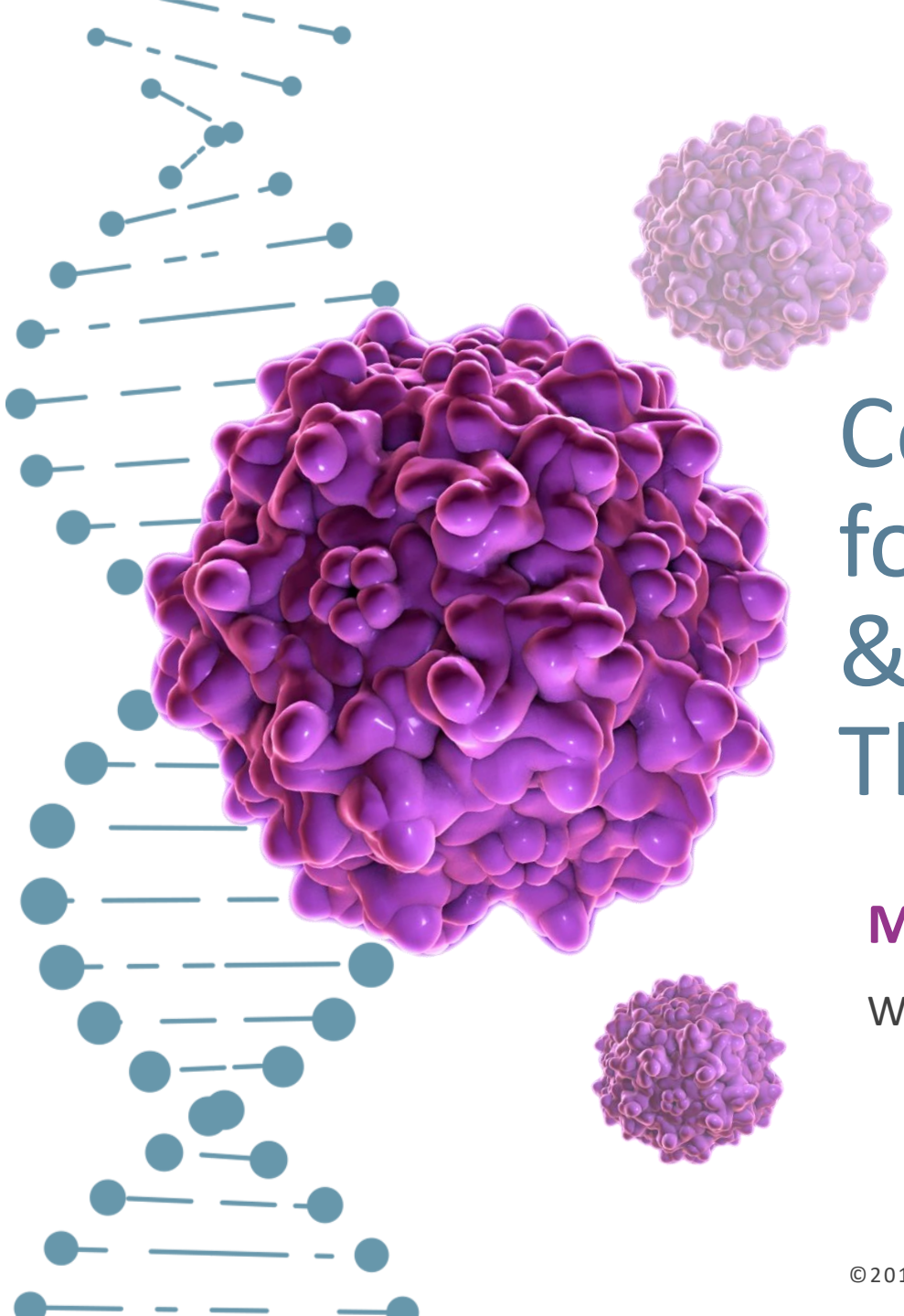


Considerations for Neuromuscular & CNS Targeted Gene Therapies

May 1, 2019

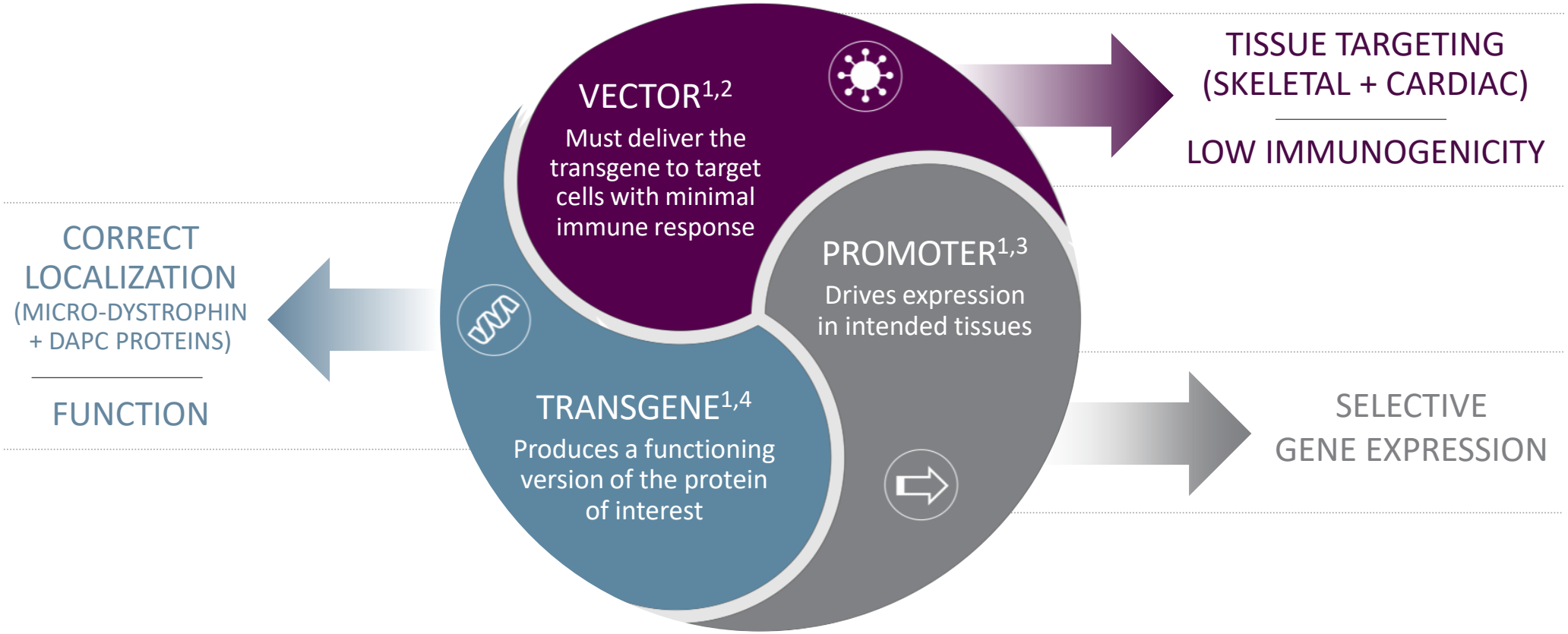
WASHINGTON, DC

Disclaimers

- AAVrh74.MHCK7.Micro-dystrophin is investigational and not approved in any country
- AAVrh74.MHCK7.beta-sarcoglycan is investigational and not approved in any country
- All pipeline therapies are investigational and have not been reviewed or approved in any country

SAREPTA THERAPEUTICS

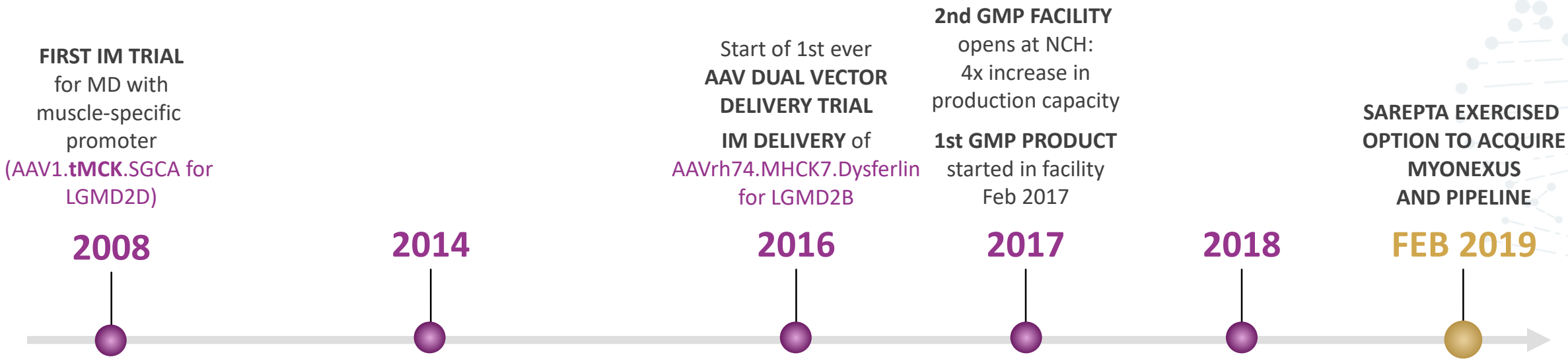
Essential Components of Gene Therapy Development



1. Naso MF, et al. *BioDrugs*. 2017;31(4):317-334. 2. U.S. National Library of Medicine. Help Me Understand Genetics: *Gene Therapy*. Bethesda, Maryland: 2013. https://ghr.nlm.nih.gov/primer/therapy/genetherapy. Accessed November 15, 2018. 3. Zheng C, Baum BJ, *Methods Mol Biol*. 2008;434:205-219. 4. Chamberlain K, et al. *Hum Gene Ther Methods*. 2016;27(1):1-12.

SAREPTA THERAPEUTICS

AAV Gene Therapy at Nationwide Children's Hospital: Over 19 Years of Development Experience



AAV, adeno-associated virus; FIH, first-in-human; GMP, good manufacturing practice; ILP, Isolated limb perfusion; IM, intramuscular; IND, investigational new drug application; MD, muscular dystrophy.
Data on file. Sarepta Therapeutics 2019.

SAREPTA THERAPEUTICS

Investment in Lacerta: Pompe & CNS-targeted Gene Therapy

- Lacerta is an AAV-based gene therapy company founded on technologies licensed from University of Florida
- August 2018: Sarepta enters into a license and option agreement with Lacerta
  - Includes access to capsid screening and proprietary OneBac manufacturing platform
  - 3 CNS development programs

News

Sarepta Therapeutics Signs Long-term Strategic Investment and License Agreements with Lacerta Therapeutics, Gaining Rights to Multiple CNS-targeted Gene Therapy programs and Access to Important Gene Therapy Talent and Tools

August 8, 2018 - … Long-term Strategic Investment and License Agreements with **Lacerta** Therapeutics, Gaining Rights to Multiple CNS-targeted … Long-term Strategic Investment and License Agreements with **Lacerta** Therapeutics, Gaining Rights to Multiple CNS-targeted … gene therapy programs, including exclusive rights to **Lacerta**'s gene therapy candidate for Pompe Disease and …

SAREPTA THERAPEUTICS

Partnership with Lysogene: MPSIIIA (Sanfilippo Syndrome)

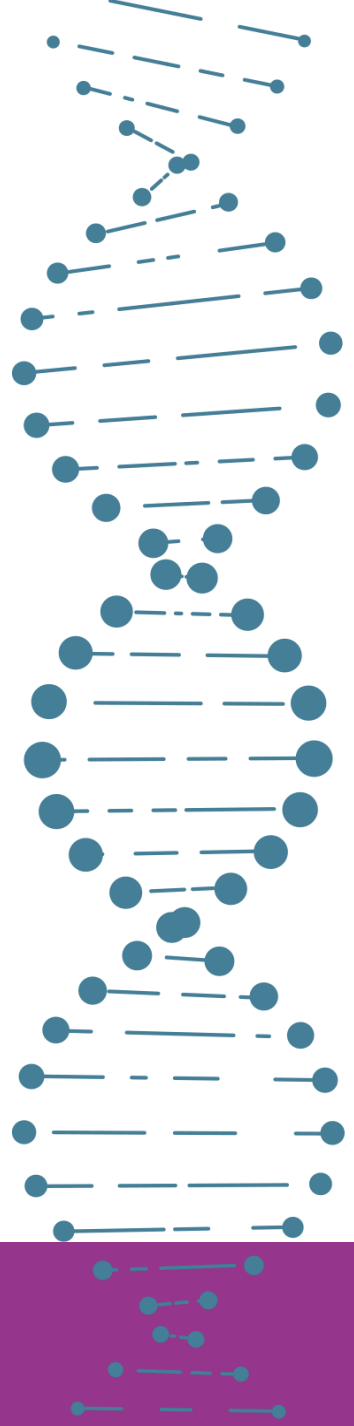
- Lysogene:
  - Specialists in gene therapy development targeting CNS diseases
- October 2018:
  - Sarepta receives full commercial rights to LYS-SAF302 in the US and other ex-EUR markets
- February 2019:
  - First Patient dosed in AAVance

News

Sarepta and Lysogene Announce Exclusive License Agreement for LYS-SAF302, a Late-stage Gene Therapy for the Treatment of MPS IIIA, and Grant of Option Rights to an Additional CNS Gene Therapy Candidate

October 15, 2018 - ... Sarepta and **Lysogene** Announce Exclusive License Agreement for LYS-SAF302, ... to an Additional CNS Gene Therapy Candidate Sarepta and **Lysogene** Announce Exclusive License Agreement for LYS-SAF302, ... in the U.S. and other markets outside of Europe , while **Lysogene** retains full commercial rights in Europe -- -- ...

SAREPTA THERAPEUTICS

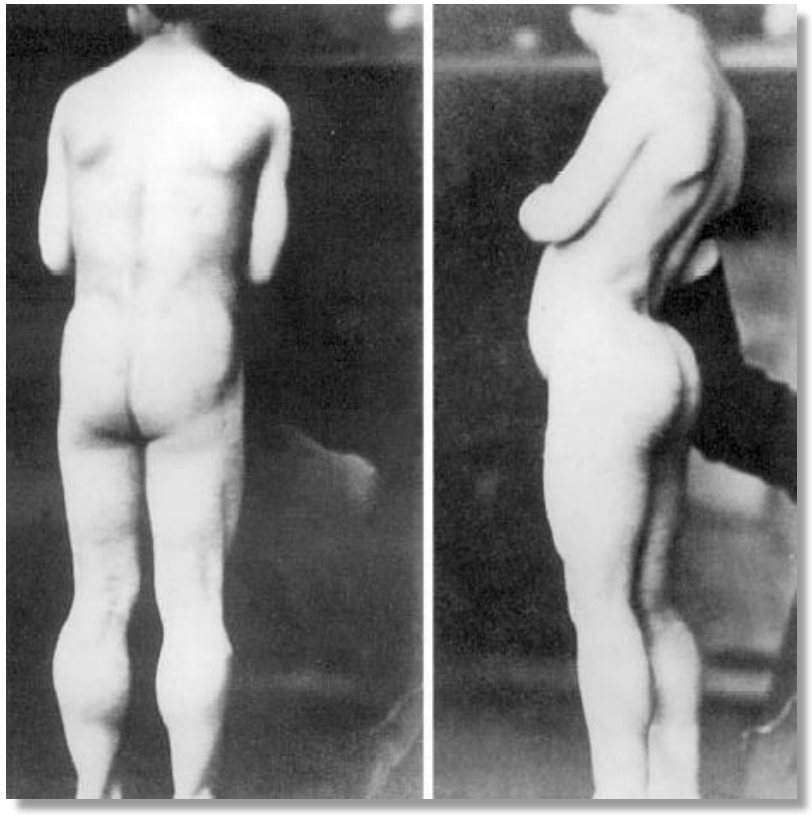


Duchenne Muscular Dystrophy (DMD)

SAREPTA THERAPEUTICS

Duchenne Muscular Dystrophy (DMD)

- **A fatal, X-linked recessive disorder[1]**
  - Estimated incidence of **1 in every 3500[2] to 5000[3]** males born worldwide
- *DMD* gene mutations reduce or prevent production of dystrophin protein, essential for muscle structure, function, and preservation [1,4,5]
- Characterized by progressive muscle weakness and degeneration[1,6,7]



Pictures of patient with DMD taken by Duchenne (1863)

1. Birkrant DJ, et al. *The Lancet Global Health*. 2018;13. 2. CDC. *MMWR Morb Mortal Wkly Rep*. 2009;58(40):1119-1122. 3. Mendell JR, et al. *Ann Neurol*. 2013;74(5):637-647.
4. Kole R, et al. *Nat Rev Drug Discov*. 2012;11(2):125-140. 5. Koenig M, et al. *Am J Hum Genet*. 1989;45(4):498-506. 6. Bushby K, et al. *Lancet Neuro*l. 2010;9(1):77-93.
7. Verhaart IE, et al. *Hum Gene Ther*. 2012;23(3):262-273.

SAREPTA THERAPEUTICS

Dystrophin Is Essential for Muscle Integrity[1]

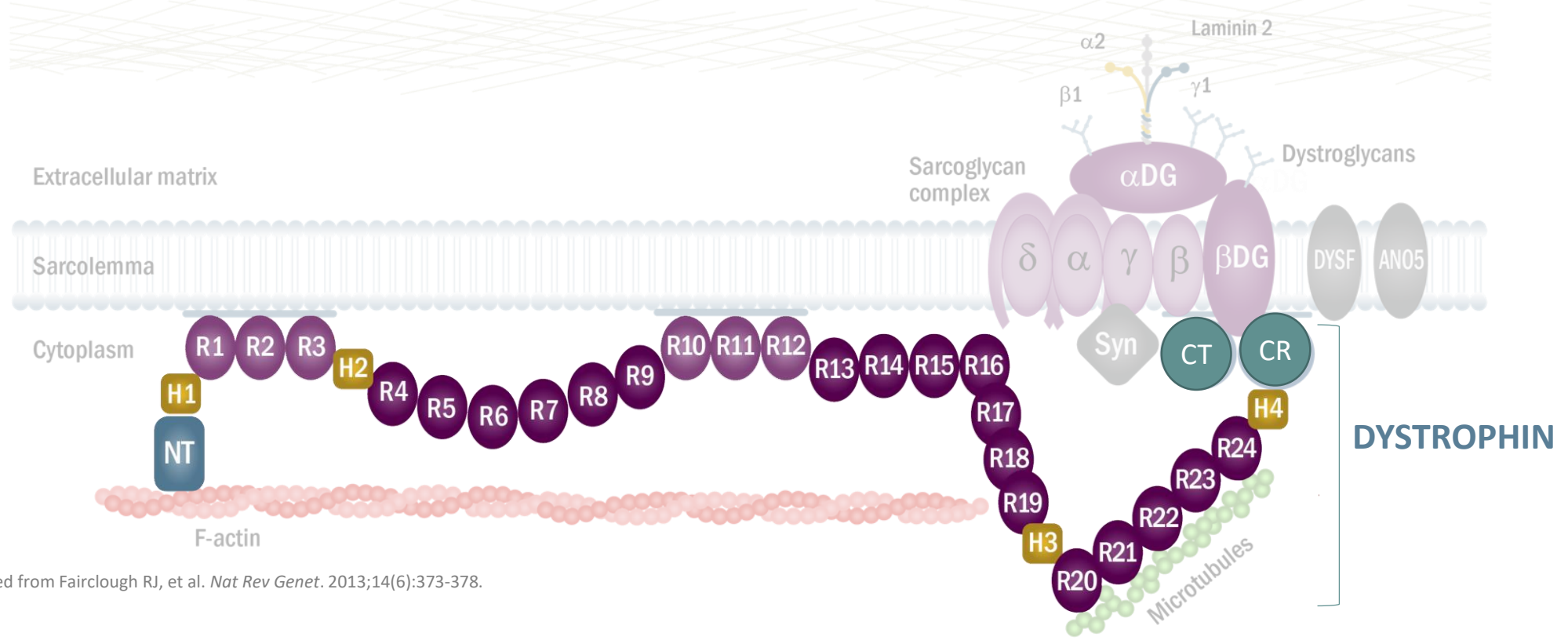


Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

Mutations in the *DMD* gene cause inadequate production of dystrophin protein[2]

ANO5, anoctamin-5; CR, cysteine-rich; CT, C-terminus; DG, dystroglycan; DYSF, dysferlin; NT, N-terminus; R, spectrin-like repeat; SG, sarcoglycan; Syn, syntrophin.

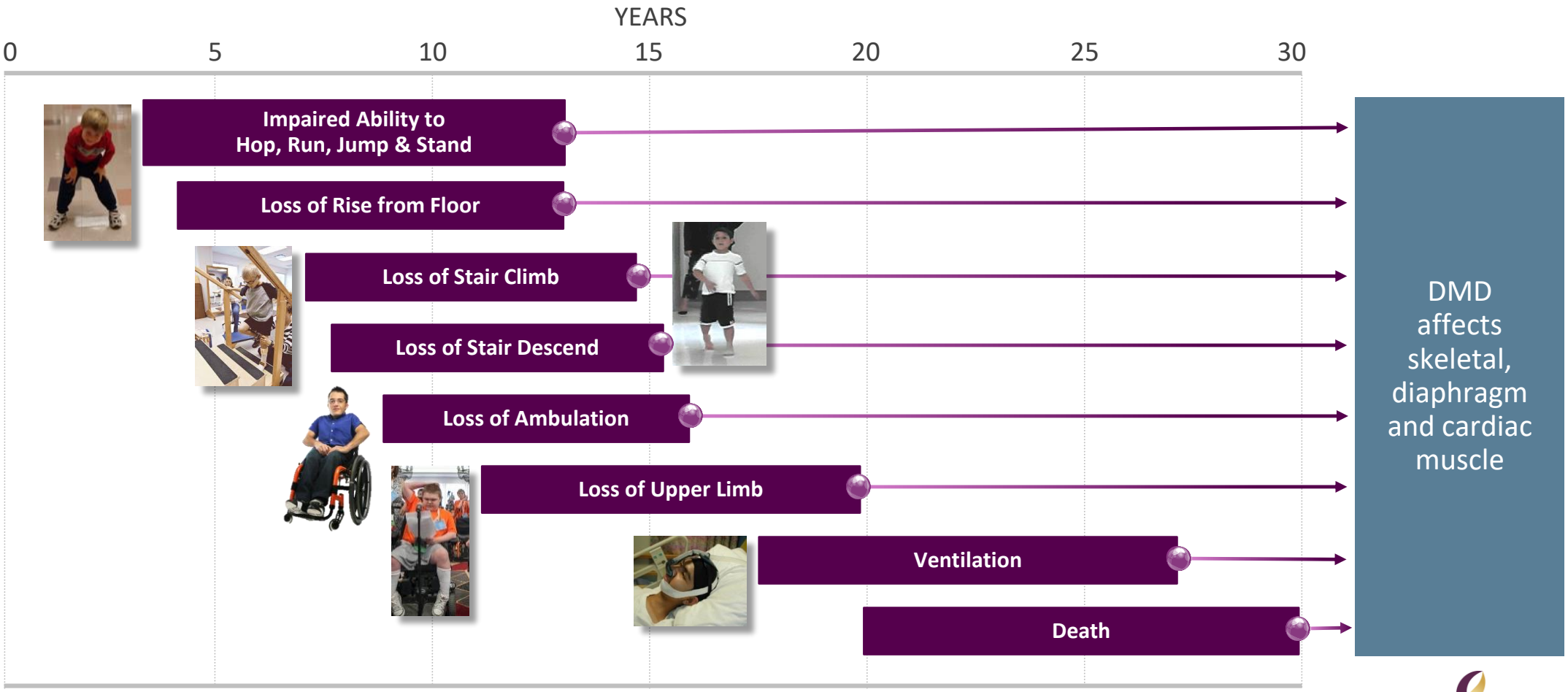
1. Verhaart IEC, Aartsma-Rus. *Neuromuscular Disorders*, InTech; 2012. https://www.intechopen.com/books/neuromuscular-disorders/aon-mediated-exon-skipping-for-duchenne-muscular-dystrophy. Accessed January 24, 2019. 2. Mosqueira M, et al. *Med Res Rev*. 2013;33:1174-1213.

SAREPTA THERAPEUTICS

DMD Disease Progression

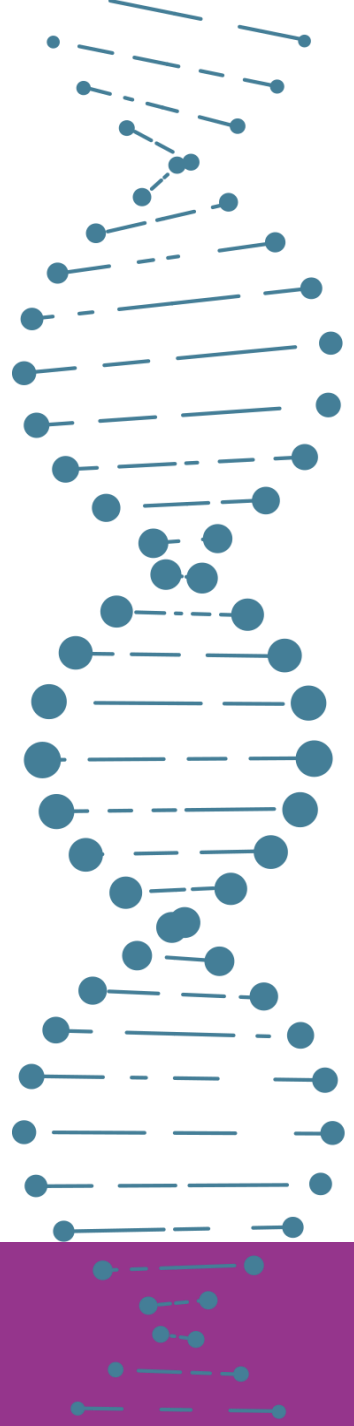
Predictable Progression Loss of Function, Resulting in Premature Death

DIFFICULTY IN GROSS MOTOR SKILLS & AMBULATION[1,2]



1. Bushby K, Connor E. *Clin Investig (Lond).* 2011;1(9):1217-1235. 2. Cruz Guzman OR, et al. *Int J Endocrinol.*2012;485376.

SAREPTA THERAPEUTICS

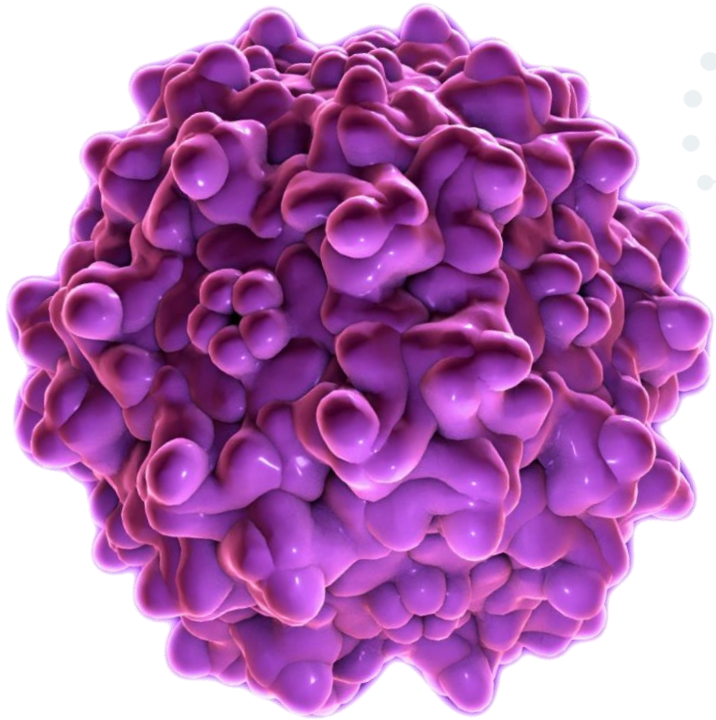


Gene Therapy for DMD:
Background & Rationale for Development

SAREPTA THERAPEUTICS

AAVrh74

- Originally isolated from NHP
- Most similar to AAV8 with regard to capsid sequence (93% identical)
- Robust affinity for muscle cells in animal models, making it an ideal choice for delivering the micro-dystrophin transgene
- Relatively low level of pre-existing immunity potentially allows more patients to be treated



Zygmunt D, et al. *Hum Gene Ther*. 2017;28(9):737-746.

SAREPTA THERAPEUTICS

Promoter: Rationale for Selecting MHCK7
Effect of Addition of α-MHC Enhancer on Cardiac Activity

Regulatory cassettes based on MCK and α-MHC regulatory elements

MCK

- Regulatory regions of the murine **muscle creatine kinase** (MCK) gene direct tissue-specific expression in both skeletal and cardiac muscle

α-MHC

- **α-myosin heavy-chain** (α-MHC) enhancer **confers high-level cardiac muscle-specific activity**

- Addition of the α-MHC enhancer boosted cardiac muscle expression beyond that observed with previous MCK-based cassettes

Salva MZ, et al. *Mol Ther*. 2007;15(2):320-329.

SAREPTA THERAPEUTICS

Transgene: Development Approach
Replace & Compensate for the Defective Gene

AAV Vector

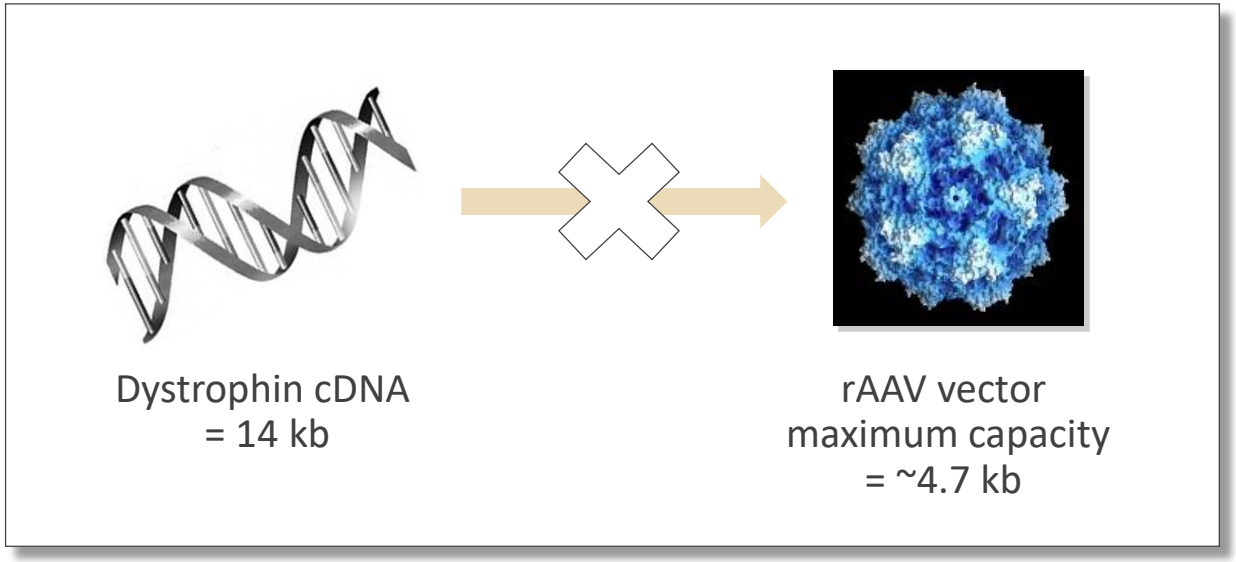


Image courtesy of Serge Braun.

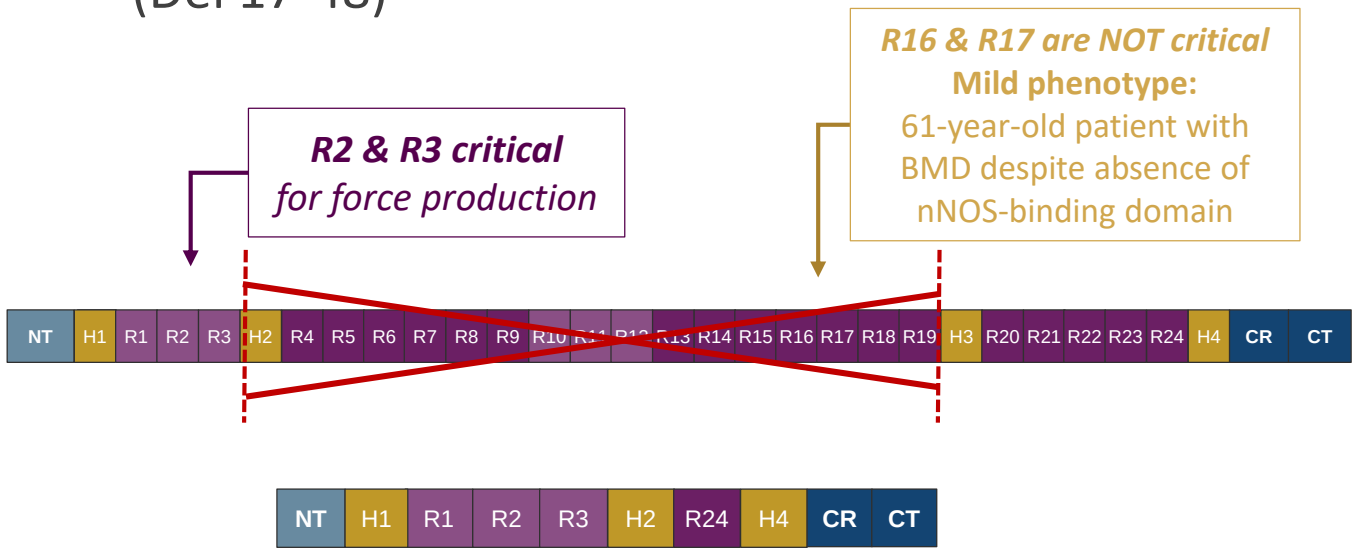
Full-length dystrophin is too big for AAV vectors

cDNA, complementary deoxyribonucleic acid; kb, kilobase; rAAV, recombinant AAV.
McClements ME, MacLaren RE. *Yale J Biol Med.* 2017;90(4):611-623.

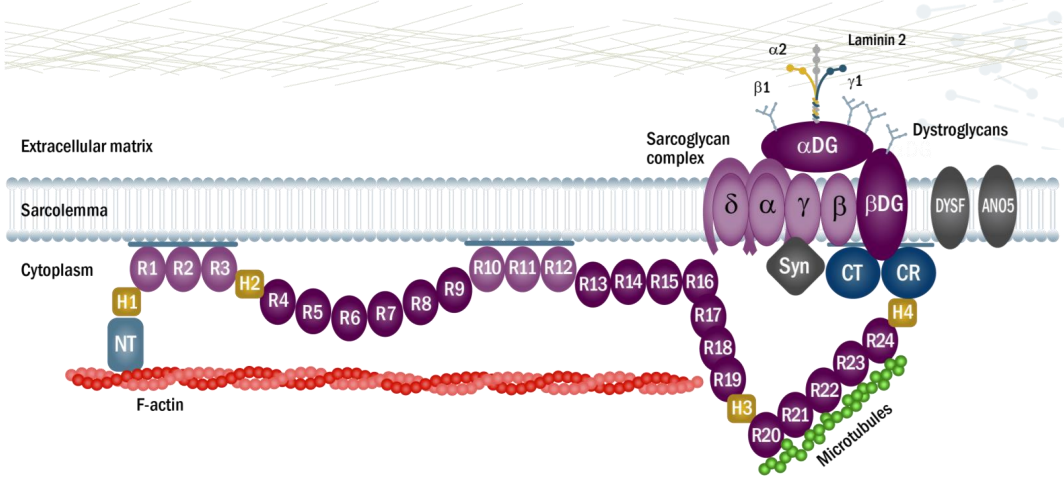
SAREPTA THERAPEUTICS

Transgene: Biological Basis for Use of Shortened Dystrophin

- Clinical observations paved the way for mini-gene therapy development
- 61-year-old ambulatory patient with BMD had 46% of dystrophin coding region deleted (Del 17-48)[1]



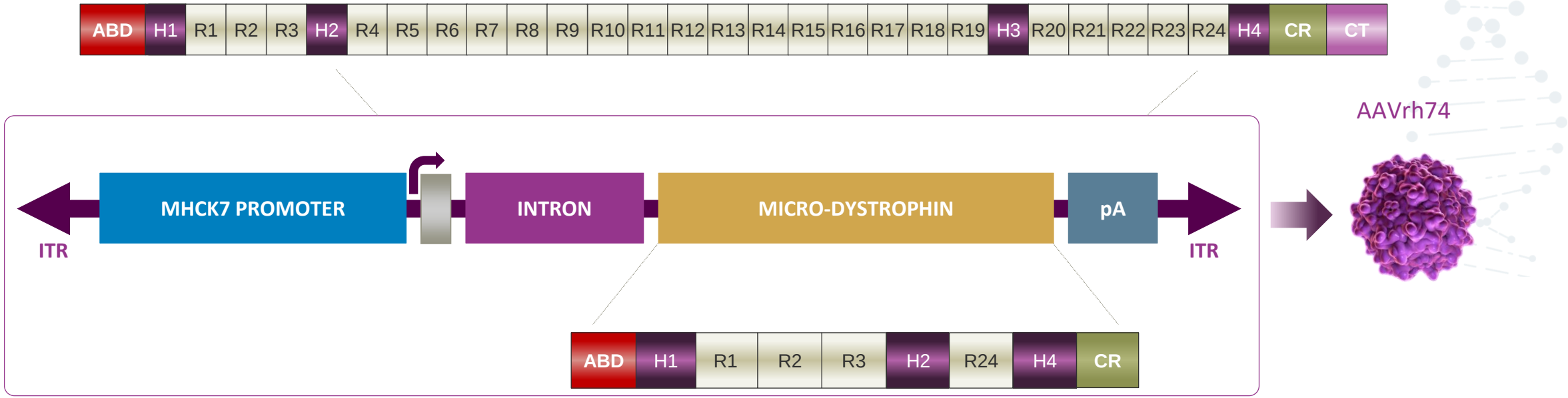
"Mini"-dystrophin[2]



1. England SB, et al. *Nature*. 1990;343(6254):180-182. 2. Wells DJ, et al. *Hum Mol Genet*. 1995;4(8):1245-1250.

SAREPTA THERAPEUTICS

Micro-dystrophin Gene Therapy Construct: Development in DMD[1-7]



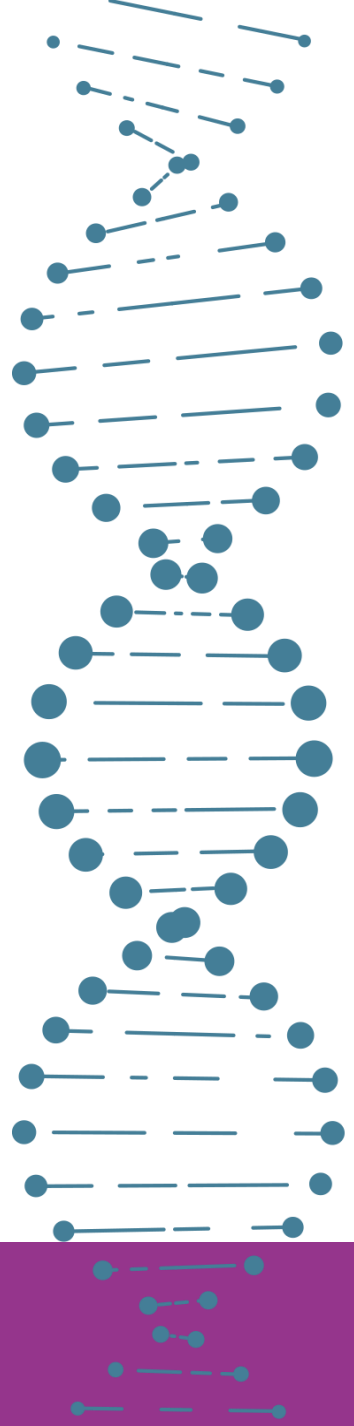
AAVrh74 Viral Vector	MHCK7 Promoter	Micro-dystrophin Transgene
Robust affinity for muscle	Specific to skeletal and cardiac muscle	Protein functionality
Relatively low level of pre-existing immunity	Drives expression in cardiac muscle	Contains spectrin-like repeats 2 and 3

ITR, inverted tandem repeat.

AAVrh74.MHCK7.Micro-dystrophin is investigational and not approved.

1. Salva MZ, et al. *Mol Ther*. 2007;15(2):320-329. 2. Mendell JR, et al. *Neurosci Lett*. 2012;527(2):90-99. 3. Rodino-Klapac LR, et al. *Hum Mol Genet*. 2013;22(24):4929-4937.
4. Velazquez VM, et al. *Mol Ther Methods Clin Dev*. 2017;4:159-168. 5. Harper SQ, et al. *Nat Med*. 2002;8(3):253-261. 6. Nelson DM, et al. *Hum Mol Genet*. 2018;27(12):2090-2100.
7. Sarepta Therapeutics Data on File.

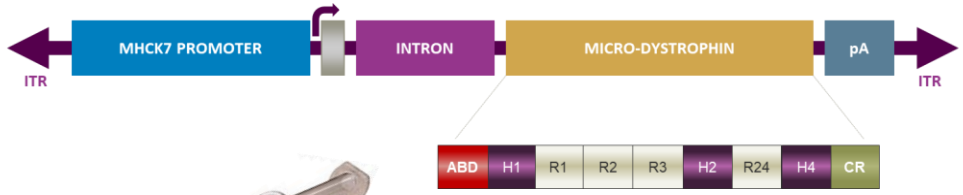
SAREPTA THERAPEUTICS

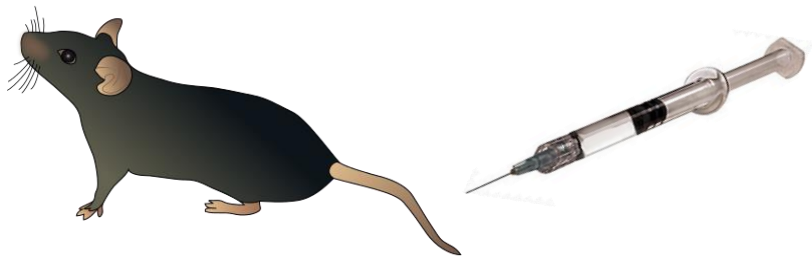


Gene Therapy Development for DMD: Pre-clinical Data

SAREPTA THERAPEUTICS

Nonclinical IV Study Design for the Delivery of AAVrh74.MHCK7.Micro-dystrophin in *mdx* mice





2 x 10^{12} vg total dose
(8×10^{13} vg/kg)

6 x 10^{12} vg total dose
(2×10^{14} vg/kg)

1.2 x 10^{13} vg total dose
(6×10^{14} vg/kg)

Assess efficacy and safety 12 weeks after gene delivery

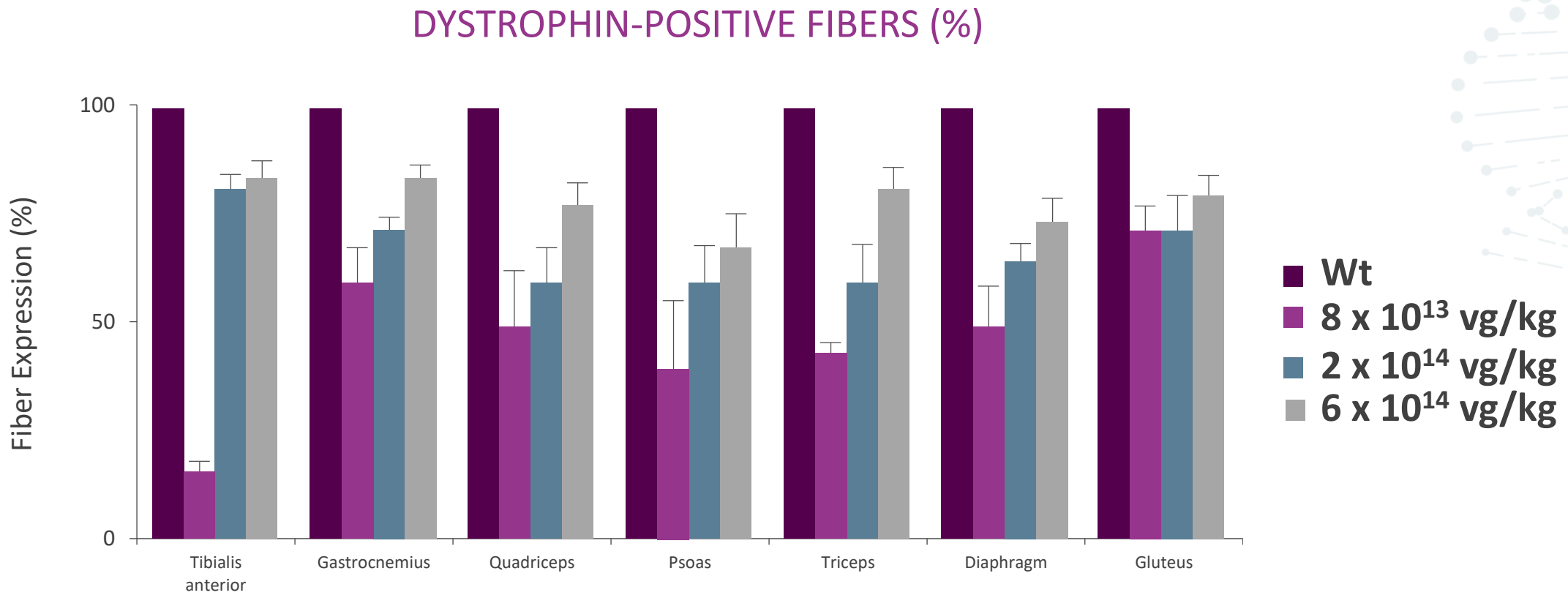
- Transgene expression and biodistribution
- Histological analysis
- Functional benefit
- Safety and toxicity

IV, intravenous; vg, viral genomes.

Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicine for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

SAREPTA THERAPEUTICS

AAVrh74.MHCK7.Micro-dystrophin Widespread Expression After Gene Delivery in *mdx* Mice



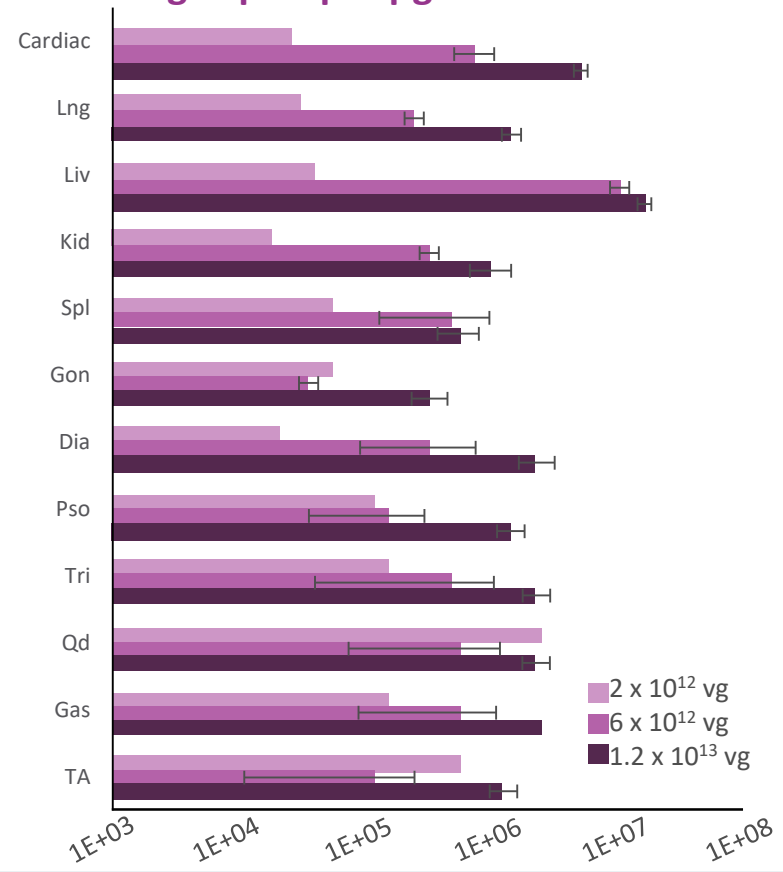
Sarepta Therapeutics 2019. Data on File.
AAVrh74.MHCK7.Micro-dystrophin is investigational and not approved.

SAREPTA THERAPEUTICS

Widespread Transduction of DNA and Selective Expression of Micro-dystrophin Protein in the *mdx* Mouse Model

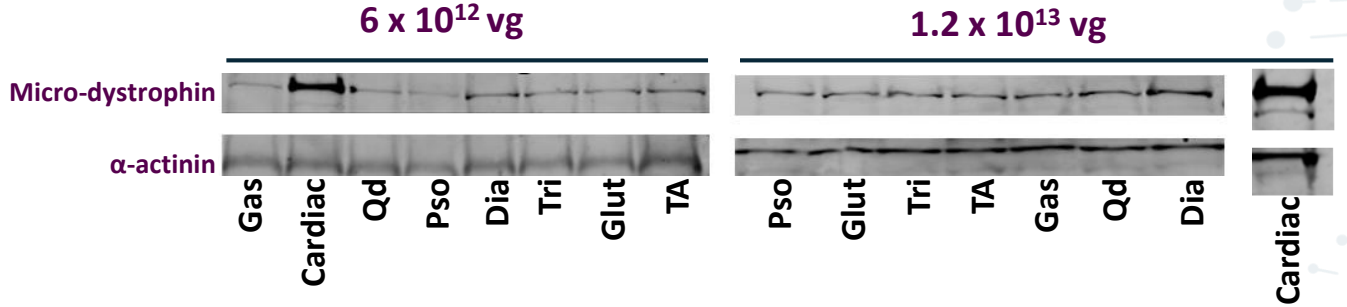
Transduction with **rh74 Vector** (qPCR)

vg copies per µg total DNA

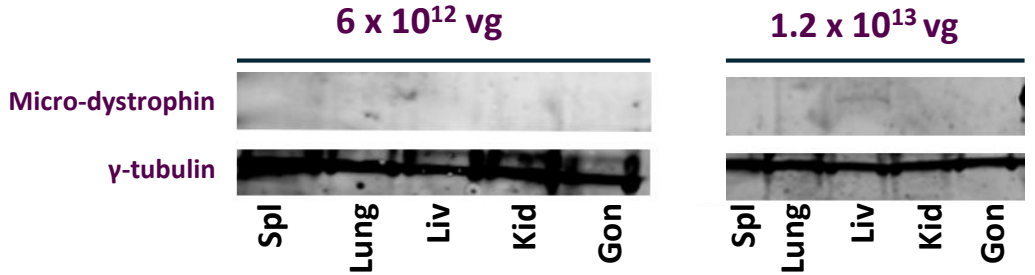


Expression With MHCK7 Promoter (WB)

MHCK7 promoter *drives* micro-dystrophin expression in muscle



MHCK7 promoter *does not drive* micro-dystrophin expression in off-target organs



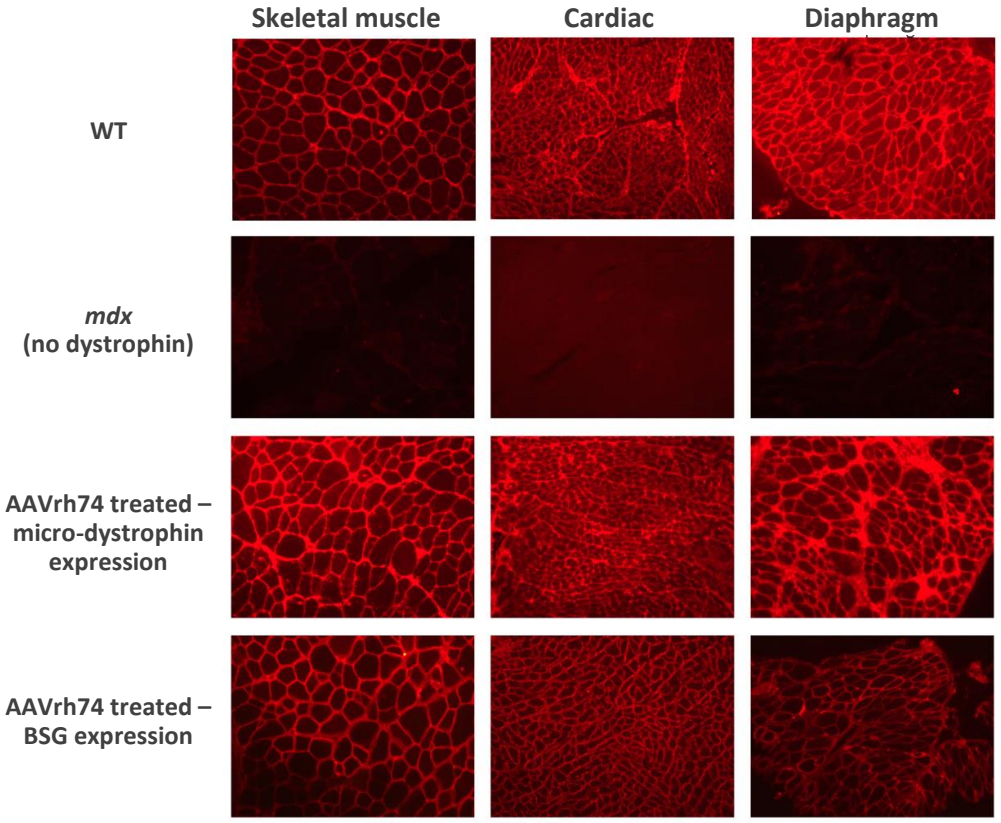
Dia, diaphragm; Gas, gastrocnemius; Gon, gonadal; Hrt, heart; Kid, kidney; Liv, liver; Lng, lung; Pso, Psoas; Qd, quadriceps; Spl, spleen; Tri, triceps; WB, Western blot.

Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

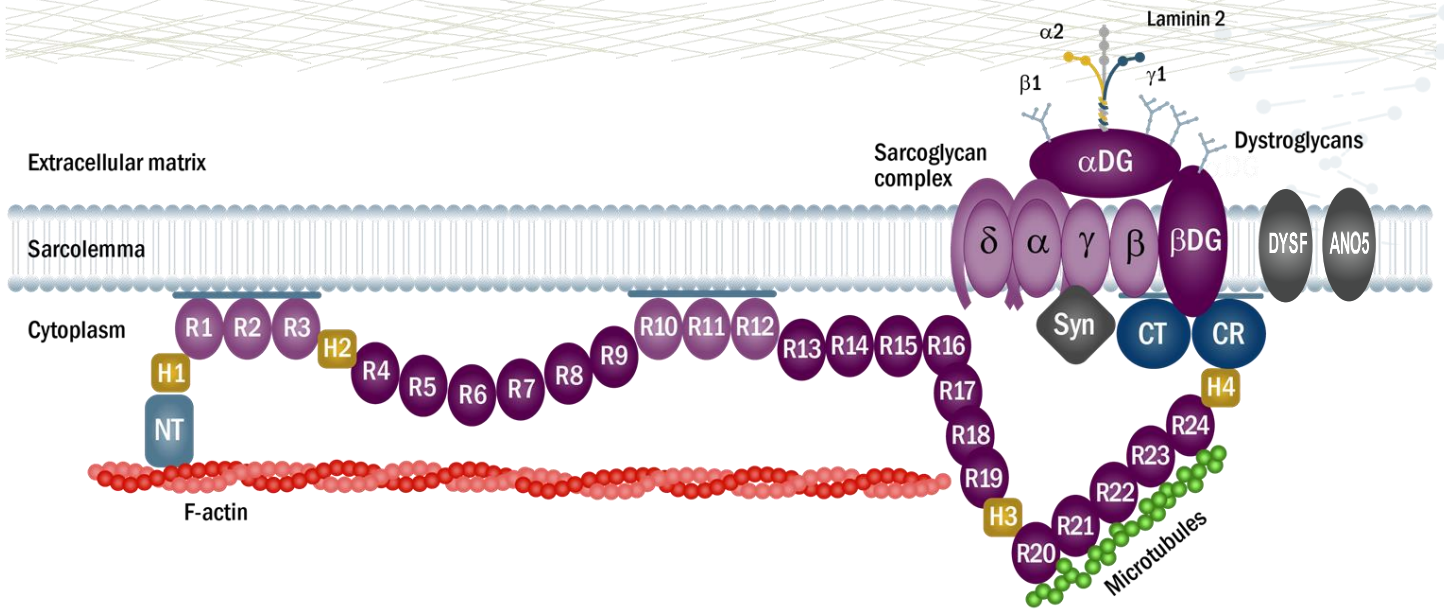
SAREPTA THERAPEUTICS

Reassembly of the Dystrophin-associated Protein Complex With Micro-dystrophin in *mdx* Mice

Dystrophin and BSG Expression (IHC)



Schematic of the DAPC



- Sarcoglycan complex associated with sarcolemma when micro-dystrophin is expressed in *mdx* mice

Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

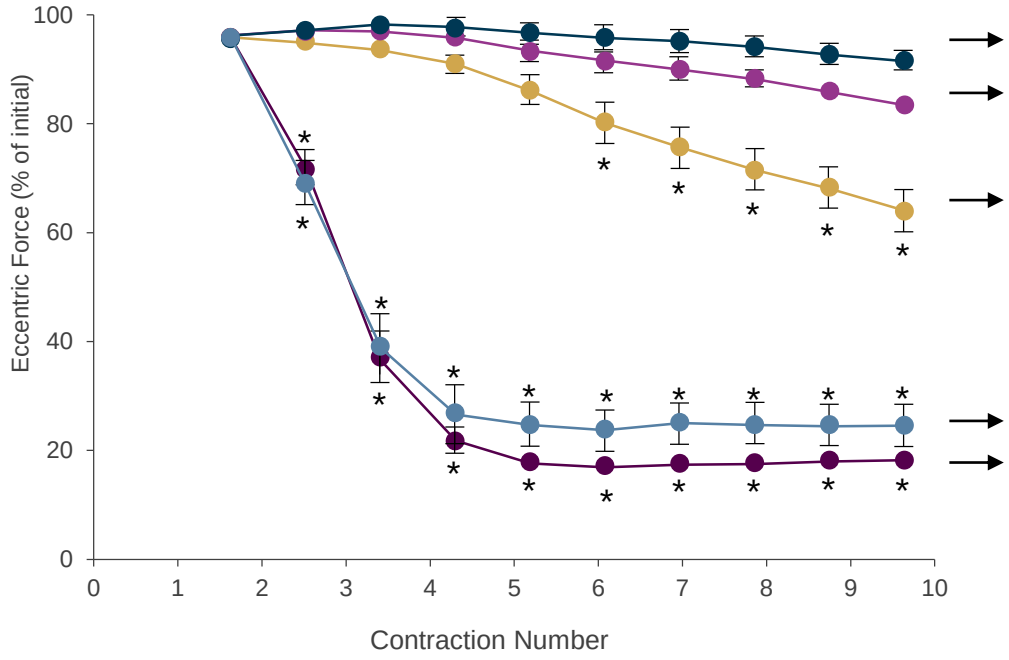
BSG, β-sarcoglycan. Data in *mdx* mice.

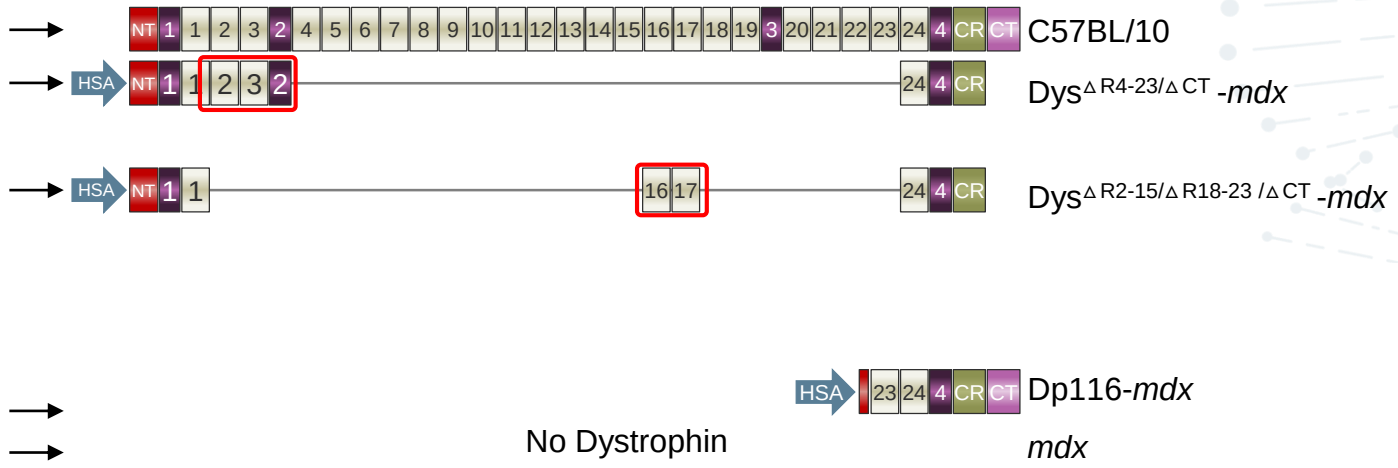
Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

SAREPTA THERAPEUTICS

R2-3 Region of Dystrophin Impacts Susceptibility to Eccentric Contraction-induced Force Drop in *mdx* Mice[1]

R2-3 of Dystrophin Required for Maximal Resistance to Eccentric Force Loss





- Eccentric force loss for Dys$^{\Delta R4\text{-}23/\Delta CT}$-*mdx* mice was comparable to that in WT (C57BL/10) mice[1]
- Dys $^{\Delta R2\text{-}15/\Delta R18\text{-}23/\Delta CT}$ -*mdx* had an intermediate eccentric force loss[1]
- Data support a role for the dystrophin **R2-3 membrane-binding domain** in modulating radial force transmission and mechanical vulnerability[1-3]

HSA, human skeletal actin; WT, wild-type.

*P<0.001 vs C57BL/10.

1. Nelson DM, et al. *Hum Mol Genet*. 2018;27(12):2090-2100. 2. Legardinier S, et al. *Biochim Biophys Acta*. 2008;1784(4):672-682.
3. Zhao J, et al. *Hum Mol Genet*. 2016;25(17):3647-3653.

SAREPTA THERAPEUTICS

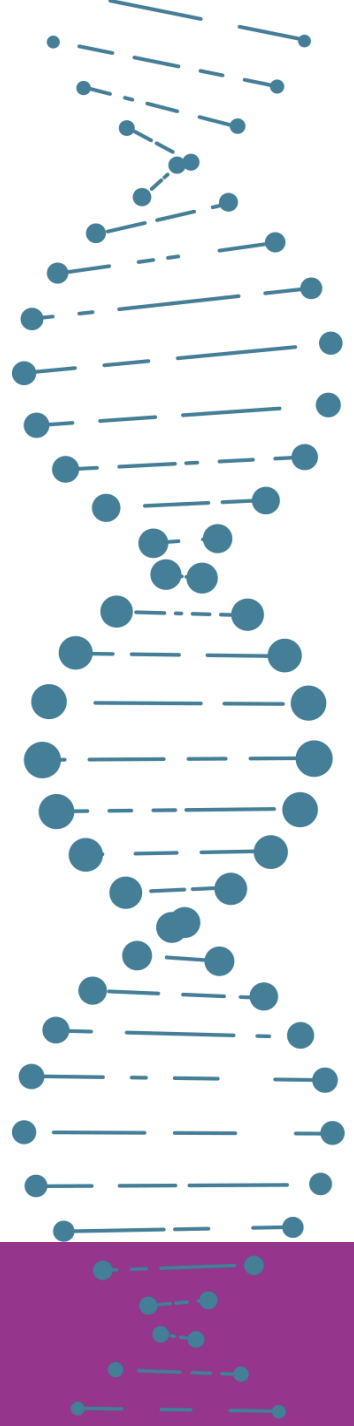
Nonclinical Summary

AAVrh74.MHCK7.Micro-dystrophin[1]

Design Consideration	Driven By	Output
Tissue Targeting (Skeletal + Cardiac)	AAVrh74	Transduction of All Muscles + Cardiac[2]
Low Immunogenicity	AAVrh74	Low Pre-existing Antibodies[3]
Selective Gene Expression (Skeletal + Cardiac)	MHCK7 Promoter	High Expression by WB in Skeletal + Cardiac Muscles[4,5] No Off-target Expression[4,5]
Correct Localization (Micro-dystrophin + DAPC Proteins)	Transgene	Restoration of DAPC by IHC[5]
Function	Transgene	Specific Force[5] Eccentric Force Drop[6]

1. Duan D. *Mol Ther*. 2018;26(10):1-20. 2. Chicoine LG, et al. *Mol Ther.* 2014;22(4):713-724. 3. Zygmunt DA, et al. *Hum Gene Ther.* 2017;28(9):737-746. 4. Salva MZ, et al.*Mol Ther.* 2007;15(2):320-329. 5. Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina. 6. Nelson DM, et al. *Hum Mol Genet.* 2018;27(12):2090-2100.

SAREPTA THERAPEUTICS



Gene Therapy for DMD: Clinical Data

SAREPTA THERAPEUTICS

AAVrh74.MHCK7.Micro-dystrophin: Goal of Study 1 Was to Validate Pre-clinical Results

AAVrh74.MHCK7.Micro-dystrophin[1]

Characteristic	Driven By	Expectations based on pre-clinical models
Transduction	AAVrh74	AAVrh74 efficient transduction to all muscle types[2]
Expression	MHCK7 Promoter	MHCK7 selective for cardiac and skeletal transgene muscle expression[3,4] Widespread micro-dystrophin expression in all biopsied muscles[3,4]
Efficacy	Transgene	Reduction in CK[5] Functional Outcomes[5]
Safety	Vector + Transgene	Favorable safety profile with no unexpected immunological responses[6]

1. Duan D. *Mol Ther*. 2018;26(10):1-20. 2. Chicoine LG, et al. *Mol Ther.* 2014;22(4):713-724. 3 Salva MZ, et al.*Mol Ther.* 2007;15(2):320-329. 4. Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina. 5. Nelson DM, et al. *Hum Mol Genet.* 2018;27(12):2090-2100. 6. Zygmunt DA, et al. *Hum Gene Ther.* 2017;28(9):737-746.

SAREPTA THERAPEUTICS

Study 1: Open-label Trial Design

- 4 subjects with DMD – open-label trial
  - 4-7 years of age
  - Confirmed *DMD* mutation within exons 18 to 58
  - Negative for AAVrh74 antibodies
- Stable steroid dosing for at least 3 months (range: 6 months to 2 years)
- Subjects were put on prednisone 1 mg/kg daily dosing starting 1 day before treatment for ≥30 days

ClinicalTrials.gov Identifier: NCT03375164.
Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

SAREPTA THERAPEUTICS

Study 1: Endpoints

Primary endpoint

- Safety

Key Secondary endpoints

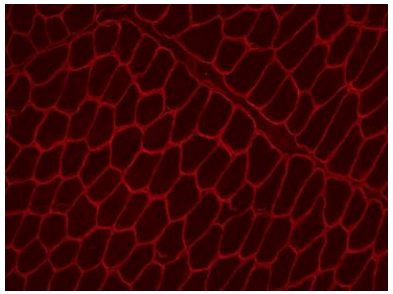
- Change in micro-dystrophin expression pre- vs post-treatment
- Decrease in CK
- 100-meter timed test (100 m)
- North Star Ambulatory Assessment (NSAA; 10-meter timed test included)
- Ascend 4 steps
- Cardiac magnetic resonance imaging (at 1 year)

ClinicalTrials.gov Identifier: NCT03375164.
Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

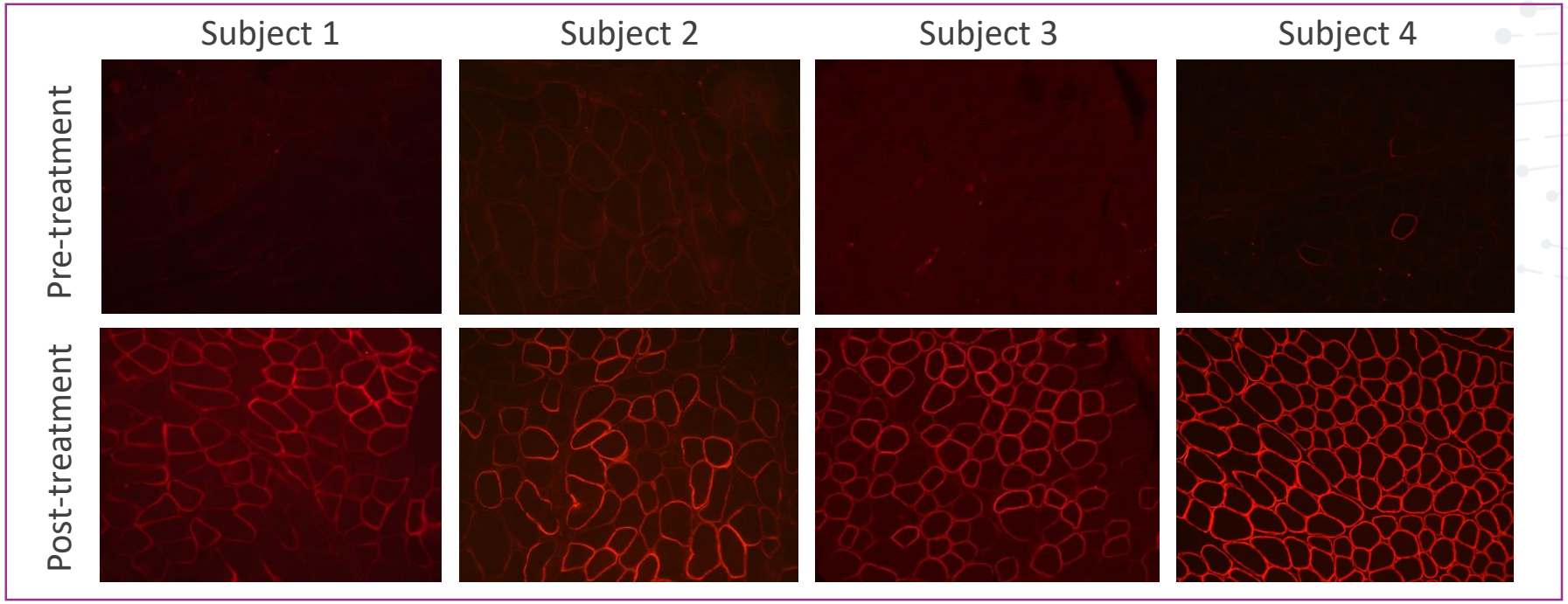
SAREPTA THERAPEUTICS

Micro-dystrophin Expression in Muscle Fibers From the Gastrocnemius in All 4 Subjects at Day 90

Normal Control



Micro-dystrophin Expression (IHC)



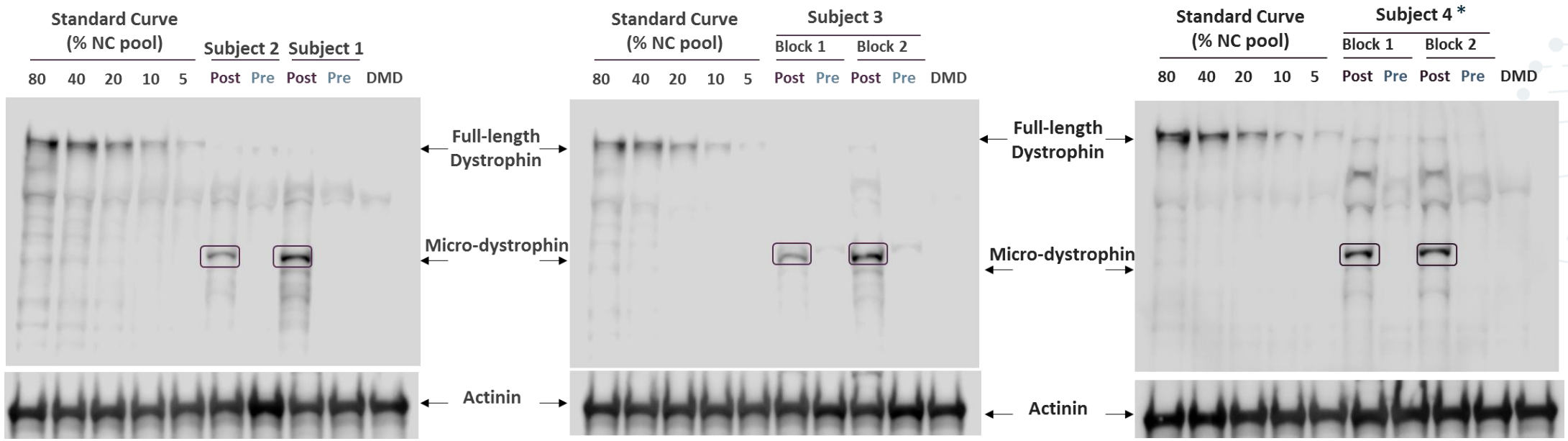
	Intensity	Percentage of Dystrophin-positive Fibers
Mean (n=4)	96.0%	81.2%

ClinicalTrials.gov Identifier: NCT03375164.

Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

SAREPTA THERAPEUTICS

Detection of Micro-dystrophin Protein by Western Blot Post-treatment in All 4 Subjects at Day 90



Western Quantitation Method	Mean Micro-dystrophin Expression (N=4) vs Normal	
Sarepta	74.3%	(not adjusted for fat and fibrotic tissue)
Nationwide Children's	95.8%	(adjusted for fat and fibrotic tissue)

NC, normal control; ULOQ, upper limit of quantitation.
*Samples diluted 1:4 because ULOQ (>80%) was exceeded in initial analysis. Mean values were multiplied by correction factor for final value compared with NC.
ClinicalTrials.gov Identifier: NCT03375164.
Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

SAREPTA THERAPEUTICS

Micro-dystrophin Expression Is Supported by a Vector Genome Count in All 4 Subjects

Micro-dystrophin Expression (IHC)

	Intensity	Percentage of Dystrophin-positive Fibers
Mean (n=4)	96.0%	81.2%

Micro-dystrophin Expression (Western Blot)

	Sarepta (not adjusted for fat/fibrosis)	Nationwide Children's (adjusted for fat/fibrosis)
Mean (n=4)	74.3%	95.8%

Vector Genome Number

	Vector Copies/µg DNA	Copies per Nucleus
Mean (n=4)	$>10^5$	3.3

ClinicalTrials.gov Identifier: NCT03375164.

Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina.

SAREPTA THERAPEUTICS

Summary of NSAA Data for All 4 Patients

NSAA Change from Baseline to Day 270

Patient	Baseline	Day 30	Day 60	Day 90	Day 180	Day 270	Change from Baseline
1	18	22	24	23	25	26	**+8**
2	19	21	23	25	27	27	**+8**
3	26	28	28	30	30	28	**+2**
4	19	20	20	25	25	27	**+8**
Mean	**20.5**	**22.75**	**23.75**	**25.75**	**26.75**	**27**	**+6.5**

ClinicalTrials.gov Identifier: NCT03375164.

Presented at Myology 2019 (Sarepta Therapeutics). 25-28 March 2019. Bordeaux, France. AAVrh74.MHCK7.Micro-dystrophin is investigational and not approved.

SAREPTA THERAPEUTICS

Summary of Clinical Data at 9 Months

Change from Baseline to Day 270

Subject	Age	Assessment	NSAA (Δ)
1	5	Baseline	18
		Day 270	26
2	4	Baseline	19
		Day 270	27
3	6	Baseline	26
		Day 270	28
4	4	Baseline	19
		Day 270	27
Average Change from Baseline			**6.5-point Improvement**

ClinicalTrials.gov Identifier: NCT03375164.

Presented at Myology 2019 (Sarepta Therapeutics). 25-28 March 2019. Bordeaux, France. AAVrh74.MHCK7. Micro-dystrophin is investigational and not approved.

SAREPTA THERAPEUTICS

Summary of Clinical Data at 9 Months

Change from Baseline to Day 270

Subject	Age	Assessment	NSAA (Δ)	Time to Rise (sec)	4 Stairs Up (sec)	100 m (sec)
1	5	Baseline	18	3.7	3.4	49.3
		Day 270	26	3.0	2.3	43.2
2	4	Baseline	19	3.0	3.8	49.9
		Day 270	27	3.3	2.7	50.3
3	6	Baseline	26	3.9	1.9	59.3
		Day 270	28	2.8	1.9	50.7
4	4	Baseline	19	4.1	4.8	67.2
		Day 270	27	2.4	2.2	49.7
Average Change from Baseline			**6.5-point Improvement**	**0.8 s Improvement**	**1.2 s Improvement**	**7.95 s Improvement**

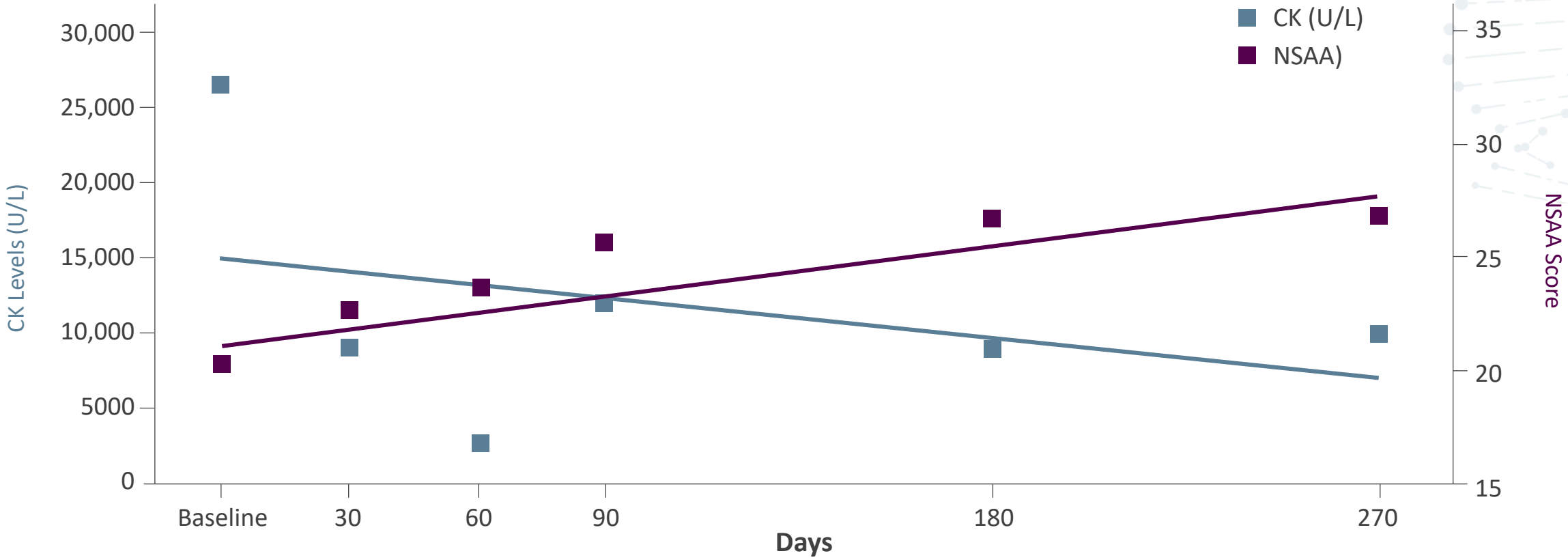
ClinicalTrials.gov Identifier: NCT03375164.

Presented at Myology 2019 (Sarepta Therapeutics). 25-28 March 2019. Bordeaux, France. AAVrh74.MHCK7.
Micro-dystrophin is investigational and not approved.

SAREPTA THERAPEUTICS

NSAA Score and CK Levels Over Time

Mean NSAA and CK Change from Baseline to Day 270



ClinicalTrials.gov Identifier: NCT03375164.

Sarepta Therapeutics 2019. Data on File. AAVrh74.MHCK7.Micro-dystrophin is investigational and not approved in any country.

SAREPTA THERAPEUTICS

Safety Experience (n=4)

- No serious adverse events in this study
- 3 subjects had elevated γ-glutamyl transpeptidase, which resolved with steroid treatment within a week
- No other clinically significant laboratory findings
- Subjects had transient nausea generally within the first week coincident with increased steroid dosing
  - Did not correlate with liver enzyme elevations or any other abnormality

ClinicalTrials.gov Identifier: NCT03375164.

Sarepta Therapeutics Data on File. AAVrh74.MHCK7.Micro-dystrophin is investigational and not approved in any country.

SAREPTA THERAPEUTICS

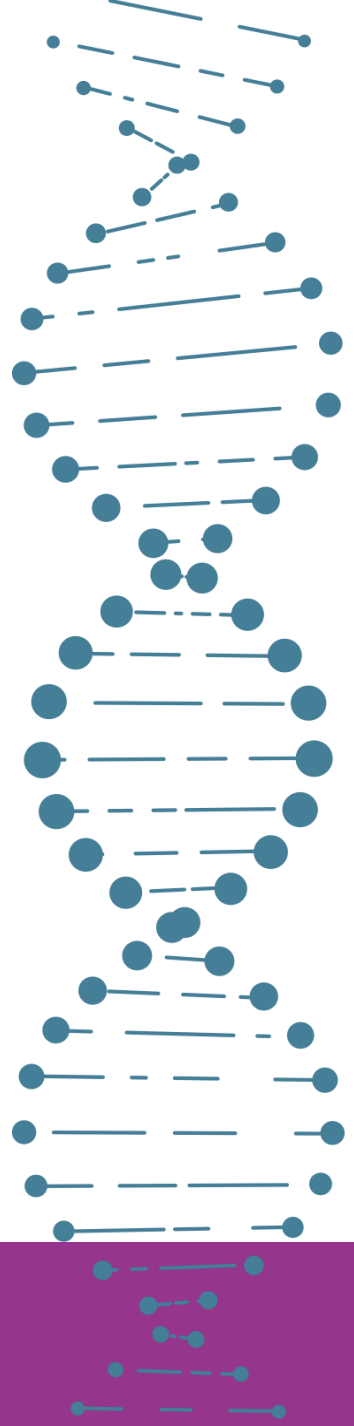
AAVrh74.MHCK7.Micro-dystrophin Study 1 Summary (N=4)

AAVrh74.MHCK7.Micro-dystrophin[1]

Characteristic	Driven by	Findings to Date
Transduction	AAVrh74	AAVrh74 efficient transduction to gastrocnemius[2]
Expression	MHCK7 Promoter	Micro-dystrophin expression post-gene transfer in biopsied muscle[3,4]
Efficacy	Transgene	Reduction in CK[5] Improved functional outcomes[5]
Safety	Vector + Transgene	No unexpected immunological responses in these patients[6]

1. Duan D. *Mol Ther*. 2018;26(10):1-20. 2. Chicoine LG, et al. *Mol Ther.* 2014;22(4):713-724. 3. Salva MZ, et al. *Mol Ther.* 2007;15(2):320-329. 4. Presented at the 23rd Annual Meeting of the World Muscle Society. Precision Genetic Medicines for Neuromuscular Diseases (Sarepta Therapeutics). 3 October 2018. Mendoza, Argentina. 5. Nelson DM, et al. *Hum Mol Genet.* 2018;27(12):2090-2100. 6. Zygmunt DA, et al. *Hum Gene Ther.* 2017;28(9):737-746.

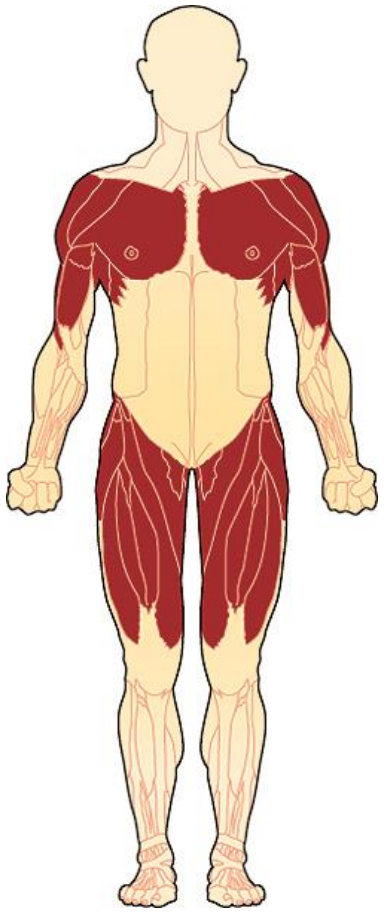
SAREPTA THERAPEUTICS



The Limb-Girdle Muscular Dystrophies (LGMDs)

SAREPTA THERAPEUTICS

LGMD



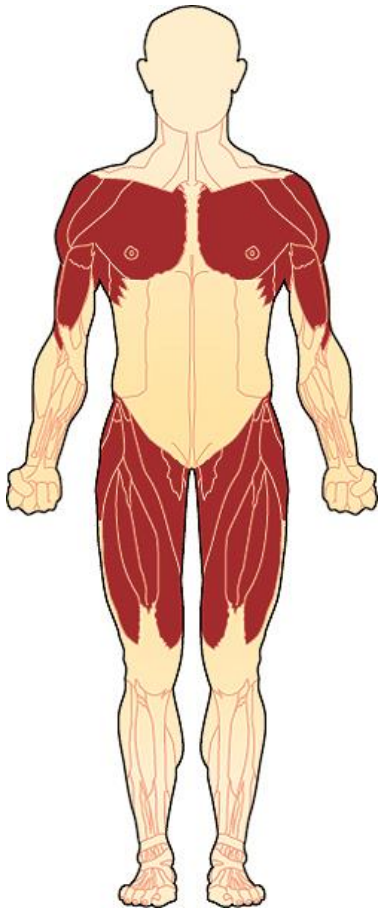
- The term “LGMD” was first coined in 1954 by John Walton and FJ Nattrass to describe a class of muscular dystrophies that were distinct from other dystrophies such as DMD and myotonic dystrophy type 1[1]
- LGMD onset can vary from early childhood to adulthood and manifests with **progressive weakness in the hip and shoulder girdle musculature**[1]
- LGMD has been **observed in both males and females** (not X-linked)[2]
- Approximate **global prevalence of LGMDs as a group is 1.63 per 100,000** (Prevalence estimates range from 0.56 to 6.90 per 100,000)[3]

DMD, Duchenne muscular dystrophy.

1. Liewluck T, Milone M. *Muscle Nerve*. 2018;58(2):167-177. 2. Pegoraro E, Hoffman EP. Limb-Girdle Muscular Dystrophy Overview. June 8, 2000 [Updated August 30, 2012]. www.ncbi.nlm.nih.gov/books/NBK1408/. Accessed December 16, 2018. 3. Mah JK, et al. *Can J Neurol Sci*. 2016;43(1):163-177.

SAREPTA THERAPEUTICS

LGMD



- In total, **34 variants of LGMD have been identified**[1]
- There is wide variation in the prevalence of LGMD subtypes, suggesting potential **founder mutations**[2]
- Each subtype represents a **unique mutation** and a **compilation of symptoms**[2]
- There is **significant heterogeneity** between the varying subtypes[2]

DMD, Duchenne muscular dystrophy.

1. Liewluck T, Milone M. *Muscle Nerve*. 2018;58(2):167-177. 2. Murphy AP, Straub V. *J Neuromuscul Dis*. 2015;2(s2):S7-S19.

SAREPTA THERAPEUTICS

The Dystrophin-Associated Protein Complex (DAPC)

- The relationship between dystrophin and the DAPC is both intricate and dependent[1]
- The dystrophin complex **stabilizes the plasma membrane (sarcolemma)** of striated & cardiac muscle cells[1]
- Loss-of-function **mutations** in the genes encoding dystrophin, or other proteins in the DAPC, **results in destabilization of the plasma membrane and loss of myofibers and cardiomyocytes[2]**

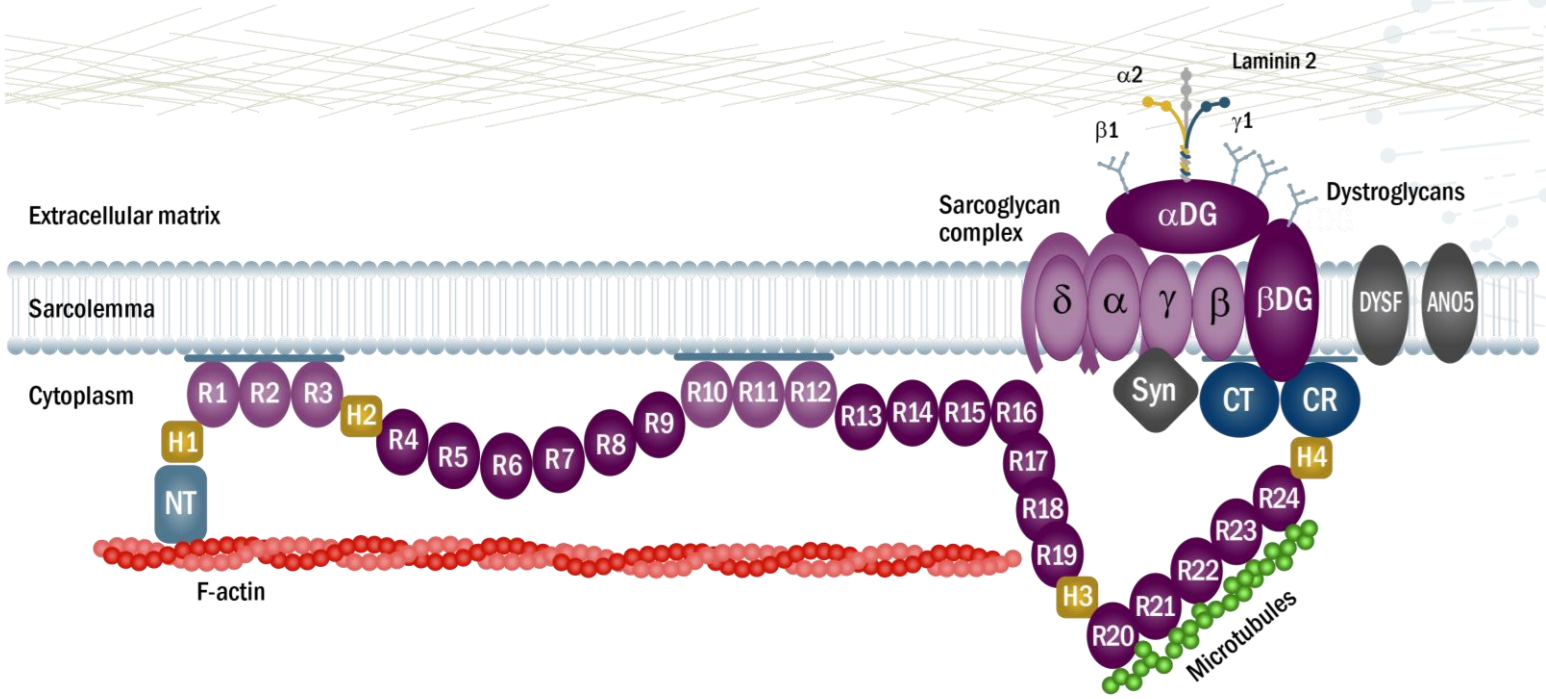


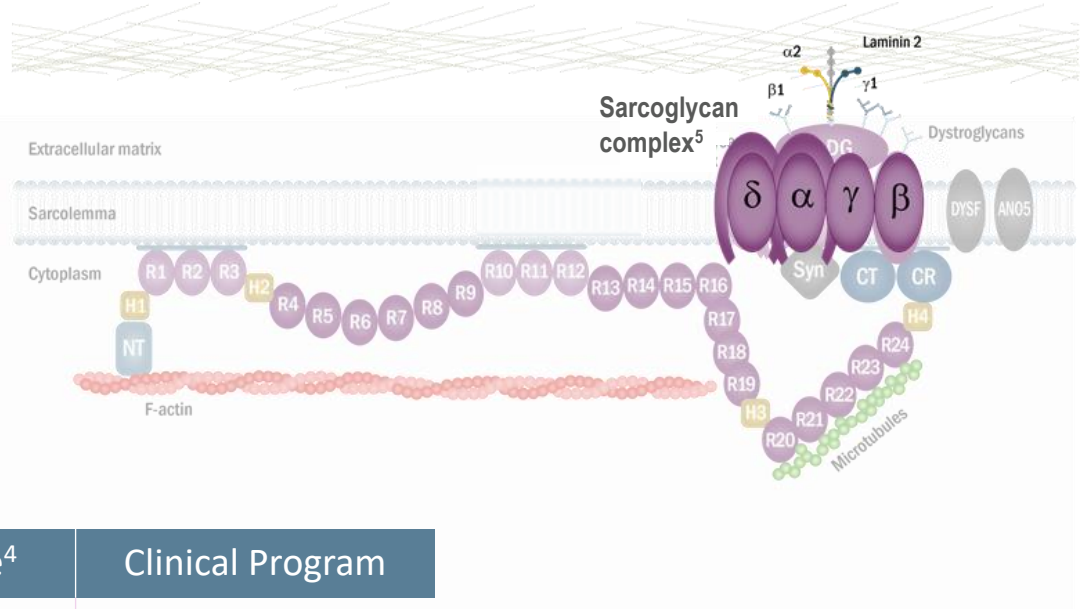
Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

1. Bhat HF, et al. *J Cell Physiol*. 2018;233(7):5142-5159. 2. Gao Q, McNally EM. *Compr Physiol.* 2015;5(3):1223-1239.

SAREPTA THERAPEUTICS

The Sarcoglycan Complex: Essential Proteins of the DAPC

- **LGMD is caused by a broad range of mutations occurring in multiple genes** that encode for proteins that play vital roles in muscle function, regulation and repair[1]
- Sarepta/NCH focus:
  - **Sarcoglycans prevent muscle damage during contraction[2]**
  - All 4 functional sarcoglycans must be present to form a functional sarcoglycan complex[3]



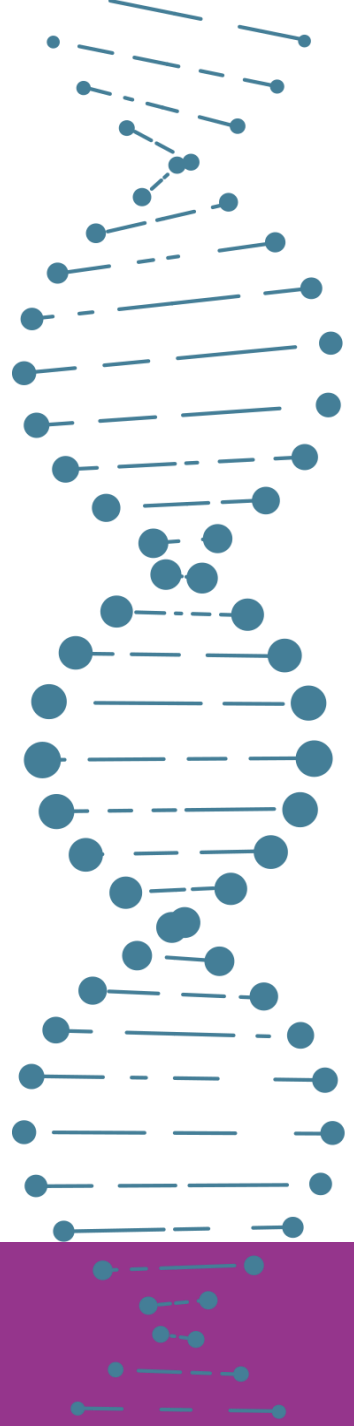
Gene/Protein[4]	Function[2]	Disease[4]	Clinical Program
SGCA α-sarcoglycan	Stabilizes DAPC, prevents muscle damage during contraction	LGMD2D	MYO-102
SGCB β-sarcoglycan		LGMD2E	MYO-101
SGCG γ-sarcoglycan		LGMD2C	MYO-103
SGCD δ-sarcoglycan		LGMD2F	—

β-sarcoglycan and δ-sarcoglycan act as the structural core of the sarcoglycan complex[2]

NCH, Nationwide Children's Hospital.

1. Mah JK, et al. *Can J Neurol Sci.* 2016;43(1):163-177. 2. McNally EM. The Sarcoglycans. Landes Bioscience 2000-2013. www.ncbi.nlm.nih.gov/books/NBK6317/. Accessed March 21, 2019. 3. Allen DG, et al. *Physiol Rev*. 2016;96(1):253-305. 4. Liewluck T, Milone M. *Muscle Nerve.* 2018;58(2):167-177. 5. Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

SAREPTA THERAPEUTICS



Overview of Sarepta's Gene Therapy Development for LGMD2E (β-sarcoglycanopathy)

SAREPTA THERAPEUTICS

AAVrh74 Vector Design

Full-length Transgene: β-sarcoglycan

- AAV expression cassette carrying the human β-sarcoglycan (hSCGB) cDNA

Vector chosen based on skeletal muscle transduction in pre-clinical testing[2]

Promoter optimized for desired skeletal muscle and cardiac muscle expression levels[1,3,4]

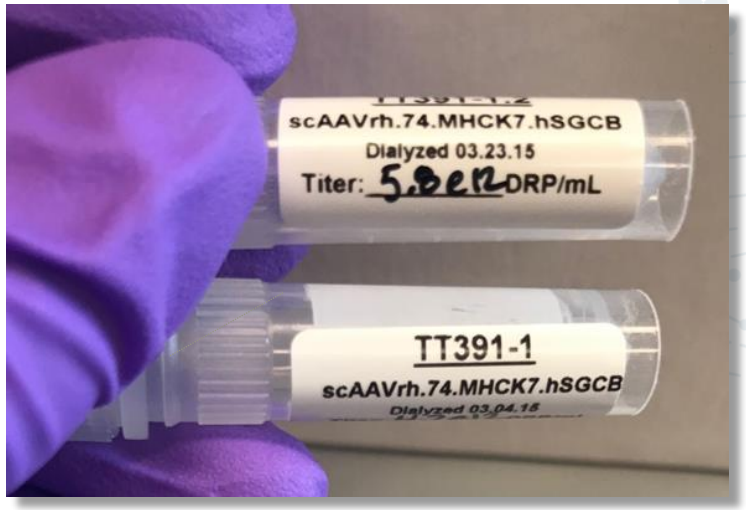
Sarepta gene of interest is specific to β-sarcoglycanopathy

1. Pozsgai ER, et al. Mol Ther. 2017;25(4):855-869. 2. Chicoine LG, et al. *Mol Ther*. 2014;22(2):338-347. 3. Salva MZ, et al. *Mol Ther*. 2007;15(2):320-329. 4. Wang B, et al. *Gene Ther*. 2008;15(22):1489-1499.

SAREPTA THERAPEUTICS

AAVrh74.MHCK7.SCGB Development Program Synopsis (LGMD2E)

- Systemic delivery of the construct by self-complementary AAV vector reconstitutes full-length SGCB in systemic mice studies[1]
  - ~98% of muscle fibers expressed SGCB
  - Diaphragm muscle function restored to 94.4% of WT
  - Overall ambulation increased by 57%
  - No safety issues were observed in pre-clinical safety studies
- Systemic Phase 1/2a IV trial has been initiated[2]
  - 60-day biopsy data now available
- US Orphan Drug Designation application was granted in February 2018[3]
- Rare Pediatric Disease Designation was granted in May 2018[3]



cDNA, complementary deoxyribonucleic acid; ITR, inverted terminal repeat; WT, wild-type.

1. Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869. 2. ClinicalTrials.gov Identifier: NCT03652259. 3. Myonexus website. Press Release May 2018. https://myonexustx.com/2018/05/16/myonexus-therapeutics-receives-fda-rare-pediatric-drug-designation-pioneering-treatment-limb-girdle-muscular-dystrophy-type-2e/. Accessed March 30, 2019.

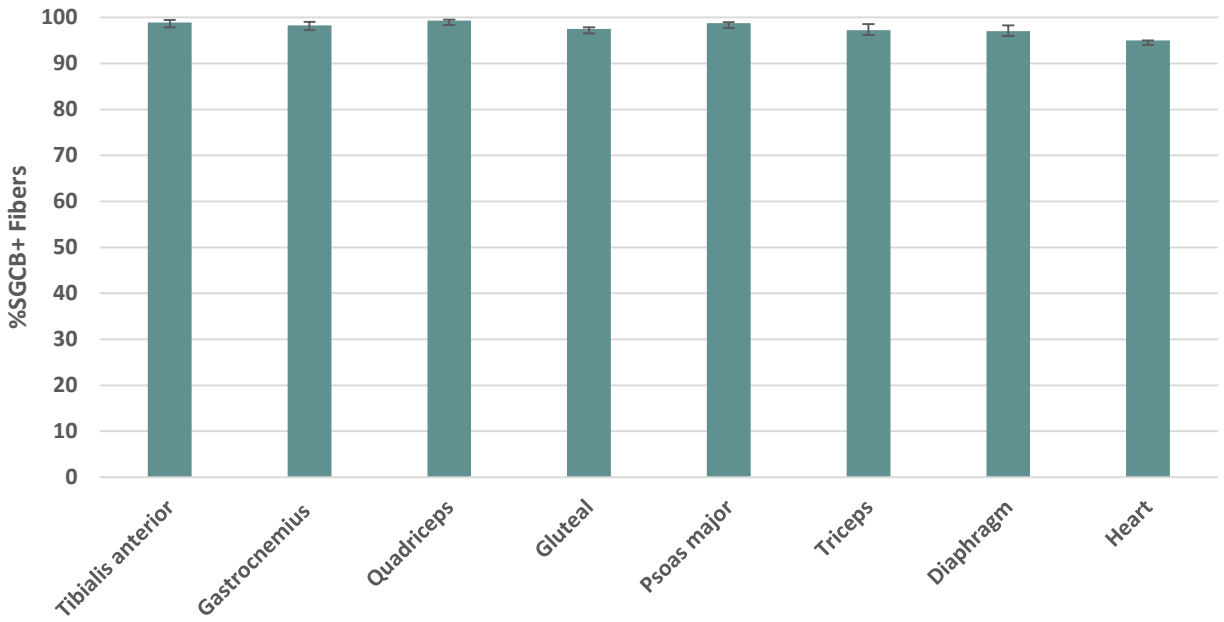
SAREPTA THERAPEUTICS

Transduction and Localization of AAVrh74.MHCK7.hSGCB Led to Restoration of DAPC Proteins in *LGMD2E-/-* Mice

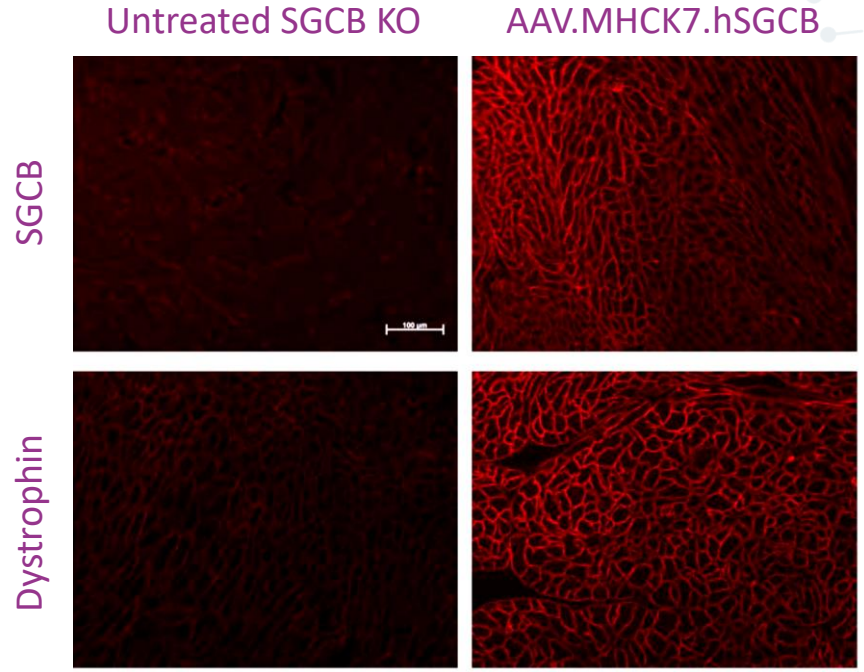
SGCB AND DYSTROPHIN EXPRESSION 6 MONTHS AFTER IV TREATMENT ($1x10^{12}$ VG TOTAL DOSE)

SGCB EXPRESSION IN TARGET MUSCLES (IF)

% Fibers Expressing SGCB
6 Months (N=5)



SGCB AND DYSTROPHIN EXPRESSION 6 MONTHS POST-INJECTION (IF)



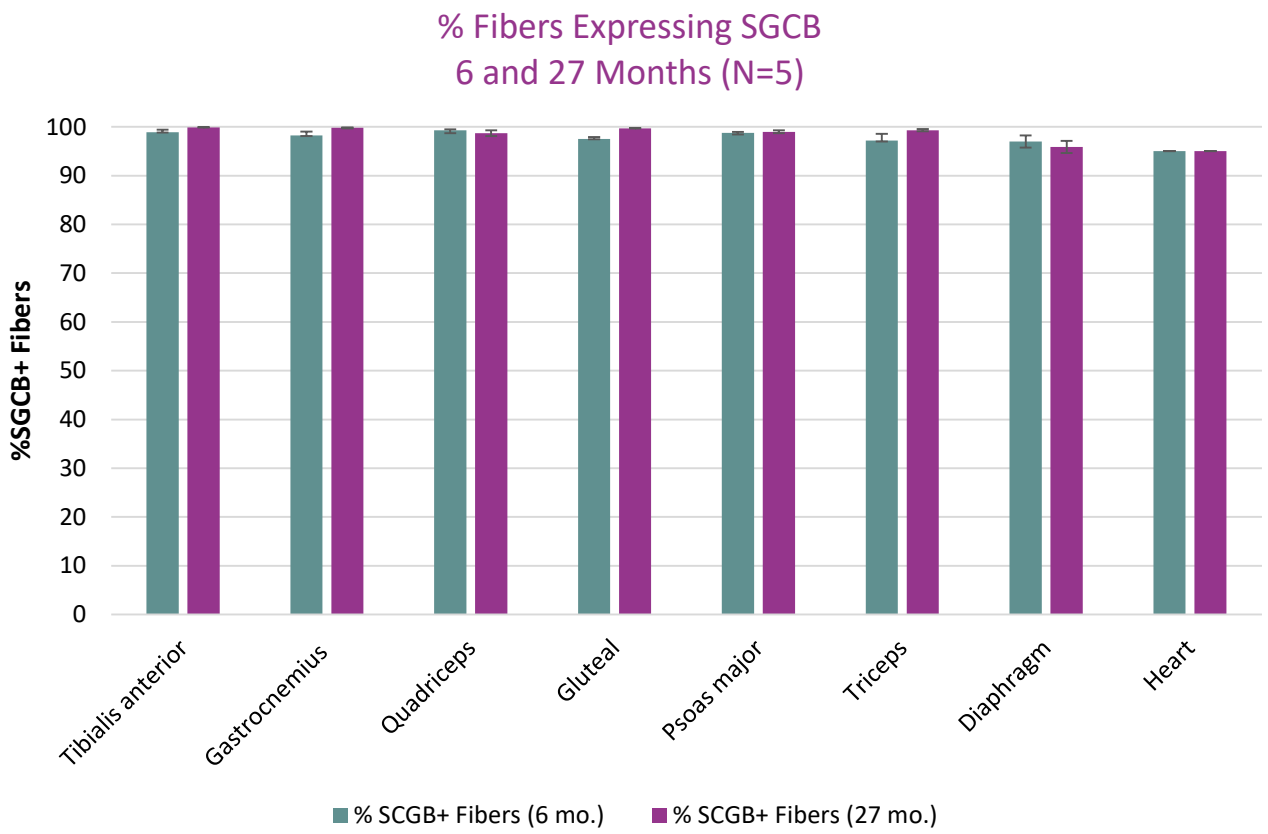
IF, immunofluorescence; SGCB, β-sarcoglycan; KO, knockout; vg, vector genome.
Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

SAREPTA THERAPEUTICS

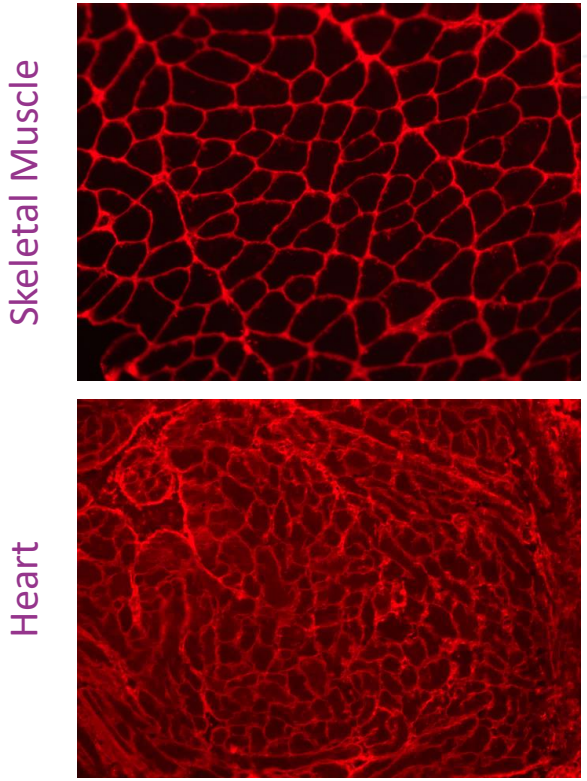
Durability: Sustained Expression for Mouse Lifespan

SGCB AND DYSTROPHIN EXPRESSION 27 MONTHS AFTER IV TREATMENT ($1x10^{12}$ VG TOTAL DOSE)

SGCB EXPRESSION IN TARGET MUSCLES (IF)



hSGCB EXPRESSION 27 MONTHS POST-INJECTION (IF)



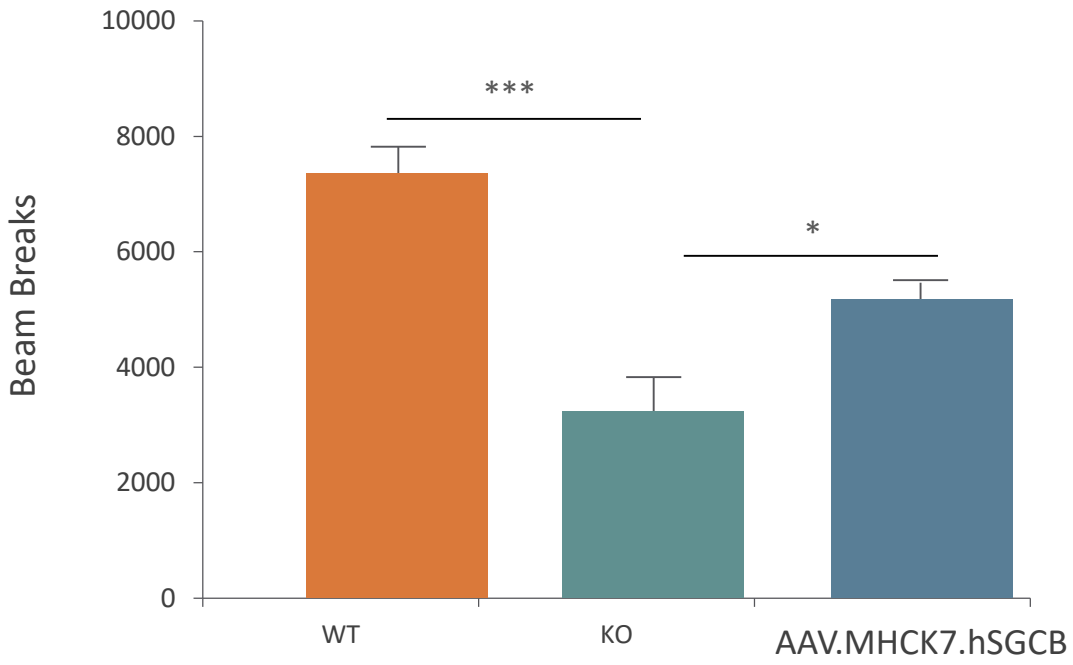
Sarepta Therapeutics 2019. Data on file.

SAREPTA THERAPEUTICS

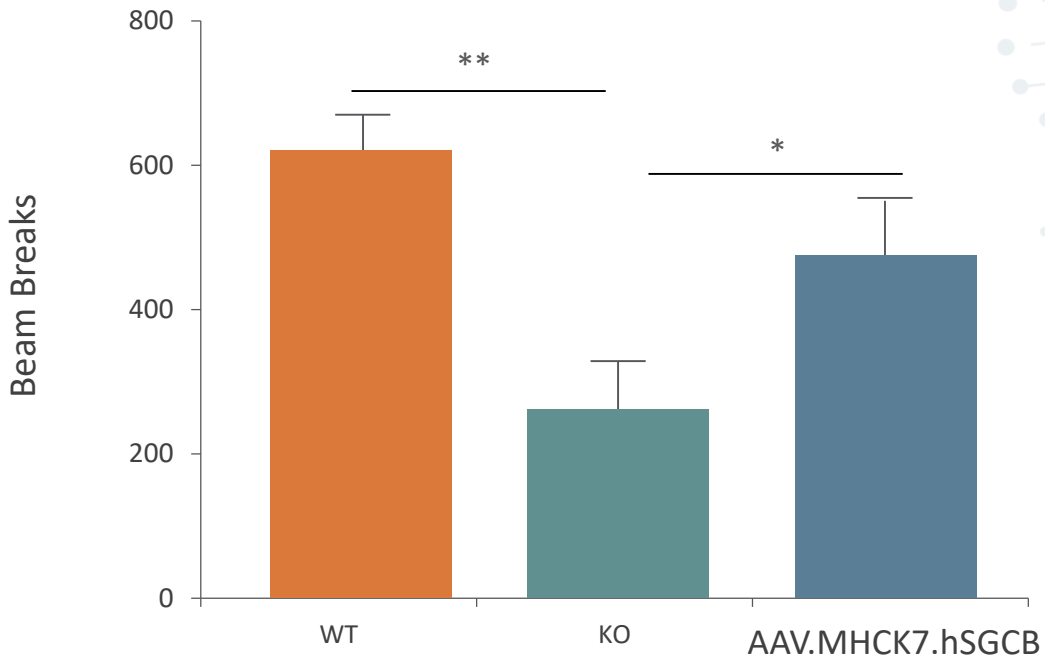
Systemic Gene Therapy Improved Activity and Movement 6 Months Post-Injection

Overall Ambulation and Hindlimb Vertical Activity Increased Upon Systemic Delivery to LGMD2E Mice

AMBULATION



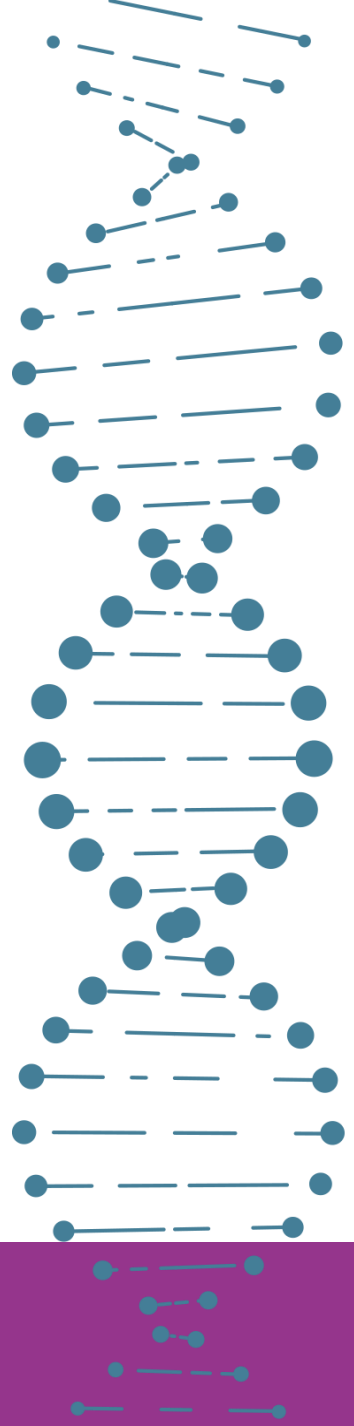
VERTICAL ACTIVITY



*P< 0.05; **P< 0.01; ***P< 0.0001.

Pozsgai ER, et al. *Mol Ther.* 2017;25(4):855-869.

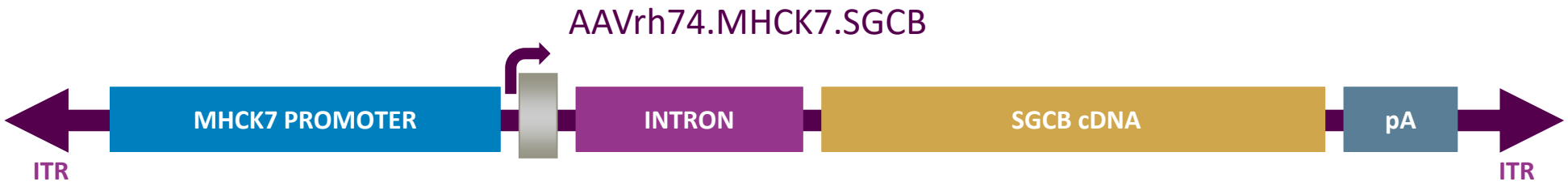
SAREPTA THERAPEUTICS



Clinical Results:
LGMD2E (β-sarcoglycanopathy)

SAREPTA THERAPEUTICS

AAVrh74.MHCK7.β-sarcoglycan
Goal to Validate Pre-clinical Results



Characteristic	Driven By	Expectations based on pre-clinical models
Transduction	AAVrh74	AAVrh74 efficient transduction to all muscle types[1]
Expression	MHCK7 Promoter	MHCK7 selective for cardiac and skeletal transgene muscle expression[2,3] Widespread SGCB expression in all muscles[3]
Efficacy	Transgene	Reduction in CK[3] Improved functional outcomes[3]
Safety	Vector and Transgene	Favorable safety profile[3]

1. Chicoine LG, et al. *Mol Ther*. 2014;22(2):338-347. 2. Salva MZ, et al. *Mol Ther*. 2007;15(2):320-329. 3. Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

SAREPTA THERAPEUTICS

LGMD2E Open-Label Trial Design

- Up to 9 subjects with LGMD
  - Cohort 1: 3 subjects
  - 4-15 years of age
  - 5 x 10^{13} vg/kg AAVrh74.MHCK7.SGCB*
- Inclusion criteria
  - A confirmed *SGCB* mutation in both alleles
  - Negative for AAVrh74 antibodies
  - >40% of normal 100-meter walk test
- 60-day muscle biopsy
- Prednisone 1 day prior to gene transfer, 30 days 1 mg/kg, taper

*Equivalent to a total dose of 1 x 10^{12} vg in mice.

ClinicalTrials.gov Identifier: NCT03652259.

SAREPTA THERAPEUTICS

Endpoints in the LGMD2E Study

- Primary endpoints
  - Expression: ≥20% SGCB-positive fibers
  - Safety
- Secondary endpoints include:
  - Change in CK
  - Functional endpoints

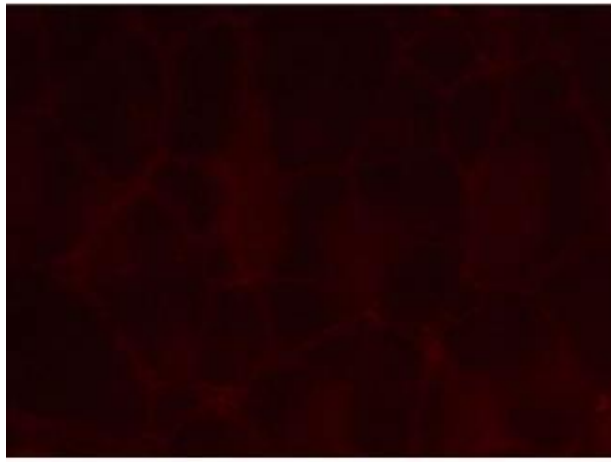
ClinicalTrials.gov Identifier: NCT03652259.

SAREPTA THERAPEUTICS

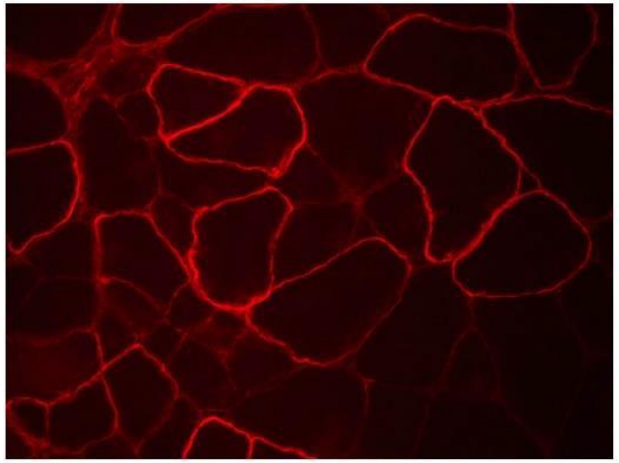
Pre-clinical Models Correlated Expression With Function

≥20% SGCB EXPRESSION LEADS TO INCREASED FUNCTION IN LGMD2E MICE

Pre-treatment

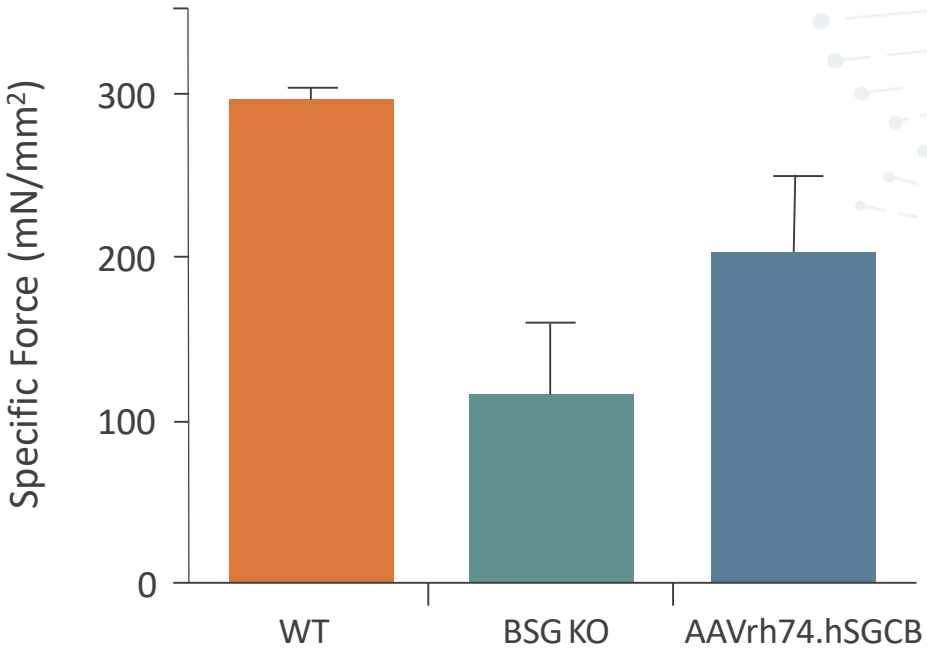


Post-treatment



5 x 10^{12} vg/kg

FUNCTION



Sarepta Therapeutics 2019. Data on file.

SAREPTA THERAPEUTICS

LGMD2E Subject Demographics at Baseline[1]

Subject	Age (years)	Mutation	Weight (kg)	CK Levels (U/L)
1	13	Exon 3	55	10,727
2	4	Exon 4	17	12,826
3	13	Exon 3	50	10,985

- Exons 3-6 encode for the extracellular domain of SGCB
- Mutations in these exons lead to complete absence of or severely reduced expression of SGCB, and a severe phenotype that includes cardiomyopathy[2]

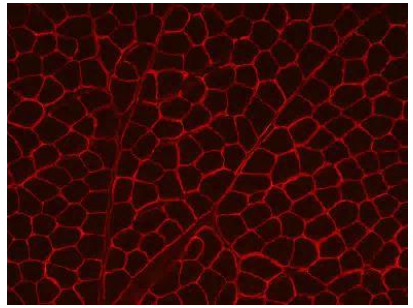
ClinicalTrials.gov Identifier: NCT03652259.

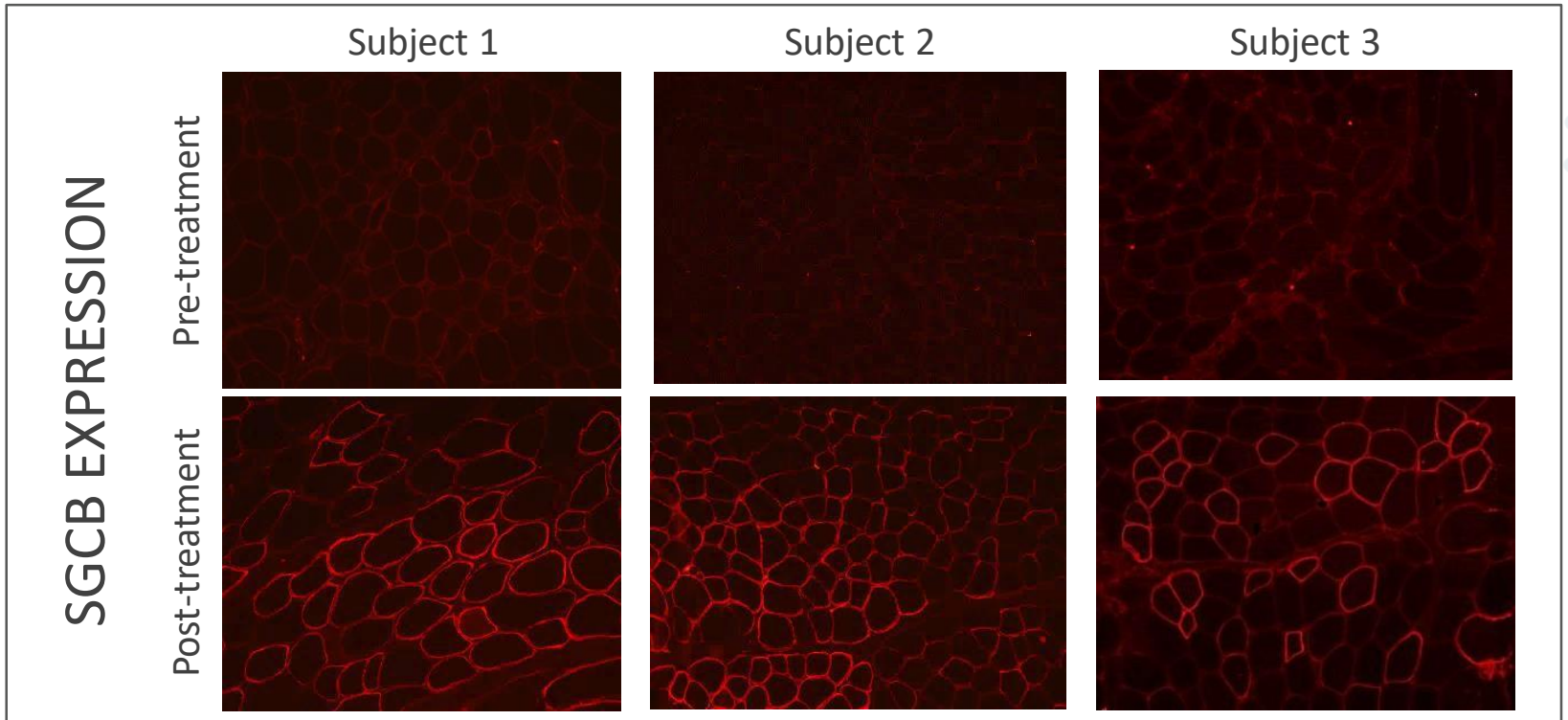
1. Sarepta Therapeutics 2019. Data on file. 2. Semplicini C, et al. *Neurology.* 2015;84(17):1772-1781.

SAREPTA THERAPEUTICS

SGCB Expression in Muscle Biopsies in 3 Subjects at a Dose of 5 x 10^{13} vg/kg

Normal Control





	Percentage of SGCB-positive Fibers	Intensity
Mean (N=3)	51%	47%

ClinicalTrials.gov Identifier: NCT03652259.

SAREPTA THERAPEUTICS

SGCB Expression in Muscle Biopsies in 3 Subjects at a Dose of 5 x 10^{13} vg/kg

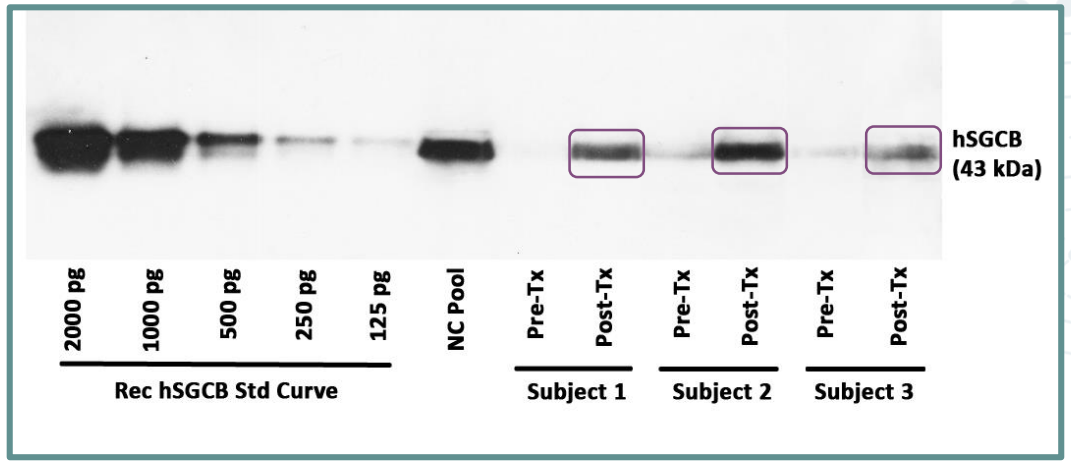
Subject	Percentage of SGCB-Positive Fibers	Mean Intensity
1	63%	47%
2	49%	57%
3	42%	38%
Mean	**51%**	**47%**

ClinicalTrials.gov Identifier: NCT03652259.

SAREPTA THERAPEUTICS

SGCB Expression in 3 Subjects as Measured by Western Blot Post-treatment

Subject	Mean SGCB Expression vs Normal
1	34.7%
2	39.2%
3	34.5%
Mean	**36.1%**



Pre-Tx Below LOQ || LOQ = 5% NC

The gene transfer delivers full-length SGCB

ClinicalTrials.gov Identifier: NCT03652259. LOQ, Limit of Quantitation

SAREPTA THERAPEUTICS

The Optimized Vector and Promoter Provided Expression at a Dose of 5 x 10^{13} vg/kg

Vector

Vector Genome Number

	Vector Copies/µg DNA	Copies per Nucleus
Mean (n=3)	8.4 x 10^4	0.60

Vector/ Promoter

SGCB Expression (IHC)

	Percentage of Beta-Sarcoglycan-positive Fibers	Intensity
Mean (n=3)	51%	47%

Promoter/ Transgene

SGCB Expression (WB)

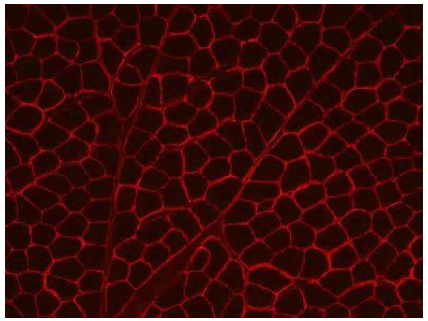
	Percentage of Normal
Mean (n=3)	36.1%

ClinicalTrials.gov Identifier: NCT03652259.

SAREPTA THERAPEUTICS

SGCB Expression Significantly Upregulated SGC Complex at a Dose of 5 x 10^{13} vg/kg

Normal Control



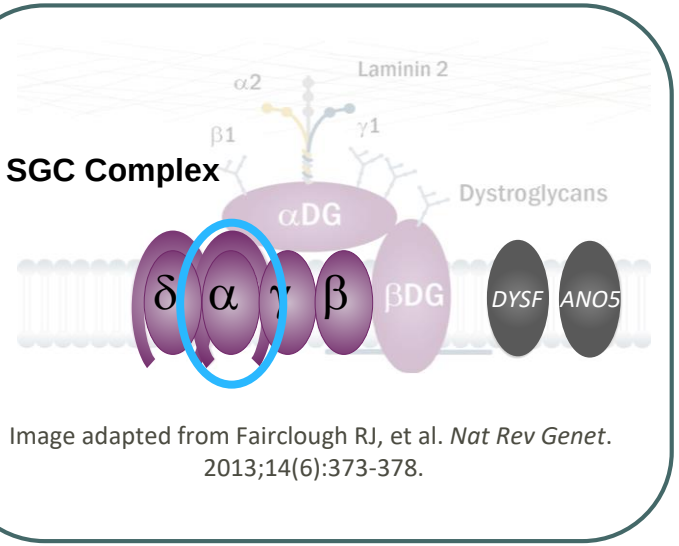
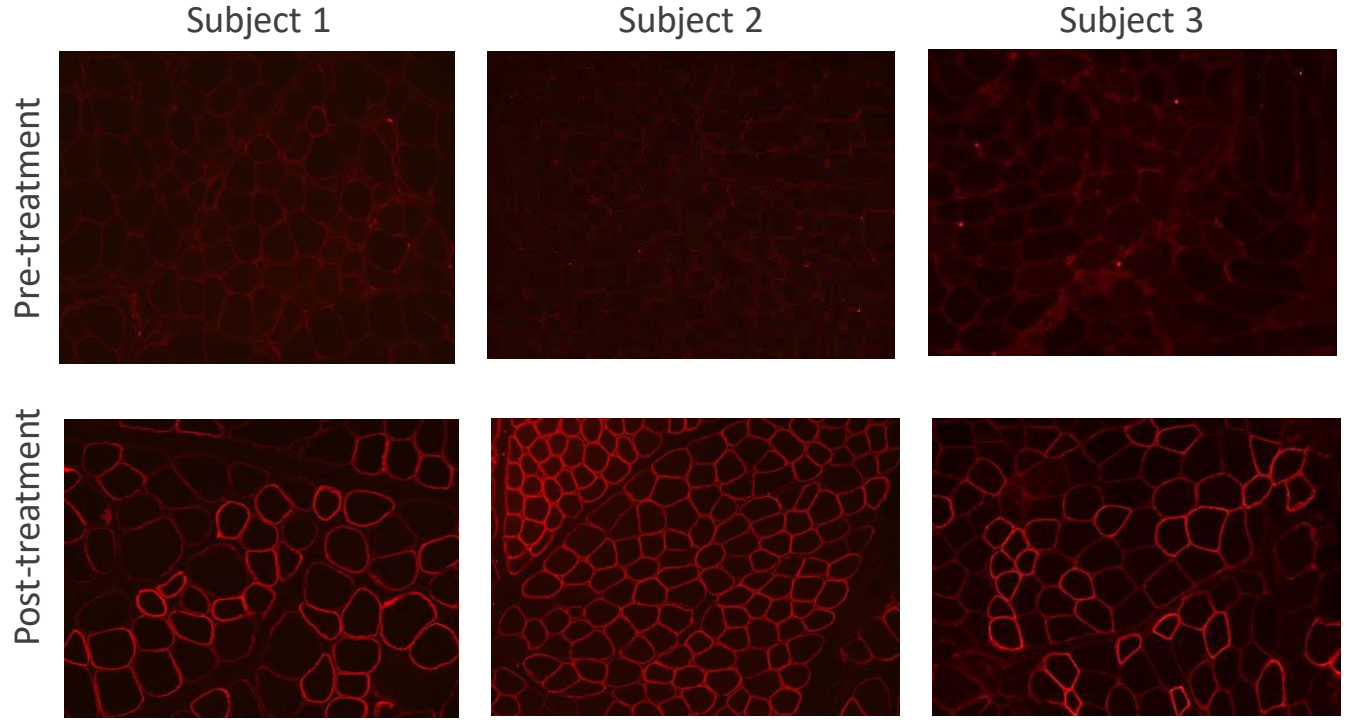


Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

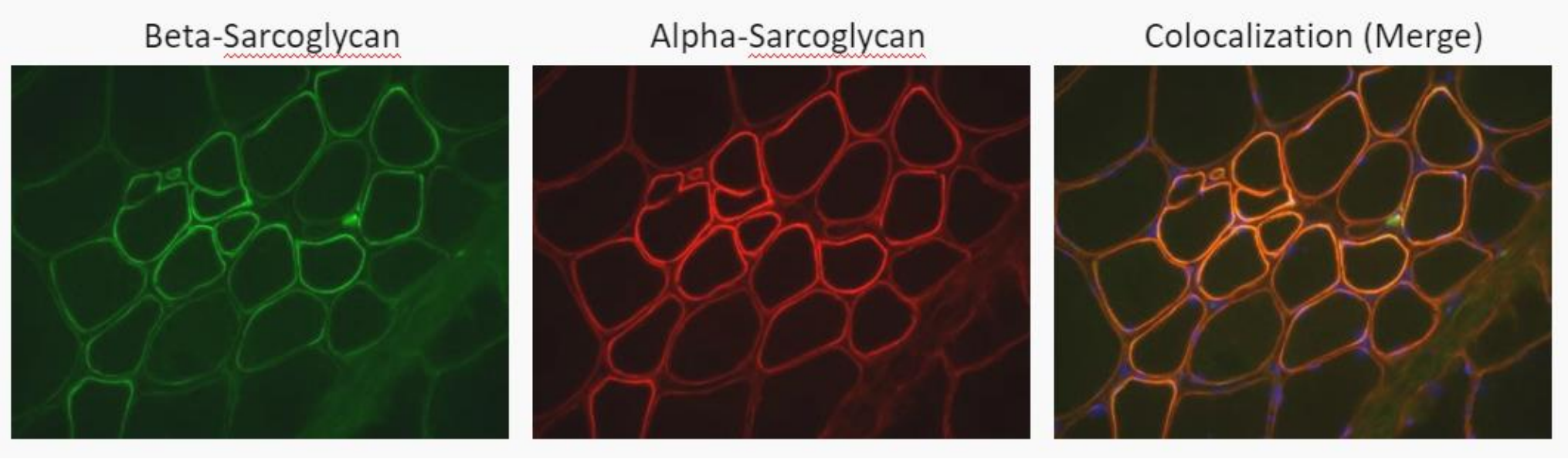
α-SARCOGLYCAN EXPRESSION (IHC)



ClinicalTrials.gov Identifier: NCT03652259.

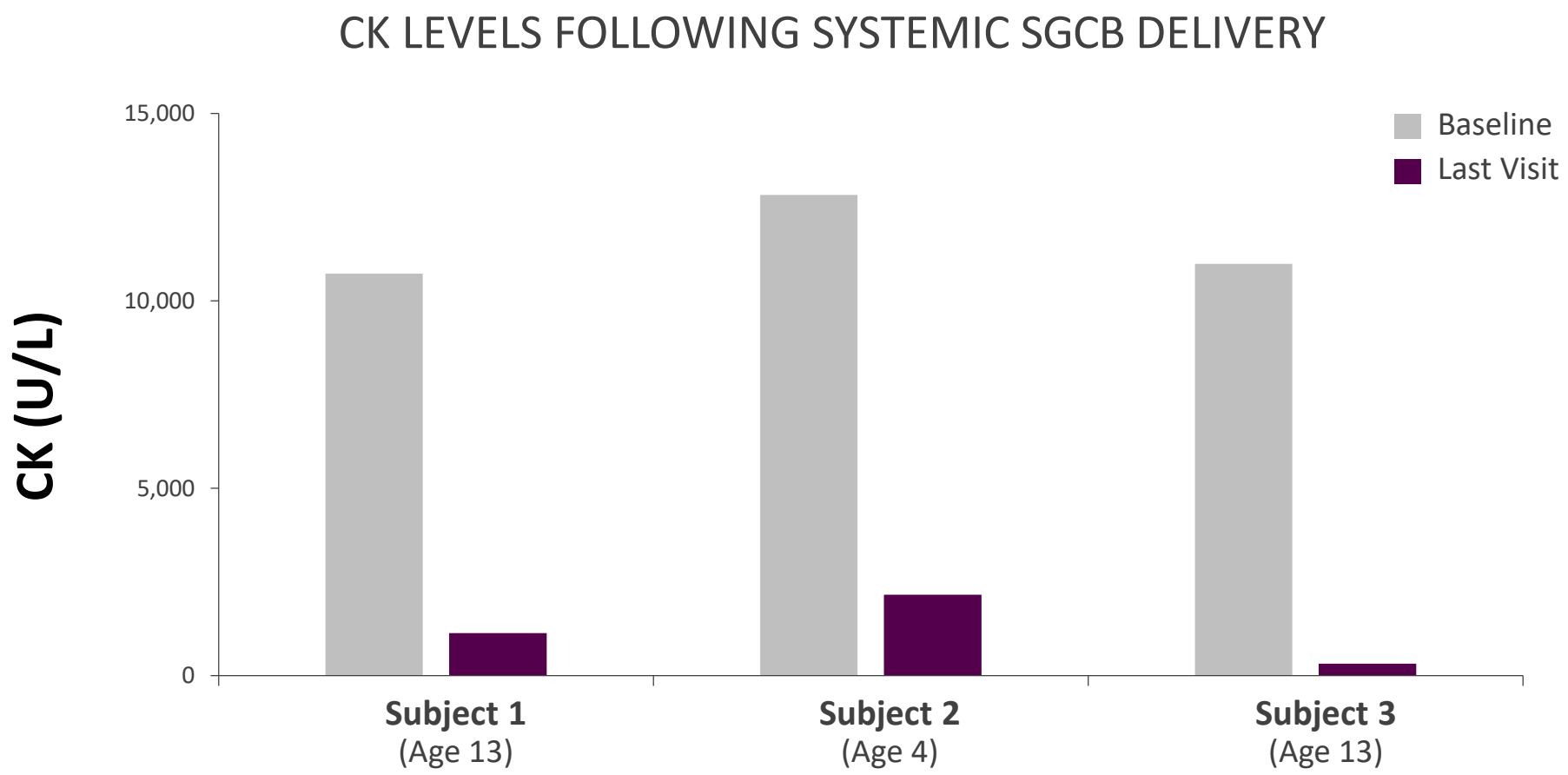
SAREPTA THERAPEUTICS

Beta-Sarcoglycan Gene Therapy Restores Sarcoglycan Complex to the Membrane



NCT03652259; Data on file from Patient 3, Sarepta Therapeutics Inc: IHC staining of tissue sample for members of the dystrophin-associated protein complex (beta- and alpha-sarcoglycan).

90% Mean Reduction of CK Levels Observed With *Systemic* SGCB Gene Therapy



ClinicalTrials.gov Identifier: NCT03652259.

Sarepta Therapeutics 2019. Data on file.

SAREPTA THERAPEUTICS

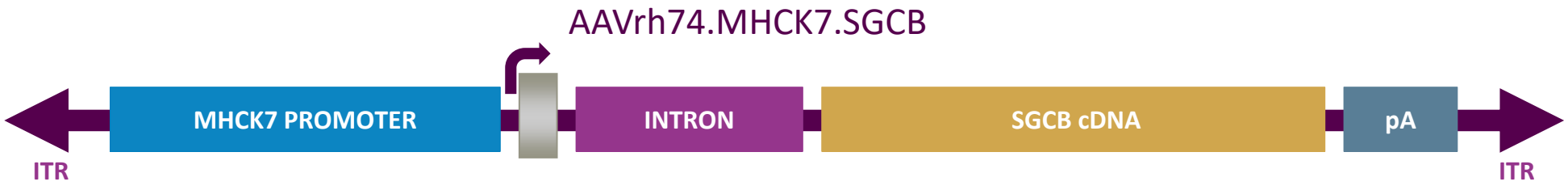
Safety Data (N=3)

- 90 days follow-up to date for all subjects
- 2 subjects had elevated liver enzymes, 1 of which was designated an SAE, as the subject had associated transient increase in bilirubin
  - Both events occurred when the subjects were tapered off oral steroids
  - Elevated liver enzymes returned to baseline and symptoms resolved within days following supplemental steroid treatment
- No other clinically significant laboratory findings
- 2 patients had transient mild nausea generally within the first week coincident with increased steroid dosing
  - Did not correlate with liver enzyme elevations or any other abnormality

SAE, serious adverse event.
ClinicalTrials.gov Identifier: NCT03652259.

SAREPTA THERAPEUTICS

AAVrh74.MHCK7.SGCB Clinical Summary (N=3)

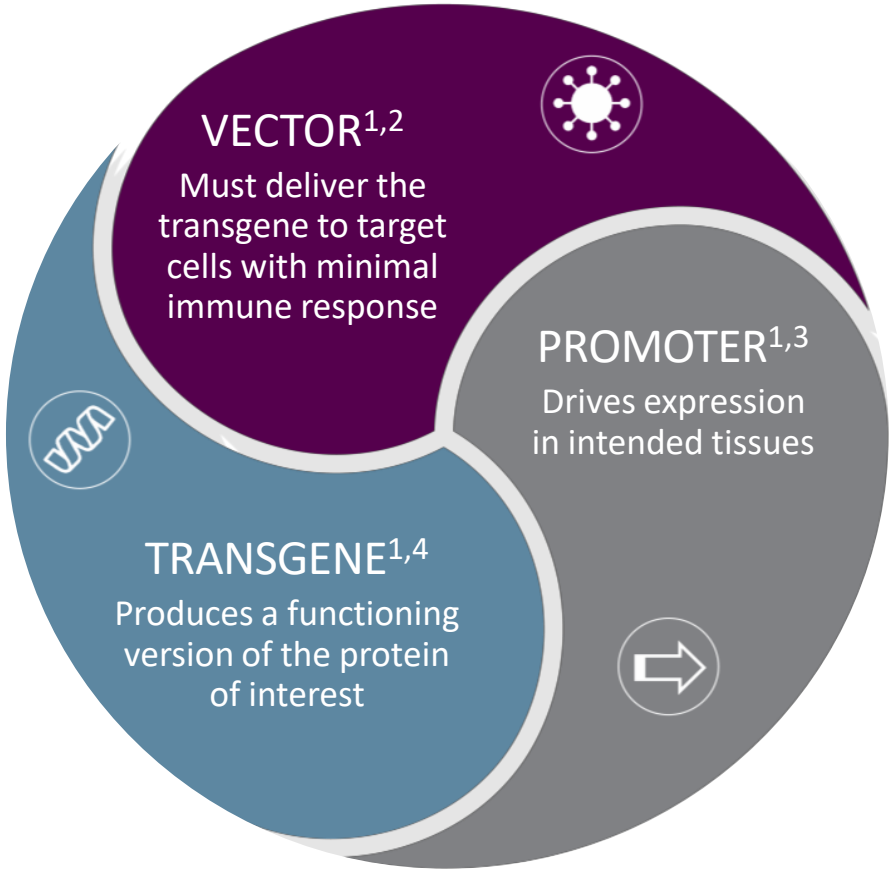


Characteristic	Driven By	Findings to Date[4]
Transduction	AAVrh74[1]	AAVrh74 efficient transduction to skeletal muscle
Expression	MHCK7 Promoter[2,3]	SGCB expression in biopsied muscle
Efficacy	Transgene[3]	Reduction in CK
Safety	Vector and Transgene[3]	No unexpected immunological responses in these patients

1. Chicoine LG, et al. *Mol Ther*. 2014;22(2):338-347. 2. Salva MZ, et al. *Mol Ther*. 2007;15(2):320-329. 3. Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869. 4. Sarepta Therapeutics 2019. Data on file.

SAREPTA THERAPEUTICS

Sarepta's Gene Therapy Engine at Work
3 Essential Elements in Rationally Designed Therapeutic Development



- Platform approach
- 2 therapeutic areas with clinical data to date
- Transduction, localization & expression shown in both programs

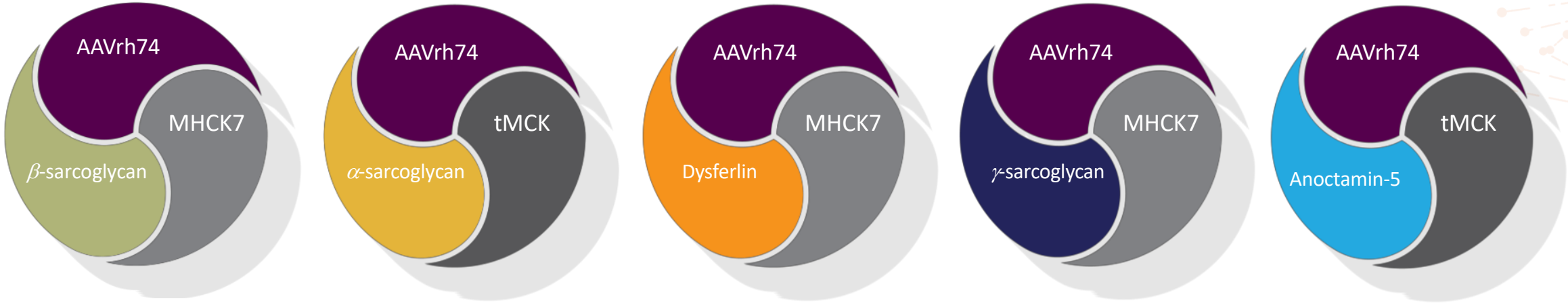
1. Naso MF, et al. *BioDrugs*. 2017;31(4):317-334. 2. US National Library of Medicine, Lister Hill National Center for Biomedical Communications. Genetics Home Reference. Help me Understand Genetics: *Gene Therapy*. Bethesda, Maryland: 2013. https://ghr.nlm.nih.gov/primer/therapy/genetherapy. Accessed August 29, 2018.
3. Zheng C, Baum J. *Methods Mol Biol*. 2008;434:205-219. 4. Chamberlain K, et al. *Hum Gene Ther Methods*. 2016;27(1):1-12.

SAREPTA THERAPEUTICS

Gene Therapy Engine at Work Across LGMD Portfolio

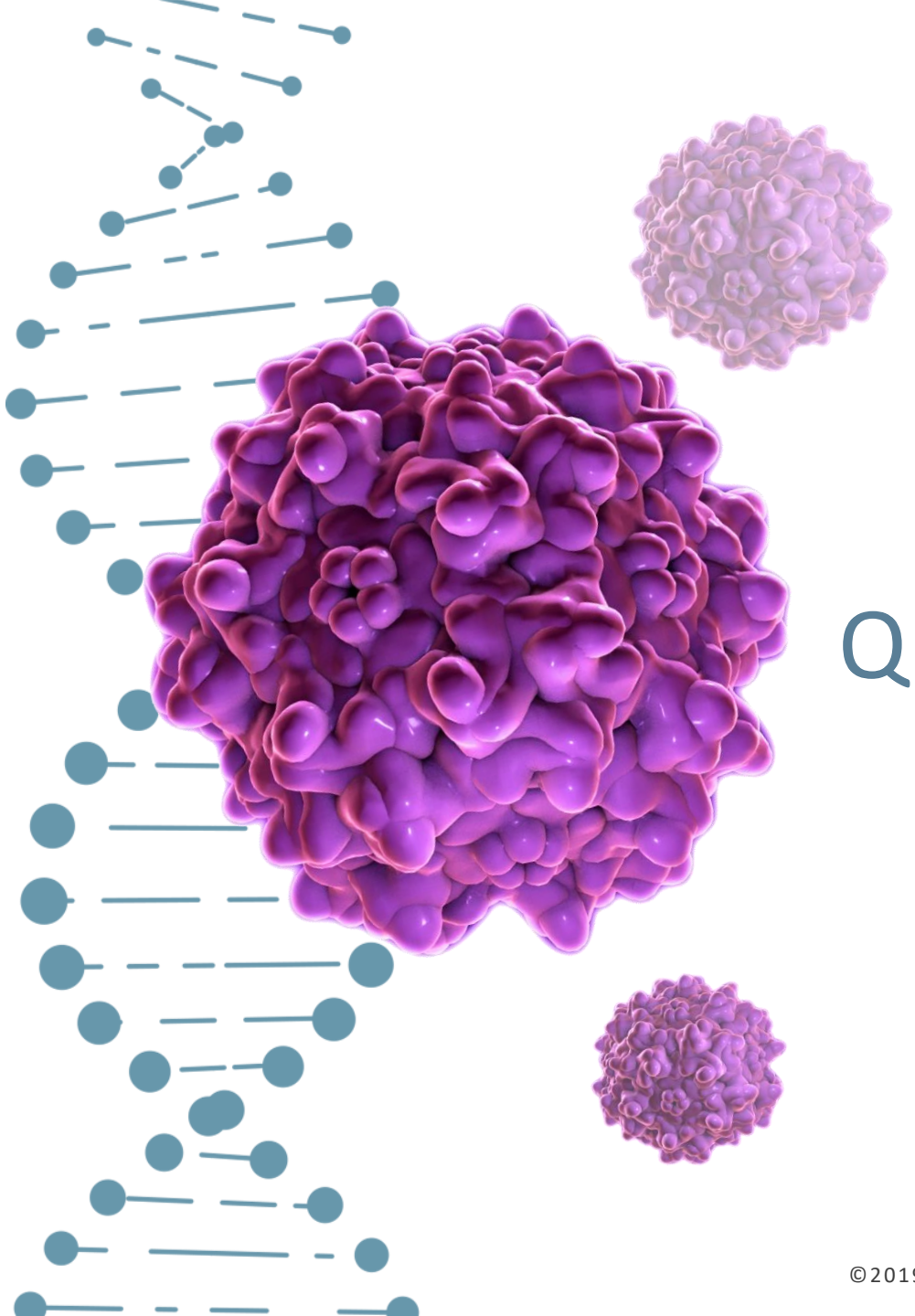
Opportunity to Generate a Steady Stream of Gene Therapy Candidates

LGMD PORTFOLIO



Sarepta Therapeutics 2019. Data on file.

SAREPTA THERAPEUTICS



Question and Answer