Impact of vamorolone, prednisone and placebo on linear growth in the VISION-DMD study, as measured by changes in height over 24 weeks

Ana de Vera,[1*] Wido Tilmann,[2†] Aki Linden,[1] Raoul Rooman,[1] Eric P Hoffman,[3] Paula R Clemens,[4] Michela Guglieri,[5] VISION-DMD (VBP15-004) Investigators

[1]Santhera Pharmaceuticals (Switzerland) Ltd, Hohenrainstrasse 24, 4133 Pratteln, Switzerland; [2]Santhera (Germany) GmbH, Leopoldstrasse 31, 80802 München, Germany;
[3]ReveraGen BioPharma, Rockville, Maryland, USA; [4]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA;
[5]John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK. [*]Corresponding author: ana.devera@santhera.com; [†]Presenting author

Background

- Corticosteroids are recommended as standard of care for patients with Duchenne muscular dystrophy (DMD).[1] However, children with DMD are on average shorter than the general population by the age of 5 years, and daily dosing with prednisone or deflazacort leads to further stunting of growth.[2,3]
- Vamorolone, a novel drug with a chemical structure distinct from classic corticosteroids, was recently approved for the treatment of patients with DMD by the FDA (in patients aged ≥2 years) and EMA (in patients aged ≥4 years).[4–7]
  - 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 demonstrated an amenable safety and tolerability profile.[4–7]
- In the VISION-DMD study, a decline in height percentile (adjusted by age using US Centers for Disease Control and Prevention growth charts) was observed over a 24-week period in patients treated with prednisone, but not in those treated with vamorolone at 6.0 mg/kg/day.[4]
- Here we further characterise the impact of vamorolone vs prednisone compared with placebo on linear growth in the VISION-DMD study by reporting unadjusted changes in height in cm and patient-level changes in height over a 24-week period.

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 mg/kg/day or 6.0 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for 24 weeks.
- Height was recorded at baseline and at 12-week intervals. This analysis included 118 participants in the safety population.
- Changes from baseline in absolute height (cm) and height z-scores (calculated using growth charts from the Centers for Disease Control and Prevention) were estimated at 24 weeks and analysed with a Mixed Model for Repeated Measures (MMRM).
  - To improve reliability in modelling, implausible height measurements, which arose due to the unique challenges of measuring height in patients with DMD, were removed prior to the MMRM analysis.
  - Post-baseline height measurement values were considered implausible if there was a weekly increase >0.4 cm or decrease >0.08 cm compared to the previous visit or baseline.
  - For pre-treatment records, all measurements were considered providing at least one could be used as baseline record (i.e. demonstrated a plausible change to the corresponding post-baseline measurement using the criteria defined above).
- A post-hoc analysis of the proportion of patients with change from baseline in height z-scores ±0.2 standard deviations (SD) at 24 weeks was undertaken based on longitudinal data from the UK NorthStar database published in 2022.[3]

Results

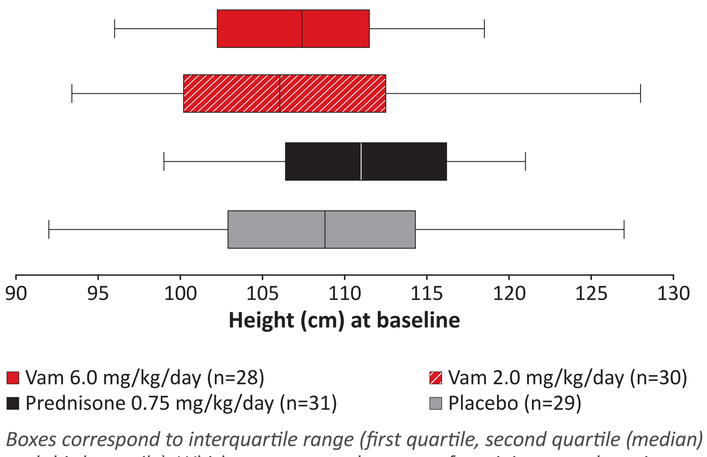
- At baseline, median age was similar across the treatment groups, and median height was higher in the prednisone group than in the other treatment groups **(Table 1, Figure 1)**.
- After 24 weeks of treatment, median height (cm) increases were 3.55 (Q1 [first quartile], Q3 [third quartile]: 2.95, 4.25) in the placebo group, 3.50 (Q1, Q3: 2.80, 4.00) in the vamorolone 6.0 mg/kg/day group, 3.40 (Q1, Q3: 2.50, 3.70) in the vamorolone 2.0 mg/kg/day group and 2.60 (Q1, Q3: 1.70, 3.10) in the prednisone group **(Figure 2)**.
- In the MMRM analysis, mean height increases were lower in the prednisone group than in the placebo group (p=0.015) or vamorolone 6.0 mg/kg/day group (p=0.002) at Week 24. There were no significant differences in mean height increases between either vamorolone group and placebo (p>0.3) at Week 24 **(Figure 3)**.
- In the prednisone group, 30.0% of children showed reductions in height z-score ≥0.2 SD after 24 weeks, compared with 18.5% in the vamorolone 2.0 mg/kg/day group, 10.7% in the placebo group and 0 children in the vamorolone 6.0 mg/kg/day group **(Figure 4)**.
  - In contrast, similar proportions of subjects in the placebo and vamorolone 6.0 mg/kg/day groups showed increases of ≥0.2 SD in height z-score (32.1% and 34.6%, respectively) compared with 16.7% in the prednisone group and 18.5% in the vamorolone 2.0 mg/kg/day group.

Table 1. Characteristics at baseline, ISS-controlled safety population

Characteristic	Statistics	Placebo (n=29)	Prednisone 0.75 mg/kg/day (n=31)	Vam 2.0 mg/kg/day (n=30)	Vam 6.0 mg/kg/day (n=28)	Vam 2–6.0 mg/kg/day (n=58)
Age (years)	Mean (SD)	5.4 (0.83)	5.5 (0.86)	5.3 (0.91)	5.4 (0.88)	5.4 (0.89)
	Median	5.3	5.3	5.2	5.5	5.3
	Min, Max	4.1, 7.0	4.0, 7.0	4.1, 7.0	4.1, 6.8	4.1, 7.0
Height (cm)	Mean (SD)	109.2 (8.90)	110.8 (6.49)	107.8 (8.82)	107.1 (6.64)	107.5 (7.78)
	Median	108.8	111.0	106.1	107.4	106.7
	Min, Max	92.0, 127.0	99.0, 121.0	93.4, 128.0	96.0, 118.5	93.4, 128.0
Height z-score	Mean (SD)	-0.6 (1.21)	-0.4 (1.03)	-0.8 (1.10)	-1.0 (1.05)	-0.9 (1.08)
	Median	-0.5	-0.6	-0.7	-1.0	-0.9
	Min, Max	-2.7, 2.7	-2.2, 1.9	-2.4, 1.4	-3.5, 1.0	-3.5, 1.4

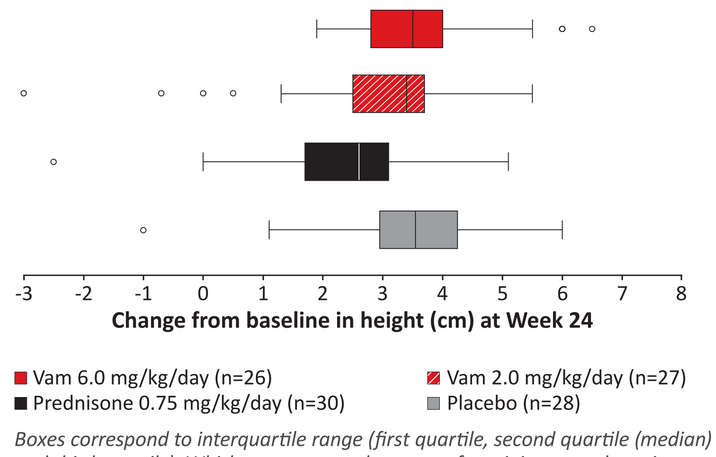
ISS, integrated summary of safety; Max, maximum; Min, minimum; SD, standard deviation; Vam, vamorolone.

Figure 1. Absolute height distribution across treatment groups at baseline



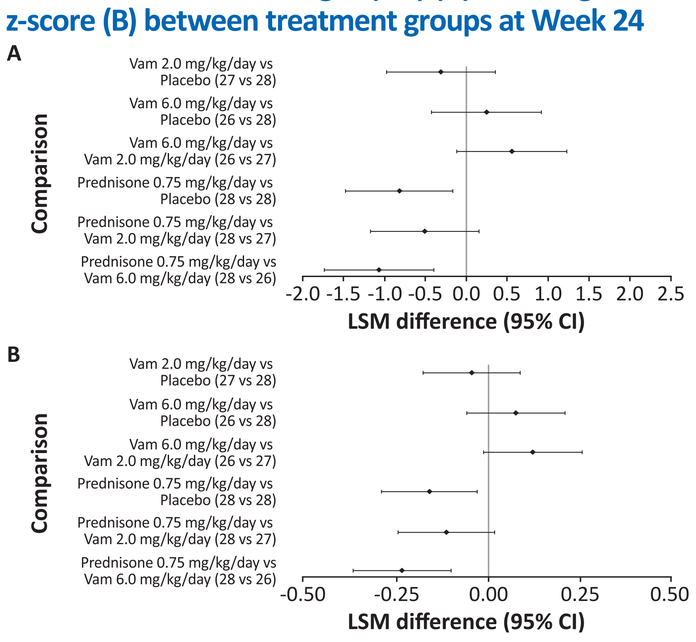
Boxes correspond to interquartile range (first quartile, second quartile (median) and third quartile). Whiskers represent the ranges for minimum and maximum values. Vam, vamorolone.

Figure 2. Change in absolute height across treatment groups at Week 24



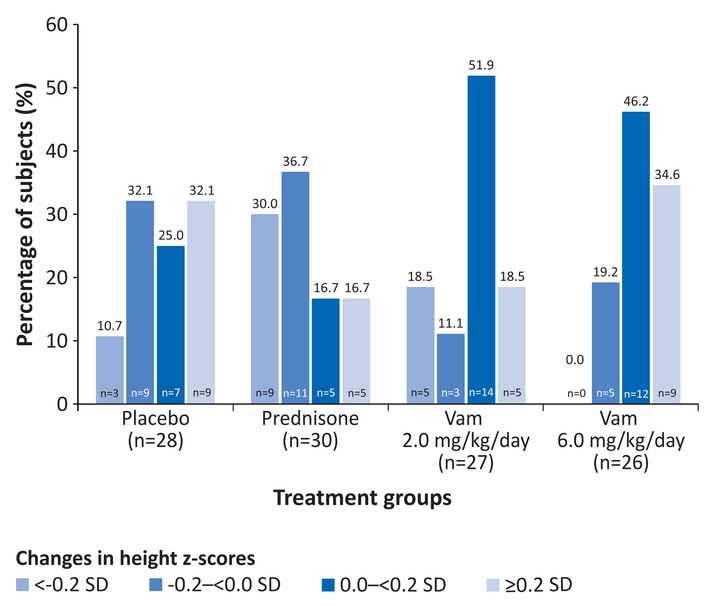
Boxes correspond to interquartile range (first quartile, second quartile (median) and third quartile). Whiskers represent the ranges for minimum and maximum values, excluding outliers >1.5 times the interquartile range. Open circles represent outliers. Vam, vamorolone.

Figure 3. MMRM analysis: LSM difference from baseline in absolute height (cm) (A) and height z-score (B) between treatment groups at Week 24



CI, confidence interval; LSM, least squares mean; MMRM, mixed model for repeated measures; Vam, vamorolone.

Figure 4. Categorical changes in height z-scores at Week 24



SD, standard deviation; Vam, vamorolone.

Conclusions

- In patients with DMD aged 4 to <7 years, absolute height (cm) values after 24 weeks of treatment showed similar increases with vamorolone and placebo, while significantly less growth (i.e. growth stunting) was observed with prednisone.
- Interpretation of this post-hoc analysis may be limited by the relatively small sample sizes and the challenges associated with measuring height consistently in patients with DMD due to the presence of contractures.

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 Ben Holtom and Isabella Janowski, Elements Communications Ltd, UK, and was funded by Catalyst Pharmaceuticals and Santhera Pharmaceuticals.

References

1. Birnkrant DJ, et al. Lancet Neurol. 2018;17:251–67;
2. Bello L, et al. Neurology. 2015;85:1048–55;
3. Stimpson G, et al. Orphanet J Rare Dis. 2022;17:20;
4. Guglieri M, et al. JAMA Neurol. 2022;79:1005–14;
5. ClinicalTrials.gov. NCT03439670. clinicaltrials.gov/study/NCT03439670;
6. 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 February 2024);
7. 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 February 2024).

Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, 3–6 March 2024, Orlando, USA