Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

Nuovi approcci terapeutici nelle malattie neuromuscolari

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Ricercatrice

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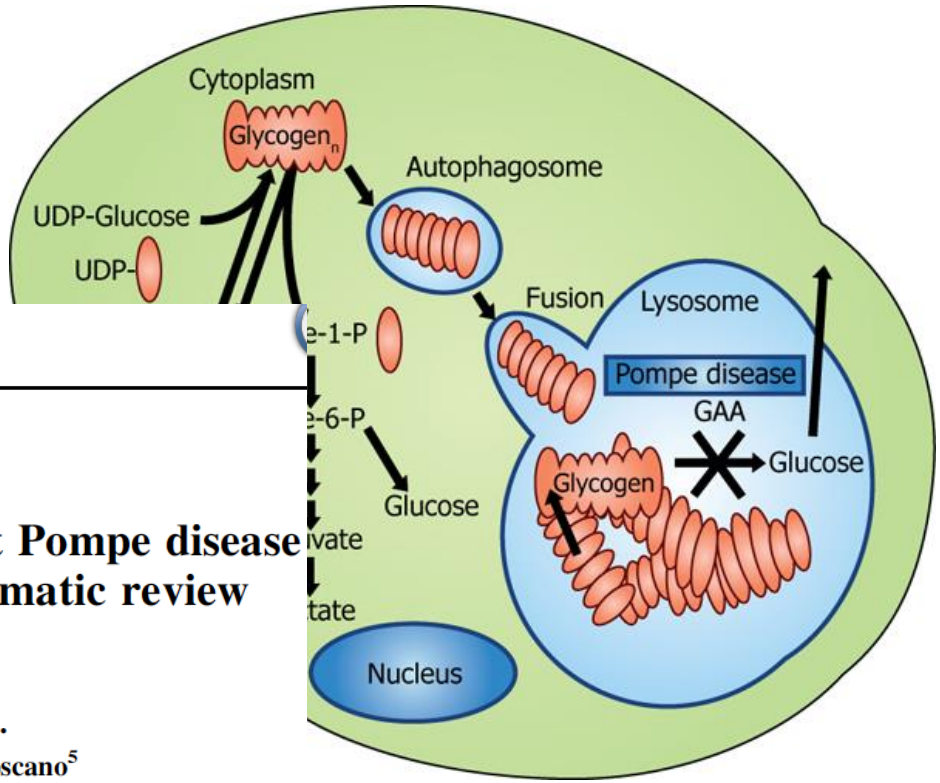
scienze Riproduttive ed Odontostomatologiche

Università degli Studi di Napoli Federico II

2006

Myozyme®
(alglucosidase alfa)



J Neurol (2017) 264:621–630
DOI 10.1007/s00415-016-8219-8

REVIEW

Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis

Benedikt Schoser[1] · Andrew Stewart[2] · Steve Kanters[3,4] · Alaa Hamed[2] · Jeroen Jansen[4] · Keith Chan[4] · Mohammad Karamouzian[3,4] · Antonio Toscano[5]

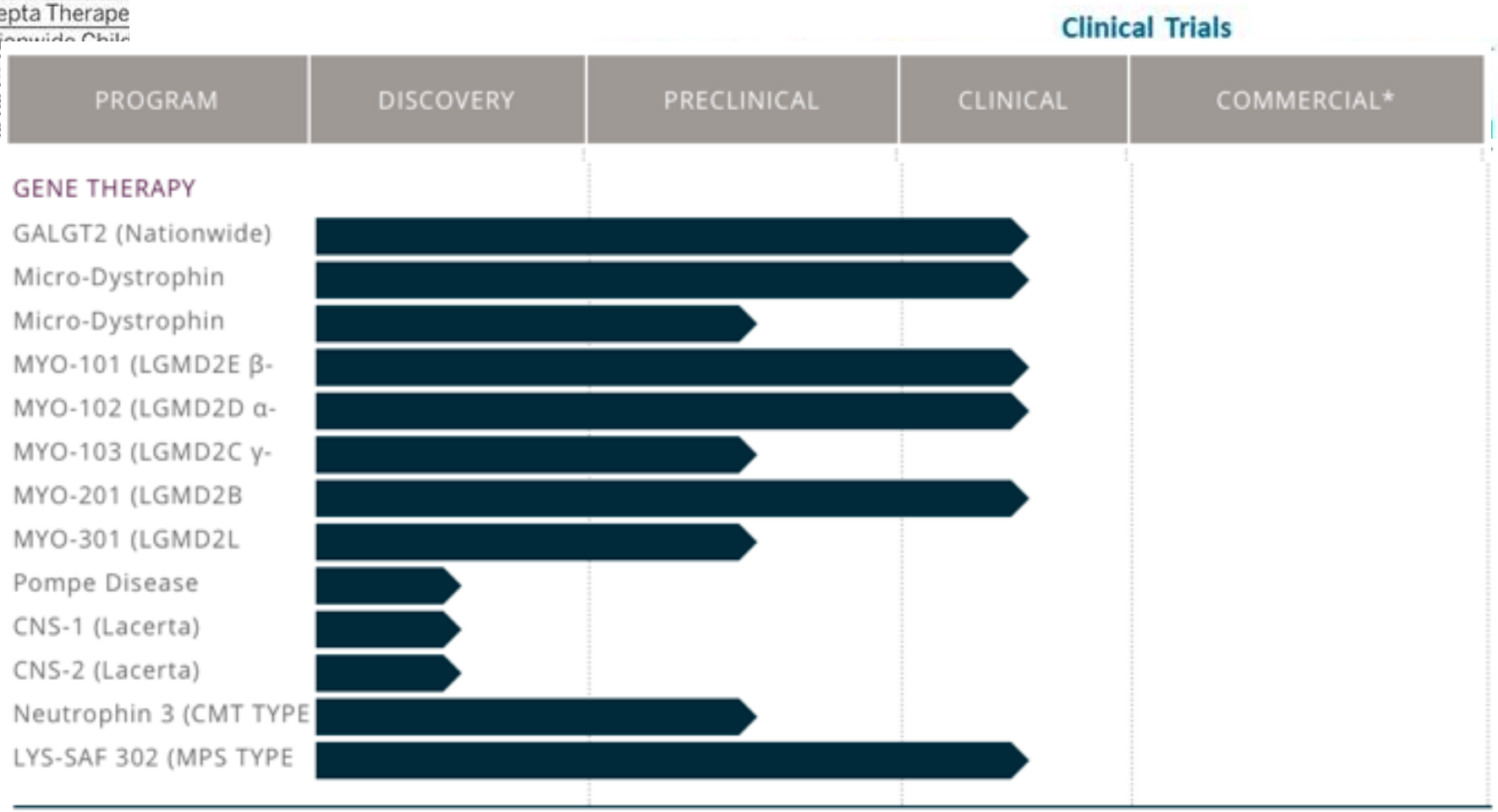
2006 2019

FILLING THE PIPELINE

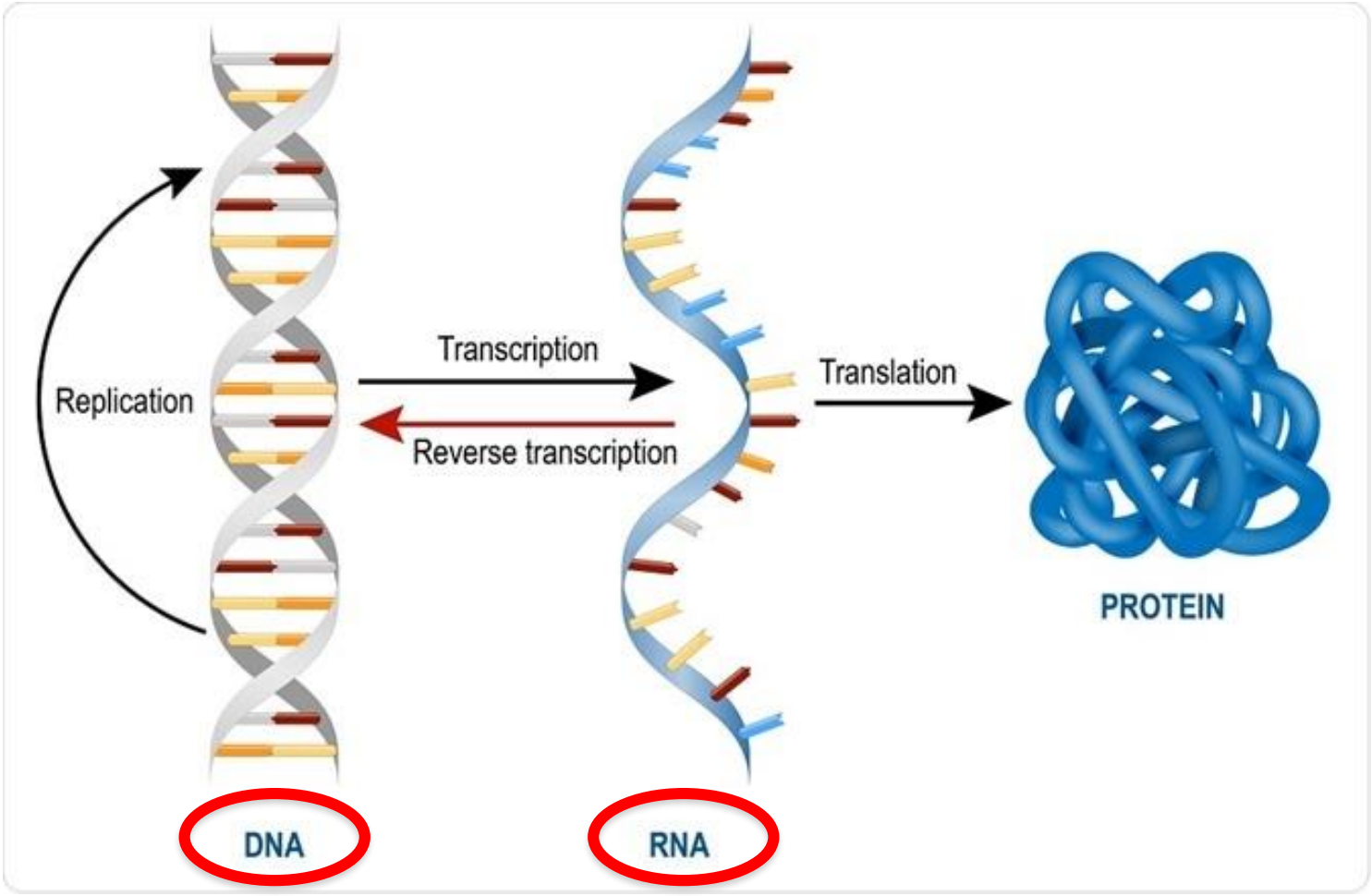
Select DMD therapies in clinical development

COMPANY	DRUG	PHASE	MOLECULE TYPE	MECHANISM OF ACTION
Eli Lilly & Co.				
Prosensa				
PTC Therapeutics				
Santhera Pharm				
Sarepta Therape				
Nati				
Aka				
Pros				
Pros				
Pro				
Su				
Aka				
Bri				
Pfi				
Re				
Tiv				
Sa				

SMA DRUGS APPROVED AND IN CLINICAL TRIALS



Modalità di approccio

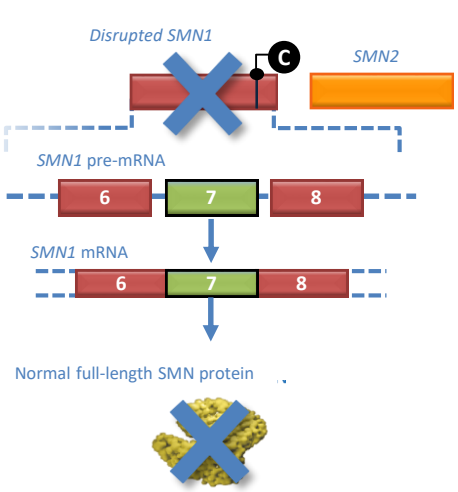


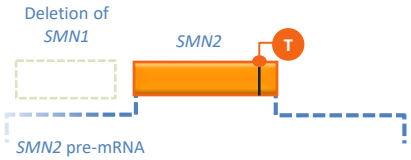
AVXS-101 (Zolgensma)
Micro -distrofine

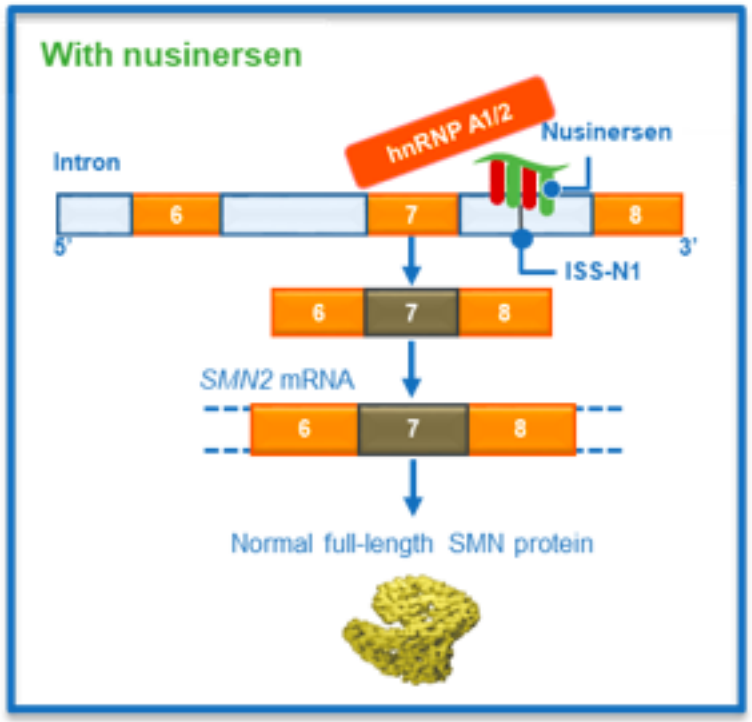
Oligonucleotidi antisenso
Exon skipping
Read-trough

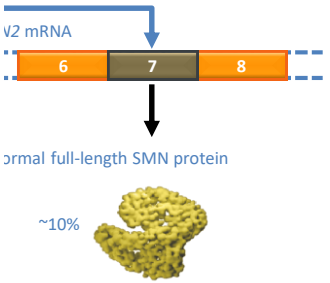
Farmaci che agiscono sull'RNA:
Oligonucleotidi anti senso (ASO)
Nusinersen

Atrofia muscolare spinale









Aumenta la quantità di SMN stabile

Nusinersen: efficacia

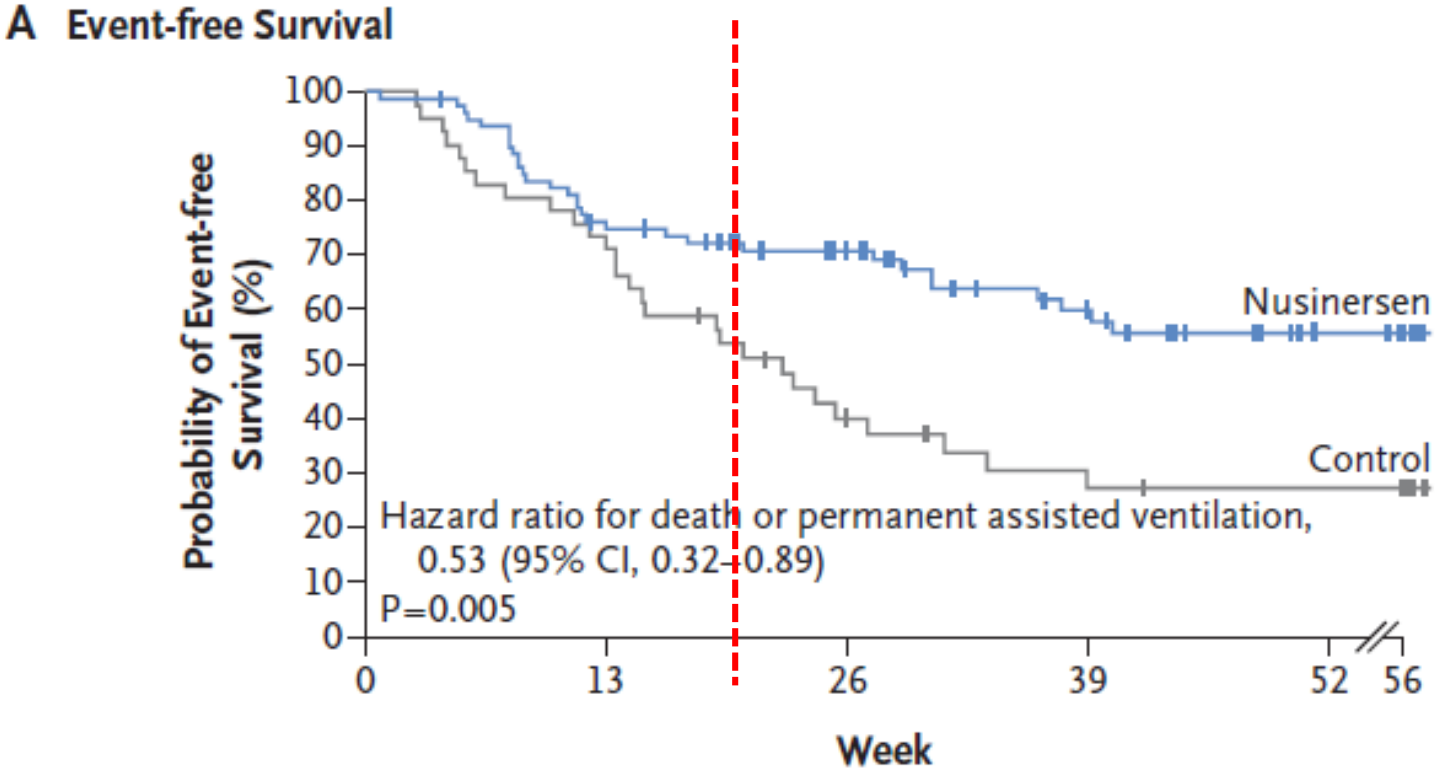
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

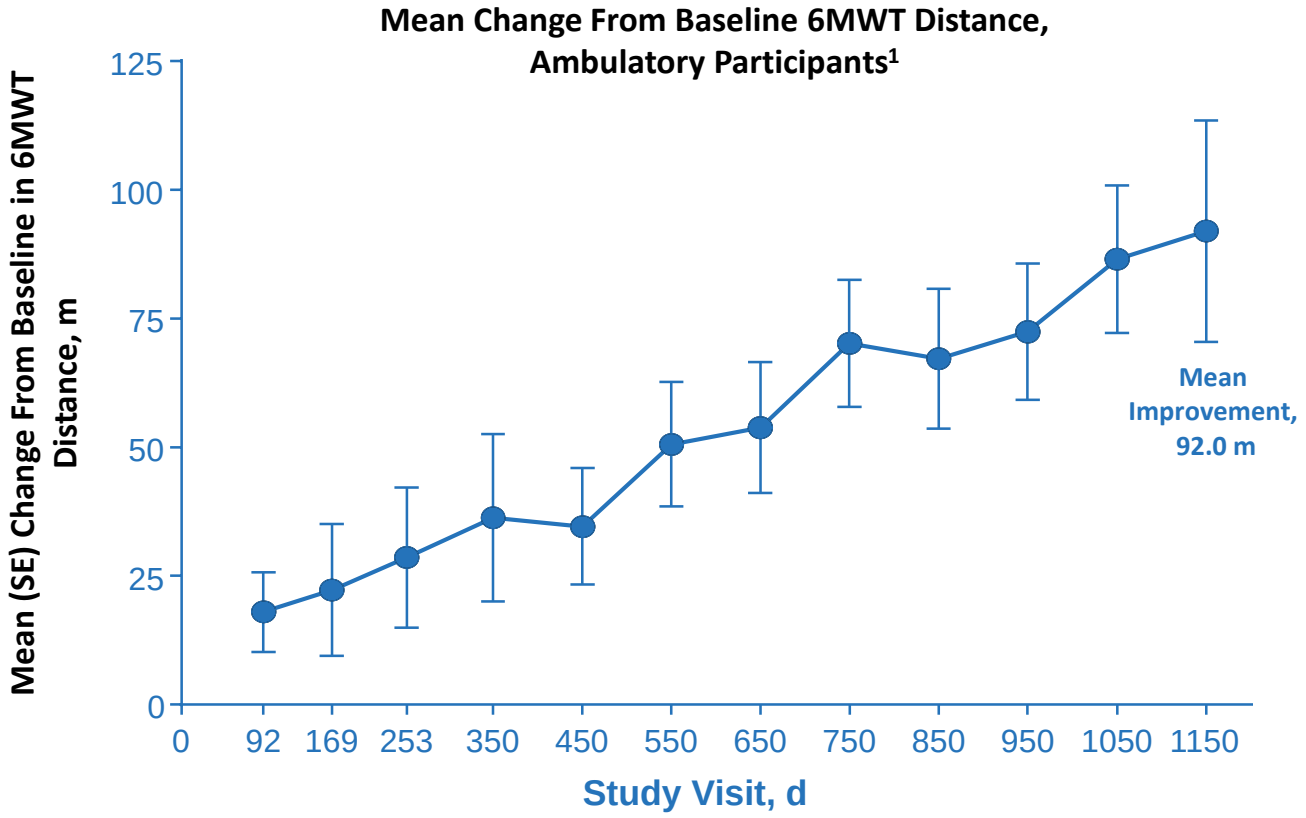
R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

N ENGL J MED 377;18 NEJM.ORG NOVEMBER 2, 2017



Nusinersen: efficacia

Nusinersen in later-onset spinal muscular atrophy
Long-term results from the phase 1/2 studies
Basil T. Darras, *Neurology*® 2019;92:e1-e15.



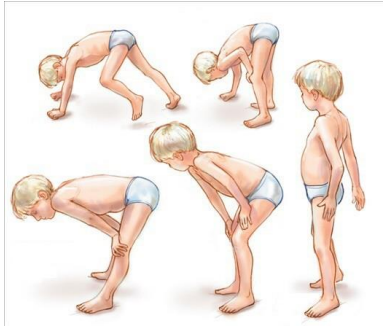
- SMA Type III individuals treated with nusinersen demonstrated a mean (SE) change from baseline 6MWT distance of:
  - **28.6** (13.6) meters at Day 253
  - **92.0** (21.5) meters by Day 1150
- In a natural history cohort SMA Type III, mean change over 12 months was −1.5 meters[9]

Farmaci che agiscono sull'RNA: Oligonucleotidi anti senso

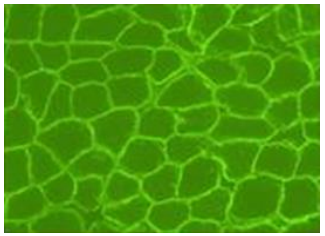
Eteplirsen

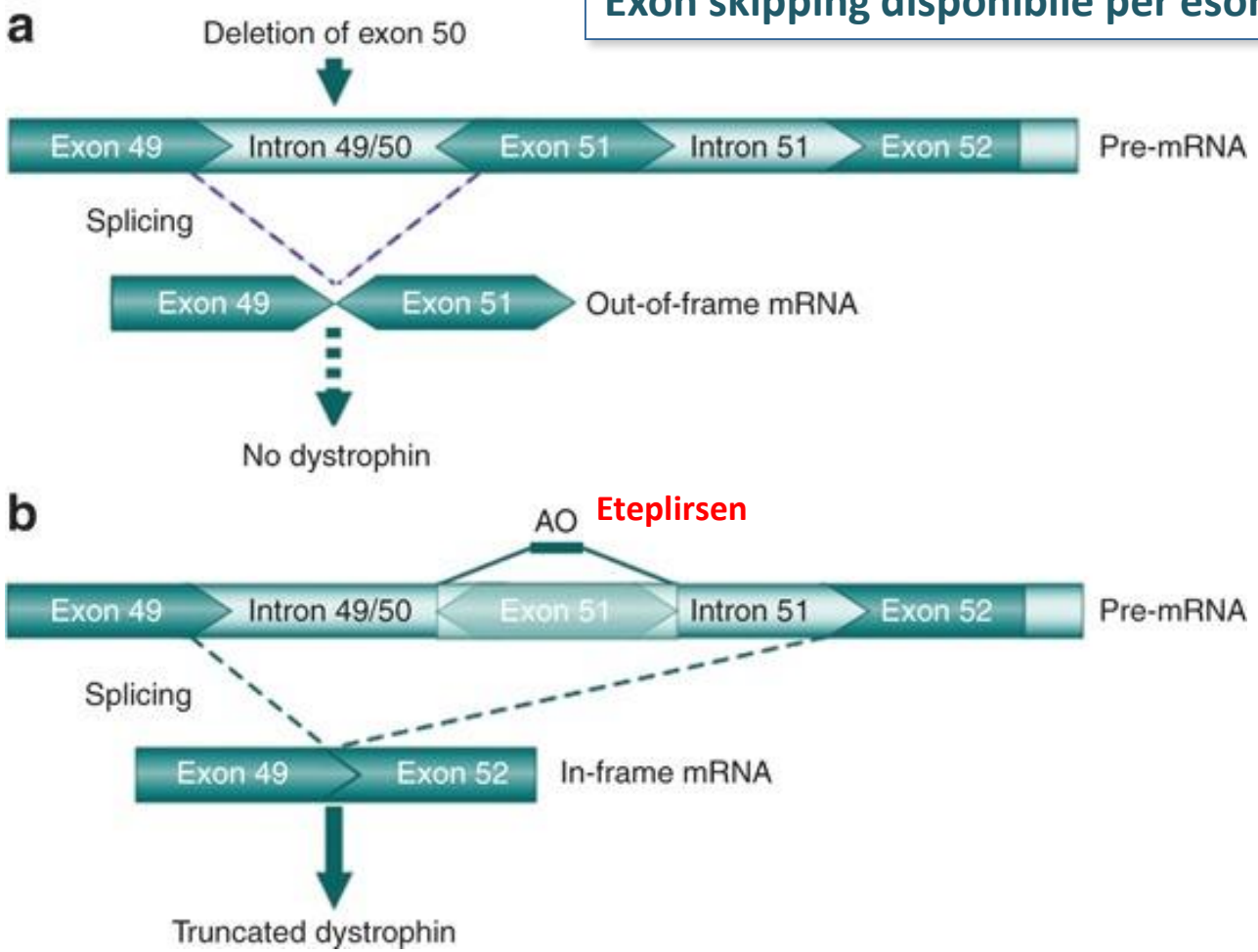
Approvato dall'FDA

Exon skipping disponibile per esone 51

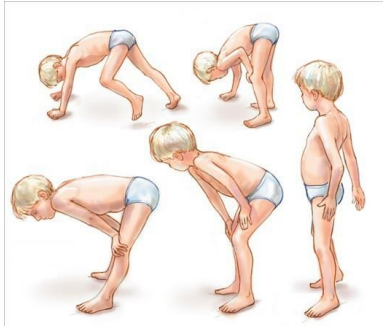


Distrofia muscolare di Duchenne

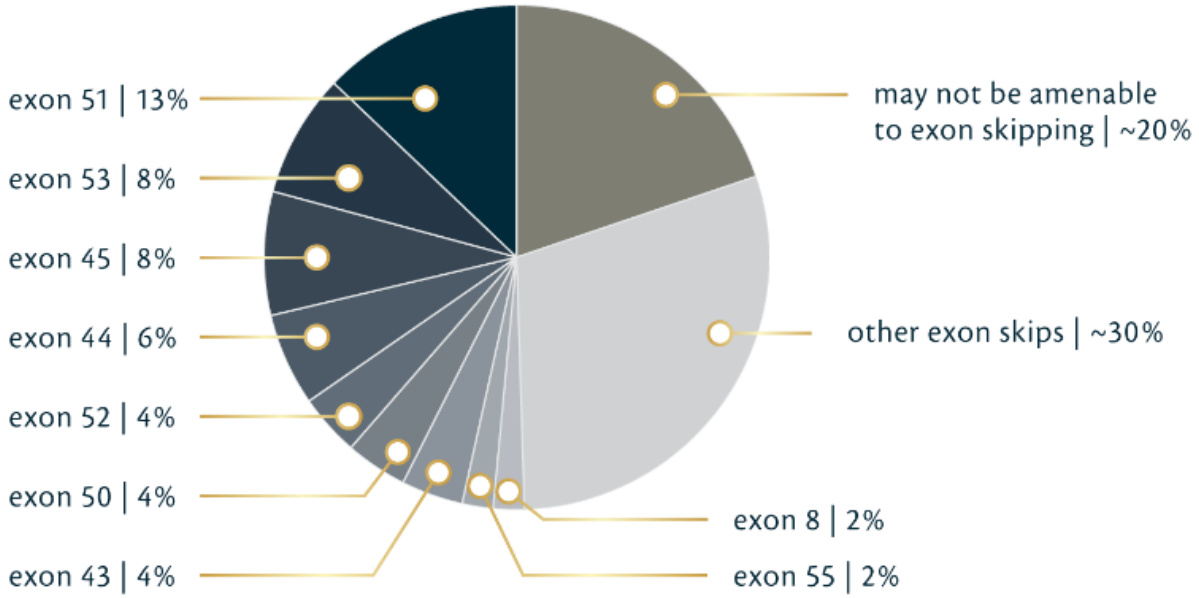




Farmaci che agiscono sull'RNA:
Oligonucleotidi anti senso
Exon skipping



Distrofia muscolare
di Duchenne



60% pazienti DMD

Farmaci che agiscono sull'RNA:
Oligonucleotidi anti senso
Sclerosi laterale amiotrofica

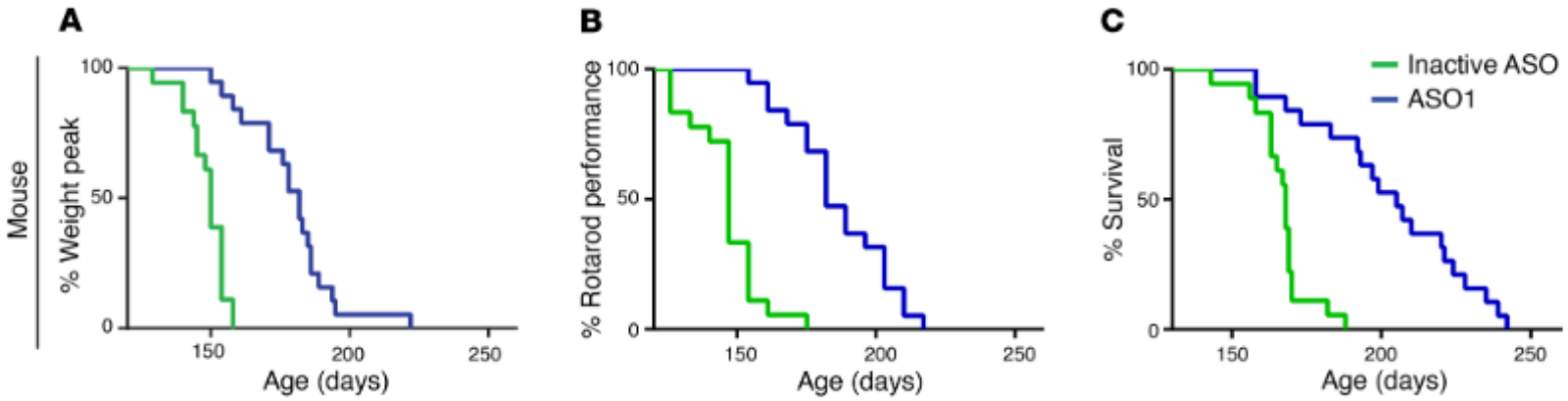
RESEARCH ARTICLE

The Journal of Clinical Investigation

Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models

Alex McCampbell,[1] Tracy Cole,[2] Amy J. Wegener,[3] Giulio S. Tomassy,[1] Amy Setnicka,[3] Brandon J. Farley,[1] Kathleen M. Schoch,[3] Mariah L. Hoye,[3] Mark Shabsovich,[3] Linhong Sun,[1] Yi Luo,[1] Mingdi Zhang,[1] Nicole Comfort,[1] Bin Wang,[1] Jessica Amacker,[1] Sai Thankamony,[1] David W. Salzman,[1] Merit Cudkowicz,[4] Danielle L. Graham,[1] C. Frank Bennett,[2] Holly B. Kordasiewicz,[2] Eric E. Swayze,[2] and Timothy M. Miller[3]

[1]Biogen, Inc., Cambridge, Massachusetts, USA. [2]Ionis Pharmaceuticals, Carlsbad, California, USA. [3]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA. [4]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.



Neuron. 2016 May 4; 90(3): 535–550. doi:10.1016/j.neuron.2016.04.006.

Gain of toxicity from ALS/FTD-linked repeat expansions in *C9ORF72* is alleviated by antisense oligonucleotides targeting GGGGCC-containing RNAs

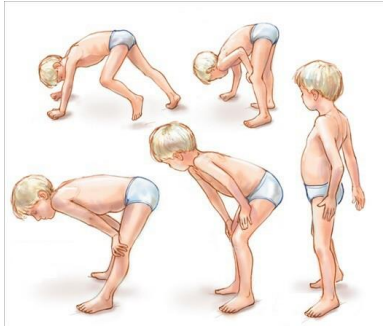
Farmaci che agiscono sull'RNA:

Read-through

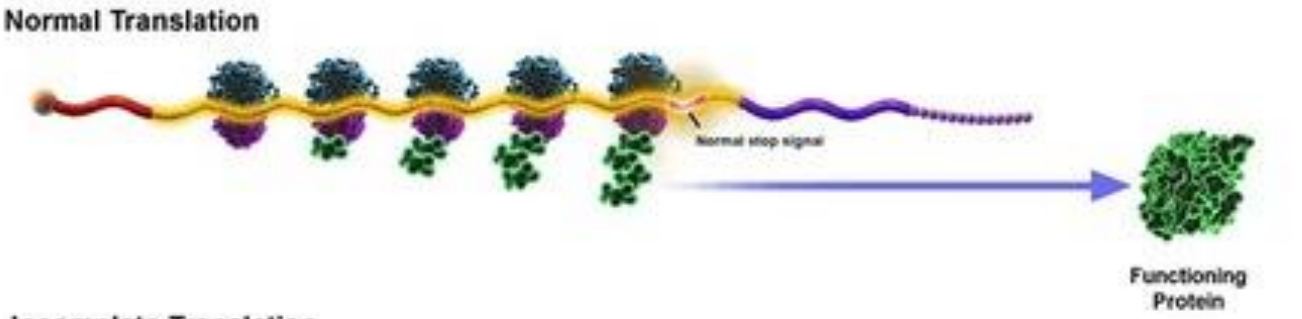
Ataluren

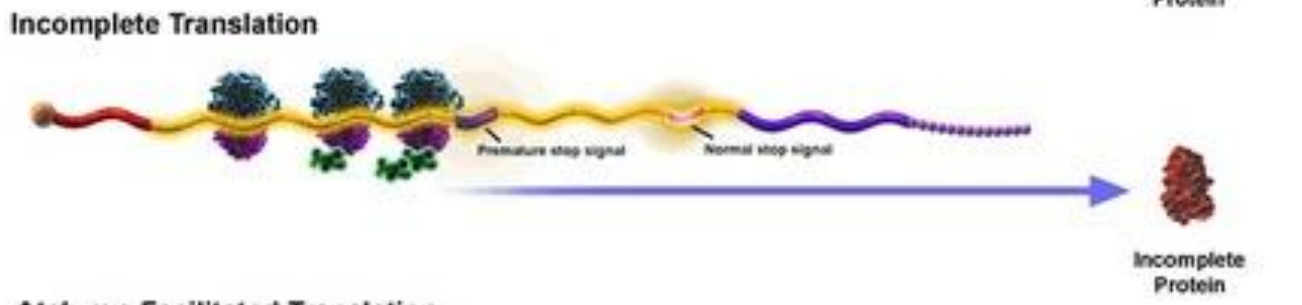
Approvato dall'EMA

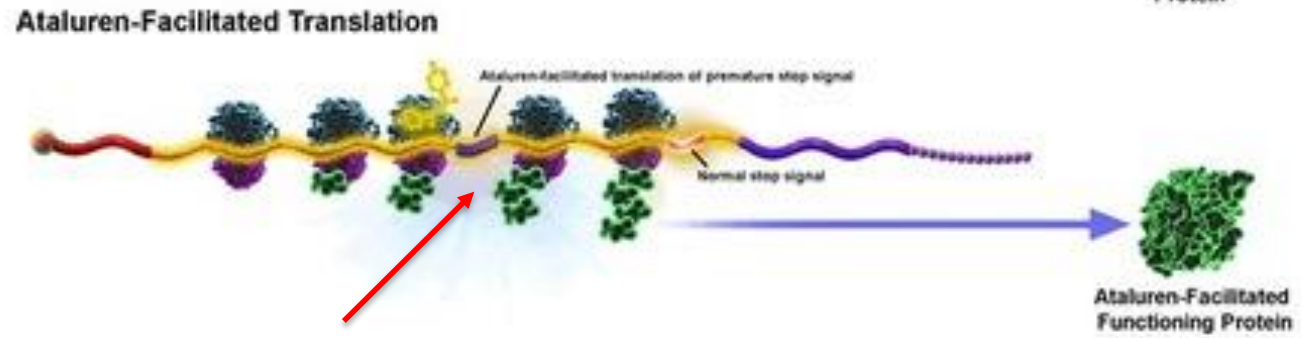
Pazienti con mutazione non-senso (stop codon prematuro)

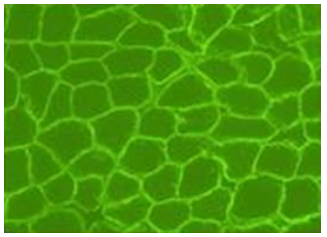


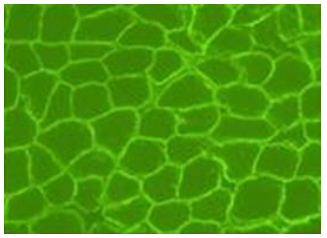
Distrofia muscolare di Duchenne











Ataluren: efficacia

www.thelancet.com Published online July 17, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31611-2

Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Craig M McDonald, Craig Campbell, Ricardo Erazo Torricelli, Richard S Finkel, Kevin M Flanigan, Nathalie Goemans, Peter Heydemann, Anna Kaminska, Janbernd Kirschner, Francesco Muntoni, Andrés Nascimento Osorio, Ulrike Schara, Thomas Sejersen, Perry B Shieh

Therapeutic Advances in Neurological Disorders Case Series

1-year follow up of three Italian patients with Duchenne muscular dystrophy treated with ataluren: is earlier better?

Lucia Ruggiero, Rosa Iodice, Marcello Esposito, Raffaele Dubbioso, Stefano Tozza, Floriana Vitale, Lucio Santoro and Fiore Manganelli

Registro Stride

Ataluren use in patients with nonsense mutation Duchenne muscular dystrophy: patient demographics and characteristics from

Journal of Comparative Effectiveness Research

Francesco M
Osorio[5], Ja
Christian W
Delage[11], C

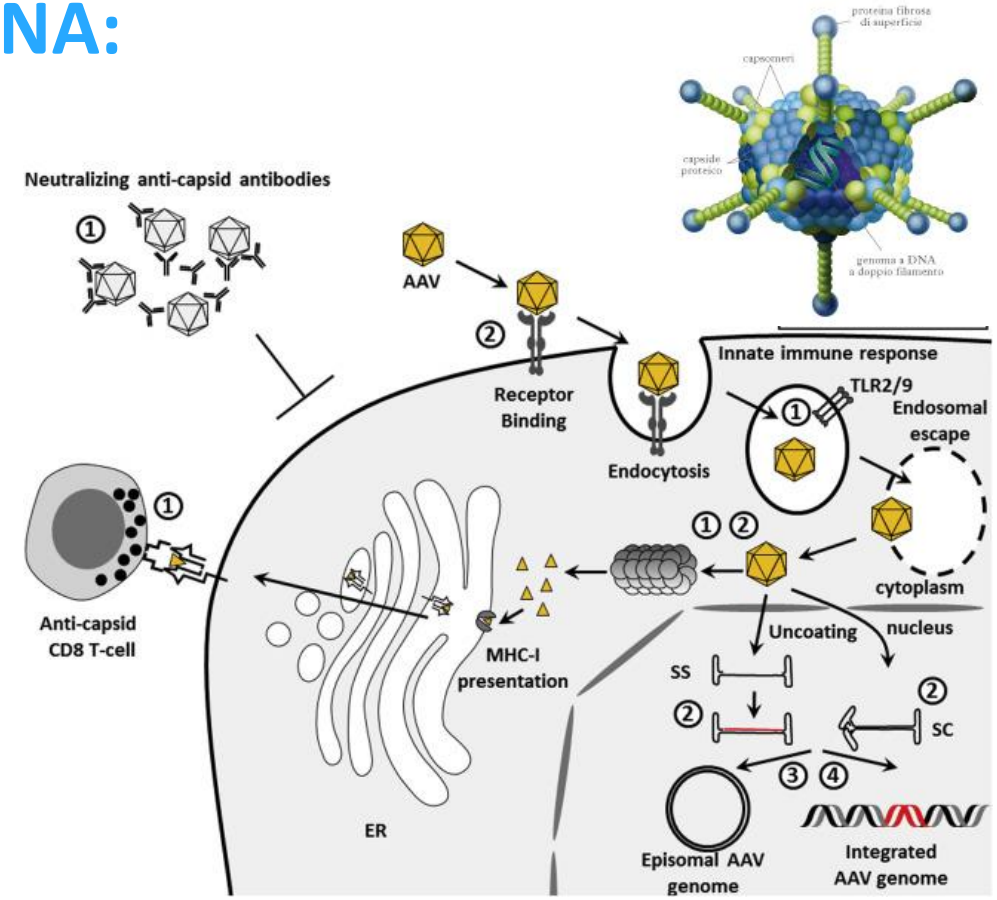
<u>Lo studio di real life ha confermato</u>

- ✓ Buona tollerabilità del trattamento
- ✓ Rallentamento del declino al Six Minute Walk Test
- ✓ Ritardo della perdita della deambulazione
  (alcuni pazienti deambulanti hanno anche più di 18 anni)

Romania	2	11 (5.2)
Sweden	1	11 (5.2)
United Kingdom	7	37 (17.4)
Latvia	1	0 (0.0)
Norway	1	0 (0.0)
Portugal	1	0 (0.0)

- ✓ Follow-up di 5 anni (media di trattamenti 640 giorni)

Farmaci che agiscono sul DNA:
Gene therapy
Vettori virali



Sono eliminati:

- ✓ geni virali
- ✓ capacità replicativa
- ✓ capacità immunogenica

Tipologie:

- ✓ Retrovirus (8 kb)
- ✓ Lentivirus (8 kb)

Si integrano nel genoma dell'ospite

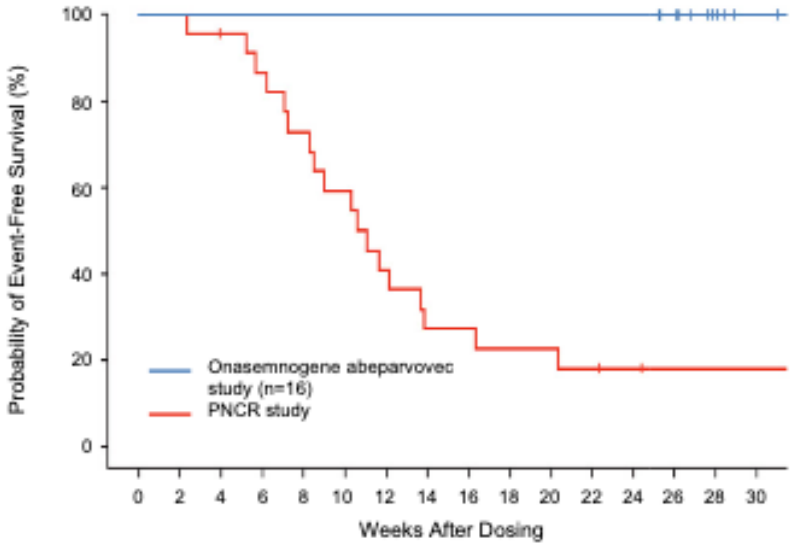
- ✓ HSV-1 (40-150 kb)
- ✓ Adenovirus (8-30 kb)
- ✓ AAV (< 5 kb)

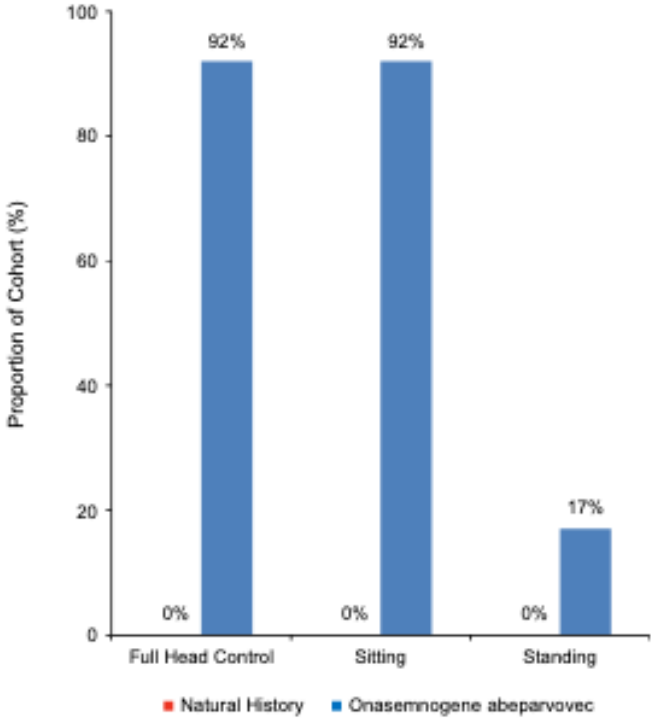
Non si integrano nel genoma dell'ospite
Persistono nel nucleo dell'ospite come episomi

Farmaci che agiscono sul DNA:
Gene therapy
Vettori virali: AVXS-101 (Zolgensma)

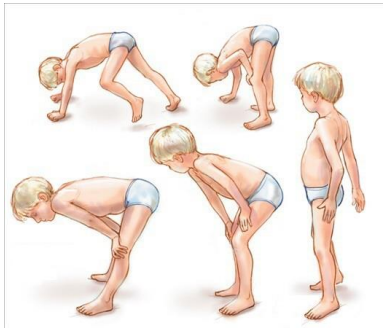
Atrofia muscolare spinale

S.A. Al-Zaidy, J.R. Mendell / Pediatric Neurology 100 (2019) 3–11

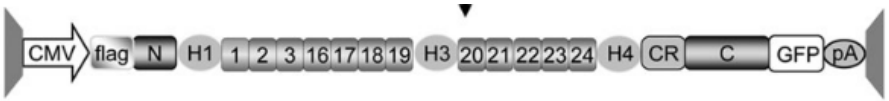




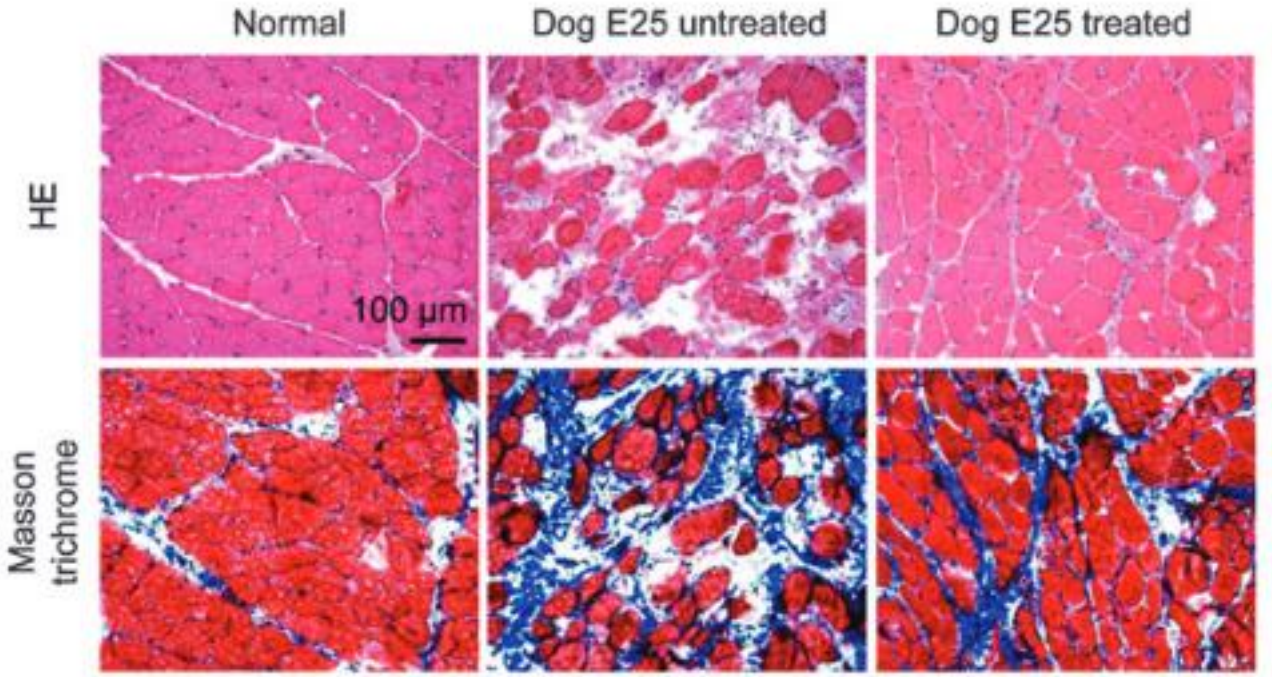
Farmaci che agiscono sul DNA:
Gene therapy
Vettori Virali: mini distrofine



Distrofia muscolare
di Duchenne



Reconstituted 7-kb mini-dystrophin gene
(corresponding to a 250 kDa protein)



DUAL AAV MINI-DYSTROPHIN FOR DMD DOG

HUMAN GENE THERAPY, VOLUME 29, NUMBER 3

Kasun Kodippili,[1]

Farmaci che agiscono sul DNA:
Gene therapy
Vettori Virali: miotubularina

Farmaci che agiscono sul DNA:
Gene therapy
Vettori Virali: are coming…

LGMD2E *LGMD R4* *β-sarcoglycan-related*	NCT03652259
LGMD2D *LGMD R3* *α-sarcoglycan-related*	NCT01976091
LGMD2C *LGMD R5* *γ-sarcoglycan-related*	NCT01344798
LGMD2B *LGMD R2* *dysferlin-related*	NCT02710500
MTM	NCT03199469 *ASPIRO*
CMT1A	NCT03520751

Afshin Saffari[1] · **M**

1007/s00115-019-0761-z

Verlag GmbH, ein Teil von
19

Implicazioni future dei nuovi trattamenti:

Gestione dei costi

Efficacia e sicurezza a lungo termine

Conseguenze a lungo termine

Nuovi fenotipi
Screening neonatali

Grazie!