Vamorolone dose titration in expanded access protocols and its impact on rates of weight change in subjects with Duchenne muscular dystrophy (DMD)

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Background

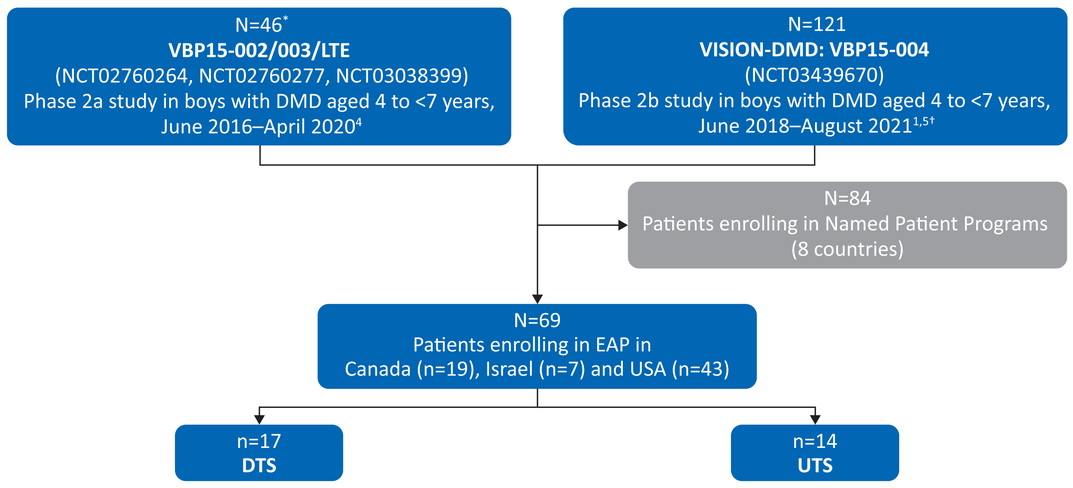
- Vamorolone, a novel drug with a chemical structure distinct from classic corticosteroids, was recently approved for the treatment of patients with DMD by the FDA (in patients aged ≥2 years) and EMA (in patients aged ≥4 years).[1–3]
  - It was approved on the basis of the pivotal VISION-DMD study (VBP15-004, 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.[1–3]
- The recommended dose of vamorolone in children with DMD is 6.0 mg/kg/day (in patients weighing <40 kg [EMA] or <50 kg [FDA]) but doses may be titrated down to as low as 2.0 mg/kg/day, based on tolerability.[2,3*]
- Vamorolone is associated with a dose-dependent risk for weight gain, but prior studies have not investigated the impact of dose titration on weight gain.[2,3]
- At the time of this post hoc study, 167 subjects had completed studies VBP15-LTE (n=46) or VBP15-004 (n=121); nearly all requested continued access to vamorolone.
- The subset of participants from the USA, Canada and Israel enrolled in Expanded Access Programs (EAPs) and participants from the remaining 8 countries could continue treatment by enrolling in the Named Patient Programs.
- Here we report experience with vamorolone dose titration in EAPs and the impact of down-titration on weight gain.

**EMA: in patients weighing ≥40 kg the recommended daily dose is 240 mg;*
FDA: in patients weighing >50 kg the recommended maximum daily dose is 300 mg.

Methods

- Data were collated from 69 subjects who had completed studies VBP15-002/003/LTE or VBP15-004 and enrolled in one of three EAPs in the USA, Canada and Israel, as of 21 July 2023 **(Figure 1)**.
  - Most subjects (60.9%; n=42) exited the double-blinded VBP15-004 study, where the dose of vamorolone administered during the trial was unknown, and thus, all subjects were encouraged to use an intermediate dose in the EAPs (4.0 mg/kg/day).
  - The majority of subjects were white (87.0%; n=60) and a smaller number were Asian (4.3%; n=3), black (2.9%; n=2), multiple (1.4%; n=1), American Indian or Alaska native (1.4%; n=1) or unknown (2.9%; n=2).
  - Most subjects were from the USA (62.3%; n=43) or Canada (27.5%; n=19) and the rest were from Israel (10.1%; n=7).
  - The mean age of subjects was as follows:
    - 5.4 years at VBP15-002/003/LTE and VBP15-004 baselines
    - 7.1 years at the start of the EAPs
- Available data were pooled to explore the effect of dose titration on weight changes, with two analysis sets created based on the availability of at least three weight measurements before and after dose titration **(Figure 1)**.
  - Down-titration set (DTS): subjects with ≥3 weight measurements on vamorolone 6.0 mg/kg/day followed by ≥3 weight measurements after down-titrating to 4.0 mg/kg/day
  - Up-titration set (UTS): subjects with ≥3 weight measurements on vamorolone 2.0 mg/kg/day followed by ≥3 weight measurements after up-titrating to 4.0 mg/kg/day
  - Treatment Period 1 started at the first dose of 6.0 mg/kg/day for the DTS and 2.0 mg/kg/day in the UTS and Treatment Period 2 started at dose titration to 4.0 mg/kg/day
- Annualised changes in weight percentiles before and after titration were estimated using mixed models (unstructured covariance) with random slope and intercept:
  - Weight Percentile = Intercept + Annual Change*Time

Figure 1. Identification of up- and down-titration sets



DTS, down-titration set; EAP, Expanded Access Programs; UTS, up-titration set.
**48 subjects enrolled in study VBP15-002 but two subjects withdrew during study VBP15-003, so 46 subjects enrolled in study VBP15-LTE.*
†Subjects could not be up- or down-titrated from their vamorolone 2.0 or 6.0 mg/kg/day starting dose while participating in study VBP15-004.

Table 1. Patient characteristics at Treatment Period 1 and 2 baselines

	DTS (n=17)		UTS (n=14)	
	Treatment Period 1	Treatment Period 2	Treatment Period 1	Treatment Period 2
Age (years)				
Mean (SD)	6.4 (1.05)	7.5 (1.53)	6.5 (1.36)	7.2 (1.62)
Median (Q1; Q3)	6.4 (5.8; 6.9)	7.3 (6.7; 7.9)	5.9 (5.6; 7.5)	6.6 (6.3; 7.9)
Min, Max	4.6, 8.6	5.4, 12.3	5.0, 9.5	5.4, 10.8
Weight percentile (%)				
Mean (SD)	48.6 (26.81)	60.6 (26.12)	54.9 (27.52)	63.6 (25.04)
Median (Q1; Q3)	50.5 (32.0; 70.0)	62.6 (55.0; 75.2)	53.5 (31.0; 80.7)	52.2 (43.3; 91.0)
Min, Max	2.7, 97.3	3.3, 99.4	16.6, 94.6	28.7, 95.2

DTS, down-titration set; Max, maximum; Min, minimum; SD, standard deviation; Q1, first quartile; Q3, third quartile; UTS, up-titration set.

Results

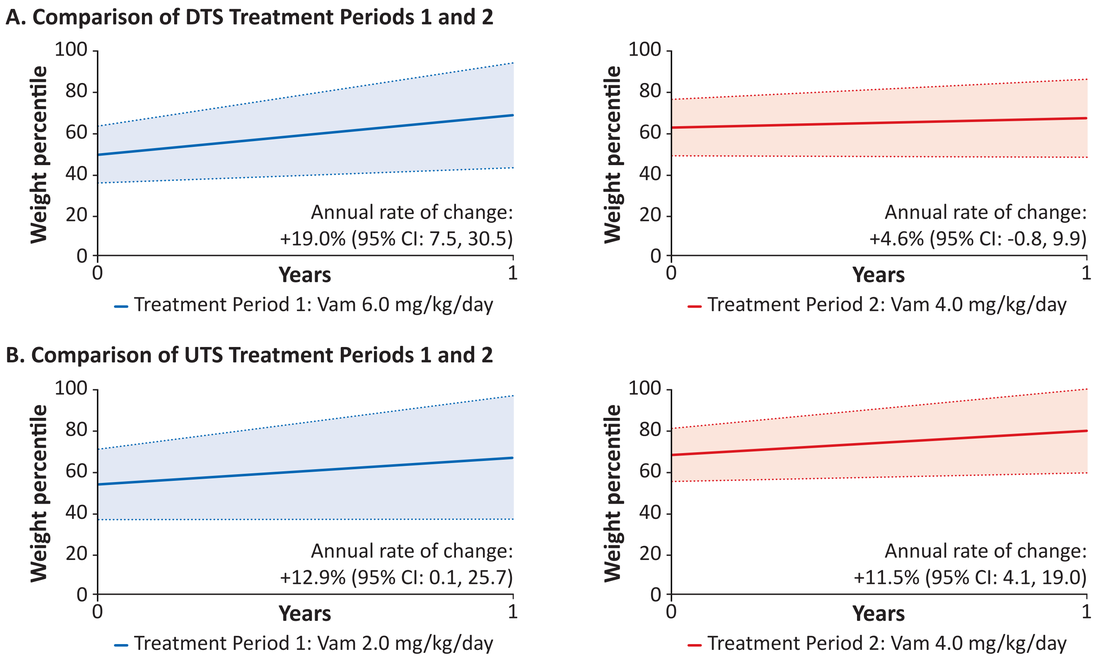
- 17 subjects were included in the DTS and 14 subjects in the UTS **(Table 1)**.
  - Median age immediately prior to dose titration was higher in the DTS (6.4 years) than in the UTS (5.9 years).
  - The median duration of exposure to vamorolone across both treatment periods is presented in **Table 2**.
- In the DTS, the annual rate of change in weight percentiles decreased **(Figure 2A)**:
  - 19.0% (95% confidence interval [CI]: 7.5, 30.5) during Treatment Period 1 (vamorolone 6.0 mg/kg/day) vs
  - 4.6% (95% CI: -0.8, 9.9) during Treatment Period 2 (vamorolone 4.0 mg/kg/day)
- In the UTS, the annual rate of change in weight percentiles remained similar **(Figure 2B)**:
  - 12.9% (95% CI: 0.1, 25.7) during Treatment Period 1 (vamorolone 2.0 mg/kg/day) vs
  - 11.5% (95% CI: 4.1, 19.0) during Treatment Period 2 (vamorolone 4.0 mg/kg/day)

Table 2. Vamorolone exposure at the end of Treatment Period 1 (before dose titration) and 2 (after dose titration)

	DTS (n=17)		UTS (n=14)	
	Treatment Period 1	Treatment Period 2	Treatment Period 1	Treatment Period 2
Duration of exposure (years)				
Mean (SD)	1.1 (1.03)	2.1 (0.95)	0.8 (0.53)	2.2 (1.17)
Median (Q1; Q3)	0.6 (0.4; 0.9)	2.5 (1.7; 2.7)	0.7 (0.4; 0.9)	2.3 (1.2; 3.0)
Min, Max	0.4, 3.7	0.2, 3.5	0.4, 2.4	0.2, 4.2
Sum of exposure (patient-years)				
	17.9	35.1	10.8	30.1

DTS, down-titration set; Max, maximum; Min, minimum; SD, standard deviation; Q1, first quartile; Q3, third quartile; UTS, up-titration set.

Figure 2. Linear model of weight percentiles in Treatment Periods 1 and 2 by analysis set



*CDC, Centers for Disease Control and Prevention; CI, confidence interval; DTS, down-titration set; UTS, up-titration set; Vam, vamorolone. 2000 CDC Growth Charts were used.[6] The annual change in weight percentiles (slope of the regression line) within each treatment period has been estimated using a mixed model with random slope and intercept. Thick lines: Weight Percentile = Intercept + Annual Change*Time (years); dotted lines: upper and lower confidence limits.*

Conclusions

- Dose titration experience in the EAPs showed that vamorolone 6.0 mg/kg/day is associated with weight gain.
- A clear increase in weight percentile was not observed in subjects who were up-titrated from vamorolone 2.0 mg/kg/day to 4.0 mg/kg/day.
- Subjects that down-titrated from 6.0 to 4.0 mg/kg/day experienced a smaller increase in weight percentile on 4.0 mg/kg/day than on 6.0 mg/kg/day.
- Overall, these results suggest that down-titration from vamorolone 6.0 mg/kg/day to 4.0 mg/kg/day may be considered in patients experiencing weight gain.
- Limitations of this exploratory, post hoc analysis include the small sample sizes of the dose titration sets, and inherent bias when selecting subjects from existing studies based on dose titration. Further study is required to characterise the relationship between vamorolone dosage and weight gain.

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References

1. Guglieri M, et al. JAMA Neurol. 2022;79:1005–14;
2. 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);
3. 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);
4. Mah JK, et al. JAMA Netw Open. 2022;5:e2144178;
5. ClinicalTrials.gov. NCT03439670. clinicaltrials.gov/study/NCT03439670;
6. CDC. Growth charts. Available at: https://www.cdc.gov/growthcharts/cdc_charts.htm (accessed February 2024).

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