Vision DMD: vamorolone drug development program for Duchenne muscular dystrophy

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Characteristics of Vamorolone

- A new chemical entity in the class of dissociative steroid
- First-in-human dissociative steroid that has shown improved safety and efficacy in mouse models of Duchenne muscular dystrophy compared to corticosteroids.
- Preserves the anti-inflammatory actions of glucocorticoids
- Protects the muscle membrane
- Lacks transactivation subproperties that may cause side effects of glucocorticoids, such as short stature and osteopenia

Phase I Study Results

- *Pharmacokinetic data in* Phase I single ascending dose up to 20.0 mg/kg and multiple ascending dose up to 20 mg/kg/day for 14 days- study in healthy adult volunteers *shows* strong adherence to dose linearity and dose proportionality. No drug accumulation was observed, consistent with the short half-life.
- A food effect was observed, with an increased absorption by 2.5-fold by the high fat meal (Fig. 1)
- No adverse events precluding further escalations in dosing were observed. One subject (20 mg/kg/day cohort) showed mild elevations of liver enzymes, and drug dosing was halted.

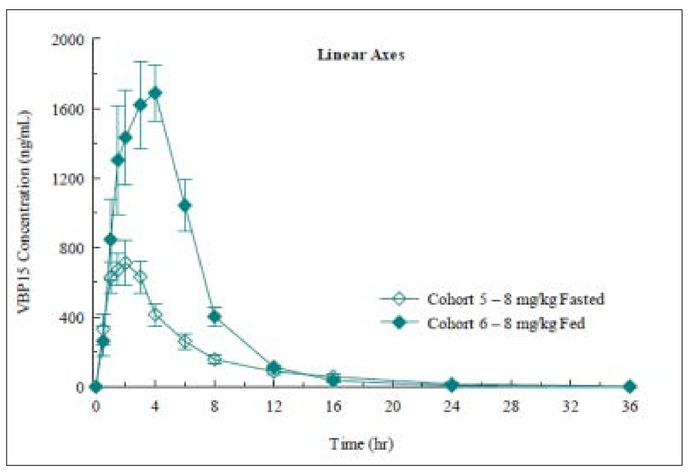


Fig 1. Arithmetic mean ± standard error plasma concentrations of vamorolone (VBP15) after single dose oral administration to healthy subjects under fed and fasted conditions

- Safety pharmacodynamics biomarker studies showed that vamorolone had an improved safety window for adrenal suppression (100-fold increase in therapeutic window), and no evidence of insulin resistance or immune suppression, compared to prednisone studies reported in the literature.

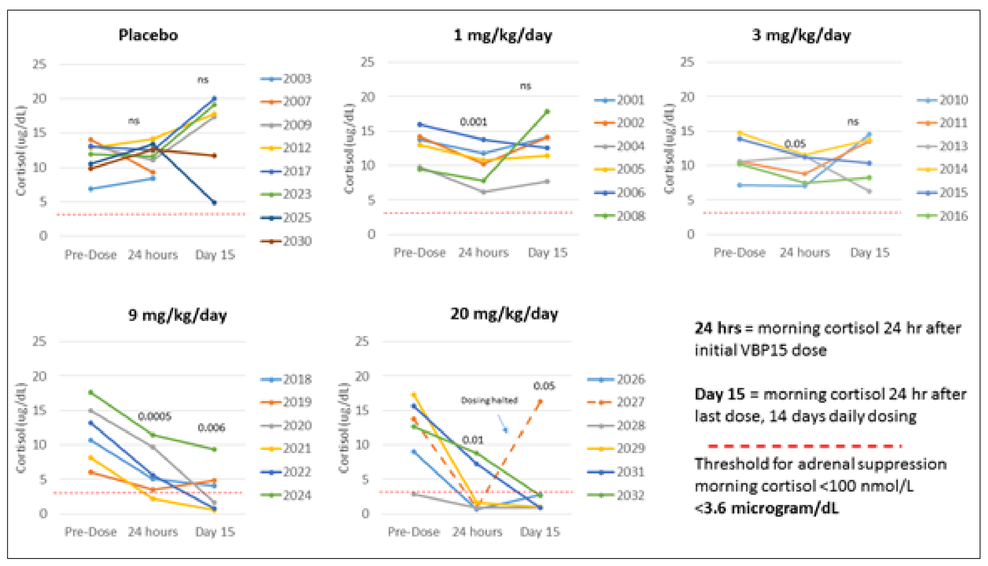


Fig 2. Morning cortisol measures in the vamorolone Phase I MAD volunteers.*

DMD Clinical Development Plan

Phase IIa study

Planned Dose Level Group-	No. Subjects in Dose Level 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

- 12 sites: USA (6), Canada(1), UK (1), Australia (2), Israel (1), Sweden (1)
- Multiple ascending dose-finding and safety study
- Inclusion Criteria: 4 - <7 years, genetically confirmed, steroid naive
- 14-day treatment trial followed by 6 month extension
- Opened recruitment in the USA, Canada, Israel, and Australia
- Recruitment expected to be opened in all sites in April 2017
- UK (Newcastle) target 4-5 patients
- DSMB report for the first cohort expected in March 2017

Primary Objective
To evaluate the safety and tolerability of multiple ascending doses of vamorolone in ambulant 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

Phase IIb

Planned Cohort	No. Subjects in Dose Level Group	Dose
1	25	2.0 mg/Kg
2	25	6.0 mg/Kg
3	25	Steroid
4	25	Placebo

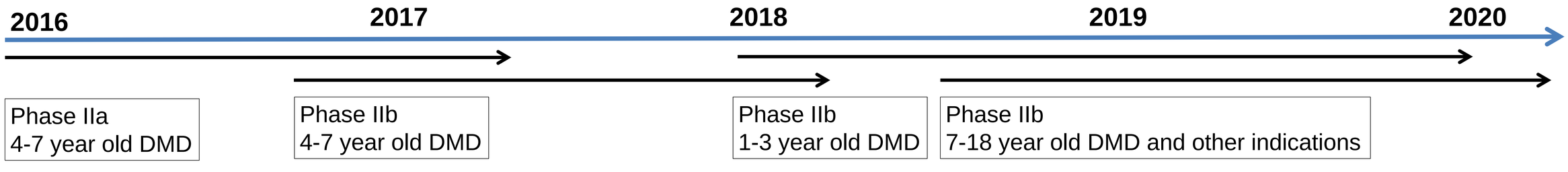
- 33 sites: EU (19), USA (8), Canada (3), Australia (2), Israel (1)
- Randomized, placebo-controlled study to include steroid and placebo arms
- Inclusion Criteria: 4 - <7 years, genetically confirmed, steroid naive
- 24-weeks treatment followed by 6 month extension
- Exploratory Muscle MRI protocol to assess feasibility in a large study
- Expected recruitment start: August 2017

Primary Objectives
1. To evaluate the efficacy of multiple ascending doses of vamorolone vs. placebo in ambulant boys ages 4- <7 years with DMD, measured by the time to Stand (TTSTAND)
2. To evaluate the safety of multiple ascending doses of vamorolone vs. prednisone, as measured by body mass index (BMI) z-score

Secondary Objectives
1. To evaluate the safety and tolerability of vamorolone administered orally at daily doses over 24 week treatment
2. To compare the efficacy vs. placebo
3. To compare the effects of vamorolone vs. prednisone on serum pharmacodynamics (PD) biomarkers of safety

Projected Vamorolone Drug Development Timeline

The phase IIa and IIb will be followed by extension and a long term extension studies to assess the long term safety and efficacy of vamorolone in DMD



References: Heier CR, et al. **VBP15**, a novel anti-inflammatory and membrane-stabilizer, improves muscular dystrophy without side effects. EMBO Mol Med. 2013 Oct;5(10):1569-85.; Reeves EK, et al. **VBP15**: preclinical characterization of a novel anti-inflammatory delta 9,11 steroid. Bioorg Med Chem. 2013 Apr 15;21(8):2241-9.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 667078