Spinal muscular atrophy (SMA)

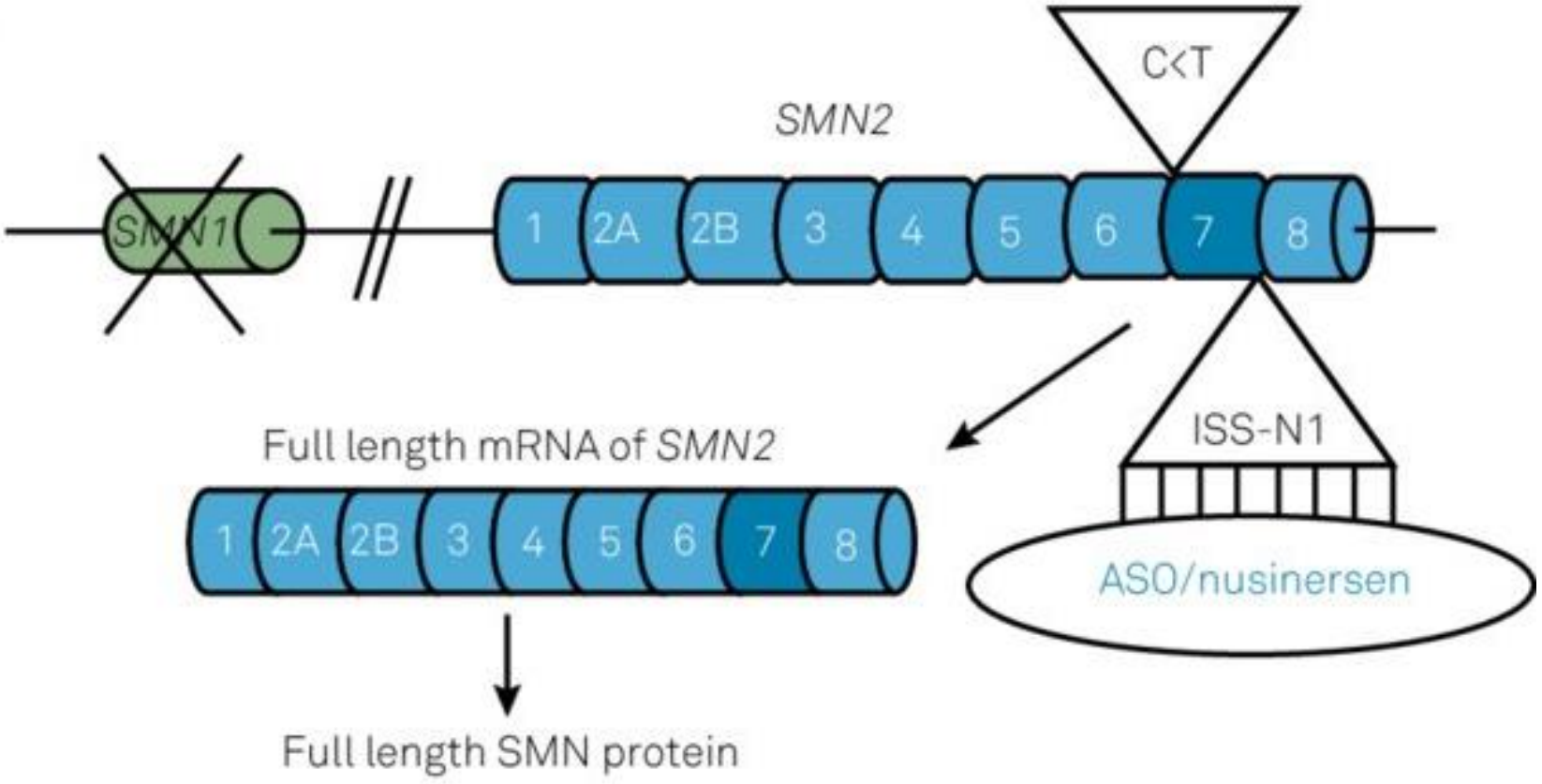
The future is bright?

SMA can be treated!

Spinraza (Biogen)

Approved by the Food and Drug Administration (FDA) in December 2016 and by the European Medicines Agency (EMA) in May 2017.

Nusinersen (Spinraza, Biogen)



Reed and Zanoteli Arq Neuropsiquiatr. 2018;76(4):265-272

Nusinersen (Spinraza, Biogen)

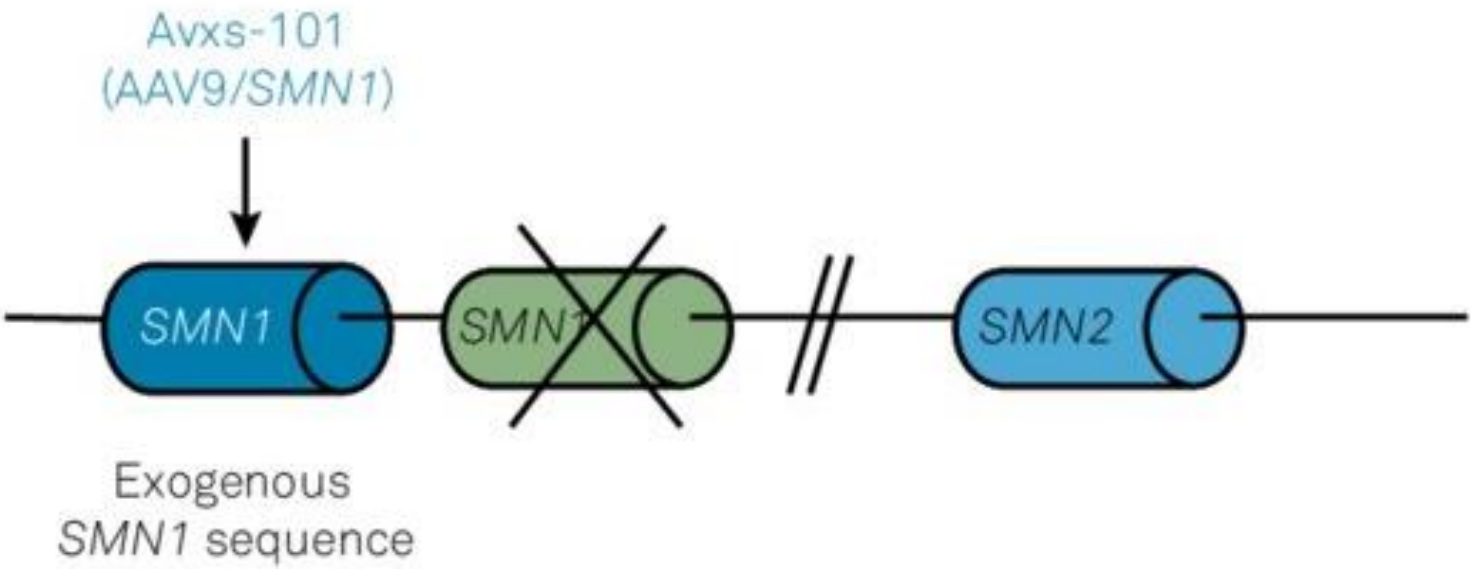
- Maintenance dose every four months (intrathecal route)
- Cost: $125,000 per dose
- Most common adverse events: fever, constipation, rash, respiratory tract infection, pneumonia, nasopharyngitis and bronchiolitis and reactions associated with lumber puncture

Risdiplam (Evrysdi; Roche and PTC Therapeutics)

- Approved by FDA in August 2020
- Oral administration
- Patients 2 months of age and older
- Side effect: fever, diarrhea, rash

… or maybe gene therapy?

SMA gene therapy



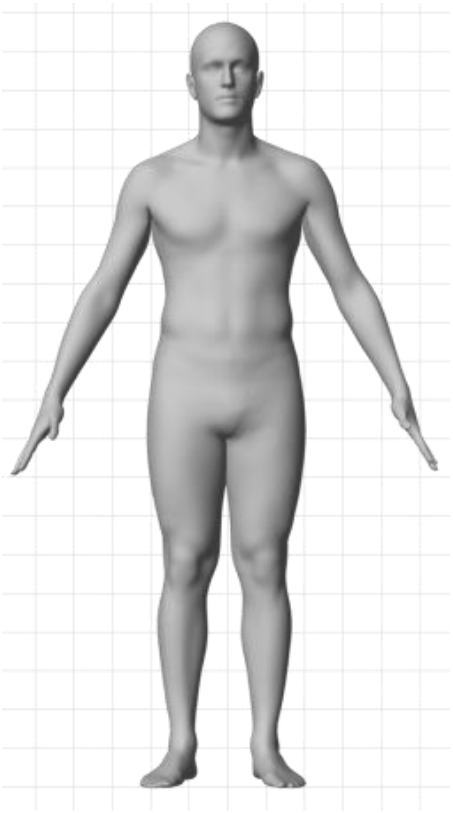
Reed and Zanoteli Arq Neuropsiquiatr. 2018;76(4):265-272

Transfer of necleic acids into the patient's cells

Directly (naked DNA)

Physical methods

Non-viral vectors:
- Calcium phosphate
- Lipids and liposomes
- Cationic polypeptides
- Cationic polymers and copolymers
- Oligodendromers
- Gold nanoparticles
- Lipid-polymer hybrids



Varial vectors:
- Retroviruses (also Lentiviruses)
- Adenoviruses
- Adenovirus-associated viruses (AAV)
- Herpetowiruses
- Poxviruses
- Alphaviruses
- Baculoviruses

Onasemnogene abeparvovec-xioi (Zolgesma, AveXis)

- Approved by the FDA in May 2019 and by EMA in May 2020 (conditional approval)

Onasemnogene abeparvovec-xioi (Zolgesma, AveXis)

- One-time treatment (intravenous)
- Patients less than 2 years of age with SMA, with bi-allelic mutations in the *SMN1* gene
- Cost: 425 000 USD per year for 5 years (above 2,1 mln USD totally)
- Side effects: acute serious liver injury

SMA therapy

Strategy for SMA treatment	Name of drug	Mode of action	Phase of clinical trials
***SMN2* gene expression modyfications**	Nusinersen (Spinraza)	Increases inclusion of exon 7	Approved
	Risdiplam (Evrysdi)	Increases inclusion of exon 7	Approved
	Branaplam	Increases exon 7 retention	Phase I/II
Gene therapy	Onasemnogene abeparvovec-xioi (Zolgesma)	Delivery of *SMN1* gene	Approved
Skeletal muscle contractility and muscle mass enchancment	Reldesemtiv	Fast skeletal muscle troponin activator	Phase II
	Apitegromab	Inhibits the latent form of miostatin	Phase II

Challenge to treatment for SMA

- Presence of a therapeutic window
- Difficulty in fully understanding the role of SMN protein.

Summary

- SMA affects the α-motor neurons leading to muscle weakness and atrophy
- Caused by mutations in *SMN1* gene
- *SMN2* gene is main modificator of phenotype
- Currently efficient therapies are avaliable (nusinersen (Spinraza), gene therapy (Zolgesma), Risdiplam (Evrysdi))

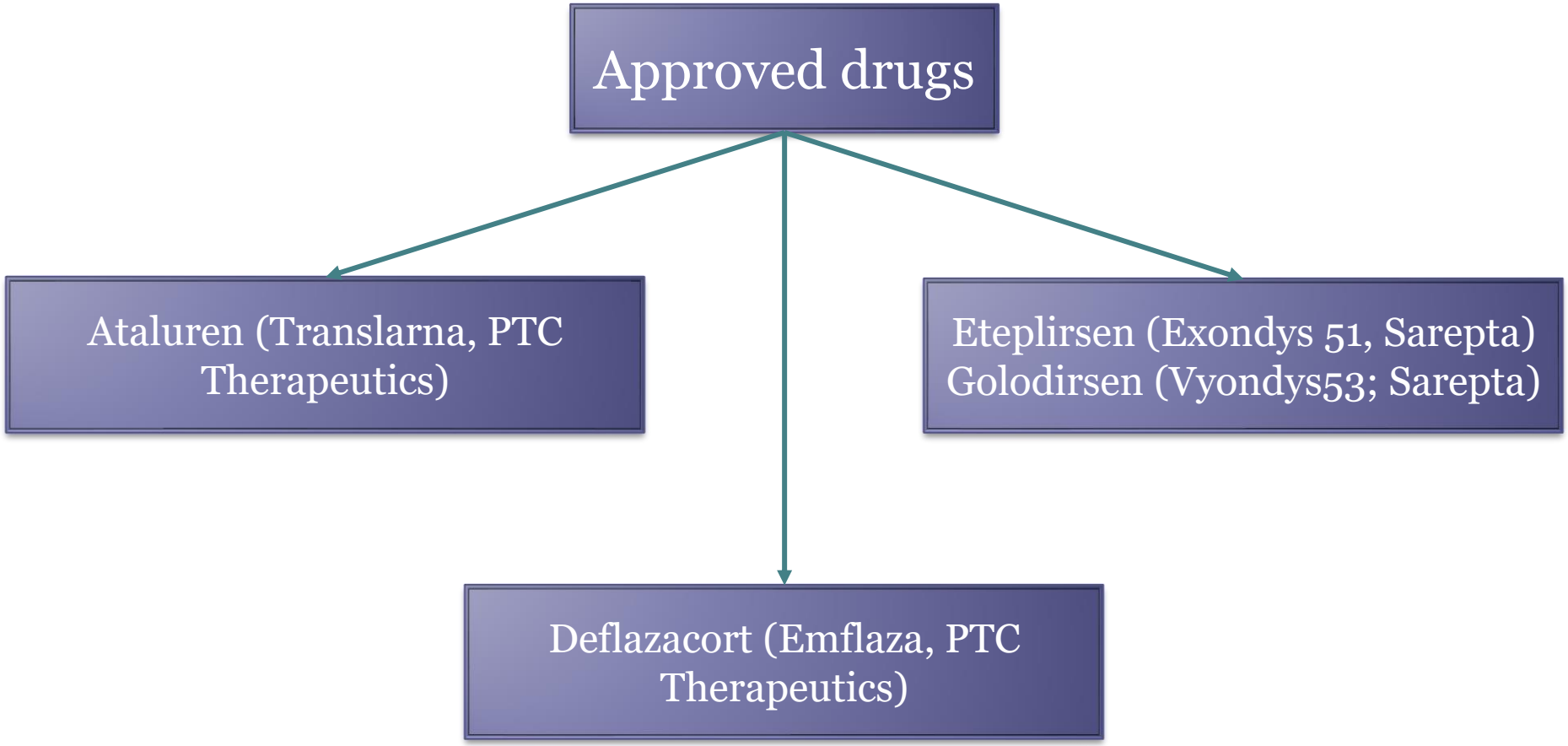
Muscular dystrophies

Duchenne (DMD) and Becker (BMD) muscular dystrophies

Muscular dystrophy treatment

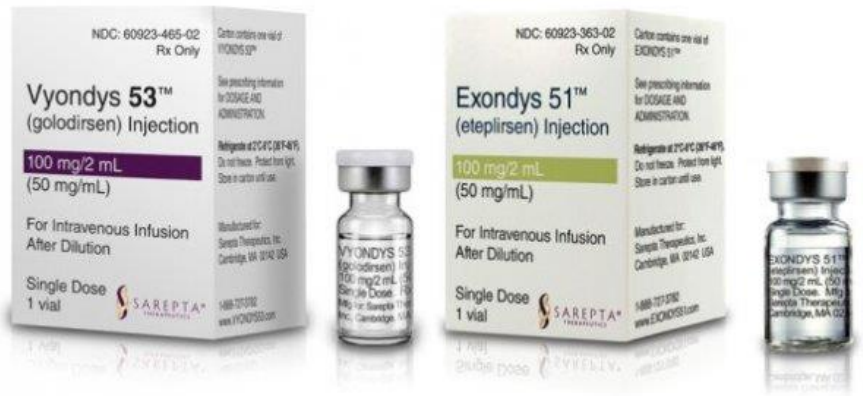
- Corticosteroids
- Anticonvulsants
- Immunosuppressive drug
- Antibiotics
- Drugs to treat heart problems
- Physiotherapy
- Occupational therapy and assistive equipment
- Surgery

Drugs dedicated for DMD



Deflazacort (Emflaza, PTC Therapeutics)

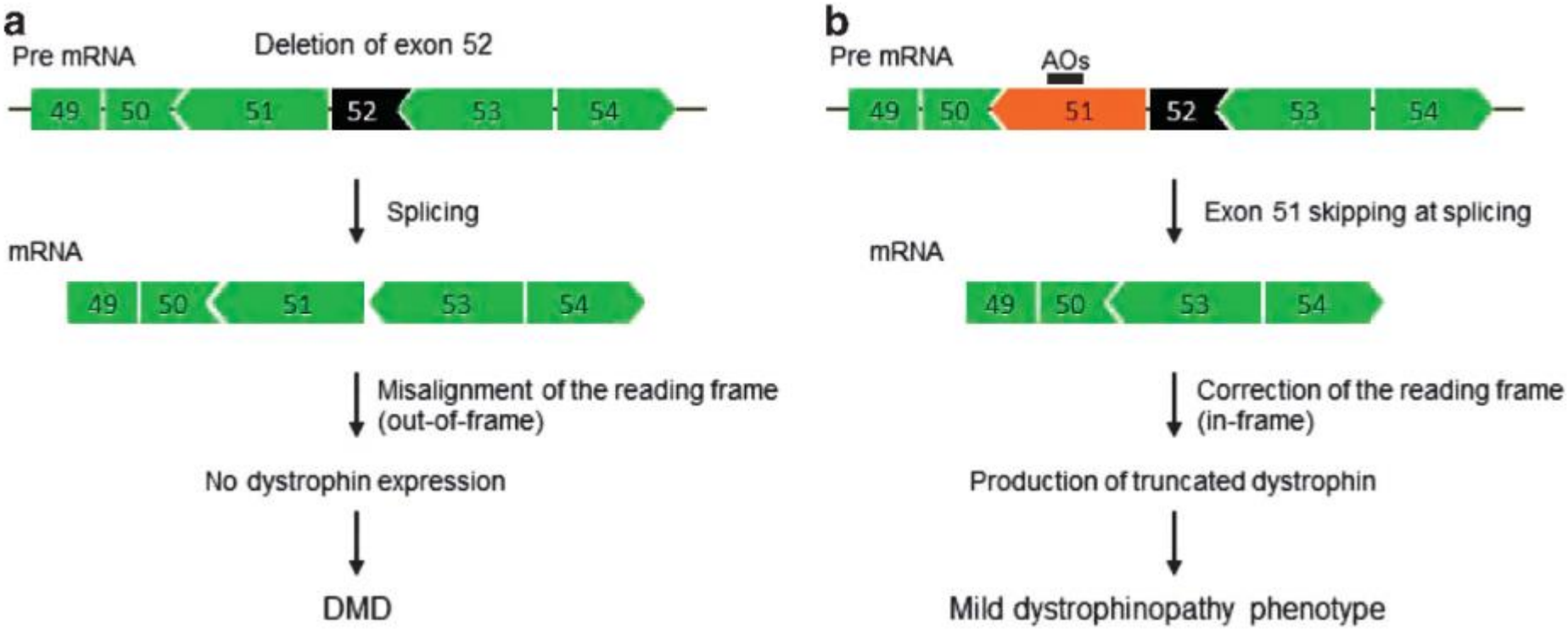
- Approved by FDA in 2017
- Patients at least 2 years of age
- Corticosteroids (it is NOT a cure)
- The common side effects: weight gain, increased appetite, upper respiratory tract infection, cough, extraordinary daytime urinary frequency (pollakiuria), unwanted hair growth (hirsutism) and changes in the shape or location of body fat



Eteplirsen (Exondys51) and Golodirsen (Vyondys53; Sarepta)

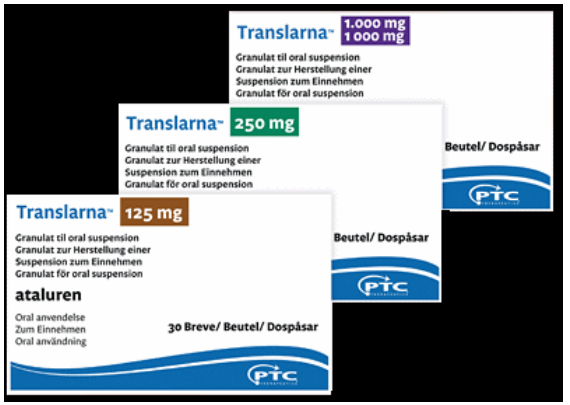
- Approved by FDA under accelerated approval in 2016 (Eteplirsen) and 2019 (Golodirsen)
- Intravenous infusion once per week
- Antisense oligonucleotide
- Promote exon skipping
- Common side effects: hypersensitivity reaction

Exon-skipping therapy for DMD



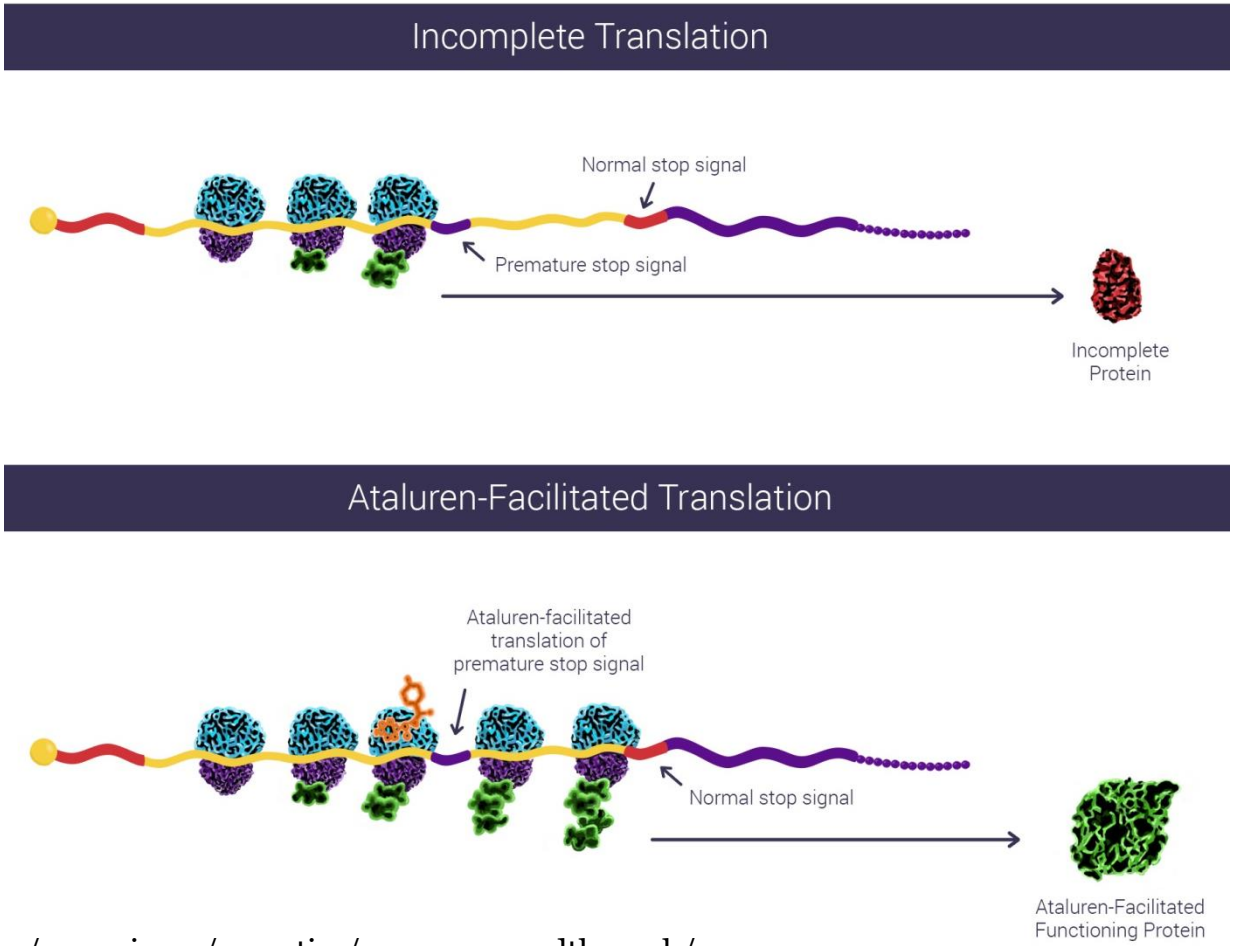
Nakamura Journal of Human Genetics (2017) 62,871–876

Ataluren (Translarna, PTC Therapeutics)



- Conditional approval by EMA in 2014
- 2 years old or older DMD patients with nonsense mutations
- Oral administration
- Promotes nonsense read through
- The most common adverse effects: vomiting, diarrhea, nausea, headache, stomachache and flatulence.

Nonsense read through



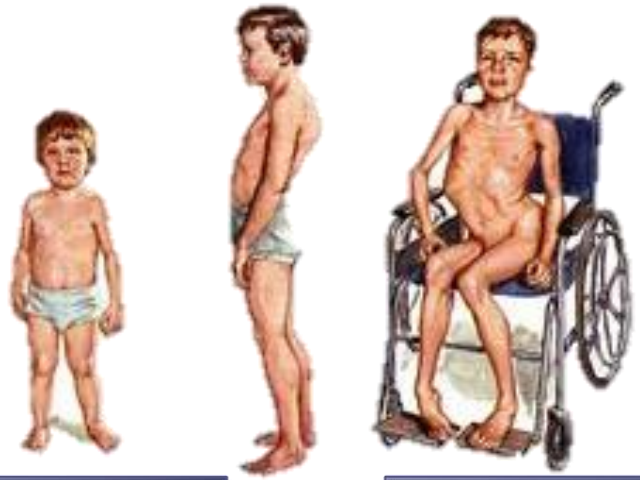
https://www.ptcbio.com/our-science/expertise/nonsense-readthrough/

Other strategies for treatment of muscular dystrophy

Modulation of utrophin level

Other

Regulation of calcium homeostasis



Micro-dystrophin gene therapy

Reduction of oxidative stress

Cell therapy

Anti-fibrotic therapy

Summary

- DMD is the most common type of muscular dystrophy (1:5000)
- It is characterised by muscle weakness associated with muscle wasting
- Caused by mutations in gene encoding dystrophin (X-linked recessive)
- Therapies: supportive, corticosteroids, Ataluren (Translarna), Eteplirsen (Exondys 51), Golodirsen (Vyondys53); other therapies in cinical trials

Take-home message

- The genetic neuromuscular diseases (gNMD) are rare but there are many of them, thus many people are affected eventually
- Usually there is no efficient cure for these disorders
- Currently different drugs for gNMD are in clinical trials
- There are several strategies for treatment of particular gNMD, including gene therapy