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Efficacy and Safety of Vamorolone Over 48 Weeks in Boys With Duchenne Muscular Dystrophy

A Randomized Controlled Trial

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Abstract

Background and Objectives

Vamorolone is a dissociative agonist of the glucocorticoid receptor that has shown similar efficacy and reduced safety concerns in comparison with prednisone in Duchenne muscular dystrophy (DMD). This study was conducted to determine the efficacy and safety of vamorolone over 48 weeks and to study crossover participants (prednisone to vamorolone; placebo to vamorolone).

Methods

A randomized, double-blind, placebo-controlled and prednisone-controlled clinical trial of 2 doses of vamorolone was conducted in participants with DMD, in the ages from 4 years to younger than 7 years at baseline. The interventions were 2 mg/kg/d of vamorolone and 6 mg/kg/d of vamorolone for 48 weeks (period 1: 24 weeks + period 2: 24 weeks) and 0.75 mg/kg/d of prednisone and placebo for the first 24 weeks (before crossover). Efficacy was evaluated through gross motor outcomes and safety through adverse events, growth velocity, body mass index (BMI), and bone turnover biomarkers. This analysis focused on period 2.

Results

A total of 121 participants with DMD were randomized. Vamorolone at a dose of 6 mg/kg/d showed maintenance of improvement for all motor outcomes to week 48 (e.g., for primary outcome, time to

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Glossary

6MWD = 6-minute walk distance; **AE** = adverse event; **AESI** = adverse events of special interest; **BMI** = body mass index; **COVID-19** = coronavirus disease 2019; **CS** = corticosteroid; **DMD** = Duchenne muscular dystrophy; **mITT-2** = modified intention to treat–2; **NSAA** = North Star Ambulatory Assessment; **P1NP** = procollagen 1 intact N-terminal propeptide; **PDN** = prednisone; **PODCI** = Pediatric Outcomes Data Collection Instrument; **PRED-VAM2** = prednisone → vamorolone 2 mg/kg/d; **PRED-VAM6** = prednisone → vamorolone 6 mg/kg/d; **SE** = standard error; **TEAE** = treatment-emergent adverse event; **TTCLIMBV** = time to climb 4 steps velocity; **TTRWV** = time to run/walk 10 m velocity; **TTSTANDV** = time to stand from supine velocity; **VAM** = vamorolone; **VAM2** = vamorolone 2 mg/kg/d; **VAM6** = vamorolone 6 mg/kg/d.

stand from supine [TTSTAND] velocity, week 24 least squares mean [LSM] [SE] 0.052 [0.0130] rises/s vs week 48 LSM [SE] 0.0446 [0.0138]). After 48 weeks, vamorolone at a dose of 2 mg/kg/d showed similar improvements as 6 mg/kg/d for North Star Ambulatory Assessment (NSAA) (vamorolone 6 mg/kg/d–vamorolone 2 mg/kg/d LSM [SE] 0.49 [1.14]; 95% CI −1.80 to 2.78, $p = 0.67$), but less improvement for other motor outcomes. The placebo to vamorolone 6 mg/kg/d group showed rapid improvements after 20 weeks of treatment approaching benefit seen with 48-week 6 mg/kg/d of vamorolone treatment for TTSTAND, time to run/walk 10 m, and NSAA. There was significant improvement in linear growth after crossover in the prednisone to vamorolone 6 mg/kg/d group, and rapid reversal of prednisone-induced decline in bone turnover biomarkers in both crossover groups. There was an increase in BMI after 24 weeks of treatment that then stabilized for both vamorolone groups.

Discussion

Improvements of motor outcomes seen with 6 mg/kg/d of vamorolone at 24 weeks of treatment were maintained to 48 weeks of treatment. Vamorolone at a dose of 6 mg/kg/d showed better maintenance of effect compared with vamorolone at a dose of 2 mg/kg/d for most (3/5) motor outcomes. Bone morbidities of prednisone (stunting of growth and declines in serum bone biomarkers) were reversed when treatment transitioned to vamorolone.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT03439670.

Classification of Evidence

This study provides Class I evidence that for boys with DMD, the efficacy of vamorolone at a dose of 6 mg/kg/d was maintained over 48 weeks.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked, progressive neuromuscular disorder caused by out-of-frame pathogenic variants in the *DMD* gene.[1,2] DMD is a rare disease affecting approximately 1 in 5,050 male births.[3] The standard of care is treatment with daily oral corticosteroids (CS; e.g., prednisone, deflazacort), which has been consistently shown to delay loss of ambulation and other motor abilities.[4-7] However, chronic treatment with CS causes growth stunting, weight gain, mood disturbances, adrenal insufficiency, Cushing syndrome, low bone density, fragility fractures, etc., which can preclude treatment with recommended doses.[8] The efforts of families and physicians to balance the efficacy with safety concerns leads to major variations in clinical practice.[9]

Vamorolone is a first-in-class, dissociative, steroidal anti-inflammatory drug that has shown similar efficacy and reduced safety concerns when compared with CS in both double-blind placebo-controlled and open-label trials.[10-12] Vamorolone lacks a 11β hydroxy-carbonyl group,[13] found in all 30+ CS drugs, which removes a contact site with the target glucocorticoid receptor and modifies structure/activity relationships. As well, vamorolone is not a substrate for 11β-hydroxysteroid dehydrogenase regulatory enzymes, which are known to mediate CS-associated bone morbidities in mice.[14] Furthermore, in contrast to all CS, vamorolone is a potent antagonist of the mineralocorticoid receptor.[15]

Vamorolone has had preclinical and clinical findings reported including dose-ranging findings and comparisons with long-term CS-treated boys (2.5 years treatment from steroid-naïve baseline) from natural history cohorts.[10,11,13,16-18] The pivotal clinical trial for vamorolone in DMD is VBP15-004 (ClinicalTrials.gov: NCT03439670). This trial randomized 121 participants with DMD, in the age group from 4 years to younger than 7 years, who had not been treated with CS at baseline. The trial had 2 sequential 24-week periods. Period 1 had 4 groups (placebo, prednisone, vamorolone 2 mg/kg/d, and vamorolone 6 mg/kg/d). In period 2, the placebo and prednisone groups randomly crossed over to vamorolone

treatment (either 2 or 6 mg/kg/d). The blind was maintained for the full 48 weeks of treatment period. The vamorolone-treated groups in period 1 were maintained on the same dose of vamorolone in period 2 (Figure 1, eFigure 1, links.lww.com/WNL/D407).

We previously reported the period 1 data (placebo-controlled portion), where the trial met the primary outcome (vamorolone 6 mg/kg/d vs placebo; time to rise from floor velocity) and met the initial 4 secondary outcomes.[8] Daily vamorolone at a dose of 6 mg/kg showed similar efficacy to daily prednisone at a dose of 0.75 mg/kg/d for all 5 motor outcomes studied. Vamorolone also showed a superior safety profile compared with prednisone, with improved linear growth, absence of reduction in serum bone turnover markers, and a lower incidence of mood disturbance.[12]

Herein we report the findings from the complete 48-week study (period 1 and period 2), including comparison of 48 weeks of treatment with vamorolone at a dose of 2 vs 6 mg/kg/d, and findings in crossover participants (placebo to vamorolone and prednisone to vamorolone). The primary research questions being addressed in the study were the durability of efficacy of vamorolone treatment and whether safety concerns seen with prednisone were reversed on crossover to vamorolone treatment.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical standards committee approvals on the VBP15-004 clinical trial were obtained for each of the 33 participating clinical trial recruitment sites, either for individual institutional or regional approvals. Written informed consent was obtained from all parents/guardians of participants in the VBP15-004 study (consent for research). The VBP15-004 clinical trial has been registered at ClinicalTrials.gov, at registration number NCT03439670.

Participants

A randomized double-blind trial of CS-naive participants with DMD, ages from 4 years to younger than 7 years at baseline, was conducted at 33 sites in 11 countries from 2018 to 2021.[12] Inclusion criteria included a molecularly confirmed DMD diagnosis and time to stand from supine in less than 10 seconds (full inclusion/exclusion criteria are in Protocol).

Study Design

Participants were randomized at a 2:2:1:1:1:1 ratio to the following 6 groups: vamorolone at a dose of 2 mg/kg/d throughout, vamorolone at a dose of 6 mg/kg/d throughout, prednisone at a dose of 0.75 mg/kg/d (period 1) crossover to vamorolone at a dose of 2 mg/kg/d or to vamorolone at a dose of 6 mg/kg/d (period 2), and placebo (period 1) crossover to vamorolone at a dose of 2 mg/kg/d or to vamorolone at a dose of 6 mg/kg/d (period 2), respectively. Hence, period 1 involved 4 treatment groups. After period 1, there was a 4-week transition period for participants who received either placebo or prednisone in period 1, during which the dose of prednisone (or placebo for prednisone) was tapered to zero. Participants who crossed over received vamorolone for the last 20 weeks (eFigure 1, links.lww.com/WNL/D407).

The study was designed by integrating the advice received from the European Medicines Agency and US Food and Drug Administration before starting the study. Details on sample size determination (powered for efficacy compared with placebo after 24 weeks of treatment [period 1]), stratified randomization (age younger than 6 years vs 6 years or older), multiple testing considerations through prespecified sequential testing process, and blinding through double-dummy design have previously been reported[12] and are in eMethods (links.lww.com/WNL/D407). Analyses through 48 weeks of treatment were prespecified in a Statistical Analysis Plan (eMethods).

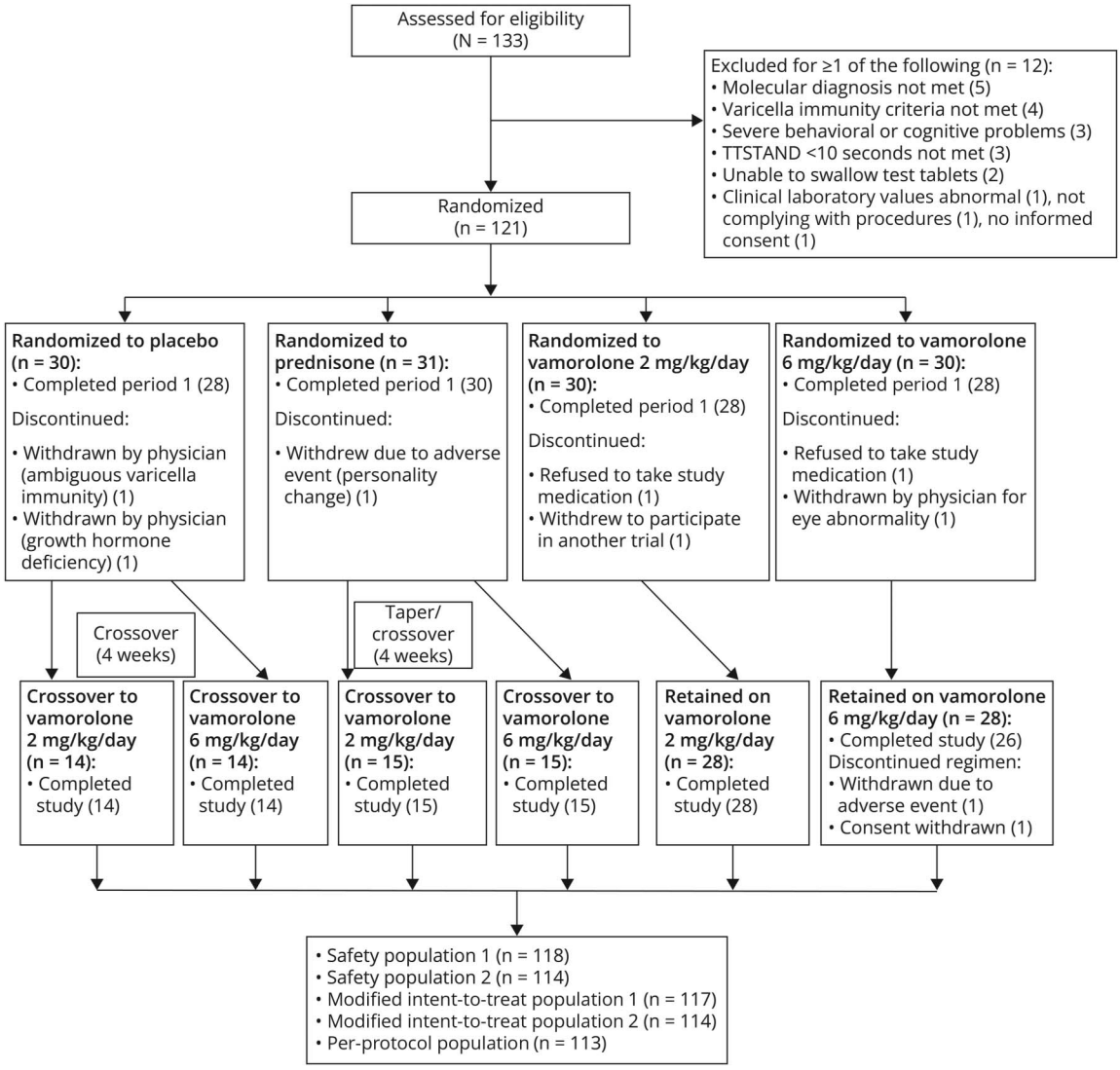
Outcomes and Assessments

Efficacy was assessed using 5 motor outcomes: time to stand from supine velocity (TTSTANDV; primary endpoint at week 24), 6-minute walk test distance (6MWD; secondary at week 24), time to run/walk 10 m velocity (TTRWV; secondary at week 24), time to climb 4 stairs velocity (TTCLIMBV; exploratory), and North Star Ambulatory Assessment (NSAA; exploratory). Velocities were calculated for the 3 timed function tests by taking the reciprocal of time taken for test (TTSTANDV, TTCLIMBV) or dividing 10 by time in seconds (TTRWV). Isometric muscle strength was measured through myometry (elbow flexors, knee extensors) and range of motion of the ankle by goniometer. Parent-reported functional outcomes were collected through the Pediatric Outcomes Data Collection Instrument (PODCI). Due to the coronavirus disease 2019 (COVID-19) pandemic, the protocol was modified to allow for remote assessments of safety and efficacy. For efficacy (motor outcomes), only the TTSTAND test (primary endpoint at 24 weeks) was performed remotely using a videoconferencing interface between the clinical evaluator and the patient family and only performed when a participant could not attend a scheduled on-site visit due to COVID restrictions. Trained clinical evaluators performed motor testing at screening, baseline, 12 weeks, 24 weeks, 40 weeks, and 48 weeks (with TTSTAND testing also performed at 6 weeks and 34 weeks).

The objectives of period 2 were to evaluate the efficacy and safety of continuous 48 weeks of vamorolone treatment (2 vs 6 mg/kg/d) and to assess vamorolone efficacy and safety in crossover participants (placebo [period 1] to vamorolone [period 2]; prednisone [period 1] to vamorolone [period 2]) (Figure 1).

Clinical and laboratory safety endpoints were assessed during screening, baseline, day 1, and week 2, 6, 12, 18, 24, 28, 30, 34, 40, and 48 visits. Adverse events of special interest (AESI)

Figure 1 Study Participant Flowchart



TTSTAND = time to stand from supine.

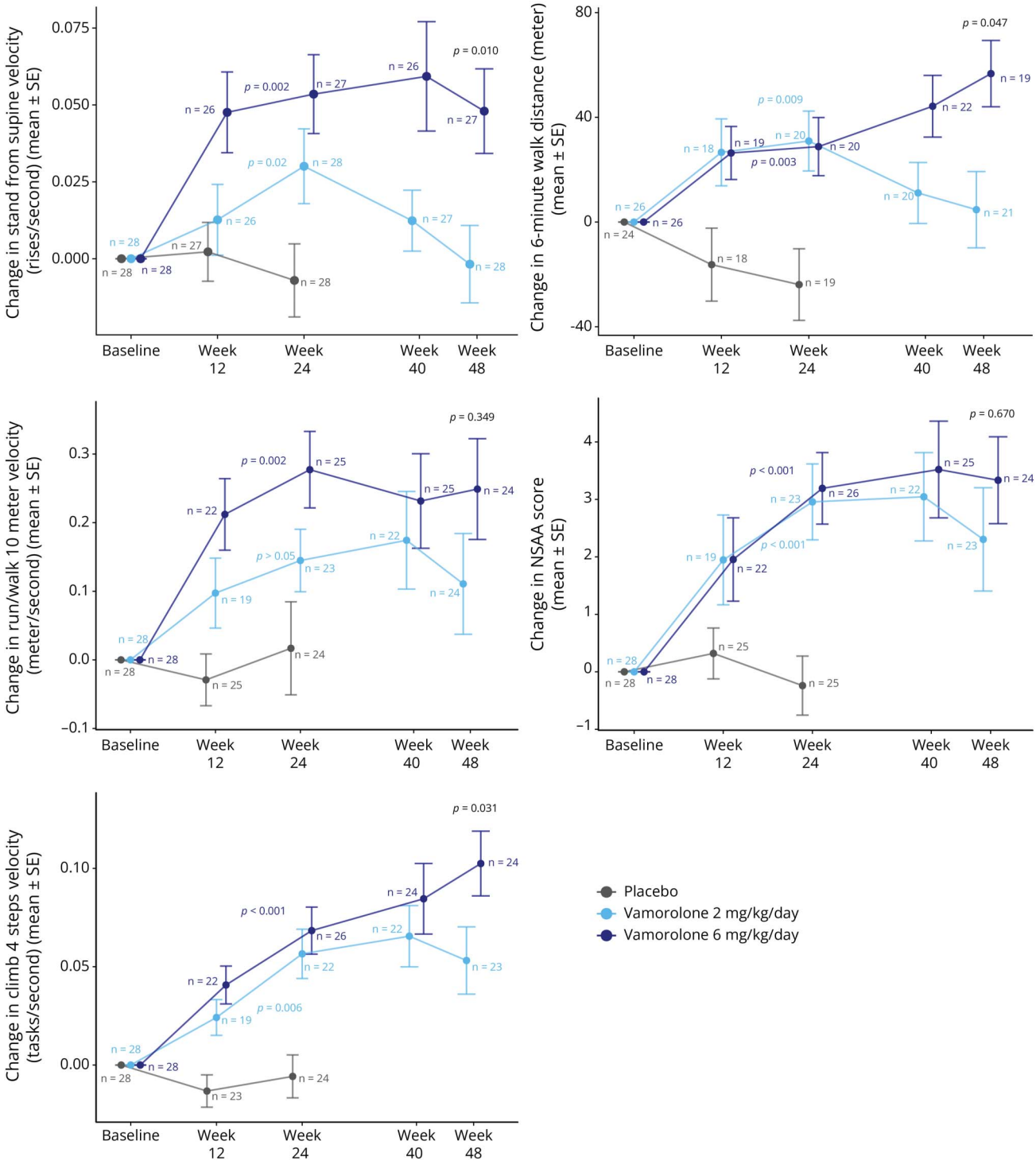
were predefined based on the safety profile known for CS including gastrointestinal symptoms, immune suppression, Cushingoid features, behavior problems, weight gain, skin/hair changes, hypertension, insulin resistance, adrenal suppression and insufficiency, and fractures. Height and body mass index (BMI) *z* scores were also evaluated as safety endpoints. Pharmacodynamic biomarkers including morning cortisol, osteocalcin, procollagen 1 intact N-terminal propeptide (P1NP), and type 1 collagen cross-linked C-telopeptide (CTX1) were collected on day 1 and weeks 12, 24, 28, 40, and 48. Bone health assessments included a DXA scan at screening, week 24, and week 48. DXA and spine x-ray assessments were performed but will be compared with an external control cohort (FOR-DMD[7]) and reported separately. The full schedule of assessments is in the Protocol. The trial was cleared by the ethics committee at each participating institution and conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice.

Statistical Analyses

Analysis populations relevant to period 2 analyses included a safety population (safety-2), which included all participants who completed period 1 and received at least 1 dose of vamorolone during period 2, and a modified intent-to-treat (mITT-2) population, which included participants from the safety-2 population with at least 1 postbaseline efficacy assessment during period 2 (eTable 1, links.lww.com/WNL/D407).

Analyses were conducted in SAS, release 9.4 (SAS Institute) and R, version 4.2.1 (R Foundation[19]; *ggplot*, *mmrm* packages[20,21]). Formal statistical analysis was performed after week 24 using the period 1 mITT population and compared between the 4 treatment groups of period 1.[12] No formal interim statistical

Figure 2 Motor Endpoints Over 48 Weeks of Treatment Period for Vamorolone 2 and 6 mg/kg/d Groups (Placebo Over Initial 24 Weeks of Treatment Serves as Reference) (mITT-2 Population)



Unadjusted mean values and SEs are plotted for placebo and 2 vamorolone dose groups using the mITT-2 population. *p* Values are provided for LSM comparisons from MMRM between the vamorolone dose groups at 48 weeks (mITT-2 population). For context, *p* values reported from comparison of performance on each of 2 vamorolone dose groups vs placebo (mITT-1 population) as previously reported[8] are overlaid. Color-coded (corresponding to legend) sample sizes at each time point are overlaid. LSM = least squares mean; mITT-1 = modified intention to treat–1; mITT-2 = modified intention to treat–2; MMRM = mixed model for repeated measures.

analyses were conducted, apart from the data reviews and presentations created for the data safety monitoring board. Categorical data counts were analyzed with χ^2 tests (with Monte Carlo simulation in case of low expected counts as a sensitivity analysis). Delayed start and dose response analyses were performed as additional exploratory analyses. Longitudinal analyses

were performed using restricted maximum likelihood–based mixed model for repeated measures on change from baseline in outcome at follow-up visits, adjusting for baseline outcome, baseline age, treatment arm, visit week, and treatment-by-week interaction. An unstructured covariance structure and the Kenward-Roger approximation for denominator degrees of freedom was used. Pairwise comparisons (using least squares mean [LSM] contrasts) of outcome were made between treatment groups at follow-up visits. The trial was powered for primary TTSTANDV endpoint comparison of vamorolone with placebo with sequential multiple testing correction specified at week 24 for secondary outcomes, but not for week 48 analysis. Hence, week 48 efficacy analyses presented here were not corrected for multiple testing, and *p* values were considered exploratory. All statistical tests were 2-sided with $\alpha = 0.05$.

Data Availability

Researchers may propose use of these data by submission of a Data Summary Request application at the CINRG website (cinrgresearch.org/publications/data-summary-requests/). Types of analyses: For any purpose, including a study protocol and analysis plan. Mechanisms of data availability: After approval of a proposal and with a signed data access agreement.

Results

Participant Demographics

A total of 121 participants were randomly assigned to 6 groups (Figure 1), with 114 participants continuing to period 2 of the study (eTable 1, links.lww.com/WNL/D407). Baseline characteristics were overall balanced; however, the 2 vamorolone dose group participants were weaker, on average at baseline in motor outcomes (eTable 2). The prednisone-treated (n = 30) and placebo-treated (n = 28) boys who completed period 1 underwent a 4-week taper period before treatment with vamorolone in period 2.

Most of the participants (112/121; 92.6%) completed the study through week 48. Seven participants withdrew in period 1 and 2 participants in period 2. In period 2, 1 withdrew consent and 1 withdrew because of an adverse event (acute hepatitis) (both in vamorolone 6 mg/kg/d group) (Figure 1, eTable 3, links.lww.com/WNL/D407).

Efficacy Outcomes at 48 Weeks of Vamorolone Treatment

The previously reported (period 1; mITT-1 population) 24-week treatment motor outcome data for 2 mg/kg/d and 6 mg/kg/d vamorolone groups vs placebo data are shown,[8] with new data reported on the period 2 extension of the 2 mg/kg/d and 6 mg/kg/d vamorolone to 48 weeks treatment (Figure 2; mITT-2 population). For context, in the previously reported analysis of 24-week treatment data, clinically meaningful and statistically significant improvements on vamorolone were seen in comparisons with placebo for 5 sequential endpoints (TTSTANDV, vamorolone 6 mg/kg/d and vamorolone 2 mg/kg/d vs placebo; 6-minute walk test, vamorolone 6 mg/kg/d and vamorolone 2 mg/kg/d vs placebo; TTRWV, vamorolone 6 mg/kg/d vs placebo). Exploratory motor outcomes (NSAA and TTCLIMBV) were also statistically significant and clinically meaningful for vamorolone-treated groups vs placebo at 24 weeks of treatment.

The improvements seen in all 5 clinical outcomes with vamorolone 6 mg/kg/d after 24 weeks of treatment (period 1) were maintained at 48 weeks of treatment (period 2) (Table 1; Figure 2). For the primary outcome, TTSTANDV, the improvement seen with vamorolone 6 mg/kg/d after 24 weeks of treatment was maintained (week 24 LSM [SE] 0.052 [0.0130] rises/s vs week 48 LSM [SE] 0.0446 [0.0138]).

The 2 mg/kg/d vamorolone group showed improvement to 24 weeks of treatment and then maintenance or some decline by 48 weeks treatment in all 5 motor outcomes. Mean declines were small in magnitude for TTRWV, NSAA, and TTCLIMBV, that is, relatively stable compared with improvements from baseline to 24 weeks of treatment (Figure 2; eTable 4, links.lww.com/WNL/D407). Declines were relatively greater for TTSTANDV and 6MWD, where motor function at week 48 was closer to that at baseline (Figure 2).

Table 1 Vamorolone Dose-Dependent Change From Baseline for Motor Endpoints Over 48-Week Treatment (mITT-2 Population)

End point (n for vamorolone 6 vs vamorolone 2 mg/kg/d)	Vamorolone 6 mg/kg/d LSM (SE) vs vamorolone 2 mg/kg/d LSM (SE)	LSM difference (SE)	LSM difference (95% CI)	*p* Value
TTSTAND velocity (rises/s) (27 vs 28)	0.0446 (0.0138) vs −0.0053 (0.0135)	0.0500 (0.0186)	0.0126 to 0.0874	0.010
6MWD (m) (19 vs 21)	49.6823 (12.5359) vs 14.9190 (12.3367)	34.7634 (17.0194)	0.4506 to 69.0761	0.047
TTCLIMB velocity (tasks/s) (24 vs 23)	0.1120 (0.0169) vs 0.0589 (0.0172)	0.0531 (0.0238)	0.0052 to 0.1010	0.031
TTRW velocity (m/s) (24 vs 24)	0.2519 (0.0747) vs 0.1544 (0.0746)	0.0976 (0.1032)	−0.1099 to 0.3051	0.349
NSAA (score) (24 vs 23)	3.0834 (0.8287) vs 2.5933 (0.8259)	0.4901 (1.1404)	−1.8041 to 2.7843	0.670

Abbreviations: 6MWD = 6-minute walk distance; LSM = least squares mean; mITT-2 = modified intention to treat–2; NSAA = North Star Ambulatory Assessment; SE = standard error; TTCLIMB = time to climb 4 steps; TTRW = time to run/walk 10 m; TTSTAND = time to stand from supine.

Assessment of dose dependency of motor outcomes showed a difference between vamorolone at a dose of 2 mg/kg/d vs 6 mg/kg/d for TTSTANDV (Table 1) after 48 weeks of treatment (LSM [SE] 0.0500 [0.0186] rises/s; 95% CI 0.0126–0.0874; p = 0.010). Similarly, significant differences between 2 vamorolone dose levels at week 48 were seen for 6MWD (LSM [SE] 34.7634 [17.0194] m; 95% CI 0.4506–69.0761 m; p = 0.047) and TTCLIMBV (LSM [SE] 0.0531 [0.0238] m; 95% CI 0.0052–0.1010 m; p = 0.031). Significant differences were not seen between dose groups for TTRWV (LSM [SE] 0.0976 [0.1032] m/s; 95% CI −0.1099 to 0.3051 m/s; p = 0.349), and NSAA (LSM [SE] 0.4901 [1.1404]; 95% CI −1.8041 to 2.7843; p = 0.670), although performance remained better, on average, on vamorolone at a dose of 6 mg/kg/d.

Other outcome measures (handheld myometry, Treatment Satisfaction Questionnaire, PODCI physical function, and Psychosocial Adjustment and Role Skills Scale III) showed no differences between vamorolone dose groups after 48 weeks of treatment.

Efficacy Outcomes in Crossover Groups (Placebo to Vamorolone; Prednisone to Vamorolone)

Of note, the sample sizes in both crossover groups (placebo crossover; prednisone crossover) were small due to stratification of the single period 1 group into 2 vamorolone dose groups in period 2 (eTables 1, 5, links.lww.com/WNL/D407). We had previously shown significant improvements of motor outcomes of both vamorolone at a dose of 2 and 6 mg/kg/d vs placebo over a 24-week treatment period (period 1).[12] The placebo participants in period 1 crossed over to vamorolone in period 2, and a delayed-start analysis of placebo (period 1) to vamorolone 6 mg/kg/d (period 2) showed improvements in all 5 efficacy outcomes in delayed starters post crossover (20 weeks of treatment) (eFigure 2; eTable 4, links.lww.com/WNL/D407), consistent with our previous period 1 data. The placebo to vamorolone 2 mg/kg/d group showed smaller improvements in delayed-start analysis relative to vamorolone 6 mg/kg/d group (eTable 4). On the contrary, the placebo to vamorolone 6 mg/kg/d seemed to catch up for TTSTANDV, TTRWV, and NSAA, relative to the vamorolone 6 mg/kg/d group. Testing of dose-dependent differences from crossover (week 24 assessments) to 20 weeks of treatment (week 48 assessments) showed a larger response by vamorolone 6 mg/kg/d (eTable 4) for 6MWD (LSM for difference 34.1 m; 95% CI −4.48 to 72.7 m, p = 0.082) and TTCLIMBV (LSM for difference 0.066 m; 95% CI −0.001 to 0.133 m/s, p = 0.053). Dose-dependent differences were not found to be statistically significant, possibly due to low power in this post hoc analysis.

Prednisone (period 1) to vamorolone (period 2) crossover groups showed that the crossover to vamorolone 6 mg/kg/d maintained the improvements seen with prednisone during period 1 for all 5 motor outcomes (Figure 3). Crossover to the vamorolone 2 mg/kg/d showed more variability in assessments, with maintenance of benefit for TTSTANDV, 6MWD, and NSAA and small declines in performance for TTRWV and TTCLIMBV (eTable 5, links.lww.com/WNL/D407). Testing of dose-dependent differences from crossover (week 24 assessments) to 20 weeks of vamorolone treatment (week 48 assessments) showed a significant vamorolone dose-dependent difference for TTCLIMBV (LSM for difference 0.0853 tasks/s; 95% CI 0.0096–0.161 tasks/s, p = 0.0288), but not other outcomes (eTable 6).

Safety: Adverse Events

No deaths were reported during the study. Three serious AEs were reported during the 48-week treatment period (eTable 7, links.lww.com/WNL/D407): perforated appendicitis (vamorolone 6 mg/kg/d), asthma (vamorolone 6 mg/kg/d), and viral gastroenteritis (vamorolone 2 mg/kg/d), all considered unrelated to vamorolone.

Common AEs for Vamorolone Dose Groups

The most common AEs reported during 48 weeks of vamorolone treatment were upper respiratory tract infections (vamorolone 2 mg/kg/d 35.7% [n = 10]; vamorolone 6 mg/kg/d 14.3% [n = 4]), vomiting (vamorolone 2 mg/kg/d 21.4% [n = 6]; vamorolone 6 mg/kg/d 21.4% [n = 6]), Cushingoid features (vamorolone 2 mg/kg/d 14.3% [n = 4]; vamorolone 6 mg/kg/d 32.1% [n = 9]), cough (vamorolone 2 mg/kg/d 17.9% [n = 5]; vamorolone 6 mg/kg/d 10.7% [n = 3]), pyrexia (vamorolone 2 mg/kg/d 25.0% [n = 7]; vamorolone 6 mg/kg/d 10.7% [n = 3]), and diarrhea (vamorolone 2 mg/kg/d 10.7% [n = 3]; vamorolone 6 mg/kg/d 17.5% [n = 5]).

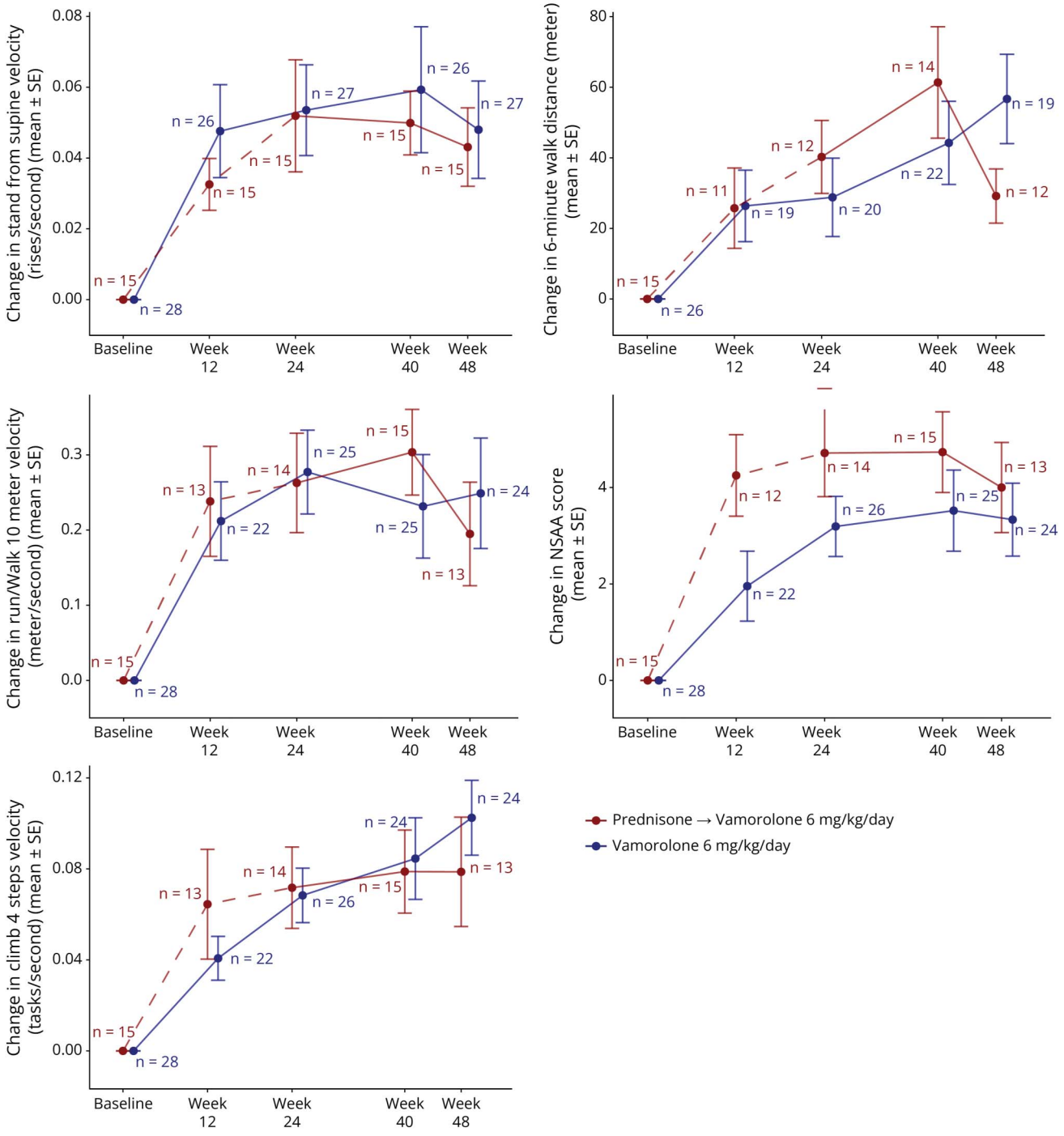
Drug-Related AEs

The percentage of participants with at least 1 drug-related AE decreased in both vamorolone groups in period 2 relative to period 1. The percentage of participants with at least 1 drug-related AE continued to be lower in the vamorolone 2 mg/kg group compared with that in the 6 mg/kg group in period 2 (17.9% vs 39.3%, respectively). There was no increase in rates of adverse events per patient per year from period 1 to period 2 for the 2 vamorolone groups (number of AEs per patient per year being 3.6 AEs per year and 2.4 AEs per year [period 1 vs 2, 2 mg/kg/d], 4.0 AEs per year and 3.0 AEs per year [period 1 vs 2, 6 mg/kg/d]).

Adverse Events of Special Interest in Crossover From Prednisone

Safety concerns associated with CS use were defined as AESI. Fewer AESI were recorded in period 2 compared with those in period 1 (eTable 8; eFigure 3, links.lww.com/WNL/D407). No serious AEs were reported after switching from prednisone to either vamorolone dose. Following the switch from prednisone (period 1) to vamorolone (period 2), annualized rates of AEs (AEs/patient/year) were reduced (all events 19.3% reduction, AESIs 39.7% reduction). Of all AESI, the largest reductions in annualized rates of AEs/patient/year were seen in behavior problems (prednisone vs vamorolone 1.08–0.51; 52.8% change) and gastrointestinal symptoms

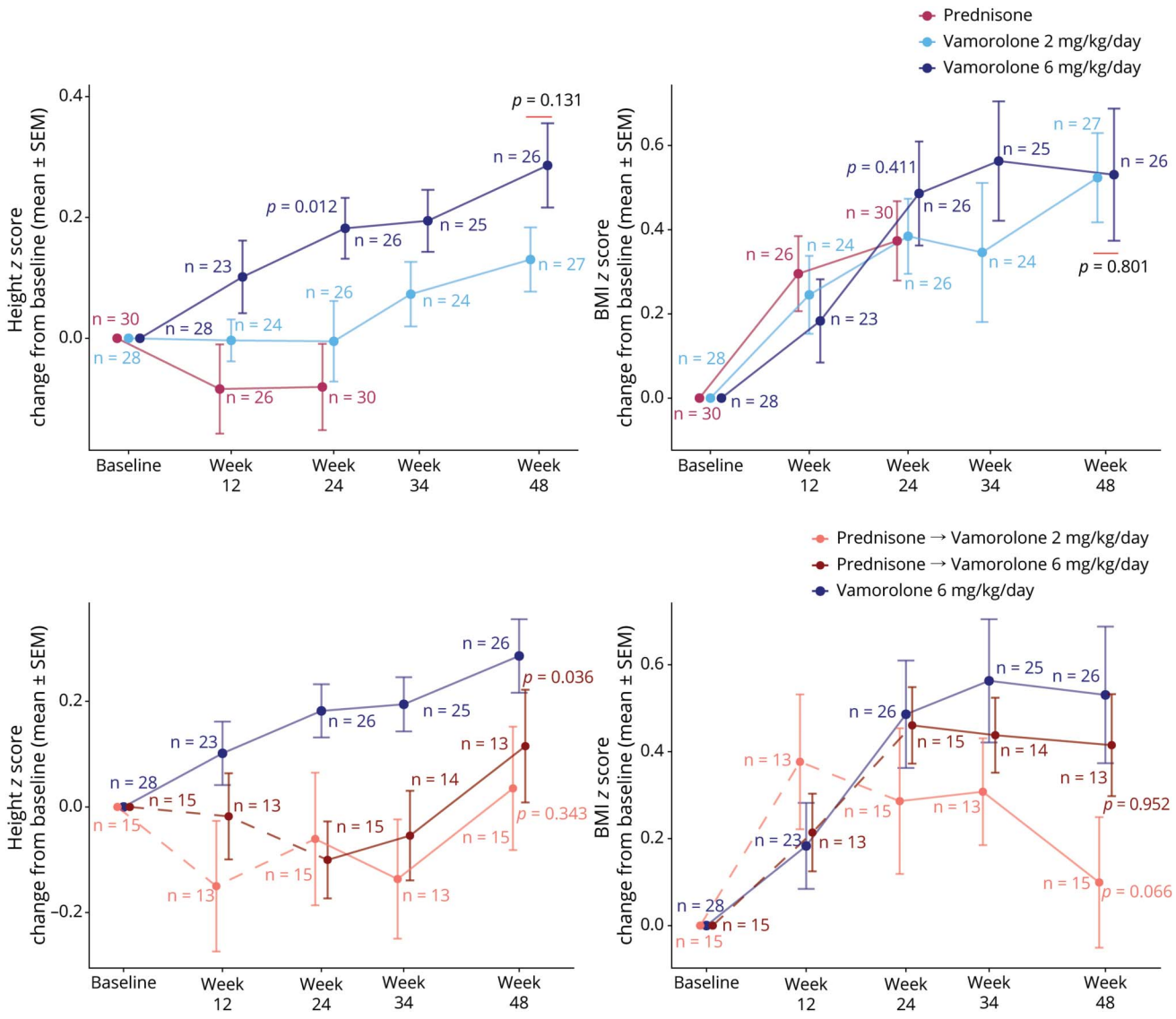
Figure 3 Motor Endpoints Over 48 Weeks of Treatment Period for Prednisone Crossover to Vamorolone 6 mg/kg/d Group With Continuous Vamorolone 6 mg/kg/d Overlaid as Reference (mITT-2 Population)



Unadjusted mean values and SEs are plotted (mITT-2 population). Color-coded (corresponding to legend) sample sizes at each time point are overlaid. mITT-2 = modified intention to treat–2.

(prednisone vs vamorolone 0.72–0.60; 16.7% change). A lower incidence of developing Cushingoid features was noted after the first 6 months of therapy at 6 mg/kg/d (1 individual in period 2 compared with 8 in period 1). Cushingoid features were not reported in participants switching from prednisone to vamorolone 2 mg/kg, and only 1 participant reported the onset of Cushingoid features after switching from prednisone to vamorolone at a dose of 6 mg/kg. Dose dependency for Cushingoid feature events may seem higher for the vamorolone 6.0 mg/kg/d dose group but a post hoc Fisher exact test of these was not statistically significant (p = 0.205). A similarly low incidence was observed for weight gain in period 2 (only in 1 participant on vamorolone 2 mg/kg/d dose group) and in those who crossed over to vamorolone from prednisone (eTable 8).

Figure 4 Safety Endpoints Over 48 Weeks of Treatment Period (mITT-2 Population)



Prednisone-treated group (period 1) is shown for reference (before cross-over to vamorolone). Unadjusted mean values and SEs are plotted using the safety-2 population. On the top panels, *p* values are provided for LSM comparisons from MMRM between the vamorolone dose groups over 48 weeks of treatment (safety-2 population). For context, a *p* value is overlaid for 24 weeks of treatment for comparison of LSM for prednisone (period 1) and vamorolone 6 mg/kg/d using the safety-2 population. On the bottom panels, *p* values are provided for within-group change for the prednisone crossover groups from week 24 (start of washout) to week 48 (including 20 weeks of treatment). Note that 1 time point (week 12 each time) for 3 participants (1 from vamorolone 2 mg/kg/d and 2 from vamorolone 6 mg/kg/d group) were removed because of suspected recording errors: patients had changed height by >10 cm by week 12 assessment, and future time points showed regression back closer to baseline height. Analysis including these values provided very similar findings and do not change interpretation. Color-coded (corresponding to legend) sample sizes at each time point are overlaid. LSM = least squares mean; mITT-2 = modified intention to treat–2; MMRM = mixed model for repeated measures

Safety: Height and BMI

Treatment with vamorolone for 48 weeks showed normal growth trajectories in participants, with no significant dose-dependent differences (LSM [CI] for vamorolone 6 mg/kg/d vs vamorolone 2 mg/kg/d comparison 0.123 [−0.038 to 0.285], $p = 0.131$) (Figure 4; Table 2). In the prednisone to vamorolone crossover participants, prednisone showed slowing of growth velocities in period 1 (Figure 4), and crossover to vamorolone 6 mg/kg/d showed reversal of growth trajectories (height *z* score) through catch-up growth (period 1 LSM −0.1001; period 2 LSM 0.1276; LSM [CI] 0.228 [0.0157 to 0.44]; $p = 0.036$). Comparing prednisone crossover to vamorolone 6 mg/kg/d dose with those on vamorolone 6 mg/kg/d dose throughout the 48-week treatment period shows good catch-up growth, although lower height at week 48 assessment for those initially treated with prednisone (LS mean [CI] 0.067 [−0.149 to 0.284]; $p = 0.53$).

BMI increased over 24 weeks of treatment in period 1 for both vamorolone dose groups and those on prednisone and then BMI stabilized for period 2 (Figure 4; Table 2). In the prednisone to vamorolone crossover groups, the weight gain

Table 2 Height, BMI, and Bone Biomarker Comparisons (Safety-2 [Height and BMI] and mITT-2 [Biomarker] Populations)

End-point	LSM difference (SE)	95% CI for LSM difference	*p* Value
Dose dependency at week 48			
Height *z* score VAM6 vs VAM2	0.123 (0.0805)	−0.0382 to 0.285	0.1312
BMI *z* score VAM6 vs VAM2	0.0463 (0.183)	−0.320 to 0.413	0.8010
Intragroup change from week 24 (prednisone) to week 48 (vamorolone)			
Height *z* score PRED-VAM6	0.228 (0.104)	0.0157 to 0.44	0.0362
Height *z* score PRED-VAM2	0.0959 (0.0993)	−0.108 to 0.299	0.3430
BMI *z* score PRED-VAM6	−0.0064 (0.104)	−0.22 to 0.207	0.952
BMI *z* score PRED-VAM2	−0.187 (0.097)	−0.387 to 0.0129	0.0655
Osteocalcin ng/mL PRED-VAM6	26.8 (5.14)	16.1 to 37.5	<0.0001
Osteocalcin ng/mL PRED-VAM2	38.5 (5.24)	27.6 to 49.5	<0.0001
CTX1 pg/mL PRED-VAM6	570 (80.3)	404 to 737	<0.0001
CTX1 pg/mL PRED-VAM2	667 (78.1)	505 to 829	<0.0001
P1NP µg/L PRED-VAM6	184 (36.2)	109 to 259	<0.0001
P1NP µg/L PRED-VAM2	317 (36.5)	242 to 393	<0.0001

Abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; CTX1 = type 1 collagen cross-linked C-telopeptide; LSM = least squares mean; NSAA = North Star Ambulatory Assessment; P1NP = procollagen 1 intact N-terminal propeptide; PRED-VAM2 = prednisone → vamorolone 2 mg/kg/d; PRED-VAM6 = prednisone → vamorolone 6 mg/kg/d; SE = standard error; VAM2 = vamorolone 2 mg/kg/d; VAM6 = vamorolone 6 mg/kg/d.

seen with prednisone in period 1 stabilized with crossover to the 6 mg/kg/d vamorolone in period 2. Prednisone to 2 mg/kg/d vamorolone showed a reduction in BMI toward baseline (Figure 4). The difference between these 2 groups was not statistically significant (LS mean [CI] 0.181 [−0.112 to 0.473]; $p = 0.21$).

Safety: Biomarkers

Bone Biomarkers

The decrease in serum bone turnover markers (osteocalcin, P1NP, CTX1) seen in the prednisone group during period 1 was quickly reversed after tapering prednisone and then switching to vamorolone during period 2 (eFigure 4, links.lww.com/WNL/D407; Table 2).

Adrenal Suppression

As previously reported,[8] all treatment groups except placebo showed evidence of adrenal suppression measured by both morning cortisol and ACTH-stimulated tests after 24 weeks of treatment. After 48 weeks of treatment, the degree of adrenal suppression was stable compared with that of week 24 assessment.

Distribution of *DMD* Gene Variant Type

Some *DMD* gene variants can be associated with a more severe phenotype (e.g., pathogenic variants of the 3′ end of the gene, involving multiple dystrophin protein isoforms including Dp71[22]), and other *DMD* gene variants can be associated with residual (non-null) dystrophin protein production and a milder phenotype[23,24] (e.g., splice-site mutations, 5′ end mutations, exon 44 skippable). To determine whether participant variant type showed comparable assignment with the 6 treatment groups, participant gene variants were curated and defined as Dp427-only vs Dp427+additional isoforms, and potential non-null vs likely null mutations. No significant differences were found in these analyses (distributions of isoform χ^2 test; $p = 0.8$ [n = 110], distribution of potential non-null variants: $p = 0.2$ [n = 111]) as expected due to randomization.

Classification of Evidence

This study provides Class I evidence that for boys with DMD, the efficacy of vamorolone 6 mg/kg/d dose was maintained over 48 weeks.

Discussion

In this 48-week, placebo-controlled and prednisone-controlled randomized crossover study of vamorolone, the efficacy of vamorolone at a dose of 6 mg/kg/d reported after 24 weeks of treatment vs placebo[12] was maintained over 48 weeks of treatment for all 5 motor outcomes (TTSTANDV, 6MWD, TTRWV, NSAA, and TTCLIMBV). Treatment with the lower dose of vamorolone, 2 mg/kg/d, for 48 weeks showed some loss of the improvements seen at week 24 assessment toward baseline function for TTSTANDV and

6MWD, but stabilization of improved function relative to baseline for TTRWV, NSAA, and TTCLIMBV. For participants crossing over from prednisone (period 1) to vamorolone (period 2), efficacy was retained for those crossing over to high-dose vamorolone (6 mg/kg/d), but those crossing over to lower-dose vamorolone (2 mg/kg/d) showed more variable retention of efficacy. A delayed-start analysis of early starters vs delayed starters (initially on placebo) showed that the initial disease-modifying effect of vamorolone with early initiation was maintained over the follow-up period (although not always statistically significant). This global assessment of efficacy supports the efficacy profile of vamorolone 6 mg/kg/d, inclusive of continuous improvements in 6MWD and TTCLIMBV to the final week 48 assessment.

Vamorolone treatment was generally well tolerated at both dose levels throughout 48 weeks of treatment with a dose-dependent profile of adverse events. For participants who continued the same dose of vamorolone throughout the study, the safety profile was consistent after 24 weeks and 48 weeks of treatment.[12] No stunting of growth was seen with either vamorolone dose, consistent with data previously presented from long-term open-label studies.[11] In our crossover design, there was a reversal of the prednisone-related growth retardation in period 1, with significant improvement in linear growth following crossover from prednisone to either dose of vamorolone. Similarly, crossing over to vamorolone from prednisone led to rapid reversal of the prednisone-induced decline in serum bone turnover markers. Fewer behavioral problems were also observed. The dose-dependent adrenal suppression observed with vamorolone in the initial 24-week treatment stabilized and did not worsen during the second period to 48-week treatment.

We had previously reported that vamorolone and prednisone groups showed similar overall gain in BMI (increase of 0.4–0.5 BMI *z* score over the initial 24-week treatment period), with high intragroup variability.[8] For the vamorolone-treated participants continuing to the 48-week treatment, the increases in period 1 were seen to stabilize in period 2, with no further substantial increase in BMI *z* score. It seems that weight gain with chronic vamorolone treatment is variable from patient to patient and that gains occur in the initial 24-week treatment and then stabilize. Note that there is considerable gain in height during the 48-week vamorolone treatment, and with increased strength likely increased muscle mass (although not measured), and this may complicate the interpretation of BMI *z* score data. We hypothesize that genetic variations (polymorphisms) unrelated to the *DMD* gene may lead to individual response to weight gain with vamorolone or CS, as has been reported with chronic CS treatment of Addison disease.[25]

Our crossover design did not enable comparison of safety outcomes of prednisone vs vamorolone after 48 weeks of treatment. The VBP15-004 study design was purposefully harmonized with the FOR-DMD study of alternative CS regimens in DMD, and comparisons of efficacy and safety outcomes over a 48-week treatment period between these 2 double-blind trials are a focus of future research.

While TTSTANDV had complete data due to use of remote recorded assessments, other outcomes had data missing due to the COVID-19 pandemic. The study was powered for analysis of the primary endpoint at 24 weeks, and had low sample sizes in the 6 treatment groups, and was underpowered for some analyses at 48 weeks. Last, some of the exploratory results should be treated with caution due to the number of comparisons/exploratory nature of the comparisons with no multiple comparison correction implemented.

In this randomized trial, vamorolone was shown to be safe and effective as treatment in boys with DMD in the age from 4 years to younger than 7 years over a 48-week treatment period. Switching from prednisone to vamorolone 6 mg/kg/d dose allowed boys to resume normal growth and experience fewer behavioral problems and fewer adverse effects typically associated with CS use, while maintaining efficacy of motor outcomes.

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Disclosure

U.J. Dang receives personal fees from ReveraGen Biopharma and grants from Foundation to Eradicate Duchenne. J.M. Damsker receives salary support and stock and stock options from ReveraGen BioPharma and support from grants from the NIH and European Horizons and holds patents related to vamorolone. M. Guglieri receives clinical trial and grant support from ReveraGen BioPharma and grants from the European Commission and the NIH. P.R. Clemens receives grants from the NIH and ReveraGen BioPharma. S.J. Perlman was a site principal investigator of the clinical investigation sponsored by ReveraGen. E.C. Smith was a site principal investigator of the clinical investigation sponsored by ReveraGen. I. Horrocks was a site principal investigator of the clinical investigation sponsored by ReveraGen. R.S. Finkel was a site principal investigator of the clinical investigation sponsored by ReveraGen. J.K. Mah was a site principal investigator of the clinical investigation sponsored by ReveraGen. N. Deconinck was a site principal investigator of the clinical investigation sponsored by ReveraGen. N. Goemans was a site principal investigator of the clinical investigation sponsored by ReveraGen. J. Haberlova was a site principal investigator of the clinical investigation sponsored by ReveraGen. V. Straub was a site principal investigator of the clinical investigation sponsored by ReveraGen. L.J. Mengle-Gaw reported receiving personal fees from ReveraGen BioPharma. B.D. Schwartz reported receiving personal fees from ReveraGen Biopharma. A.D. Harper was a site principal investigator of the clinical investigation sponsored by ReveraGen. P.B. Shieh was a site principal investigator of the clinical investigation sponsored by ReveraGen. L. De Waele was a site principal investigator of the clinical investigation sponsored by ReveraGen. D. Castro was a site principal investigator of the clinical investigation sponsored by ReveraGen. M.L. Yang was a site principal investigator of the clinical investigation sponsored by ReveraGen. M. Ryan was a site principal investigator of the clinical investigation sponsored by ReveraGen. C.M. McDonald was a site principal investigator of the clinical investigation sponsored by ReveraGen. M. Tulinius was a site principal investigator of the clinical investigation sponsored by ReveraGen. R. Webster was a site principal investigator of the clinical investigation sponsored by ReveraGen. H.J. McMillan was a site principal investigator of the clinical investigation sponsored by ReveraGen. N.L. Kuntz was a site principal investigator of the clinical investigation sponsored by ReveraGen. V.K. Rao was a site principal investigator of the clinical investigation sponsored by ReveraGen. G. Baranello was a site principal investigator of the clinical investigation sponsored by ReveraGen. S. Spinty was a site principal investigator of the clinical investigation sponsored by ReveraGen. A.M. Childs was a site principal investigator of the clinical investigation sponsored by ReveraGen. A.M. Sbrocchi was a site principal investigator of the clinical investigation sponsored by ReveraGen. K.A. Selby was a site principal investigator of the clinical investigation sponsored by ReveraGen. M. Monduy was a site principal investigator of the clinical investigation sponsored by ReveraGen. Y. Nevo was a site principal investigator of the clinical investigation sponsored by ReveraGen. J.J. Vilchez-Padilla was a site principal investigator of the clinical investigation sponsored by ReveraGen. A. Nascimento-Osorio was a site principal investigator of the clinical investigation sponsored by ReveraGen. E.H. Niks was a site principal investigator of the clinical investigation sponsored by ReveraGen. I.J.M. de Groot was a site principal investigator of the clinical investigation sponsored by ReveraGen. M. Katsalouli was a site principal investigator of the clinical investigation sponsored by ReveraGen. J. van den Anker received salary support and stock options from ReveraGen. L.M. Ward received contract support from ReveraGen and a grant from Foundation to Eradicate Duchenne. M. Leinonen received salary support from Santhera Pharmaceuticals. A. D'alessandro received contract support from ReveraGen. E.P. Hoffman received salary support and stock from ReveraGen BioPharma and is a PI on grants from the NIH and Food and Drug Administration. Go to Neurology.org/N for full disclosures.

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