

# Long-term impact of vamorolone on bone health compared to standard of care glucocorticoids (SoC-GC) in boys with Duchenne Muscular Dystrophy (DMD)

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## Background

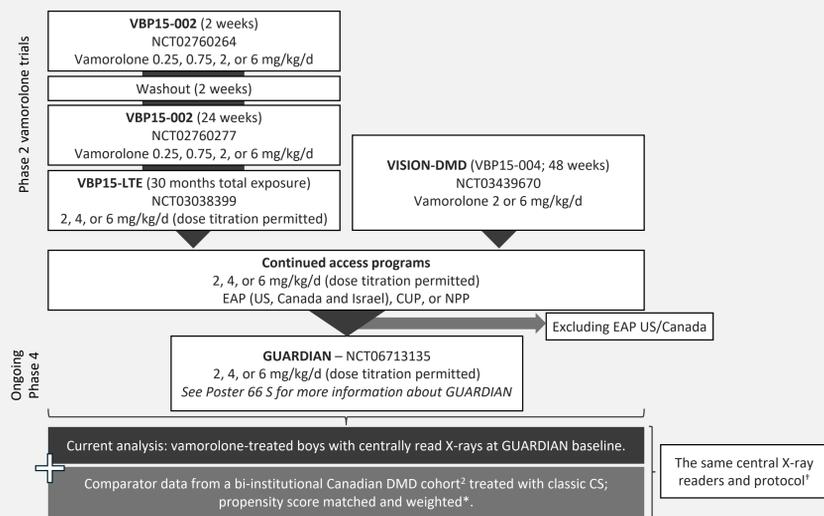
- Classic corticosteroids (CS, prednisone and deflazacort) for Duchenne muscular dystrophy (DMD) can induce bone toxicity that leads to inhibition of growth and increased risk of vertebral fractures.<sup>1,2</sup>
  - The adverse effect profile of classic CS can lead to non-treatment, discontinuation, and suboptimal dosing.<sup>3</sup>
- Vamorolone is a first-in-class dissociative corticosteroid for DMD that has demonstrated similar efficacy and fewer adverse effects versus classic CS, including maintenance of growth trajectories and serum bone turnover markers.<sup>4-6</sup>
  - Long-term effectiveness and anthropometric outcomes are presented at Poster 23 S.

## Objective

- To indirectly compare the prevalence and burden of vertebral fractures, plus bone age delay, between long-term vamorolone and classic CS data.

## Methods

### Figure 1. Data sources

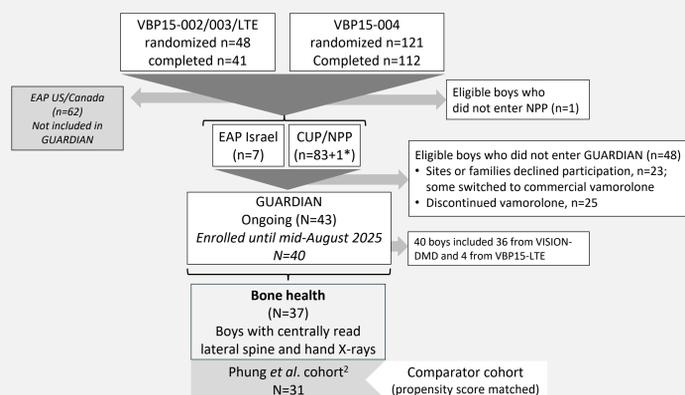


\*Propensity score matching criteria: age at treatment start and time from treatment initiation to X-ray. <sup>1</sup>Performed in an academic setting. CINRG-DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; CUP, compassionate use program; EAP, expanded access program; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; NPP, named patient program; US, United States.

- Vertebral fracture prevalence defined by degree of vertebral height loss was determined using the semi-quantitative Genant method.<sup>7</sup>
  - The assessment of vertebral fractures and grading was performed in an academic setting by two blinded expert radiologists, with a third expert adjudicating discrepancies.
  - A weighted logistic regression model was used to compare between-group vertebral fracture prevalence.
- The burden of vertebral fractures was calculated as Spinal Deformity Index (SDI) by summing Genant grades.
  - A prorated SDI was calculated as (sum of observed scores/number of observed vertebrae)×13 when 1–2 vertebrae were missing from the analysis for any individual.
- Bone age relative to chronological age was quantified via the modified Greulich and Pyle method using BoneXpert™ (Visiana ApS, Denmark).<sup>8</sup>
- All studies were conducted according to good clinical practice.

## Results

### Figure 2. Subject flow from the Phase 2 studies through to the long-term bone-health analyses



\*A single boy was originally in the US EAP and transferred to the UK continued access program. CUP, compassionate use program; EAP, expanded access program; NPP, named program; US, United States.

## Conclusions

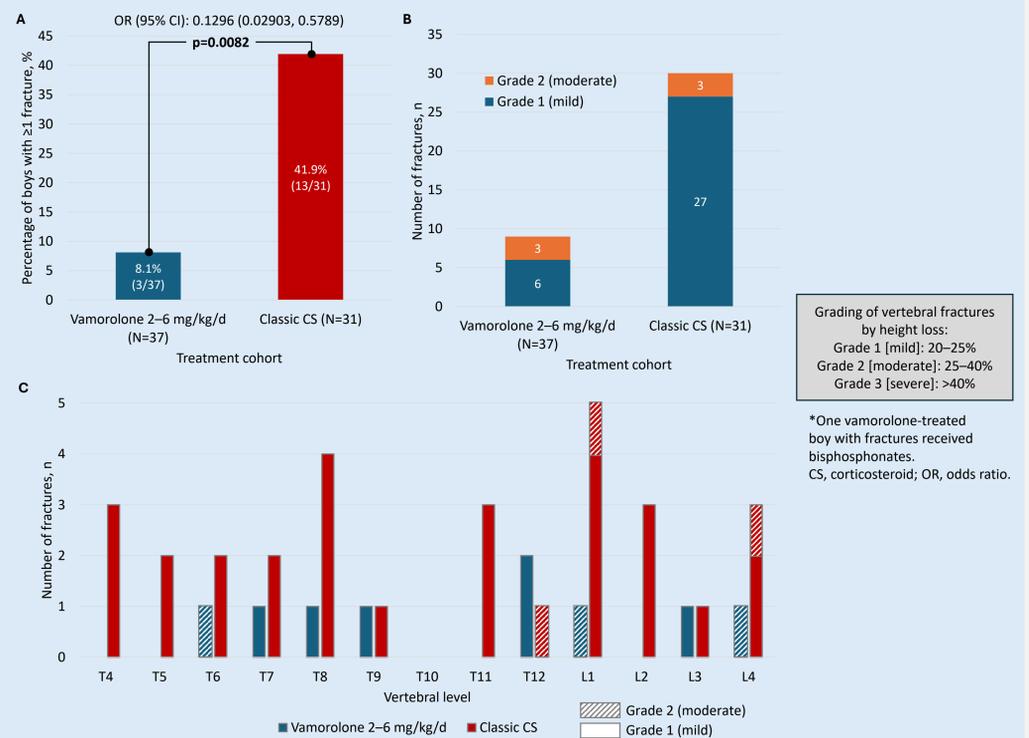
- The prevalence of boys with vertebral fractures was significantly lower on vamorolone versus classic CS after a median treatment time of ~5 years.
- Vertebral fracture burden was lower in the full vamorolone cohort compared with the classic CS cohort.
- Most (6/9) vertebral fractures on vamorolone occurred in a single boy, the cause of this concentration of vertebral fractures has yet to be determined.
- Bone age delay was not clinically meaningful on vamorolone.
- Vertebral fractures occurred in both treatment groups and continued monitoring is recommended.

Table 1. Cohort characteristics at time of X-ray

| Parameters                                   | Vamorolone cohort (N=37*) | Classic CS comparator cohort (N=31) | *37/40 boys in GUARDIAN had readable baseline X-rays interpreted by central readers (Children's Hospital of Eastern Ontario, Ottawa). Exclusions were for IT firewalls preventing sharing of images (2) and unable to X-ray (1). †Mean daily dose is for deflazacort-treated boys n=30, a boy treated with prednisone in this cohort had a mean daily dose of 0.52 mg/kg (n=1). |
|--|---------------------------|-------------------------------------|---|
| Mean age, years ± SD                         | 10.9 ± 1.3                | 11.7 ± 1.5                          |   |
| Mean age at treatment initiation, years ± SD | 5.8 ± 0.8                 | 6.3 ± 2.1                           |   |
| Mean treatment duration, years ± SD          | 5.2 ± 1.0                 | 5.4 ± 2.1                           |   |
| Total exposure, -years                       | 190.6                     | 167.5                               |   |
| Mean daily dose at X-ray, mg/kg ± SD         | 4.9 ± 1.3                 | 0.65 ± 0.2†                         |   |
| Mean duration of treatment, years            | 5.2 ± 1.0                 | 5.4 ± 2.1                           |   |

## Key Vertebral Fracture Findings

### Figure 3. Prevalence of boys with ≥1 vertebral fracture (A), vertebral fracture severity (B), and distribution (C) by treatment\*



- The prevalence of boys with vertebral fractures was significantly lower on vamorolone versus classic CS (Figure 3A).
- In total, 3/37 boys (8.1%) on vamorolone had a total of 9 vertebral fractures; one boy had 6 vertebral fractures (2 moderate and 4 mild), and the other two boys had 1 (mild) and 2 (1 mild and 1 moderate + additional at L5) fractures, respectively (Figure 3B).
- The fractures were distributed across the vertebrae (Figure 3C).

- The prorated SDI was lower on vamorolone (13.7) versus on classic CS (34.1).
  - The mean prorated SDI across the entire cohorts was 0.37 for vamorolone and 1.10 for classic CS.
- The mean prorated SDI in boys with ≥1 vertebral fracture was 4.6 on vamorolone and 2.6 in the classic CS cohort.
  - The higher SDI on vamorolone was predominantly driven by the concentration of fractures in one boy (SDI score of 8).
- Boys on vamorolone had a mean bone age within normal limits versus chronological age, which was delayed on classic CS (Table 2); threshold of normal: ± 1 year; however, the difference between vamorolone and classic CS was not statistically different.

Table 2. Bone age delay

| Parameters                                      | Vamorolone cohort (N=37) | Classic CS cohort (N=31)      |
|---|--------------------------|-------------------------------|
| Mean bone age, years ± SD                       | 10.2 ± 1.7               | 10.1 ± 1.8                    |
| Mean chronological age, years ± SD              | 10.9 ± 1.2               | 11.7 ± 1.4                    |
| Bone age delay, years                           | 0.8 ± 1.5                | 1.6 ± 1.6                     |
| Mean ± SD                                       | 0.6 (-0.4; 1.9)          | 1.3 (0.5; 2.7)                |
| Median (Q1; Q3)                                 | -1.8; 4.3                | -1.3; 4.9                     |
| Min; max  |                          |                               |
| Mean bone age delay difference estimate (95%CI) |                          | -0.6 years (-1.4, 0.2) p=0.12 |

CI, confidence interval; CS, corticosteroid; max, maximum; min, minimum; Q, quartile; SD, standard deviation.

Study limitations: data are from an indirect historical comparison of classic CS including individuals with DMD who were predominantly (30/31) treated with deflazacort.

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