Gene therapy for Duchenne Muscular Dystrophy

Prof. Dr. Nicolas Deconinck

H.U.B
HÔPITAL UNIVERSITAIRE DE BRUXELLES
ACADEMISCH ZIEKENHUIS BRUSSEL

INSTITUT JULES BORDET INSTITUUT
Hôpital Erasme | ULB
Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

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Overview

- Some words about « Gene Therapy »
- Current status of gene therapy trials in the World / Belgium
- What to conclude at this stage?

AAV Vectors are Versatile Gene Therapy Vehicles

AAV vectors have well-characterized clinical efficacy and safety profiles[1]

Transduction

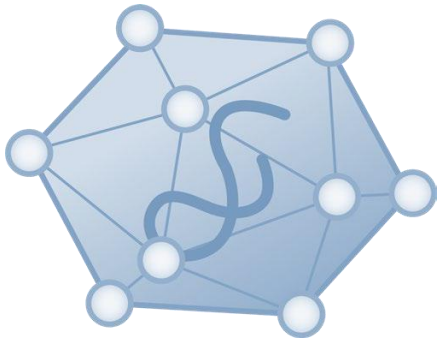
AAVs can be engineered for selective cell targeting and optimized transduction[1,2]

AAVs cross the cell membrane and deliver genetic cargo to the nucleus[1]

Safety

In comparison to other viral vectors (eg, retrovirus, lentivirus), AAVs are generally regarded as non-pathogenic[3,4]

AAVs are less immunogenic than other viruses[1,2]



Tropism

AAVs target numerous cell/tissue types; ≥12 distinct serotypes display varying efficiencies in different cell types[5,6]

A few naturally occurring serotypes (eg, AAV9) efficiently cross the blood–brain barrier[7]

Versatility

AAV vectors are very stable; they are able to withstand wide temperature and pH changes with little to no loss in activity[1]

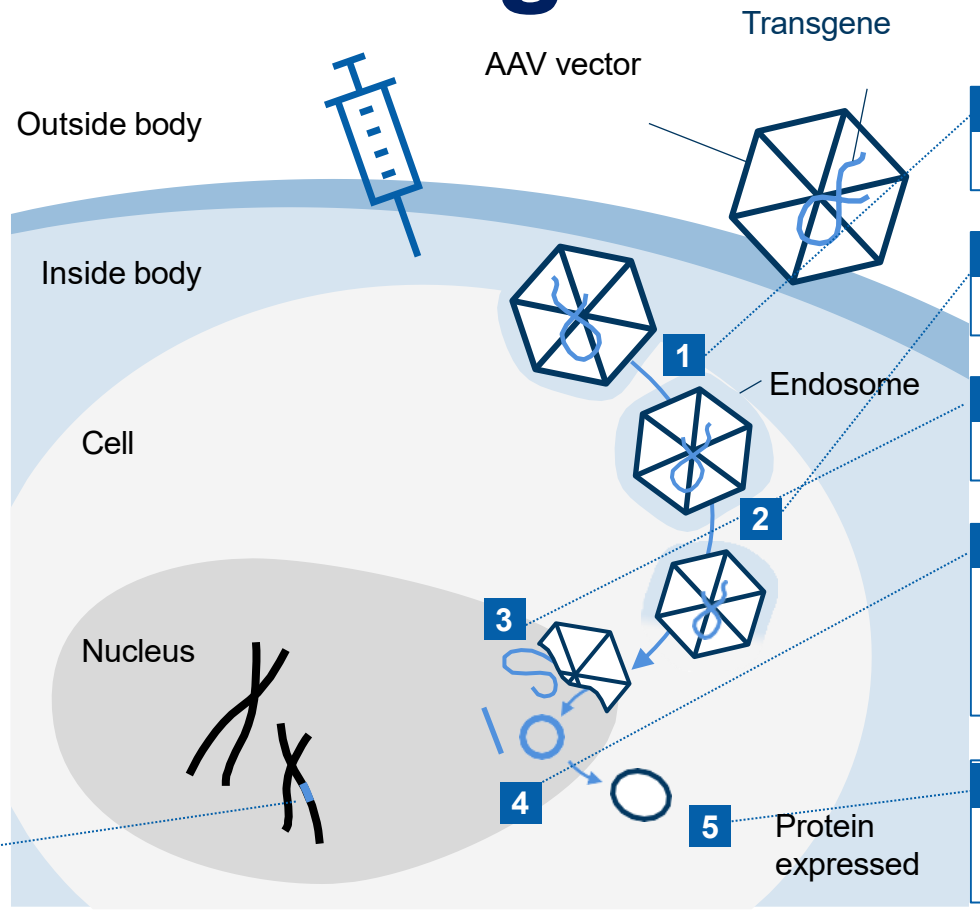
This robust stability allows for different administration routes and specialized delivery strategies[1]

AAV, adeno-associated virus; AAV9, adeno-associated virus serotype 9.

1. Naso MF et al. *BioDrugs*. 2017;31(4):317-334. **2.** Thomas CE et al. *Nat Rev Genet*. 2003;4(5):346-358. **3.** FDA. Briefing Document: Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT). 2021. A14, 2025. https://www.nxgenvectorsolutions.com/wp-content/uploads/2024/01/FDA_CTGTAC-09.02.21-09.03.21-Meeting-Briefing-Document-FDA.pdf **4.** Sabatino DE et al. *Mol Ther*. 2022;30(8):2646-2663. **5.** Ai J et al. *Sci Rep*. 2017;7:40336. **6.** Vance MA et al. AAV Biology, Infectivity.

AAV Vectors are Designed to Deliver Transgenes to Target Cells[1]

Episomal and Integrated DNA Delivery With AAV Vectors[2]



1. AAV vector enters cell via an endosome[2]
2. Endosome breaks down, allowing vector to bind to cell nucleus[2]
3. Vector enters the cell nucleus[2]
4. Vector DNA persists as a linear or circular episome (genetic material existing outside host genome)[2,3]
   - Random integration into host DNA has been observed[4-6]
5. Upon promoter activation, transcription occurs. Resulting transcript leaves the nucleus and is translated at ribosome (protein synthesis)[3]

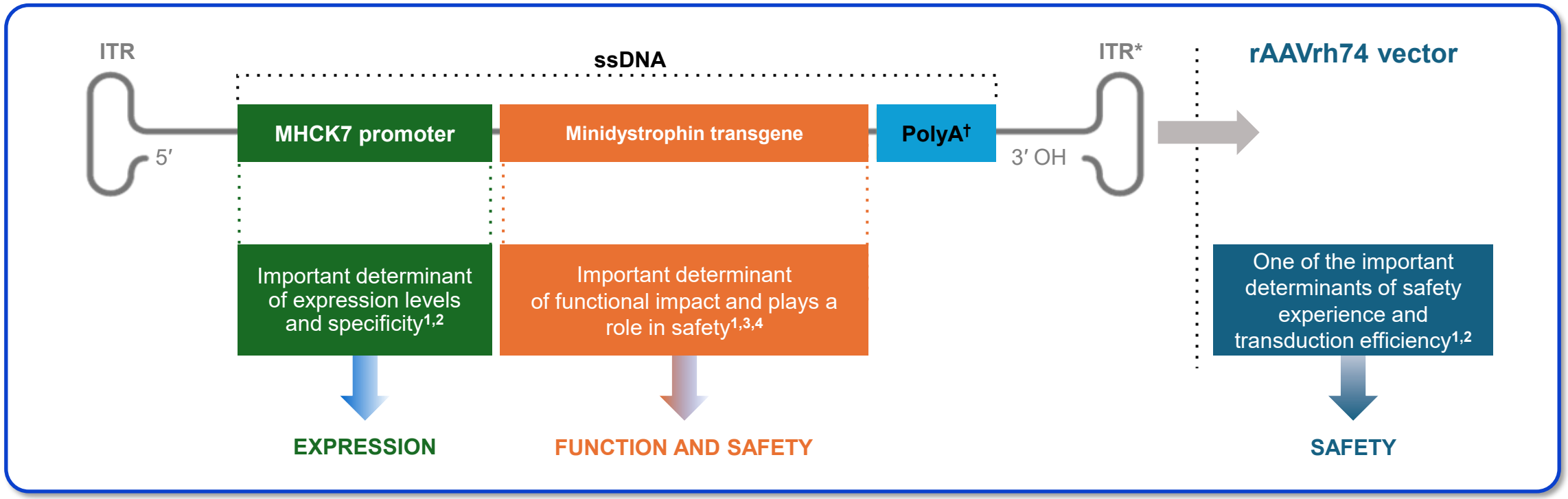
Modified from Colella et al., *Mol Ther Methods Clin Dev*. 2017;1:8:87-104[7]

MOA data is based on in vitro/in vivo data.

AAV, adeno-associated virus; MOA, mechanism of action.

1. Naso MF et al. *BioDrugs*. 2017;31(4):317-334. **2.** Akst J. Targeting DNA. The Scientist. Accessed February 14, 2025. https://www.the-scientist.com/features/targeting-dna-40937 **3.** Nakai H et al. *Mol Ther*. 2003;7(1):112-121. **4.** Sabatino DE et al. *Mol Ther*. 2022;30(8):2646-2663. **5.** Roctavian. Summary of product characteristics. BioMarin International Ltd. **6.** Hemgenix. Prescribing information. CSL Behring LLC. **7.** Colella P et al. *Mol Ther Methods Clin Dev*. 2017;1:8:87-104.

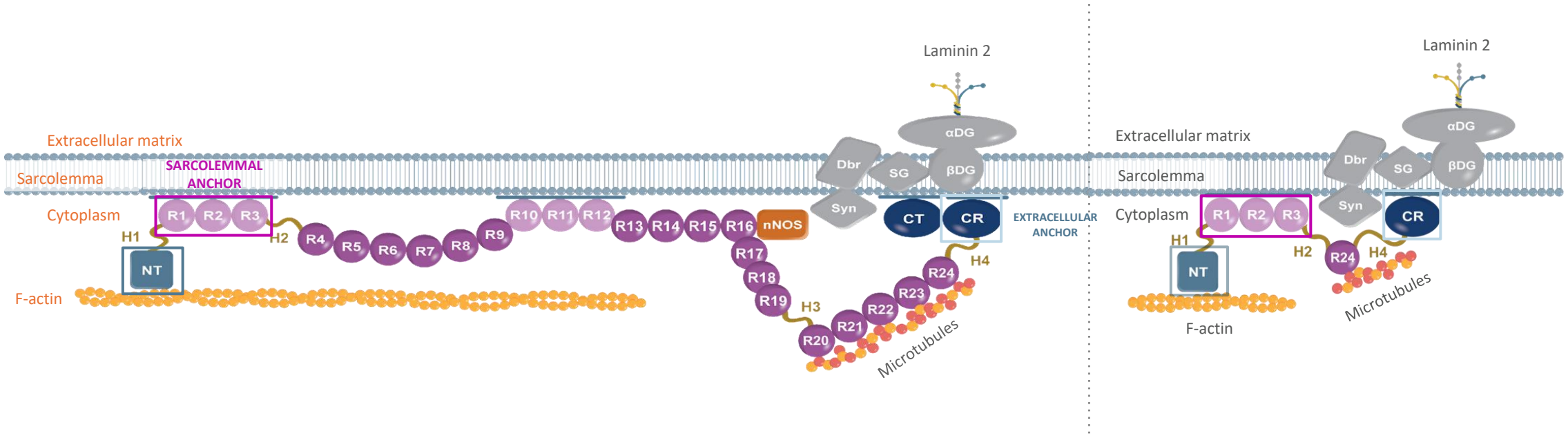
Essential components of DNA inside of modified AAV vectors



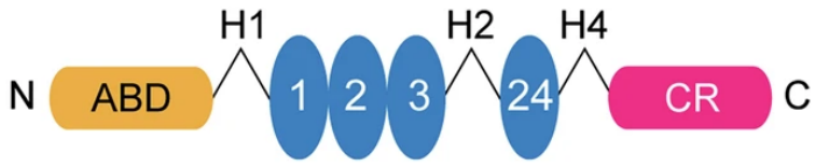
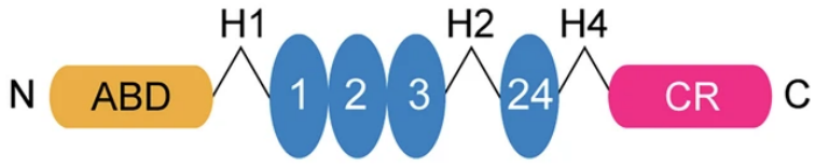
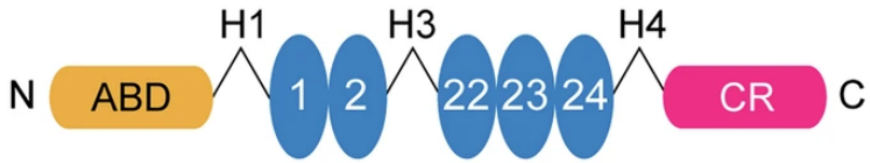
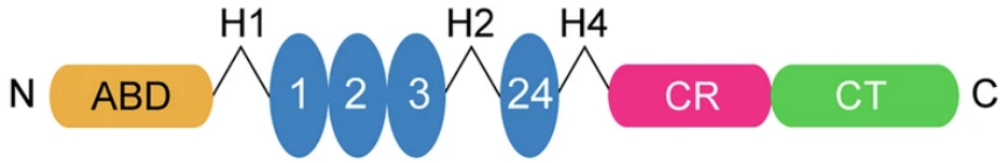
The micro-dystrophin transgene replicates key elements of wild-type dystrophin

Healthy muscle[1-7]

Delandistrogene moxeparvovec micro-dystrophin[1-7]

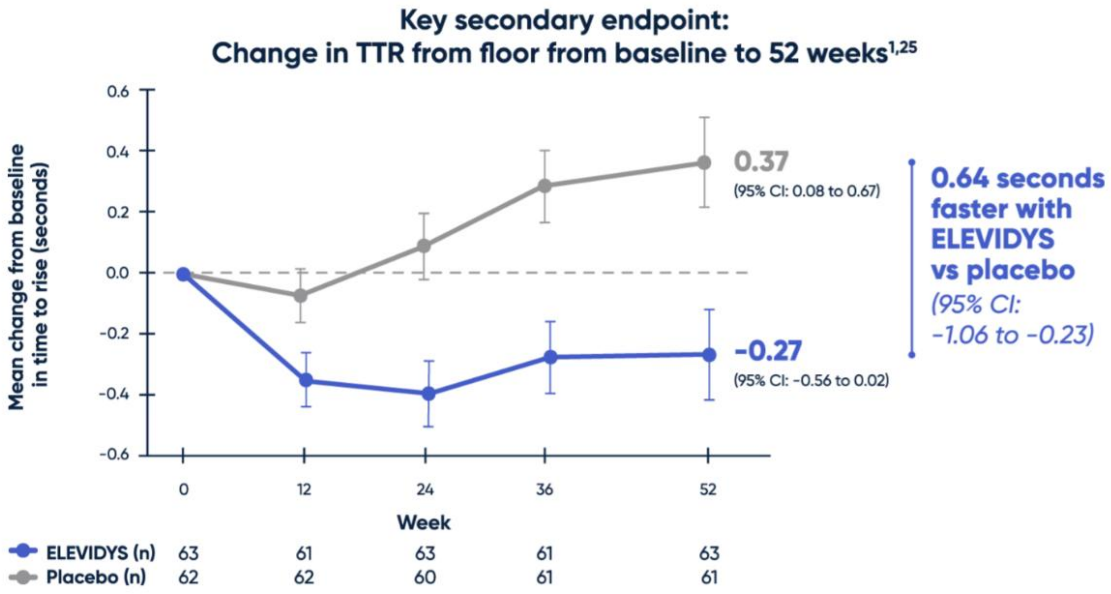


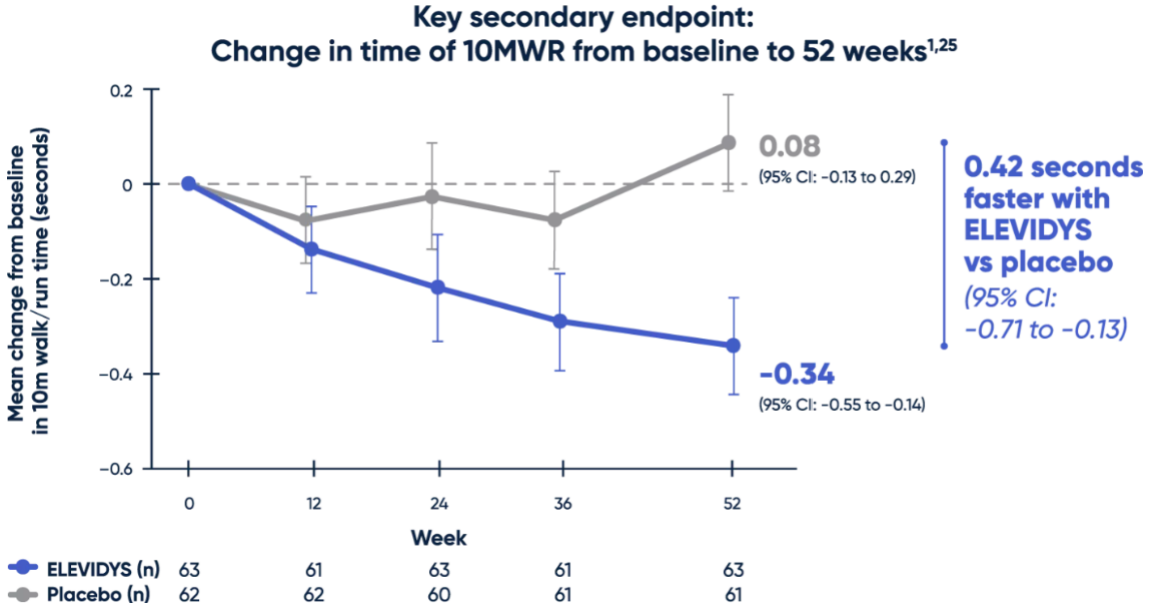
Fairclough RJ. *Nat Rev Genet* 2013;14:373–8;
5. Aartsma-Rus A. *Muscle Nerve* 2006;34:135–44; 6. Zhao J. *Hum Mol Genet* 2016;25:3647–53; 7. Asher DR. *Expert Opin Biol Ther* 2020;20:263–74.

Name	Microdystrophin transgene structure	AAV serotype	Promoter	Notes
Elevidys Delandistrogene moxeparvovec SRP-9001 (Sarepta Tx)		AAVrh74	MHCK7	Approved by US FDA, 2024
GNT0004 (Genethon/Sarepta Tx)		AAV8	Spc5-12	
PF-06939926 Fordadistrogene movaparvovec (Pfizer)		AAV9	MSP	Discontinued
SGT-001 (Solid Biosciences)		AAV9	CK8	Deprioritzed: focusing on SGT-003
RGX-202 (REGENXBIO)		AAV8	Spc5-12	

Elevidys

SAREPTA THERAPEUTICS

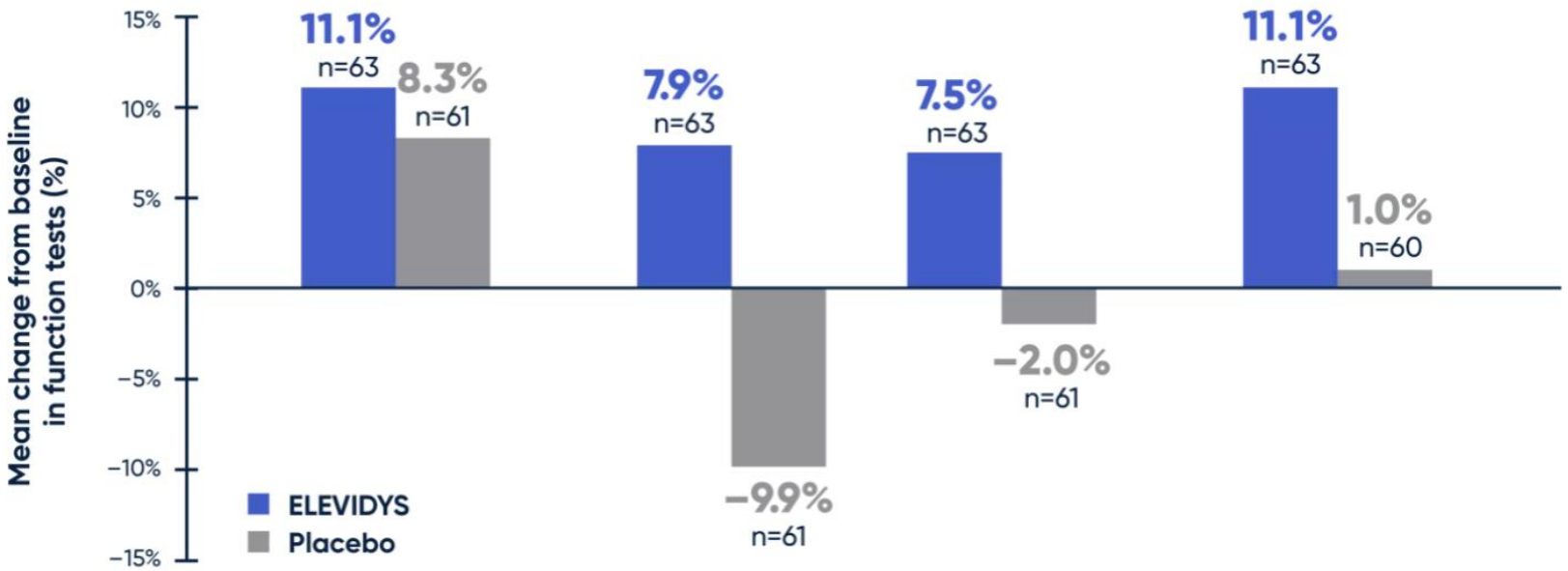




Elevidys

SAREPTA THERAPEUTICS

Change in function tests from baseline to 52 weeks[1,2,25]



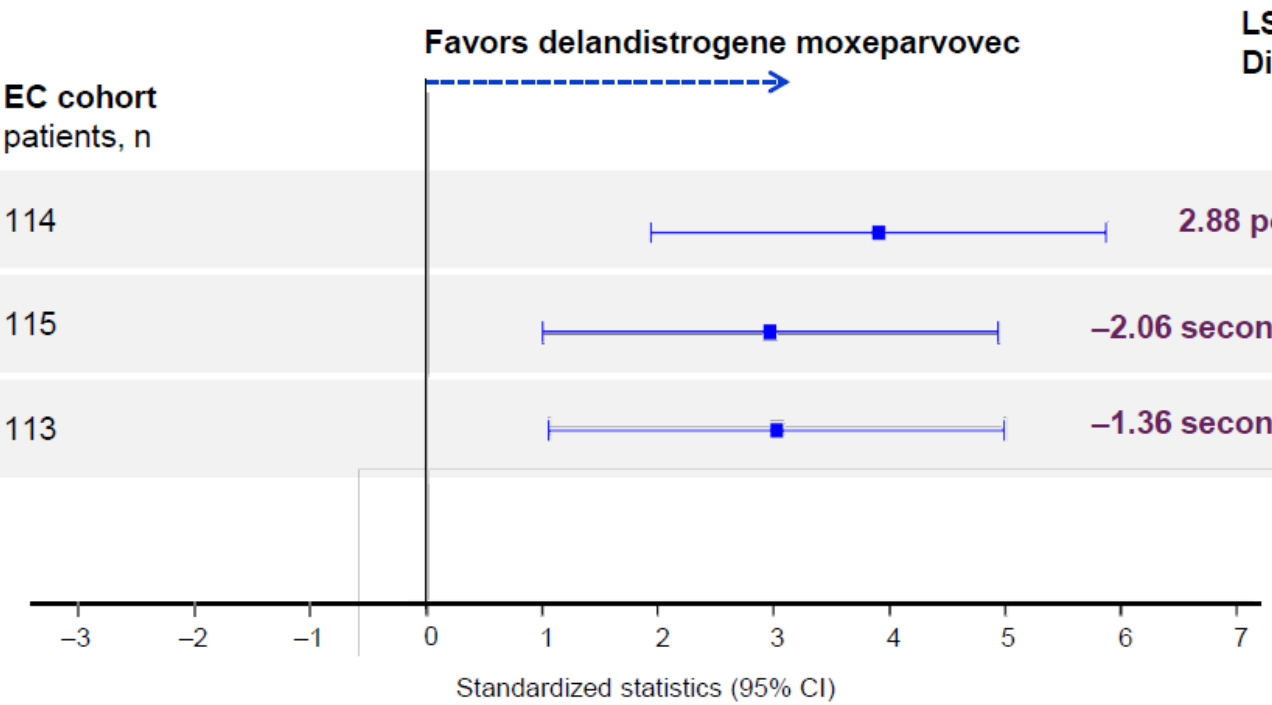
	PRIMARY ENDPOINT	KEY SECONDARY ENDPOINTS		OTHER TIMED SECONDARY ENDPOINT
Least squares mean difference from placebo	NSAA 0.7	TTR from floor −0.64*	Time of 10MWR −0.42*	Time to ascend 4 steps −0.36*
	(95% CI: -0.5 to 1.7; *P*=0.2441)	(95% CI: -1.06 to -0.23)	(95% CI: -0.71 to -0.13)	(95% CI: -0.71 to -0.01)

Positive percentage on graph indicates functional improvement, while negative percentage indicates functional decline.

EMBARK Part 1: Functional outcomes at 2 years

At 2 years, Part 1-treated patients demonstrated **statistically significant and clinically meaningful functional benefit** versus a propensity-score-weighted EC cohort

		Delandistrogene moxeparvovec patients, n	EC cohort patients, n	LSM change Diff (95% CI)	*P*-value
Primary endpoint	NSAA	63	114	**2.88 points** (1.43 to 4.33)	0.0001
Key secondary endpoints	TTR	63	115	**–2.06 seconds** (–3.43 to –0.70)	0.0033
	10MWR	63	113	**–1.36 seconds** (–2.24 to –0.47)	0.0028



LSMs (of change from baseline) and CIs were standardized by dividing by the SE. Negative values for timed function tests (TTR and 10MWR) show an improvement in the time taken to achieve these endpoints. LSMs difference are on original scale (without SE adjustment). Signs of timed function tests were reversed in the forest plot to align favorable directions among endpoints. Numerical results of LSM difference kept the original signs. All *P*-values reported are nominal and have not been adjusted for multiple comparisons.

10MWR, 10-meter Walk/Run; CI, confidence interval; Diff, difference; EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error; TTR, Time to Rise.

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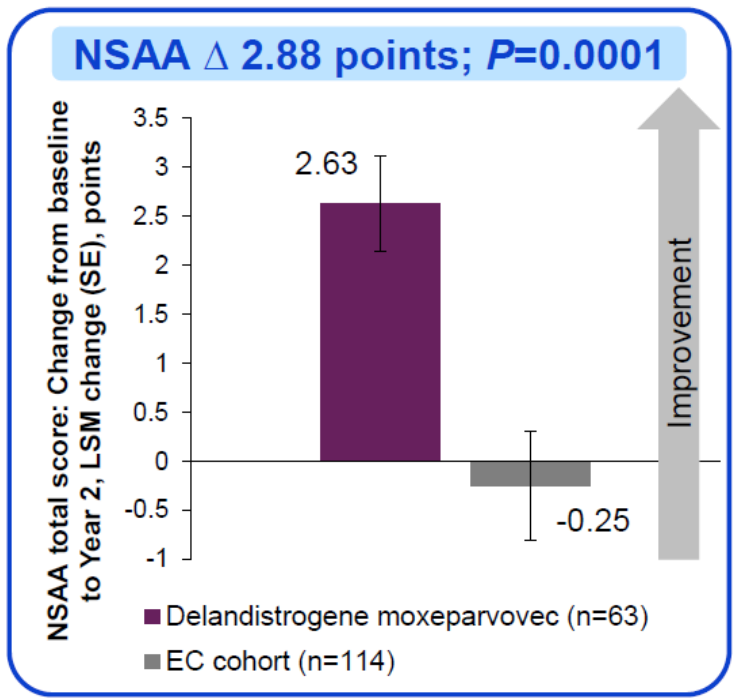

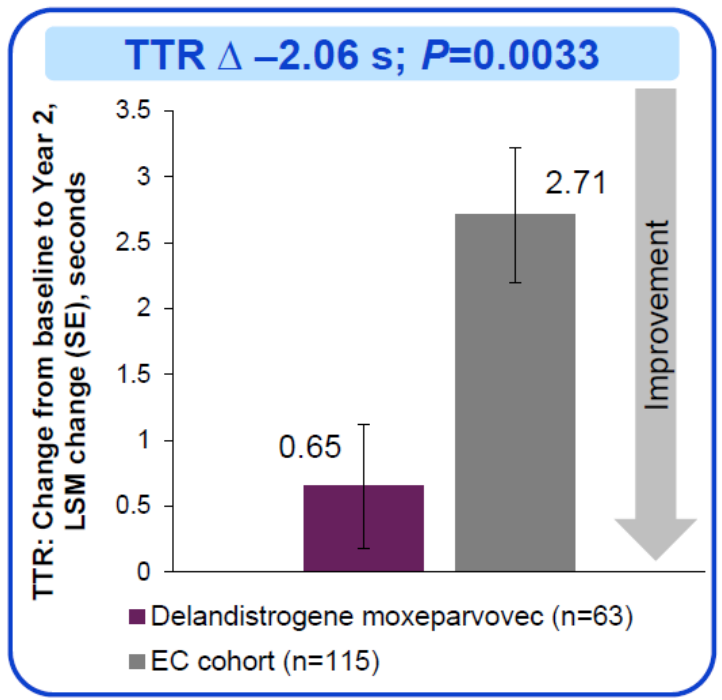

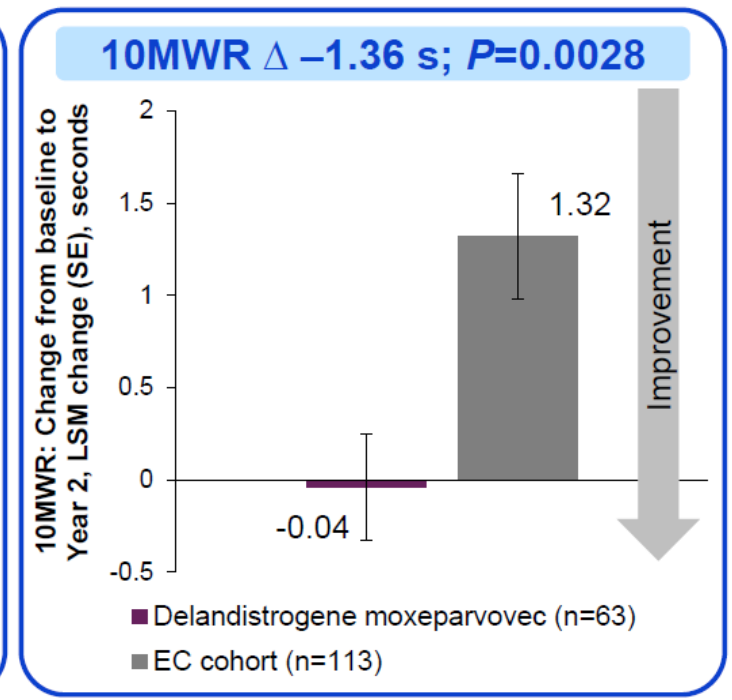

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Elevidys

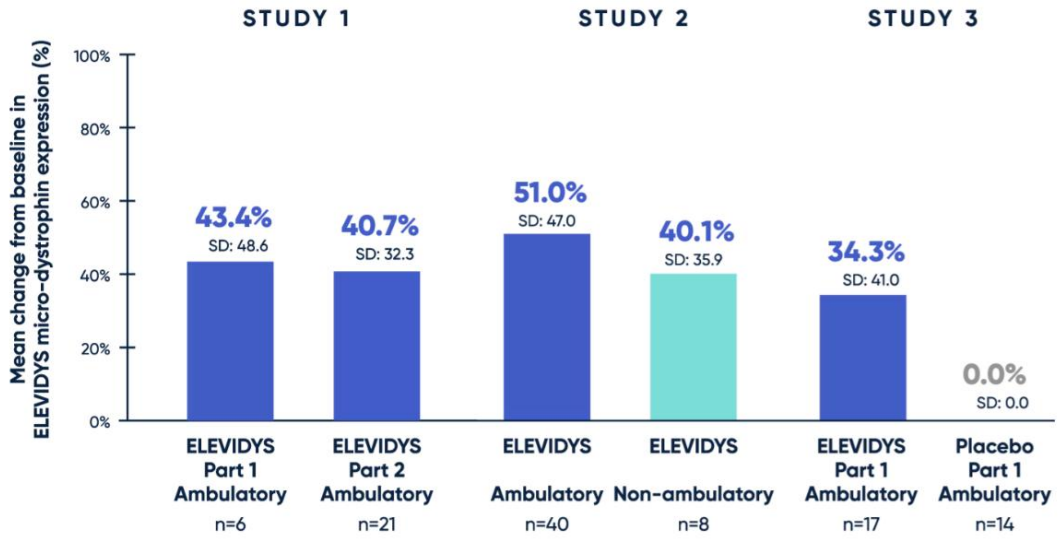
SAREPTA THERAPEUTICS

Statistically significant and highly expressed ELEVIDYS micro-dystrophin in treated patients[1]

Clinical trials confirmed targeted ELEVIDYS micro-dystrophin expression in skeletal muscle cells across ambulation status and ages studied.

ELEVIDYS micro-dystrophin expression via western blot at 12 weeks*†‡

– AMBULATORY & NON-AMBULATORY PATIENTS –



* All patients received 1.33 x 10^{14} vg/kg, as measured by ddPCR.
† Change from baseline was statistically significant.
‡ Adjusted for muscle content. Control was level of wild-type (normal) dystrophin in normal muscle.
ddPCR=droplet digital polymerase chain reaction.

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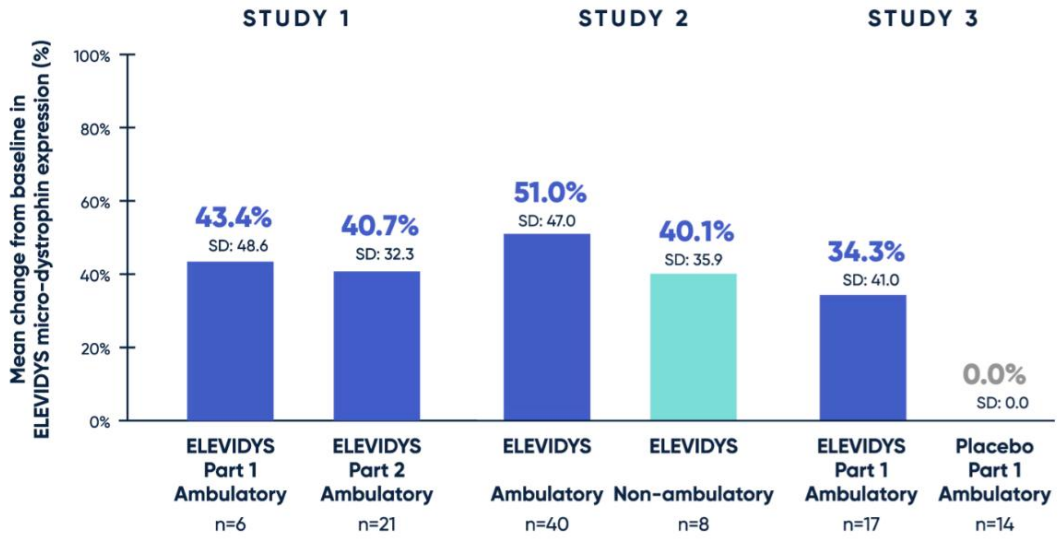

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Elevidys on the market? In the US

Initial Approval & Expansion

- **June 2023**
  - The FDA granted accelerated approval to Elevidys for a narrower group of ambulatory DMD patients aged 4 to 5 years with a confirmed DMD gene mutation.

- **June 2024**
  - The FDA expanded the approval, granting traditional approval for ambulatory DMD patients aged 4 and older and accelerated approval for non-ambulatory patients in the same age range. This expansion was based on data from a Phase 3 clinical trial that showed some clinical benefit.

Recent Regulatory Action

- **July 2025:**
  - In response to safety concerns, particularly reports of acute liver failure and deaths, the FDA requested that the manufacturer, Sarepta Therapeutics, voluntarily suspend distribution of Elevidys.

Current Status

- Shipments were later allowed to resume but were restricted to ambulatory patients, while the FDA continues to investigate the safety risks associated with the gene therapy's delivery mechanism.

But EMA negative opinion

- *In July 2025, the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) issued **a negative opinion**, recommending **against the conditional marketing authorization for Elevidys** (delandistrogene moxeparvovec) for treating ambulatory individuals aged three to seven with Duchenne muscular dystrophy (DMD). The decision was based on finding that the **supporting study failed to demonstrate Elevidys's effect on movement abilities after 12 months**, even though some patients produced dystrophin*.

GNT-004

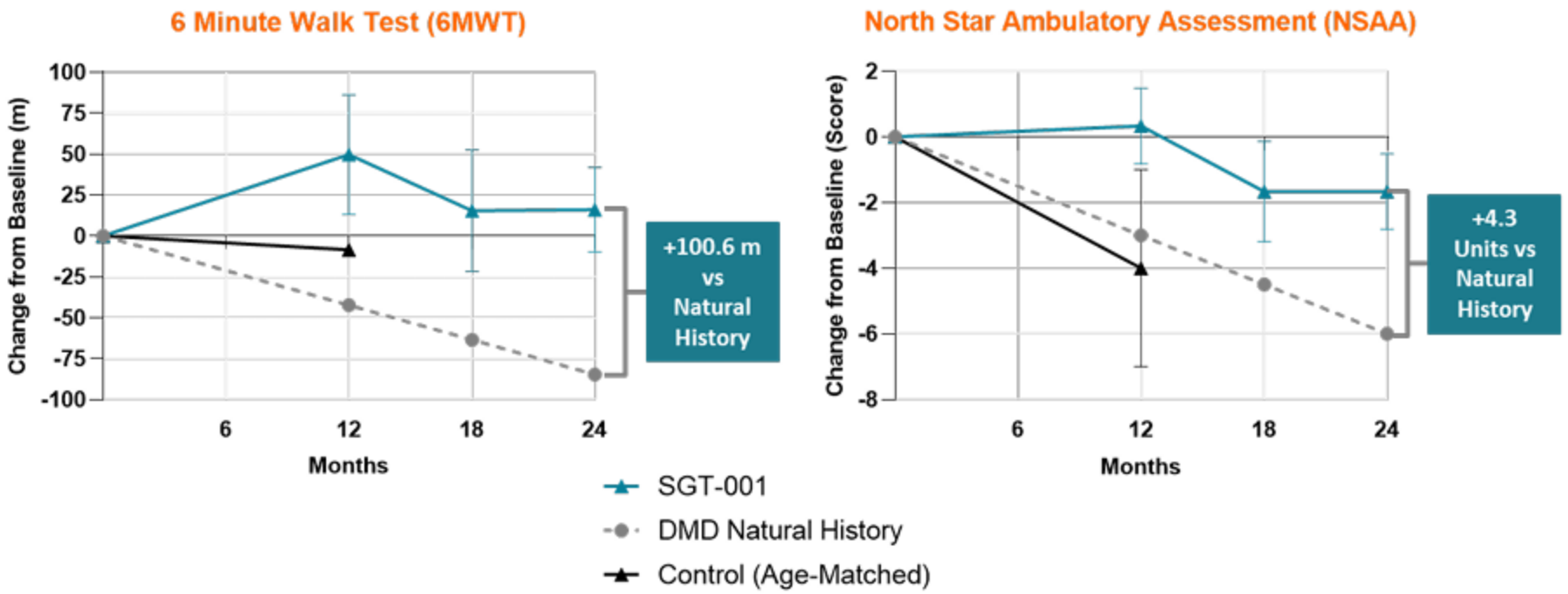
- AAV8
- Preliminary results
  - Stabilization NSAA in higher dose
  - 85% muscle fibers expressed micro-dystrophin (8w post dose)
  - CK fall between 50-87%
  - Results from phase I/II
  - Phase I/II/III about to start Q3-4 2025

Pf-06939926

DISCONTINUED

SGT-001

SGT-001 Treated Patients 4-6 Continue to Show Consistent, Stable Motor Function by 6MWT and NSAA at 2 Years Post-Dosing Compared to Natural History



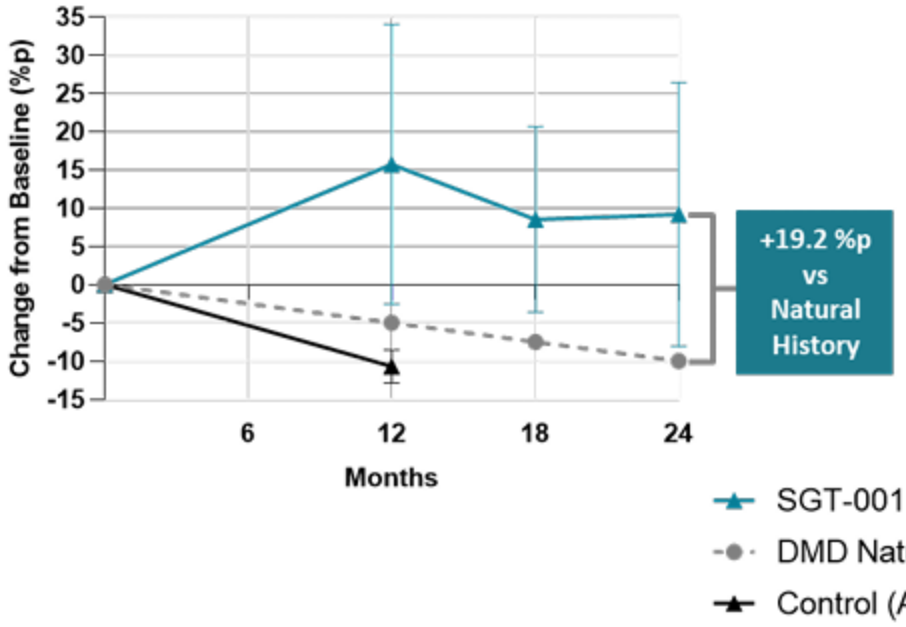
-84.6 m expected decline in 24 months after age 7 (Mercuri et al 2016)

-6.0 unit expected decline in 24 months after age 6.3 (Muntoni et al 2019)

SGT-001

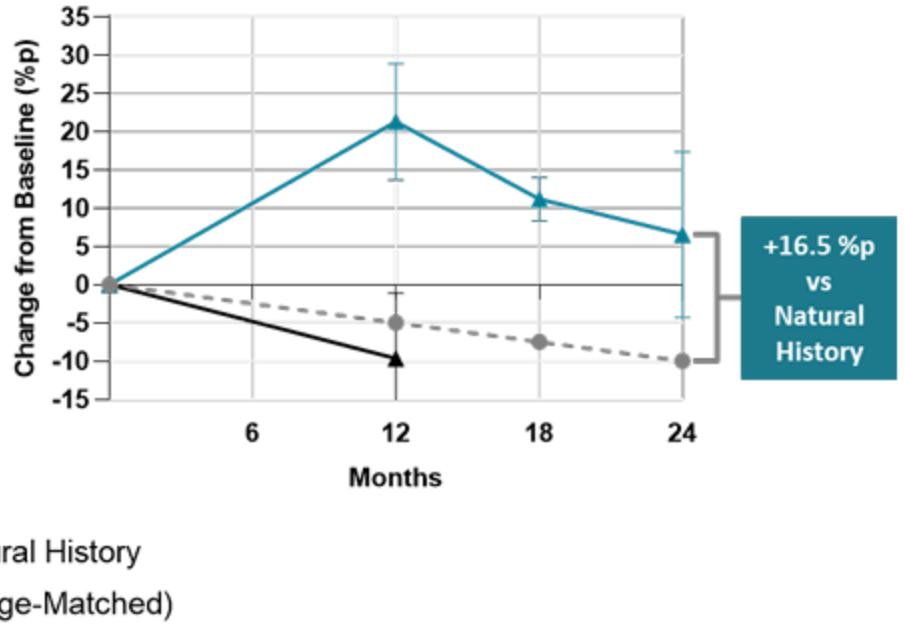
Pulmonary Function Tests Show Durable Improvements in SGT-001 Treated Patients 4-6 across 2 Years after Dosing

Forced Vital Capacity % Predicted (FVC %p)



-10.0 %p expected decline in 24 months after age 6 (Mayer et al 2015)

Peak Expiratory Flow % Predicted (PEF %p)



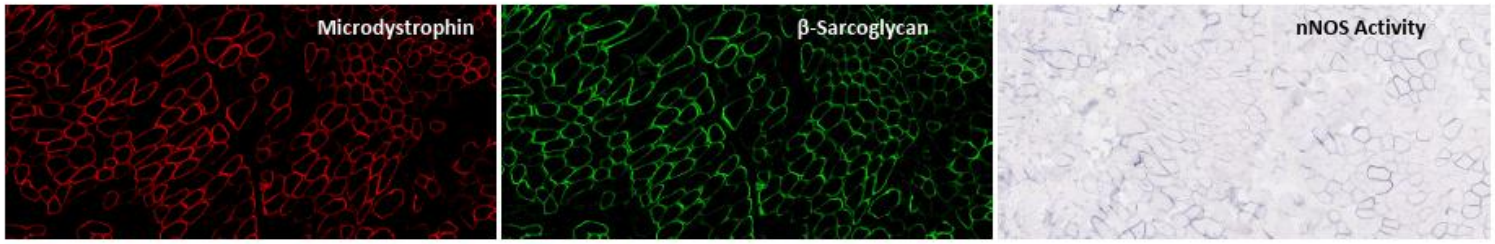
-10.0 %p expected decline in 24 months after age 6 (Mayer et al 2015)

SGT-001
DMD Natural History
Control (Age-Matched)

SGT-001

SOLID BIOSCIENCES

Durable Microdystrophin Expression and Protein Function are Observed Between 3-Month and Long-Term 12 to 24-Month Biopsies



Biopsy from Pt. 5 at 18 months

Biopsy Results (2E14 vg/kg Cohort)	3 months (Mean % - Pts. 4-9)	12 months (Mean % - Pts. 6-8)	18 months (Pt. 5)	24 months (Pt. 4)
% Normal Dystrophin (Western Blot)	6.6%	8.4%	70%	BLQ*
% Positive Fibers (Immunofluorescence)				
Blinded Assessment (Pathologist)	31%	30%	85%	10%
Automated Assessment (Flagship)	40%	40%	84%	32%

*BLQ: Below the 5% limit of quantification by Western blot
BLQ values assigned 0.5*LLOQ for Mean calculations (=2.5%)

RGX-202

https://www.regenxbio.com/therapeutic-programs/rgx-202/

Safety Considerations

Altough generally not regarded as pathogenic[1]; specific adverse safety events have been reported following AAV vector exposure

Most AAV Vectors Display Liver Tropism[1-3]

Acute effects on the liver reported, including[4,5]:

- Asymptomatic and symptomat aminotransferase elevations
- Acute serious liver injury and acute liver failure, including a cases with fatal outcomes

In general, patients responds well corticosteroid treatmentadministere before and after AAV vector IV infusion[4,5]

Thrombocytopenia

TMA

Theoretical Risk of Tumorigenicity

egration has been tients treated with AAV 0

nce of individual nts is unknownty[5]

as caausing tumors in such as dogs or non- es (NHP), no reports of ributed to rAAV therapy in

Involvement of:

- ✓ **Innate Immune Response,**
- ✓ **Adaptive Immune Response (capside, transgene, promoter)**
- ✓ **Preexisting Immune Response,**
- ✓ **Dose-Efficacy Relationship mechanisms**

AAV, adeno-associated virus; IV, intravenous; rAAV, recombinant adeno-associated virus; TMA, thrombotic microangiopathy.

1. Naso MF et al. *BioDrugs*. 2017;31(4):317-334. **2.** DiMattia MA et al. *J Virol*. 2012;86(12):6947-6958. **3.** Shen S et al. *J Virol*. 2012;86(19):10408-10417. **4.** Lillicrap D. *Cell*. 2017;171(7):1478-1480. **5.** Zolgensma. Prescribing information. Novartis Gene Therapies, Inc. **6.** Stone D et al. *J Virol*. 2008;82(15):7711-7715. **7.** Duan D. *Mol Ther*. 2018;26(10):2337-2356. **8.** Chand DH et al. *J Pediatr*. 2021;231:265-268. **9.** Sabatino DE et al. *Mol Ther*. 2022;30(8):2646-2663. **10.** Roctavian. Summary of product characteristics. BioMarin International Ltd.

Limitations of AAV based microdystrophin approach in DMD

- Despite high transduction efficiency, relatively durable therapeutic benefits, and remarkable clinical successes, the AAV platform suffers from several limitations:

  - Limited cargo capacity limiting the delivery options: for example micro-dystrophin might not be fully functional: missing of important binding proteins
  - Immunogenicity remains a challenge: innate immunity understudied
  - Currently limited to « One shot therapy »: no redosing possibility
  - Managing dosage and Manufacturing issue
  - Risk of transgene dilution during muscle cell divisions
  - …

Conclusions

- Elevidys is conditionally approved in the U.S. for young boys with Duchenne muscular dystrophy (DMD), under accelerated approval and age restrictions.
- In Europe, it is not yet approved; regulatory agencies are still reviewing clinical data, especially regarding long-term efficacy.
- Current limitations: partial and variable clinical benefit, short durability, immune response risks, and high treatment cost.
- Therapeutic hopes: targets the genetic cause of DMD, increases microdystrophin levels, and may slow disease progression.
- Next steps: larger trials, long-term data collection, better vector technology, and potential expansion of approvals.

Thank you

Thank you – Team UZ Gent

Thank you – Team HUDERF (HUB)