Long-term dose-titration experience with vamorolone in subjects with Duchenne muscular dystrophy (DMD) enrolled in expanded access programs

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and VISION-DMD (VBP15-004) Investigators

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Introduction

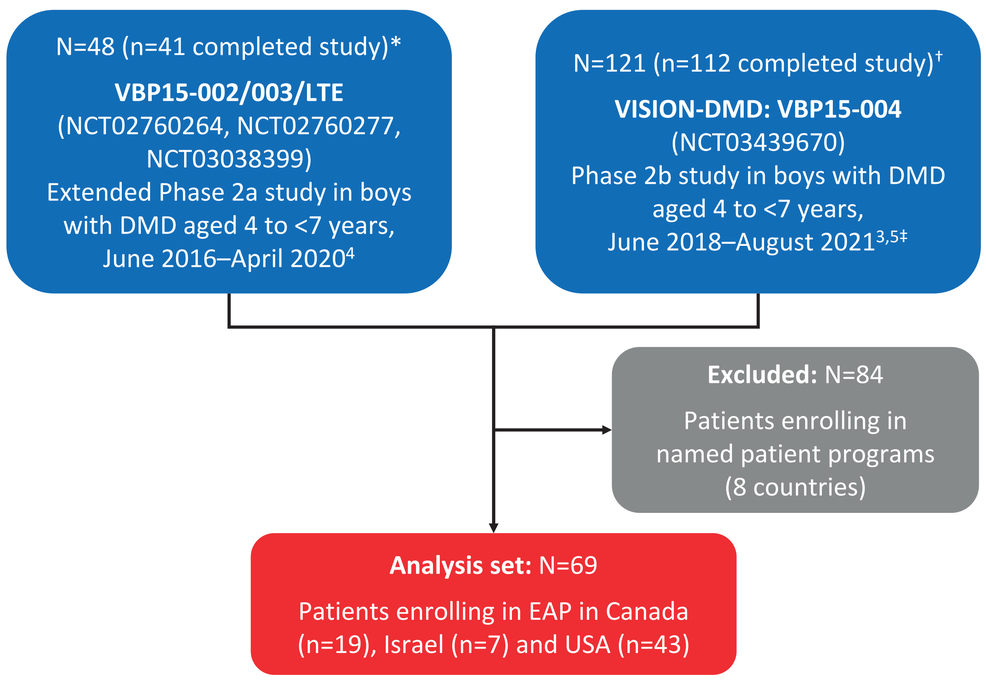
- Vamorolone, a novel dissociative corticosteroid with a chemical structure distinct from classic corticosteroids, was recently approved for the treatment of patients with DMD by the FDA (in patients aged ≥2 years) and EMA (in patients aged ≥4 years).[1–3]
  - The efficacy and safety of vamorolone in boys with DMD was previously investigated in a randomised Phase 2b study (VBP15-004 [VISION-DMD]) and an extended Phase 2a study (VBP15-002/003/LTE).[3–4]
  - Patients from the USA, Canada and Israel who participated in these studies were able to continue vamorolone treatment in expanded access programs (EAPs), whereas participants from the remaining eight countries could continue treatment by enrolling in the named patient programs.
- 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 gradually titrated down to 4.0 or 2.0 mg/kg/day, based on tolerability.[1,2]
- The EAPs allowed for up- or down-titration of vamorolone as medically warranted.
- Here we report experience with vamorolone dose titration in EAPs.

**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

- At the time of this post hoc analysis, 167 subjects had completed studies VBP15-LTE (n=46) or VBP15-004 (n=121); nearly all requested continued access to vamorolone.
- Data were collated from subjects who had completed studies VBP15-LTE or VBP15-004 and enrolled in one of three EAPs in the USA, Canada and Israel, respectively **(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).
  - At the start of the EAPs:
    - The mean age of subjects was 7.1 years.
    - The median height was 118.0 cm.
    - The median weight was 26.0 kg.
- Available data were pooled to explore the frequency of dose titration during the EAPs.
- The EAPs are ongoing; a cut-off date of 3 April 2024 was used for the analysis presented.

Figure 1. Analysis set

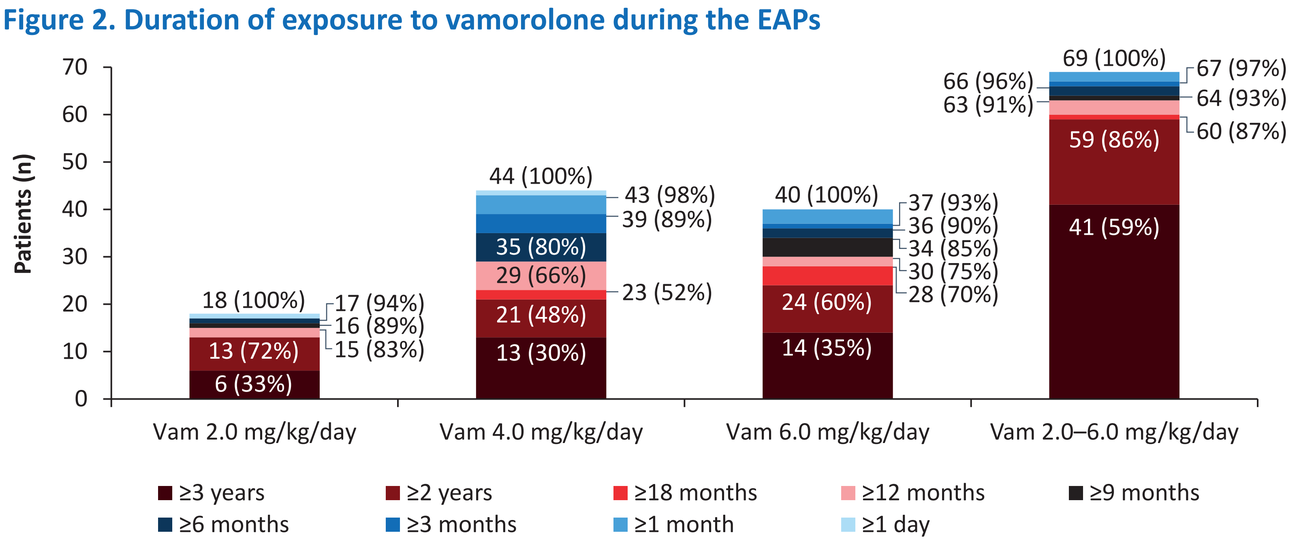


EAP, expanded access programs.
**Reasons for discontinuation: withdrawn by parent/guardian (n=7).*
†Reasons for discontinuation: withdrawn by parent/guardian (n=3), adverse event (n=2), physician decision (n=1), other (n=3).
‡Subjects could not be up- or down-titrated from their vamorolone 2.0 or 6.0 mg/kg/day starting dose while participating in study VBP15-004.

Results

- At the start of the EAPs, most subjects were dosed at vamorolone 4.0 mg/kg/day (43.5%; n=30) or 6.0 mg/kg/day (40.6%; n=28), with fewer dosed at 2.0 mg/kg/day (15.9%; n=11).
- The median duration of vamorolone exposure during the EAPs was 3.3 years with a maximum of 4.9 years.
- Duration of vamorolone exposure during the EAPs is reported in **Figure 2**.
- The majority of subjects did not change dose, and up- and down-titrations occurred at a similar frequency **(Table 1)**.
- Up-titration from 4.0 to 6.0 mg/kg/day and down-titration from 6.0 to 4.0 mg/kg/day were the most common dose changes, and the least common changes were down-titrations from the higher doses to 2.0 mg/kg/day **(Table 1)**.
- Treatment-emergent adverse events during the EAPs are reported in **Table 2**.
- During the EAPs, 16 subjects discontinued treatment **(Figure 3)**.
- By the end of the EAP or treatment cut-off, most subjects were dosed at vamorolone 4.0 mg/kg/day (40.6%; n=28) or 6.0 mg/kg/day (40.6%; n=28), and fewer were dosed at 2.0 mg/kg/day (18.8%; n=13).

Figure 2. Duration of exposure to vamorolone during the EAPs



EAP, expanded access program; Vam, vamorolone.
Dose levels 3.0–5.0 mg/kg/day are included in 4.0 mg/kg/day; these data represent all subjects who received each dose during the EAPs, so patients who changed dose are represented in multiple bars.

Table 1. Dose changes during the EAPs

Dose change	Vam 2.0–6.0 mg/kg/day (N=69)	
	n (%)	f
Any dose changes	29 (42.0)	42
Up-titrations	16 (23.2)	22
Down-titrations	18 (26.1)	20
4.0 mg/kg/day to 6.0 mg/kg/day	14 (20.3)	16
6.0 mg/kg/day to 4.0 mg/kg/day	11 (15.9)	12
2.0 mg/kg/day to 4.0 mg/kg/day	4 (5.8)	6
6.0 mg/kg/day to 2.0 mg/kg/day	4 (5.8)	4
4.0 mg/kg/day to 2.0 mg/kg/day	4 (5.8)	4

EAP, expanded access program; f, frequency of events; Vam, vamorolone. Dose levels 3.0–5.0 mg/kg/day are included in 4.0 mg/kg/day; dose changes as part of tapering to discontinue vamorolone in two subjects were excluded.

Figure 3. Reasons for discontinuation

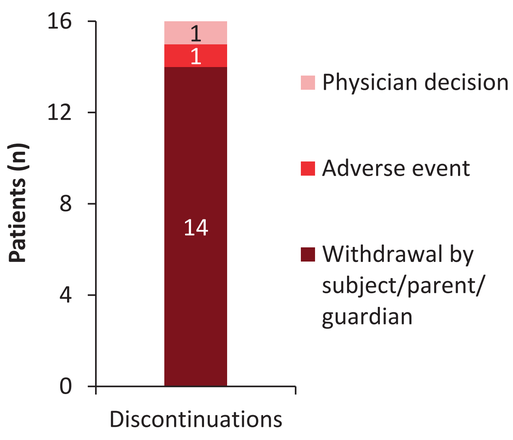


Table 2. Summary of TEAEs by dose at onset

Type of TEAE	Vam 2.0 mg/kg/day (n=18)		Vam 4.0 mg/kg/day (n=44)		Vam 6.0 mg/kg/day (n=40)		Vam 2.0–6.0 mg/kg/day (N=69)	
	n (%)	f (rate)*	n (%)	f (rate)*	n (%)	f (rate)*	n (%)	f (rate)*
Total TEAEs	11 (61.1)	37 (0.83)	27 (61.4)	87 (1.05)	31 (77.5)	105 (1.08)	53 (76.8)	229 (1.02)
Any drug-related TEAEs	3 (16.7)	3 (0.07)	5 (11.4)	7 (0.08)	12 (30.0)	16 (0.16)	18 (26.1)	26 (0.12)
Severe TEAEs	0	0	4 (9.1)	7 (0.08)	2 (5.0)	4 (0.04)	5 (7.2)	11 (0.05)
Serious TEAEs	1 (5.6)	1 (0.02)	5 (11.4)	8 (0.10)	4 (10.0)	11 (0.11)	8 (11.6)	20 (0.09)
TEAEs leading to withdrawal from study	1 (5.6)	1 (0.02)	0	0	0	0	1 (1.4)	1 (0.00)
TEAEs leading to drug interruption	1 (5.6)	2 (0.04)	5 (11.4)	11 (0.13)	2 (5.0)	4 (0.04)	7 (10.1)	17 (0.08)
TEAEs leading to dose reduction	0	0	4 (9.1)	4 (0.05)	8 (20.0)	10 (0.10)	11 (15.9)	14 (0.06)
TEAEs leading to dose increase	2 (11.1)	2 (0.04)	1 (2.3)	2 (0.02)	0	0	3 (4.3)	4 (0.02)

f, frequency of events; TEAE, treatment-emergent adverse event; Vam, vamorolone.
**Rate per patient-year of exposure. Dose levels 3.0–5.0 mg/kg/day are included in 4.0 mg/kg/day; the columns represent the dose at the time of the TEAE, so patients who changed dose may be represented in multiple columns.*

Conclusions

- Long-term experience in the EAPs shows that vamorolone 4.0 and 6.0 mg/kg/day are the most frequently used doses and that most patients do not change dose.
- The therapeutic dose range from 2.0 to 6.0 mg/kg/day allows physicians to up- or down-titrate dosing based on individual tolerability.
- The number of TEAEs was dose dependent, with the highest number occurring in the 6.0 mg/kg/day group.
- The majority of TEAEs did not lead to a dose reduction or interruption.
- Interpretation of this exploratory post hoc analysis may be limited by relatively small sample sizes and the impact of patients who participated in the VBP15-004 study being encouraged to use an intermediate dose (4.0 mg/kg/day) at the start of the EAPs.

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