LB.08 Vamorolone versus corticosteroid real-word experience: Comparisons of 2-year treatment period with NorthStar UK Network and CINRG Duchenne Natural History

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Background

- Vamorolone is a novel steroidal drug that differs from conventional corticosteroids (CS) in lacking an 11β-hydroxy/carbonyl group.[1] This change removes a contact site with the target glucocorticoid receptor significantly altering structure/activity relationships.[2]
- Three consecutive open-label vamorolone trials (VBP15-002, NCT02760264; VBP15-003, NCT02760277; VBP15-LTE, NCT0303839) were conducted by the Cooperative International Neuromuscular Research Group (CINRG) from 2016 to 2020.[3,4,5]
- Participants (n=48) were CS-naïve boys ages 4 to <7 years with Duchenne muscular dystrophy (DMD) at start of VBP15-002.
- Participants received vamorolone at one of 4 dose levels (0.25, 0.75, 2.0, or 6.0 mg/kg/day) and remained at the same dose level during the 2-week VBP15-002 and the 24-week VBP15-003 trials.
- The 24-month VBP15-LTE protocol permitted multiple dose escalations to higher doses; de-escalations were also allowed at site investigator's discretion.

Objectives

- We present 2-year treatment outcomes of vamorolone (VBP15-LTE) in boys with DMD and compare them to CS-treated historical controls from CINRG Duchenne Natural History Study (DNHS) and NorthStar UK Network (NSUK).
- Given the variable timing of dose escalations, pre-specified analyses focused on VBP15 participants (n=23) who were initially assigned and maintained on ≥2.0 mg/kg/day of vamorolone throughout the VBP15-002/-003 trials.

Corticosteroid Real-world Comparators

- Corticosteroid (CS)-treated participants from the DNHS and NSUK cohorts were matched with higher-dose (≥2.0 mg/kg/day) VBP15-LTE participants for comparison of timed function tests, 6MWT, NorthStar Ambulatory Assessment (NSAA), height, and BMI.
- Data on DNHS participants was collected between December 2005 and November 2016. The NSUK DMD participants were recruited from August 2005 to October 2019.
- Participants from the DNHS and NSUK cohorts were first eligible as controls once they had at least 6 months of continuous CS (any type or dose) exposure, with age between 4.5 to 7.5 years old at baseline, similar to VBP15-LTE participants with 6 months of vamorolone exposure at baseline after completing the VBP15-002/-003 trials.

Statistical Analysis

- Comparison of higher-dose VBP15-LTE participants with CS-treated historical controls from DNHS was based on longitudinal outcome data using mixed-effect models with repeated measures (MMRM).
- The NSAA data were analyzed separately by the NSUK team due to data sharing restrictions; summaries of change were compared with higher-dose VBP15-LTE participants using independent *t*-tests.
- Nonparametric maximum likelihood estimation (NPMLE) was used to estimate the observed survival curve for the first Time-To-Stand (TTSTAND) outcome of ≥ 10 seconds event.

Results

- 41 DMD participants completed the VBP15-LTE study. 3/23 (13%) higher-dose participants withdrew before their Month 24 visit.
- 75 DNHS and 110 NSUK CS-treated participants were group-matched to the 23 higher-dose (≥2.0 mg/kg/day) VBP15-LTE participants. Their baseline characteristics are shown in **Table 1** below.

Table 1 Baseline characteristics of VBP15-LTE, DNHS, & NSUK Cohorts[a]

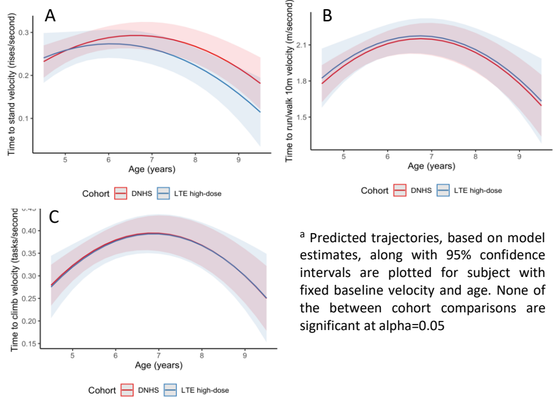
	Statistic	Higher-dose[b] VBP15-LTE	CS-treated DNHS	CS-treated NSUK[c]
Age at baseline comparison (years)	N	23	75	110
	Mean (SD)	5.83 (0.88)	6.08 (0.81)	6.00 (0.77)
Steroid exposure at baseline comparison visit (days)	Mean (SD)	200.57 (7.54)	227.73 (61.91)	264.84 (57.39)
Duration of follow up from baseline visit (yr)	Mean (SD)	1.85 (0.46)	1 (2.6)	-
Participants with >18 months follow up	Number	21 (91.3%)	30 (40.0%)	-
Weight	N	23	73	-
	Mean (SD)	21.98 (3.78)	20.35 (3.55)	-
Height (cm)	N	22	73	-
	Mean (SD)	111.80 (6.94)	109.86 (6.86)	-
Body Mass Index (kg/m2)	N	22	72	-
	Mean (SD)	17.68 (1.23)	16.68 (1.55)	-

[a] Baseline comparator visit corresponds to approximately 6 months of steroid exposure for the NorthStar UK Network and CINRG DNHS participants; [b] Higher-dose refers to participants assigned and maintained on vamorolone at ≥2 mg/kg/day from VBP15-002/-003/-LTE baseline; [c] Due to NSUK subject-level data sharing restrictions, limited summary information was available

Outcomes: Vamorolone LTE vs. DNHS Group

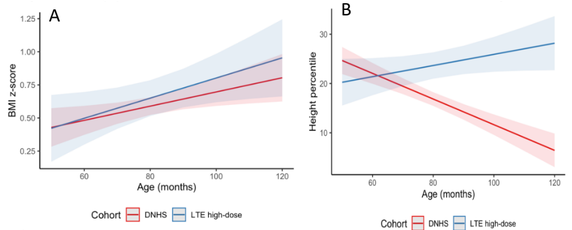
- Timed function tests: Mean TTSTAND, TTRW, and TTCLIMB trajectories were not significantly different between higher-dose VBP15-LTE (n=23) and CS-treated DNHS participants (n=75) over 2-years (**Figure 1**) .
- Anthropometric measures: Higher-dose VBP15-LTE and CS-treated DNHS participants were not significantly different in mean BMI z-score trajectories (**Figure 2A**); however, there was a significant difference in mean height percentile change (0.37/month; p=8.94 ×10^{-07}, **Figure 2B**).

Figure 1. Comparison of mean time to stand (A), time to run/walk 10 m (B), and time to climb (C) velocities in vamorolone LTE vs. CS-treated DNHS cohorts[a]



[a] Predicted trajectories, based on model estimates, along with 95% confidence intervals are plotted for subject with fixed baseline velocity and age. None of the between cohort comparisons are significant at alpha=0.05

Figure 2. Comparison of mean Body Mass Index z-score (A) and height percentile (B) in vamorolone LTE vs. CS-treated DNHS cohorts over 2-year[b]



[b] Predicted trajectories, based on model estimates, along with 95% confidence intervals are plotted for subject with fixed baseline values. For BMI z-score, the between cohort comparison is not significant at alpha=0.05 while for height, the comparison was significant (p=8.94 ×10^{-07}; 0.37/month; CI: 0.23, 0.52).

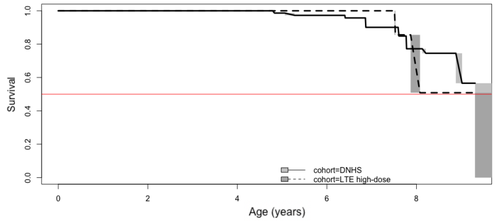
Total NSAA Score: Vamorolone LTE vs. NSUK Group

- The change in mean total NSAA scores for higher-dose vamorolone (-0.61, CI: -4.65, 3.43; n=18) and CS-treated (-0.39, CI: -1.91, 1.13; n=49) NSUK participants at 2-year follow up was not significantly different (p=0.92; CI: -4.48, 4.04).
- A relative risk analysis of NSAA scores also showed no significant difference in the risk of losing a motor function between the two cohorts: NSUK participants lost 139/1734 functions while VBP15-LTE participants lost 26/335 functions (RR 1.03, CI: 0.69, 1.544).

Time to reach TTSTAND milestone ≥ 10 seconds: Vamorolone LTE vs. DNHS and NSUK Groups

- There was no significant difference in the nonparametric maximum likelihood estimate of median time to reach a TTSTAND milestone of ≥10 seconds for higher-dose VBP15-LTE participants (>9.31 years, CI: 7.51, Inf, n=22) and CS-treated DNHS (>9.31 years, CI: 8.29, Inf; n=74) participants (asymptotic logrank two-sample test p=0.744, **Figure 3**).

Figure 3. Survival analysis of time to reach first TTSTAND ≥10 second: LTE vs. DNHS



- The median time to reach a TTSTAND milestone ≥10 seconds for NSUK was 9.55 years (CI: 8.87, Inf; n=108), similar to DNHS and LTE cohorts.

Discussion

- The study design allowed for comparison of vamorolone with corticosteroids (CS) in two independent DMD cohorts (DNHS and NSUK).
- Analysis of disease trajectories and safety data showed consistent long-term benefit of vamorolone, with fewer adverse events compared to CS.

Conclusion

- Vamorolone showed a disease-modifying effect in boys with DMD, with maintenance of muscle function similar to corticosteroid real-world data observed in the NSUK and DNHS cohorts over a 2-year treatment period.
- A randomized study (VBP15-004, NCT03439670) of 121 DMD participants will provide Class 1 evidence for vamorolone safety and efficacy.

References

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