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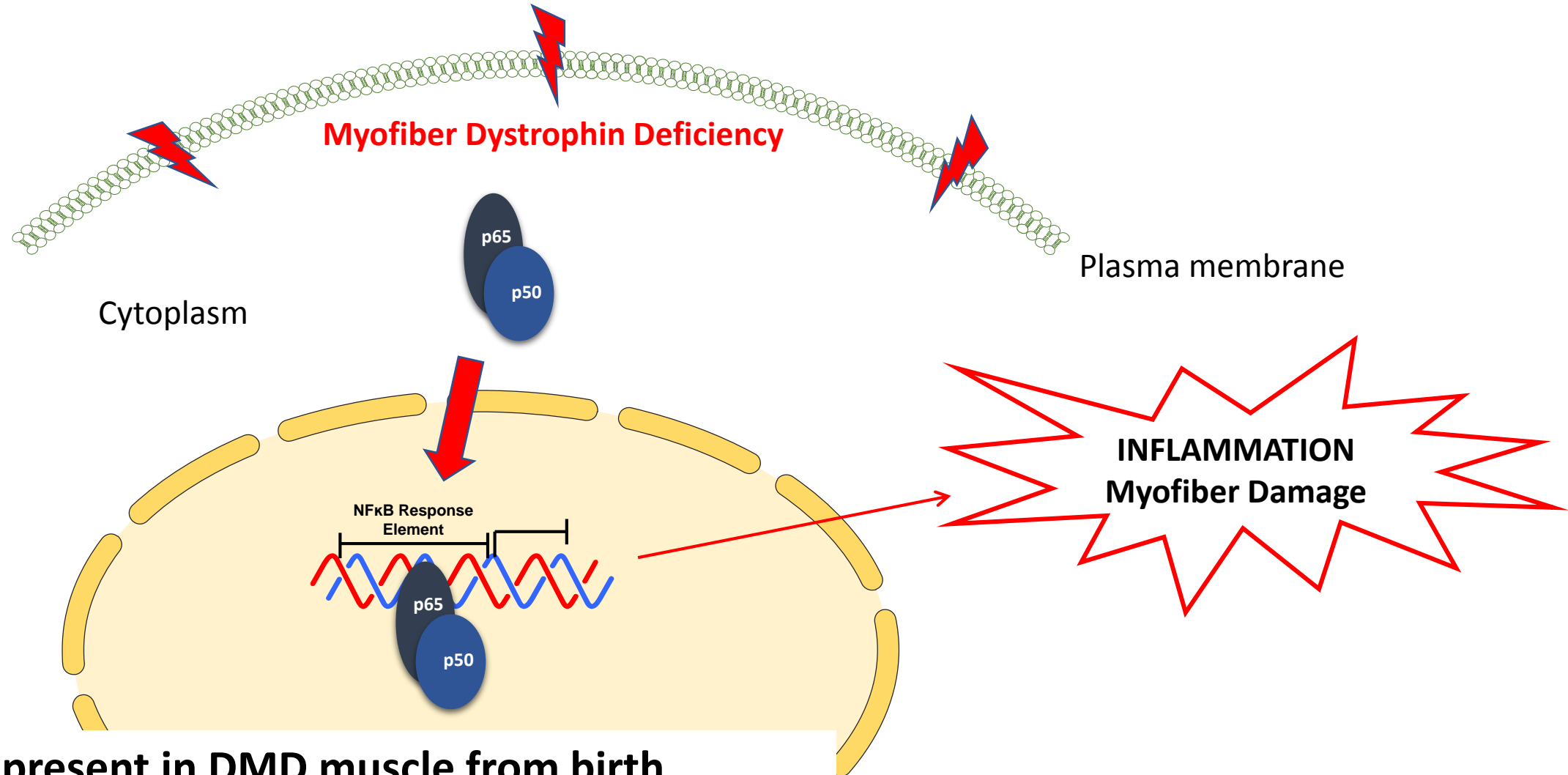
VAMOROLONE: CLINICAL STAGE

*FIRST DISSOCIATIVE STEROIDAL ANTI-INFLAMMATORY*

ReveraGen  
BioPharma

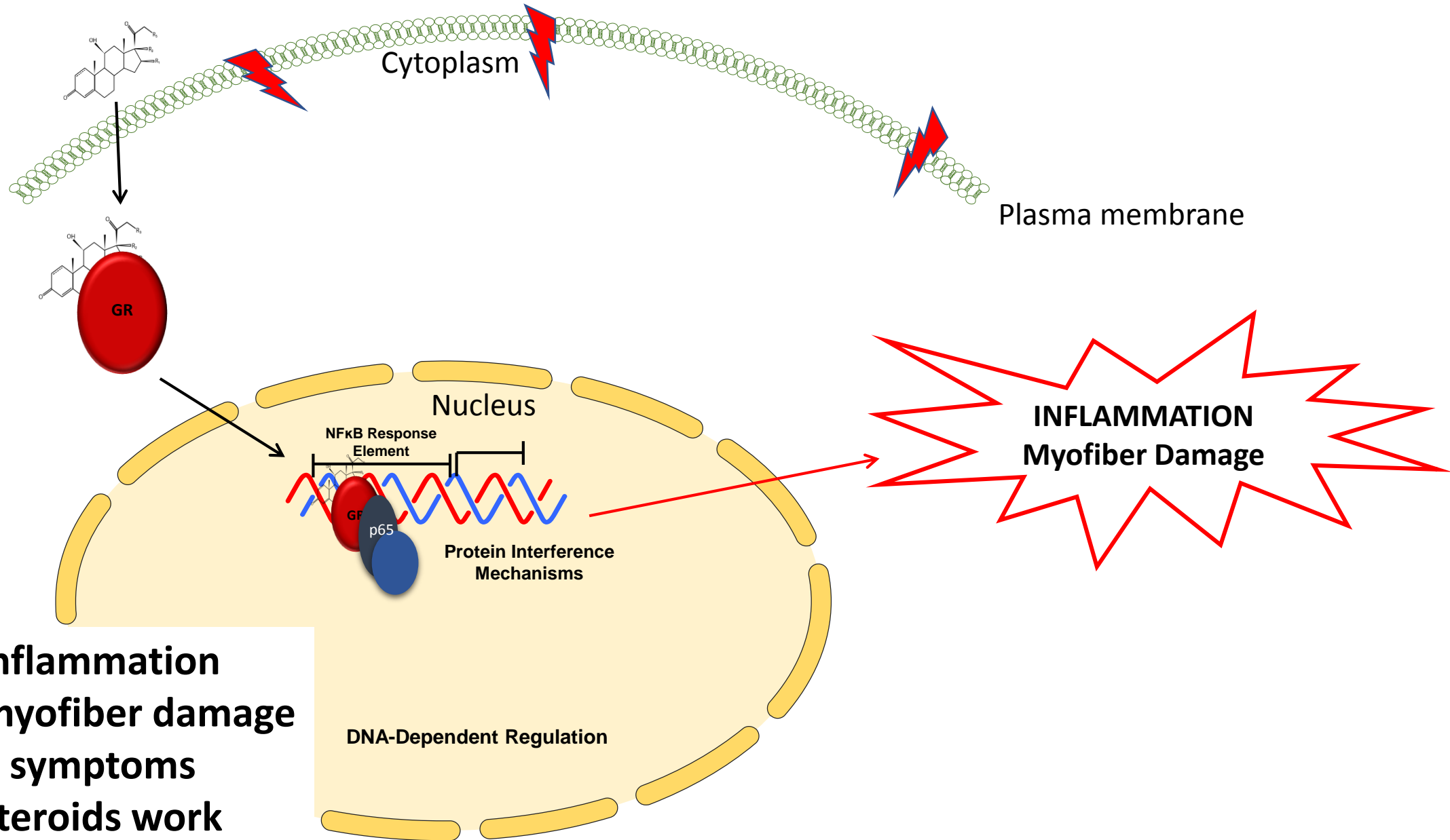
Eric Hoffman, CEO [ericphoffman@gmail.com](mailto:ericphoffman@gmail.com)

# DMD NFkB danger signals – inflammation – myofiber damage



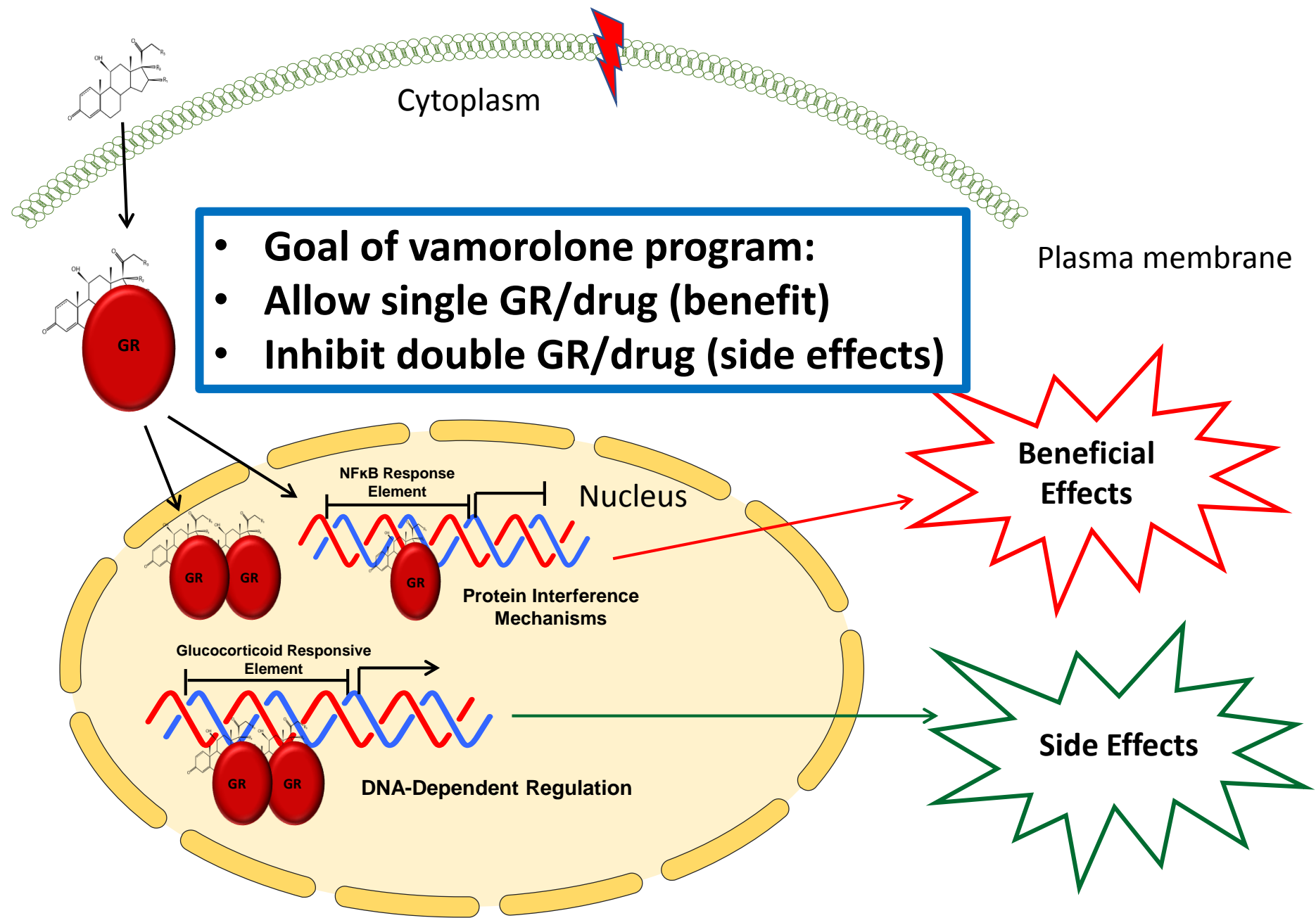
- Process present in DMD muscle from birth
- Shared with many chronic inflammatory states
- Target of corticosteroids (deflazacort, prednisone)

# General mechanisms of action of glucocorticoids



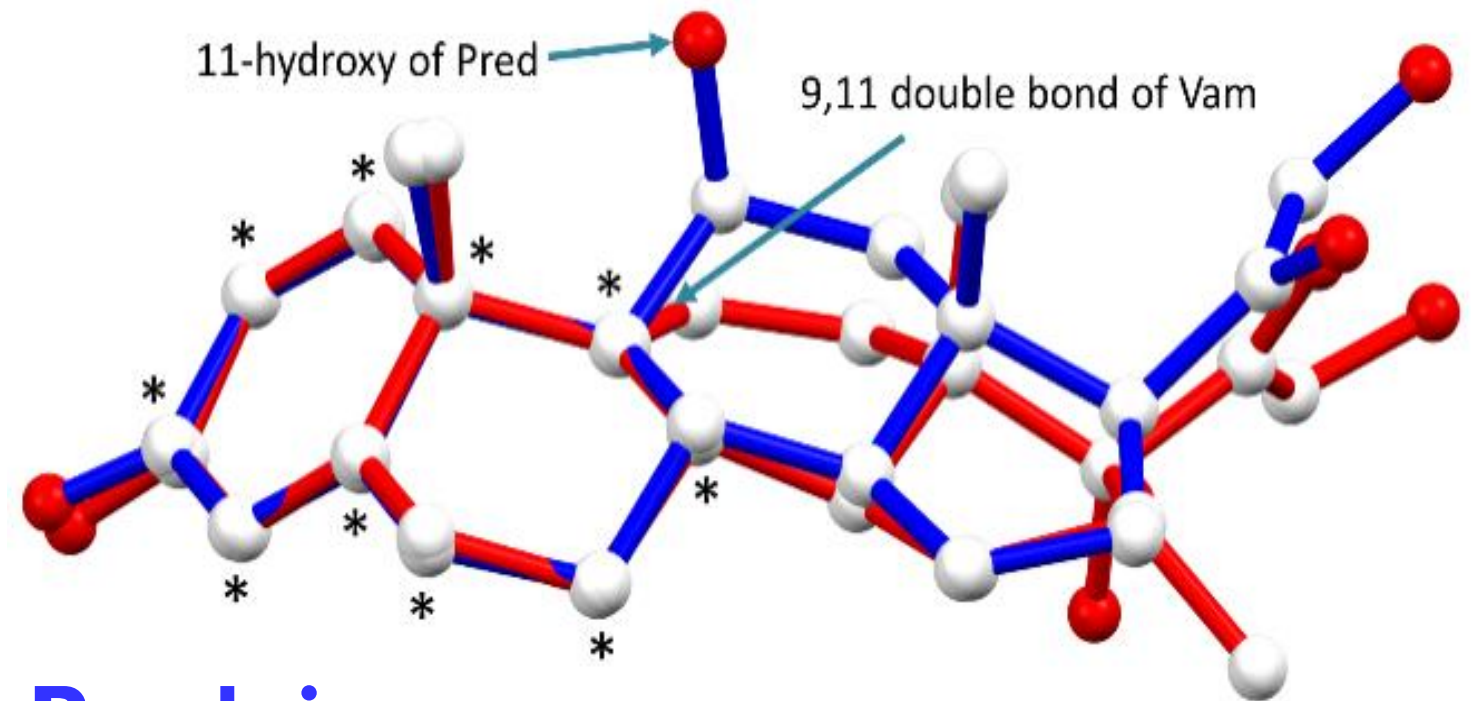
- Inhibit inflammation
- Lessen myofiber damage
- Improve symptoms
- Corticosteroids work

# General mechanisms of action of glucocorticoids



# 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)

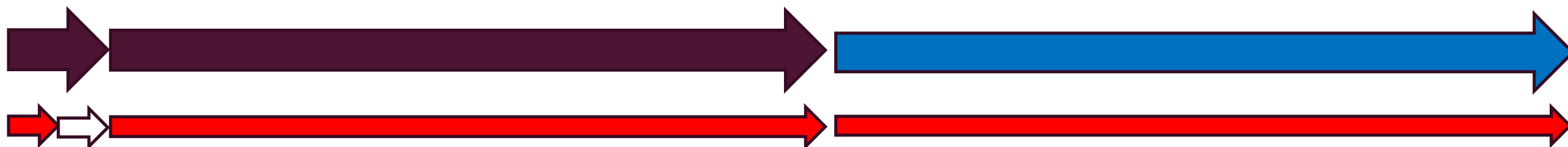
# PHASE 2A DESIGN = OPEN LABEL DOSE ESCALATION

Phase 2a  
VBPI5-002

Phase 2a extension  
VBPI5-003

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

Long term extension  
VBPI5-LTE



2 weeks on  
2 weeks off

6 months on drug

2 years on drug

**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

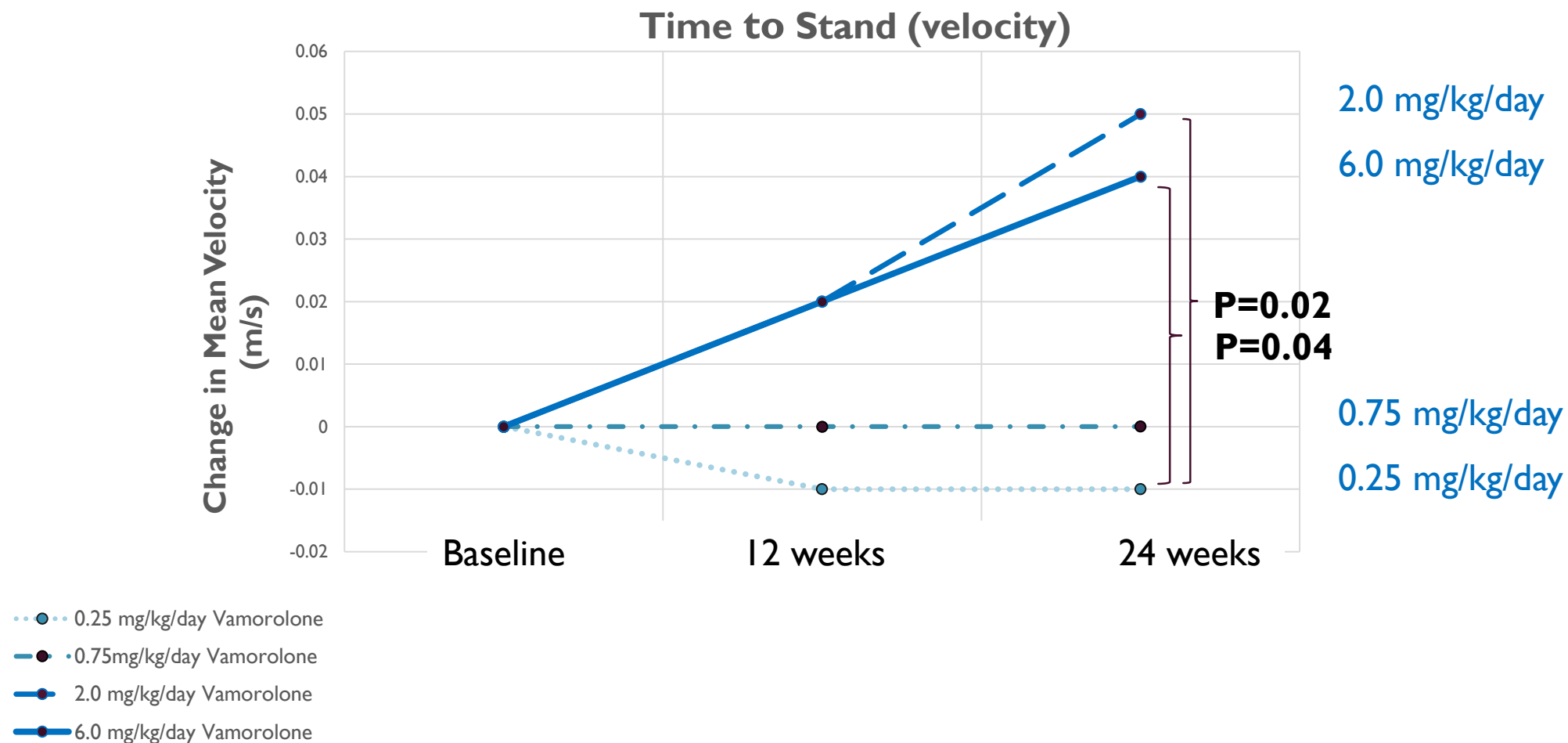
- **Primary: Time to stand**
- Secondary:
  - 10 meter walk
  - 6 minute walk
  - 4 stair climb
  - NorthStar Ambulatory Assessment
  - Quantitative muscle testing

Study Measurement	%CV Mean Intra-patient variance (precision)
Time to Stand	62.0
<b>Time 10 m Run/Walk</b>	<b>23.8</b>
Time to Climb 4 Stairs	71.0
<b>6 Minute Walk Test</b>	<b>19.5</b>
NSAA	28.1
QMT Elbow Flexion	42.5
QMT Elbow Extension	45.0
QMT Knee Flexion	58.4

**Four measures/patient in ~6 weeks**

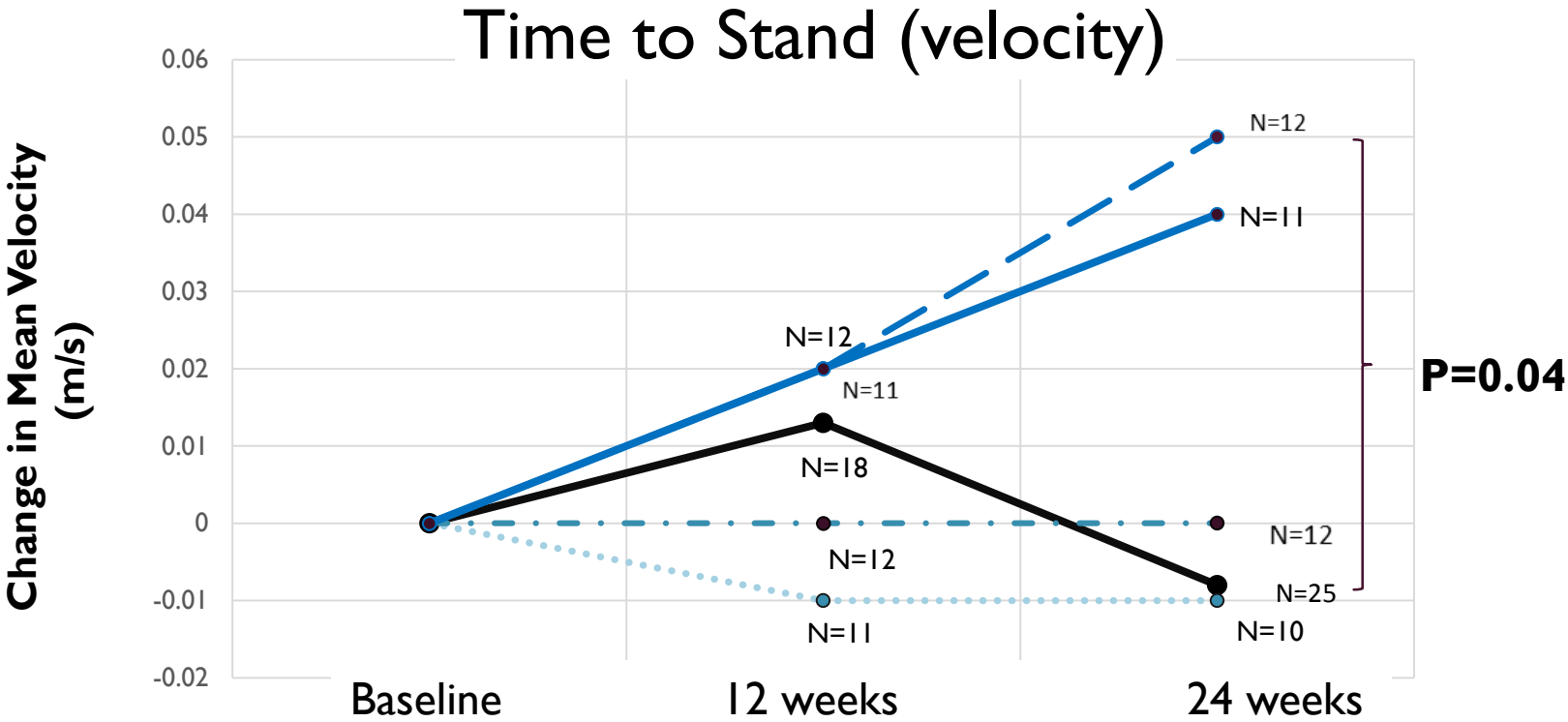
# Primary clinical efficacy outcome – Mixed model repeated measure

Change from baseline at 12 weeks and 24 weeks



# Primary clinical efficacy outcome: Meets primary outcome Comparison to CINRG Duchenne Natural History Study (DNHS)

Change from baseline at  
12 weeks and 24 weeks

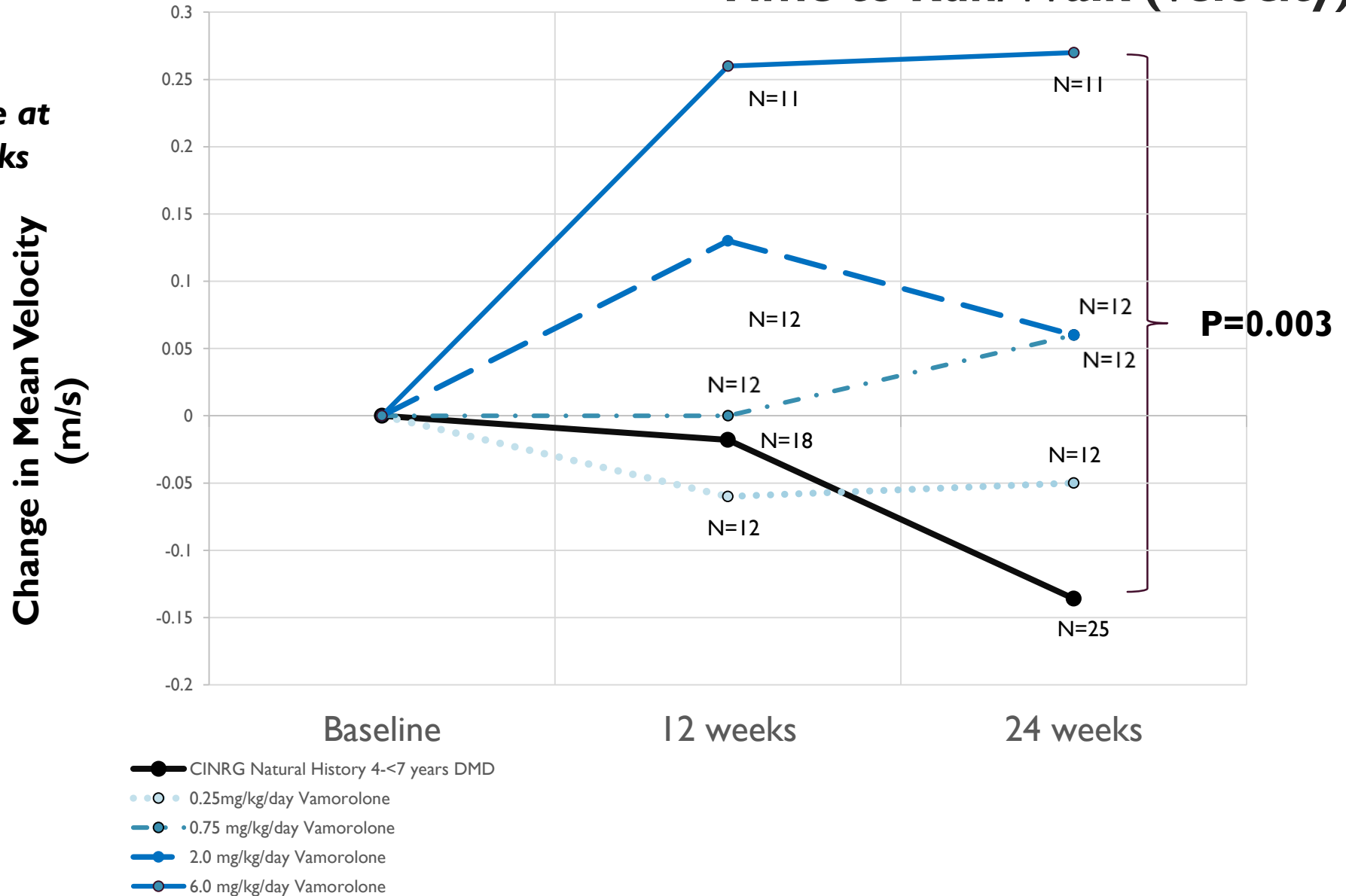


- CINRG Natural History 4- <7 years DMD
- ... 0.25 mg/kg/day Vamorolone
- - 0.75mg/kg/day Vamorolone
- 2.0 mg/kg/day Vamorolone
- 6.0 mg/kg/day Vamorolone

# Secondary clinical efficacy outcome:

# Time to Run/Walk (velocity)

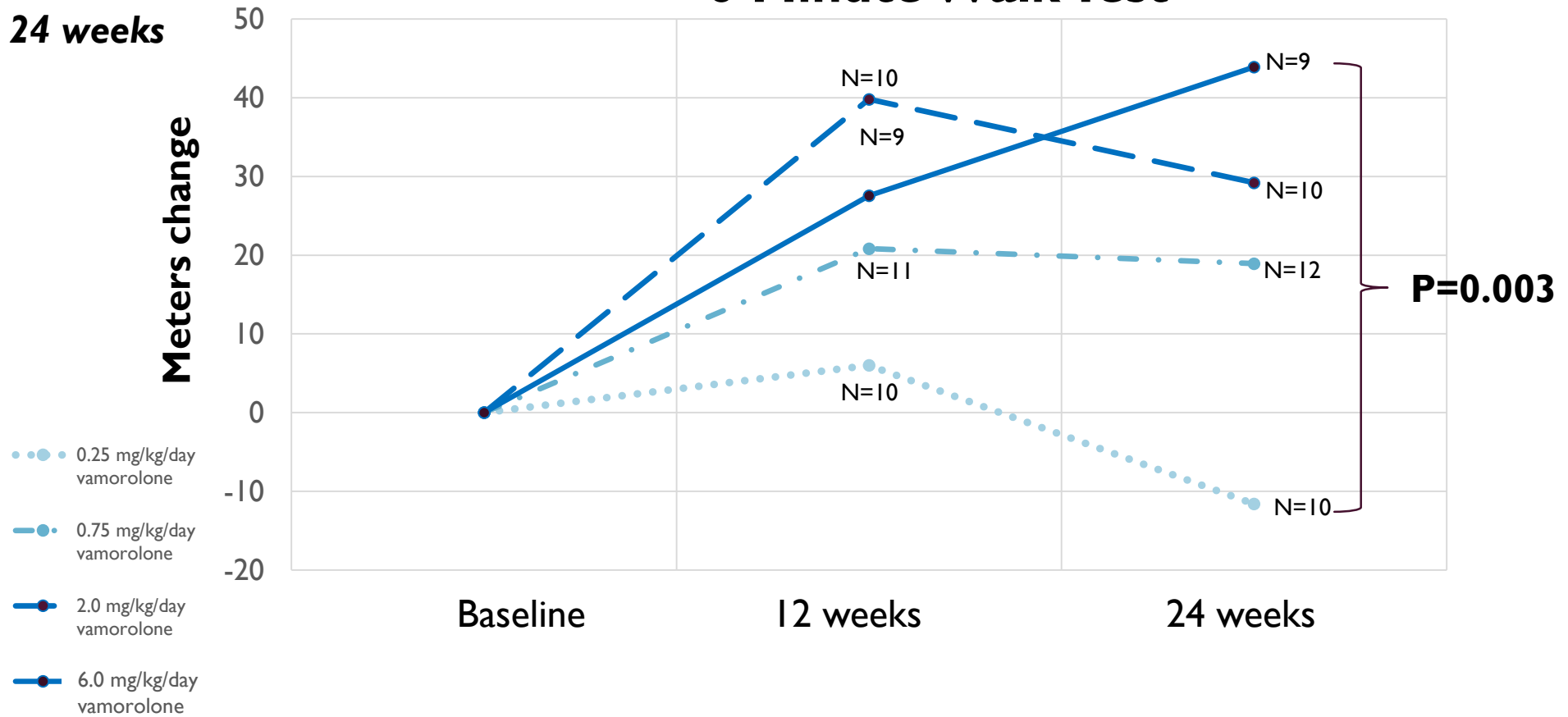
Change from baseline at 12 weeks and 24 weeks



# Secondary clinical efficacy outcome

Change from baseline at 12 weeks and 24 weeks

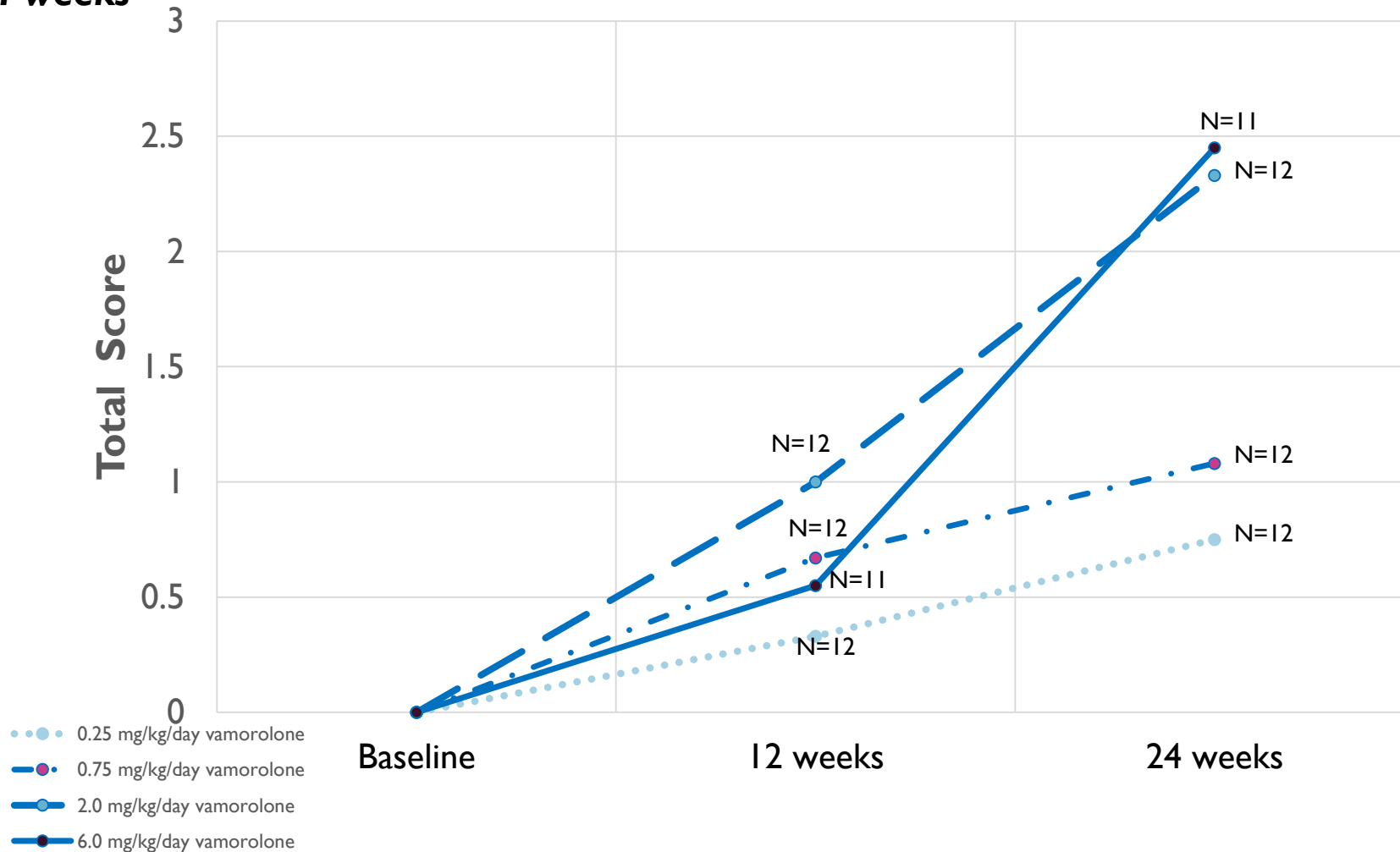
## 6 Minute Walk Test



# Secondary clinical efficacy outcome

Change from baseline at 12 weeks and 24 weeks

## North Star Ambulatory Assessment



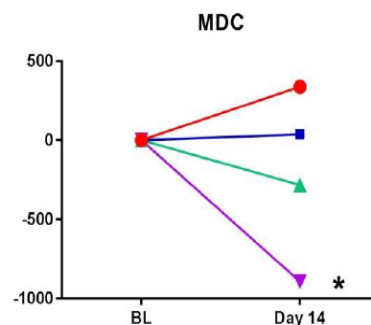
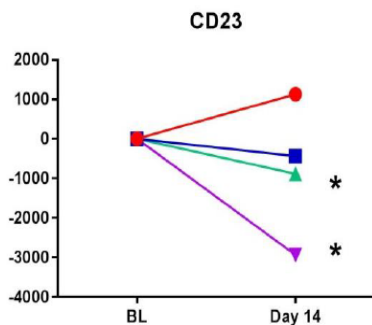
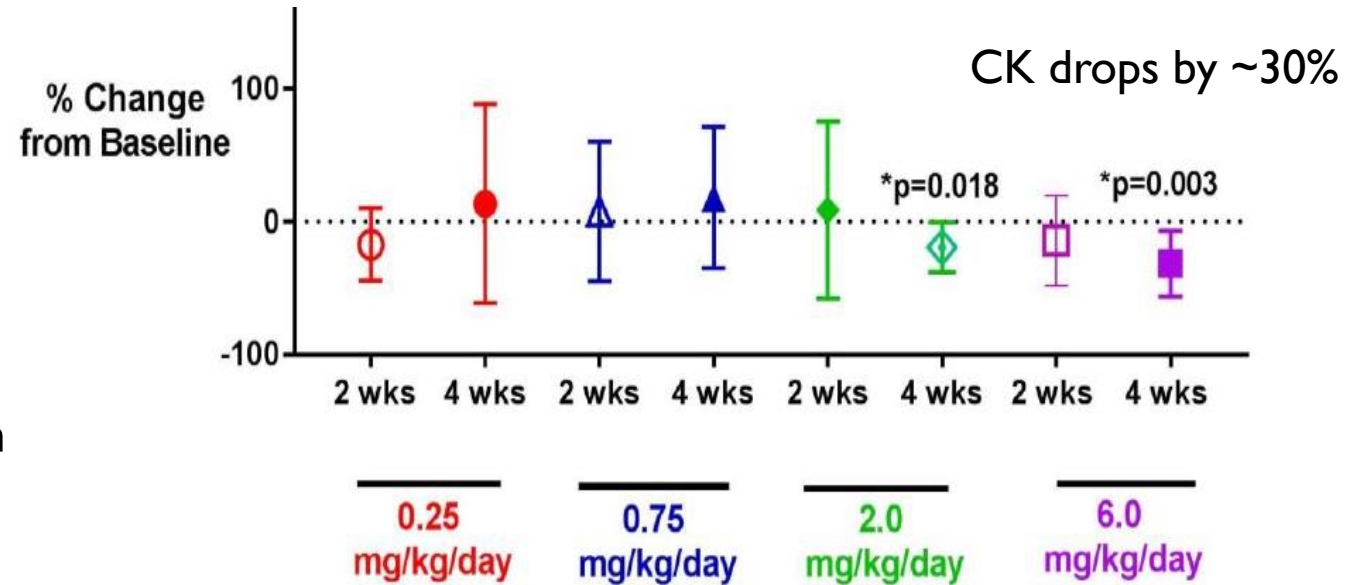
# Exploratory Efficacy Biomarkers

- 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



- 0.25 mg/kg
- 0.75 mg/kg
- 2.0 mg/kg
- 6.0 mg/kg

# Safety – side effects

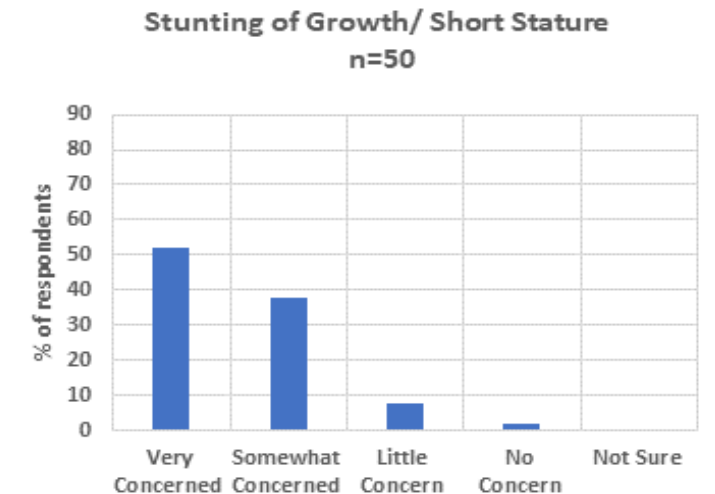
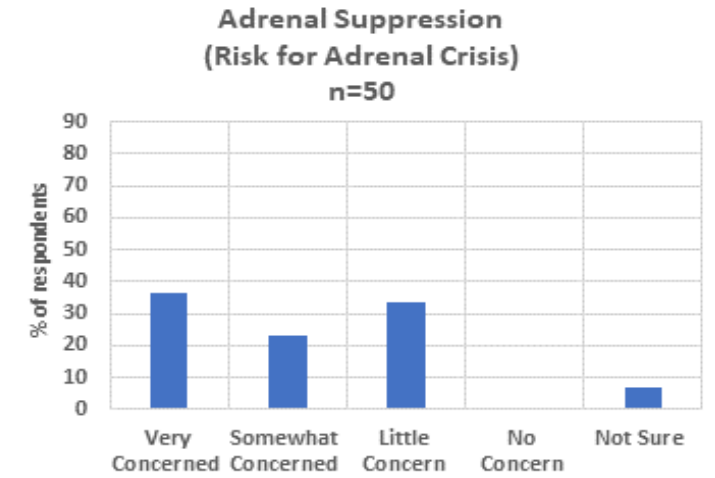
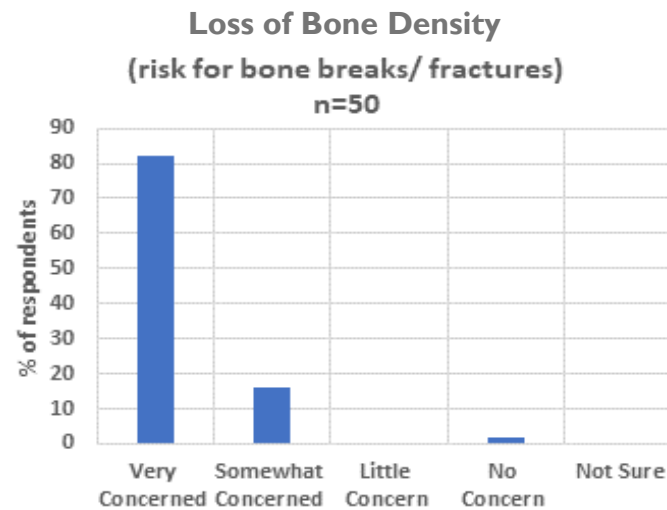
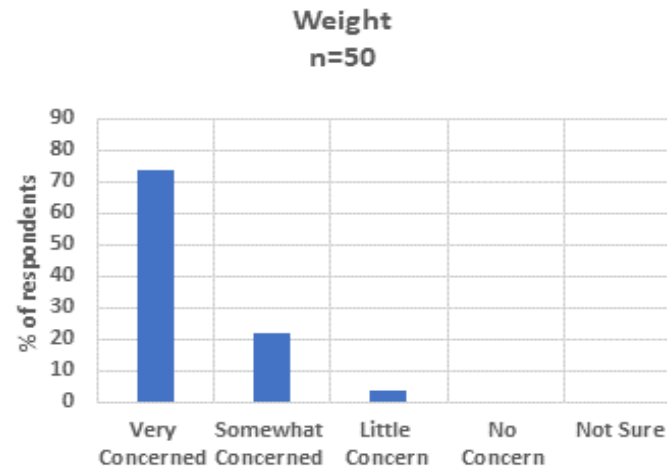
- **Clinical Safety – Adverse events, serious adverse events**
  - Adult volunteers – 2 weeks treatment – **safe to highest dose tested** – 20 mg/kg/day
  - DMD Phase IIa – 2 weeks treatment – **safe to highest dose tested** – 6 mg/kg/day
  - Phase IIa extension – 24 weeks treatment – **under analysis**
  - Long-term extension – 2 years treatment – **ongoing**
- **No dose-limiting safety concerns in adult volunteers or DMD**

# Corticosteroid (prednisone, deflazacort) pharmacodynamic safety concerns

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



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- **Pharmacodynamic Safety – Potential side effects**

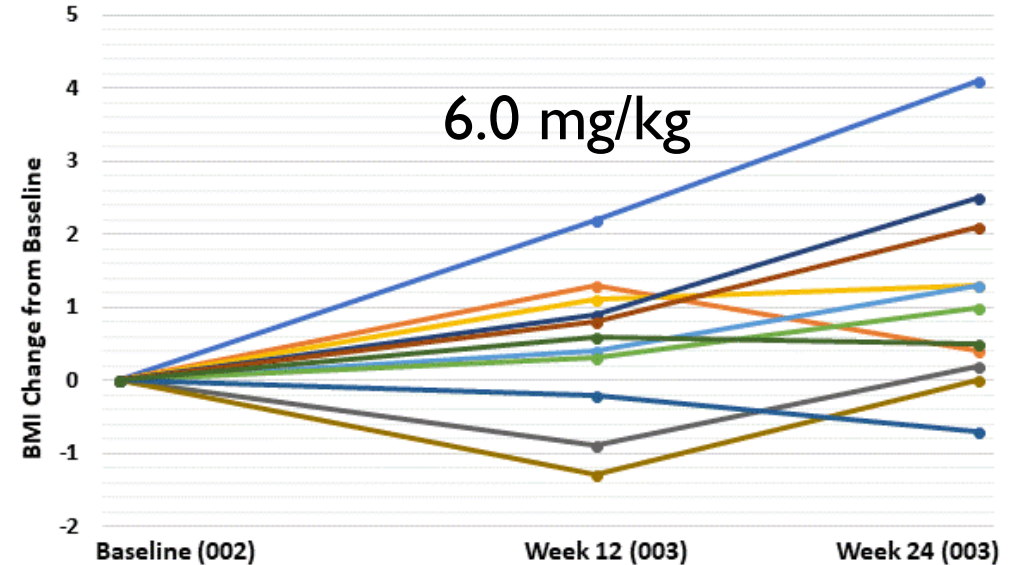
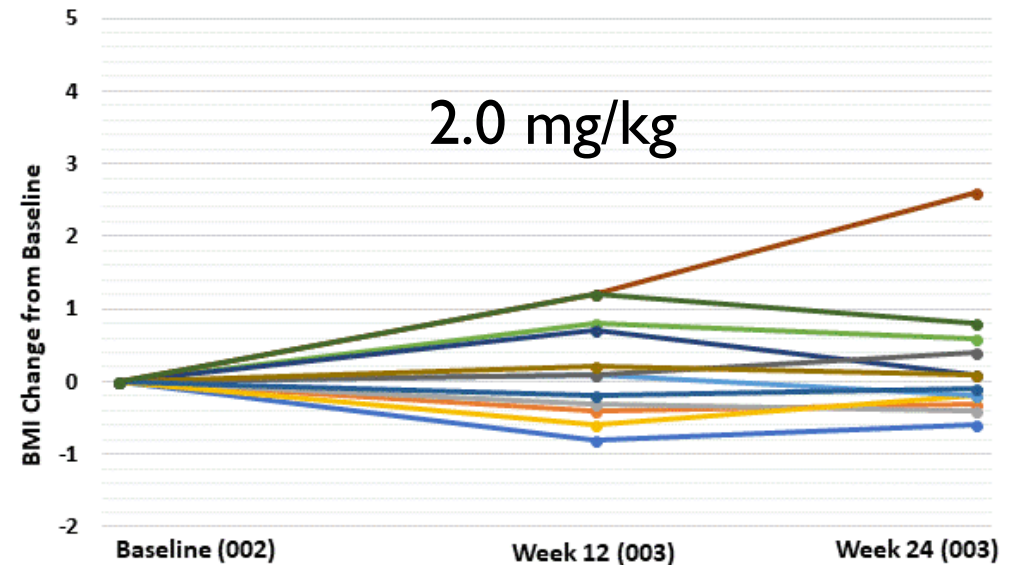
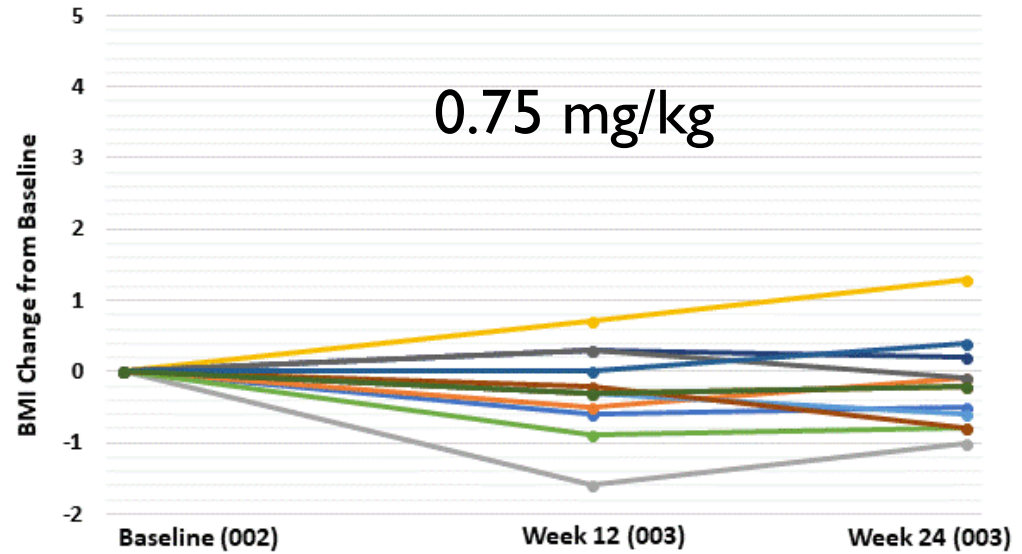
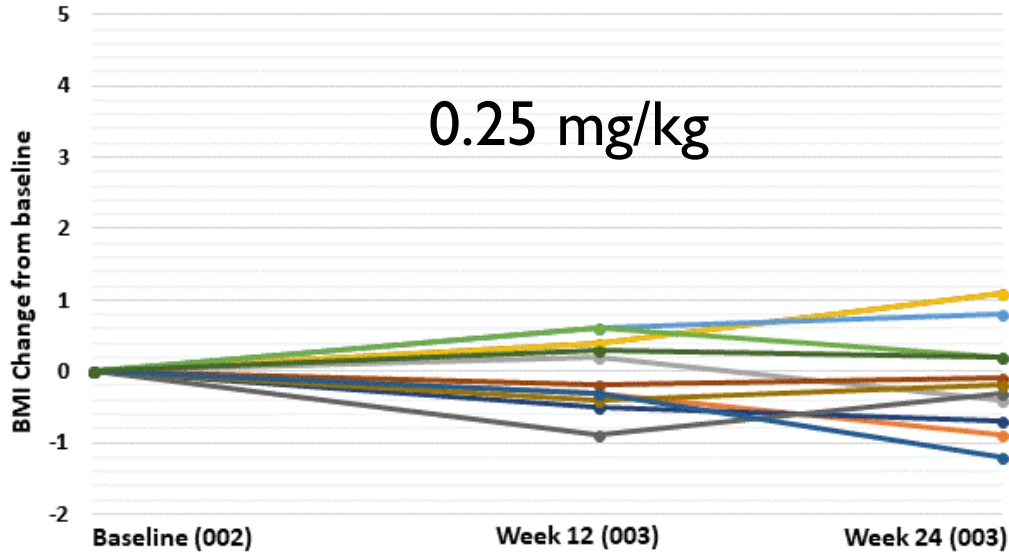
- **Adult volunteers – 2 weeks treatment**

- **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)





## 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 I, Phase 2a)
- Phase 2a data consistent with 2.0, 6.0 mg/kg advancing to Phase 2b

## PHASE 2B

- Study Chairs: Michela Guglieri (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](https://clinicaltrials.gov) **NCT03439670**

# SITES PHASE 2B: TRANCHE I NORTH AMERICA

**PHASE 2A SITES – THANKS!**

Tranche	Country	Institution	City, State	Site Principal Investigator
I	US	<b>Duke University</b>	<b>Durham, North Carolina</b>	<b>Edward Smith</b>
		<b>University of Texas</b>	<b>Dallas, Texas</b>	<b>Diana Castro</b>
		<b>Southwestern Medical Center</b>		
		<b>University of California Davis</b>	<b>Sacramento, California</b>	<b>Craig McDonald</b>
		<b>Ann &amp; Robert H. Lurie</b>	<b>Chicago, Illinois</b>	<b>Nancy Kuntz</b>
		<b>Children's Hospital</b>		
		Seattle Children's Hospital	Seattle, Washington	Susan Apkon
		UCLA	Los Angeles, California	Perry Shieh
		Children's Hospital Colorado	Denver, Colorado	Michele Yang
		<b>Nemours Children's Hospital</b>	<b>Orlando, Florida</b>	<b>Rich Finkel</b>
	Richmond Children's Hospital	Richmond, Virginia	Amy Harper	
	CANADA	<b>Alberta Children's Hospital</b>	<b>Calgary, Alberta</b>	<b>Jean Mah</b>
Children's Hospital of Eastern Ontario (CHEO)		Ottawa, Ontario	Hugh McMillan	
BC Children's Hospital		Vancouver, British Columbia	Kathy Selby	
Montreal Children's Hospital		Montreal, Quebec	Anne Marie Sbrocchi	

# SITES PHASE 2B TRANCHE 2

**PHASE 2A SITES – THANKS!**

2	UNITED KINGDOM	Royal Hospital for Children	Glasgow, UK	Iain Horrocks
		Alder Hey Children's Hospital	Liverpool, UK	Stefan Spinty
		University College London	London, UK	Francesco Muntoni
		<b>Newcastle University</b>	<b>Newcastle, UK</b>	<b>Michela Guglieri</b>
		Leeds Teaching Hospitals Trust	Leeds, UK	Anne-Marie Childs
	ISRAEL	<b>Schneider Children's Medical Center</b>	<b>Tel Aviv, Israel</b>	<b>Yoram Nevo</b>
	AUSTRALIA	<b>Royal Children's Hospital</b>	<b>Melbourne, Australia</b>	<b>Monique Ryan</b>
		<b>The Children's Hospital at Westmead</b>	<b>Sydney, Australia</b>	<b>Richard Webster</b>
	SWEDEN	<b>Queen Silvia Children's Hospital</b>	<b>Gothenburg, Sweden</b>	<b>Mar Tulinius</b>
		Karolinska Institutet	Stockholm, Sweden	Thomas Sejersen

## KEY QUESTIONS

- **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**