VISION-DMD

Project website: www.vision-dmd.info

VISION-DMD: Clinical development of an innovative designer drug for the rare disease Duchenne Muscular Dystrophy (DMD).

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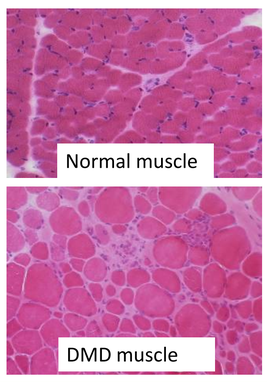
VISION-DMD is a collaborative project undertaking Phase 2 Clinical Trials of Vamorolone - an Innovative Steroid-like Intervention for Duchenne Muscular Dystrophy.

Duchenne Muscular Dystrophy

- 1:5000 male births worldwide
- Onset is usually between 2 and 6 years of age
- Caused by mutations in the dystrophin gene
- Progressive muscle weakness and wasting
- Early death from cardiorespiratory failure
- Treatments generally palliative in nature



Glucocorticoids – Standard of Care for DMD

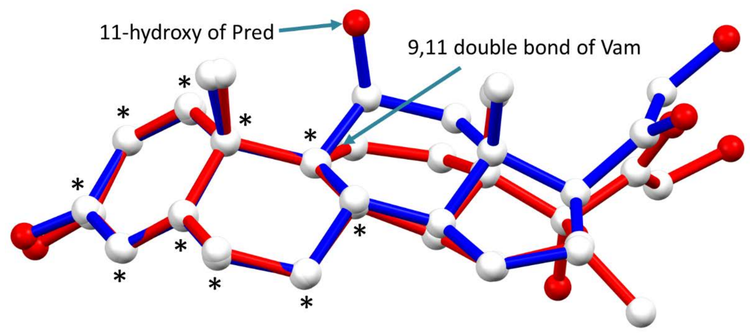
- Prednisone and deflazacort are the only treatment option for DMD that is independent of mutation type
- Mechanism of action is as an anti-inflammatory
- Glucocorticoids improve muscle strength, prolong ambulation, delay respiratory and orthopaedic complications and very likely prolong survival

Glucocorticoids show severe safety concerns: Multiple side effects detract from patient quality of life, lead to variation in practice

Vamorolone: A first-in-class dissociative steroid

- ✓ An innovative steroid-like drug designed to retain or improve glucocorticoid anti-inflammatory efficacy
- ✓ Mineralocorticoid receptor antagonist – additional efficacy
- ✓ Reduced side effects
- ✓ Membrane stabilizing activity
- ✓ Better safety profile enables higher dosing

Comparison of the experimentally determined crystal structures of vamorolone and prednisone.



Structure overlay of Vamorolone (Vam, red) and Prednisone (Pred, blue).

Phase 1 clinical trial in adult volunteers

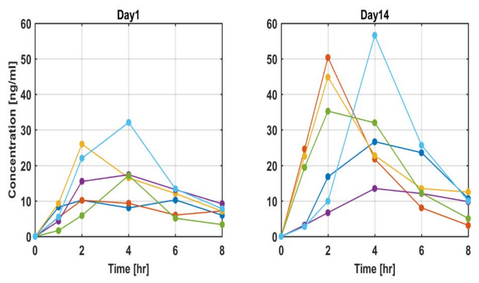
- Pharmacokinetic (PK) data in single and multiple ascending doses up to 20 mg/kg/day for 14 days: strong adherence to dose linearity and dose proportionality
- No drug accumulation observed, consistent with short half-life
- No adverse events precluding further escalations in dosing observed
- Safety pharmacodynamics (PD) biomarker studies showed loss of insulin resistance, loss of bone safety concerns, increased window for adrenal suppression
- Published: Hoffman et al. 2018; *Steroids*

Phase 2a in 4 to <7 years DMD boys

Phase 2a: Multiple ascending dose, 2 weeks on, 2 weeks washout - complete
Phase 2a extension: 6 months at same dose - complete
Phase 2a Long-term extension: 2 years with dose escalations permitted - ongoing

- 48 patients recruited at 11 Cooperative International Neuromuscular Research (CINRG) sites: USA (5), Canada (1), UK (1), Australia (2), Israel (1), Sweden (1)
- Four dose groups: 0.25, 0.75, 2.0, 6.0 mg/kg/day (12 patients/dose group)
- All doses well tolerated; PK and metabolites in DMD children similar to healthy adults (Phase 1)
- Considered safe to 6.0 mg/kg/day (~10x typical prednisone dose)
- High retention of patients through sequential studies (95% in LTE)

Dose Level Group-	No. Subjects/ Group	Vamorolone Dose
1	12	0.25 mg/Kg
2	12	0.75 mg/Kg
3	12	2.0 mg/Kg
4	12	6.0 mg/Kg



- PK run on initial 6 boys in 0.25 mg/kg/day
- PK in DMD children similar to fasted adults
- Increased bioavailability with milk likely offset by faster metabolism in children

*Bill Jusko, SUNY Buffalo

Phase 2b study - Recruiting May 2018

- Randomised, Double-blind, Parallel Group, placebo and active controlled study
- >30 sites: EU (18), USA (9), Canada (4), Australia (2), Israel (1)
- 120 steroid naïve genetically confirmed DMD boys 4-<7 years
- 24-week placebo and active controlled treatment period 1 followed by 24 week extension
- Primary efficacy outcome: time to stand
- Primary safety outcome: change in body mass index
- Exploratory biomarkers and muscle MRI

Primary Objectives

1. To compare the efficacy of vamorolone administered orally at daily doses of 2 mg/kg and 6 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD
2. To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2 mg/kg and 6 mg/kg in ambulant boys ages 4 to <7 years with DMD.

Secondary Objectives

1. To compare the safety of vamorolone over a 24-week treatment period vs. prednisone
2. To compare the efficacy of vamorolone over a 24-week treatment period vs. prednisone
3. To compare the efficacy of 2 mg/kg vamorolone vs. 6 mg/kg vamorolone over a 24 week treatment period
4. To compare the efficacy of 2 mg/kg vamorolone vs. 6 mg/kg vamorolone over a 48 week treatment period vs. untreated DMD historical controls
5. To compare the efficacy of 2 mg/kg vamorolone vs. 6 mg/kg vamorolone over a 48 week treatment period vs. prednisone treated DMD historical controls
6. To evaluate the population pharmacokinetics (PK) of vamorolone at daily doses of 2 mg/kg and 6 mg/kg in ambulant boys ages 4 to <7 years with DMD

Group	No Subjects/ group	Treatment period 1	Treatment period 2
1	30	Vamorolone, 2.0 mg/kg/day →	Vamorolone, 2.0 mg/kg/day
2	30	Vamorolone, 6.0 mg/kg/day →	Vamorolone, 6.0 mg/kg/day
3	15	Prednisone, 0.75 mg/kg/day →	Vamorolone, 2.0 mg/kg/day
4	15	Prednisone, 0.75 mg/kg/day →	Vamorolone, 6.0 mg/kg/day
5	15	Placebo →	Vamorolone, 2.0 mg/kg/day
6	15	Placebo →	Vamorolone, 6.0 mg/kg/day

VISION-DMD International Consortium

ReveraGen BioPharma; United Parent Projects Muscular Dystrophy; CERATIUM helping research happen; FN MOTOL; The John Walton Muscular Dystrophy Research Centre; The Newcastle upon Tyne Hospitals NHS Foundation Trust; Newcastle University; ECRIN European Clinical Research Infrastructure Network; TRiNDS; CINRG; University of Pittsburgh

Vamorolone Development through Grants & Venture Philanthropy

Ryan's Quest; Cure Duchenne; Duchenne Alliance; CDMRP Department of Defense; Duchenne Research Fund; MDA Fighting Muscle Disease; Joiningjack; Action Duchenne; Alex's Wish; NIH National Center for Advancing Translational Sciences; Pietrosfight.org; michael's cause; Save Our Sons Help Cure DMD; Parent Project Muscular Dystrophy; Foundation to Eradicate Duchenne; Duchenne UK

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