Ontsteking en fibrose in DMD

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Disclosures

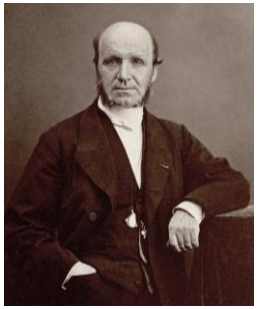
- clinical trial activities (PI and sub-I) for Sarepta Therapeutics, Pfizer, Italfarmaco, FibroGen, ReveraGen, PTC Therapeutics, Biomarin, GlaxoSmithKline, Santhera Pharmaceuticals, Lilly, Prosensa, Wave Life Sciences
- ad hoc scientific advisory board activities for Santhera Pharmaceuticals, Pfizer, Italfarmaco

Duchenne spierdystrofie (DMD)

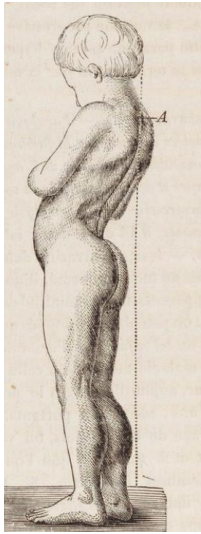
- X-linked progressieve spieraandoening
- 1/3.500-7.000 levend geboren jongens

- skeletspieraantasting met verlies van ambulantie op jonge leeftijd
- aantasting van hartspier en ademhalingsspieren
- cognitieve en neuropsychologische moeilijkheden

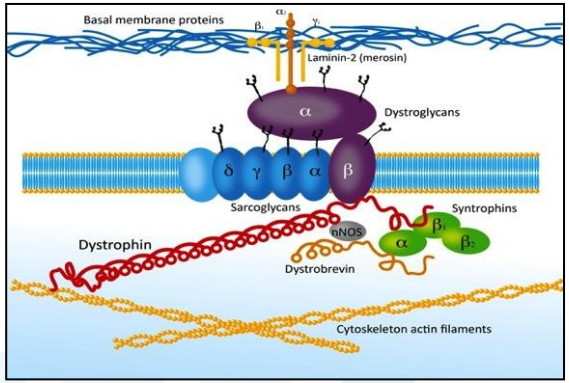
- geen curatieve behandeling, enkele genetische therapieën met beperkte werkzaamheid, vooral multidisciplinaire supportieve/symptomatische aanpak

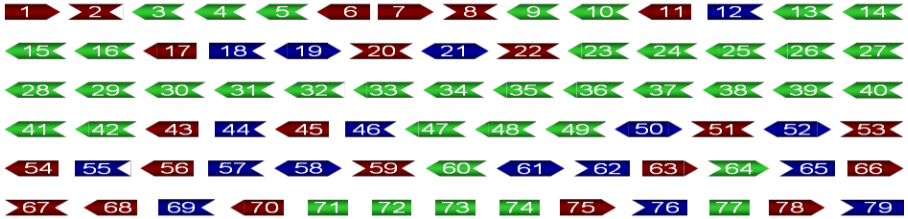


Guillaume Duchenne de Boulogne (1861)

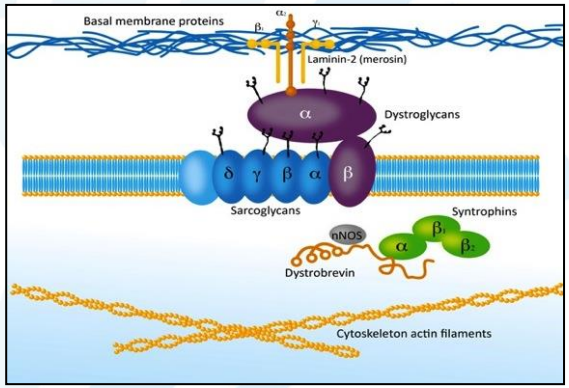


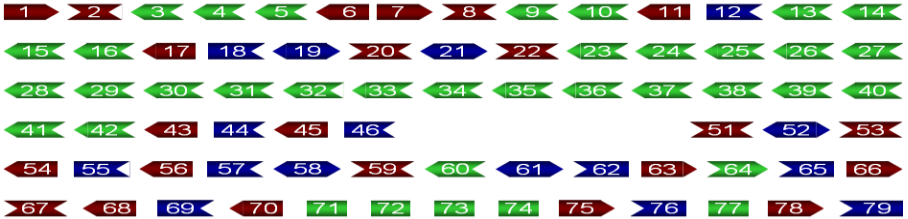
DMD gen codeert voor het dystrofine eiwit





grootste gen
2.6 miljoen bp
79 exonen
chromosoom Xp21





out of frame transcript
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afwijkende pre-mRNA translatie
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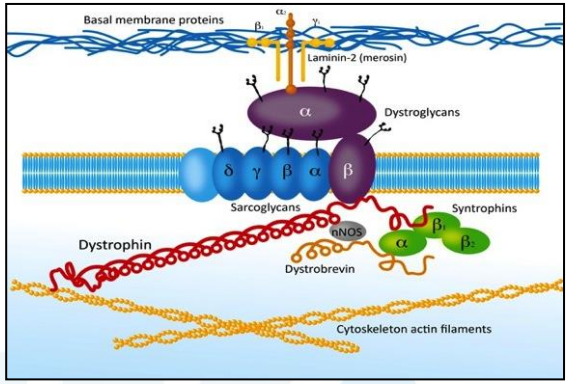
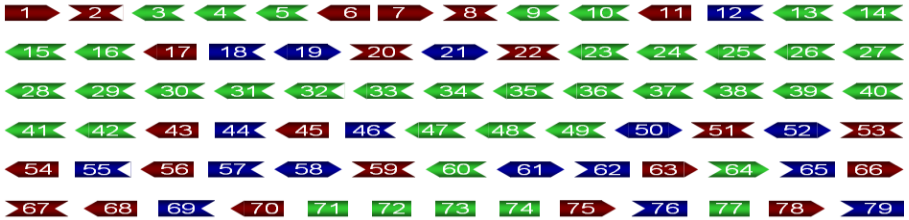
afwezigheid van dystrofine
↓
DMD

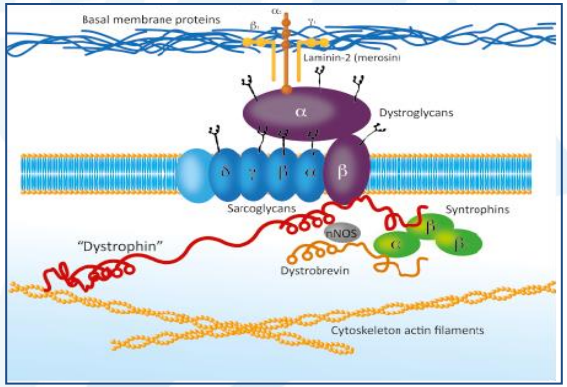
courtesy of Dr. Goemans

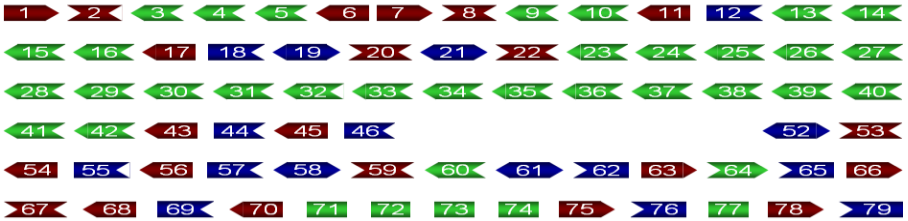
Becker musculaire dystrofie (BMD)





grootste gen
2.6 miljoen bp
79 exonen
chromosoom Xp21





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intern getrunceerd dystrofine
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functionele domeinen bewaard
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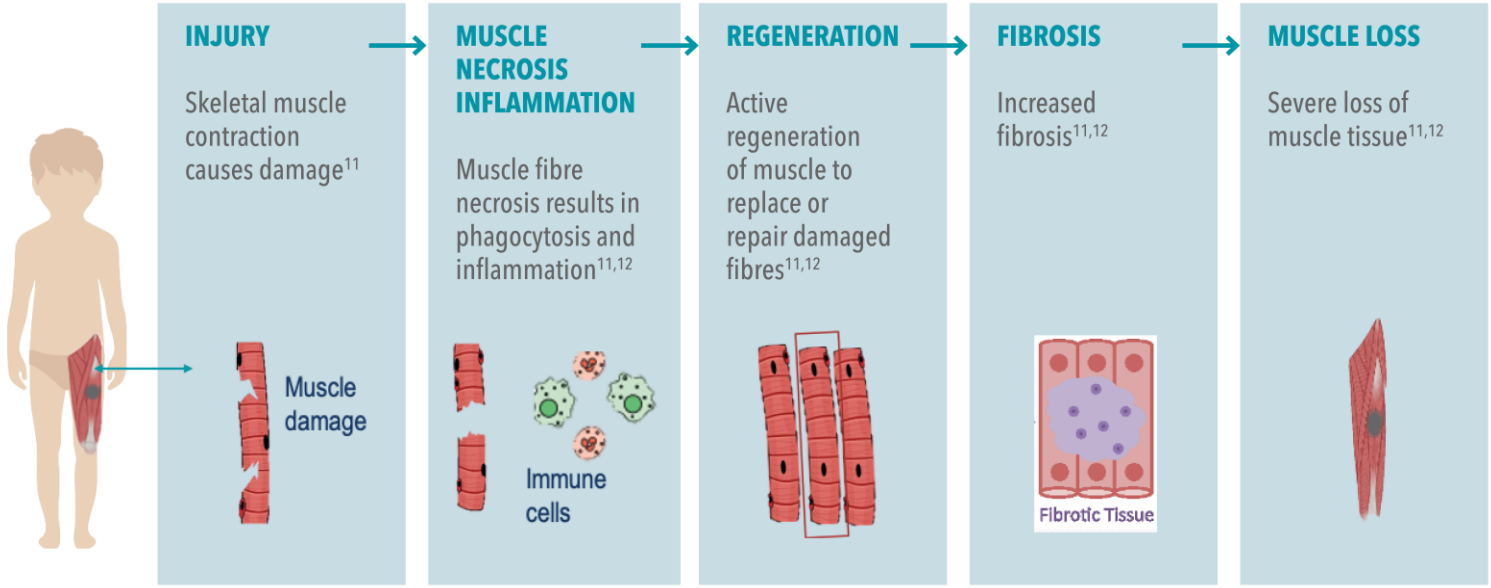
BMD

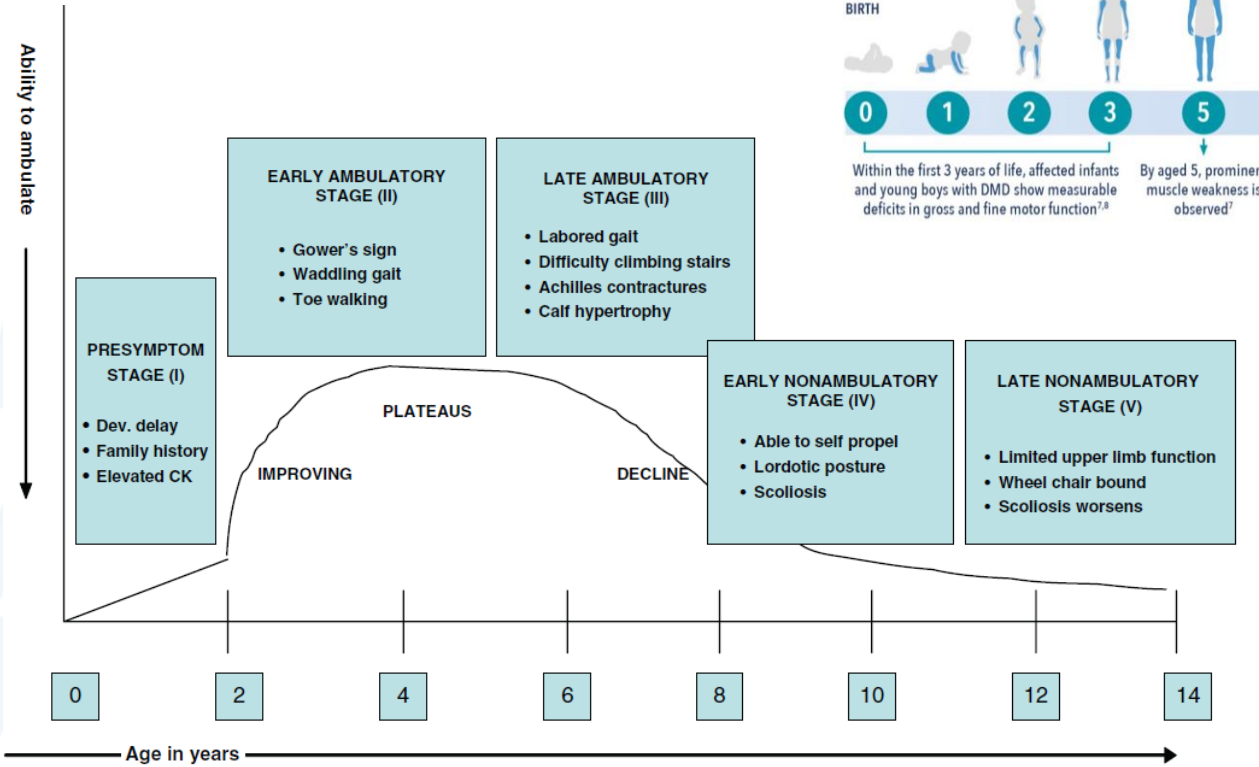
courtesy of Dr. Goemans

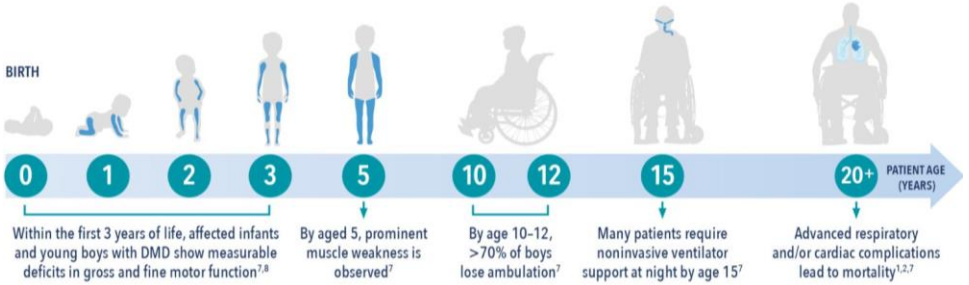
Spierschade resulteert in ontsteking, necrose en fibrosevorming



takeonduchenne.eu; Loboda et al. *Pharmacol Reports* 2020

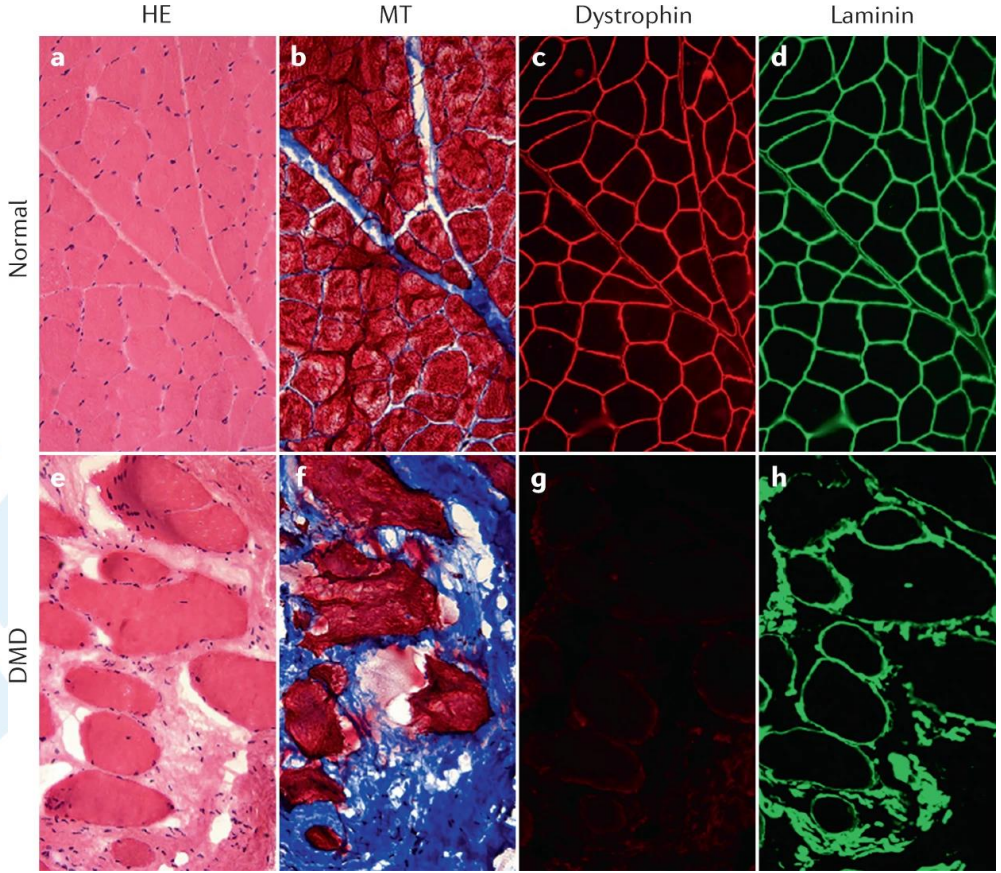
Traag degeneratief verloop





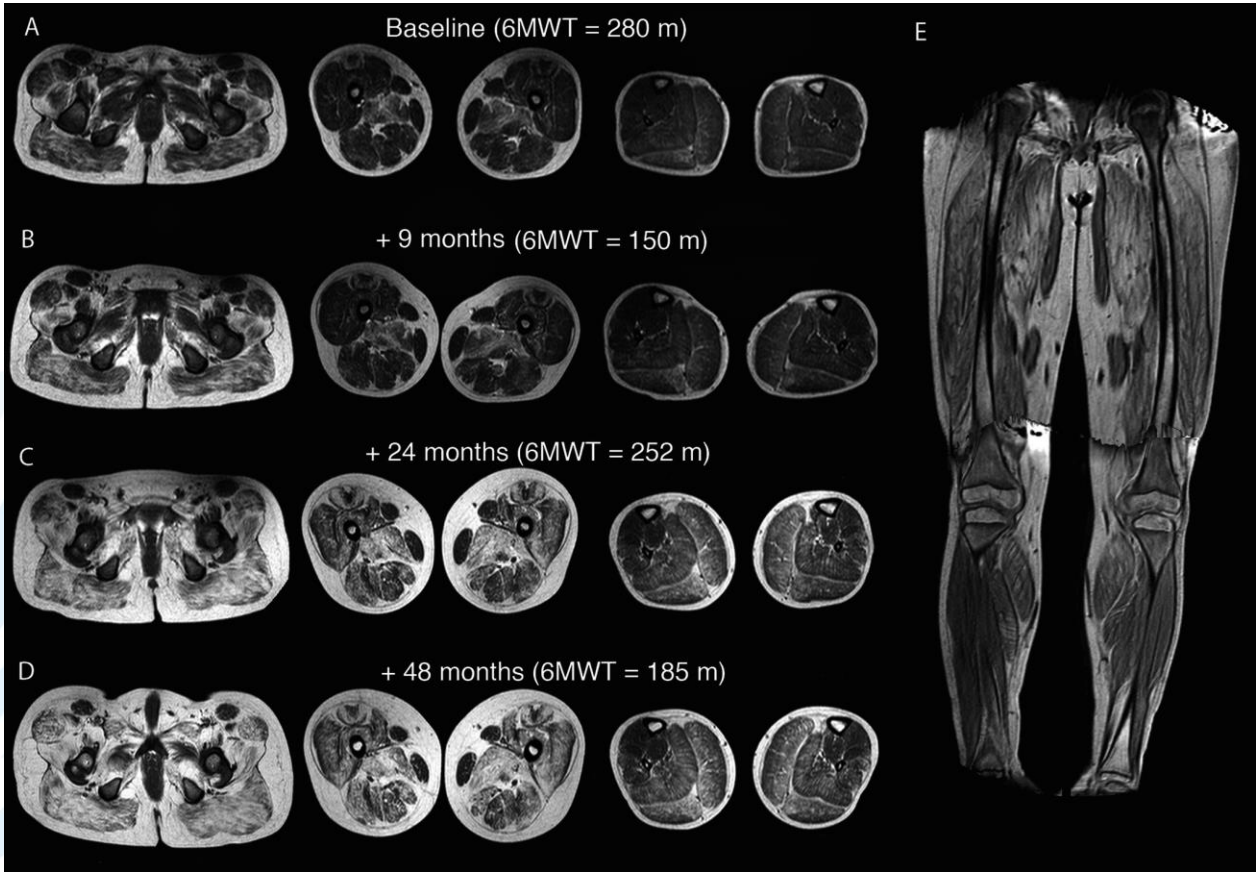
courtesy of Dr. Goemans; takeonduchenne.eu

Spierschade resulteert in ontsteking, necrose en fibrose



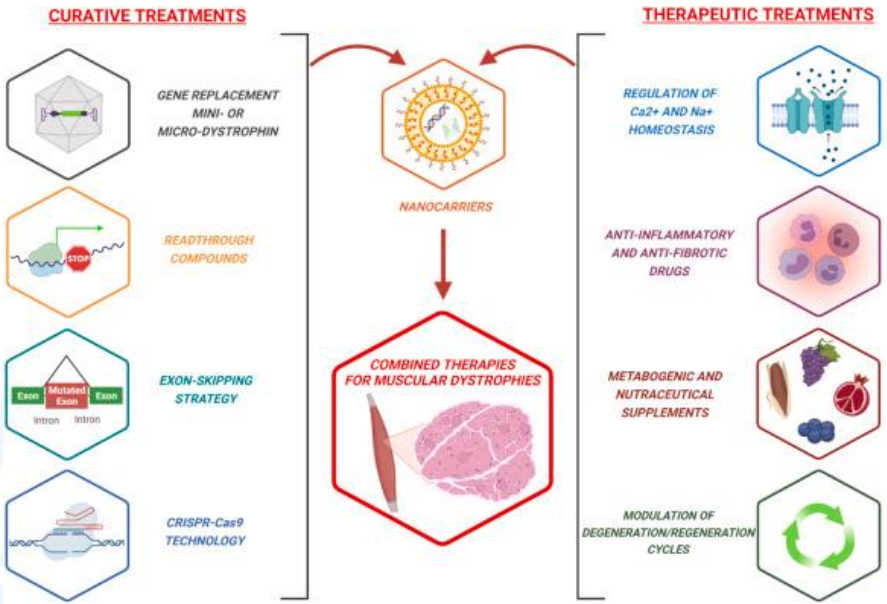
Duan et al. *Nat Rev Dis Prim* 2021

Spierschade resulteert in ontsteking, necrose en fibrose



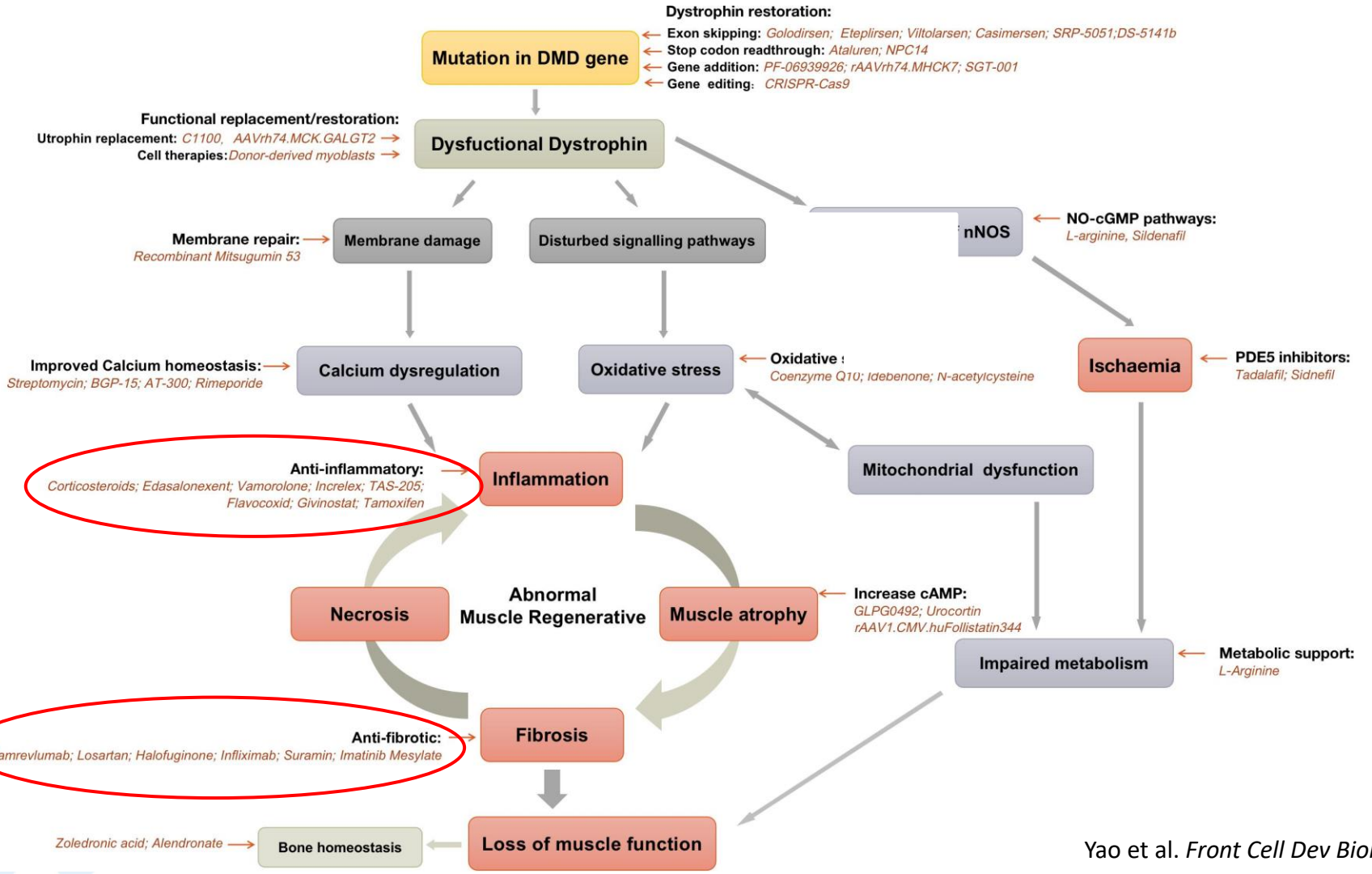
Godi et al. *Ann Clin Transl Neurol* 2016

Behandeling van Duchenne spierdystrofie



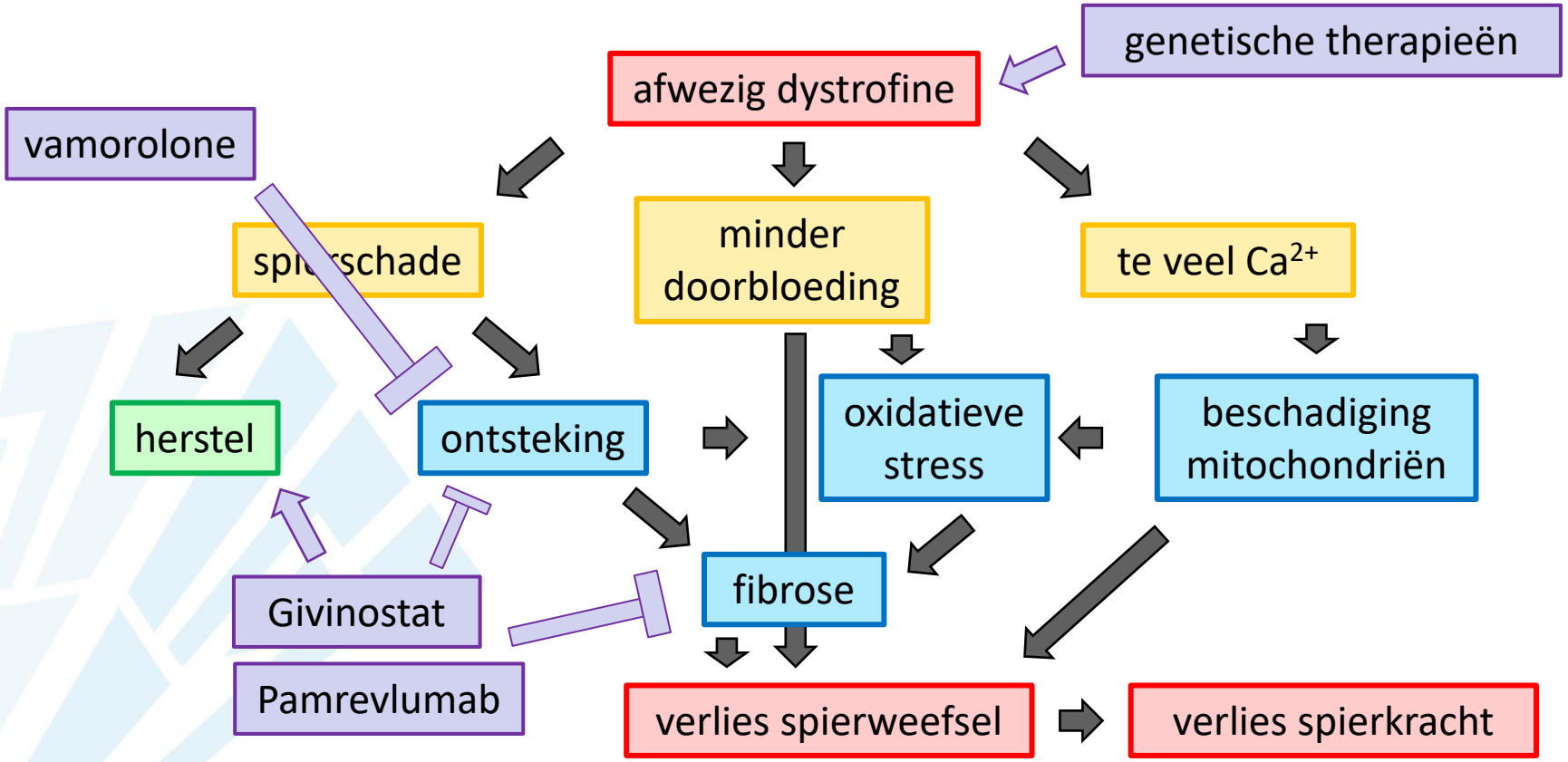
- de productie van dystrofine herstellen
  - ✓ gentherapie
  - ✓ exon skipping
  - ✓ non-sense mutation read-through

- de symptomen van het tekort aan dystrofine behandelen
  - ✓ ontsteking verminderen
  - ✓ fibrose tegengaan
  - ✓ verbeteren van spiergroei en bescherming van spieren
  - ✓ calcium evenwicht herstellen
  - ✓ herstel energie cellen
  - ✓ hartfunctie verbeteren



Yao et al. *Front Cell Dev Biol* 2021

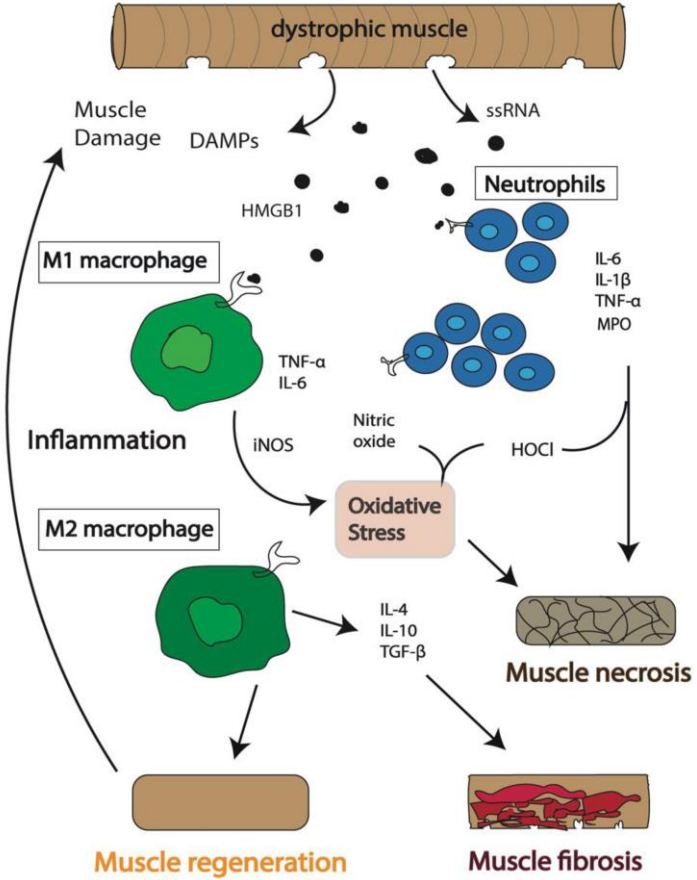
Aangrijpingspunten voor therapieën in DMD



Ontsteking verminderen

ANTI-INFLAMMATORY THERAPY				
Mechanism	**Company**	**Drug**	**Status**	
Corticosteroid **standard of care**	PTC Therapeutics	Emflaza	Approved	
Non-hormonal steroid **submitted FDA/EMA**	Reveragen	Vamorolone	Clinical	■
NHE-1 Inhibitor	EspeRare	Rimeporide	Clinical	
CD49d expression inhibitor	Antisense Therapeutics	ATL1102	Clinical	
Estrogen receptor inhibitor	University Hospital in Basel	Tamoxifen	Clinical	
Anti-IL1beta antibody	Children's Research Institute	Ilaris	Clinical	
Nitric oxide donator Ca+ modulator	Myotherix	MRX-1043	Preclinical	■
Steroid alternative	Mallinckrodt	Cosyntropin	Discontinued*	
Non-steroid anti-inflammatory	Catabasis	Edasalonexent	Discontinued*	

Ontsteking in DMD

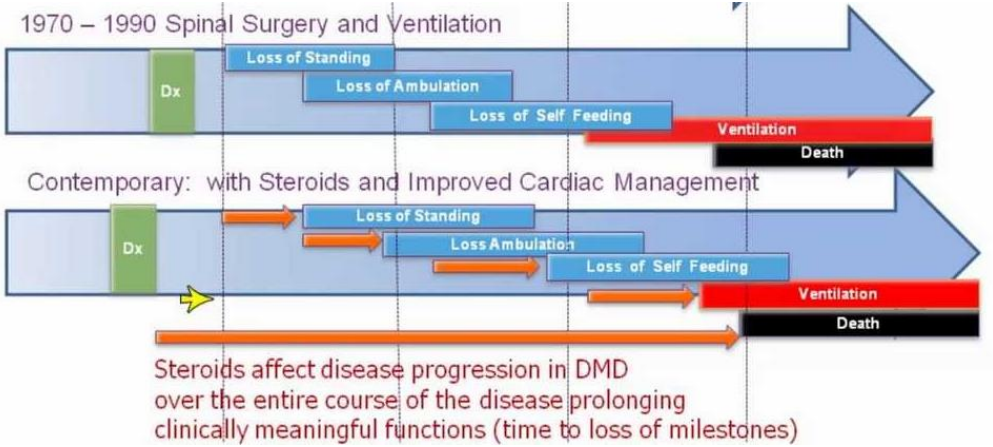


Tulangekar et al. *Biomed* 2021

Deflazacort/Prednisone

standard of care: consistent gedemonstreerd effect

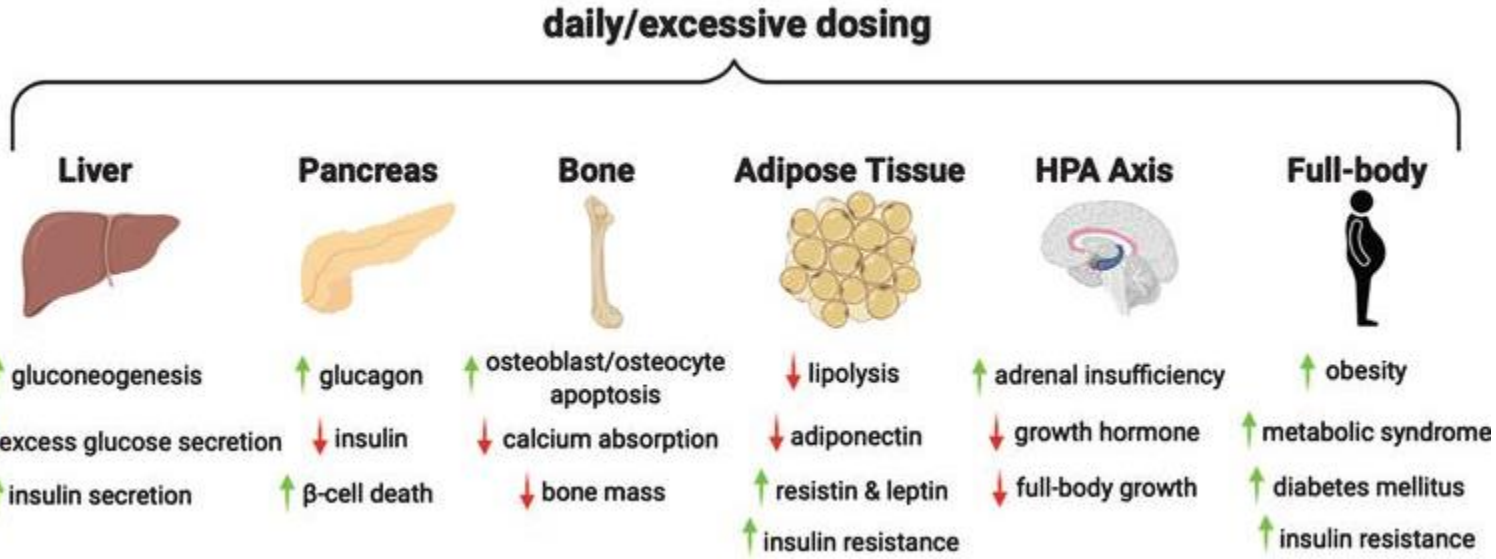
- langer bewaren spierkracht en motorische functie
- uitstel verlies van ambulantie
- langer bewaren longfunctie
- vermijden/uitstellen scoliose chirurgie
- verbeterde overleving



Lynn et al. *Neuromusc Dis* 2015

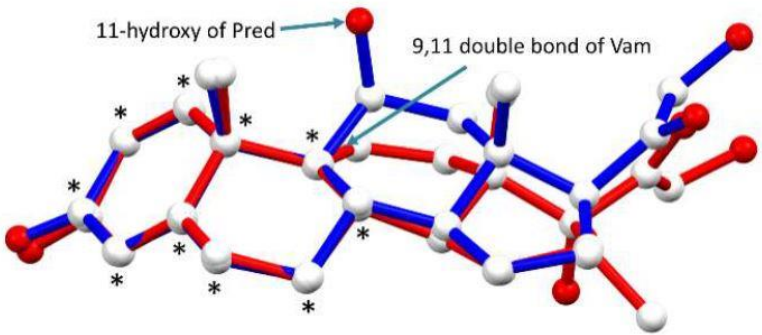
SIDE EFFECTS

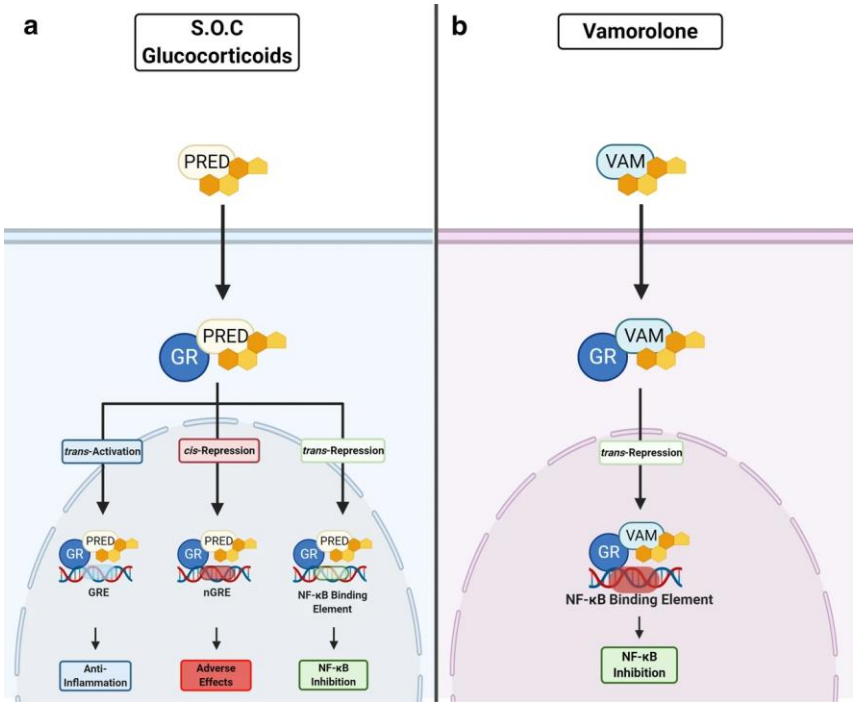
Corticosteroïden in DMD



Quattrocelli et al. *J Neuromusc Dis* 2021

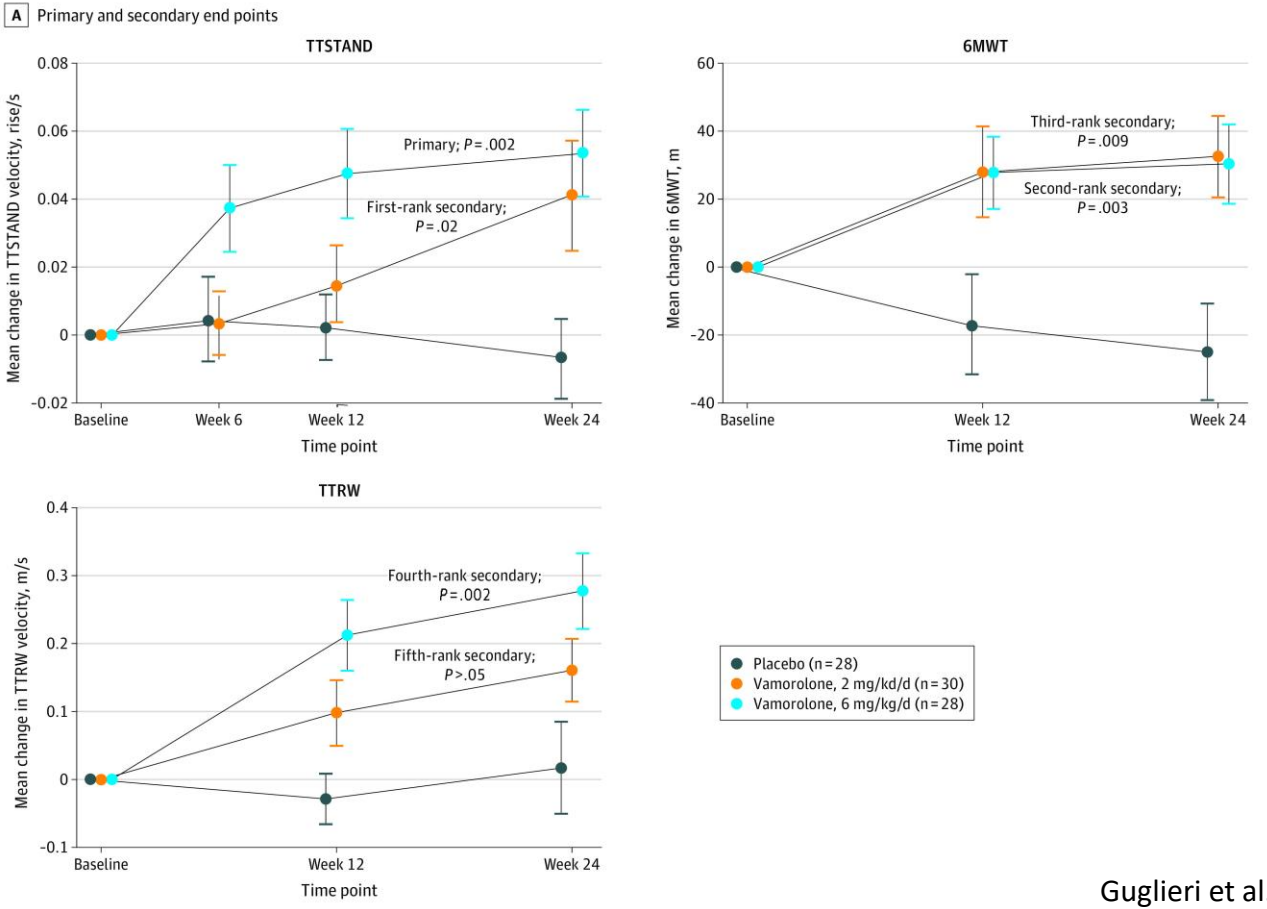
Vamorolone (Reveragen)





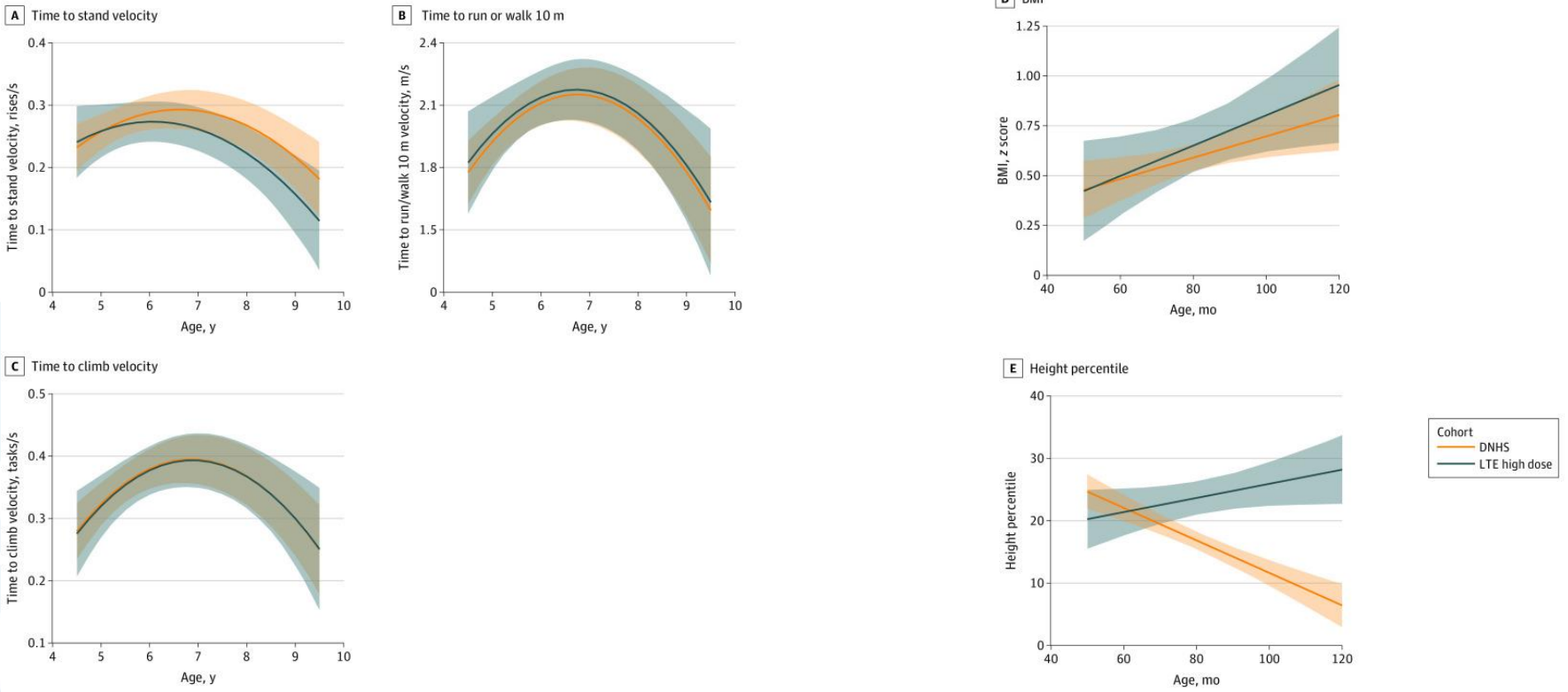
Kourakis et al. *Orphanet J Rare Dis* 2021

Vamorolone (Reveragen)



Guglieri et al. *JAMA Neurology* 2022

Vamorolone (Reveragen)



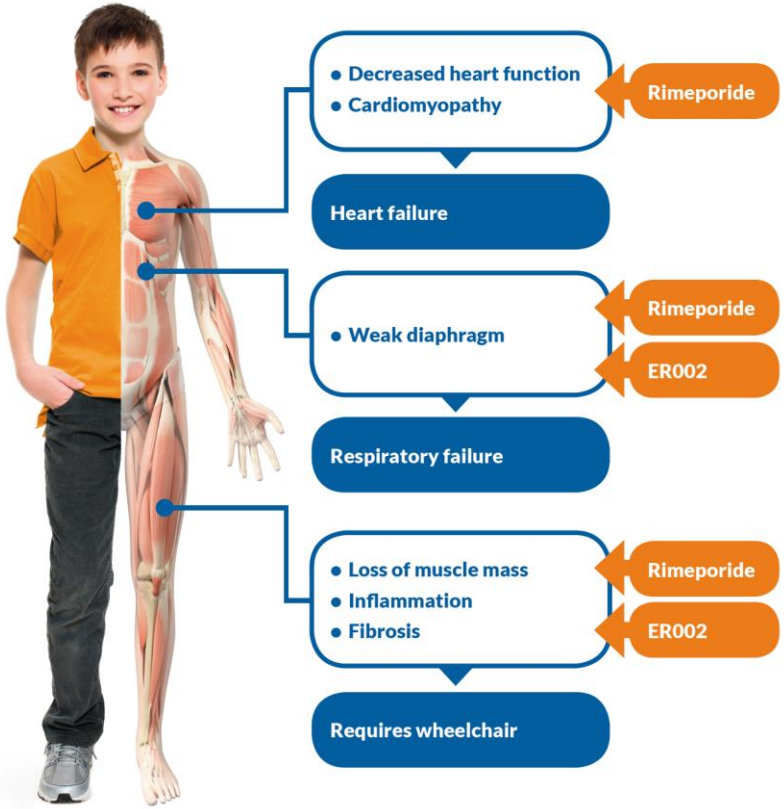
Mah et al. *JAMA Netw Open* 2022

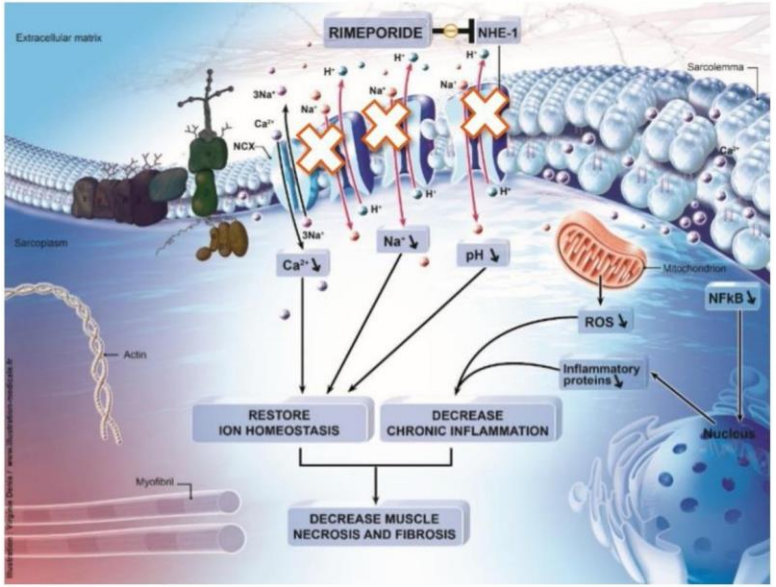
Vamorolone (Reveragen)

- vergelijkbare werkzaamheid als predisone
- minder nevenwerkingen
  - ✓ betere lengtegroei
  - ✓ botmetabolisme
  - ✓ minder effect op gedrag

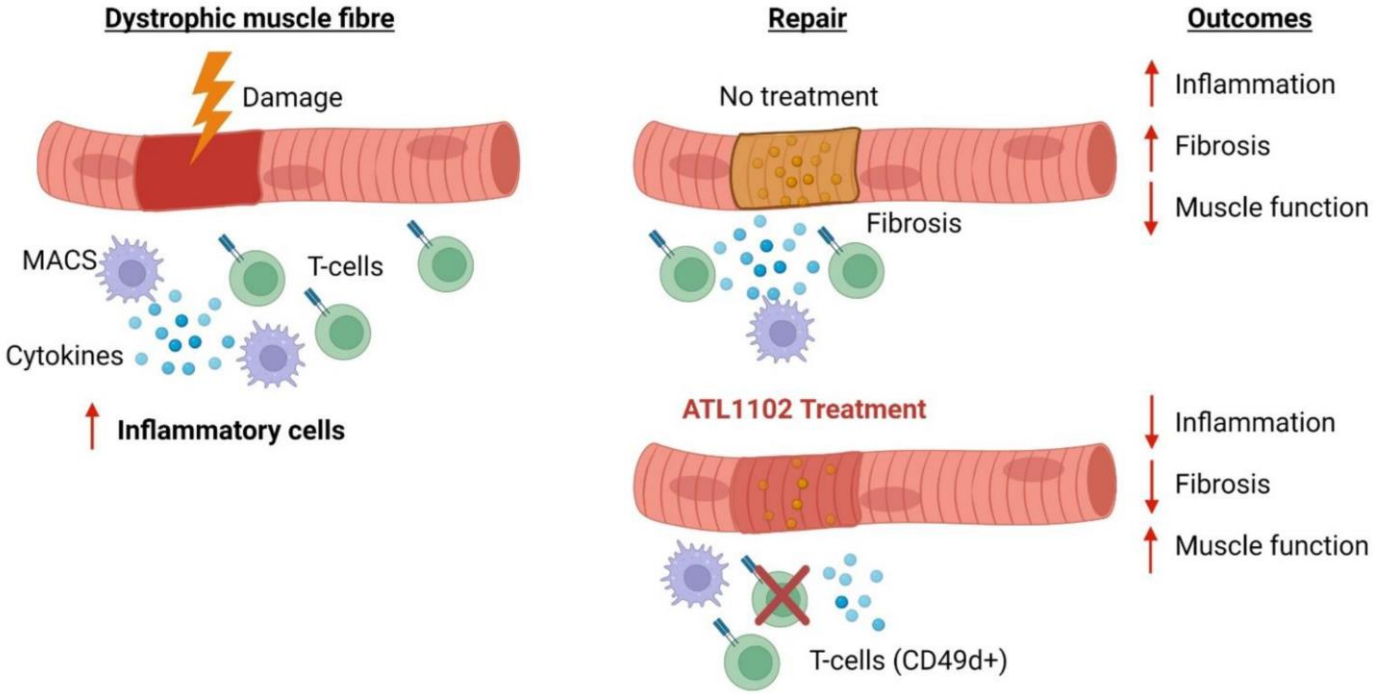
- in review bij FDA en EMA
- mogelijks op de markt eind 2024

Rimeporide (EspeRare Foundation)



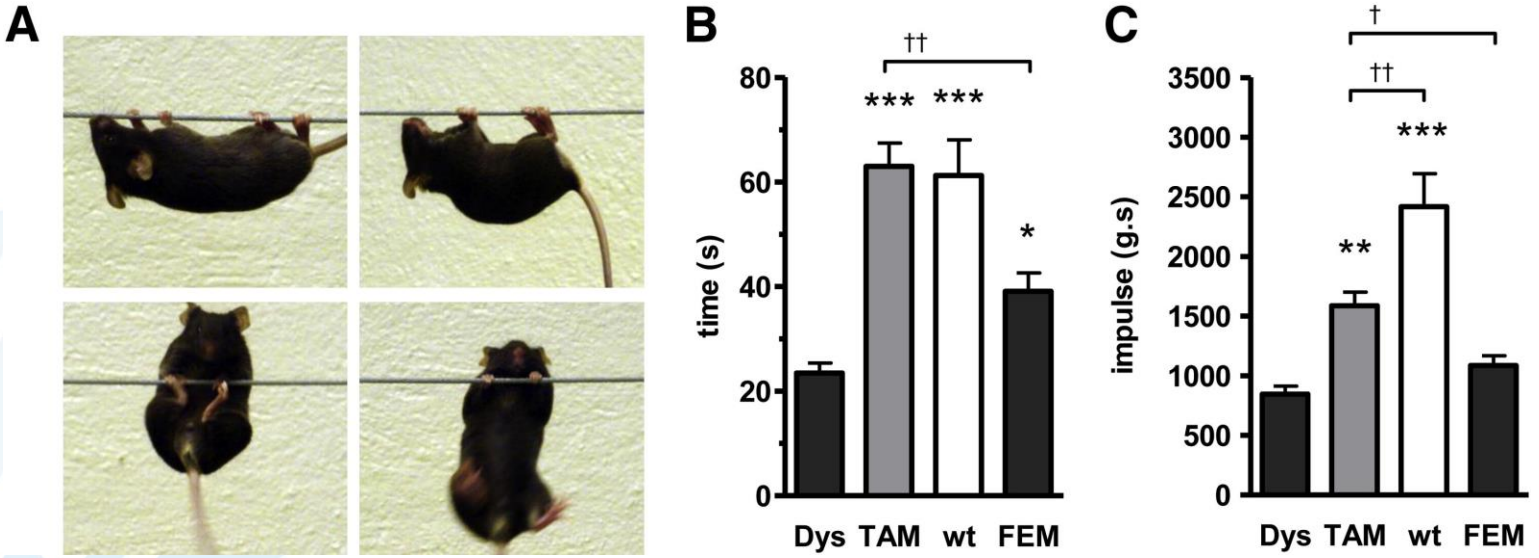


ATL1102 (Antisense Therapeutics)



Coles et al. *Biomedicines* 2022

Tamoxifen (University Hospital Basel)

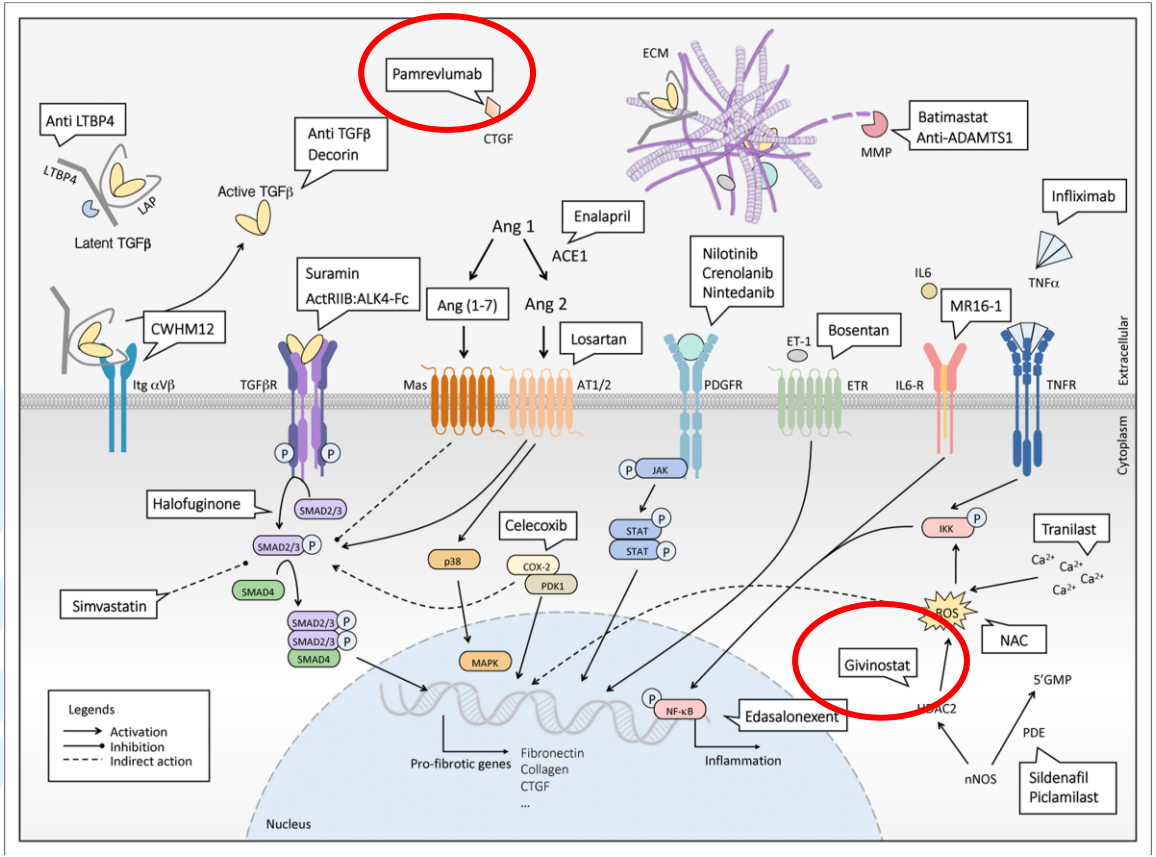


Dorchies et al. *Am J Pathol* 2013

Fibrose tegengaan

ANTI-FIBROSIS THERAPY				
Mechanism	**Company**	**Drug**	**Status**	
Anti-CTGF antibody	FibroGen	Pamrevlumab	Clinical	
HDAC inhibitor	Italfarmaco	Givinostat	Clinical	
Renin-Angiotensin System Agonists	BioPhytis	BIO101	Preclinical	■
Anti-fibrotic	Akashi	HT100	Discontinued*	■

Fibrose in DMD



Muraine et al. *Cur Opin Pharm* 2023

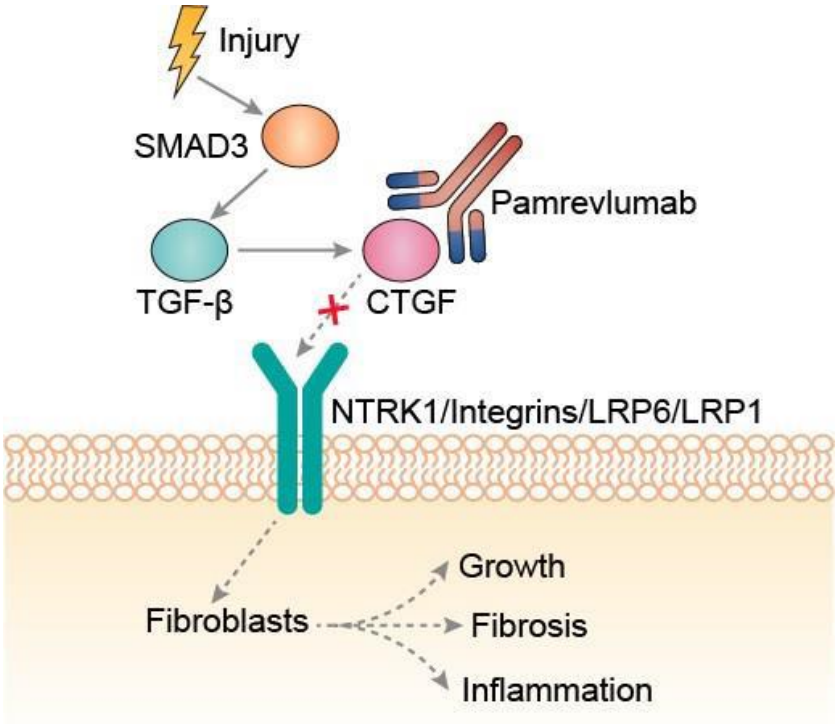
Pamrevlumab (Fibrogen)

- humane recombinante monoclonale antistof tegen CTGF
- fibrose tegengaan

- IV 1 x/2 weken

- goed veiligheidsprofiel

- primaire eindpunt **niet** behaald in LELANTOS en LELANTOS TWO



Givinostat (Italfarmaco)

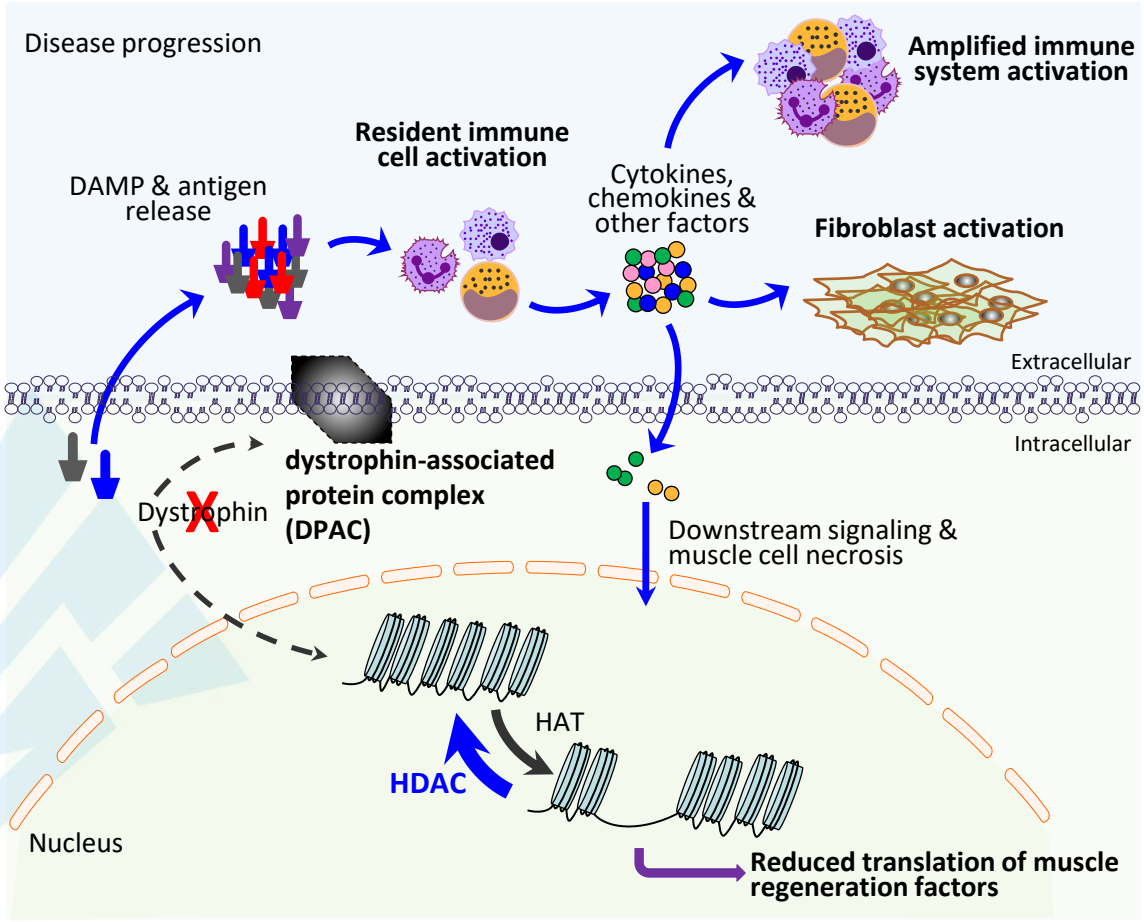
- HDAC inhibitor: verhogen expressie factoren spierherstel
- 3-voudige werking
  - ✓ ontsteking verminderen
  - ✓ fibrose tegengaan
  - ✓ spierherstel

- orale oplossing

- goed veiligheidsprofiel, wel diarree, braken, thrombocytopenie, koorts, hypertriglyceridemie, arthralgia beschreven

- primaire eindpunt werd bereikt in studie met ambulante patiënten (EPIDYS)

ROLE OF HDAC IN THE PATHOGENESIS OF DMD

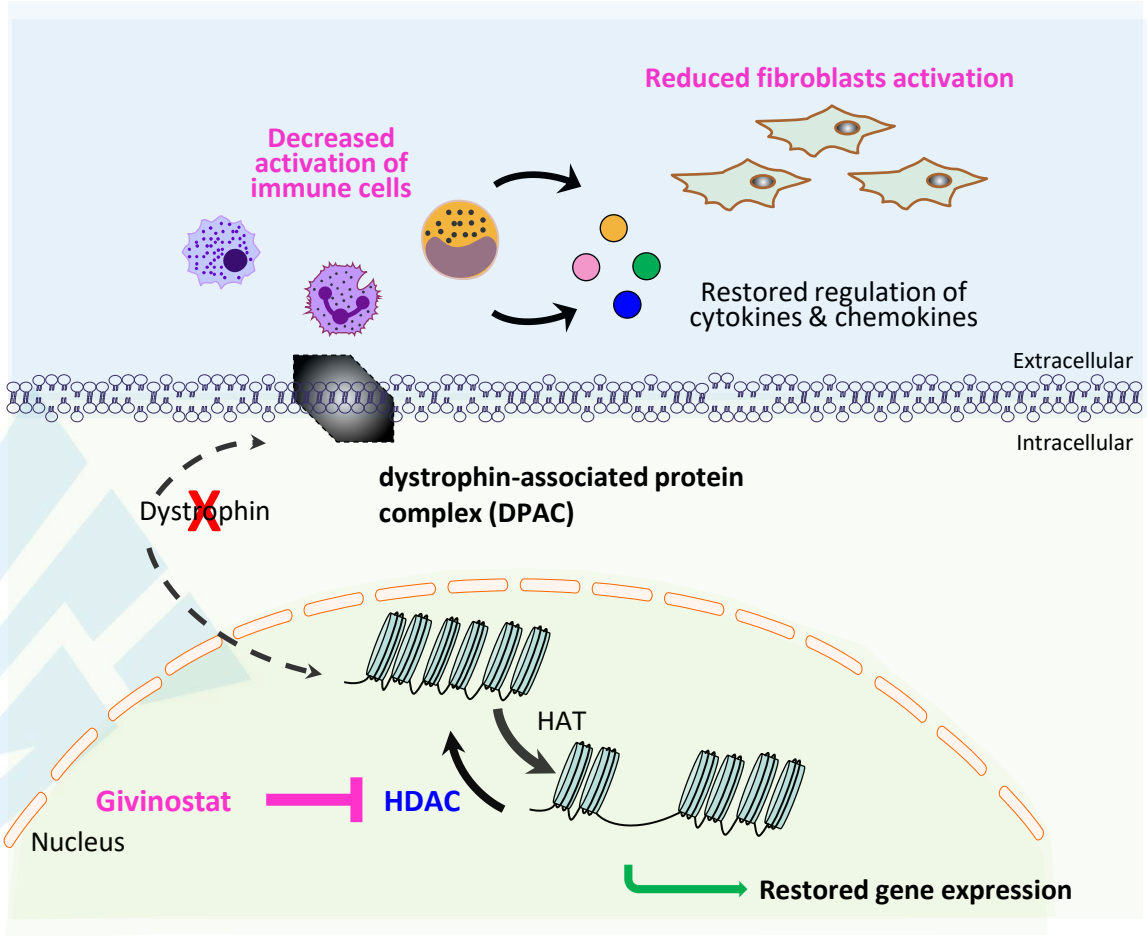


MODE OF ACTION

Data presented at 7th International Myology Congress and mitoNice 12-17 September 2022

GIVINOSTAT MECHANISM OF ACTION IN DMD PATIENTS

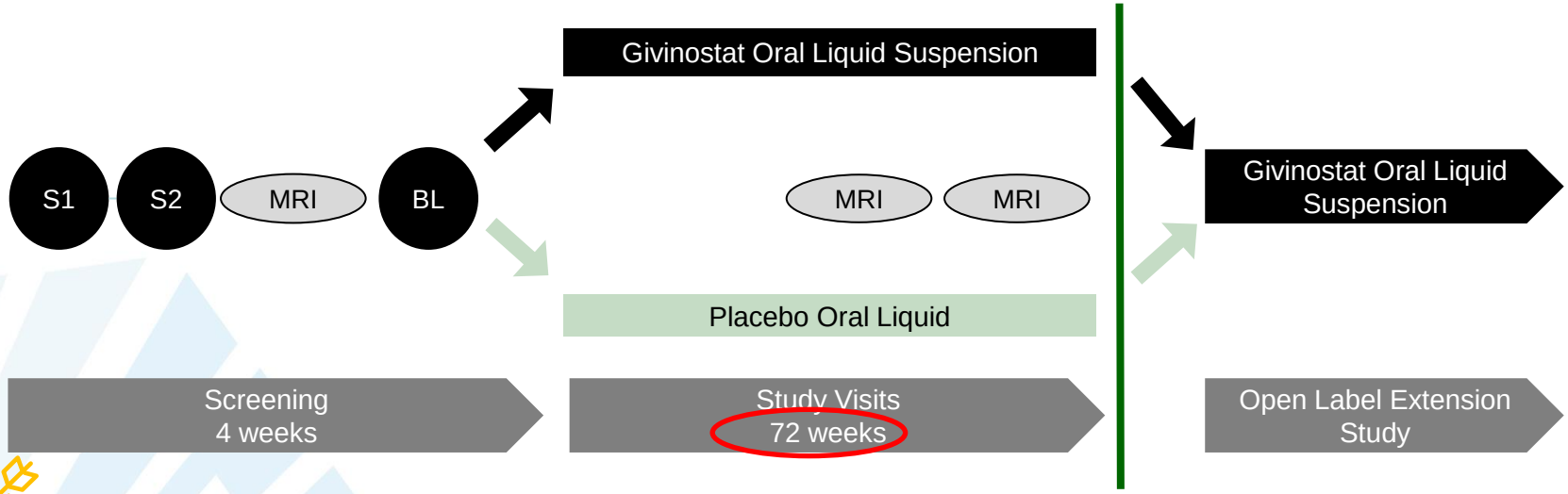
MODE OF ACTION



Data presented at 7th International Myology Congress and mitoNice 12-17 September 2022

Epidys - Phase 3 Study design

- Randomized, double blind, placebo-controlled study with 179 male ambulant subjects randomized 2:1 (Givinostat:placebo).



Primary Objective:
Givinostat preserves muscle mass and delays disease progression

Clinicaltrials.gov: NCT02851797

Epidys - Phase 3 Endpoints

- Endpoints were assessed before and after **18 months** of treatment of Givinostat versus placebo in target population

Primary Endpoint	✓ Mean change in 4 standard stairs climb (4SC) test
Secondary Endpoint	✓ Mean change in NSAA ✓ Cumulative loss of function on the NSAA ✓ Mean change in Time to Rise from Floor ✓ Mean change in 6MWT ✓ Mean change of muscle strength evaluated by knee extension; elbow flexion as measured by hand-held myometry (HHM) ✓ Mean change in fat fraction of vastus lateralis muscles using Magnetic Resonance Spectroscopy

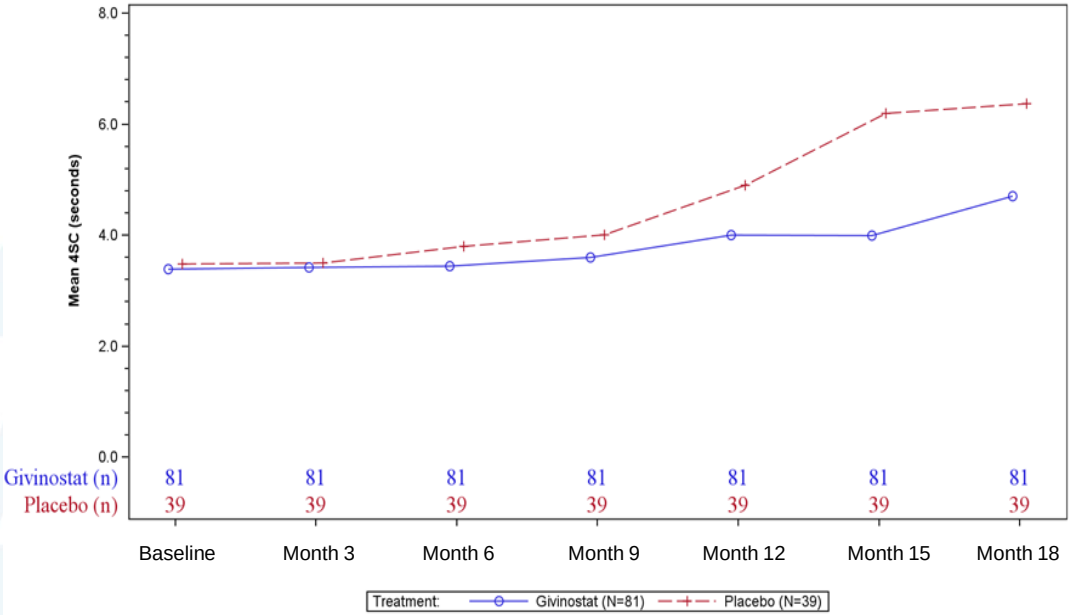
6MWT=6-minute walking test; MRS=magnetic resonance spectroscopy; NSAA=North Start Ambulatory Assessment; VL MFF=vastus lateralis muscle fat fraction

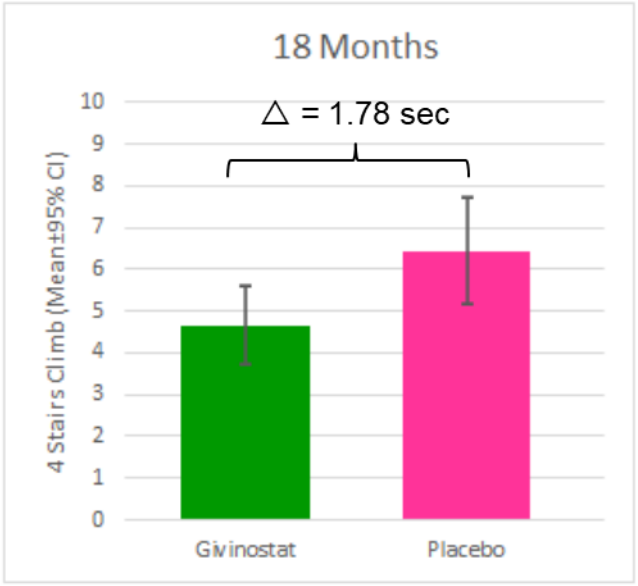
EPIDYS study; ClinicalTrials.gov identifier: NCT02851797

The EPIDYS study met its primary endpoint

Givinostat reduces by ≈40% the decline in time to climb 4 stairs (4SC, Primary Endpoint).

Results are statistically significant and clinically meaningful[1].



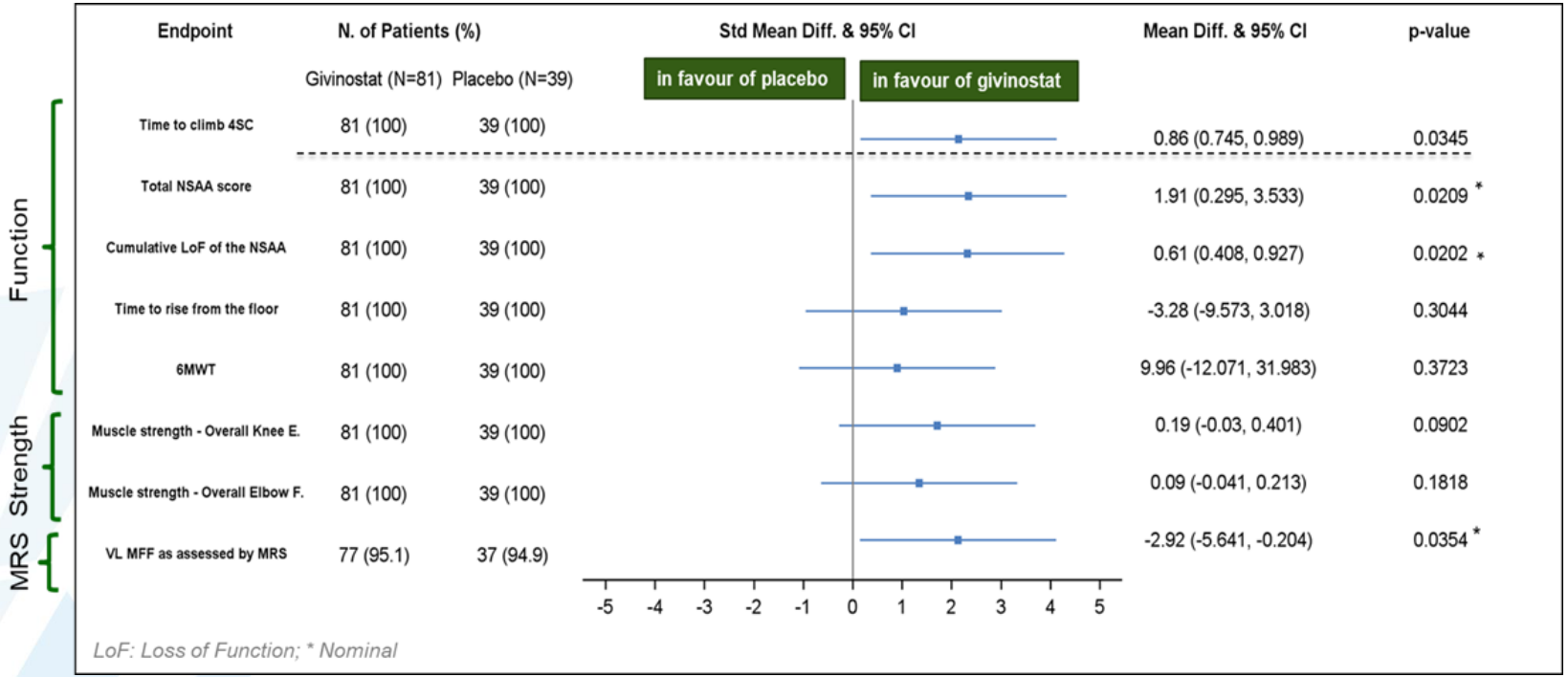


p-value = 0.0345

Compared to published literature: Bendixen et al. Disabil Rehabil 2014;36:1918-23; Duong et al. J Neuromuscul Dis. 2021;8(6):939-948

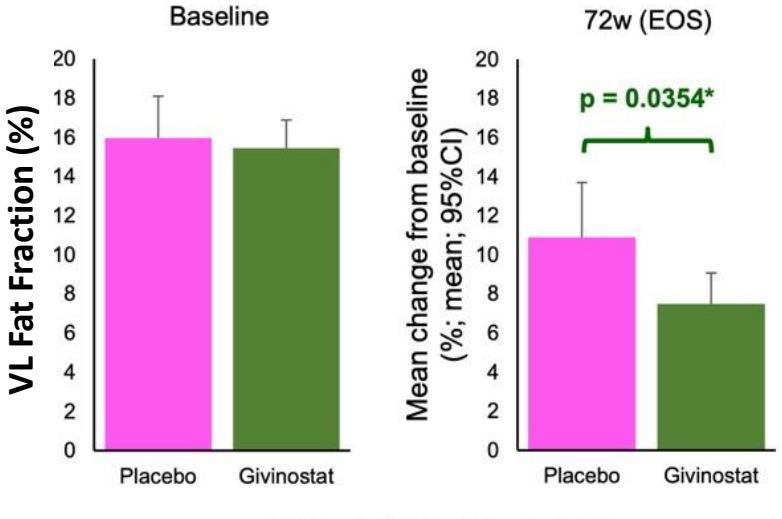
Data presented at 7th International Myology Congress and mitoNice 12-17 September 2022

Key secondary endpoints consistent with primary endpoint

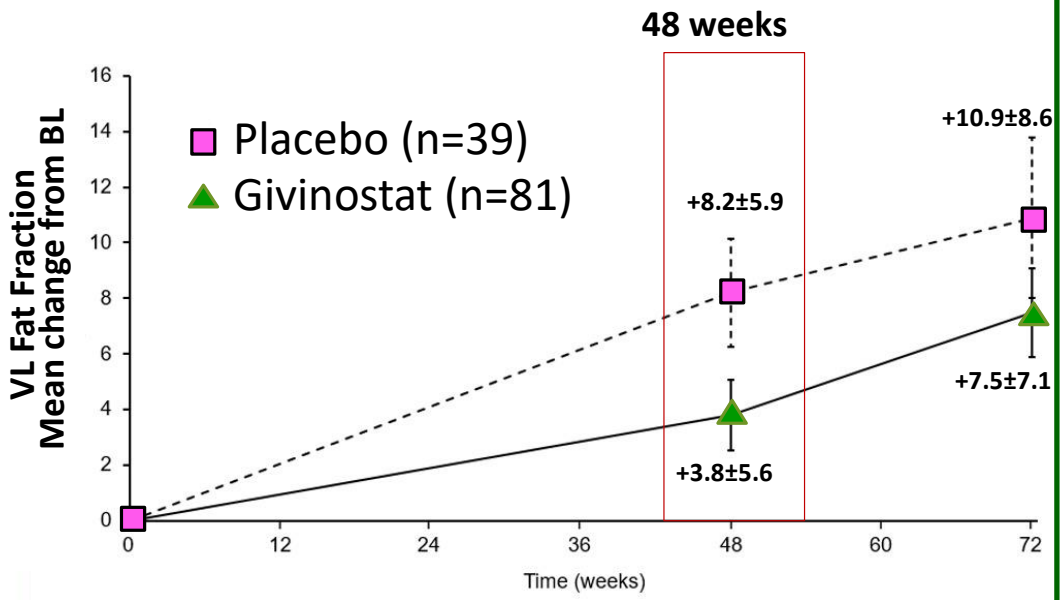


Givinostat consistently reduces muscle function and strength decline and fatty infiltration over time

Givinostat reduced by ≈30 % muscle fatty infiltration measured by MRI



n (Givinostat): 77; n (placebo): 37

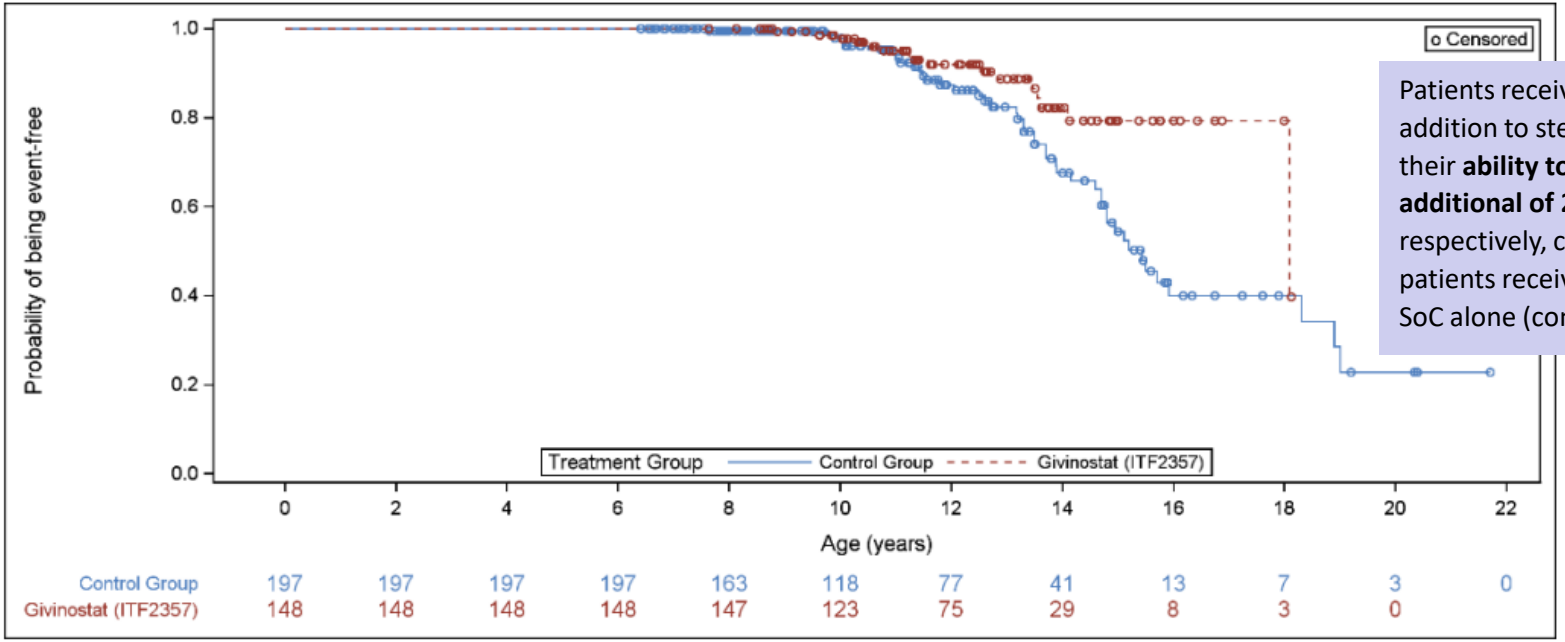


* Nominal

Presented at the 2023 MDA Clinical & Scientific Conference, Dallas, USA, 19-21 March 2023

GIIVINOSTAT IN DMD: Results of the EPIDYS Study with particular attention to MR measures of muscle fat fraction
KRISTA VANDENBORNE, PhD Director, ImagingNMD

Givinostat delays age at persistent loss of ambulation versus natural history matched patients



Patients receiving givinostat in addition to steroids preserved their **ability to walk** for an **additional of 2.7 years**, respectively, compared with patients receiving SoC alone (control group)

Givinostat in Duchenne Muscular Dystrophy: Effect on Disease Milestones

Craig McDonald1, M.D., Ph.D., Laurent Servais2, M.D., Francina Munell3, M.D., Ulrike Schara-Schmidt4, M.D., Enrico Bertini5, M.D., Giacomo Comi6, M.D., Astrid Blaschek7, M.D., Sara Cazzaniga8, M.Sc., Paolo Bettica8, M.D., Ph.D., Krista Vandenborne9 P.T., Ph.D., Eugenio Mercuri, M.D.10

Presented at the 2023 MDA Clinical & Scientific Conference, Dallas, USA, 19-21 March 2023

Groei en bescherming van spier verbeteren

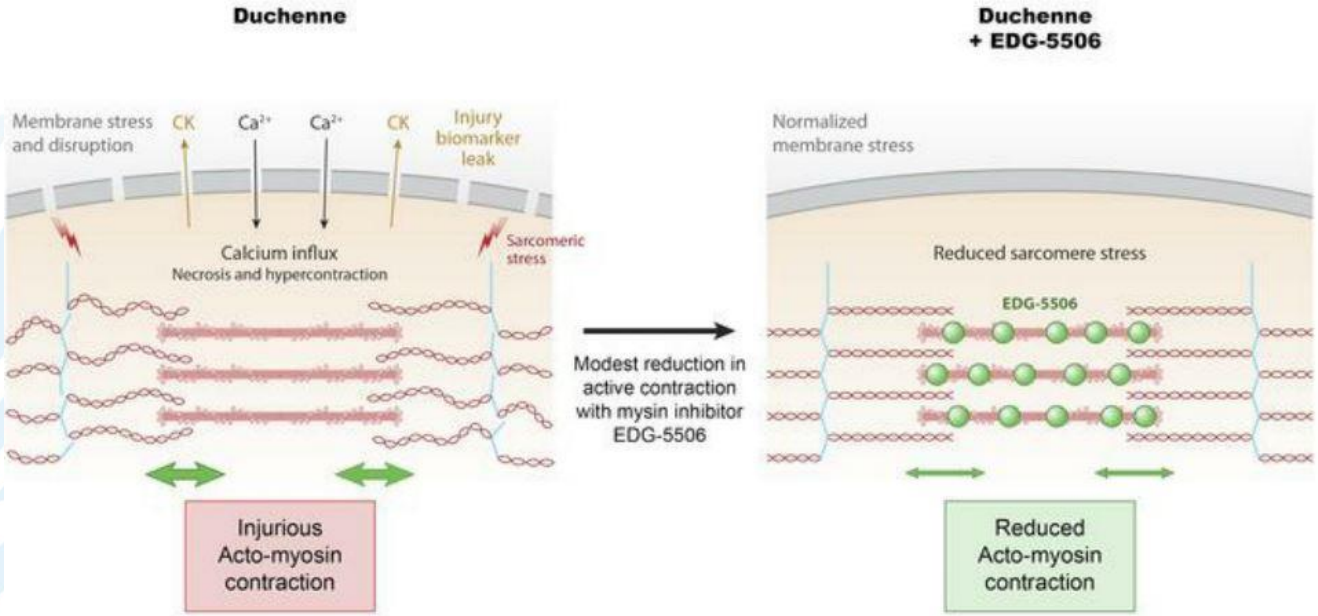
MUSCLE REGENERATION				
Mechanism	**Company**	**Drug**	**Status**	
Follistatin gene therapy	Milo Biotechnology	rAAV1-Follistatin	Discontinued*	
Myostatin Antibody	Roche	RO7239361	Discontinued*	
Myostatin Antibody	Pfizer	PF-06252616	Discontinued*	

No treatment effect

MUSCLE STABILIZATION				
Mechanism	**Company**	**Drug**	**Status**	
Muscle Stabilizer	Edgewise Therapeutics	EDG-5506	Clinical	

EDG-5506 (Edgewise Therapeutics)

- inhibeert fast myosin isovormen – sterkere binding tussen actine en myosine
- oraal small molecule



Rusell et al. *J Clin Invest* 2023

Te onthouden…

- ontsteking en fibrose spelen een belangrijke rol in het ziektemechanisme bij DMD
- corticosteroïden verminderen ontsteking en remmen ziekteprogressie af, vamorolone met een beter nevenwerkingenprofiel
- Givinostat mogelijks 1ste niet-genetische therapie voor DMD
- combinatie van genetische en ‘symptomatische’ therapieën in de toekomst?

NMRC Kinderen
UZ Leuven

Kinderneurologen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Benedicte Eyskens


Bjorn Cools

Paediatric pulmonologists


Mieke Boon


Marijke Proesmans

Dank u wel!