Feasibility of switch from prednisone to vamorolone in patients with DMD in the VBP15-004 study

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Background

- Vamorolone is a dissociative steroidal anti-inflammatory drug that seeks to retain efficacy and reduce safety concerns in patients with Duchenne muscular dystrophy (DMD) 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 DMD suggested a favorable efficacy–safety profile over 30 months of exposure.[2]
- The efficacy and safety of vamorolone were investigated during the first 24 weeks (Period 1) of the VISION-DMD (VBP15-004, NCT03439670) study:
  - The results of the primary analysis at 24 weeks have been reported previously.[3]
  - The study met its primary endpoint; both doses of vamorolone (6 mg/kg/day and 2 mg/kg/day) showed statistically significant and clinically meaningful improvement in functional outcomes vs. placebo after 24 weeks of treatment.

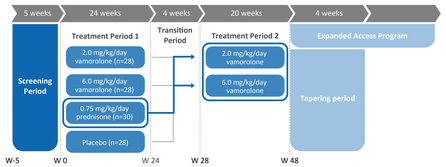
Objectives

- The objective of this analysis was to evaluate the efficacy and safety in patients who switched from prednisone 0.75 mg/kg/day to vamorolone 2 or 6 mg/kg/day during Period 2.

Methods

- VISION-DMD (VBP15-004) is a 48-week randomized, double-blind study comprising two periods:
  - During Period 1, 121 patients were randomized 1:1:1:1 to vamorolone 2 or 6 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for 24 weeks.
  - During Period 2, patients continued their initial vamorolone dose or crossed over from placebo or prednisone to vamorolone 2 or 6 mg/kg/day.
- This analysis was conducted in patients randomized to receive prednisone during Period 1 and who had at least 1 post cross-over efficacy assessment during Period 2 (mITT-2), and for safety analyses include all patients who had at least one dose of study medication during Period 2 (SAF-2) **(Figure 1)**.
- Global efficacy was assessed as change from baseline to week 48 in time to stand (TTSTAND) velocity, 6-minute walk distance (6-MWT), Time to run/walk 10 m (TTRW) velocity, North Star Ambulatory Assessment (NSAA) score, Time to climb 4 steps (TTCLIMB) velocity and was modelled using restricted maximum likelihood-based mixed model for repeated measures (MMRM).

Figure 1. Study design for VISION-DMD (VBP15-004)



This poster focuses on analysis of patients who switched from prednisone 0.75 mg/kg/day to vamorolone 2 or 6 mg/kg/day.

Results

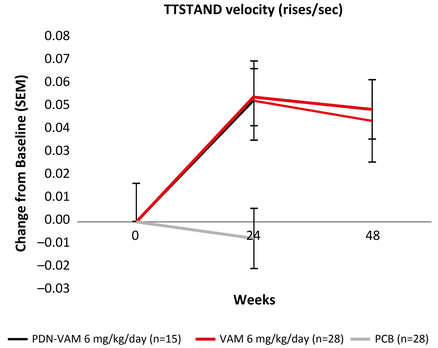
- Out of 121 patients randomized to the study, 30 received prednisone during Period 1 followed by vamorolone treatment during Period 2 **(Table 1)**.
  - All 30 patients completed vamorolone treatment at Week 48.

Table 1. Characteristics at prednisone baseline (study entry), m-ITT-2 / Safety-2 Population

	Prednisone to vamorolone 2 mg/kg/day group (n=15) Mean (SD)	Prednisone to vamorolone 6 mg/kg/day group (n=15) Mean (SD)	Continuous vamorolone 6 mg/kg/day (n=28) Mean (SD)
Age (years)	5.4 (0.9)	5.6 (0.8)	5.4 (0.9)
TTSTAND (sec)	5.4 (1.9)	4.5 (0.8)	6.0 (2.0)
6-MWT (m)	329 (52)	360 (58)	313 (56.2)
NSAA (points)	21.1 (5.4)	21.4 (5.8)	18.9 (4.1)
Height (percentile)	34.2 (30.1)	41.1 (29.1)	23.2 (24.6)
Weight (percentile)	53.0 (28.7)	61.1 (28.2)	43.7 (26.7)
BMI (percentile)	73.6 (24.0)	77.4 (17.5)	69.8 (23.0)

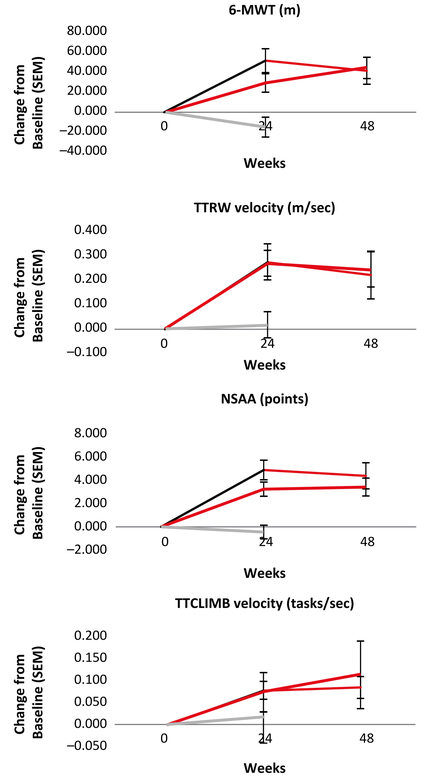
6-MWD, six-minute walk distance; BMI, body mass index; mITT-2, modified intention to treat-2 population; TTSTAND, time to stand from supine; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

Figure 2. TTSTAND velocity (rises/sec), switch from prednisone 0.75 mg/kg /day to vamorolone 6 mg/kg/day vs. continuous treatment with vamorolone 6 mg/kg/day (mITT-2 population, MMRM)



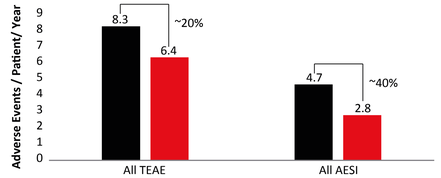
mITT-2, modified intention to treat-2 population; MMRM, mixed model for repeated measures; PCB, placebo; PDN, prednisone; SEM, standard error of the mean; TTSTAND, time to stand from supine; VAM, vamorolone.

Figure 3. 6MWT distance (m), TTRW velocity (m/sec), NSAA score (points) and TTCLIMB velocity (tasks/sec), switch from prednisone 0.75 mg/kg/day to vamorolone 6 mg/kg/day vs. continuous treatment with vamorolone 6 mg/kg/day (mITT-2 population, MMRM)



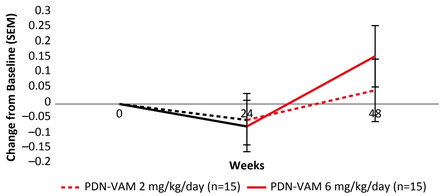
6MWD, six-minute walk distance; mITT-2, modified intention to treat-2 population; MMRM, mixed model for repeated measures; TTCLIMB, time to climb 4 steps; TTRW, time to run/walk 10 m; NSAA, North Star Ambulatory Assessment; PCB, placebo; PDN, prednisone; SEM, standard error of the mean; VAM, vamorolone.

Figure 4. Rates of all TEAEs and AESIs, in patients who switched from prednisone 0.75 mg/kg/day to vamorolone 2 or 6 mg/kg/day (Safety-2 population)



AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.

Figure 5: Change in height z-scores, in patients who switched from prednisone 0.75 mg/kg/day to vamorolone 2 or 6 mg/kg/day (Safety-2 population)



PDN, prednisone; SEM, standard error of the mean; VAM, vamorolone.

Table 2. Serum bone biomarker concentrations (mean ± SD) in patients who switched from prednisone 0.75 mg/kg/day to either 2 or 6 mg/kg/day of vamorolone

		Mean (SD)		
Bone biomarker	Study group	Baseline	Week 24 (PDN)	Week 48 (VAM)
Osteocalcin (ng/ml)	PDN-VAM 2 mg/kg/day (n=15)	58.3 (14.0)	40.8 (9.3)	76.9 (14.0)
	PDN-VAM 6 mg/kg/day (n=15)	54.4 (12.0)	41.6 (8.4)	66.8 (15.7)
PINP (ng/ml)	PDN-VAM 2 mg/kg/day (n=15)	493 (139)	323 (72)	621 (117)
	PDN-VAM 6 mg/kg/day (n=15)	478 (87)	344 (72)	543 (143)
CTX (pg/ml)	PDN-VAM 2 mg/kg/day (n=15)	1116 (112)	749 (147)	1414 (228)
	PDN-VAM 6 mg/kg/day (n=15)	1166 (166)	853 (209)	1392 (277)
ALP (U/ml)	PDN-VAM 2 mg/kg/day (n=15)	116.8 (28.9)	87 (134.2)	129.3 (36)
	PDN-VAM 6 mg/kg/day (n=15)	141.1 (20.9)	104.7 (123.8)	146.1 (26.5)

ALP, alkaline phosphatase; CTX, C-terminal telopeptide; PDN, prednisone; procollagen I N-terminal propeptide; SD, standard deviation; VAM, vamorolone.

Summary

- For the primary endpoint, TTSTAND velocity improvements seen at Week 24 with prednisone 0.75 mg/kg/day was maintained after switching to vamorolone 6 mg/kg/day during Period 2 (0.05 vs. 0.04 rises/sec, compared to baseline) and similar in magnitude to that seen with continuous treatment with vamorolone 6 mg/kg/day throughout the study. **(Figure 2)**.
- Consistent outcomes were seen for 24 vs. 48 week timepoints for other secondary efficacy measures 6-MWT (40 vs. 29 m), TTRW velocity (0.26 vs. 0.19 m/sec), NSAA (4.7 vs. 4.0 points) and TTCLIMB (0.07 vs. 0.08 tasks/sec). These changes were similar in magnitude to that seen with continuous treatment with vamorolone 6 mg/kg/day throughout the study **(Figure 3)**.
- For the vamorolone 2 mg/kg/day, statistically significant differences were seen vs. placebo at Week 24, but overall, the effect was lower than for vamorolone 6 mg/kg/day or prednisone 0.75 mg/kg/day and not consistently maintained for all efficacy endpoints.
- No serious adverse events (AEs) were reported after the switching from prednisone to either vamorolone dose.
- Annualized rates of AEs (AEs/patient/year) were reduced after the switch from prednisone to vamorolone (all events: ~20% reduction, AEs of special interest [AESIs]: ~40% reduction) **(Figure 4)**.
  - Out of all AESIs, the largest reductions in annualized rates of AEs/patient/year were seen in behavior problems (prednisone vs. vamorolone: 1.1 to 0.5; 52.5% change) and gastrointestinal symptoms (prednisone vs. vamorolone: 0.75 to 0.6; 20.0% change).
- Stunting of growth observed with prednisone during Period 1 was reversed during treatment with vamorolone during Period 2 **(Figure 5)**.
- The decrease in serum bone biomarkers (osteocalcin, procollagen I N-terminal propeptide [PINP]) and collagen I C-Telopeptide [CTX], and alkaline phosphatase [ALP]) seen in the prednisone group during Period 1 was quickly reversed after the switch to vamorolone during Period 2 **(Table 2)**.

Conclusions

- There was no loss of efficacy after switching from prednisone to vamorolone 6 mg/kg/day.
- Switching from prednisone to vamorolone allowed boys to resume normal growth, and experience fewer behavioral problems in addition to other side effects typically associated with corticosteroid use such as the inhibition of height and bone metabolism.
- The longer-term results of the VISION-DMD (VBP15-004) study confirm earlier findings regarding the efficacy of vamorolone and support the potential benefits of switching to vamorolone following treatment with prednisone.

References

1. Heier CR, et al. *Life Sci Alliance*. 2019;2(1):e201800186
2. Mah JK, et al. *JAMA Netw Open*. 2022 Jan 4;5(1):e2144178.
3. Hoffman E. Presented at PPMD Annual Conference, June 22–26, 2021 (Virtual)

Acknowledgments

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