Pipeline studier
Duchenne muskeldystrofi

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FDA NEWS RELEASE

FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy

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For Immediate Release: June 22, 2023

Español

Today, the U.S. Food and Drug Administration approved Elevidys, the first gene therapy for the treatment of pediatric patients 4 through 5 years of age with Duchenne muscular

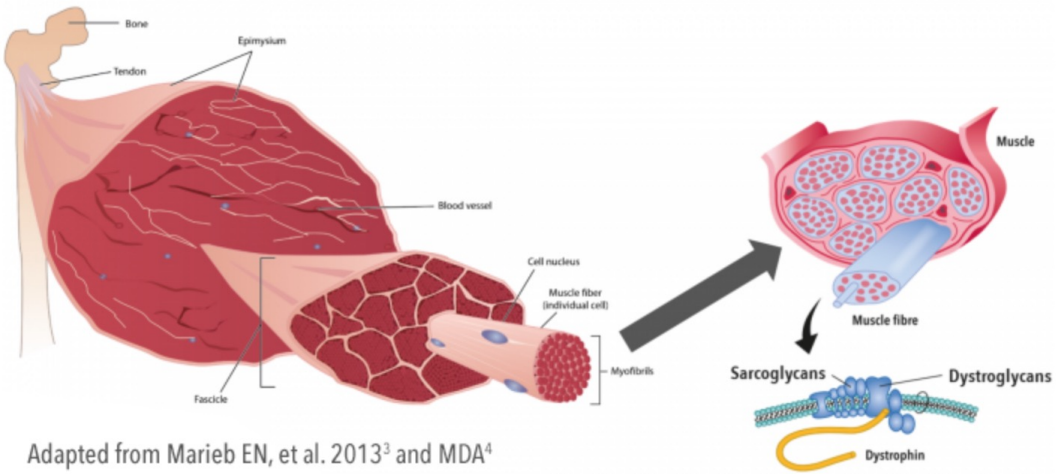
Content current as of:
06/23/2023

Regulated Product(s)
Biologics

DMD behandling

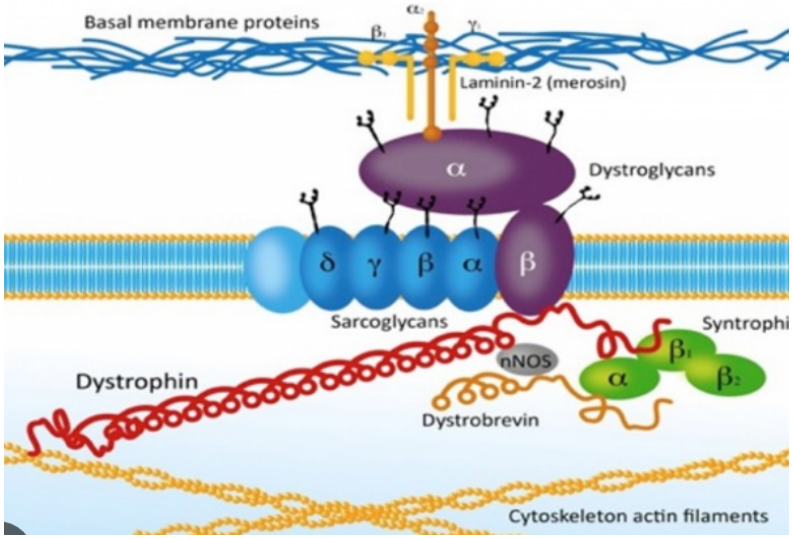
- Baggrund
- Eksisterende behandlinger
- Exon-skipping
- Stop codon readthrough behandling
- Microdystrophin-baseret genterapi
- Vamorolone
- Andre behandlinger

Duchenne muskeldystrofi



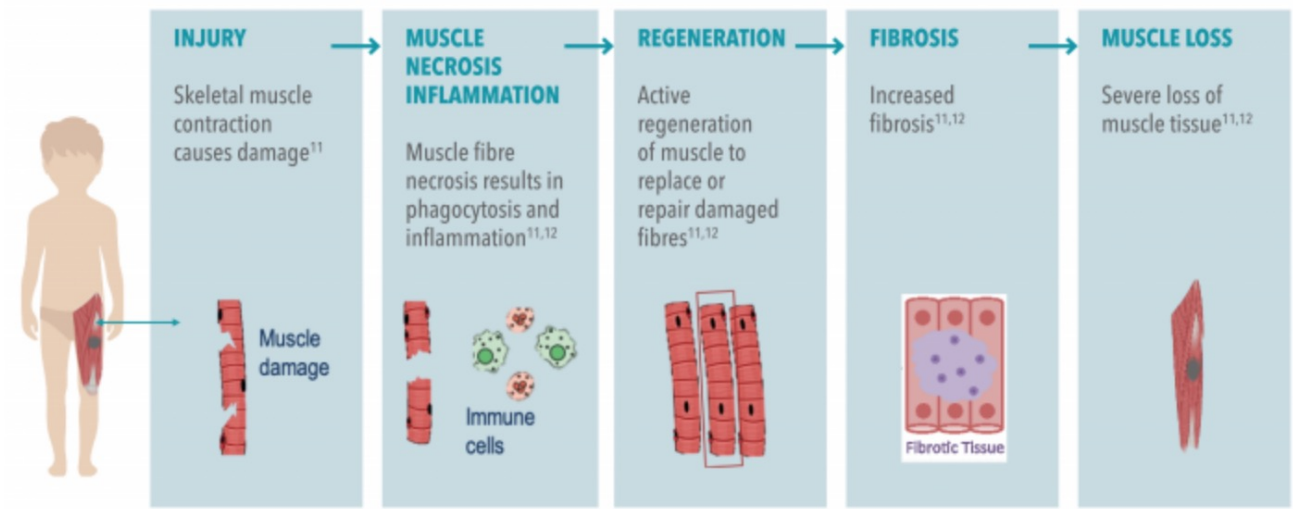
Adapted from Marieb EN, et al. 2013[3] and MDA[4]

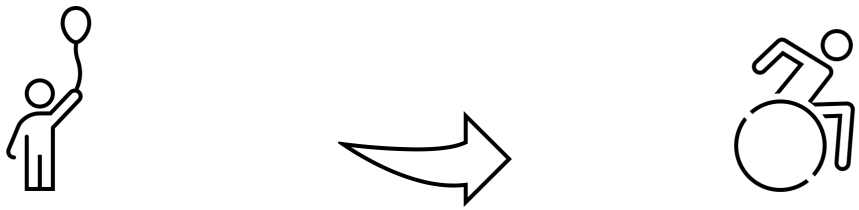
- Skyldes mutation i dystrofin genet, der giver stabilitet under muskelkontraktioner
- Ca. 1:5000 drengebørn



Duchenne muskeldystrofi

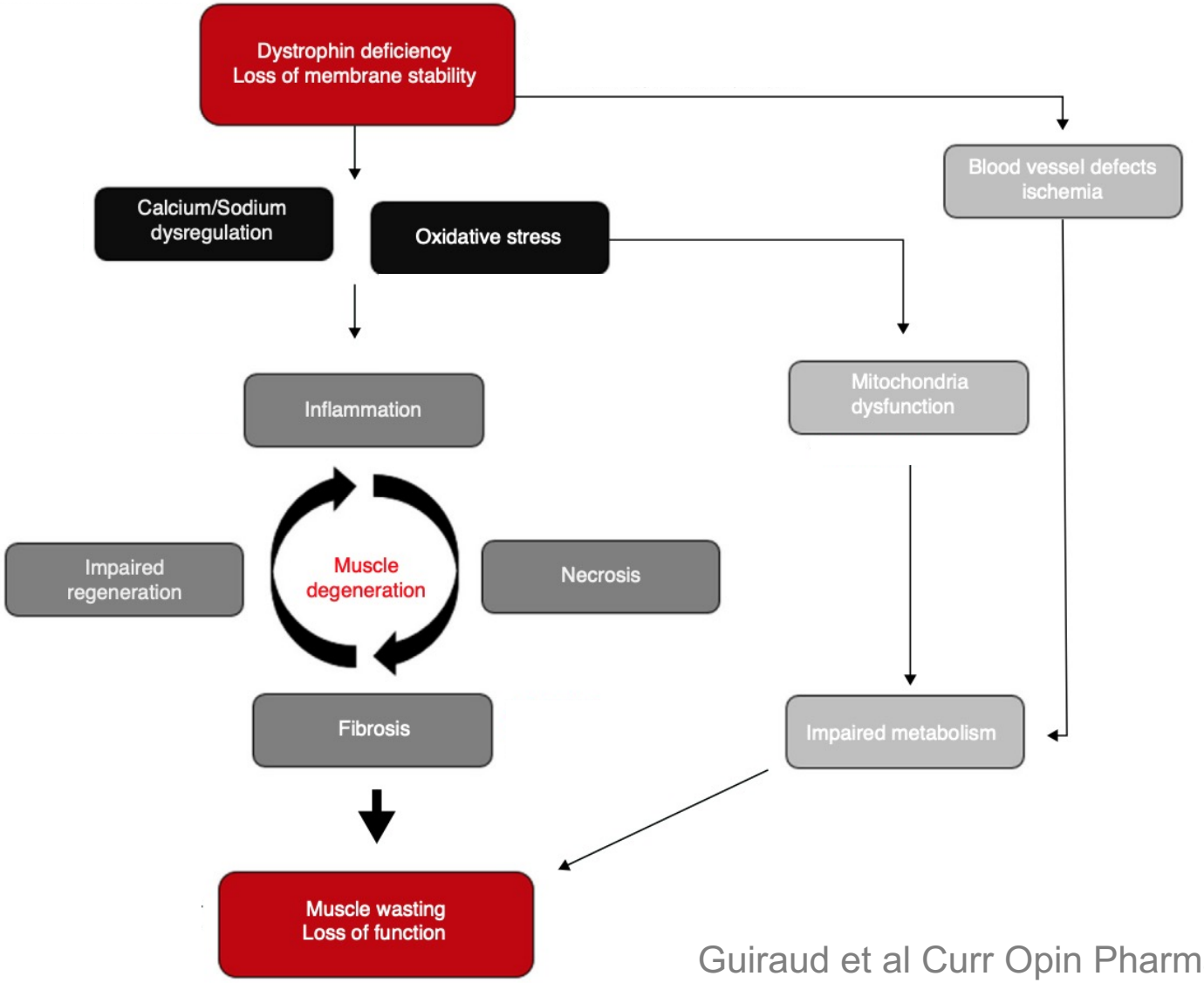
- Manglende eller defekt dystrofin fører til muskel degeneration og fibrose





www.takeonduchenne.eu

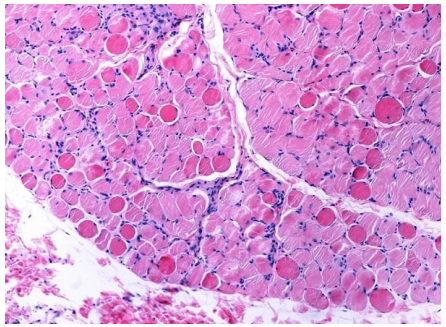
DMD patogenese



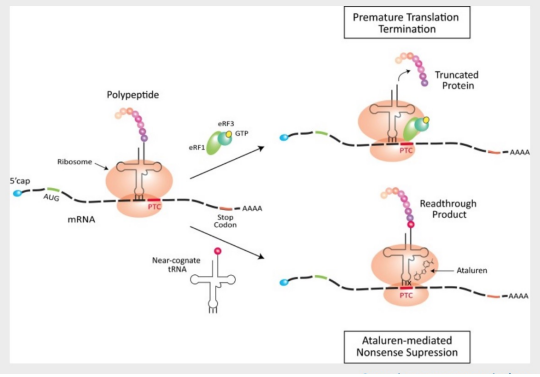
Guiraud et al Curr Opin Pharmacol 2017

Nuværende behandlingsmuligheder

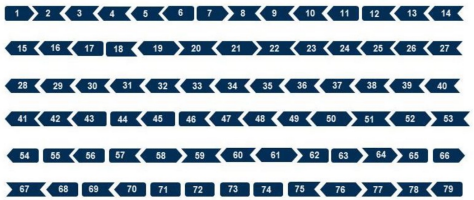
- Prednisolon
- Deflazacort



- Ataluren

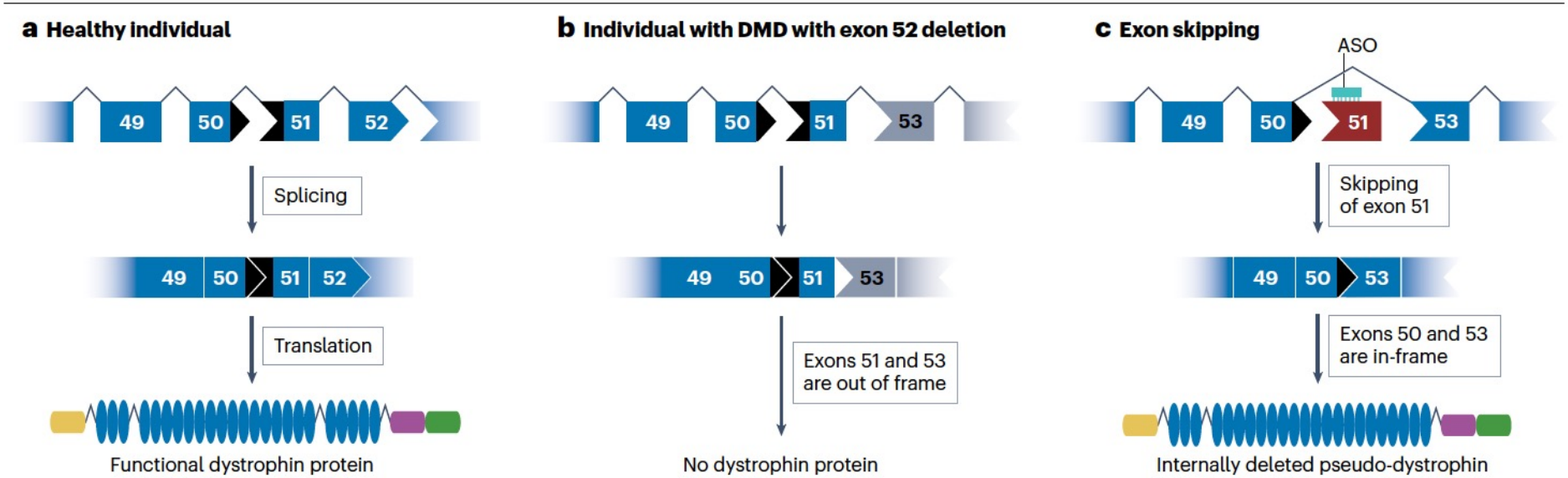


- Eteplirsen
- Golodirsen
- Viltolarsen
- Casimersen



Exon-skipping metoden

Re-etablering af dystrophin expression ved exon skipping



Roberts et al Nat Rev Aug 2023

Exon-skipping evidens

Golodirsen exon 53 og casimersen exon 45

- Godkendelse FDA hhv. dec 2019 og feb 2021
- Fase III open label langtidseffekt studie pågår.

Eteplirsen exon 51

- Enkelte langtidsstudier, senest Mendell et al 2021,der ser på gangfunktion efter 4 års behandling. Forskel i 6MWT på 159m efter år 4 (12 patienter). Flere var gående efter 4 år (10/12 eteplirsen beh. vs. 3/11 kontroller fra registre)

Godkendelser baseret på dokumenteret øget dystrofin i skeletmuskulatur

Bivirkninger: få

Flere firmaer med studier med **andre tilgange til exon-skipping**, bla.

- small nuclear RNAs (snRNAs), der kan indgives med adeno-associated virus til duplikationer
- self-complementary AAV9 der koder forU7 snRNA exon skipping transgene cassetter, der kan skippe en kopi af DMD exon 2 og generere et fuld-længde dystrofin.

Roberts et al Nat Rev Aug 2023

Exon-skipping studier

Table 1 | Exon skipping drugs approved and in clinical development

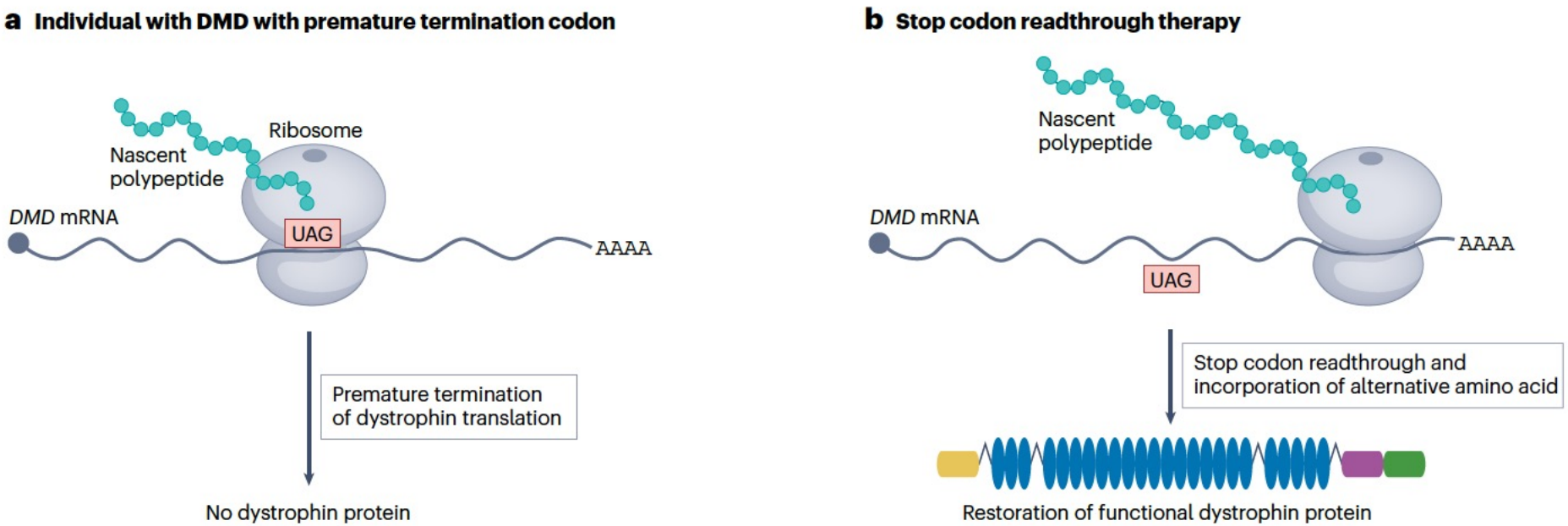
Name	Company	Chemistry	Target exon	Approval or clinical stage
Eteplirsen	Sarepta Therapeutics	PMO	51	FDA
Viltolarsen	NS Pharma	PMO	53	FDA, Japan
Golodirsen	Sarepta Therapeutics	PMO	53	FDA
Casimersen	Sarepta Therapeutics	PMO	45	FDA
Vesleteplirsen	Sarepta Therapeutics	PPMO (R_6Gly)	51	Phase II
WVE-N531	Wave Life Sciences	PS/PN stereoselective	53	Phase Ib/II
Renadirsen	Daiichi Sankyo	2′OMe/ENA mixmer	45	Phase II
AOC 1044	Avidity Biosciences	PMO–antibody conjugate	44	Phase I/II
DYNE-251	Dyne Therapeutics	PMO–Fab fragment conjugate	51	Phase I/II
ENTR-601-44	Entrada Therapeutics	PPMO (EEV)	44	Preclinical
PGN-EDO51	PepGen	PPMO (EDO)	51	Phase I
SQY51	SQY Therapeutics	Tricylco-DNA	51	Phase I/II (in 2023)

EDO, enhanced delivery oligonucleotide; EEV, enhanced endosomal escape vehicle; ENA, ethylene-bridged nucleic acid; PMO, phosphorodiamidate morpholino oligonucleotide; PPMO, peptide–PMO conjugate; PS/PN, phosphorothioate and phosphoryl guanidine linkages.

Roberts et al Nat Rev Aug 2023

Ataluren

Re-etablering af dystrophin expression ved stop codon read-through behandling



Juli 2014 blev Ataluren betinget godkendt af EMA.
FDA kunne ikke godkende Ataluren på de samme data.
Der er fortsat kontrovers om effekt, og flere studier pågår (fase II, NCT04336826 og fase III, NCT02369731, NCT01247207, NCT03179631

Roberts et al Nat Rev Aug 2023

Genterapi

22/6-23 FDA godkendelse

Adeno-associated virus vector-based gene therapy Elevidys
(delandistrogene moxeparvovec-rokl, SRP-9001)

- Etablerer micro-dystrophin
- Første genterapi til DMD, til drenge 4-5 år
- Kontraindikation ved deletioner exon 8 eller 9.
- Bivirkninger rapportereret: leverpåvirkning, immunmedieret myositis og myokarditis.

Flere afprøvningsstudier

- A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of Delandistrogene Moxeparvovec (SRP-9001) in Non-Ambulatory and Ambulatory Participants With Duchenne Muscular Dystrophy (DMD) (ENVISION)
- A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of Delandistrogene Moxeparvovec (SRP-9001) in Participants With Duchenne Muscular Dystrophy (DMD) (EMBARK)
- A Gene Transfer Therapy Study to Evaluate the Safety of Delandistrogene Moxeparvovec (SRP-9001) in Participants With Duchenne Muscular Dystrophy (DMD)

Elevidys - effekt

- Baggrund for godkendelsen

CENTER DIRECTOR DECISIONAL MEMO

BLA 125781

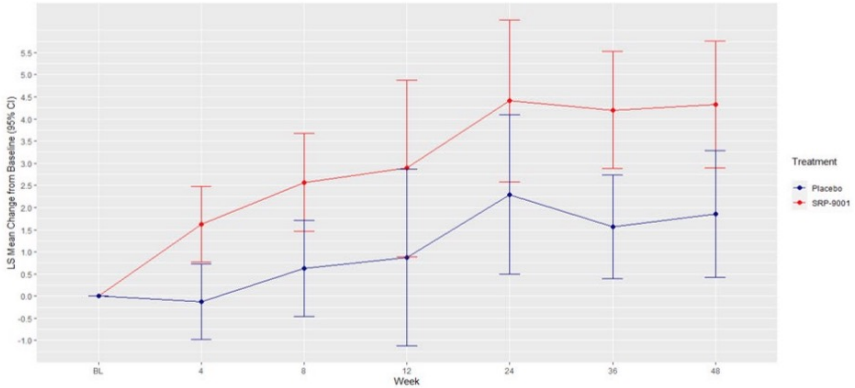
Product Name: ELEVIDYS (delandistrogene moxeparvovec-rokl)

Indication: Duchenne Muscular Dystrophy (DMD) in Ambulatory Individuals

Applicant: Sarepta Therapeutics, Inc.

Author: Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research (CBER), FDA

LS Mean Change in NSAA Total Score From Baseline Over Time in 4-5 Year Age Group



Source: FDA statistical reviewer's analysis
Abbreviation: LS, least square; NSAA, North Star Ambulatory Assessment.

settings, a somewhat greater risk of false positive conclusions (compared to placebo-controlled or other randomized superiority trials)—and, therefore, less certainty about effectiveness—may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy for an unmet medical need. The data supporting effectiveness could, despite the greater risk of error, support a conclusion in certain circumstances that there is substantial evidence of effectiveness. See, e.g., 21 CFR 601.41, and FDA's Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (December 2019).[5] Here, given the unmet medical need, the serious nature of the underlying disease entity, and the progressive and irreversible nature of the disease with onset in early childhood, it is reasonable to accept less certainty about effectiveness than in other circumstances. An additional randomized clinical trial will be required as a condition of accelerated approval to verify and describe the predicted clinical benefit. The trial is fully enrolled at this time and data from the study will be available by fall of 2023 as a condition of accelerated approval.

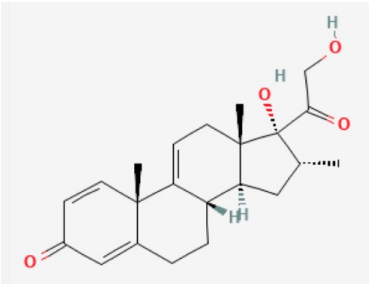
Genterapi
Mikrodystrofin replacement behandlinger

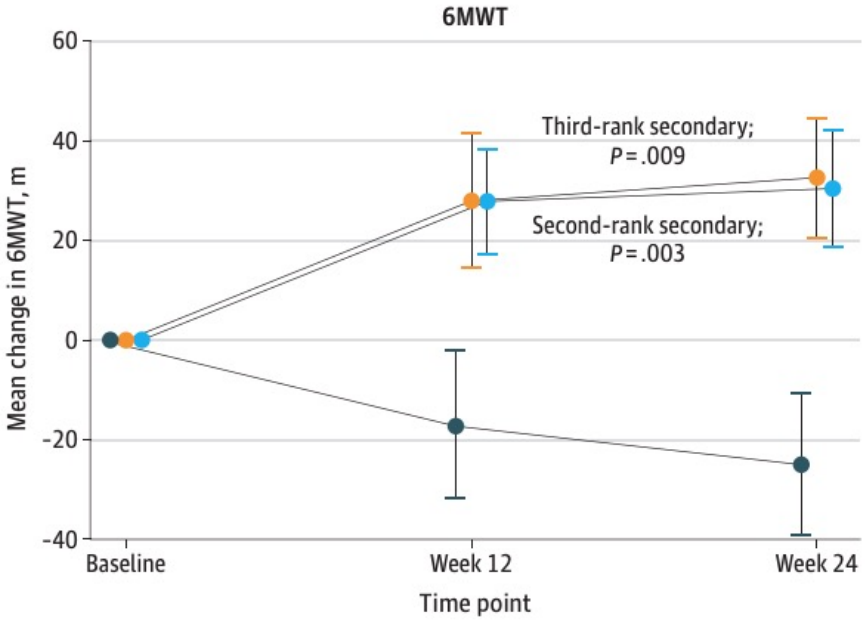
Table 2 | Micro-dystrophin gene replacement therapies in clinical development

Name	Company	Micro-dystrophin	AAV serotype	Promoter	Approval or clinical stage
SRP-9001	Sarepta Therapeutics	ΔR4-23/ΔCT	AAVrh74	MHCK7	FDA
PF-06939926	Pfizer	ΔR3-19/20-21/ΔCT	AAV9	hMSP	Phase III
SGT-001	Solid Biosciences	ΔR2-15/R18-22/ΔCT	AAV9	CK8	Phase I/II
GNT 0004	Genethon–Sarepta	ΔR4-23/ΔCT	AAV8	Spc5-12	Phase I/II/III
RGX-202	REGENXBIO	ΔR4-23 (Includes CT)	AAV8	Spc5-12	Phase I/II

AAV, adeno-associated virus.

Vamorolone





- Minder om binyrebarkhormon: anti-inflammatorisk
- Potentielt færre bivirkninger

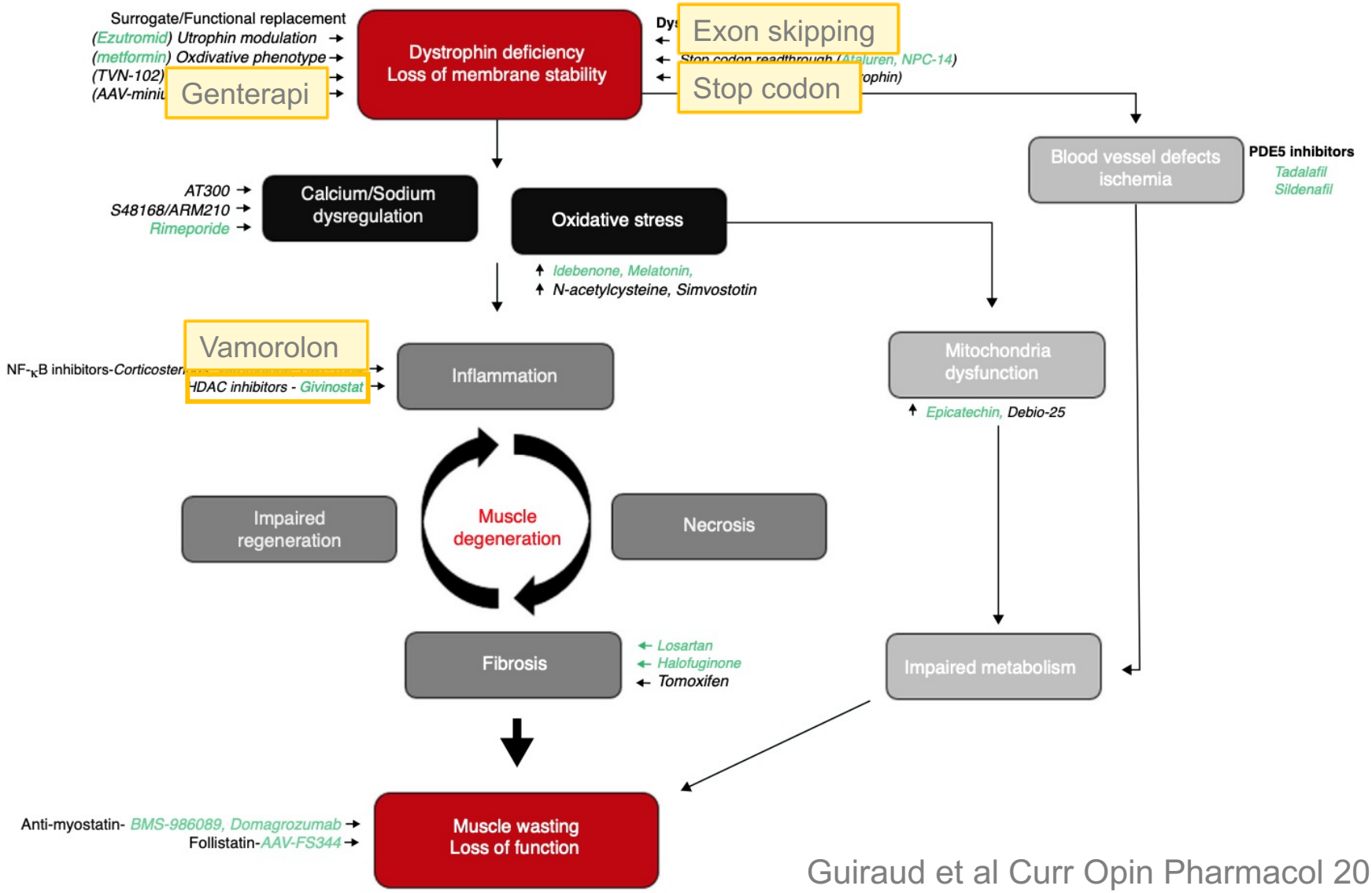
Table 2. Primary and Secondary Efficacy End Points vs Placebo and Safety End Points vs Prednisone[a]

	Vamorolone							
	6 mg/kg/d group			2 mg/kg/d group				
End point	Change from baseline, mean (SD) [No.]	End point rank LSM difference (95% CI)	P value	Change from baseline, mean (SD) [No.]	End point rank LSM difference (95% CI)	P value	Placebo group, change from baseline, mean (SD) [No.]	Prednisone group, change from baseline, mean (SD) [No.]
Efficacy vs placebo[b]								
TTSTAND velocity, rise/s	0.05 (0.07) [27]	Primary: 0.06 (0.02 to 0.10)	.002	0.04 (0.09) [29]	First-rank secondary: 0.05 (0.01 to 0.08)	.02	−0.01 (0.06) [28]	NA
6MWT, m	28.8 (49.7) [20]	Second-rank secondary: 41.6 (14.2 to 68.9)	.003	31.0 (51.1) [20]	Third-rank secondary: 37.1 (9.6 to 64.7)	.009	−23.9 (59.6) [19]	
TTRW velocity, m/s	0.28 (0.28) [25]	Fourth-rank secondary: 0.24 (0.09 to 0.39)	.002	0.16 (0.23) [24]	Fifth-rank secondary: 0.13 (−0.03 to 0.28)	>.05	0.02 (0.33) [24]	
Safety vs prednisone[c]								
Height percentile	3.86 (6.16) [26]	4.98 (0.75 to 9.21)	.02	0.26 (9.22) [27]	1.86 (−2.27 to 6.00)	>.05	NA	−1.88 (8.81) [30]
BMI z score	0.52 (0.62) [27]	0.09 (−0.19 to 0.36)	>.05	0.40 (0.45) [27]	−0.06 (−0.34 to 0.22)	>.05		0.41 (0.51) [30]

NDA submitted 1Q2023
EMA submitted 1Q2023
Ongoing study VBP-006

Guglieri et al
JAMA Neurol 2022

Duchenne muskel



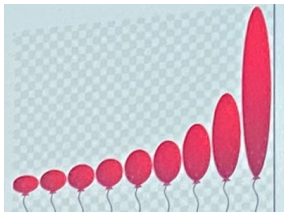
Guiraud et al Curr Opin Pharmacol 2017

DMD behandling – next steps

- Effekt
- Sikkerhed
- Bedste tidspunkt for behandling
- Holdbarhed af behandling

- Kombination af behandlinger
- Nye metoder (CRISPR/Cas9 gene editing)
- Effekt af behandlinger på DMD som multi-system sygdom

- Patient forventninger



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