VAMOROLONE: CLINICAL STAGE

FIRST DISSOCIATIVE STEROIDAL ANTI-INFLAMMATORY

Eric Hoffman, CEO ericphoffman@gmail.com
DMD NFkB danger signals – inflammation – myofiber damage

- Process present in DMD muscle from birth
- Shared with many chronic inflammatory states
- Target of corticosteroids (deflazacort, prednisone)
General mechanisms of action of glucocorticoids

- Inhibit inflammation
- Lessen myofiber damage
- Improve symptoms
- Corticosteroids work
General mechanisms of action of glucocorticoids

- Goal of vamorolone program:
  - Allow single GR/drug (benefit)
  - Inhibit double GR/drug (side effects)
NEW CHEMISTRY: FIRST-IN-CLASS

- A key change in the steroid backbone (9,11 bond)
- Binds receptors, but prevents dimerization
- Full dissociation of efficacy and side effects

Prednisone
Vamorolone
VAMOROLONE GOALS

- Retain anti-inflammatory efficacy
- Add additional new aspects of potential efficacy
  - Eplerenone activity (MR antagonist; aids heart)
  - Membrane stability (counteracts dystrophin-deficiency)
- Reduce drug-associated safety concerns (side effects)
Phase 2a Design = Open Label Dose Escalation

Phase 2a
VBP15-002

Phase 2a extension
VBP15-003

Long term extension
VBP15-LTE

4 to <7 years, never taken steroids
12 boys/group. 48 boys total

2 weeks on                             6 months on drug                                                            2 years on drug
2 weeks off

Dose group 1 = 0.25 mg/kg/day

Dose group 2 = 0.75 mg/kg/day

Dose group 3 = 2.0 mg/kg/day

Dose group 4 = 6.0 mg/kg/day

Patients on LTE can dose escalate
0.25 to 0.75 to 2.0 to 6.0 mg/kg/day
Phase 2a studies:
Phase 2a (VBP15-002)
Phase 2a extension (VBP15-003)
Long term extension (VBP15-LTE)

- **Study Chair:** Paula Clemens, University of Pittsburgh
- **Sponsor:** Eric Hoffman, ReveraGen
- **Coordinating center:** TRiNDS (CINRG), Andrea Smith
- **Recruitment sites:** CINRG sites
- **Patients:** 48 DMD 4 to <7 years, steroid naïve
- **Sample size calculations:** CINRG DNHS vs. CINRG prednisone trial
- **Design:** Broad dose range (0.25 – 6.0 mg/kg/day); 12 boys per dose group
  - 1/3 prednisone dose – 10-times prednisone dose in DMD
Outcome measures - Efficacy

- **Primary:** Time to stand
- **Secondary:**
  - 10 meter walk
  - 6 minute walk
  - 4 stair climb
  - NorthStar Ambulatory Assessment
  - Quantitative muscle testing

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<tr>
<th>Study Measurement</th>
<th>%CV Mean Intra-patient variance (precision)</th>
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<tr>
<td>Time to Stand</td>
<td>62.0</td>
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<tr>
<td>Time 10 m Run/Walk</td>
<td>23.8</td>
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<td>Time to Climb 4 Stairs</td>
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<td>6 Minute Walk Test</td>
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<td>QMT Elbow Flexion</td>
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<td>QMT Knee Flexion</td>
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Four measures/patient in ~6 weeks
Primary clinical efficacy outcome – Mixed model repeated measure

Change from baseline at 12 weeks and 24 weeks

![Graph showing changes in Mean Velocity (m/s) from baseline to 12 weeks and 24 weeks for different doses of Vamorolone: 0.25 mg/kg/day, 0.75 mg/kg/day, 2.0 mg/kg/day, and 6.0 mg/kg/day. The graph indicates significant improvements in time to stand velocity at 24 weeks for 2.0 and 6.0 mg/kg/day doses with p-values of 0.02 and 0.04, respectively.](image-url)
Primary clinical efficacy outcome: Meets primary outcome
Comparison to CINRG Duchenne Natural History Study (DNHS)

Change from baseline at 12 weeks and 24 weeks

![Change in Mean Velocity (m/s) vs Time to Stand (velocity)](image-url)

- CINRG Natural History 4-<7 years DMD
- 0.25 mg/kg/day Vamorolone
- 0.75mg/kg/day Vamorolone
- 2.0 mg/kg/day Vamorolone
- 6.0 mg/kg/day Vamorolone

Baseline 12 weeks 24 weeks

P=0.04
Secondary clinical efficacy outcome:

Change from baseline at 12 weeks and 24 weeks

Time to Run/Walk (velocity)

Change in Mean Velocity (m/s)

Baseline 12 weeks 24 weeks

CINRG Natural History 4-<7 years DMD
0.25mg/kg/day Vamorolone
0.75 mg/kg/day Vamorolone
2.0 mg/kg/day Vamorolone
6.0 mg/kg/day Vamorolone

N=11
N=11
N=12
N=12
N=12
N=18
N=25

P=0.003
Secondary clinical efficacy outcome

*Change from baseline at 12 weeks and 24 weeks*

![6 Minute Walk Test Graph](image)

- **Baseline**: Meters change
- **12 weeks**: Meters change
- **24 weeks**: Meters change

- **0.25 mg/kg/day vamorolone**
- **0.75 mg/kg/day vamorolone**
- **2.0 mg/kg/day vamorolone**
- **6.0 mg/kg/day vamorolone**

**N=10**

**N=11**

**N=12**

**P=0.003**
Secondary clinical efficacy outcome

*Change from baseline at 12 weeks and 24 weeks*

North Star Ambulatory Assessment

- 0.25 mg/kg/day vamorolone
- 0.75 mg/kg/day vamorolone
- 2.0 mg/kg/day vamorolone
- 6.0 mg/kg/day vamorolone
Exploratory Efficacy Biomarkers

- **Serum creatine kinase**
  - Biomarker membrane stability
  - Reductions at 2.0 and 6.0 mg/kg

- **Steroid-responsive serum proteins**
  - Anti-inflammatory mechanism of action
  - 7 pre-specified inflammatory proteins
    - DMD, IBD, JDM, vasculitis
  - 6 of 7 show Vamorolone dose response

CK drops by ~30%
Safety – side effects

• **Clinical Safety** – Adverse events, serious adverse events
  
  • Adult volunteers – 2 weeks treatment – **safe to highest dose tested** – 20 mg/kg/day
  • DMD Phase IIa – 2 weeks treatment – **safe to highest dose tested** – 6 mg/kg/day
  • Phase IIa extension – 24 weeks treatment – **under analysis**
  • Long-term extension – 2 years treatment – **ongoing**

• **No dose-limiting safety concerns in adult volunteers or DMD**
Survey of DMD parents with children on prednisone/deflazacort Binghamton University – SUNY (n=50)

What side effects are of most concern?

- #1: Loss of bone density  
  - 80% very concerned
- #2: Weight gain  
  - 75% very concerned
- Tied #3: 50% very concerned  
  - Stunting of growth
  - Delayed puberty
  - Suppressed immunity

Corticosteroid (prednisone, deflazacort) pharmacodynamic safety concerns
• **Pharmacodynamic Safety – Potential side effects**

  • **Adult volunteers – 2 weeks treatment**
    • Bone markers – no changes through 20 mg/kg/day
    • Insulin resistance – no changes through 20 mg/kg/day
    • Incidence of adrenal suppression – 0% 1, 3 mg/kg; 50% 9 mg/kg; 100% 20 mg/kg

  • **Phase IIa – 2 weeks treatment, 24 weeks treatment - DMD**
    • Bone markers – osteocalcin (bone formation) no decreases 24 weeks any dose
    • Insulin resistance – no increases 24 weeks any dose
    • Incidence of adrenal suppression – 18% 2 mg/kg; 60% 6 mg/kg at 2 weeks
Change in body mass index relative to baseline (to six months)

- 0.25 mg/kg
- 0.75 mg/kg
- 2.0 mg/kg
- 6.0 mg/kg
Prednisone
CINRG
0.75 mg/kg/day

Vamorolone
2.0 mg/kg

Vamorolone
6.0 mg/kg
PHASE 2A - CONCLUSIONS

- Efficacy at 24 weeks - 2.0 and 6.0 mg/kg/day
- Pharmacodynamic biomarkers
  - Creatine kinase levels reduced 2.0, 6.0 mg/kg/day up to 4 weeks
  - Improved safety relative to published studies of prednisone/deflazacort (Phase 1, Phase 2a)

- Phase 2a data consistent with 2.0, 6.0 mg/kg advancing to Phase 2b
PHASE 2B

- Study Chairs: Michela Guglieni (Newcastle University), Paula Clemens (University of Pittsburgh)
- Coordination: TRiNDS LLC, Newcastle University
- Design:
  - **Period 1: 24 weeks.** 50% DMD patients vamorolone (2 doses), 25% placebo, 25% prednisone
  - **Period 2: 24 weeks.** 100% patients vamorolone (2 doses)
  - 120 DMD boys, 4 to <7 years, not previously treated with steroids
  - **Visits:** Designed with DMD parent involvement, burden kept to minimum. ~1 visit per month
  - **Dosing:** Daily by mouth in morning at home
- **Info:** clinicaltrials.gov  NCT03439670
### SITES PHASE 2B: TRANCHE I NORTH AMERICA

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- **When will trials of older and younger DMD patients be carried out?**
  - There is a Pediatric Investigation Plan approved by the EMA for Vamorolone that plans trials for the complete pediatric age range (newborn to 18 years)
  - The next anticipated clinical trial of Vamorolone is in a broad age range (2-4 years, and 7-18 years) that we have planned to initiate in 2019

- **Why the 3-fold jump from 2.0 to 6.0? Why not try an intermediate dose, or higher than 6.0?**
  - The goal is to find therapeutic index (window); lowest efficacious dose, and highest safe dose
  - This is always challenging – the group felt that 3-fold was aggressive, but appropriate.
  - Regulators often accuse programs of not going high enough.
  - It is all a balance, and at the end of the day, patients are individuals and doses may need to be optimized
PROGRAM MADE POSSIBLE BY:
PARENTS, FOUNDATIONS, GOVERNMENTS

$40M in non-dilutive capital to date