Delayed-start analysis of efficacy outcomes in placebo-to-vamorolone crossover participants in VBP15-004

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Background

- Vamorolone is a novel dissociative steroidal anti-inflammatory drug (DSAID) that seeks to retain efficacy and reduce safety concerns compared to corticosteroids via changes to structure/activity relationships with the glucocorticoid receptor.[1]
- A series of open-label studies (VBP15-LTE, NCT03038399) in boys with Duchenne muscular dystrophy (DMD) suggested a favorable efficacy–safety profile over 30 months of exposure.[2–5]
- A double blinded, prednisone- and placebo-controlled 48-week vamorolone trial with crossover (VBP15-004; NCT03439670) conducted by the Cooperative International Neuromuscular Research Group (CINRG) confirmed efficacy–safety findings.
- In this study, steroid-naïve boys with DMD (5.4±0.9 years; N=121) randomized to placebo for 24 weeks in Period 1 crossed over to two vamorolone groups (2.0 or 6.0 mg/kg/day) for Period 2.

Objectives

- To present delayed-start analysis of efficacy outcomes from VBP15-004.
- This comparison will focus on a global assessment of efficacy by evaluating a disease-modifying effect shown through a delayed-start analysis.

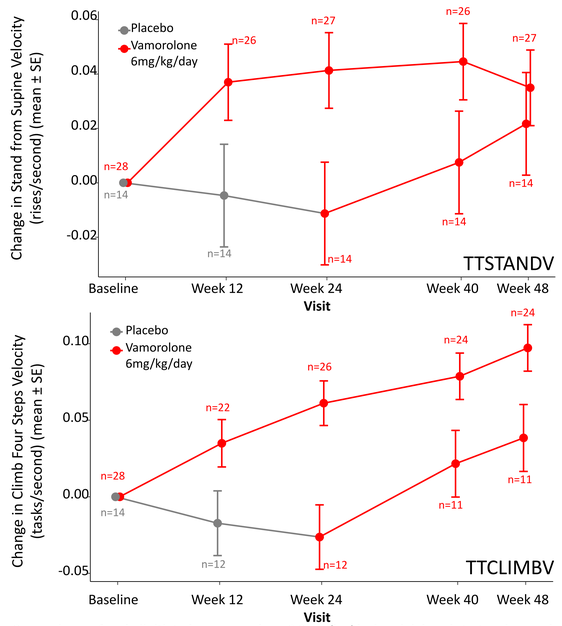
Methods

- The population was defined as all randomized patients who received ≥1 dose of study medication and had ≥1 post-baseline efficacy assessment during Period 2.
- Pre-specified comparison of participants initially assigned to placebo (delayed-starters) vs. those assigned and retained on vamorolone throughout (early-starters) was conducted on:
  1. *Time to stand from supine (TTSTAND) velocity (rises/s)*
  2. *Time to climb 4 steps (TTCLIMB) velocity (tasks/s)*
  3. *Time to run/walk 10 m (TTRW) velocity (m/s)*
  4. *Six-minute walk distance (6MWD) (m)*
  5. *North Star Ambulatory Assessment (NSAA) score*
- Change of outcome from baseline at Weeks 12, 24, 40, and 48 was modelled via a restricted maximum likelihood-based mixed model for repeated measures while adjusting for baseline age (< or ≥ 6 years of age), baseline outcome value, treatment phase (early vs. delayed), week, and the treatment phase-by-week interaction.

Results

Table. Characteristics at steroid-naïve baseline (study entry), m-ITT-2/Safety-2 Population

Characteristic mean (SD)	Vamorolone 6.0 mg/kg/day (n=28)	Vamorolone 2.0 mg/kg/day (n=28)	Control Group (placebo) (n=28)
Age in years	5.4 (0.9)	5.3 (0.9)	5.4 (0.8)
TTSTAND velocity	0.19 (0.06)	0.19 (0.06)	0.20 (0.06)
TTCLIMB velocity	0.21 (0.09)	0.20 (0.05)	0.25 (0.09)
TTRW velocity	1.6 (0.4)	1.6 (0.3)	1.7 (0.3)
6MWD	313 (56)	317 (60)	355 (78)
NSAA	18.9 (4.1)	17.5 (4.6)	18.9 (5.3)



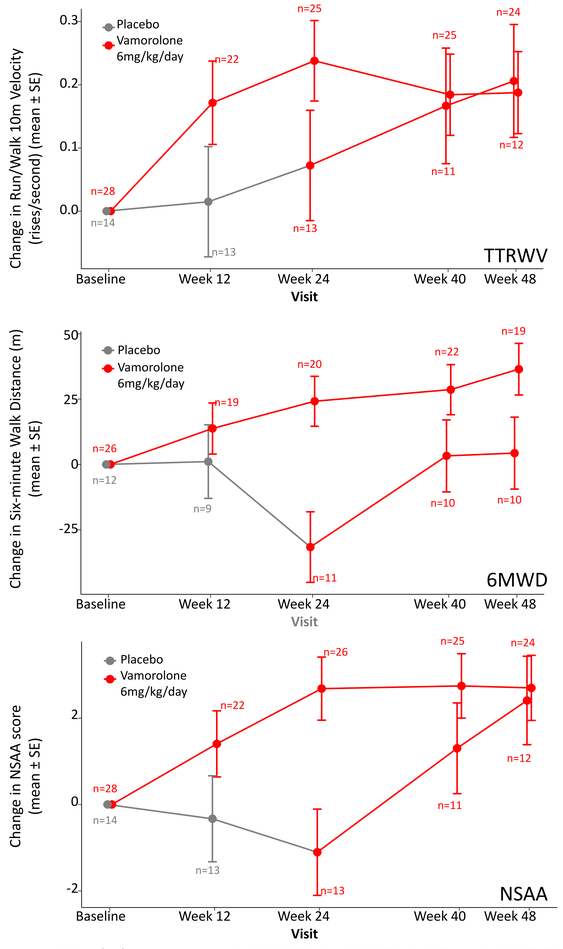


Fig. Comparisons of early (initiated on vamorolone 6.0 mg/kg/day) and delayed starters (crossed over to vamorolone 6.0 mg/kg/day from placebo) for TTSTANDV (A), TTCLIMBV (B), TTRWV (C), 6MWD (D), and NSAA (E). 6MWD, six-minute walk distance; TTCLIMBV, time to climb 4 steps velocity; TTRWV, time to run/walk 10 m velocity; NSAA, North Star Ambulatory Assessment; TTSTANDV, time to stand from supine velocity.

Summary

- Baseline characteristics were similar across groups (Table)
- The figure shows an improvement in multiple efficacy outcomes in delayed starters post-crossover to vamorolone 6.0 mg/kg/day (TTSTAND velocity, TTCLIMB velocity, 6MWD, NSAA; all p<0.05).
- Early-starters (vamorolone 6.0 mg/kg/day) had increased outcome means compared with delayed-starters (placebo → vamorolone 6.0 mg/kg/day) for all 5 outcomes at all timepoints with 1 exception (TTRW velocity at week 48).
- Other comparisons (e.g., vamorolone 2.0 mg/kg/day throughout group vs. placebo → vamorolone 2.0 mg/kg/day or comparison of pooled dose groups) yielded similar findings for the most part.
- At 48 weeks, only the mean for TTCLIMB velocity was statistically significant between early- and delayed-starters (p<0.05).
- Vamorolone 2.0 mg/kg/day showed smaller improvements than vamorolone 6.0 mg/kg/day.
- Limitations: While TTSTAND velocity had complete data due to use of remote recorded assessments, other outcomes had missingness due to the COVID-19 pandemic, leading to larger standard errors. Furthermore, while this analysis was pre-specified, the trial was not powered for this analysis.

Conclusion

- A delayed start analysis of early-starters vs. delayed-starters 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 is supportive of the efficacy profile of vamorolone.

References

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