Evaluation of behavioural problems using PARS III in the VISION-DMD study of vamorolone vs prednisone in Duchenne muscular dystrophy (DMD)

Erik Henricson,[1] Ana de Vera,[2] Kerry Nip,[2*†] Mika Leinonen,[2] Paula R Clemens,[3] Michela Guglieri,[4] Natalie Truba,[5] Eric P Hoffman,[6,7] and VISION-DMD (VBP15-004) Investigators

[1]University of California, Davis, Sacramento, California, USA; [2]Santhera Pharmaceuticals (Switzerland) Ltd, Hohenrainstrasse 24, 4133 Pratteln, Switzerland; [3]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [4]John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK; [5]Nationwide Children's Hospital, Columbus, Ohio, USA; [6]ReveraGen BioPharma, Rockville, Maryland, USA; [7]Department of Pharmaceutical Sciences, Binghamton University, State University of New York, Binghamton, New York, USA.
*Corresponding author: Kerry.Nip@santhera.com; [†]Presenting author. Please see acknowledgements and disclosures section below for conflicts of interest.

Introduction

- Corticosteroids are recommended as standard of care for patients with Duchenne muscular dystrophy (DMD). However, behavioural adverse effects during systemic corticosteroid therapy are common and well documented.[1]
- Behavioural problems are a known feature in DMD, and corticosteroids can exacerbate these challenges.[2] These adverse changes in behaviour can lead to treatment discontinuation and can have a substantial negative impact on patient and parent quality of life.[3,4]
- Vamorolone, a novel dissociative corticosteroid with a chemical structure distinct from classic corticosteroids, was recently approved for the treatment of DMD by the FDA (in patients aged ≥2 years) and EMA (in patients aged ≥4 years).[5–8]
  - It was approved on the basis of the pivotal VISION-DMD study (VBP15-004, NCT03439670), which met the primary endpoint of improved time to stand (TTSTAND) velocity with vamorolone 6.0 mg/kg/day vs placebo (p=0.002) at 24 weeks of treatment and showed a manageable safety and tolerability profile.
- Here we report the frequency of behavioural problems observed with vamorolone vs prednisone, compared with placebo, in the VISION-DMD study using the Personal Adjustment and Role Skills Scale, 3rd edition (PARS III), a validated index of youth psychosocial adjustment in DMD.

Methods

- VISION-DMD was a randomised, double-blind Phase 2b study that enrolled male participants aged 4 to <7 years at baseline with centrally confirmed DMD who could walk independently without assistive devices and were able to complete the TTSTAND test without assistance in <10 seconds.
- In the first part of the study, participants were randomised to receive daily doses of vamorolone 2.0 or 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for 24 weeks.
- The frequency of behavioural problems was recorded at Week 24. This analysis included 118 participants in the safety population.
- PARS III is a questionnaire that was completed by parents and consists of 28 items that measure psychosocial functioning in six subscales (peer relations, dependency, hostility, productivity, anxiety/depression and withdrawal).
- In order to define clinically relevant worsening on the PARS III, VISION-DMD data were normalised as z-scores using a previous study of 287 boys with DMD (aged 5–18 years) by Hendriksen et al 2009.[9]
  - Z-scores were calculated as ([Mean – Score]/standard deviation [SD]), where 'Mean' and 'SD' values correspond to the Hendriksen study, and 'Score' corresponds to the value from VISION-DMD.
  - Clinically relevant worsening was defined as a shift from normal adjustment score (z-score <1) at baseline to abnormal adjustment score (z-score ≥1) at Week 24.

Results

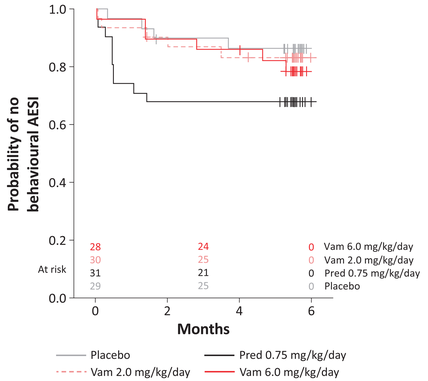
- Adverse events of special interest (AESIs) included abnormal behaviour, aggression, agitation, anger, anxiety, behaviour disorder, emotional disorder, initial insomnia, insomnia, irritability, mood alterations, mood swings, personality change, poor quality sleep, psychomotor hyperactivity, skin laceration and sleep disorder.
- Moderate or severe clinically relevant AESIs and behavioural problems were more frequent in the prednisone group (22.6%) than the placebo group (3.4%). One patient on prednisone discontinued due to a severe behavioural adverse event. Vamorolone showed no moderate or severe clinically relevant behavioural AESIs (**Table 1**).
- After 24 weeks, the probability of having experienced at least one behavioural AESI was lowest in the placebo group, followed by vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, and prednisone (**Figure 1**).
- Prednisone treatment showed the largest proportion of patients with clinically relevant worsening (>20% of patients) in three of the PARS III subscales: hostility, dependency and productivity (**Figure 2**).
  - Clinical worsening in hostility was seen in 26.1% of patients in the prednisone group, 15.4% in the vamorolone 6.0 mg/kg/day group, 9.1% in the vamorolone 2.0 mg/kg/day group, and 8.0% in the placebo group.
  - In the prednisone group, clinical worsening in dependency was seen in 24.0% and clinical worsening in productivity was seen in 26.9% compared with <10% in any other group.
- Clinical worsening in anxiety and depression was observed in a similar number of patients in both the vamorolone 6.0 mg/kg/day group and the prednisone group. However, a larger proportion of patients experienced clinically relevant worsening of withdrawal symptoms with vamorolone 6.0 mg/kg/day (12.5%) compared with prednisone (3.8%).

Table 1. Frequency of AESIs and clinically relevant AESIs (behavioural problems)

	Placebo (N=29)		Pred 0.75 mg/kg/day (N=31)		Vam 2.0 mg/kg/day (N=30)		Vam 6.0 mg/kg/day (N=28)	
Preferred term	**n (%; EAIR)‡**	**f (rate)§**	**n (%; EAIR)‡**	**f (rate)§**	**n (%; EAIR)‡**	**f (rate)§**	**n (%; EAIR)‡**	**f (rate)§**
Total AESIs (behavioural problems)	4 (13.8; 0.34)	5 (0.38)	10 (32.3; 0.99)	16 (1.14)	5 (16.7; 0.43)	5 (0.37)	6 (21.4; 0.53)	9 (0.70)
Total clinically relevant AESIs*,† (behavioural problems)	1 (3.4; 0.08)	1 (0.08)	7 (22.6; 0.59)	8 (0.57)	0	0	0	0
Abnormal behaviour	1 (3.4; 0.08)	1 (0.08)	0	0	0	0	0	0
Aggression	0	0	2 (6.5; 0.15)	2 (0.14)	0	0	0	0
Behaviour disorder	0	0	1[‖] (3.2; 0.07)	1 (0.07)	0	0	0	0
Emotional disorder	0	0	1 (3.2; 0.07)	1 (0.07)	0	0	0	0
Mood swings	0	0	1 (3.2; 0.07)	1 (0.07)	0	0	0	0
Personality change	0	0	1 (3.2; 0.07)	1 (0.07)	0	0	0	0
Psychomotor hyperactivity	0	0	1 (3.2; 0.07)	1 (0.07)	0	0	0	0
Sleep disorder	0	0	1[‖] (3.2; 0.07)	1 (0.07)	0	0	0	0

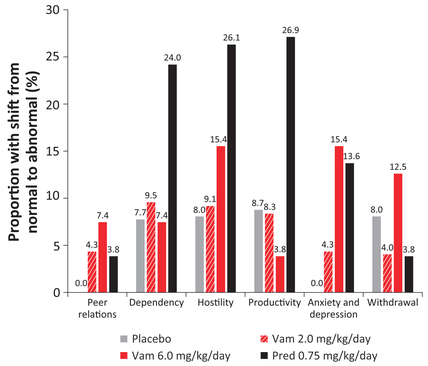
One patient had a skin laceration. Subsequent review of this case confirmed that this was due to a fall, and not related to behavioural problems. Therefore, this patient was not included in Table 1.
*Chi-square p-value for patient counts: vamorolone 6.0 mg/kg/day vs prednisone, p=0.0074; vamorolone 6.0 mg/kg/day vs placebo, p=0.3215; prednisone vs placebo, p=0.0294.
†Clinically relevant AEs were either at least moderate in severity or leading to withdrawal from study or serious event.
‡EAIR was calculated as number of patients reporting the event at least once divided by total time spent (time to first occurrence or total treatment time for patients not experiencing the event in question) at risk for the event to occur. EAIR was annualised.
§The rate of AEs was calculated as events per patient per year of exposure.
‖One patient experienced both behaviour disorder and sleep disorder.
AE, adverse event; AESI, AE of special interest; EAIR, exposure-adjusted incidence rate; f, event count; N/n, patient count; Pred, prednisone; Vam, vamorolone.

Figure 1. Kaplan–Meier curves of time to first onset of behavioural AESIs



Patients without any AESI in the respective category are censored at the date of the last dose of study medication. AESI, adverse event of special interest; Pred, prednisone; Vam, vamorolone.

Figure 2. Proportion of patients with clinically relevant worsening in PARS III adjustment at Week 24



PARS III baseline scores missing from one patient in the placebo group; therefore, N=117. Normal PARS III baseline scores were reported in most patients (>85% across subscales). PARS III, Personal Adjustment and Role Skills Scale, 3rd edition; Pred, prednisone; Vam, vamorolone.

Conclusions

- Vamorolone 6.0 mg/kg/day was associated with an increase in mainly mild behavioural AESIs compared with placebo, but with a lower frequency and severity of behavioural AESIs reported compared with prednisone.
- PARS III subscales showed a reduced risk for psychosocial adjustment in hostility, dependency and productivity with vamorolone compared with prednisone. However, with vamorolone 6.0 mg/kg/day, the risk for anxiety and depression was similar to prednisone, and there was a higher risk for withdrawal symptoms.
- Overall, these results align with adverse event data, suggesting vamorolone has a lower risk for developing behaviour problems affecting the psychosocial adjustment of children with DMD compared with prednisone.
- Limitations include small sample sizes and a potential bias in parent and child reports. The PARS III data relied solely on parent reports, which may have been influenced by parental stress and/or emotional factors. Additionally, because our PARS III data are cross-sectional, we were limited in our ability to examine change over time, such as age.

Acknowledgements

- We would like to thank all patients with DMD and their families for participating in the research studies and the study coordinators, clinical evaluators and Therapeutic Research in Neuromuscular Disorders Solutions.
- This analysis was supported by Santhera Pharmaceuticals.
- Medical writing support was provided by Isabella Janowski, Elements Communications Ltd, UK, and was funded by Catalyst Pharmaceuticals and Santhera Pharmaceuticals.

Disclosures

Erik Henricson: Consultancy: Capricor, Cardero Therapeutics, Genzyme, Sarepta, Santhera, GSK, Pfizer, PTC Therapeutics, Mallinkrodt, Bristol Myers Squibb; Part of the Executive Committee for CINRG and the Scientific Ad Com for PPMD. **Ana de Vera**, **Kerry Nip** and **Mika Leinonen**: Employees of Santhera. **Paula R Clemens**: Grants: ReveraGen, NS Pharma, Amicus, Sanofi, Spark, NIH, FDA, Foundation to Eradicate Duchenne; Consultancy: Catalyst Medical Education, Med Learning Group. **Michela Guglieri**: Grants: Edgewise, Pfizer, Italfarmaco, Santhera, Roche, ReveraGen, Dynacure, Dyne, Sarepta, PTC Therapeutics; Consultancy: Pfizer, Dyne, NS Pharma, Antisense; Honoraria: Italfarmaco, Santhera, Roche, Sarepta, Novartis. **Natalie Truba**: Consultancy: PTC, Sarepta. **Eric P Hoffman**: Stock ownership: ReveraGen, AGADA BioSciences; Employee: ReveraGen, AGADA BioSciences.

References

1. Bello L, et al. Neurology. 2015;85:1048–55;
2. Liu G, et al. Hum Mol Genet. 2024;33:211–23;
3. Cowen L, et al. BMC Neurol. 2019;19:84;
4. Sienko S, et al. PLoS Curr. 2016;8:ecurrents.md.7628d9c014bfa29f821a5cd19723bbaa;
5. Guglieri M, et al. JAMA Neurol. 2022;79:1005–14;
6. Dang UJ, et al. Neurology. 2024;102:e208112;
7. Santhera Pharmaceuticals (Deutschland) GmbH. AGAMREE 40 mg/mL oral suspension. Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/agamree-epar-product-information_en.pdf (accessed June 2024);
8. Catalyst Pharmaceuticals Inc. AGAMREE 40 mg/mL oral suspension. Prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215239s000lbl.pdf (accessed June 2024);
9. Hendriksen JG, et al. J Pediatr Psychol. 2009;34:69–78.

10th EAN Congress, 29 June – 2 July 2024, Helsinki, Finland