The Disease: Duchenne Muscular Dystrophy

- A very severe rare disease affecting 1 : 5000 male births
- Onset is usually between 2 and 4 years of age
- Caused by mutation in the dystrophin gene
- Muscles progressively weaken and eventually stop working
- Cardiac and respiratory related problems
- No cure available

VISION-DMD

Project website: www.vision-dmd.info

Advancing clinical development of the innovative orphan drug vamorolone for DMD.

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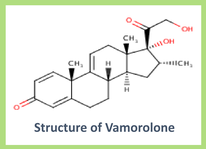

Structure of Vamorolone

VISION-DMD is a US-EU collaborative project undertaking Phase 2 Clinical Trials of vamorolone - An Innovative Steroid-like intervention for Duchenne Muscular Dystrophy.

Corticosteroids – Standard of Care for DMD

- Corticosteroids are the only treatment option for DMD that is independent of mutation type
- Corticosteroids delay the natural course of the disease
- Corticosteroids improve muscle strength, prolong ambulation, delay respiratory and orthopaedic complications and very likely prolong survival

BUT Steroids have a problem

- **Severe side effects reduce use and restricts treatment options**
- **Global implementation is variable**

Could vamorolone be the answer? A designer drug:

- ✓An innovative steroid-like drug designed to retain or improve corticosteroid efficacy
- ✓Protects the muscle membrane for membrane stabilisation
- ✓Possible reduced side effects
- ✓Lacks transactivation sub-properties that may cause side effects of steroids such as growth restriction and osteopenia
- ✓Increase the therapeutic window to slow DMD progression and improve quality of life and lifespan for DMD boys.

Made Possible by Grants & Venture Philanthropy

Phase 2a study recruitment completed

Primary Objective

To evaluate the safety and tolerability of multiple ascending doses of vamorolone in ambulant, steroid naive boys ages 4-< 7 years with DMD.

Secondary Objectives

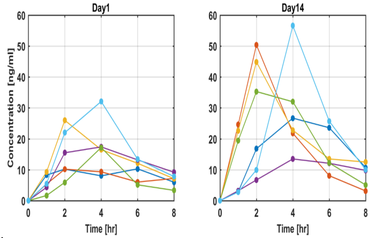
1. To investigate the single-dose and multiple-dose PK of vamorolone at multiple dose levels
2. To investigate the effects of single and multiple oral doses of vamorolone on serum PD

- 12 sites: USA(6), Canada(1), UK(1), Australia(2), Israel(1), Sweden(1)
- Multiple ascending dose-finding and safety study
- 14-day treatment followed by 6 month extension
- 48 patients completed treatment, extension study in progress
- DSMB report for the first cohort shows no alterations of pharmacodynamic biomarkers and no severe adverse events

Phase 1 study results

- Pharmacokinetic (PK) data in single and multiple ascending doses upto 20 mg/kg/day for 14 days study in healthy adult volunteers shows 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 an improved safety window for adrenal suppression (100-fold increase in therapeutic window),
- No evidence of insulin resistance or immune suppression, compared to prednisone studies reported in the literature

Dose Level Group-	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 - Start Q1 2018

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; and
2. To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 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 2.0mg/kg vamorolone vs. 6.0mg/kg vamorolone over a 24 week treatment period
4. To compare the efficacy of 2.0mg/kg vamorolone vs. 6.0mg/kg vamorolone over a 48 week treatment period vs. untreated DMD historical controls;
5. To compare the efficacy of 2.0mg/kg vamorolone vs. 6.0mg/kg vamorolone over a 48 week treatment period vs. prednisone treated DMD historical controls;
6. To evaluate the population pharmacokinetics (PK) of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD.

- Randomised, Double-blind, Parallel Group, placebo and active controlled study
- >30 sites: EU, USA, Canada, Australia, Israel
- 120 steroid naïve DMD boys 4-<7 years
- Two treatment periods. Each 24 weeks
- Primary efficacy outcome: time to stand
- Primary safety outcome: change in body mass index
- Exploratory biomarkers and muscle MRI

Group	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

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