Vamorolone for Duchenne Muscular Dystrophy

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Vamorolone is a synthetic corticosteroid designed to treat Duchenne muscular dystrophy (DMD) and potentially other inflammatory conditions.

This is a summary of current evidence on vamorolone in DMD, based on published data. A systematic review of current evidence of efficacy and safety in DMD has been recently published[1].

Indication

Duchenne muscular dystrophy, age 4 years and older (based on NICE recommendations, 10th December 2024): (**Overview | Vamorolone for treating Duchenne muscular dystrophy in people 4 years and over | Guidance | NICE**)

Mechanism of action

Vamorolone is a corticosteroid. It is often called a "dissociative corticosteroid" as it is intended to retain the therapeutic benefits of traditional corticosteroids (prednisone and deflazacort), whilst reducing some of the side effects[2].

Vamorolone has similar anti-inflammatory action to prednisone and deflazacort (*transrepression* activity as it is mediated by *repression* of a specific inflammatory pathway, NF-κB).

Vamorolone lacks the affinity for the glucocorticoid response element (GRE) binding site, which is thought to be responsible for the corticosteroid side effect profile.

In contrast to traditional corticosteroids, vamorolone is an antagonist of the mineralocorticoid receptor (like spironolactone), with potential cardioprotective benefits (which still need to be investigated).

Current evidence on vamorolone

Our current knowledge on vamorolone in DMD comes primarily from two completed phase 2 studies and two extension studies:

- Phase 2a study (VPB15-002): open label, dose escalation (vamorolone 0.25, 0.75, 2.0, and 6.0 mg/kg/day) safety study in 48 boys aged 4-6 years treated for 14 days *(number of patients: 24)*

- Open label extension study (VBP15-003): open label, dose escalation (vamorolone 0.25, 0.75, 2.0, and 6.0 mg/kg/day) long term safety and efficacy study in boys who completed the Phase 2a study and continued treatment for 24 weeks. *(number of patients: 24)*
- Long term extension study (VBP15-LTE): open label, long term, dose escalation, safety and efficacy study in boys who completed the Phase 2a and open label extension study and continued treatment up to 30 months (number of patients: 46)
- Phase 2b study (VBP15-004 or **VISION-DMD**): randomized, double-blind, parallel group, placebo and active-controlled safety and efficacy study of two doses of vamorolone (2.0 mg/kg/day and 6.0 mg/kg/day) versus prednisone 0.75 mg/kg/day and placebo in 121 boys aged 4-6 years over a treatment period of 24 weeks. After 24 weeks, boys treated with vamorolone continued to receive the same dose until week 48 (providing safety and efficacy data of continuous vamorolone treatment at two different doses of 2 and 6 mg/kg/day for up to 48 weeks) whilst boys on prednisone and placebo were tapered off treatment/placebo over 4 weeks (week 24-week 28) and randomized to either vamorolone 2 mg/kg or 6 mg/kg until week 48. The study did therefore allow comparison of vamorolone vs placebo and prednisone at week 24 (but not at week 48) (number of patients: 121)

The results of these studies have been published in peer reviewed journals.[3-7]

Patients enrolled in the above studies have been offered the option to continue receiving vamorolone at the end of the study through compassionate use (UK) and other early access programs.

Only data on up to 30 months' exposure in ambulant children have been published so far.

Longer term safety and efficacy of vamorolone and comparison with traditional corticosteroids is not available yet.

Efficacy of vamorolone

Based on the evidence available to date, vamorolone has shown similar efficacy to traditional corticosteroids across various functional outcome measures at 6 months*[6] and up to 30 months**[5].

Vamorolone 2 mg/kg/day is less effective than daily prednisone and vamorolone 6mg/kg/day, with less improvement on the majority of the motor function outcome measures at 12 months of treatment[7].

Earlier treatment initiation is associated with better clinical outcomes[7].

Longer term efficacy comparison is not available yet.

Currently, there is no published efficacy direct comparison between vamorolone and deflazacort or with intermittent regimens.

Switching from daily prednisone to vamorolone after the first 6 months of treatment showed that vamorolone 6 mg/kg/day maintained the improvements seen with prednisone during the first 6 months. Currently, there is no information on efficacy of switching to vamorolone after receiving longer term prednisolone or deflazacort. [7]

***** VISION DMD Study, *vamorolone 6 mg/kg/day versus prednisone 0.75 mg/kg/day at 6 months after treatment initiation*; outcome measures: time to rise from the floor, 6 minute walking distance, time to run/walk 10 meters, time to climb 4 steps, NSAA total score

** LTE study, vamorolone vs different corticosteroids (any type, dose and regimes) compared to CINRG natural history and UK North Star cohort. Outcome measures: time to rise from the floor, 6 minute walking distance, time to run/walk 10 meters, time to climb 4 steps, NSAA total score

Safety of vamorolone

A summary of the side effect profile of vamorolone compared to traditional corticosteroids based on the evidence available so far is provided in table 3.

Overall, vamorolone has shown a better profile compared to traditional corticosteroids with regard to two specific side effects: growth and bone health[5,6,8]. There is some evidence suggesting a favourable side effect profile with regard to behavioural problems[9].

Vamorolone has shown similar side effects related to weight gain and adrenal suppression[10].

Data on long term safety of vamorolone are missing (maximum exposure 30 months).

Following the switch from prednisone to vamorolone after the first 6 months of treatment, catch up growth was observed and a reduced frequency of some adverse events (behavioural problems and gastrointestinal symptoms) was reported. Currently, there is no information on reversal of side effects when switching to vamorolone after receiving longer term prednisolone or deflazacort.

Side effects	**Comments**	**Comparison with traditional corticosteroids**
Adrenal insufficiency	Adrenal suppression occurs in boys treated with vamorolone in a dose dependent manner. All boys treated with vamorolone regardless of the dose, should be assumed to have adrenal suppression and therefore to be at risk of adrenal crisis during acute illness, emergencies or significant stress. A sick day plan with oral hydrocortisone must therefore be in place.	The risk of adrenal insufficiency occurs with all CS types and regimens.

Weight gain	Weight gain occurs commonly with all CS, including vamorolone. Time of onset and severity can vary from patient to patient.	Vamorolone is associated with similar weight gain and increase in body mass index to daily prednisone. It is currently unclear how weight gain with daily vamorolone compares to weight gain with daily deflazacort.
Growth failure and short stature	Boys on vamorolone treated for up to 30 months did not show decline in height percentiles.	In contrast to traditional CS, vamorolone is not associated with growth failure. The negative effect of traditional CS on growth seems to be reversible after switching to vamorolone, at least after short exposure (boys switched from prednisone to vamorolone after the first 6 months of treatment showed reversal of growth trajectories through catch-up growth).
Osteoporosis and fragility fractures	Vamorolone does not suppress bone turnover marker. Vamorolone still increases risk of vertebral fractures. Further data is need on long bone fracture risk with vamorolone.	Preliminary results suggest that vertebral fractures are less common in boys treated with vamorolone compared to boys treated with daily prednisone or deflazacort; but *more common* compared to boys not treated with CS or on an intermittent prednisone regime (data up to 30 month treatment exposure). (*Data presented but not peer reviewed to date*[8]).
Behavioural issues	Behavioural problems, including anxiety, depression, temper tantrums, aggressivity, insomnia can be triggered or exacerbated by CS, including vamorolone.	Vamorolone might be associated with less behavioural problems than prednisolone. *(Data presented but not published to date*[9]*).* To date, there is no data comparing vamorolone to deflazacort with regard to behavioural problems.

Cushingoid features	Cushingoid features have been described in boys treated with vamorolone, possibly dose-dependent.	No data available
Pubertal delay	Unknown: published data only includes boys with DMD exposed to vamorolone up to the age of 11 years.	Unknown
Gastro-intestinal symptoms	No data available	Unknown
Cataracts	No data available	Unknown
Immunosuppression/increased risk of infections	No data available	Unknown
Hypertrichosis	No data available	Unknown
Hypertension	No data available	Unknown
Glucose intolerance	No data available	Unknown
Skin fragility	No data available	Unknown
Acne and other skin infections (e.g. tinea, warts)	No data available	Unknown

Ongoing studies/access programs with vamorolone in DMD

Compassionate use (UK) – open to patients who completed any of the clinical trials with vamorolone in the UK. *No data published to date.*

Early Access Programs (Australia, US, Israel) – open to patients who completed any of the clinical trials with vamorolone in Australia, US and Israel. *No data published to date.*

Licensed prescription (US, Germany) – following FDA and EMA approval in October 2023 and December 2023 respectively. *No data published to date.*

VBP15-006 study (US) – Open-label, multiple dose safety and efficacy study of vamorolone in steroid-naïve boys aged 2 to <4 years, and in previously glucocorticoid-treated (switching) and untreated boys aged 7 to <18 years with DMD over a treatment period of 12 weeks (number of participants: 54).

Guardian clinical trial (UK) – open label study of boys who completed previous studies with vamorolone (VBP15-002/003/LTE/004) and continued vamorolone under EAP or compassionate use to assess long term safety and effectiveness of vamorolone, with a specific focus on vertebral fractures, non-vertebral fractures, cataracts, delayed puberty, overall safety as well as disease milestones (ambulatory and non-ambulatory function).

Additional evidence on short term (12 months) safety and efficacy of vamorolone (focused on clinical outcome measures, anthropometric measures, vertebral fractures and behavioural

issues), are expected in the upcoming months from the comparison of the data from the **VISION DMD study and the FOR DMD study**.

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