the study in order to make recommendations concerning 475 continuation, termination, or modification of the study; 476 Reviewing important protocol deviations; 477 478 Providing expert advice to the SSC on an ad hoc basis regarding matters such as 479 safety concerns or diagnostic evaluations in individual subjects; 480 Based on the results of its deliberations, the DSMB can recommend continuation 481 of the studies unchanged, study interruption, study termination, modification of 482 the studies, or alteration in the DSMB monitoring plan. 483 **DATA COLLECTION** 484 9 485 9.1 **Source Documents** 486 487 Source documents are defined as original documents, data, and records. These 488 documents may include hospital records, clinical and office charts, laboratory 489 490 data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfilm or magnetic media, 491 and/or x-rays. Data collected during this study must be recorded in the appropriate 492 source documents. 493 Investigators will keep a record relating the names of the subjects to their enrollment 494 numbers (subject identification log) to permit efficient verification of data subject files, 495 496 when required. 497 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 498 completion/termination, and the reason the subject was not entered (if applicable). 499 500 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. 501

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

513The Coordinating Center will design an electronic database in OpenClinica for this study.514Access rights to the EDC system for the study site team members will need to be515requested. Every user of the system will be made aware of the fact that user name and516password should never be shared and their electronic signature constitutes the legally517binding equivalent of a handwritten signature. Only trained personnel certified by the518Coordinating Center will receive a user name and password.

519All data will be directly entered or collected on a source document and then entered into520OpenClinica or transferred electronically to the study database (e.g., clinical laboratory521results).

522The Coordinating Center data management team will monitor the eCRFs for523completeness and acceptability throughout the course of the study. ReveraGen personnel524(or their representatives) will be allowed read-only access to all source documents in525order to verify eCRF entries.

9.3 Data Processing

A clinical study database will be constructed from the eCRFs and any data merged electronically, and the data will be validated both manually and electronically. Clarification of data will be requested from the study site as required. The database will be quality assured in accordance to the data management plan and will be available for statistical analysis according to the methods outlined in Section 10.9 and the Statistical Analysis Plan (SAP).

9.4 Subject Diaries

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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 a randomized, double-blind, parallel group, placebo- and active-controlled study. Study medication is administered daily in this Phase IIb trial. Data for untreated subjects from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study^{38,39,40,41} and data for prednisone treated subjects from the CINRG Prednisone study⁴² were used to help estimate sample sizes for this study.

- In the vamorolone VBP15-003 study and the interim analysis of the VBP15-LTE study, doses of 0.25 and 0.75 mg/kg/day showed little evidence of clinical benefit, whereas doses of 2.0 and 6.0 mg/kg/day both showed clear evidence of clinical benefit comparable to that seen with glucocorticoids (prednisone and deflazacort).
- In consideration of the primary efficacy endpoint, comparison of 6.0 mg/kg/day vamorolone versus placebo, sample size calculations were performed using data from vamorolone-treated subjects from the VBP15-002/VBP15-003 24-week treatment period. The analysis compared TTSTAND velocity from the combined 2.0 and 6.0 mg/kg/day groups (Treatment Group) to the combined 0.25 and 0.75 mg/kg/day groups (Pseudo-Placebo Group).

Least squares (LS) means from the mixed model for repeated measures (MMRM) modeling of VBP15-002/VBP15-003 24-week data were used as parameter estimates of the population means in the sample size calculations for the comparison of the Treatment Group (2.0 + 6.0 mg/kg/day) vs. the Pseudo-Placebo Group (0.25 + 0.75 mg/kg/day) on the mean change from baseline at Week 24. For the estimates of standard deviations within each comparison group, simple descriptive statistics from the

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VBP15-002/VBP15-003 24-week data were used. Power was estimated using two-sided t-tests assuming unequal variance, with alpha =0.05.

The following table shows the resultant estimated power for various sample sizes per comparison group for comparing the Treatment Group (2.0 + 6.0 mg/kg/day) vs. the Pseudo-Placebo Group (0.25 + 0.75 mg/kg/day) on the mean change from baseline at Week 24 for the alternative hypothesis that H1: $\mu 1 \neq \mu 2$ assuming an alpha level of 0.05 and parameter estimates from the analyses described above for TTSTAND velocity:

Sample Size per Comparison Group	µ1 (Pseudo- Placebo)	μ2 (Treatment Group)	σ1 (Pseudo- Placebo)	σ2 (Treatment Group)	Estimated Power
25	-0.0052	0.0450	0.0628	0.0530	84.89%
28	-0.0052	0.0450	0.0628	0.0530	88.76%
30	-0.0052	0.0450	0.0628	0.0530	90.81%

The sample size of 25 per treatment group for 2.0 mg/kg/day, 6.0 mg/kg/day, prednisone, 575 and placebo will result in a total enrollment of 100 subjects which will provide 576 approximately 85% power at alpha level 0.05 to detect a statistically significant 577 difference between 6.0 mg/kg/day and placebo on TTSTAND velocity at Week 24. 578 Similarly, a total enrollment of 120 subjects (30 per treatment group) will provide 579 approximately 91% power at alpha level 0.05 to detect a statistically significant 580 difference between 6.0 mg/kg/day and placebo on TTSTAND velocity at Week 24. 581 Note that subjects in the prednisone and placebo groups will actually be randomized into 582 583 two groups each:

- Prednisone 0.75 mg/kg/day \rightarrow Vamorolone 2.0 mg/kg/day (n=15);
- Prednisone 0.75 mg/kg/day \rightarrow Vamorolone 6.0 mg/kg/day (n=15);
- Placebo \rightarrow Vamorolone 2.0 mg/kg/day (n=15); or
- Placebo \rightarrow Vamorolone 6.0 mg/kg/day (n=15).

These groups will be pooled by initial treatment (prednisone or placebo) for the Treatment Period #1 analyses.

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591If the number of subjects who withdraw early from the study is high, additional subjects592may be enrolled to achieve approximately 120 subjects completing the Week 24 Visit593assessments.

59410.2 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.

50510.3 Analysis Populations

Four populations will be defined for data analysis: the Safety Population, the modified Intent-to-Treat Population, the Per Protocol Population (PPP), and the Pharmacokinetic Population.

510 **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 postbaseline 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 but never have post-baseline assessments will be excluded. Results will be presented "as randomized."

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10.3.3 Per Protocol Population

The Per Protocol Population (PPP) will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data. The PPP will also exclude some subjects because of missed assessments due to the COVID-19 pandemic. Exclusion of subjects from the PPP will be made on a subject-by-subject basis prior to database hard lock

10.3.4 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.

53410.4 Measures Taken to Avoid/Minimize Bias

Not applicable.

53810.5 Interim Analysis

No formal interim statistical analyses are planned; however, interim safety data and overviews will be supplied to the DSMB. Since this is a blinded study, an unblinded and independent statistician will be involved in preparing the overviews for the DSMB. These overviews will not be shared outside the unblinded and independent statistician and the unblinded DSMB members.

545 **10.6 Week 24 Analysis**

The primary analyses for this study are the analyses which will be performed after all subjects complete Week 24 of Treatment Period #1. The results from these analyses will be provided to regulatory authorities. Investigators, study subjects, study staff, and monitors will remain blinded throughout the duration of the 52-week study. The Sponsor, including data management and statistical personnel, will be unblinded after the Week 24 analyses.

553 **10.7 Week 48 Analysis**

The Week 48 analyses will be performed after all subjects complete Week 48 of Treatment Period #2. The results from these analyses will be provided to regulatory

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658authorities. All study staff may be unblinded after database lock of Treatment Period #2659data.

10.8 Missing, Unused, and Spurious Data

The primary analyses for the primary and secondary efficacy variables will be conducted on observed data only; the MMRMs will employ appropriate covariance structures to accommodate missing data, as described in **Section 10.9.4**. Missing efficacy data will be imputed for supportive sensitivity analyses on the primary and secondary efficacy endpoints using the following methods:

- Multiple Imputations using Markov Chain Monte Carlo (MCMC); and
 - Multiple Imputations using a Control-based Pattern Mixture Model.

Full details will be provided in the SAP.

10.9 Statistical Analysis

10.9.1 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.

No formal interim statistical analyses are planned, apart from the interim data views and presentations to be created for the DSMB. Missing values for safety and exploratory outcomes will be treated as missing, unless stated otherwise.

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

Treatment Period #1 analyses will be summarized by four treatment groups:

- Vamorolone 2.0 mg/kg/day (n=30);
- Vamorolone 6.0 mg/kg/day (n=30);

placebo

- 592 593 Prednisone 0.75 mg/kg/day (n=30); and 594 Placebo (n=30). ٠ 595 Treatment Period #2 analyses (besides historical control comparison data) will be 596 597 summarized by six treatment groups: 598 Vamorolone 2.0 mg/kg/day \rightarrow Vamorolone 2.0 mg/kg/day (n=30); • Vamorolone 6.0 mg/kg/day \rightarrow Vamorolone 6.0 mg/kg/day (n=30); 599 Prednisone 0.75 mg/kg/day \rightarrow Vamorolone 2.0 mg/kg/day (n=15); 700 • Prednisone 0.75 mg/kg/day \rightarrow Vamorolone 6.0 mg/kg/day (n=15); 701 Placebo \rightarrow Vamorolone 2.0 mg/kg/day (n=15); and 702 • 703 Placebo \rightarrow Vamorolone 6.0 mg/kg/day (n=15). 704 TTSTAND, TTCLIMB, and TTRW will be analyzed using raw scores and velocity. 705 Velocity will be calculated as follows: TTSTAND velocity = 1 / TTSTAND and is expressed as rises/sec 706 707 TTCLIMB velocity = 1 / TTCLIMB and is expressed as tasks/sec 708 709 TTRW velocity = 10 / TTRW and is expressed as meters/sec 710 711 Sensitivity analyses will be performed and will be described in the SAP. **10.9.2** Adjustment for Multiple Comparisons 712 713 The primary efficacy endpoint tests vamorolone 6.0 mg/kg/day vs. placebo using 714 715 TTSTAND velocity at Week 24 and occurs during Treatment Period #1 of the study. The 716 primary efficacy endpoint supports the primary objective of this study. The study is thus powered for the efficacy comparison using an alpha level of 0.05 for success. 717 The secondary efficacy endpoints will be tested at Week 24 along with the primary 718 efficacy endpoint using a fixed sequential testing process where the fixed sequence of 719 testing will be done in the following order: 720 721 1. TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo 722 2. 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs. 723
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726	3. 6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs.		
727	placebo		
728	4. Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day vs.		
729	placebo		
730	5. Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day vs.		
731	placebo		
732	6. 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone		
733 734	7. 6MWT meters walked, vamorolone 2.0 mg/kg/day vs. prednisone		
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736	Each test in the sequence will be carried out using a two-sided alpha level of 0.05.		
737	Statistical testing of the primary/secondary efficacy endpoints will stop if a p-value >0.05		
738	occurs or if a p-value ≤ 0.05 occurs in the wrong direction. In case the fixed sequential		
739	testing process stops, the results of the subsequent tests will be reported with nominal		
740	p-values, but p-values ≤ 0.05 in the right direction will not be considered proof of		
741	statistical testing success in these subsequent tests.		
742	All other analyses will not be corrected for multiple comparisons (tests will be performed		
743	at the 0.05 alpha level), as they will be viewed and handled in the perspective of not		
744	testing a formal hypothesis.		
745	10.9.3 Subject Disposition, Demographics, and Baseline Characteristics		
746 747	Subject disposition will be summarized by analysis population. The number of subjects		
748	enrolled, the number in each population, and the reason for discontinuation from the		
749	study will be summarized and listed.		
750	Subject demographics (e.g., age, race, and ethnicity) and baseline characteristics (e.g.,		
751	height, weight, and months/years since DMD diagnosis) will be summarized		
752	descriptively by treatment group and overall, per analysis population. Baseline		
753	characteristics between groups presented in these summary tables will be reviewed for		
754	any clinically relevant differences among the treatment groups, and may be accounted for		
755	in the statistical models for the endpoints.		
10.9.4 Efficacy Analyses

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

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

The primary efficacy outcome is Time to Stand (TTSTAND) from supine (velocity), comparison of vamorolone 6.0 mg/kg/day vs. placebo. Secondary and exploratory efficacy outcomes are TTSTAND (velocity), comparison of vamorolone 2.0 mg/kg/day vs. placebo; the NSAA assessment; Time to Climb four stairs (TTCLIMB) (velocity); Time to Run/Walk 10 meters (TTRW) (velocity); the distance walked in 6 minutes (6MWT); hand-held myometry (elbow flexors and knee extensors); and ROM.

The primary efficacy outcome TTSTAND (velocity) change from baseline to Week 24 769 will be compared between the 6.0 mg/kg/day vamorolone dose group and the placebo 770 group using a restricted maximum likelihood (REML)-based mixed model for repeated 771 measures (MMRM). This model includes fixed effects for treatment (vamorolone 2.0 772 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, 773 baseline TTSTAND, age group (per stratification), and the treatment-by-week 774 775 interaction. Study week will be included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, pairwise 776 comparisons (using least squares [LS] mean contrasts) will be made to compare 777 TTSTAND velocity at 24 weeks for the vamorolone 6.0 mg/kg/day dose level with 778 779 placebo (primary efficacy outcome).

780For secondary outcomes, the same models will be used as for the primary outcome781(REML-based MMRM including fixed effects for treatment [vamorolone 2.0 mg/kg/day,782vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo], age group783[<6 years; ≥ 6 years], week, baseline, and treatment-by-week interaction).784An unstructured covariance matrix will be used, and underlying modelling assumptions

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

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789	relevant and necessary. The secondary outcome measures will be compared using similar
790	models. Full details will be provided in the SAP.
791	The following sensitivity analyses will be performed (see SAP for full details) for the
792	primary efficacy and secondary efficacy endpoints:
793	• Multiple imputations using MCMC methods for missing data;
794	• Multiple imputations using a Control-based Pattern-Mixture Model for missing
795	data.
796	Additional sensitivity analyses will be performed to assess the impact of COVID-19 on
797	the primary endpoint. Supportive analyses will also be performed on the primary
798	endpoint. Full details will be provided in the SAP.
799	Subjects who are randomized to receive vamorolone 2.0 mg/kg/day or vamorolone
300	6.0 mg/kg/day for both treatment periods will have TTSTAND velocity change from
801	baseline data captured over 48 weeks compared with untreated DMD historical control
802	data. Full details will be provided in the SAP.
803	10.9.5 Safety Analyses
804 805	The Safety Population will be used for presentations and analyses of the safety
806	parameters. Analyses will be done as per actual treatment received.
807	In general, descriptive statistics for each safety endpoint will be presented by time point
808	and treatment group. In addition, individual subject listings of all safety data will be
309	created and sorted by treatment group and time point, and will be reviewed for any
810	evidence of dose-related differences or trends in the safety profile of vamorolone. Where
811	considered relevant, plots will be created.
812	Safety data will include BMI, weight, vital signs, 2D-echocardiogram, DXA scan, spine
813	X-ray, eye examination results, and ACTH Stimulation Test results, and ECG results, and
814	these will be presented using descriptive statistics. Safety laboratory data will be
815	summarized using descriptive statistics, and out-of-range values will be listed. For safety
816	analyses, the vamorolone doses during Treatment Period #1 will be compared to
817	prednisone, as specified in the SAP.

818 In Treatment Period #1, BMI z-score change from baseline results will be compared 819 between treatment groups using an REML-based MMRM analysis with treatment group, 820 week of the visit, and the treatment-by-week interaction as factors, and baseline BMI 321 822 z-score and age group as a covariate. Week will be included in the model as a categorical variable (Week 12 and 24) along with the treatment-by-week interaction. An 323 unstructured within-subject covariance matrix will be used. If this analysis fails to 324 converge, Akaike's information criterion will be used to select the best covariance 825 structure from compound symmetry and autoregressive-1 (AR(1)). The Kenward-Roger 826 approximation will be used to estimate denominator degrees of freedom. 827 828 Change from baseline in all continuous clinical laboratory test results will be tested using one sample t-tests with p-values presented along with the descriptive statistics at each 829 830 assessment visit within each treatment group (note that pharmacodynamic biomarkers -CK for efficacy, fasting glucose and insulin for insulin resistance, and GLDH for safety -831 will be of special interest). 832 Adverse events will be coded using the Medical Dictionary for Regulatory Activities 333 (MedDRA), version 20. The incidence of AEs will be summarized overall and by 334 treatment group, SOC and preferred term; treatment group, SOC, preferred term, and 835 intensity (CTCAE v 4.03 grade); and treatment group, SOC, preferred term, and 836 relationship to study drug. Additional AE analyses will be at the subject level: the 837 number of subjects who had any AE, the distribution of number of AEs per subject within 838 a treatment group, worst intensity in a subject within a treatment group, highest level of 839 relationship to study treatment for each subject within a treatment group. Adverse events 840 associated with suicidality and abuse potential will be listed. Full details will be provided 341 in the SAP. 842

- Physical examination results will be listed only.
 - 10.9.6 Pharmacodynamic Analyses

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The evaluations of PD biomarkers will be performed using the Safety Population.

- Analyses will be done as per actually received treatment.
- All PD biomarker results will be summarized and listed.

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover will be assessed. PD biomarkers will be analyzed using MMRMs similar to the primary efficacy model. Plots will be created. Additional exploratory PD biomarkers of both safety and efficacy may be assessed. Vamorolone-treated groups will be compared to both prednisone-treated and placebo groups.

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10.9.7 Patient-Reported Outcome Exploratory Analyses

Patient Reported Outcomes including the TSQM, PODCI, PARS III, Ease of Study Medication Administration Assessment, and the Blindedness Assessment will be listed and presented using descriptive statistics by treatment and time point. In addition, comparison will be made for each vamorolone dose group with placebo for the PODCI and for each vamorolone dose group with prednisone and placebo for the PARS III, with p values computed for the comparisons. Full details will be provided in the SAP.

10.9.8 Pharmacokinetic Analyses

The 2-hr post-dose plasma concentration measurements of vamorolone at Week 30 will be used for comparison of drug exposures between the two dosing groups. They will be added to PK data from previous studies in DMD boys for comparison with measurements obtained in healthy adult male subjects. All PK data will be combined in a population assessment of plasma concentrations in relation to dose and age of subjects. The PK population will be used for these analyses. A separate PK Analysis Plan will be created to further discuss these analyses.

10.9.9 Concurrent Medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the World Health Organization (WHO) Drug classification (Version 4.3). All concomitant medications will be detailed in the subject data listings.

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380	11 STUDY MANAGEMENT AND ETHICAL AND REGULATORY
881	REQUIREMENTS
882	11.1 Regulatory Approval and Good Clinical Practice
883 884	This study will be conducted in accordance with the principles of the 18 th World Medical
885	Assembly (Helsinki, June 1964), and amendments of the 29 th (Tokyo, 1975), 35 th
886	(Venice, 1983), 41 st (Hong Kong, 1989), 48 th (Somerset West, 1996), 52 nd (Edinburgh,
887	2000), 53 rd (Washington, 2002), 55 th (Tokyo, 2004), 59 th (Seoul, 2008), and 64 th
388	(Fortaleza, 2013) World Medical Assemblies and ICH E6 Guideline for Good Clinical
889	Practice (GCP).
890	Further, the trial will be conducted in accordance with all applicable laws, guidances and
891	directives of the jurisdiction where the study is being conducted
892	11.2 Investigator Responsibilities
893	11.2.1. Subject Information and Informed Consent
894 895	11.2.1 Subject Information and Informed Consent
896	It is the Investigator's responsibility to ensure that parent(s)/guardian(s) give(s) informed
897	consent before the subject is admitted to the study, in accordance with ICH guidelines on
398	GCP and all applicable laws, guidances and directives of the jurisdiction where the study
899	is being conducted.
900	If applicable, written or verbal assent will also be obtained from each subject as required
901	per regulations.
902	An approved ICF will be given to each parent/guardian written in a language they
903	understand.
904	The Investigator or designee will review the study with the parent(s)/guardian(s) of each
905	subject. The review will include the nature, scope, procedures, and possible
906	consequences of the subject's participation in the study. The consent, assent, and review
907	must be in a form understandable to the parent(s)/guardian(s) of the subject. The
908	Investigator or designee and the parent(s)/guardian(s) of the subject must both sign and
909	date the ICF after review and before the subject can participate in the study. The
910	parent(s)/guardian(s) of the subject will receive a copy of the signed and dated form, and

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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.

916If the ICF is amended during the study, the Investigator must follow all applicable917regulatory requirements pertaining to all new subjects and repeat the consent process with918the amended ICF for any ongoing subjects.

91911.2.2 Institutional Review Board/Independent Ethics Committee Approval and Other920Institutional 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.

State concerned and/or the IEC of any substantial amendment(s) to the protocol.

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

Study medication can only be supplied to the Investigator after documentation of all 932 ethical and legal requirements for starting the study has been received by the Sponsor or 933 designee (Coordinating Center). This documentation must also include an IRB/IEC 934 membership list that contains members' occupations and qualifications. If the IRB/IEC 935 will not disclose the names of the committee members, it should be asked to issue a 936 statement confirming that the composition of the committee is in accordance with GCP. 937 The Investigator will keep the IRB/IEC informed regarding the progress of the study, per 938 939 institutional requirements. No changes will be made in the study without IRB/IEC

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941	approval, except when required to eliminate apparent immediate hazards to the subjects.
942	In cases where any implemented deviation from, or a change of, the protocol to eliminate
943	an immediate hazard(s) to trial participants is implemented without prior IRB/IEC
944	approval, the implemented deviation should be notified as soon as possible not only to
945	the IRB/IEC for review and approval/favorable opinion but also to the regulatory
946	authority(ies).
947	While the study is ongoing and at study completion/discontinuation, the Investigator must
948	submit to the IRB/IEC the following information in accordance with applicable
949	regulatory requirements where the study is being conducted:
950	1. Information on serious or unexpected AEs, showing due diligence in providing
951	this information as soon as possible
952	2. Periodic reports on the progress of the study
953 954	3. Final Study Summary upon study completion or closure.
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956	Notification of the end of the trial will be sent to the IRB/IEC within 30 days after
957	completion of the study close-out visit. In case the study is ended prematurely, the
958	IRB/IEC will be notified within 15 days, including the reasons for the premature
959	termination. The end of the trial is defined as the date of final analysis of the study data
960	according to the SAP.
961	11.2.3 Study Documentation
962	Before the Start of the Study
963	The following study documentation will be in place at the study site prior to the first
964	administration of study drug:
965	• Fully signed protocol and protocol-supporting manuals
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967 968	• Investigator's Brochure->
969	Investigator Protocol Agreement form signed by the Investigator
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9 71	• IRB/IEC-approved copy of the ICF

973	• Curriculum vitae of the Investigator and all sub-investigators listed on the FDA	
974	Form 1572	
975	• A letter of IRB/IEC approval for protocol	
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977	• A list of members of the IRB/IEC and their affiliations	
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979	 A copy of the Investigator-signed FDA 1572 form 	
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981	An Investigator-signed financial disclosure form	
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983	• Investigator/site study contract.	
984	During the Study	
985	During the Study	
980	The following documentation should be added to the site study file during study conduct:	
988	The following documentation should be added to the site study file during study conduct.	
989	• Any paper source forms completed and subsequently entered into the study	
990	database. An explanation should be given for all missing data and any protocol	
991	deviations documented in the site study file	
992	• Any changes to the documentation identified above (see <i>Before the Start of the</i>	
993	Study)	
994	• Shipping documents relating to shipment of medication (drug accountability) and	
995	bioanalytical samples	
996	• Copies of relevant correspondence such as letters, emails, meeting notes, and	
997	telephone calls.	
998	After the Study	
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000	After completion or premature termination of the trial, all of the documents identified	
001	should be in the file, together with the following:	
002	• Study drug accountability documents	
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004	Audit certificates (if applicable)	
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006	 Investigator delegation of responsibilities log 	
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800	Site signature log	

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010	Subject enrollm
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012	Subject identifi
)13	- Substantive cor
)15	• Substantive cor
016	Notification of
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018	11.2.4 Delegation of
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020	The Investigator must
021	qualified by education,
022	task; and (b) provide ad
023	sub-investigators and c
024	delegated significant st
025	11.3 Protocol Deviat
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027	11.3.1 Protocol Devia
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	Protocol deviations sho
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)29)30)31	Protocol Deviation
029 030 031 032	Protocol Deviation
029 030 031 032 033	<i>Protocol Deviation</i> A protocol deviation is
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029 030 031 032 033 034 035 036	Protocol Deviation A protocol deviation is procedures of a researc Changes or alterations subject's rights, safety
029 030 031 032 033 034 035 036 037	Protocol Deviation A protocol deviation is procedures of a researce Changes or alterations subject's rights, safety study data are consider
029 030 031 032 033 034 035 036 037	Protocol Deviation A protocol deviation is procedures of a researce Changes or alterations subject's rights, safety study data are consider Important Protocol De
029 030 031 032 033 034 035 036 037 038 039	 Protocol Deviation A protocol deviation is procedures of a researce Changes or alterations subject's rights, safety study data are consider Important Protocol Deviation
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029 030 031 032 033 034 035 036 037 038 039 040 041	 Protocol Deviation A protocol deviation is procedures of a researce Changes or alterations subject's rights, safety study data are consider Important Protocol Dee An important protocol may significantly affect

Subject enrollment	log
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- cation log
- respondence with the Sponsor and IRB/IEC
- the end of the trial to the IRB/IEC.

f Investigator Responsibilities

(a) ensure that any individual to whom a task is delegated is training, and experience (and licensure, if relevant) to perform the dequate supervision. The Investigator should maintain a list of ther appropriately qualified persons to whom he or she has udy-related duties.

ions

tion Definitions

ould be documented in accordance with the Manual of Operations.

any change, divergence, or departure from the study design or ch protocol that has not been approved by the IRB/IEC.

in the conduct of the trial which do not have a major impact on the or well-being, or the completeness, accuracy and reliability of the red minor protocol deviations.

eviation

deviation is a deviation from the IRB/IEC-approved protocol that et the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. This includes examples such as)42 043 inappropriate consent, errors in drug dosing, or lack of reporting of safety data.

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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.

D66The Sponsor reserves the right to terminate the study for refusal of the Investigator toD67supply 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

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080	6. Record of all relevant communications between the Investigator and the Sponsor	
081	(or designee)	
082	7. List of sub-investigators and other appropriately qualified persons to whom the	
083	Investigator has delegated significant study-related duties, together with their	
084	roles in the study and their signatures	
085	8. Drug accountability records (See Section 5.8.4)	
)86)87	9. Record of any body fluids or tissue samples retained	
088	5. Record of any body manas of assue samples realined	
089	10. All other source documents (subject records, hospital records, laboratory records,	
090	etc.)	
091	11. All other documents as listed in Section 8 of the ICH consolidated guideline on	
092	GCP (Essential Documents for the Conduct of a Clinical Trial).	
093	11.5 Study Monitoring	
)94)05	In accordance with analizable regulations CCD and the presedence of the Secondar on its	
	In accordance with applicable regulations, GCP, and the procedures of the Sponsor or its	
)96	designees, the Study Monitor will periodically contact the site and conduct on-site visits.	
097	The extent, nature, and frequency of on-site visits will be based on enrollment rate and	
098	data quality at the site. Through frequent communications (e.g., letter, e-mail, and	
)99	telephone), the Study Monitor will ensure that the investigation is conducted according to	
100	protocol and regulatory requirements.	
101	During these contacts, the monitoring activities will include:	
102 103	1. Checking and assessing the progress of the study	
104	2. Reviewing study data collected to date for completeness and accuracy	
105	3. Reviewing compliance with protocol assessments	
106	4. Conducting source document verification by reviewing eCRF database data	
107	against source documents when available (e.g., medical records, subject diaries,	
108	ICF [and assent, if applicable], laboratory result reports, raw data collection	
109	forms)	
110	5. Identifying any issues and addressing resolutions	
	c. radiarying any issues and addressing resonations.	

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112	These activities will be done in order to verify that the:	
113	1. Data are authentic, accurate, and complete	
115	2. Safety and rights of the subjects are being protected	
116	3. Study is conducted in accordance with the currently approved protocol (and any	
117	amendments), GCP, and all applicable regulatory requirements.	
118 119	The Investigator will allow the Study Monitor direct access to all relevant documents	
120	and allocate his/her time and the time of his/her staff to the Study Monitor to discuss	
120	findings and any relevant issues.	
122	In addition to contracte during the study, the Study Manitempiill contract the site union to	
122	in addition to contacts during the study, the Study Monitor will contact the site prior to	
123	the start of the study to discuss the protocol and data collection procedures with site	
124	personnel.	
125	At study closure, Study Monitors will conduct all activities as indicated in Section 11.7.	
120	11.6 Quality Assurance	
128 129	At its discretion, the Sponsor or its designee may conduct a quality assurance audit of this	
130	study. Auditing procedures of the Sponsor and/or its designee will be followed in order	
131	to comply with GCP guidelines and ensure acceptability of the study data for registration	
132	purposes. If such an audit occurs, the Investigator will give the auditor direct access to	
133	all relevant documents, and will allocate his/her time and the time of his/her staff to the	
134	auditor as may be required to discuss findings and any relevant issues.	
135	In addition, regulatory authorities and/or the IRB/IEC may conduct an inspection of this	
136	study. If such an inspection occurs, the Investigator will allow the inspector direct access	
137	to all source documents, eCRFs, and other study documentation for source data check	
138	and/or on-site audit inspection. The Investigator must allocate his/her time and the time	
139	of his/her staff to the inspector to discuss findings of any relevant issues.	
140	An explanation will be given for all missing, unused, and spurious data in the relevant	
141	section of the study report.	

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143	11.7 Study Termination and Site Closure	
144 145	Upon completion of the study the following activities, when applicable, must be	
146	conducted by the Study Monitor in conjunction with the Investigator, as appropriate:	
140	conducted by the Study Monitor in conjunction with the investigator, as appropriate.	
147	1. Provision of all study data to the Sponsor	
148	2. Data clarifications and/or resolutions	
149	3. Accounting, reconciliation, and final disposition of used and unused study	
150	medication	
151 152	4. Review of site study records for completeness.	
153	In addition, the Sponsor reserves the right to temporarily suspend or prematurely	
154	terminate this study for any reason.	
155	If the study is suspended or terminated for safety reason(s), the Sponsor will promptly	
156	inform the Investigator, and will also inform the regulatory authorities of the suspension	
157	or termination of the study and the reason(s) for the action. The Investigator is	
158	responsible for promptly informing the IRB/IEC, and providing the reason(s) for the	
159	suspension or termination of the study.	
160	If the study is prematurely terminated, all study data must be returned to the Sponsor. In	
161	addition, the site must conduct final disposition of all unused study medications in	
162	accordance with the Sponsor procedures for the study.	
163	11.8 Site Termination	
164 165	The Sponsor may at any time, at its sole discretion, terminate the study site for various	
166	reasons, including, without limitation, the following:	
167	1. Failure of the Investigator to enroll subjects into the study	
168	2. Failure of the Investigator to comply with applicable laws and/or pertinent	
169	regulations	
170	3. Submission of knowingly false information from the research facility to the	
171	Sponsor, Study Monitor, or regulatory authorities	
172	4. Insufficient adherence to protocol requirements.	

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If participation of a study site is terminated, the Sponsor and Study Chair will issue a written notice to the Investigator. The written notice will contain the reasons for taking such action. If the study site is terminated for noncompliance, appropriate regulatory authorities will also be notified by the Sponsor.

178Study termination and follow-up will be performed in compliance with relevant179regulations 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, and birth date will be recorded on the eCRF. If the subject's name appears on any other document collected (e.g., hospital discharge summary), the name must be obliterated before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects' parents or guardians will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB/IEC to inspect the subjects' medical records to verify the information collected. The subjects' parents or guardians will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all 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

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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

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

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

All information concerning the product as well as any information such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor or designee, and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no 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.

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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.

14 REFERENCES

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255	14 REFE	RENCES
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15 APPENDICES

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399 100	Appendix 15.1Protocol Amendment #4 Complete List of Changes
401	The following changes have been incorporated into the protocol under this protocol
402	amendment, as summarized in Protocol Amendment Tracking, Reasons for Protocol
403	Amendment #4. Protocol sections that have been changed are itemized below with the
404	original and revised text. Correction of typographical errors is not itemized.
405 406	Sections Changed:
407	Synopsis: Primary Objectives, #1
408 409	Section 2.1.1: Primary Objectives, #1
410	Original Text:
411 412	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD; and
413	Revised Text:
414 415 416	 To compare the efficacy of vamorolone administered orally at daily doses of 6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD; and
417 418	Sections Changed:
419	Synopsis: Secondary Objectives, #1-3
420 421	Section 2.1.2: Secondary Objectives, #1-3
422	Original Text:
423 424 425	 To compare the safety of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
426 427 428	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
429 430 431	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg vs. vamorolone administered orally at daily doses of 6.0 mg/kg over a 24-week treatment period in ambulant boys ages 4 to <7 years with DMD;
432	Revised Text:
433 434	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD;
435 436 437	 To compare the safety of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;
438 439 440	 To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. daily prednisone 0.75 mg/kg in ambulant boys ages 4 to <7 years with DMD;

Section Changed:

Synopsis: Synopsis, Pharmacodynamic Measures, sentence #2

Original Text:

Secondary outcomes are serum biomarkers bridged to clinical outcomes of safety, including adrenal suppression, insulin resistance, bone turnover, and immune suppression.

Revised Text:

Secondary outcomes are serum biomarkers bridged to clinical outcomes of safety, including adrenal suppression, insulin resistance, and bone turnover.

Sections Changed:

Synopsis: Statistical Methods, Sample Size, paragraphs #2 and #3 Section 10.1: Sample Size Determination, paragraphs #2 and #3

Original Text:

The primary efficacy outcome is TTSTAND (velocity) change from baseline to Week 24. A sample size of 30 subjects per treatment group (120 total subjects) will detect a 0.0674 point difference in mean change from baseline to Week 24 in TTSTAND (velocity) between a vamorolone dose level and placebo, assuming a common standard deviation of 0.08, a two-sided t test, and a Type-I error of 0.025 with approximately 83% power. The Bonferroni adjustment method will be used to control the Type-I error rate at 0.05 due to the multiple comparisons (2 vamorolone dose levels will be tested against placebo).

Based on this calculation, a total of approximately 120 subjects will be randomized to treatment with vamorolone 2.0 mg/kg/day (n=30), vamorolone 6.0 mg/kg/day (n=30), prednisone 0.75 mg/kg/day (n=30), or placebo (n=30).

Revised Text:

In the vamorolone VBP15-003 study and the interim analysis of the VBP15-LTE study, doses of 0.25 and 0.75 mg/kg/day showed little evidence of clinical benefit, whereas doses of 2.0 and 6.0 mg/kg/day both showed clear evidence of clinical benefit comparable to that seen with glucocorticoids (prednisone and deflazacort).

In consideration of the primary efficacy endpoint in the current study, comparison of 6.0 mg/kg/day vamorolone versus placebo, sample size calculations were performed using data from vamorolone-treated subjects from the VBP15-002/VBP15-003 24-week treatment period. The analysis compared TTSTAND velocity from the combined 2.0 and 6.0 mg/kg/day groups (Treatment Group) to the combined 0.25 and 0.75 mg/kg/day groups (Pseudo-Placebo Group).

Least squares (LS) means from the mixed model for repeated measures (MMRM) modeling of VBP15-002/VBP15-003 24-week data were used as parameter estimates of the population means in the sample size calculations for the comparison of the Treatment Group (2.0 + 6.0 mg/kg/day) vs. the Pseudo-Placebo Group (0.25 + 0.75 mg/kg/day) on the mean change from baseline at Week 24. For the estimates of standard deviations within each comparison group, simple descriptive statistics from the VBP15-002/VBP15-003 24-week data were used. Power was estimated using two-sided t-tests assuming unequal variance, with alpha =0.05.

The following table shows the resultant estimated power for various sample sizes per comparison group for comparing the Treatment Group (2.0 + 6.0 mg/kg/day) vs. the Pseudo-Placebo Group (0.25 + 0.75 mg/kg/day) on the mean change from baseline at Week 24 for the alternative hypothesis that H1: $\mu 1 \neq \mu 2$

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 assuming an alpha level of 0.05 and parameter estimates from the analyses described above for TTSTAND

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 velocity:

bity: Sample Size μl $\mu 2$ σl $\sigma 2$ Estimated

per Comparison Group	µ1 (Pseudo- Placebo)	μ2 (Treatment Group)	σ1 (Pseudo- Placebo)	σ2 (Treatment Group)	Estimated Power
25	-0.0052	0.0450	0.0628	0.0530	84.89%
28	-0.0052	0.0450	0.0628	0.0530	88.76%
30	-0.0052	0.0450	0.0628	0.0530	90.81%

The sample size of 25 per treatment group for 2.0 mg/kg/day, 6.0 mg/kg/day, prednisone, and placebo will result in a total enrollment of 100 subjects which will provide approximately 85% power at alpha level 0.05 to detect a statistically significant difference between 6.0 mg/kg/day and placebo on TTSTAND velocity at Week 24. Similarly, a total enrollment of 120 subjects (30 per treatment group) will provide approximately 91% power at alpha level 0.05 to detect a statistically significant difference between 6.0 mg/kg/day and placebo on TTSTAND velocity at placebo on TTSTAND velocity at Week 24.

Section Changed:

Synopsis: Statistical Methods, Analysis Populations

Original Text:

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

Safety Population

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

Modified Intent-to-Treat (mITT) Population

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

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.

Revised Text:

Four populations will be defined for data analysis: the Safety Population, the modified Intent-to-Treat Population, the Per Protocol Population (PPP), and the Pharmacokinetic (PK) Population.

Safety Population

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

525 <u>Modified Intent-to-Treat (mITT) Population</u>

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."

531 <u>Per Protocol Population</u>

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The PPP will be those subjects in the mITT Population who had no major protocol deviations and will be the secondary analysis population for analysis of the efficacy data. The PPP will also exclude some subjects because of missed assessments due to the COVID-19 pandemic. Exclusion of subjects from the PPP will be made on a subject-by-subject basis prior to database hard lock.

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.

Sections Changed:

Synopsis: Statistical Methods, Adjustment for Multiple Comparisons, paragraphs #1-4 Section 10.0.2: A directment for Multiple Comparisons, paragraphs #1.4

Section 10.9.2: Adjustment for Multiple Comparisons, paragraphs #1-4

Original Text:

The primary efficacy endpoint tests each dose of vamorolone vs. placebo using TTSTAND velocity at Week 24 and occurs during Treatment Period #1 of the study. The primary efficacy endpoint supports the primary objective of this study. The study is thus powered for the efficacy comparisons.

A multi-branched gatekeeping procedure will be utilized for the primary efficacy endpoint. The primary efficacy endpoint (TTSTAND velocity at Week 24) will be tested first using a Bonferroni adjustment. Any dose that is significant for the primary efficacy endpoint will then have the secondary efficacy endpoints tested sequentially. Further details are provided below.

For primary efficacy (TTSTAND velocity), the two vamorolone dose levels will be compared with placebo. To account for these comparisons (two vamorolone dose levels vs. placebo), Bonferroni multiple comparison adjustments will be utilized. Each comparison will be conducted at the 0.025 (0.05/2) alpha level.

Secondary efficacy endpoints will be tested sequentially on change from baseline to Week 24 values (each dose of vamorolone vs. placebo or prednisone [6MWT only]). Only the doses that are significant for the primary efficacy endpoint (change in TTSTAND velocity at Week 24) will have the secondary endpoints tested. A 0.025 alpha level will be used for the sequential testing. Testing will stop once a p-value is >0.025 for one of the secondary efficacy endpoints. The Week 24 change from baseline values will be tested using this sequential testing procedure. The order of the secondary efficacy endpoints is as follows.

- 1. Six-minute Walk Test (6MWT) vs. placebo
- 2. Time to Run/Walk 10 meters Test (TTRW) velocity vs. placebo
- 3. 6MWT vs. prednisone
- 4. North Star Ambulatory Assessment (NSAA) vs. placebo
- 5. Hand-held Myometry (knee extensors) vs. placebo
- 6. Hand-held Myometry (elbow flexors) vs. placebo
- 7. Time to Climb 4 Steps (TTCLIMB) velocity vs. placebo
- 8. Range of Motion (ROM) in the ankles vs. placebo

Revised Text:

The primary efficacy endpoint tests vamorolone 6.0 mg/kg/day vs. placebo using TTSTAND velocity at Week 24 and occurs during Treatment Period #1 of the study. The primary efficacy endpoint supports the primary objective of this study. The study is thus powered for the efficacy comparison using an alpha level of 0.05 for success.

The secondary efficacy endpoints will be tested at Week 24 along with the primary efficacy endpoint using a fixed sequential testing process where the fixed sequence of testing will be done in the following order:

- 1. TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo
- 2. 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs. placebo
- 3. 6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs. placebo
- 4. Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day vs. placebo
- 5. Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day vs. placebo
- 6. 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone
- 7. 6MWT meters walked, vamorolone 2.0 mg/kg/day vs. prednisone

Each test in the sequence will be carried out using a two-sided alpha level of 0.05. Statistical testing of the primary/secondary efficacy endpoints will stop if a p-value >0.05 occurs or if a p-value \leq 0.05 occurs in the wrong direction. In case the fixed sequential testing process stops, the results of the subsequent tests will be reported with nominal p-values, but p-values \leq 0.05 in the right direction will not be considered proof of statistical testing success in these subsequent tests.

Section Changed:

Synopsis: Statistical Methods, Efficacy Analysis, paragraphs #1 and #2

Original Text:

All evaluations of clinical efficacy will be listed and presented using descriptive statistics per treatment group and time point. The primary efficacy outcome is TTSTAND (velocity). Secondary efficacy outcomes are the NSAA assessment, TTCLIMB, TTRW, 6MWT, hand-held myometry (elbow flexors and knee extensors), and ROM. TTSTAND, TTCLIMB, and TTRW will be analyzed using raw scores and velocity.

The primary efficacy outcome TTSTAND (velocity) change from baseline to Week 24 will be compared between each of the two different vamorolone dose groups and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed effects for treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline TTSTAND, age group (per stratification), and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, pairwise comparisons (using least squares [LS] mean contrasts) will be made to compare TTSTAND at 24 weeks for each vamorolone dose level with placebo separately (primary efficacy outcome), for each vamorolone dose level with prednisone separately (secondary analysis), and for the high vamorolone dose level with the low vamorolone dose level (secondary analysis). Treatments will also be compared at other weeks as secondary analyses. An unstructured covariance matrix will be used, and underlying modelling assumptions will be checked. If differences between baseline characteristics exist between the three treatment groups in this comparison, it will be investigated if adjustment for these characteristics is clinically relevant and necessary. The secondary outcome measures will be compared using similar models.

Revised Text:

All evaluations of clinical efficacy will be listed and presented using descriptive statistics per treatment group and time point. The primary efficacy outcome is TTSTAND (velocity), comparison of vamorolone 6.0 mg/kg/day vs placebo. Secondary and exploratory efficacy outcomes are TTSTAND (velocity), comparison of vamorolone 2.0 mg/kg/day vs placebo; the NSAA assessment; TTCLIMB (velocity); TTRW (velocity); 6MWT; hand-held myometry (elbow flexors and knee extensors); and ROM.

The primary efficacy outcome TTSTAND (velocity) change from baseline to Week 24 will be compared between the 6.0 mg/kg/day vamorolone dose group and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model includes fixed

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effects for treatment (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, baseline TTSTAND, age group (per stratification), and the treatment-by-week interaction. Study week will be included in the model as a categorical variable (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, pairwise comparisons (using least squares [LS] mean contrasts) will be made to compare TTSTAND velocity at 24 weeks for the vamorolone 6.0 mg/kg/day dose level with placebo (primary efficacy outcome).

For secondary outcomes, the same models will be used as for the primary outcome (REML-based MMRM including fixed effects for treatment [vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo], age group [<6 years; \geq 6 years], week, baseline, and treatment-by-week interaction).

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

Sensitivity analyses will be performed to assess the impact of COVID-19 on the primary endpoint. Additional sensitivity and supportive analyses will be performed on the primary and secondary outcomes. Full details will be provided in the SAP.

Sections Changed:

<u>Synopsis: Statistical Methods, Patient Reported Outcome Analyses</u> <u>Section 10.9.7: Patient Reported Outcome Exploratory Analyses</u>

Original Text:

Patient Reported Outcomes including the TSQM, PODCI, PARS III, Ease of Study Medication Administration Assessment, and the Blindedness Assessment will be listed and presented using descriptive statistics by treatment and time point. In addition, comparison will be made for each vamorolone dose group with placebo for the PODCI and for each vamorolone dose group with prednisone for the PARS III, with p values computed for the comparisons. Full details will be provided in the SAP.

Revised Text:

Patient Reported Outcomes including the TSQM, PODCI, PARS III, Ease of Study Medication Administration Assessment, and the Blindedness Assessment will be listed and presented using descriptive statistics by treatment and time point. In addition, comparison will be made for each vamorolone dose group with placebo for the PODCI and for each vamorolone dose group with prednisone and placebo for the PARS III, with p values computed for the comparisons. Full details will be provided in the SAP.

Section Changed:

Synopsis: Statistical Methods, Safety Analyses

Original Text:

All evaluations of clinical safety will be listed and presented using descriptive statistics per treatment group and time point. For the safety analyses, the vamorolone dose levels will be compared to prednisone.

Safety data will include BMI, weight, vital signs, 2D-echocardiogram, DXA scan, spine x-ray, eye examination results, ACTH Stimulation Test results, and ECG results, and these will be presented using descriptive statistics. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed. Adverse events will be summarized overall and by treatment group, system organ class (SOC) and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]); by treatment group and relationship to study medication; and by treatment group and intensity (CTCAE grade).

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In Treatment Period #1, BMI z-score change from baseline data captured over 24 weeks will be compared for subjects who are randomized to receive vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day vs. subjects randomized to receive prednisone. The same MMRM that is used for the primary efficacy analysis will be used for BMI z-score. The test for statistical significance will be performed at the 0.05 level. Subjects who are randomized to receive vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for both treatment periods will have their BMI z-score change from baseline data captured over 48 weeks compared with prednisone-treated DMD historical control data. Full details will be provided in the SAP.

Revised Text:

All evaluations of clinical safety will be listed and presented using descriptive statistics per treatment group and time point. For the safety analyses during Treatment Period #1, the vamorolone dose levels will be compared to prednisone, as specified in the SAP.

Safety data will include BMI, weight, vital signs, 2D-echocardiogram, DXA scan, spine x-ray, eye examination results, ACTH Stimulation Test results, and ECG results, and these will be presented using descriptive statistics. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed. Adverse events will be summarized overall and by treatment group, system organ class (SOC) and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]); by treatment group and relationship to study medication; and by treatment group and intensity (CTCAE grade). Suicidality and abuse potential associated with treatment will be assessed by examination of adverse event data. Full details will be provided in the SAP.

In Treatment Period #1, BMI z-score change from baseline results will be compared between treatment groups using an REML-based MMRM analysis with treatment group, week of the visit, and the treatmentby-week interaction as factors, and baseline BMI z-score and age group as a covariate. Week will be included in the model as a categorical variable (Week 12 and 24) along with the treatment-by-week interaction. An unstructured within-subject covariance matrix will be used. If this analysis fails to converge, Akaike's information criterion will be used to select the best covariance structure from compound symmetry and autoregressive-1 (AR(1)). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Change from baseline in all continuous clinical laboratory test results will be tested using one sample t-tests with p-values presented along with the descriptive statistics at each assessment visit within each treatment group.

Sections Changed:

<u>Synopsis: Statistical Methods, Pharmacodynamics Analyses, sentence #1</u> <u>Section 10.9.6: Pharmacodynamic Analyses, sentence #1</u>

Original Text:

Serum PD biomarkers of adrenal axis suppression, insulin resistance, bone turnover, and immune suppression will be assessed.

Revised Text:

Serum PD biomarkers of adrenal axis suppression, insulin resistance, and bone turnover will be assessed.

721 Section Changed:

722 List of Abbreviations

723 Original Text:

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724		
123	РК	pharmacokinetics
	PODCI	Pediatric Outcomes Data Collection Instrument
	PR [PQ]	time from onset of P wave to start of the QRS complex
	QD	once daily (dosing)
726 727	Revised Text:	
	РК	pharmacokinetics
	PODCI	Pediatric Outcomes Data Collection Instrument
	PPP	Per Protocol Population
	PR [PQ]	time from onset of P wave to start of the QRS complex
700	QD	once daily (dosing)
728	Section Changed:	
730	Section Changear	
731	Section 1.4: Rationa	<u>le for Study Design, paragraph #5</u>
733	Original Text:	
734	The primary efficacy	outcome is the Time to Stand (TTSTAND) from the floor
735	(velocity), and compa	risons will be made between each dose level of vamorolone and the
736	placebo group at Wee	k 24. Multiple secondary efficacy outcomes will be measured,
737	including Time to Ru	n/Walk 10 meters (TTRW), Time to Climb four stairs (TTCLIMB),
738	North Star Ambulator	ry Assessment (NSAA), 6-Minute Walk Test (6MWT), Range of
739	Motion test (ROM), a	nd hand-held myometry (elbow flexors and knee extensors).
740	Exploratory measures	of efficacy include PD biomarkers that have previously been
741	shown to be glucocor	ticoid-responsive in DMD boys and inflammatory bowel disease in
742	children. ³¹ Moreover,	physical functioning, behavior, neuropsychology, and satisfaction
743	with treatment will be	measured as exploratory efficacy outcomes using the parent proxy-
744	report of Pediatric Ou	tcomes Data Collection Instrument (PODCI), PARS III, Treatment
745	Satisfaction Question	naire (TSQM), and Ease of Study Medication Administration
746	Assessment for the stu	udy medication suspension, respectively.
747 748	Revised Text:	
749	The primary efficacy	outcome is the Time to Stand (TTSTAND) from the floor
750	(velocity), and compa	rison will be made between the 6.0 mg/kg/day dose level of
751	vamorolone and the p	lacebo group at Week 24. Multiple secondary and exploratory

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753	efficacy outcomes will be measured, including TTSTAND, Time to Run/Walk 10 meters
754	(TTRW), Time to Climb four stairs (TTCLIMB), North Star Ambulatory Assessment
755	(NSAA), 6-Minute Walk Test (6MWT), Range of Motion test (ROM), and hand-held
756	myometry (elbow flexors and knee extensors). Additional exploratory measures of
757	efficacy include PD biomarkers that have previously been shown to be glucocorticoid-
758	responsive in DMD boys and inflammatory bowel disease in children. ³¹ Moreover,
759	physical functioning, behavior, neuropsychology, and satisfaction with treatment will be
760	measured as exploratory outcomes using the parent proxy-report of Pediatric Outcomes
761	Date Collection Instrument (BODCI), BABS III, Treatment Satisfaction Questionneire
701	(TSON) = 15 = 52(-1, M, 1) + (1, -1, 1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1, -1) + (1, -1) + (1, -1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1) + (1, -1
/62	(ISQM), and Ease of Study Medication Administration Assessment for the study
763	medication suspension, respectively.
764	Section Changed:
765 766	Section 1.4: Pationals for Study Design paragraph #6 item #4
767	Section 1.4: Kationale for Study Design, paragraph #0, item #4
768	Original Text:
769	4. Immune suppression. Glucocorticoids can cause immunosuppression. The
770	measure of differential lymphocyte percentage can be a biomarker for immune
771	suppression.
772	Revised Text:
773	none
774	
775	Section Changed:
770	Section 1.5: Overall Benefit/Risk, naragranh #1
778	Steash field Stefan Denend Hish, purugruph #1
779	Original Text:
780	It is anticipated that the adverse effect profile of the investigational product will be more
781	favorable than standard of care glucocorticoids in the long term. There were no serious
782	adverse events (SAEs) reported over the 14-day treatment in the Phase I clinical trial in
783	healthy adult volunteers, nor in the four cohorts (0.25 mg/kg, 0.75 mg/kg, 2.0 mg/kg, and
784	6.0 mg/kg) of the Phase IIa study (VBP15-002; 14-day treatment) in boys ages 4 to
785	<7 years with DMD. There have been a total of 7 SAEs in the Phase II VBP15-003 and

VBP15-LTE extension studies in DMD boys: two SAEs of pneumonia in two different 787 subjects (both subjects receiving vamorolone 0.75 mg/kg/day), one SAE of bilateral 788 testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day, 789 one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day, and 790 two SAEs of acute myoglobinuria in the same subject receiving 6.0 mg/kg/day. Each of 791 these SAEs was considered unrelated to study drug, and none of them resulted in 792 discontinuation from the study. In the Phase I clinical trial in adult volunteers, 793 794 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 795 levels up to 6.0 mg/kg/day did not appear to induce liver toxicity over a 24-week 796 treatment period in the VBP15-003 study. In the VBP15-002 study, after 2 weeks of 797 treatment, 0 of 11 tested participants who received vamorolone 0.25 mg/kg/day, 0 of 11 798 tested participants who received vamorolone 0.75 mg/kg/day, 2 of 11 (18.2%) tested 799 participants who received vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested 800 participants who received vamorolone 6 mg/kg/day had a depressed morning cortisol 801 (<3.6 µg/dL [100 nmol/L]) consistent with chronic adrenal suppression. In the 802 803 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%) 804 tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%) tested participants 805 (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 µg/dL [100 nM]) consistent with 806 807 chronic adrenal suppression. Instructions for detecting adrenal crisis and the circumstances in which stress dose steroids should be provided will be included in the 808 Informed Consent Form (ICF) and Manual of Operations, and Investigators should 309 monitor clinical study participants closely to identify elevations in liver-specific 810 enzymes. 811

812 **Revised Text:**

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It is anticipated that the adverse effect profile of the investigational product will be more favorable than standard of care glucocorticoids in the long term. There has been a total of 11 SAEs in the vamorolone program to date: a total of 4 SAEs in the VBP15-003 study, a total of 3 SAEs in the VBP15-LTE study, a total of 3 SAEs in the VBP15-004

study, and 1 SAE in the VBP15-EAP program. There have been two SAEs of pneumonia 819 in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day); one SAE 820 of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 821 mg/kg/day; one SAE of influenza associated dehydration in a subject receiving 6.0 822 mg/kg/day; two SAEs of acute myoglobulinemia in the same subject receiving 6.0 823 mg/kg/day; one SAE of viral gastroenteritis with secondary dehydration in a subject 824 receiving blinded study drug; one SAE of asthma exacerbation in the setting of 825 826 respiratory syncytial virus and bronchiolitis in a subject receiving vamorolone at either 2.0 mg/kg/day or 6.0 mg/kg/day; one SAE of perforated appendicitis occurring with 30 827 days after the subject completed the VBP15-004 study, and one SAE of viral 828 gastroenteritis requiring hospitalization for hydration. Each of these SAEs was 329 considered unrelated to study drug, and none of them resulted in discontinuation from the 830 831 study.

832 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. One subject 333 834 participating in VBP15-004 developed an AE of acute cholestatic hepatitis manifested by elevated transaminases, direct bilirubin, ALP and GGT during Treatment Period #1 and 835 after study drug interruption and restart, redeveloped acute cholestatic hepatitis in 836 Treatment Period #2. Unblinding of the treatment assignment for this subject, to 837 facilitate decisions regarding subsequent standard of care corticosteroid therapy, 838 839 indicated that the subject had been on vamorolone 6.0 mg/kg/day in both Treatment Period #1 and Treatment Period #2. 840

In the VBP15-002 study, after 2 weeks of treatment, 0 of 11 tested participants who 841 received vamorolone 0.25 mg/kg/day, 0 of 11 tested participants who received 842 vamorolone 0.75 mg/kg/day, 2 of 11 (18.2%) tested participants who received 843 vamorolone 2 mg/kg/day, and 6 of 10 (60.0%) tested participants who received 844 vamorolone 6 mg/kg/day had a depressed morning cortisol (<3.6 µg/dL [100 nmol/L]) 845 consistent with chronic adrenal suppression. In the VBP15-003 study, after 24 weeks of 846 treatment, 0 of 8 tested participants (0.25 mg/kg/day), 1 of 12 (8.3%) tested participants 847 848 (0.75 mg/kg/day), 5 of 12 (41.7%) tested participants (2.0 mg/kg/day), and 8 of 9 (88.9%)

849	
850	tested participants (6.0 mg/kg/day) had a depressed morning cortisol (<3.6 μ g/dL
851	[100 nM]) consistent with chronic adrenal suppression. Instructions for detecting adrenal
852	crisis and the circumstances in which stress dose steroids should be provided will be
853	included in the Informed Consent Form (ICF) and Manual of Operations, and
854	Investigators should monitor clinical study participants closely to identify elevations in
855	liver-specific enzymes.
856 857 858	Section Changed:
859	Section 2.2.1. Safety Endpoints, #1, #2, and #12
860	Original Text:
861	1. BMI z-score: Comparison of each vamorolone dose level group with the prednisone
862	group in change from baseline to each of the scheduled on-treatment and post-
863	treatment assessment time points.
864	Original Text:
865	9. Dual-energy x-ray absorptiometry (DXA) scan: Change from baseline to Week 24
866	and Week 48 in spine BMD, spine BMD z-score, total body BMD, spine and total
867	body bone mass, and total body composition (lean mass, fat mass, fat-free mass, Lean
868	Mass Index, and Fat Mass Index);
869	Original Text:
870	12. ACTH Stimulation Test: measure of adrenal suppression at Week 24 and Week 48.
871	Adrenal suppression is likely if cortisol levels $<18 \mu g/dL$ (or 500 nM) 30 or
872	60 minutes after stimulation with Cosyntropin.
873 874	Revised Text.
875	1 BMI z-score: Change from baseline to each of the scheduled on-treatment and post-
876	treatment assessment time points;
877	Revised Text:
878	9. Dual-energy x-ray absorptiometry (DXA) scan: Change from baseline to Week 24
879	and Week 48 in spine BMD, total body BMD, spine and total body bone mass, and

880	
881	total body composition (lean mass, fat mass, fat-free mass, Lean Mass Index, and Fat
882	Mass Index);
883	Revised Text:
884	12. ACTH Stimulation Test: measure of adrenal suppression at Week 24 and Week 48.
385	Percentage of subjects in each treatment group with cortisol levels $<18 \mu g/dL$ (or
886	500 nM) 30 or 60 minutes after stimulation with Cosyntropin.
887	13. Linear growth velocity: Change from baseline to each of the scheduled on-treatment
888	and post-treatment assessment time points in height percentile for age.
889	Section Changed:
890 801	Section 2.2.1: Sefety Endnoints, nergarenh #15
892	Section 2.2.1. Safety Enupoints, paragraph #15
893	Original Text:
894	none
895	
896	Revised Text:
897	Tolerability Endpoint
898	1. Premature discontinuations of study treatment due to adverse events.
899	Section Changed
900 901	<u>section Changed:</u>
902	Section 2.2.2: Clinical Efficacy Endpoints
903 904	Original Text:
905	Primary Clinical Efficacy Endpoint
906	1. Time to Stand Test (TTSTAND) velocity (rise/second): Comparison of each
907	vamorolone dose level group versus the placebo group in change from baseline
908	to the Week 24 assessment.
909	Secondary Efficacy Endpoints
910	1. Change from baseline to each of the scheduled study assessment time points for
911	each treatment group up to Week 48, with comparison of each vamorolone dose
912	level group versus the placebo group at each of the scheduled study assessment
913	time points up to and including Week 24 for:

914	
915	• Time to Stand Test (TTSTAND) velocity (rise/second) (other than Week 24);
916	
917	 Time to Climb (4 Steps) Test (TTCLIMB) velocity (tasks/second);
918	
919	• Time to Run/Walk Test (TTRW) velocity (meters/second) to complete
920	10 meters of a 14 meter course;
921	• Total distance traveled, in meters, in completing the Six-minute Walk Test
922	(6MWT);
923	• North Star Ambulatory Assessment (NSAA);
924	
925	 Hand-held myometry (elbow flexors and knee extensors); and
926	
927	• Range of motion in the ankles (ROM).
928	
929	2. Change from baseline with comparison of each vamorolone dose level group
930	versus the prednisone group at each of the scheduled study assessment time
931	points up to and including Week 24 for:
932	• Total distance traveled, in meters, in completing the Six-minute Walk Test
933	(6MWT).
934	
935	Revised Text:
936	Primary Clinical Efficacy Endpoint
937	1. Time to Stand Test (TTSTAND) velocity (rise/second): Comparison of the
938	vamorolone 6.0 mg/kg/day dose level group versus the placebo group in change
939	from baseline to the Week 24 assessment.
940	Secondary Efficacy Endpoints
941	1. Change from baseline to Week 24 for the following comparisons:
942	
943	• TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo
944	
945	• 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs.
946	placebo
947	• 6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs.
948	placebo
	а.
949	
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950	• Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day
951	vs. placebo
952	• Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day
953	vs. placebo
954	• 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone
955	• (NWT meters welled versueland 2.0 mg/kg/day versus and biggers
950	• 61vi w 1 meters walked, vamorolone 2.0 mg/kg/day vs. prednisone
958	2. Change from baseline to each of the scheduled study assessment time points for
959	each treatment group up to Week 48 for:
960	• Time to Stand Test (TTSTAND) velocity (rise/second);
901	• Time to Climb (4 Store) Test (TTCL IMP) valasity (tasks/second);
902	• Thile to Chillo (4 Steps) Test (TTCLIMB) velocity (tasks/second),
964	• Time to Run/Walk Test (TTRW) velocity (meters/second) to complete
965	10 meters of a 14 meter course;
966	• Total distance traveled, in meters, in completing the Six-minute Walk Test
967	(6MWT);
968	• North Star Ambulatory Assessment (NSAA);
969	
$\frac{9}{10}$	• Hand-held myometry (elbow flexors and knee extensors); and
9/1 770	• Panga of motion in the anklos (POM)
972	• Range of motion in the anxies (ROM).
974	Exploratory Efficacy Endpoints
975	1. Change from baseline to each of the scheduled study assessment time points up
976	to and including Week 24 for the following comparisons:
977	• TTSTAND velocity, vamorolone 6.0 mg/kg/day vs placebo (Week 6 and 12
978	only)
979	• TTSTAND velocity, vamorolone 2.0 mg/kg/day vs placebo (Week 6 and 12
980	only)
981	• 6 Minute Walk Test (6MWT) meters walked, vamorolone 6.0 mg/kg/day vs.
982	placebo (Week 12 only)

6 Minute Walk Test (6MWT) meters walked, vamorolone 2.0 mg/kg/day vs. 984 placebo (Week 12 only) 985 Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 6.0 mg/kg/day 986 vs. placebo (Week12 only) 987 Time to Run/Walk (TTRW) 10 meters velocity, vamorolone 2.0 mg/kg/day 988 vs. placebo (Week12 only) 989 6MWT meters walked, vamorolone 6.0 mg/kg/day vs. prednisone (Week 12 990 991 only) 6MWT meters walked, vamorolone 2.0 mg/kg/day vs. prednisone (Week 12 992 993 only) NSAA total score, vamorolone 6.0 mg/kg/day vs. placebo 994 NSAA total score, vamorolone 2.0 mg/kg/day vs. placebo 995 Hand-held Myometry knee extensors, vamorolone 6.0 mg/kg/day vs. 996 placebo 997 Hand-held Myometry knee extensors, vamorolone 2.0 mg/kg/day vs. 998 999 placebo 000 Hand-held Myometry elbow extensors, vamorolone 6.0 mg/kg/day vs. 001 placebo Hand-held Myometry elbow extensors, vamorolone 2.0 mg/kg/day vs. 002 003 placebo TTCLIMB velocity, vamorolone 6.0 mg/kg/day vs. placebo 004 TTCLIMB velocity, vamorolone 2.0 mg/kg/day vs. placebo 005 ROM in the ankles, vamorolone 6.0 mg/kg/day vs. placebo 006 007 ROM in the ankles, vamorolone 2.0 mg/kg/day vs. placebo 008)09 Section Changed: 010 011 Section 2.2.3: Exploratory Endpoints, #3 and #4)12 **Original Text:** 013 2.2.3 Exploratory Endpoints)14

015				
016	3. Behavioral changes (PARS III): Comparison of each vamorolone dose level group			
017	to the prednisone group for change from baseline to each of the scheduled study			
018	assessment time points up to the Week 24 assessment; comparison of each			
019	treatment group for change from baseline to the Week 48 assessment;			
020	4. Ease of study medication administration assessed at each of the scheduled study			
021	assessment time points;			
022	Revised Text:			
023	2.2.3 Additional Exploratory Endpoints			
024	3. Behavioral changes (PARS III): Comparison of each vamorolone dose level group			
026	to the prednisone group and to the placebo group for change from baseline to each			
027	of the scheduled study assessment time points up to the Week 24 assessment;			
028	comparison of each treatment group for change from baseline to the Week 48			
029	assessment;			
030	4. Ease of study medication administration (Question 1 only: tablet vs liquid)			
031	assessed at each of the scheduled study assessment time points;			
032	Section Changed:			
)33)34	Section 2.2.4. Pharmacodynamic Endpoints #1b and #1d			
035	Section 2.2.4. That macodynamic Endpoints, "To and "To			
036	Original Text:			
037	2.2.4 Exploratory Endpoints			
038	b. Bone turnover. Measures of serum osteocalcin are reflective of bone			
039	formation, and measures of serum CTX1 are reflective of bone			
040	reabsorption. Ratios of osteocalcin and CTX1 predict later clinical safety			
041	concerns of osteopenia and bone fragility.			
042	d. Immune suppression. Glucocorticoids can cause immunosuppression.			
043	Measure of differential lymphocyte percentage can be a biomarker for			
044	immune suppression.			
045	Revised Text:			
046	2.2.4 Exploratory Endpoints			

)48	b. Bone turnover. Measures of serum osteocalcin are reflective of bone
)49	formation, and measures of serum CTX1 are reflective of bone
)50	reabsorption. Levels of osteocalcin and CTX1 predict later clinical safety
)51	concerns of osteopenia and bone fragility.

Section Changed:

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Section 5.4: Rationale for Dose Selection, paragraph #5

Original Text:

Vamorolone at doses of 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day and 6.0 mg/kg/day has been demonstrated to be safe and well-tolerated in a 2-week Phase IIa study (VBP15-002) in 4 to <7 years DMD boys. The safety of these four doses continued to be studied in the 24-week Phase II extension study (VBP15-003) in 4 to 7 year-old DMD boys, and continues to be studied in the ongoing VBP15-LTE long-term extension study. There were a total of 4 SAEs in the Phase II VBP15-003 study and three SAEs to date in the VBP15-LTE extension 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, and two SAEs of acute myoglobinuria in the same subject receiving 6.0 mg/kg/day. 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.²⁹ Thus, based on the available data in the Phase I and Phase II studies 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.

Revised Text:

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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 a 2-week Phase IIa study (VBP15-002) in 4 to <7 years DMD boys. - There has been a total of 11 SAEs in the vamorolone program to date: a total of 4 SAEs in the VBP15-003 study, a total of 3 SAEs in the VBP15-LTE study, a total of 3 SAEs in the VBP15-004 study, and 1 SAE in the VBP15-EAP program. There have been two SAEs of pneumonia in two different subjects (both subjects receiving vamorolone 0.75 mg/kg/day); one SAE of bilateral testicular torsion and one SAE of hypoxia in the same subject receiving 6.0 mg/kg/day; one SAE of influenza associated dehydration in a subject receiving 6.0 mg/kg/day; two SAEs of acute myoglobulinemia in the same subject receiving 6.0 mg/kg/day; one SAE of viral gastroenteritis with secondary dehydration in a subject receiving blinded study drug; one SAE of asthma exacerbation in the setting of respiratory syncytial virus and bronchiolitis in a subject receiving vamorolone at either 2.0 mg/kg/day or 6.0 mg/kg/day; one SAE of perforated appendicitis occurring with 30 days after the subject completed the VBP15-004 study, and one SAE of viral gastroenteritis requiring hospitalization for hydration. Each of these SAEs was considered unrelated to study drug, and none of them resulted in discontinuation from the study. 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.²⁹ Thus, based on the available data in the Phase I and Phase II studies 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.

107 <u>Section Changed:</u>

Section 7.1.1: Genetic Modifiers of DMD, paragraph #4

110				
111	Original Text:			
112	none			
113 114	Revised Text:			
115	Results will be presented in an addendum report.			
116				
117	Section Changed:			
1 1 8 1 1 9	Section 7.2.6: Pharmacodynamic Biomarker Panel, naragranhs #1 and #2			
120				
121	Original Text:			
122	Blood samples will be collected to explore the effect of vamorolone on biomarkers			
123	associated with glucocorticoid safety concerns (secondary outcomes for adrenal			
124	suppression, insulin resistance, bone turnover and immune suppression), as listed in			
125	Table 19.			
126	Blood samples will be collected pre-dose at the Day 1 and Weeks 12, 24, 28, 40, and 48			
127	Visits, and at the final Week 52 Dose-tapering Period Visit for analysis of biomarkers for			
128	secondary outcome measures of adrenal suppression, bone turnover, and insulin			
129	resistance. Approximately 2 mL of blood will be collected for the PD biomarker panel			
130	(osteocalcin, P1NP, and CTX bone turnover markers) at each scheduled collection time			
131	point; blood samples for analysis of morning cortisol levels (adrenal suppression			
132	biomarker) and fasting glucose and insulin (insulin resistance biomarkers) will be			
133	collected as part of the clinical laboratory tests and require no additional blood volume.			
134	All samples will be collected after the subject has fasted for ≥ 6 hours and prior to			
135	administration of the daily dose of study medication at dosing visits. Blood samples for			
136	analysis of immune suppression (differential lymphocyte percentage) will be collected as			
137	part of the clinical laboratory tests (see Section 7.2.4). Blood remaining from collected			
138	samples not needed for protocol-specified analyses at each of these time points may be			
139	stored for future exploratory biomarker studies for aspects of safety and efficacy. These			
140	remaining blood samples may be released to scientists worldwide for research purposes,			
141	including research on biomarkers in DMD. Any released samples will have no			
142	identifying subject information.			

144 **Revised Text:**

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Blood samples will be collected to explore the effect of vamorolone on biomarkers associated with glucocorticoid safety concerns (secondary outcomes for adrenal suppression, insulin resistance, and bone turnover), as listed in **Table 19**.

Blood samples will be collected pre-dose at the Day 1 and Weeks 12, 24, 28, 40, and 48 148 Visits, and at the final Week 52 Dose-tapering Period Visit for analysis of biomarkers for 149 secondary outcome measures of adrenal suppression, bone turnover, and insulin 150 resistance. Approximately 2 mL of blood will be collected for the PD biomarker panel 151 (osteocalcin, P1NP, and CTX bone turnover markers) at each scheduled collection time 152 153 point; blood samples for analysis of morning cortisol levels (adrenal suppression biomarker) and fasting glucose and insulin (insulin resistance biomarkers) will be 154 collected as part of the clinical laboratory tests and require no additional blood volume. 155 All samples will be collected after the subject has fasted for ≥ 6 hours and prior to 156 157 administration of the daily dose of study medication at dosing visits. Blood remaining from collected samples not needed for protocol-specified analyses at each of these time 158 points may be stored for future exploratory biomarker studies for aspects of safety and 159 efficacy. These remaining blood samples may be released to scientists worldwide for 160 research purposes, including research on biomarkers in DMD. Any released samples will 161 have no identifying subject information. 162

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econdary Safety Outcomes

64	Section Changed:
165	
166	Section 7.2.6: Pharmacodynamic Biomarker Panel, Table 19
67	
168	Original Text:
68	Table 21. Pharmacodynamic Biomarkers – Secondary Safet
	Adrenal Suppression
	Cortisol - morning
	Insulin Resistance
	Glucose – fasting
	Insulin - fasting
	Bone Turnover
	Osteocalcin
	CTX1
	P1NP

Immune Suppression

Differential lymphocyte percentage

Revised Text:

Table 22. Pharmacodynamic Biomarkers – Secondary Safety Outcomes

Adrenal Suppression		
Cortisol - morning		
Insulin Resistance		
Glucose – fasting		
Insulin - fasting		
Bone Turnover		
Osteocalcin		
CTX1		
P1NP		

Section Changed:

Section 7.2.13: Bone Health and DXA Scan (total body and spine), paragraph #2

Original Text:

Antero-posterior spine (L1-L4) and total body (without head) bone mineral density (BMD) by DXA scan will be collected. DXA quality control will be performed as described in the Manual of Operations. DXA scans will be analyzed centrally by a certified medical radiation technologist at Children's Hospital of Ottawa in Ottawa, Canada, and then age-specific z-scores will be generated in order to chart the differences in the change in BMD z-scores among the different groups participating in this trial. The

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188	Screening result will represent a baseline assessment for long-term follow up. Additional		
189	DXA scanning may be arranged if clinically indicated throughout the study.		
190	Revised Text:		
191	Antero-posterior spine (L1-L4) and total body (without head) bone mineral density		
192	(BMD) by DXA scan will be collected. DXA quality control will be performed as		
193	described in the Manual of Operations. DXA scans will be analyzed centrally by a		
194	certified medical radiation technologist at Children's Hospital of Ottawa in Ottawa,		
195	Canada. The Screening result will represent a baseline assessment for long-term follow		
196	up. Additional DXA scanning may be arranged if clinically indicated throughout the		
197	study.		
198	Section Changed:		
199			
200	Section 7.2.14: Spine X-rays, paragraph #2		
201	Original Text:		
203	none		
204			
205	Revised Text:		
206	Spine x-ray data will be analyzed in an addendum report.		
207	Section Changed:		
208	Section Changed.		
210	Section 7.5.6: Serious Adverse Events, paragraph #9		
211	Original Toxts		
212	Original Text:		
213	none		
214	Revised Text:		
216	Hospital admissions scheduled prior to the study are not considered SAEs unless the		
217	hospitalization is prolonged due to an adverse event. Planned admissions as part of the		
218	study, hospitalizations for scheduled treatment of a preexisting condition that has not		
219	worsened, and hospitalization for an elective procedure are not considered SAEs.		
220	Hospitalizations for fewer than 24 hours and emergency room/department visits are not		
221	considered SAEs.		

222	
223	Section Changed:
224	
225 226	Section 10.3: Analysis Populations
227	Original Text:
228	Three populations will be defined for data analysis: the Safety Population, the modified
229	Intent-to-Treat Population, and the Pharmacokinetic Population.
230	Revised Text:
231	Four populations will be defined for data analysis: the Safety Population, the modified
232	Intent-to-Treat Population, the Per Protocol Population (PPP), and the Pharmacokinetic
233	Population.
234	Section Changed:
235	Section 10.2.2. Dharmanalringtia (DK) Domulation
236 237	Section 10.3.3: Pharmacokinetic (PK) Population
238	Original Text:
239	10.3.3 Pharmacokinetic (PK) Population
240	All subjects who receive at least one dose of vamorolone study medication and have
241	sufficient data for PK analysis will be included in the PK Population.
242	Revised Text:
243	10.3.3 Per Protocol Population
244	The Per Protocol Population (PPP) will be those subjects in the mITT Population who
245	had no major protocol deviations and will be the secondary analysis population for
246	analysis of the efficacy data. The PPP will also exclude some subjects because of missed
247	assessments due to the COVID-19 pandemic. Exclusion of subjects from the PPP will be
248	made on a subject-by-subject basis prior to database hard lock
249	10.3.4 Pharmacokinetic (PK) Population
250	All subjects who receive at least one dose of vamorolone study medication and have
251	sufficient data for PK analysis will be included in the PK Population.
252	Section Changed:
255 254 255	<u>Section 10.9.3: Subject Disposition, Demographics, and Baseline Characteristics, paragraph #2</u>

257 Original Text:

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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 treatment group and overall, per analysis population. In addition, tables will be presented according to age stratification. Baseline characteristics between groups 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.

265 **Revised Text**:

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 treatment group and overall, per analysis population. Baseline characteristics between groups presented in these summary tables will be reviewed for any clinically relevant differences among the treatment groups, and may be accounted for in the statistical models for the endpoints.

272 <u>Section Changed:</u> 273

274 <u>Section 10.9.4: Efficacy Analyses</u> 275

Original Text:

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

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

The primary efficacy outcome is the Time to Stand (TTSTAND) from supine (velocity). Secondary efficacy outcomes are the NSAA assessment, Time to Climb four stairs (TTCLIMB), Time to Run/Walk 10 meters (TTRW) the distance walked in 6 minutes (6MWT), hand-held myometry (elbow flexors and knee extensors), and ROM. TTSTAND, TTCLIMB, and TTRW will be analyzed using raw scores and velocity.

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The primary efficacy outcome TTSTAND (velocity) change from baseline to Week 24 287 will be compared between each of the two different vamorolone dose groups and the 288 placebo group using a restricted maximum likelihood (REML)-based mixed model for 289 repeated measures (MMRM). This model includes fixed effects for treatment 290 (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and 291 placebo), week, baseline TTSTAND, age group (per stratification), and the treatment-by-292 293 week interaction. Study week will be included in the model as a categorical variable 294 (Weeks 6, 12, and 24) along with the treatment-by-week interaction. Within this model, pairwise comparisons (using least squares [LS] mean contrasts) will be made to compare 295 TTSTAND at 24 weeks for each vamorolone dose level with placebo separately (primary 296 efficacy outcome), for each vamorolone dose level with prednisone separately (secondary 297 analysis), and for the high vamorolone dose level with the low vamorolone dose level 298 (secondary analysis). Treatments will also be compared at other weeks as secondary 299 analyses. An unstructured covariance matrix will be used, and underlying modelling 300 assumptions will be checked. If differences between baseline characteristics exist 301 302 between the three treatment groups in this comparison, it will be investigated if 303 adjustment for these characteristics is clinically relevant and necessary. The secondary outcome measures will be compared using similar models. Full details will be provided 304 in the SAP. 305

The following sensitivity or supportive analyses will be performed (see SAP for full details) for the primary efficacy and secondary efficacy endpoints:

- Multiple imputations using MCMC methods for missing data;
- Multiple imputations using a Control-based Pattern-Mixture Model for missing data.

Subjects who are randomized to receive vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for both treatment periods will have TTSTAND velocity change from baseline data captured over 48 weeks compared with untreated DMD historical control data. Full details will be provided in the SAP.

316 **Revised Text:**

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

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

The primary efficacy outcome is Time to Stand (TTSTAND) from supine (velocity), comparison of vamorolone 6.0 mg/kg/day vs. placebo. Secondary and exploratory efficacy outcomes are TTSTAND (velocity), comparison of vamorolone 2.0 mg/kg/day vs. placebo; the NSAA assessment; Time to Climb four stairs (TTCLIMB) (velocity); Time to Run/Walk 10 meters (TTRW) (velocity); the distance walked in 6 minutes (6MWT); hand-held myometry (elbow flexors and knee extensors); and ROM.

The primary efficacy outcome TTSTAND (velocity) change from baseline to Week 24 327 will be compared between the 6.0 mg/kg/day vamorolone dose group and the placebo 328 group using a restricted maximum likelihood (REML)-based mixed model for repeated 329 measures (MMRM). This model includes fixed effects for treatment (vamorolone 2.0 330 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo), week, 331 baseline TTSTAND, age group (per stratification), and the treatment-by-week 332 interaction. Study week will be included in the model as a categorical variable (Weeks 6, 333 12, and 24) along with the treatment-by-week interaction. Within this model, pairwise 334 comparisons (using least squares [LS] mean contrasts) will be made to compare 335 TTSTAND velocity at 24 weeks for the vamorolone 6.0 mg/kg/day dose level with 336 placebo (primary efficacy outcome). 337

For secondary outcomes, the same models will be used as for the primary outcome (REML-based MMRM including fixed effects for treatment [vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, and placebo], age group [<6 years; \geq 6 years], week, baseline, and treatment-by-week interaction).

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

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346	relevant and necessary. The secondary outcome measures will be compared using similar
347	models. Full details will be provided in the SAP.
348	The following sensitivity analyses will be performed (see SAP for full details) for the
349	primary efficacy and secondary efficacy endpoints:
350	• Multiple imputations using MCMC methods for missing data;
351	• Multiple imputations using a Control-based Pattern-Mixture Model for missing
352	data.
353	Additional sensitivity analyses will be performed to assess the impact of COVID-19 on
354	the primary endpoint. Supportive analyses will also be performed on the primary
355	endpoint. Full details will be provided in the SAP.
356	Subjects who are randomized to receive vamorolone 2.0 mg/kg/day or vamorolone
357	6.0 mg/kg/day for both treatment periods will have TTSTAND velocity change from
358	baseline data captured over 48 weeks compared with untreated DMD historical control
359	data. Full details will be provided in the SAP.
360	Section Changed:
361 362	Section 10.9.5: Safety Analyses, paragraphs #3-5
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364	Original Text:
365	Safety data will include BMI, weight, vital signs, 2D-echocardiogram, DXA scan, spine
366	X-ray, eye examination results, and ACTH Stimulation Test results, and ECG results, and
367	these will be presented using descriptive statistics. Safety laboratory data will be
368	summarized using descriptive statistics, and out-of-range values will be listed. For safety
369	analyses, the vamorolone doses will be compared to prednisone.
370	In Treatment Period #1, BMI z-score change from baseline data captured over 24 weeks
371	will be compared for subjects who are randomized to receive vamorolone 2.0 mg/kg/day
372	or vamorolone 6.0 mg/kg/day vs. subjects randomized to receive prednisone. The same
373	MMRM that is used for the primary efficacy analysis will be used for BMI z-score. The
374	test for statistical significance will be performed at the 0.05 level. Subjects who are
375	randomized to receive vamorolone 2.0 mg/kg/day or vamorolone 6.0 mg/kg/day for both

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377treatment periods will have their BMI z-score change from baseline data captured over 48378weeks compared with prednisone-treated DMD historical control data. Full details will379be provided in the SAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities 380 (MedDRA), version 20. The incidence of AEs will be summarized overall and by 381 382 treatment group, SOC and preferred term; treatment group, SOC, preferred term, and intensity (CTCAE v 4.03 grade); and treatment group, SOC, preferred term, and 383 relationship to study drug. Additional AE analyses will be at the subject level: the 384 number of subjects who had any AE, the distribution of number of AEs per subject within 385 a treatment group, worst intensity in a subject within a treatment group, highest level of 386 relationship to study treatment for each subject within a treatment group. 387

Revised Text:

Safety data will include BMI, weight, vital signs, 2D-echocardiogram, DXA scan, spine X-ray, eye examination results, and ACTH Stimulation Test results, and ECG results, and these will be presented using descriptive statistics. Safety laboratory data will be summarized using descriptive statistics, and out-of-range values will be listed. For safety analyses, the vamorolone doses during Treatment Period #1 will be compared to prednisone, as specified in the SAP.

395 In Treatment Period #1, BMI z-score change from baseline results will be compared between treatment groups using an REML-based MMRM analysis with treatment group, 396 week of the visit, and the treatment-by-week interaction as factors, and baseline BMI z-397 score and age group as a covariate. Week will be included in the model as a categorical 398 399 variable (Week 12 and 24) along with the treatment-by-week interaction. An unstructured within-subject covariance matrix will be used. If this analysis fails to 400 converge, Akaike's information criterion will be used to select the best covariance 401 structure from compound symmetry and autoregressive-1 (AR(1)). The Kenward-Roger 402 approximation will be used to estimate denominator degrees of freedom. 403

Change from baseline in all continuous clinical laboratory test results will be tested using one sample t-tests with p-values presented along with the descriptive statistics at each

407	assessment visit within each treatment group (note that pharmacodynamic biomarkers -
408	CK for efficacy, fasting glucose and insulin for insulin resistance, and GLDH for safety -
409	will be of special interest).
410	Adverse events will be coded using the Medical Dictionary for Regulatory Activities
411	(MedDRA), version 20. The incidence of AEs will be summarized overall and by
412	treatment group, SOC and preferred term; treatment group, SOC, preferred term, and
413	intensity (CTCAE v 4.03 grade); and treatment group, SOC, preferred term, and
414	relationship to study drug. Additional AE analyses will be at the subject level: the
415	number of subjects who had any AE, the distribution of number of AEs per subject within

416a treatment group, worst intensity in a subject within a treatment group, highest level of417relationship to study treatment for each subject within a treatment group. Adverse events418associated with suicidality and abuse potential will be listed. Full details will be provided419in the SAP.

VBP15-004-A4 (Version 1.4) FINAL 28AUG2020

Final Audit Report

2020-09-02

By: Jess	
	sse Damsker (jesse.damsker@reveragen.com)
Status: Sigr	ned
Transaction ID: CBJ	JCHBCAABAAbFhYlqGUrdWv25eDMyi7p3bM08_NC-eU

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