Santhera Pharmaceuticals

Developing medicines to meet the needs of patients living with rare diseases

June 2021

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Pipeline offers promising therapeutic options in rare disease areas

Development Stage

Indication	Molecule	Preclinical / Ph 1 / Ph 2 / Pivotal / Filing / Market	Milestones	Remarks
Duchenne muscular dystrophy	**vamorolone** (oral suspension)	VISION-DMD	Q2-2021: Positive top line data at 6 months	Licensed from ReveraGen
Cystic fibrosis	**lonodelestat** (inhaled)		Q1-2021: Successfully completed Phase 1	Licensed from Polyphor
Congenital muscular dystrophy	**Gene therapy**		Animal PoC ongoing	Collab. Univ. Basel & Rutgers
Inflammatory diseases e.g. IBD, COPD, Asthma	**vamorolone**		Preclinical biomarker studies published	Rationale for multiple diseases
Diseases associated with high hNE activity	**lonodelestat**		Under evaluation	Rationale for multiple diseases

Vamorolone option rights assigned from Idorsia and license taken from ReveraGen in Sep 2020
IBD: Inflammatory Bowel Disease; COPD: Chronic Obstructive Pulmonary Disease
hNE: Human Neutrophil Elastase; Lonodelestat was formerly known as POL6014
PoC: Proof of Concept

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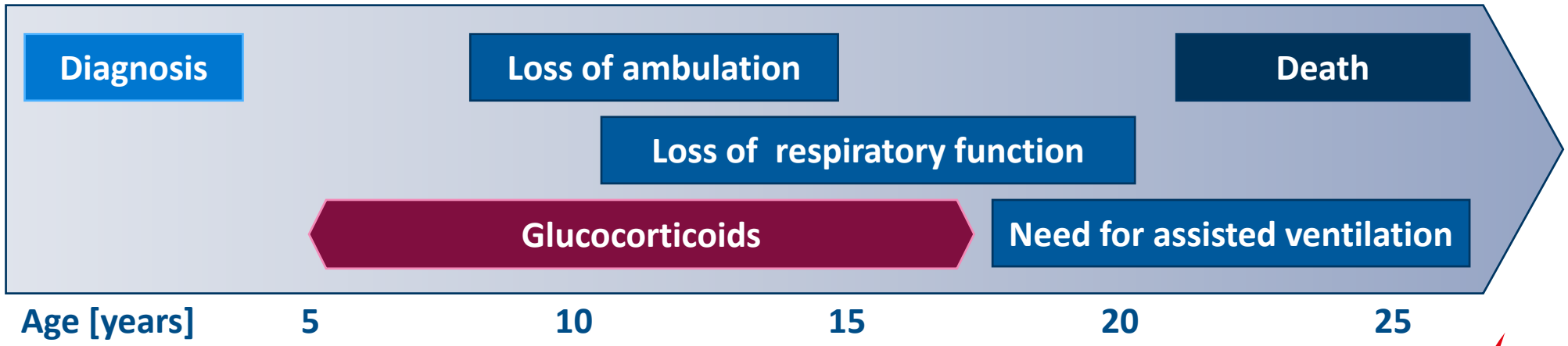
DMD is a rare genetic disorder with very limited treatment options

Genetics	Patients	Cause	Symptoms	Late stage
X-linked recessive, rare genetic disorder and most common type of muscular dystrophy	Affecting primarily boys at early age with incidence of 1 in 3,500 – 5,000 male births	Caused by loss of the protein dystrophin in muscle cells as a result of genetic mutations	Associated with chronic muscle damage, inflammation and eventual loss of function	Early death due to cardio-respiratory failure



Birnkrant et al. (2018) Lancet Neurology, 1474-4422(18)30024-3 ; Cowen et al. BMC Neurology (2019) 19:84

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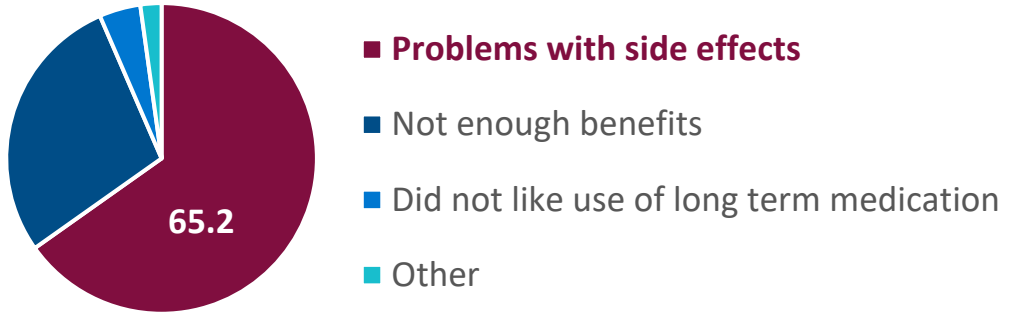
Glucocorticoids in DMD

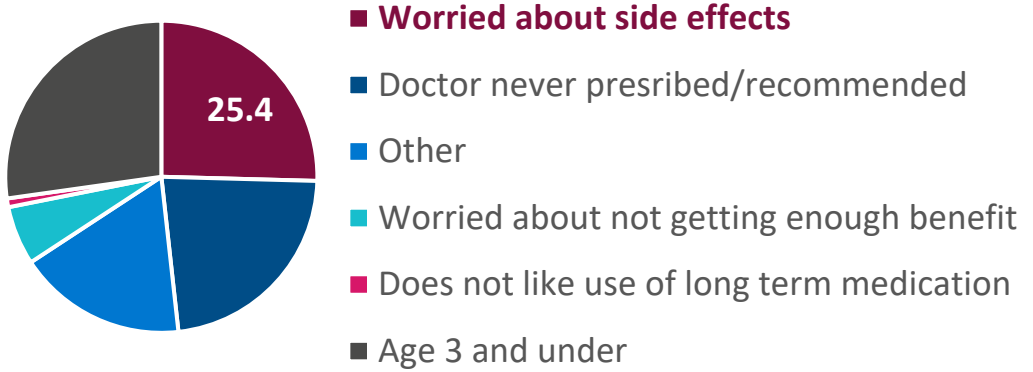
Glucocorticoids

- Glucocorticoids (GC) improve muscle strength, slow disease progression and early use can change natural history of the disease [1-3]
- Use of GCs in DMD is high, particularly in ambulatory patients but declines with age [4]
- The main reason for discontinuation or reason for not initiating GC treatment is associated with well-established side effects [4]

Reasons for Discontinuing [4]



Reasons for not Initiating [4]



1: McDonald Lancet 2017; 2: Goemans Lancet 2018; 3:McDonald Mucle&Nerve 2020 ; 4: Cowen BMC Neurology 2019;

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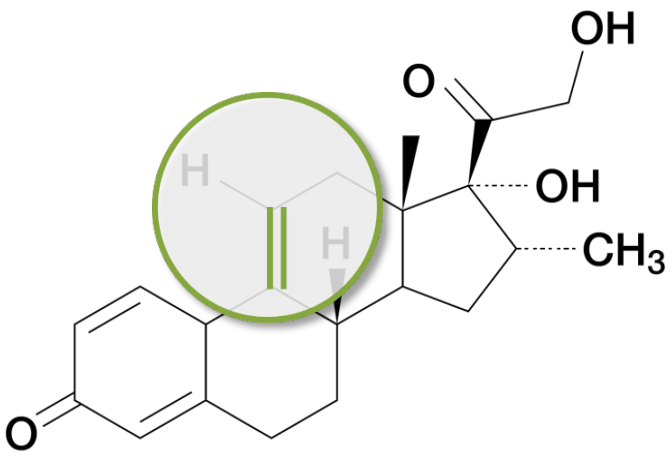
Vamorolone: Engineered to uncouple anti-inflammatory effects from corticosteroid-mediated adverse effects



Vamorolone Molecular Structure

Like corticosteroids, inhibits NF-κB activity

Retained efficacy due to anti-inflammatory action

Reduced Muscle Inflammation

Unlike corticosteroids, reduced activation of GREs

Significant improvement of steroid-associated side effect profile

- Bone fragility & fractures
- Reduced / delayed growth
- Hypogonadism
- Weight gain
- Behavioral effects
- Diabetes
- Cushingoid features
- Hypertension

GRE=glucocorticoid response elements; NF-κB=nuclear factor kappa B; MoA: Mode of action

1. Barnes P. Pharmaceuticals. 2010;3:514-540. 2. Heier CR, et al. EMBO Mol Med. 2013;5:1569-1585.
3. Saag K, Furst DE. https://www.uptodate.com/contents/major-side-effects-of-systemic-glucocorticoids

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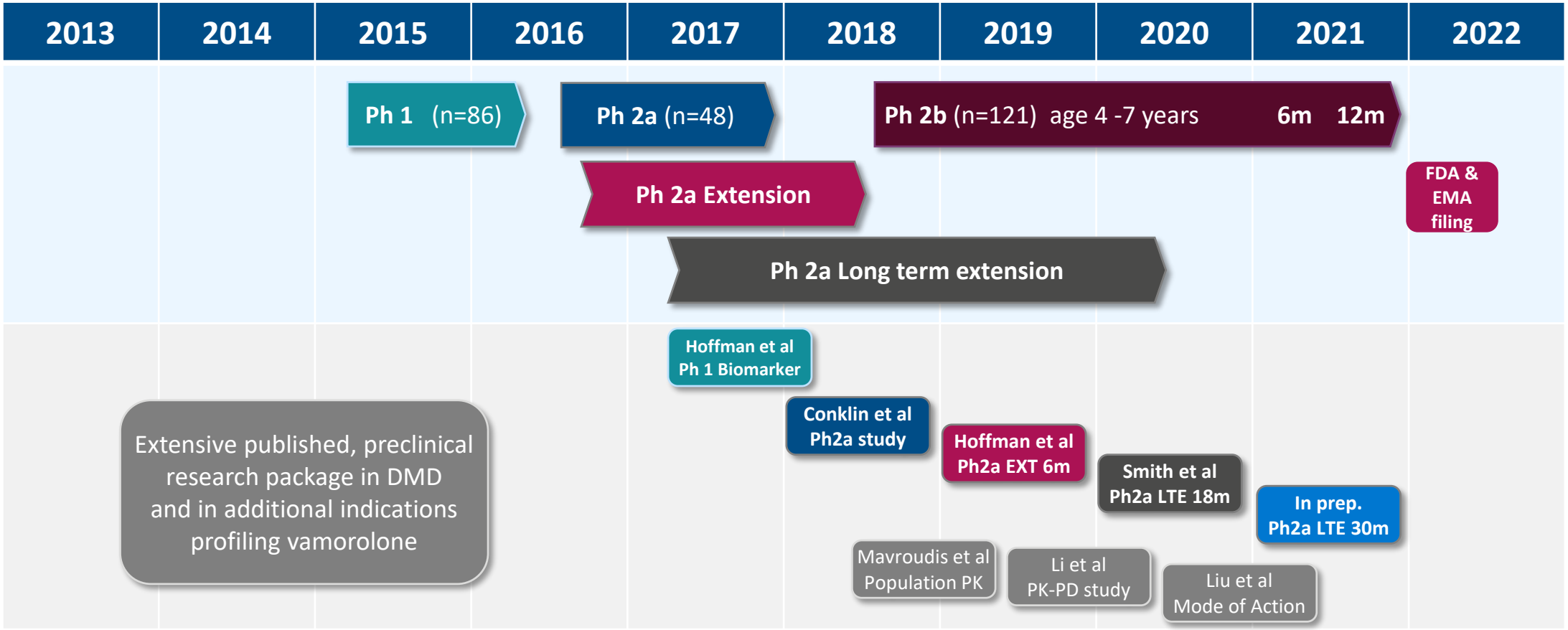
Vamorolone clinical development timeline and associated publications

Vamorolone pharmacology and clinical evidence has been published in > 20 peer reviewed articles



Hoffman et al. Steroids (2018); Conklin et al. Ph. Res. (2018); Hoffman et al. Neurology. (2019); Smith et al. PLOS Med. (2020); Dang et al. MDA Abstr. #47 (2021); Mavroudis et al. J. Clin. Ph. (2019); Li et al. J. Clin Ph. (2020); Liu et al. PNAS (2020)

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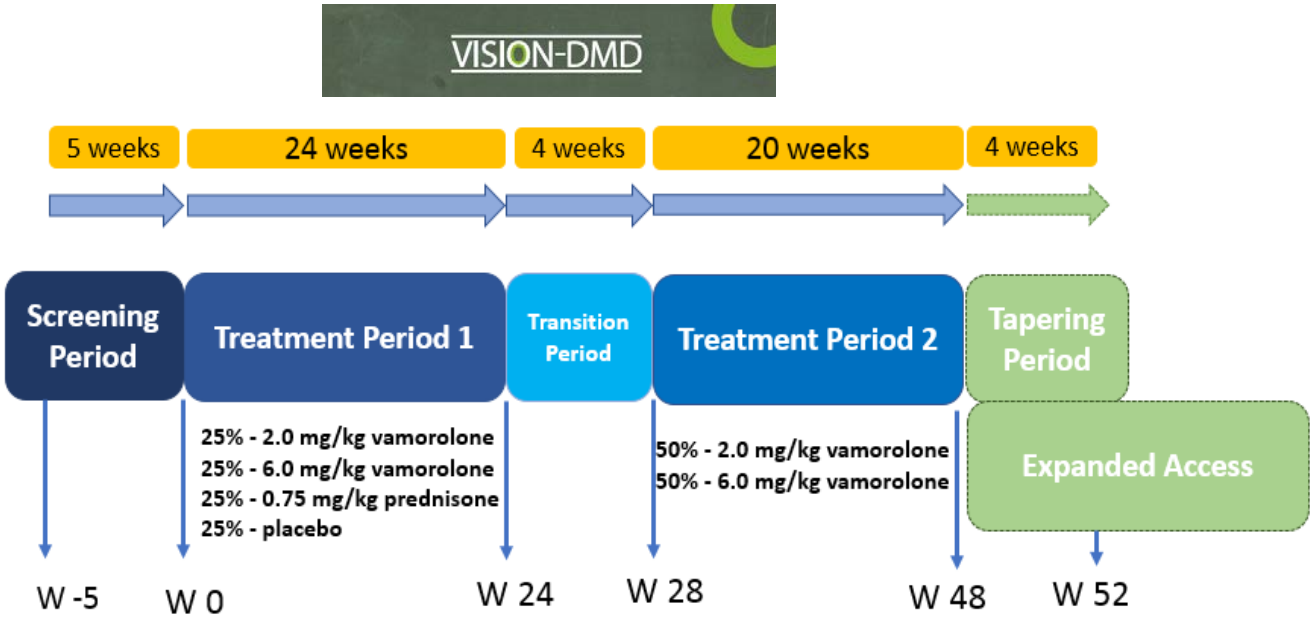
Pivotal Phase 2b study design in patients with DMD

Pivotal, randomized, double-blind, placebo controlled trial in 121 steroid-naive patients

- Developed under FDA and EMA scientific advice
- Boys aged 4 - <7 years in 4 groups
- 30 sites in US, EU, Canada, Australia, Israel
- Readout after 24 and 48 weeks
- 24-week last patient last visit completed
- 24-week readout Q2-2021



6MWT: six minute walk test; NSAA: North Star Ambulatory Assessment

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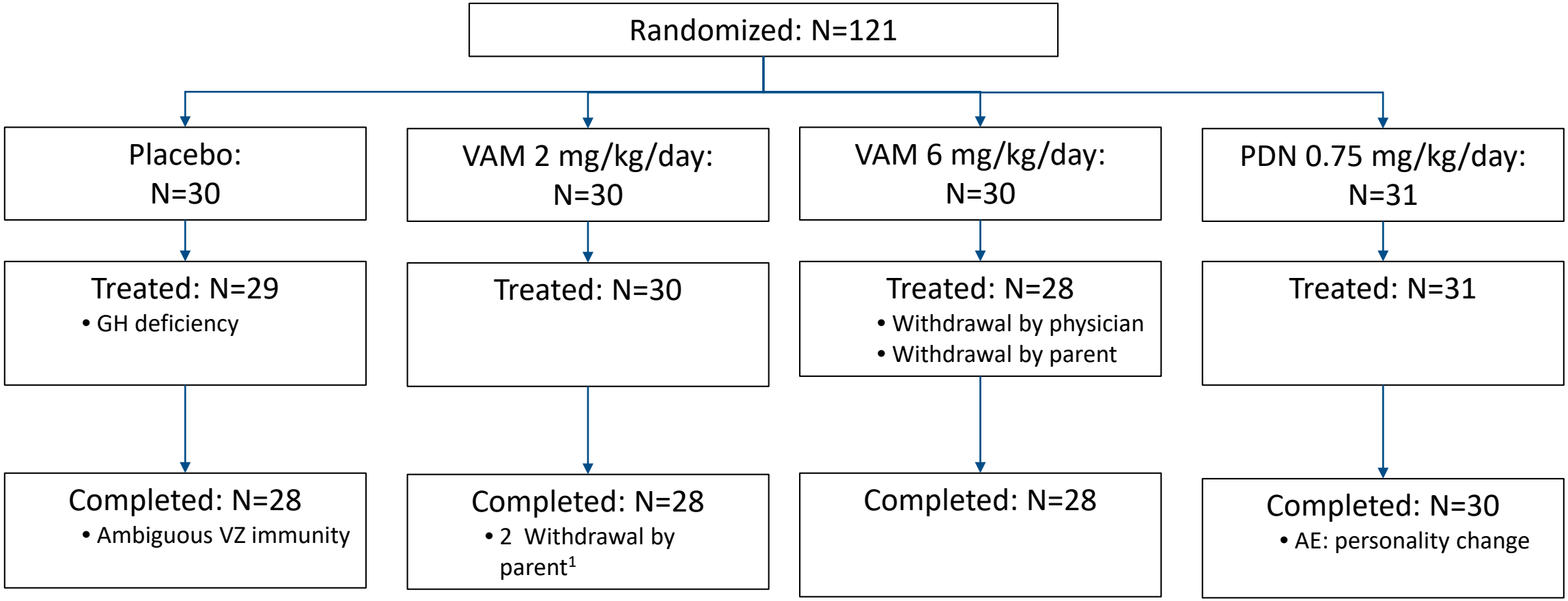
Pivotal Phase 2b study: methods for 3 endpoints & 8 comparisons

- **Primary endpoint:**
  - Change baseline to wk 24 in Time to Stand (TTSTAND) velocity, Vamorolone 6 mg/kg versus placebo

- **Secondary endpoints were tested in pre-defined hierarchical order (all at Week 24):**
  - TTSTAND velocity, Vamorolone 2 mg versus placebo
  - 6-minute walk test (6-MWT) distance, Vamorolone 6 mg versus placebo
  - 6-minute walk test (6-MWT) distance, Vamorolone 2 mg versus placebo
  - Time to Run/Walk 10 meters (TTRW) velocity, Vamorolone 6 mg versus placebo
  - Time to Run/Walk 10 meters (TTRW) velocity, Vamorolone 2 mg versus placebo
  - 6-minute walk test distance, Vamorolone 6 mg versus prednisone 0.75 mg/kg
  - 6-minute walk test distance, Vamorolone 2 mg versus prednisone 0.75 mg/kg

- **This 24-week analysis is the primary analysis of the study**

Pivotal Phase 2b study: Disposition of subjects



[1]Patient refused to take the syrup, participation to exon skipping study

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Pivotal Phase 2b study: Demographics characteristics

	Placebo (N=29)	PDN 0.75 mg (N=31)	VAM 2 mg (N=30)	VAM 6 mg (N=28)	Total[1] (N=118)
Age (years)	5.4 (0.8)	5.5 (0.9)	5.3 (0.9)	5.4 (0.9)	5.4 (0.9)
Height (cm)	109 (9)	111 (6)	108 (9)	107 (7)	109 (8)
Weight (kg)	20 (3)	21 (3)	19 (4)	19 (3)	20 (3)
BMI (kg/m^2)	16.3 (1.2)	16.8 (1.3)	16.2 (1.2)	16.6 (1.4)	16.5 (1.3)

Data shown as mean (SD) or % of patients
[1]Safety population

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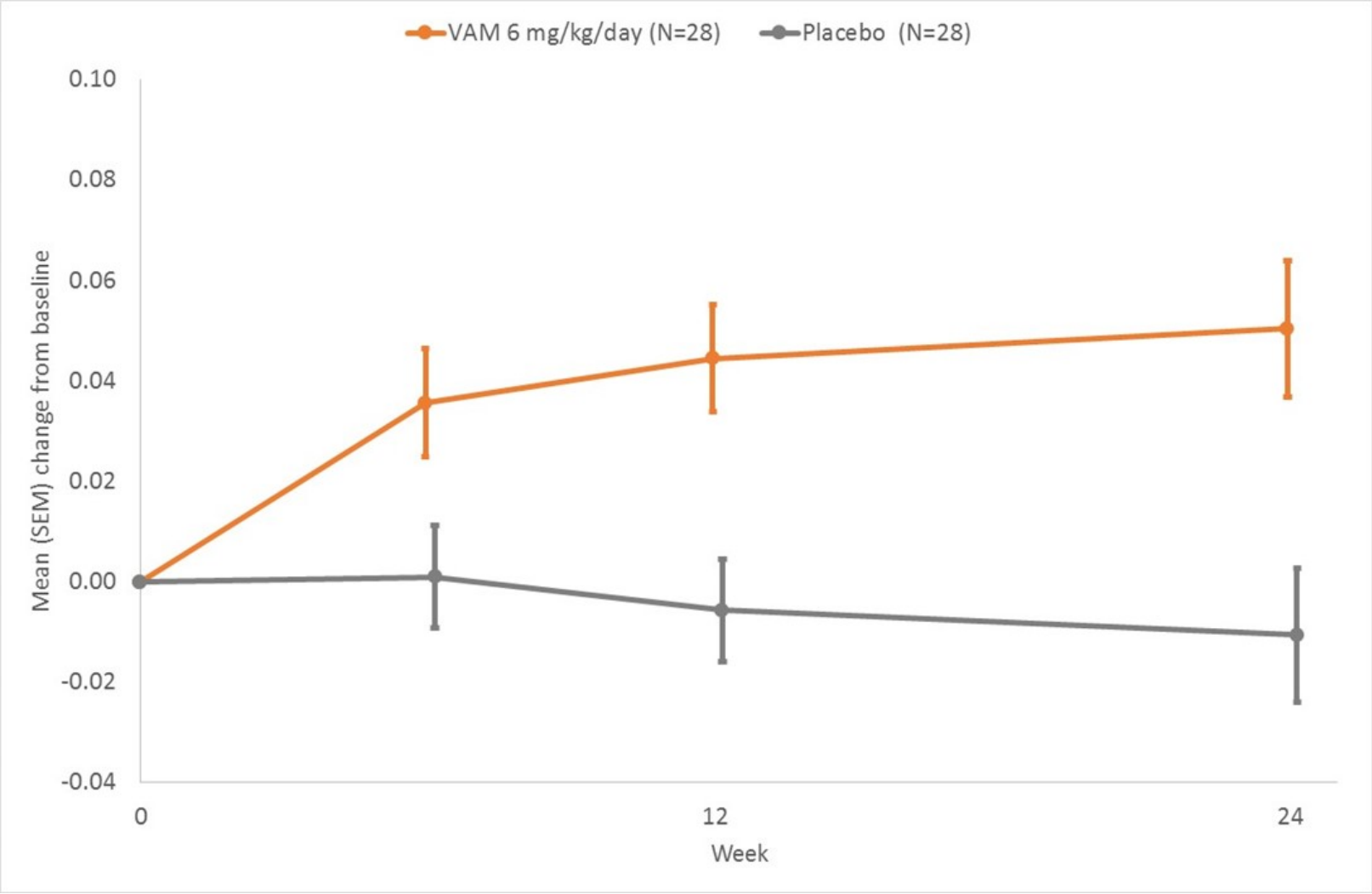
Primary Endpoint: Change in TTSTAND velocity (rises/sec)

Baseline to Week 24 (mITT Set, MMRM)



Mean (SEM) difference at Week 24:

VAM 6 mg/kg/day vs Placebo: 0.06 (0.02) rises/sec; p=0.002

TTSTAND – time to stand

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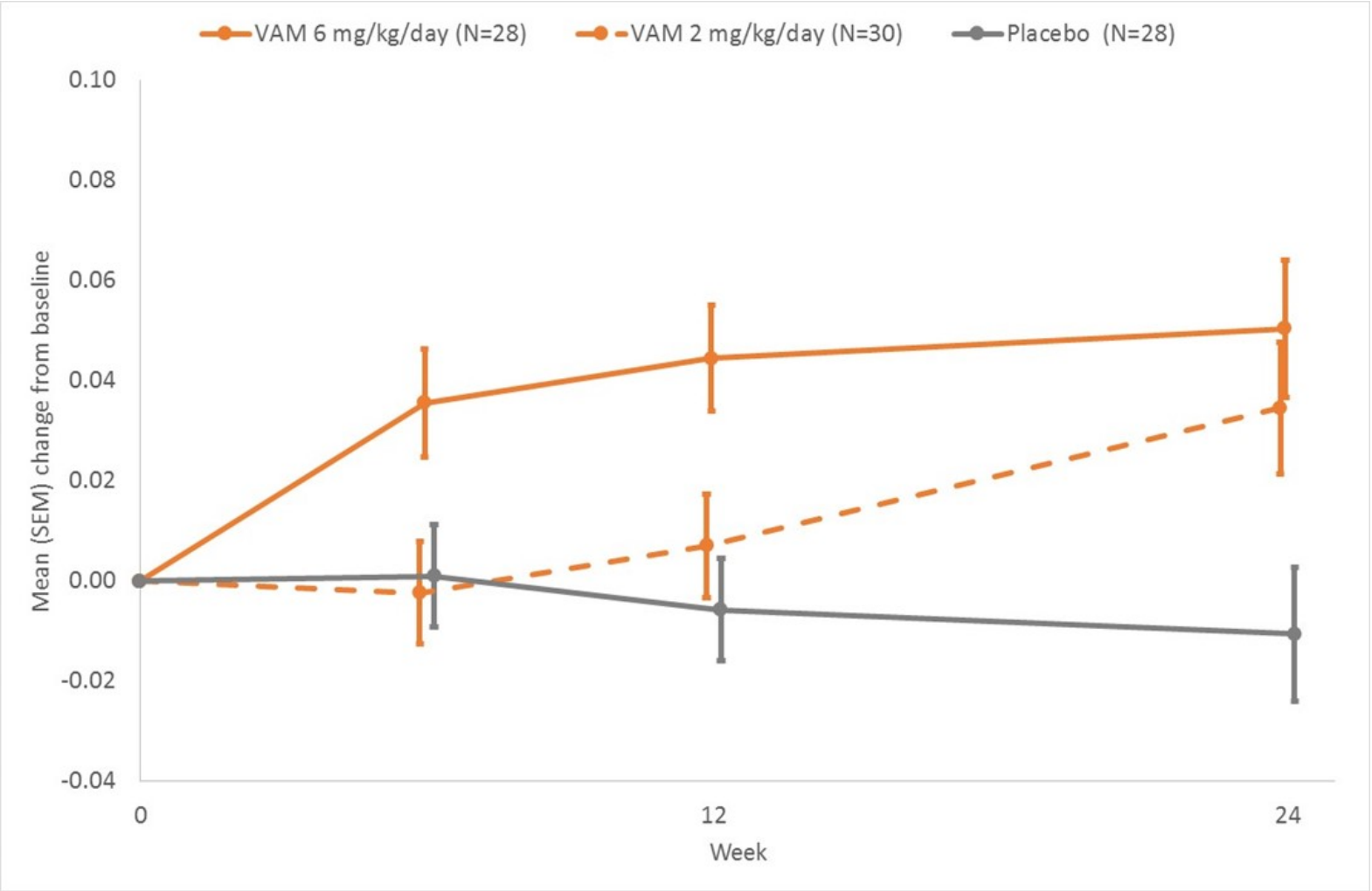
Change in TTSTAND velocity (rises/sec)

Vamorolone doses vs placebo, (mITT Set, MMRM)



Mean (SEM) difference at Week 24:

VAM 6 mg/kg/day vs Placebo: 0.06 (0.02) rises/sec; p=0.002

VAM 2 mg/kg/day vs Placebo: 0.04 (0.02) rises/sec; p=0.017

TTSTAND – time to stand

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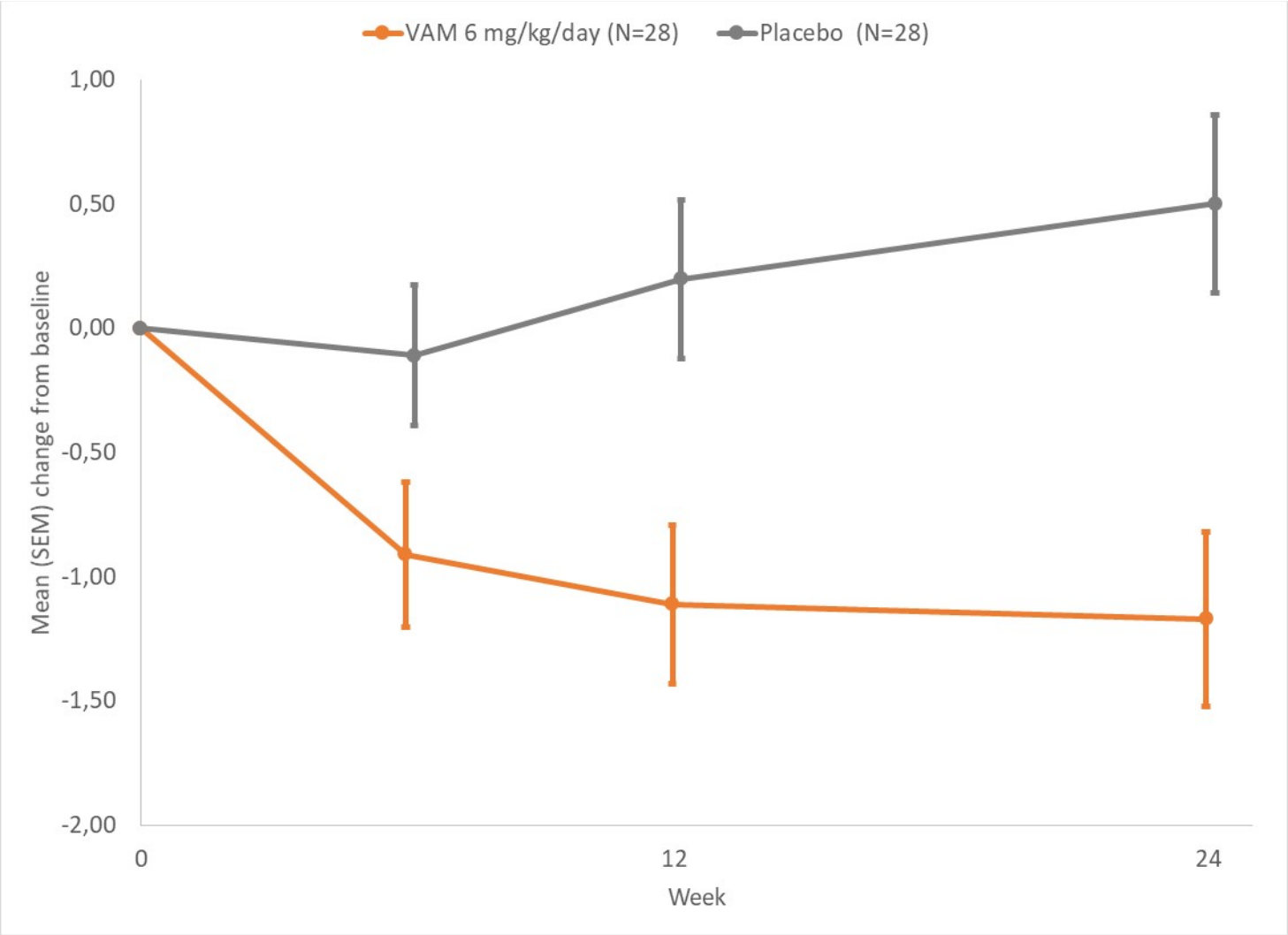
Change in TTSTAND (sec)
Baseline to Week 24 (mITT Set, MMRM)



Mean (SEM) difference at Week 24:

VAM 6 mg/kg/day vs Placebo: -1.7 (0.5) sec

TTSTAND – time to stand

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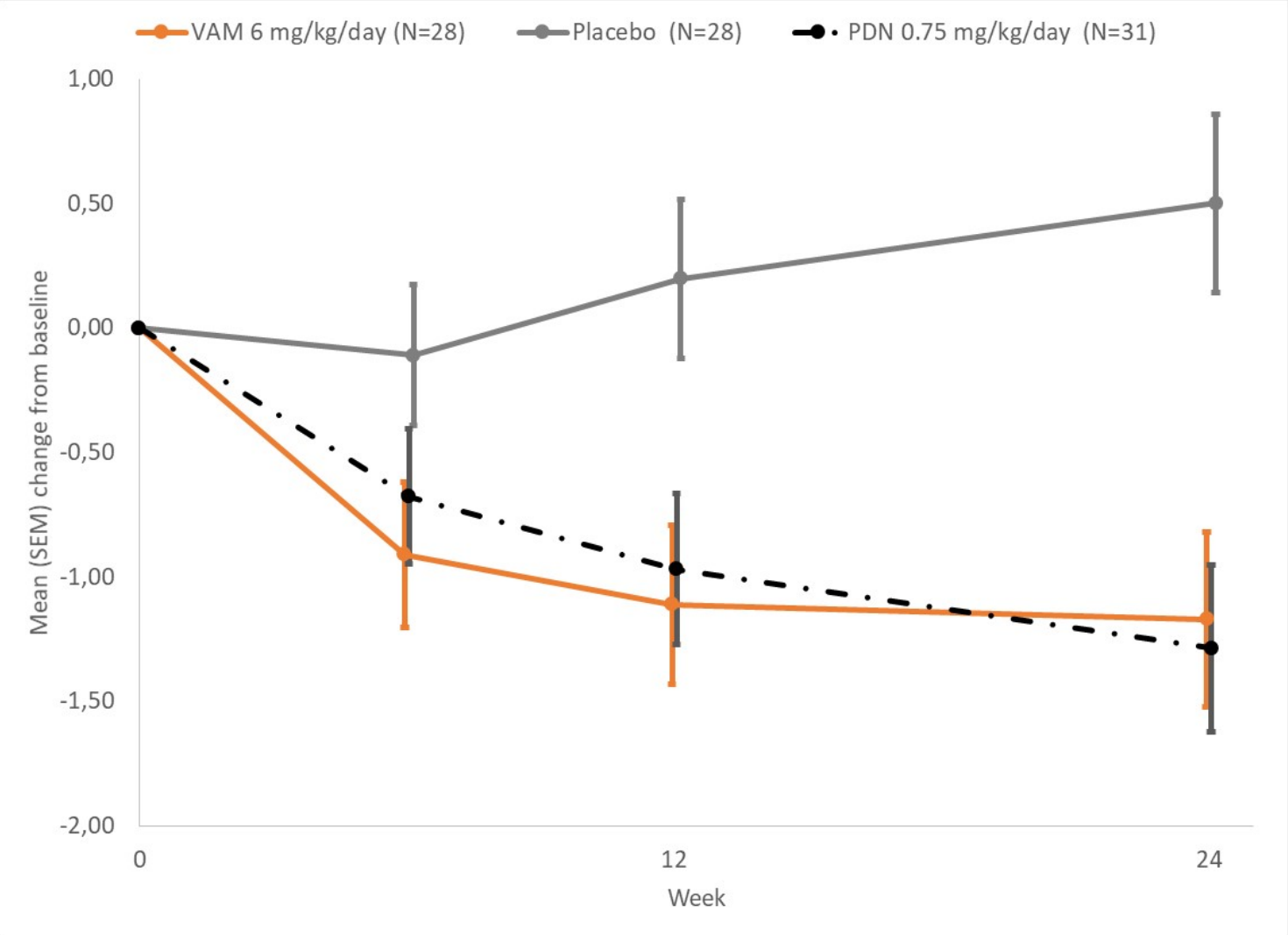
Change in TTSTAND (sec) from baseline to Week 24

Exploratory comparison to prednisone, (mITT Set, MMRM);



Mean (SEM) difference at Week 24:

VAM 6 mg/kg/day vs Placebo:
-1.7 (0.5) sec

VAM 6 mg/kg/day vs Prednisone:
0.2 (0.5) sec

TTSTAND – time to stand

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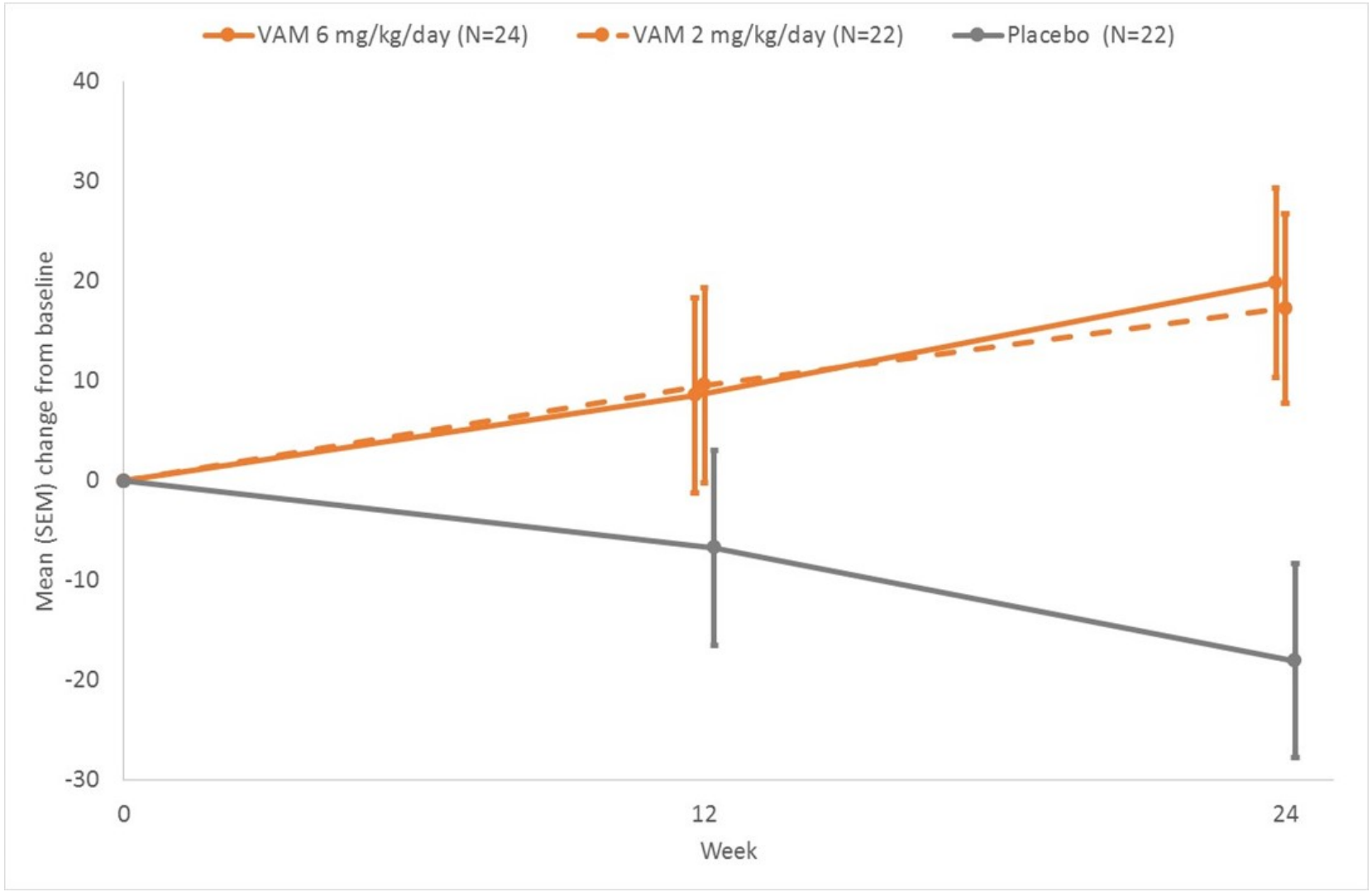
Change in 6-MWT (m)

Comparison of vamorolone doses to placebo (mITT Set, MMRM)



Mean (SEM) difference at Week 24:

VAM 6 mg/kg/day vs Placebo: 42 (14) m; p=0.003

VAM 2 mg/kg/day vs Placebo: 37 (14) m; p=0.009

6MWT: six minute walk test

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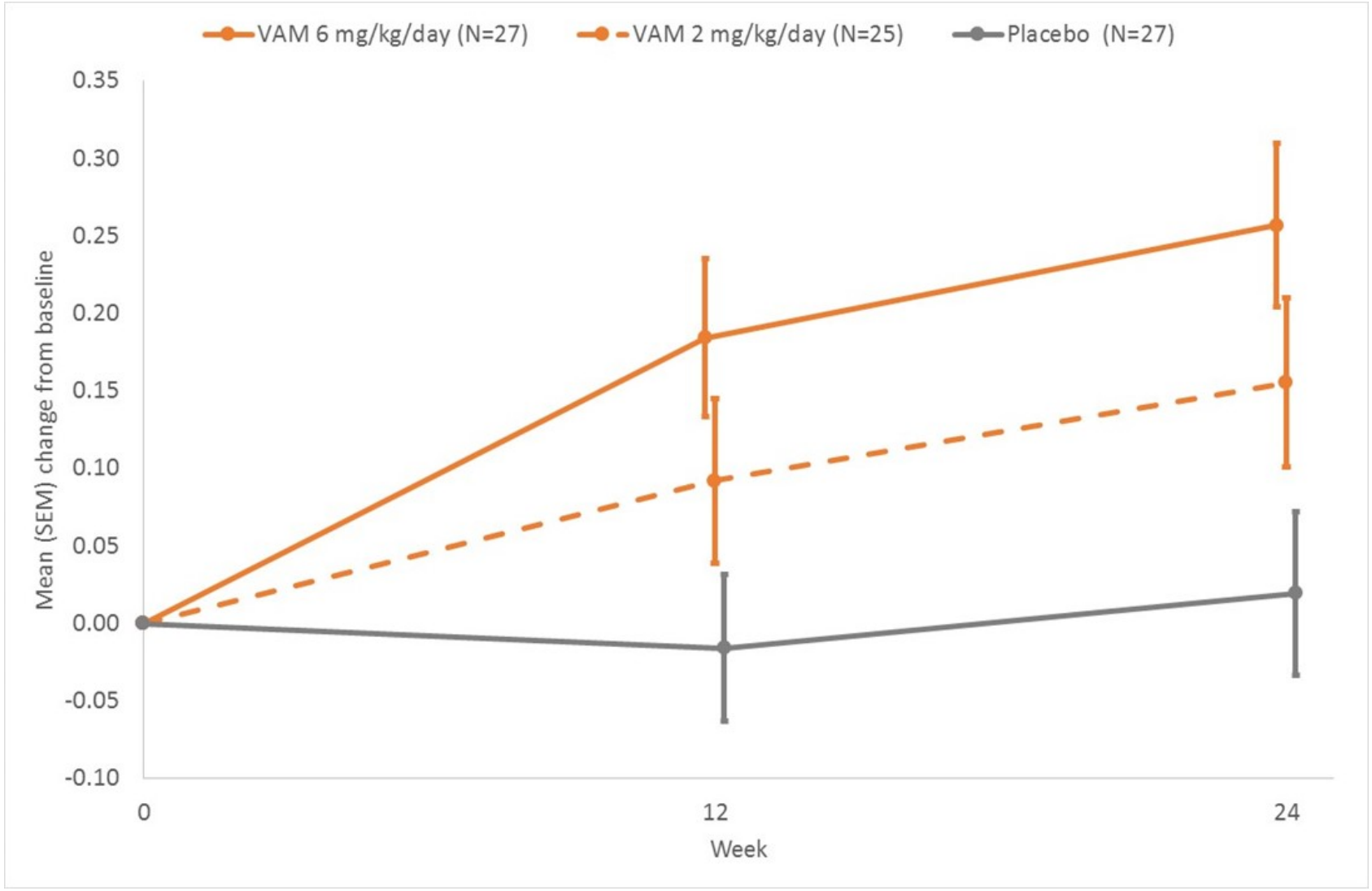
Change in TTRW (m/s)

Comparison of vamorolone doses to placebo (mITT Set, MMRM)



Mean (SEM) difference at Week 24:

VAM 6 mg/kg/day vs Placebo: 0.24 (0.08) m/sec; p=0.002

VAM 2 mg/kg/day vs Placebo: 0.13 (0.08) m/sec; p=0.103

TTRW – time to run/walk 10m

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Summary of efficacy data

Rank	Endpoint	Comparison	Difference	P-value	Interpretation
1	TTSTAND	VAM 6 mg vs Placebo	0.06 rises/s	0.002	Statistically significant
2	TTSTAND	VAM 2 mg vs Placebo	0.04 rises/s	0.017	Statistically significant
3	6MWT	VAM 6 mg vs Placebo	42 m	0.003	Statistically significant
4	6MWT	VAM 2 mg vs Placebo	37 m	0.009	Statistically significant
5	TTRW	VAM 6 mg vs Placebo	0.24 m/s	0.002	Statistically significant
6	TTRW	VAM 2 mg vs Placebo	0.13 m/s	0.103	Non-significant

Safety Summary: All Treatment Emergent Adverse Events

Event type	Placebo (N=29) N (%); F	PDN 0.75 mg (N=31) N (%); F	VAM 2.0 mg (N=30) N (%); F	VAM 6.0 mg (N=28) N (%); F
Total TEAEs	23 (79.3) ; 77	26 (83.9) ; 120	25 (83.3) ; 96	25 (89.3) ; 91
Drug-related TEAEs[5]	10 (34.5) ; 19	15 (48.4) ; 59	11 (36.7) ; 17	20 (71.4) ; 38
Severe (or worse) TEAEs	-	1 (3.2) ; 1[2]	-	-
Serious TEAEs (other than deaths)	-	-	1 (3.3) ; 1[3]	-
Deaths	-	-	-	-
TEAEs leading to discontinuation[1]	-	1 (3.2) ; 1[4]	-	-

[1]Leading to permanent discontinuation of study treatment

[2] Severe TEAE Gastroenteritis viral
[3]Serious TEAE: Aggression
[4]TEAE leading to discontinuation: Personality change
[5]Remotely, possibly, probably or definitely related

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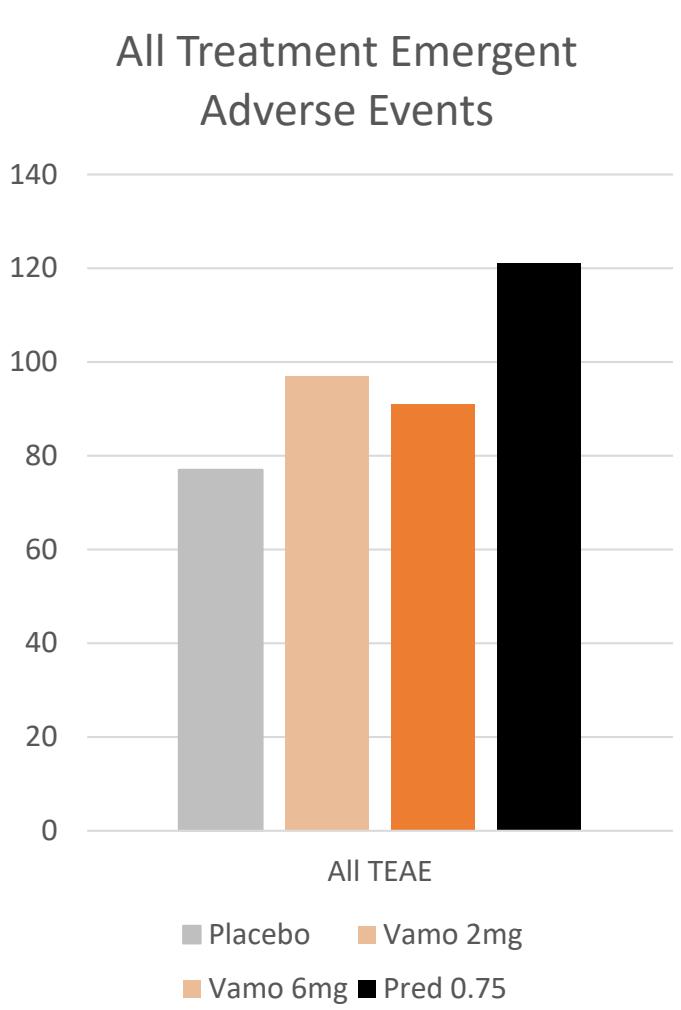
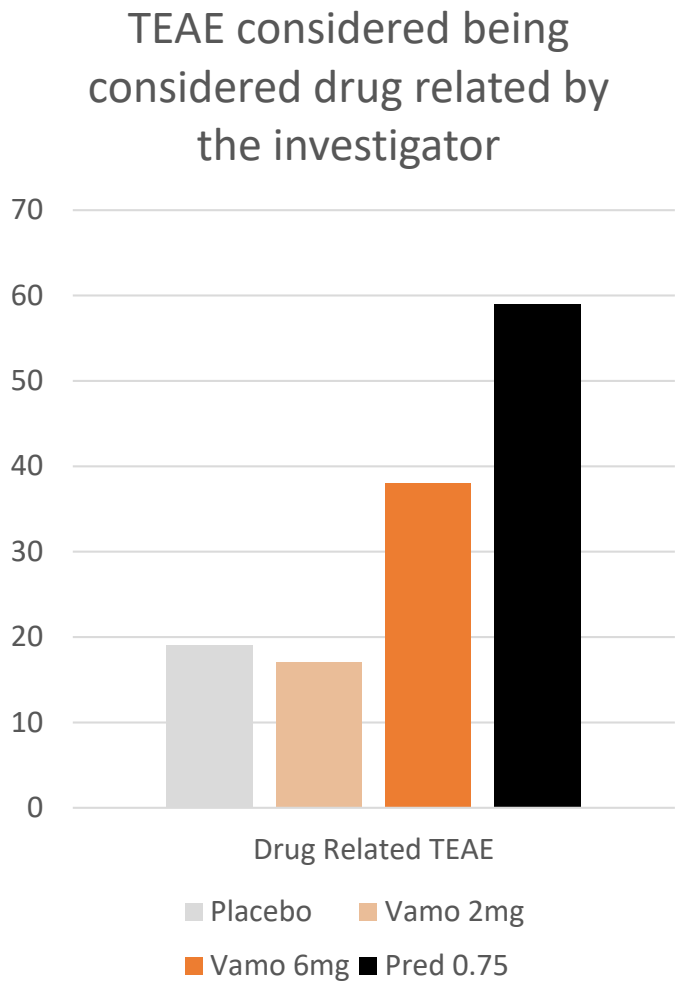
Clinically relevant TEAEs (pre-defined safety analysis)

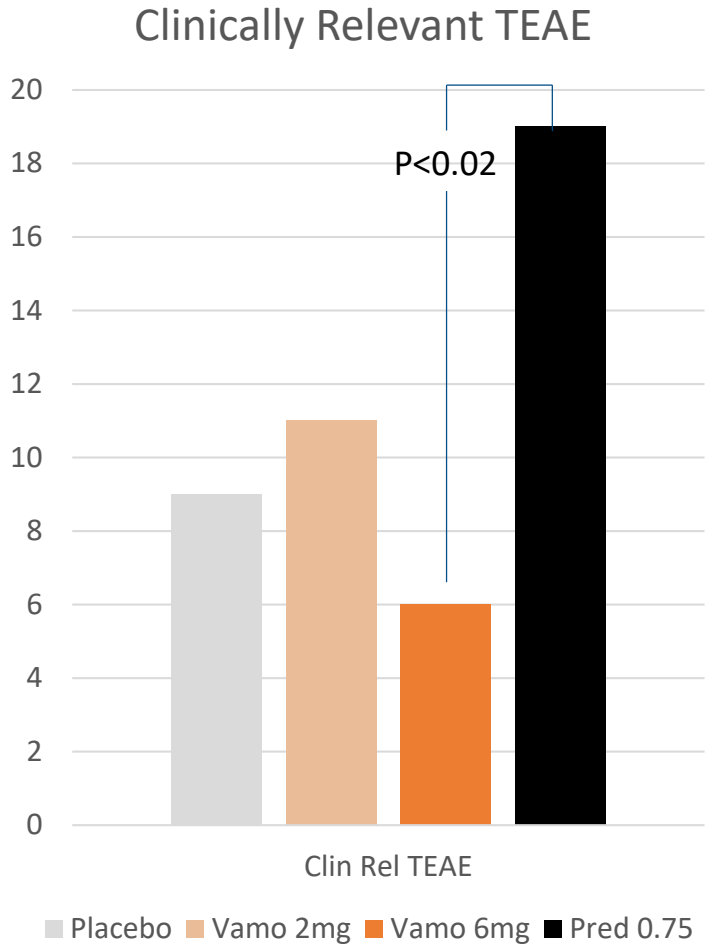
Graded as moderate, severe, serious or leading to discontinuation

Event type	Placebo (N=29) N (%); F	PDN 0.75 mg (N=31) N (%); F	VAM 2.0 mg (N=30) N (%); F	VAM 6.0 mg (N=28) N (%); F
Clinically relevant TEAEs	9 (31.0) ; 9	13 (41.9) ; 19	8 (26.7) ; 11	4 (14.3) ; 6

Summary of Safety Findings of VISION-DMD







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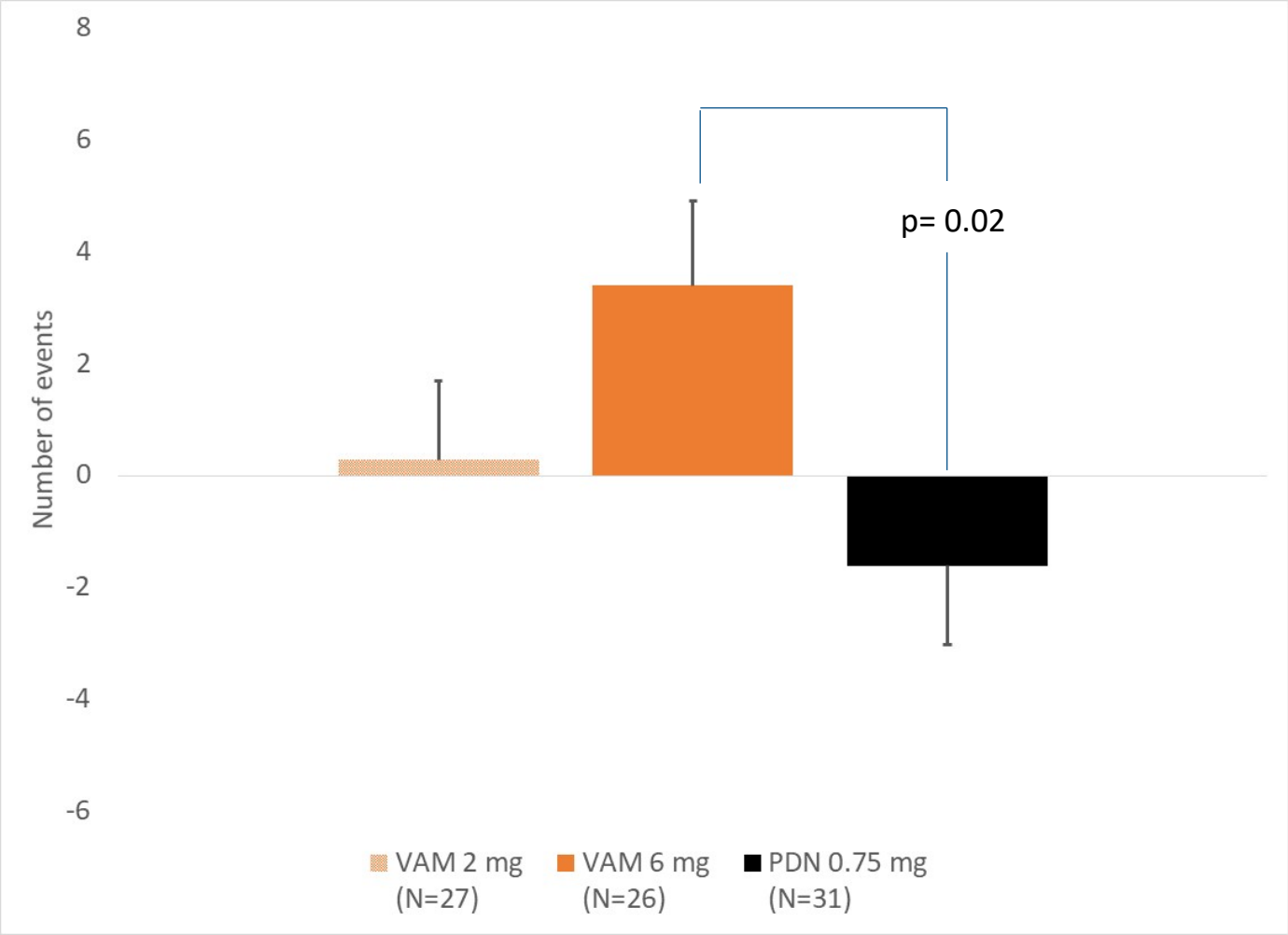
Change from baseline to Week 24 in height z-score[1]



[1]Mean(SEM) change from baseline; MMRM,Safety population

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Comparison to vamorolone phase IIa data
Study VBP15-002/003/LTE

- **The treatment effect of vamorolone seen after 24 weeks was comparable between the studies**
  - Across all efficacy endpoints
  - For both dose levels (2 mg/kg/day and 6 mg/kg/day)

- **Study VBP15-002/003/LTE collected long-term safety data over 2.5 years**
  - 113 patient years of vamorolone treatment exposure
  - Vamorolone did not show stunting of growth
  - Rate of adverse events typically seen with glucocorticoid treatments remained low throughout the study

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“The strength of evidence for both efficacy and safety of vamorolone over such a wide dose range from 2 to 6 mg/kg/day allows clinicians to individually tailor treatment of Duchenne patients by starting at the higher 6 mg/kg/day dose of vamorolone with equivalent efficacy to daily prednisone and titrate the dose according to how well the treatment is tolerated, whilst maintaining optimal efficacy. I am enthusiastic that this approach may allow patients to avoid side effects that currently lead to discontinuing steroid treatment, meaning they are able stay on for longer.”

Craig McDonald, MD, Professor and Chair, Department of Physical Medicine & Rehabilitation and Director of Neuromuscular Disease Clinics, UC Davis Health, USA.

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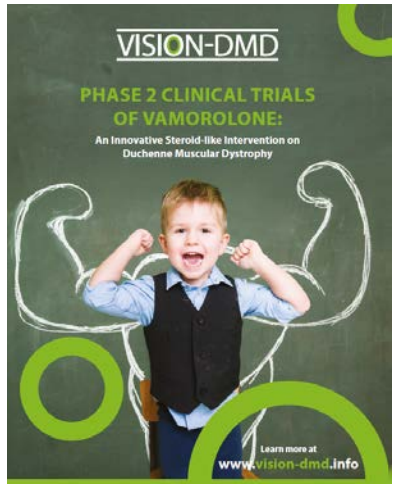
Summary

- Strong efficacy across primary and secondary endpoints in both doses of 6 and 2 mg/kg/day
- Primary endpoint for time to stand TTSTAND velocity met for vamorolone 6 mg/kg/day versus placebo (p=0.002)
- Secondary endpoints Six-Minute Walk (6MWT) and Time to Run/Walk 10 meters (TTRW) tests achieve statistical significance versus placebo
- Study confirmed good safety and tolerability profile of vamorolone for both doses
- Early confirmation of preservation of growth consistent with outcomes seen in long-term open label study
- Provides evidence base for 2 effective doses to allow for a tailored approach to treating individual patients
- Strength of data allows for path towards NDA & MAA with single pivotal study

NDA filing for vamorolone in DMD is expected in Q1-2022

VISION-DMD positive pivotal trial at recent 6-month data readout



Regulatory incentives

Orphan Drug Designation (EU, US) & FDA Fast Track Designation

Rare Pediatric Disease Designation, eligibility for US Priority Review Voucher

TIMELINES DMD	2020		2021				2022				2023	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	H1	H2
Vamorolone	VISION-DMD		VISION-DMD	VISION-DMD 6-month			NDA Filing			Approval Launch		
	Full enrollment		Last patient last visit	Positive outcome		VISION-DMD 12-month data		MA Application				Approval Launch

MoA: Mode of action; LTE: Long term extension; Smith 2020, Liu 2020

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Q & A Session

June 2021