# SESSIONE su
# INNOVAZIONE TERAPEUTICA:

# MALATTIE NEUROMUSCOLARI

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# Atrofia Muscolare Spinale (SMA)

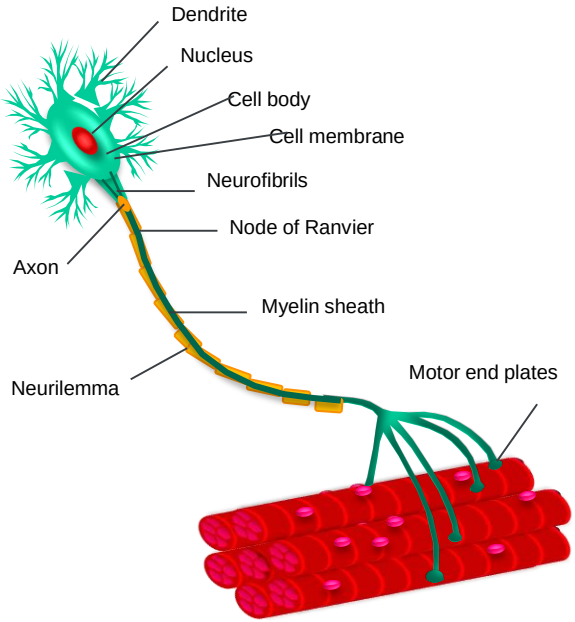
- Trasmissione **AR** cromosoma 5 (gene SMN)
- **Degenerazione progressiva dei motoneuroni** delle corna anteriori del midollo spinale
- Incidenza: 1:10.000; prevalenza 3/100.000
- 1 persona su 40-60 è portatore sano
- In base al decorso clinico è classificata:

  - tipo I Malattia Werdnig-Hoffmann, forma infantile acuta

  - tipo II Malattia Werding-Hoffmann, forma intermedia

  - tipo III Sindrome Kugelberg-Welander, forma cronica

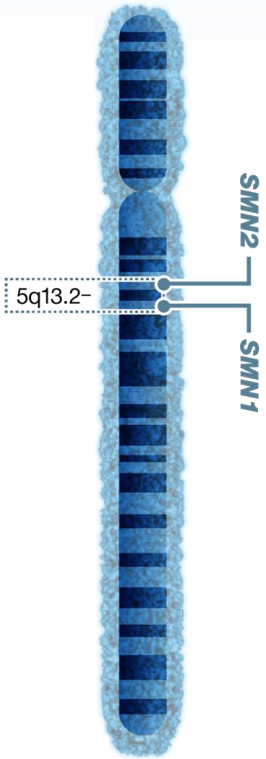
  - tipo IV Esordio 2°-3° decade

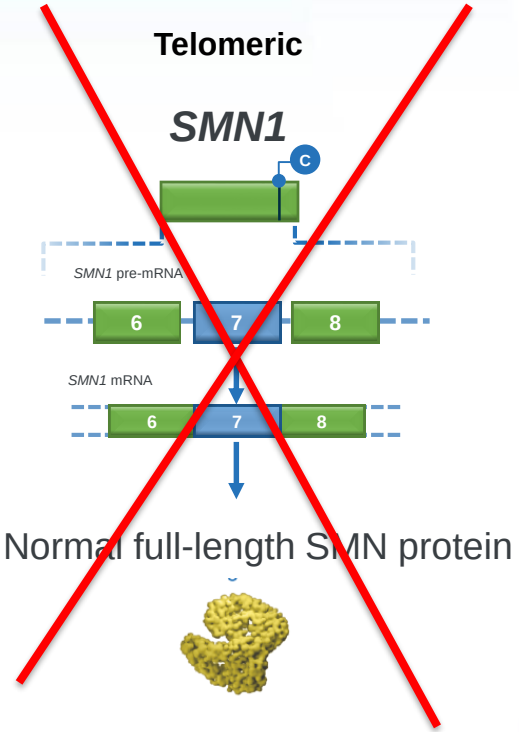


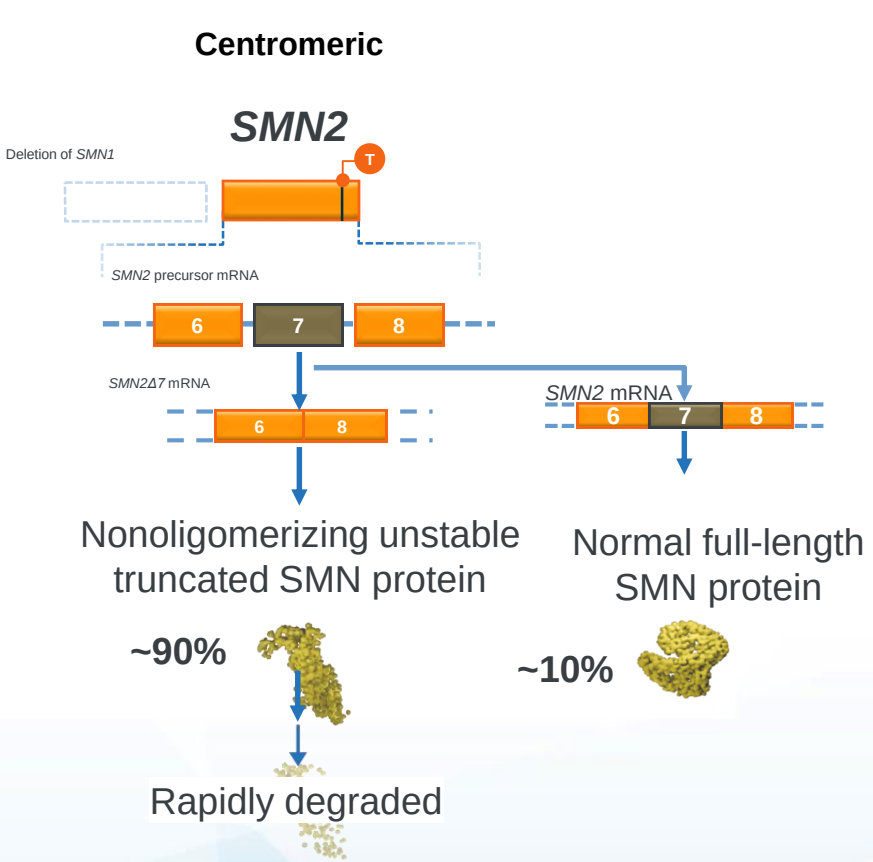
# Types of SMA 5q

| SMA type | Age at symptom onset | Maximal motor function achieved | Incidence | Survival |
|---|---|---|---|---|
| **Type 0** | Prenatal | __ | | < 1month |
| **Type I** | 0–6 mo | Never sits unsupported | • 3.2–7.1 per 100,000 live births<br>• Due to high mortality rate (often not surviving beyond 2 years of age without intervention) | < 2 years (10% survival) |
| **Type II** | 7–18 mo | Sits, may stand, never walks | 1.0–5.3 per 100,000 live births[3] | = 70% alive at 25 years |
| **Type III** | >18 mo | Walks | 1.5–4.6 per 100,000 live births | Almost normal |
| **Type IV** | Second or third decade | Walks unaided | 1 in 300,000 live births | Normal |

# Summary of the genetics of SMA

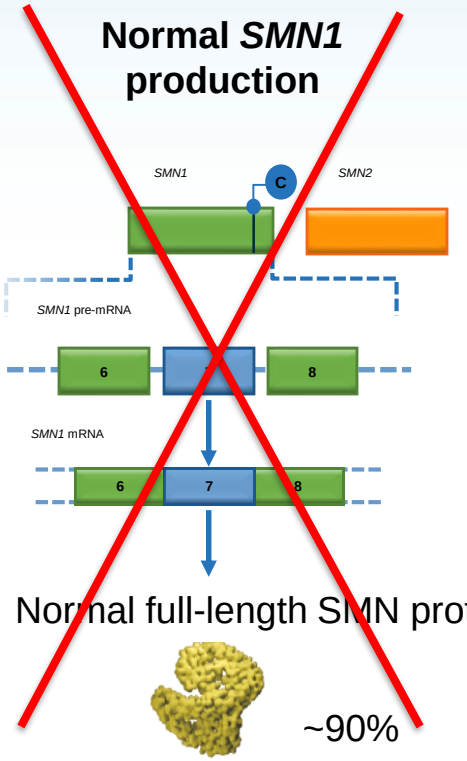


# Nusinersen: Mechanism of action

**Normal *SMN1* production**

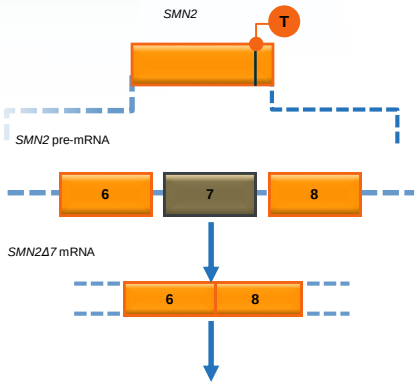



Normal full-length SMN protein

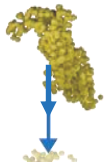


~90%

***SMN2* production in patients with SMA**



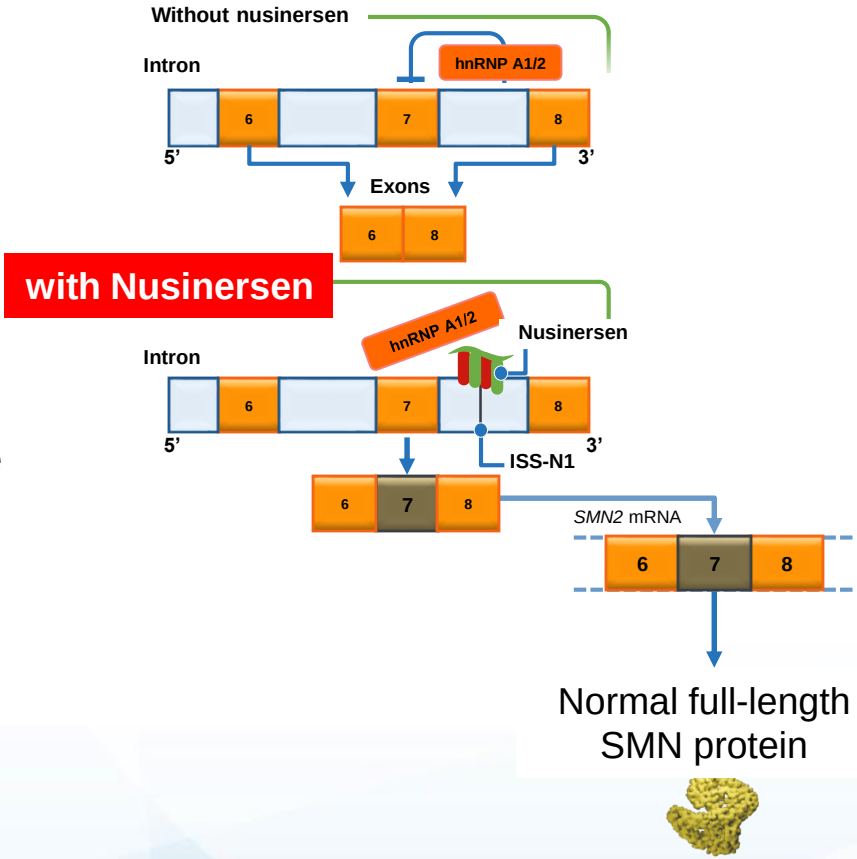

Nonoligomerizing unstable truncated SMN protein



~10%

Rapidly degraded

**with Nusinersen**

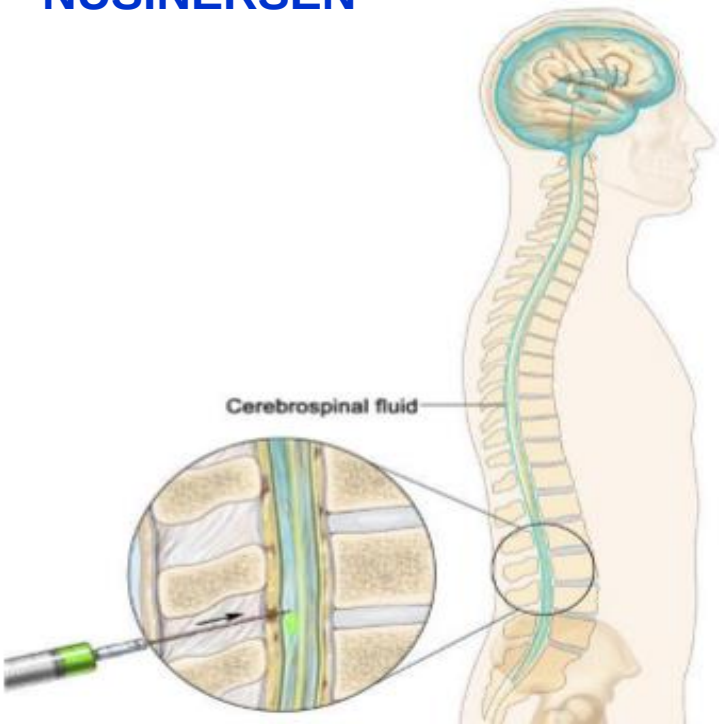



Normal full-length SMN protein



**Nusinersen modifies splicing of *SMN2* precursor mRNA, thereby promoting increased production of full-length SMN protein**

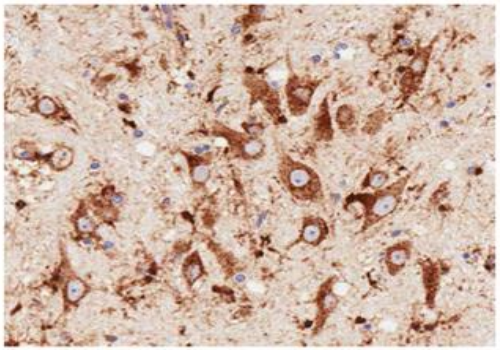
# NUSINERSEN




- Intrathecal drug administration – Lumbar Puncture bolus injection
- Precedence for IT drug delivery with anesthetics, pain medications, and chemotherapeutics
- ASOs have long half-lives (several months) in CNS tissue, with even longer duration of action, so enables infrequent dosing
- For more frequent dosing, there are implantable devices that can also be used

Antisense oligonucleotides (ASOs) do not cross an intact BBB

ASOs distribute broadly into spinal cord and specific brain tissues following intrathecal delivery

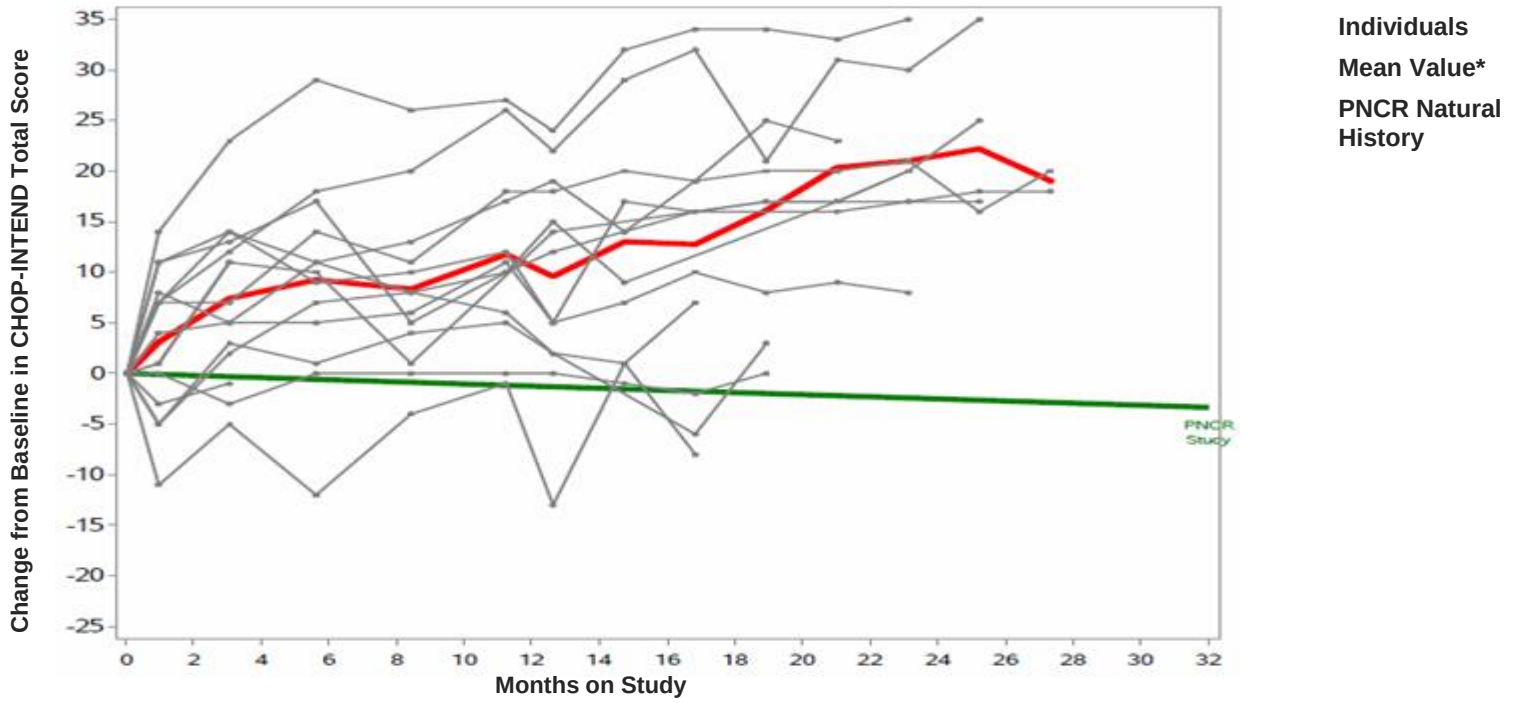


IHC against drug in monkey spinal cord following intrathecal delivery of ASO

# Increased Muscle Function Scores in Nusinersen-treated Infants with SMA Compared to Natural History (PNCR)

As of January 26th, 2016

## Individual CHOP INTEND Change Scores: 12 mg Cohort (N=15)




- **Infants continue to demonstrate increases in motor function scores with a mean increase of 22.2 points at 26 months**

*Mean value calculated based on patient values at each time point.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

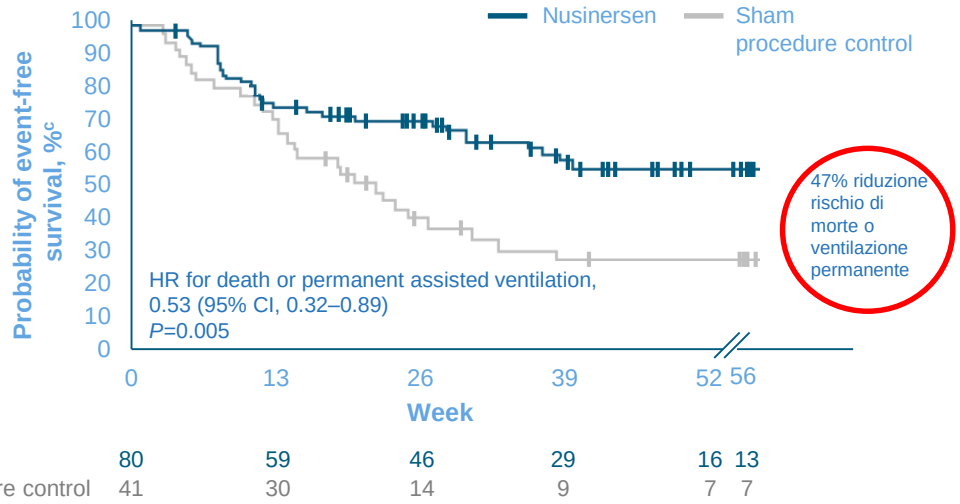
# Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

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*

# ENDEAR (CS3B) EOS analysis: Event-free survival

## Significantly prolonged event-free survival[a] in nusinersen-treated infants (HR, 0.53; *P*=0.005[b])

| Outcome, n (%) | Sham procedure control | Nusinersen |
|---|---|---|
| Death or permanent ventilation | 28 (68) | 31 (39) |
| Alive and no permanent ventilation | 13 (32) | 49 (61) |

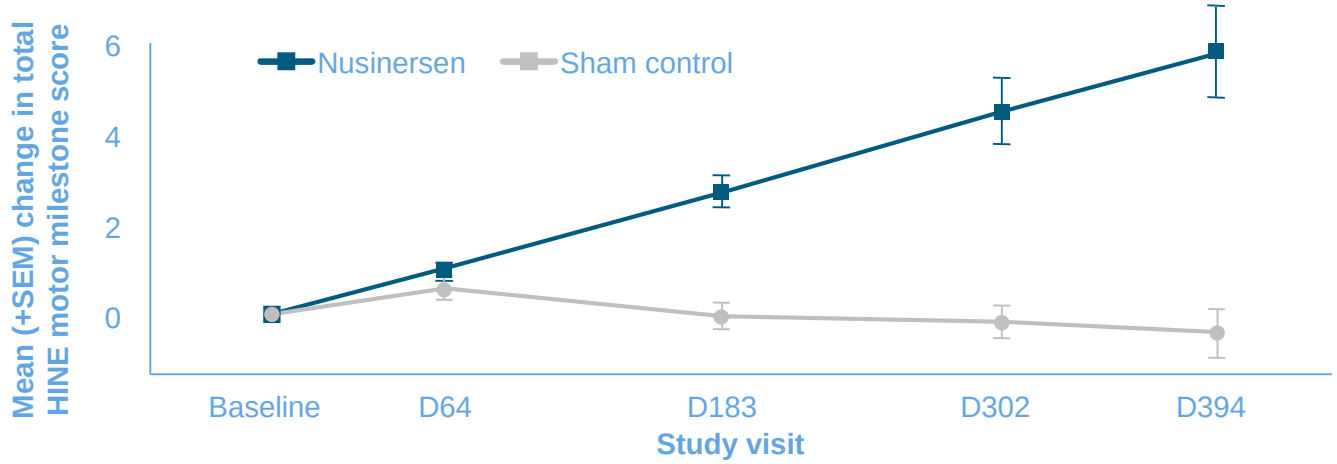



All infants randomized who received at least one dose of nusinersen or sham procedure control were included in the analysis. [a]Event-free survival = time to death or permanent ventilation (permanent ventilation was defined as tracheostomy or ≥16 hours ventilatory support per day for >21 days in the absence of acute reversible event in the determination of an independent endpoint adjudication committee). [b]Log-rank statistical test stratified by disease duration. [c]Estimated from the Kaplan-Meier method. Finkel R, et al. N Engl J Med 2017;377:1723-1732

# ENDEAR (CS3B) EOS analysis: Change in total motor milestones (HINE Section 2) over time[a]



**Improvements in HINE motor milestone total scores in nusinersen-treated infants did not plateau compared with an overall decrease in sham control infants**




| | | | | | |
|---|---|---|---|---|---|
| Sham control | 37 | 30 | 23 | 16 | 11 |
| Nusinersen | 73 | 66 | 59 | 36 | 26 |

[a]Mean changes from Baseline in HINE-2 total motor milestone scores including al 8 assessments at the Day 64, 183, 302, or 394 study visits among all infants in the efficacy set. Finkel R, et al. N Engl J Med 2017;377:1723-1732



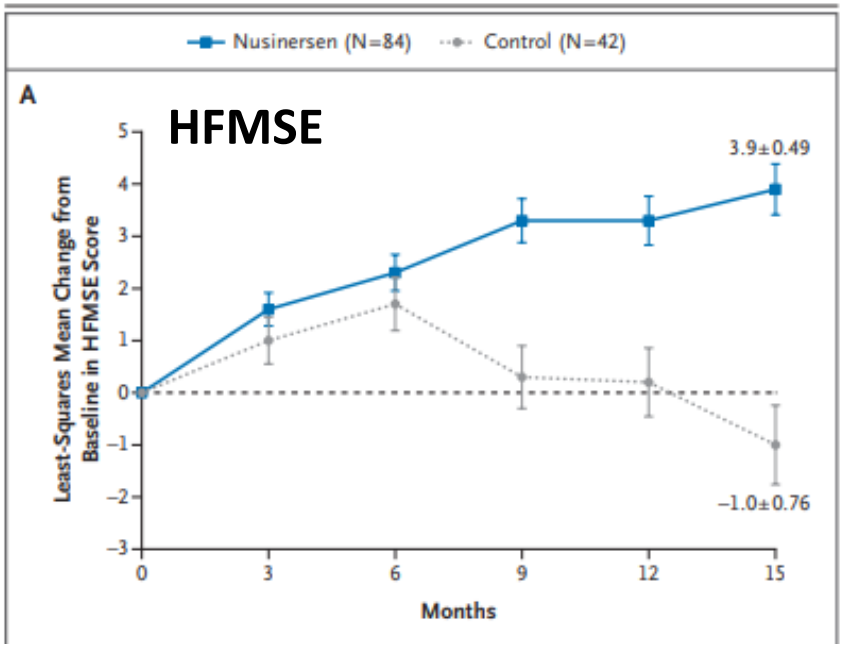
Biogen

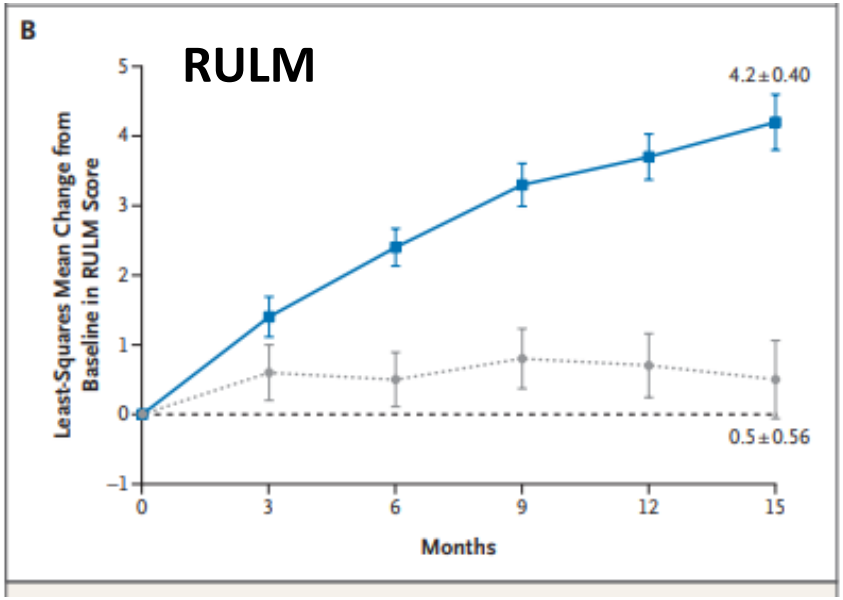
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

E. Mercuri, B.T. Darras, C.A. Chiriboga, J.W. Day, C. Campbell, A.M. Connolly, S.T. Iannaccone, J. Kirschner, N.L. Kuntz, K. Saito, P.B. Shieh, M. Tulinius, E.S. Mazzone, J. Montes, K.M. Bishop, Q. Yang, R. Foster, S. Gheuens, C.F. Bennett, W. Farwell, E. Schneider, D.C. De Vivo, and R.S. Finkel, for the CHERISH Study Group*



Domenica, 07 Agosto 2016

## Verso l'approvazione di nusinersen!

Biogen e Ionis Pharmaceuticals hanno diramato un comunicato ufficiale alla Comunità SMA sulla decisione di presentare alla FDA la richiesta di approvazione del farmaco nusinersen.

"Cari Membri della Comunità SMA, oggi è un giorno importante nella nostra ricerca collettiva di un trattamento significativo per l'atrofia muscolare spinale (SMA). Siamo lieti di condividere la notizia entusiasmante che un'analisi intermedia dei dati dello studio Endear nei bambini con l'atrofia muscolare spinale ha evidenziato risultati positivi. Di conseguenza sono in corso gli adempimenti per trasferire tutti i partecipanti allo studio Endear in un nuovo studio di estensione in aperto con somministrazione a tutti di nusinersen e chiusura dello studio Endear.

Famiglie SMA
Genitori per la Ricerca sull'Atrofia Muscolare Spinale


**Novembre 2016**: avvio in Italia del programma di accesso ampliato (EAP) basata sull'uso di nusinersen. 5 Centri italiani coinvolti. Nusinersen disponibile per uso compassionevole per neonati e bambini con **SMA di tipo 1**.

Trattati bambini di diverse età e differenti stadi di malattia.

**Creazione di una lista nazionale**

**Criteri di priorità:** età come primo filtro; neonati appena diagnosticati in cima alla lista.

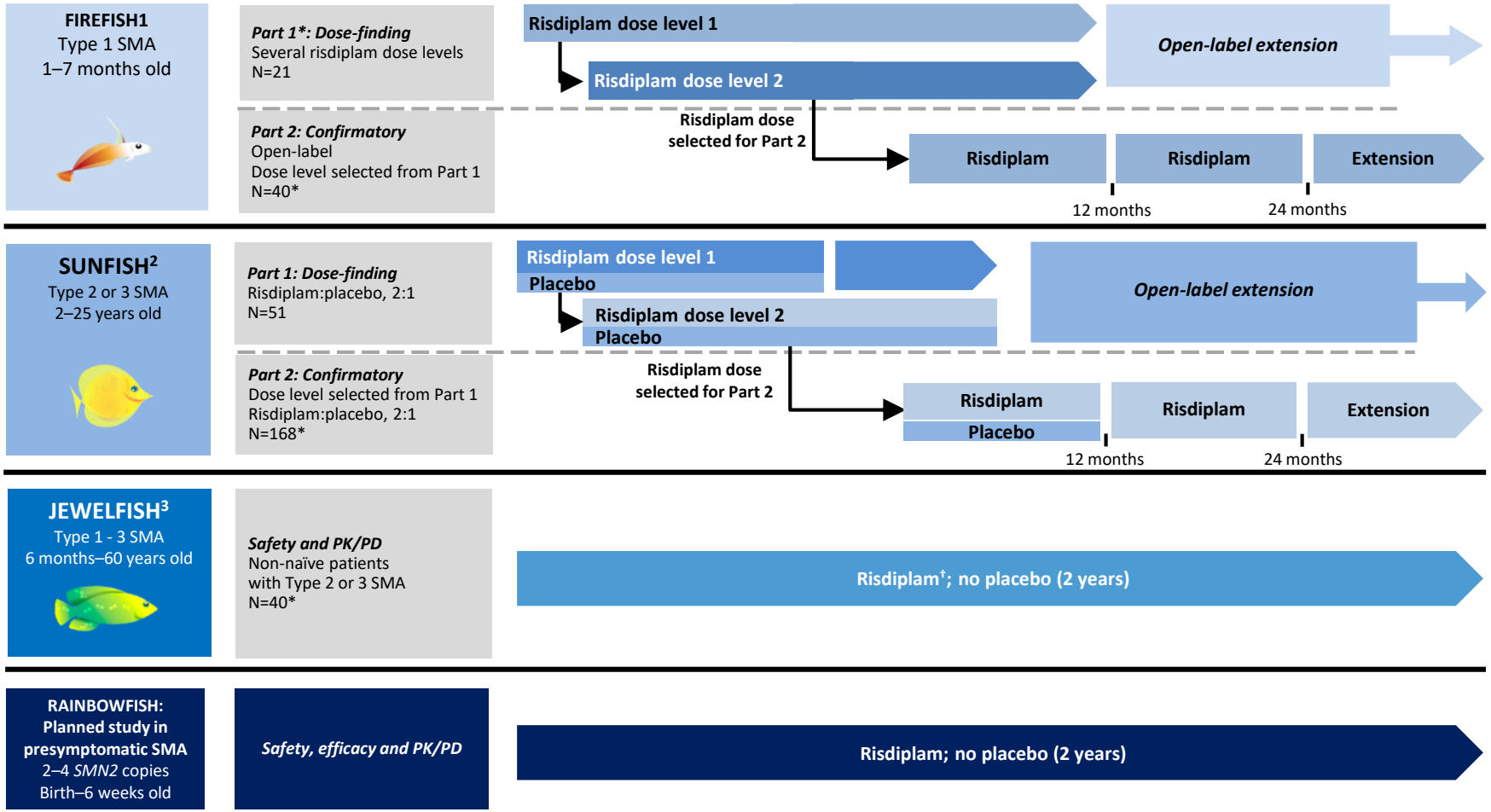
## EAP in Italian Centres

- **Spinraza è il primo ed unico farmaco indicato per il trattamento della SMA), che è una delle principali cause genetiche di mortalità infantile**

- Spinraza è un farmaco "*disease-modifying*" in grado di aumentare il livello della proteina SMN nei pazienti con SMA in modo tale da ottenere miglioramenti nella sopravvivenza e le capacità motorie, rallentando notevolmente la progressione della malattia.
- Poiché il numero di pazienti affetti da SMA è basso, Spinraza è stato qualificato come "*medicinale orfano*".

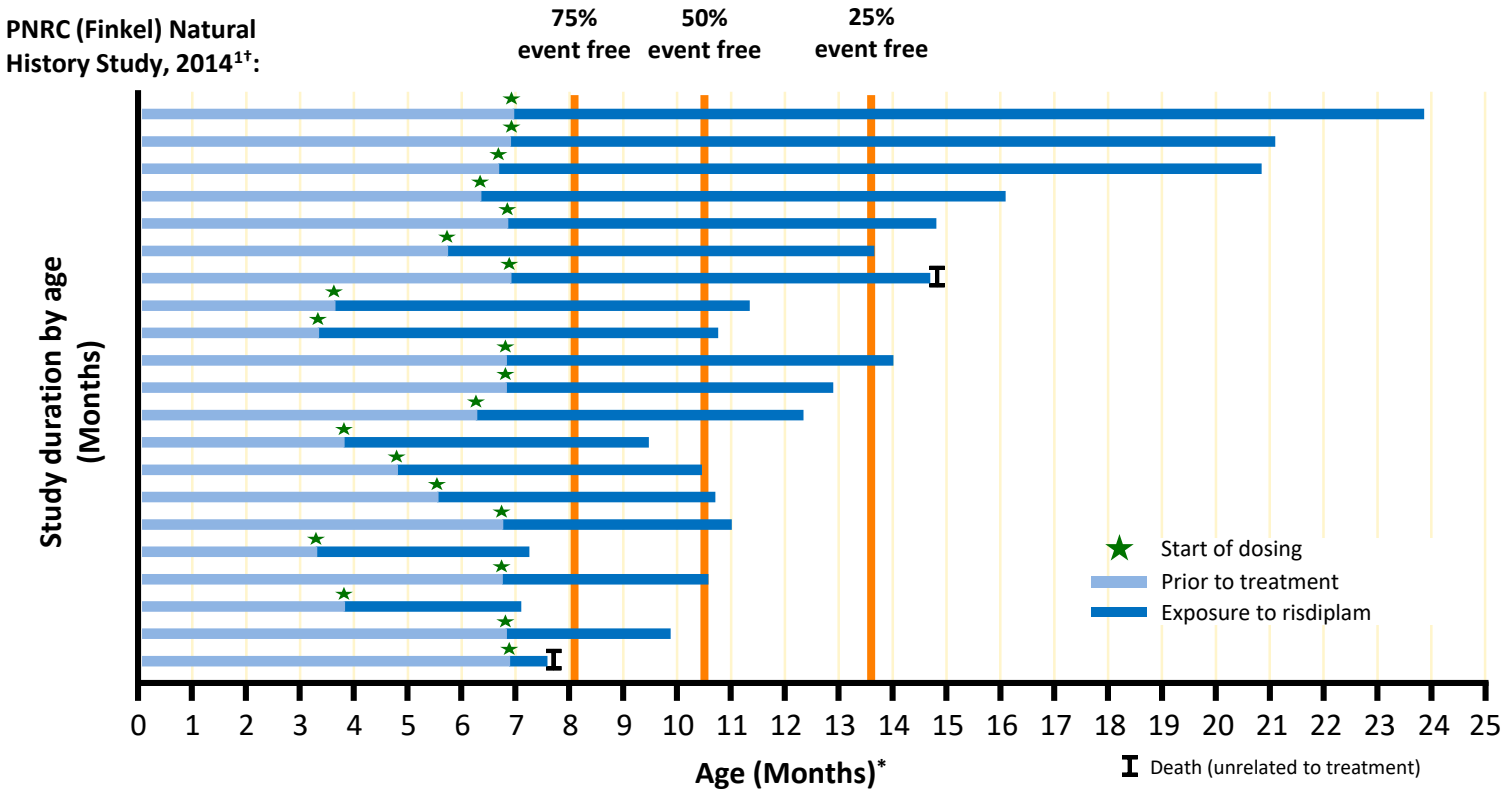
- E' **stata riconosciuta a Spinraza, da parte di AIFA, l'innovatività permettendo l'inclusione del farmaco nel fondo per l'aquisto dei medicinali innovativi.**

# Risdiplam Clinical Development Program




*Target enrollment; †same dose as in SUNFISH.
PK, pharmacokinetics; PD, pharmacodynamics; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Gorni K, et al.; Presented at Cure SMA - 2018 Annual Conference CSMA.
Clinicaltrials.gov; 1. NCT02913482; 2. NCT02908685; 3. NCT03032172. (Accessed March 2018).

# FIREFISH Part 1 Interim Data: Age of Babies and Duration of Exposure to Treatment




- Median exposure to treatment: 6.05 months (range: 0.7–16.9 months).

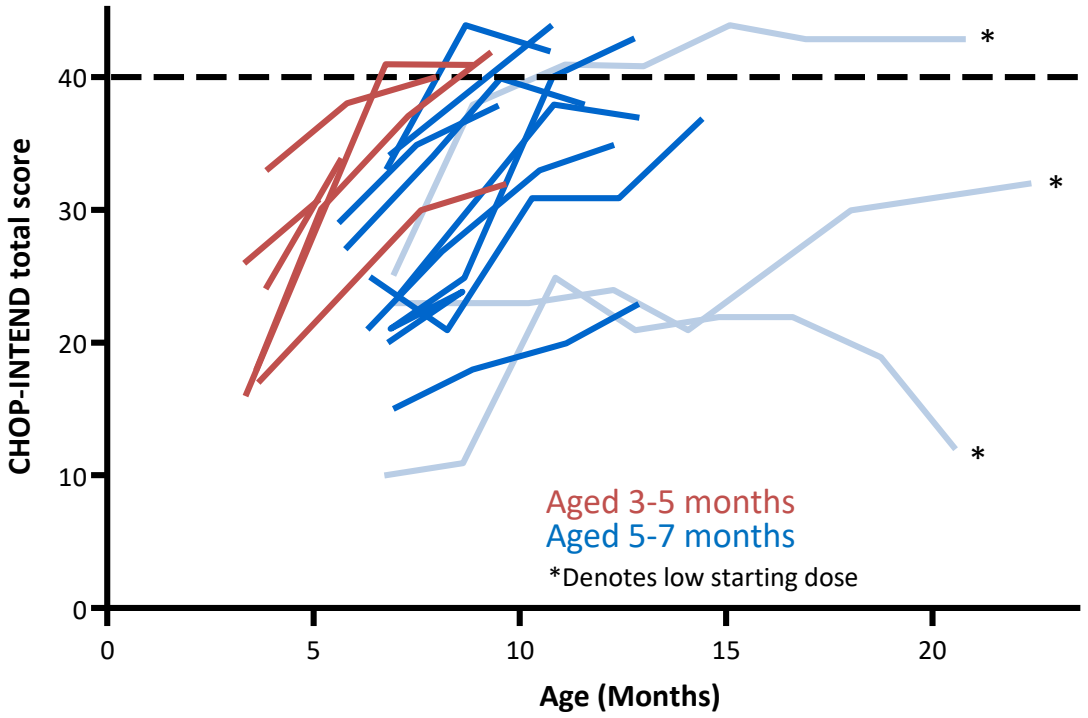
**Study duration is measured from the start date of the first dose to the date of data extraction. Deaths were not related to study treatment, one death was due to aspiration and one death was due to pneumonia. Data cut: 24 May 2018.*

*†The median age at the combined endpoint for subjects with two SMN2 copies was 10.5 months (IQR 8.1–13.6);[1] event free = alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks).[1]*

*Baranello G, et al.; Presented at Cure SMA - 2018 Annual Conference CSMA.*

*1. Finkel R, et al. Neurology 2014; 83(9): 810-817.*

# CHOP-INTEND Score: Individual Patient Plots Show Continuous Improvement from Baseline




**Median change from baseline in CHOP-INTEND score was:**

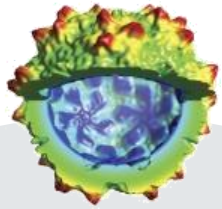
| | Aged 3-5 months | Aged 5-7 months | Overall |
|---|---|---|---|
| **Day 56** | **8.0** (n=6) | **4.5** (n=14) | **5.5** (n=20) |
| **Day 119** | **13.5** (n=4) | **11.0** (n=12) | **12.5** (n=16) |
| **Day 182** | **20.5** (n=2) | **11.0** (n=9) | **14.0** (n=11) |

*Intent-to-treat patients from FIREFISH Part 1. Data cut-off: 24th May 2018.*
*CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; IQR, interquartile range.*
*Baranello G, et al.; Presented at Cure SMA - 2018 Annual Conference CSMA.*

# AVXS-101: An Innovative Treatment Approach for SMA

***Gene therapy is the right approach for SMA: Monogenic mutation that drives the pathology***

**Recombinant AAV9 Capsid Shell**



| scAAV ITR | Continuous Promoter | Human SMN Transgene | scAAV ITR |
|---|---|---|---|

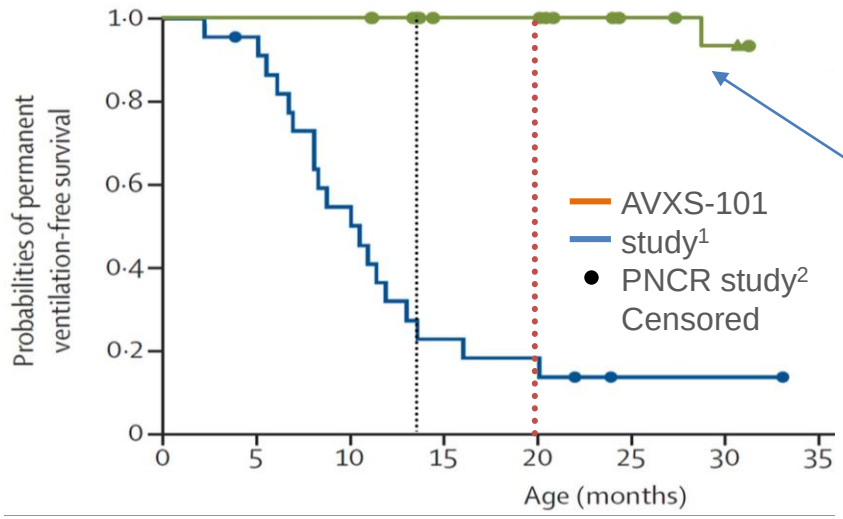
| KEY COMPONENTS | PURPOSE |
|---|---|
| **Recombinant AAV9 capsid shell** | • Ability to deliver across the blood brain barrier (BBB) and into the spinal cord<br>  - Avoids the need for intrathecal delivery when treating infants<br>• Non-replicating virus does not modify the existing DNA of the patient |
| **scAAV ITR (self-complementary DNA technology)** | • Enables rapid onset of effect, which is key in a quickly deteriorating population |
| **Continuous promoter** | • Activates the transgene to allow for continuous and sustained SMN expression |
| **Human SMN transgene** | • Full copy of a stable, functioning SMN gene that is introduced into the cell's nucleus |

Rendering adapted from DiMattia MA, et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9. J *Virol* 2012;86:6947–58

# Effect on Survival*:
# 100% Survival vs 8% for Natural History at 20 Months of Age

**SURVIVAL DATA SUMMARY**

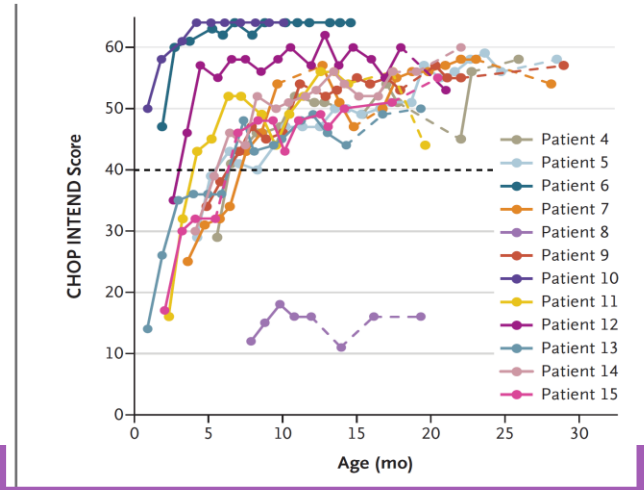
**15/15 (100%) reached 20 months of age event-free[1] (vs 8% natural history[2])**




**SURVIVAL DATA**

- 15/15 reached 20 mo. event-free (8% NHx)
- 15/15 reached 13.6 mo. event-free (25% NHx)
- 15/15 reached 10.5 mo. event-free (50% NHx)
- 15/15 reached 8.1 mo. event-free (75% NHx)

- One subject in low-dose cohort ($6.7x10^{13}$ vg/kg) met ventilatory endpoint (16 hours of use daily) at age 28.8 months
- This was due to hypersalivation. Following surgical ligation of the salivary glands, the child's ventilatory requirement subsequently lessened to less than 16 hours per day



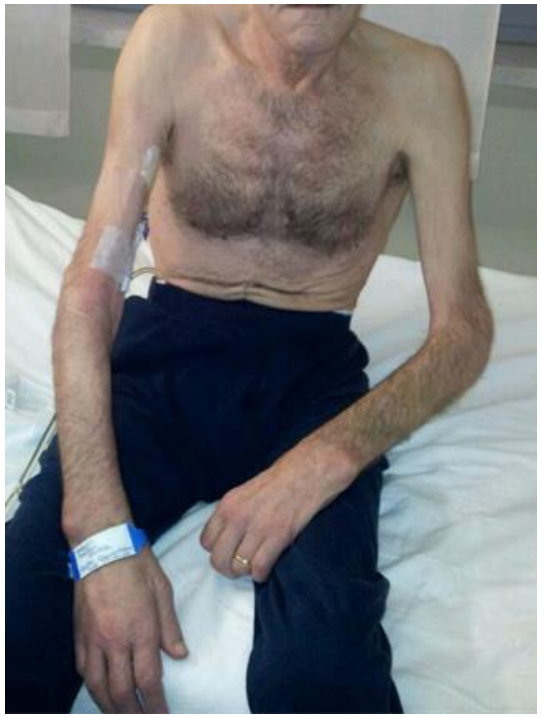

**Cohort 2 (n=12)**

Baseline Age (months): **3.1** [median]
Current Age (months): **25.7** [median]
Mean CHOP INTEND Increase: **24.7** points


# IN LAZIO E TOSCANA PROGETTO PILOTA DI SCREENING NEONATALE PER LA DIAGNOSI PRECOCE

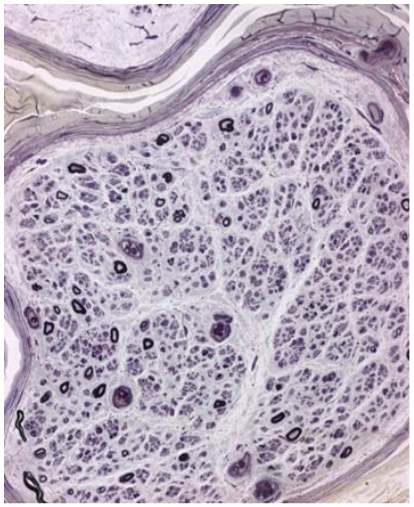
È possibile salvare i nuovi nati dalle difficoltà di una malattia genetica rara come l'**atrofia muscolare spinale**? La risposta affermativa è nel test molecolare sviluppato presso l'**Istituto di Medicina Genomica dell'Università Cattolica del Sacro Cuore**, e la dimostrazione è nell'avvio del **progetto pilota di screening neonatale** che partirà in **Lazio e Toscana** nei **primi mesi del 2019**, grazie alla collaborazione tra la stessa Università e il **Policlinico Gemelli di Roma**, i due **governi regionali**, **l'Ospedale Meyer di Firenze**, l'azienda farmaceutica **Biogen** e **Famiglie SMA**, l'associazione dei genitori di bimbi e pazienti con questa patologia prima incurabile e mortale (*SMA* dall'acronimo dell'inglese *Spinal Muscolar Atrophy).*

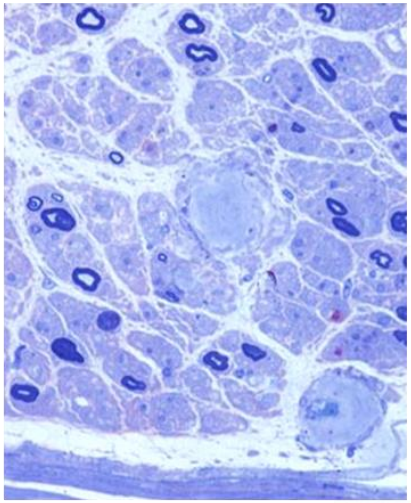
## LE NEWS

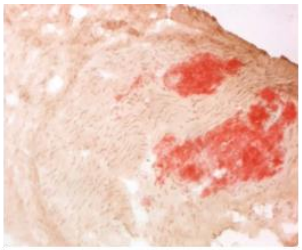


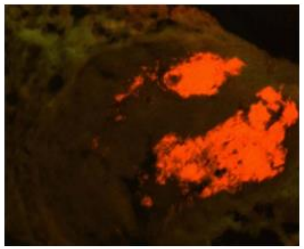
# Polineuropatia amiloidosica legata alla transtiretina (TTR-FAP o hATTR)

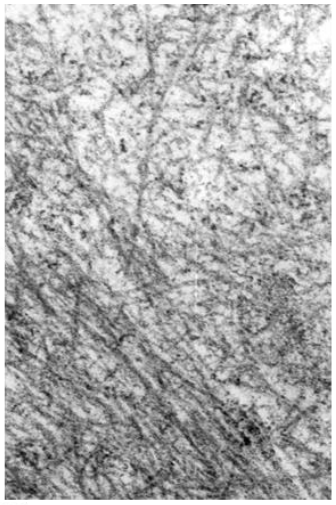
- Sindrome del Tunnel carpale
- Polineuropatia assonale sensori-motoria
- Cardiopatia
- Disautonomia
  - Ipotensione ortostatica
  - Diarrea/Stipsi
  - Impotenza
  - Disturbi della sudorazione
  - Salivazione ridotta
- Perdita di peso
- Opacità del vitreo

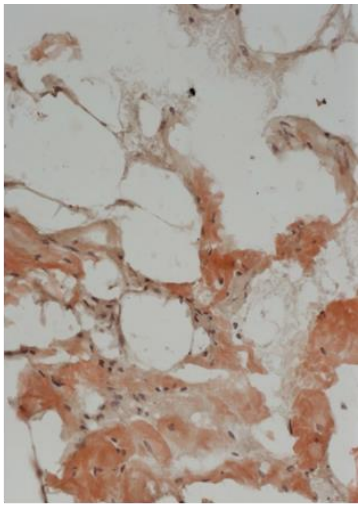






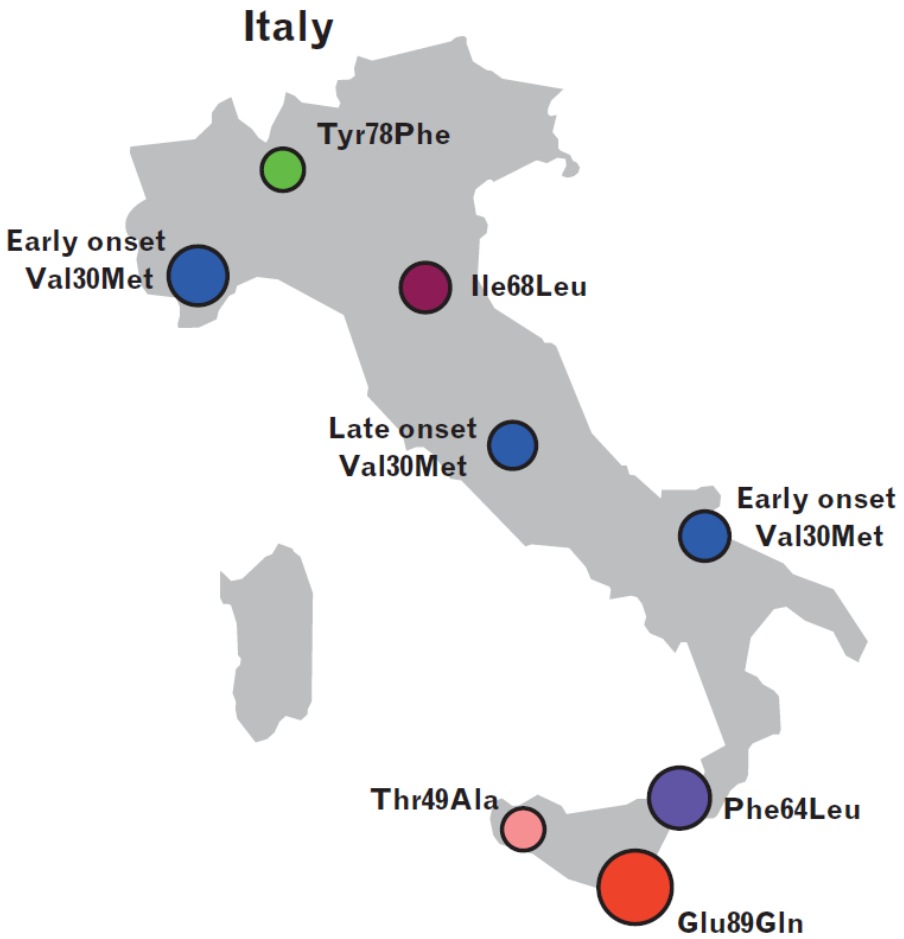






**Prevalence**

| | | | |
|---|---|---|---|
| North Portugal: | 151 | / | 100,000 |
| North Sweden: | 104 | / | 100,000 |
| Majorca, Spain: | 5 | / | 100,000 |
| Cyprus: | 3.7 | / | 100,000 |
| Japan: | 0.87-1.1 | / | 1,000,000 |
| Nagano: | 11-15.5 | / | 1,000,000 |
| Kumamoto: | 10.2 | / | 1,000,000 |
| France | 3-4 | / | 1,000,000 |
| **Sicily** | **8.8** | **/** | **1,000,000** |




Journal of Neuromuscular Diseases 2 (2015) S39–S48
DOI 10.3233/JND-150091
IOS Press

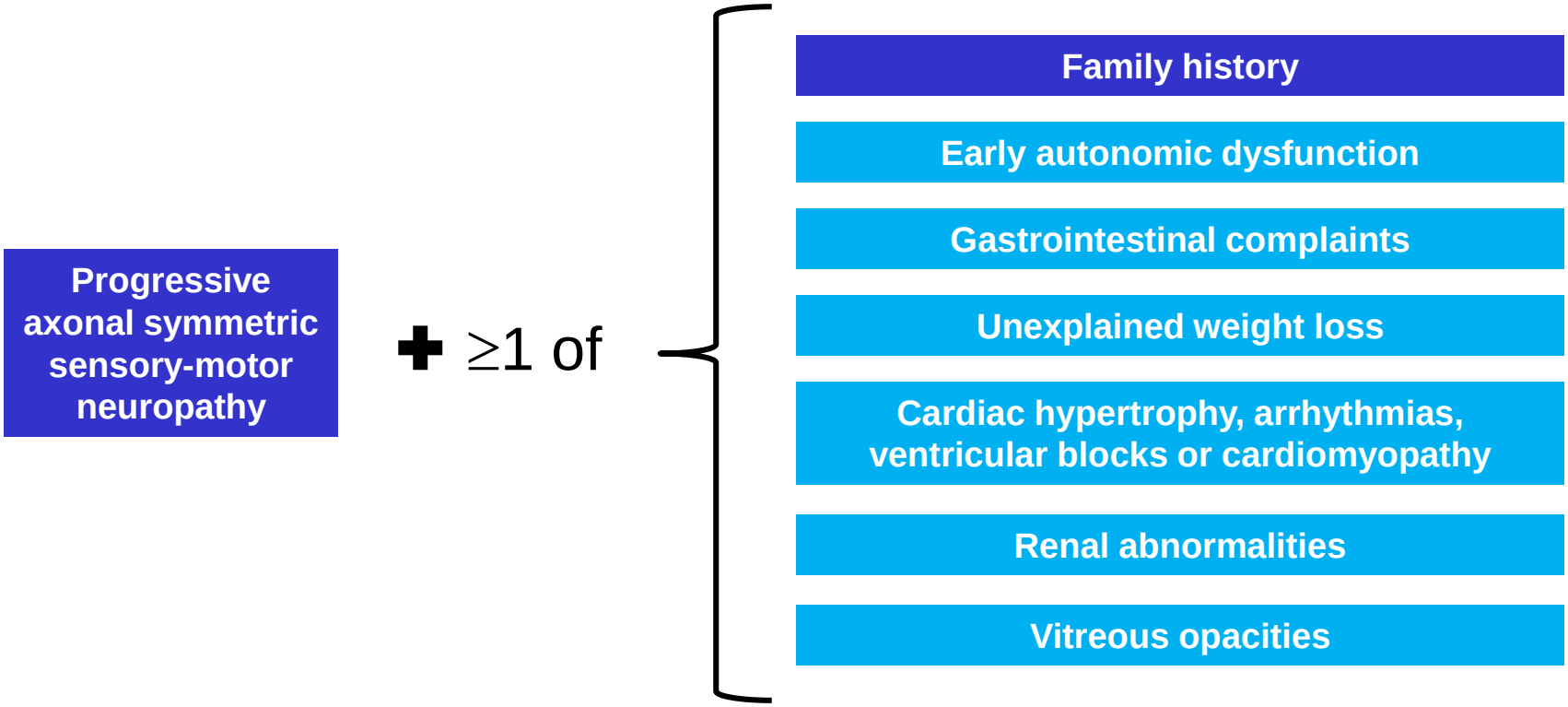


Research Report

# Transthyretin-Related Familial Amyloid Polyneuropathy (TTR-FAP): A Single-Center Experience in Sicily, an Italian Endemic Area

Anna Mazzeo[a], Massimo Russo[b], Gianluca Di Bella[c], Fabio Minutoli[d], Claudia Stancanelli[a,c], Luca Gentile[a], Sergio Baldari[d], Scipione Carerj[c], Antonio Toscano[a] and Giuseppe Vita[a,b,*]

# "Red-flag" symptom cluster recommended for hATTR amyloidosis presenting with polyneuropathy

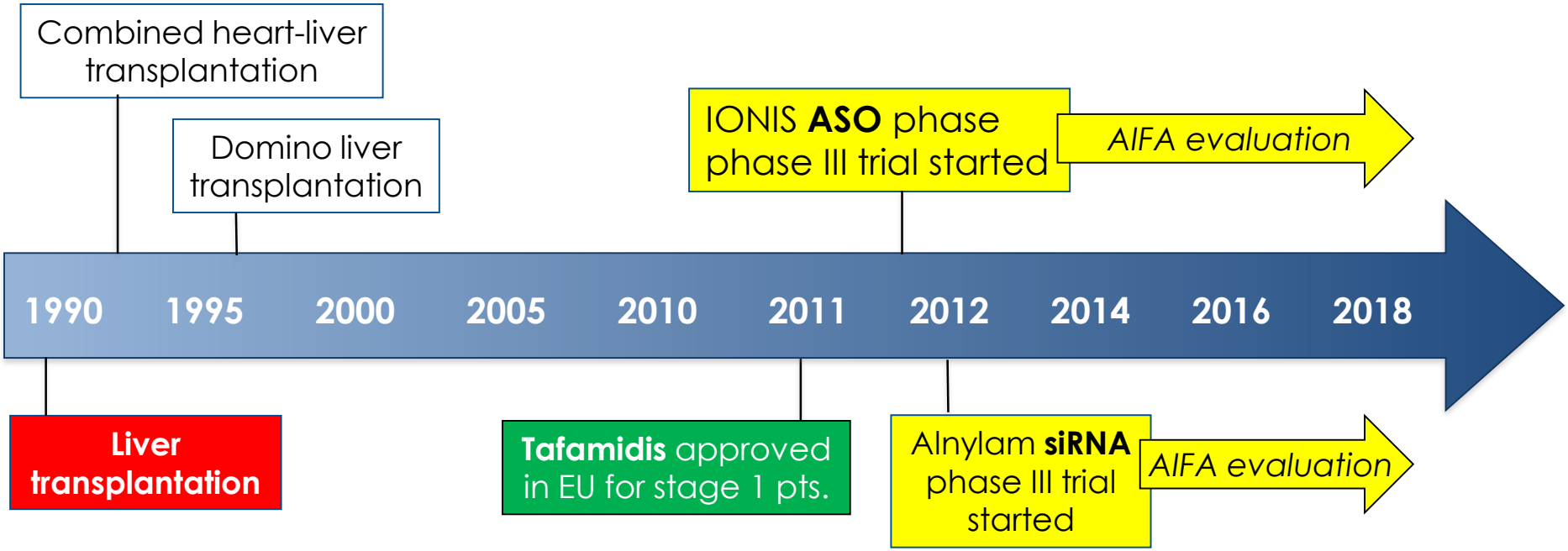



**Additional alert signs:**

- Rapid disease progression
- Lack of response to prior therapies

# Disease-modifying treatments

*Approved and in development treatment options*



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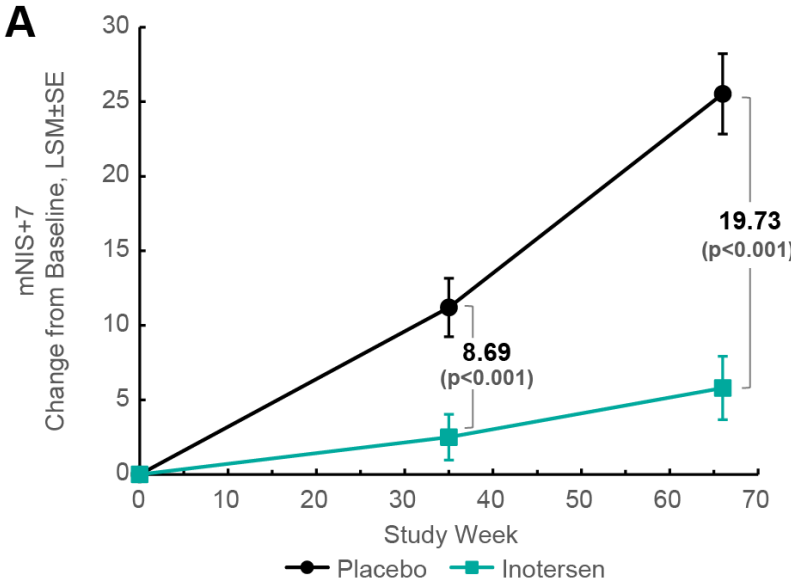
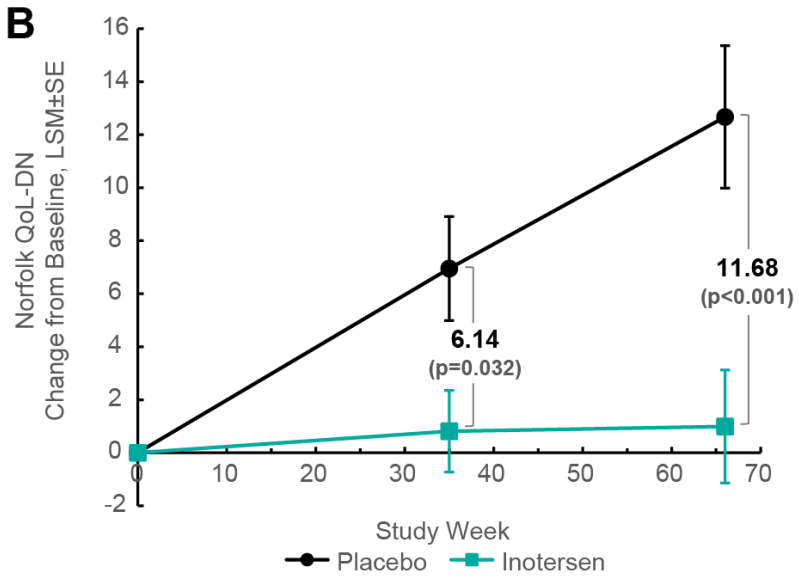


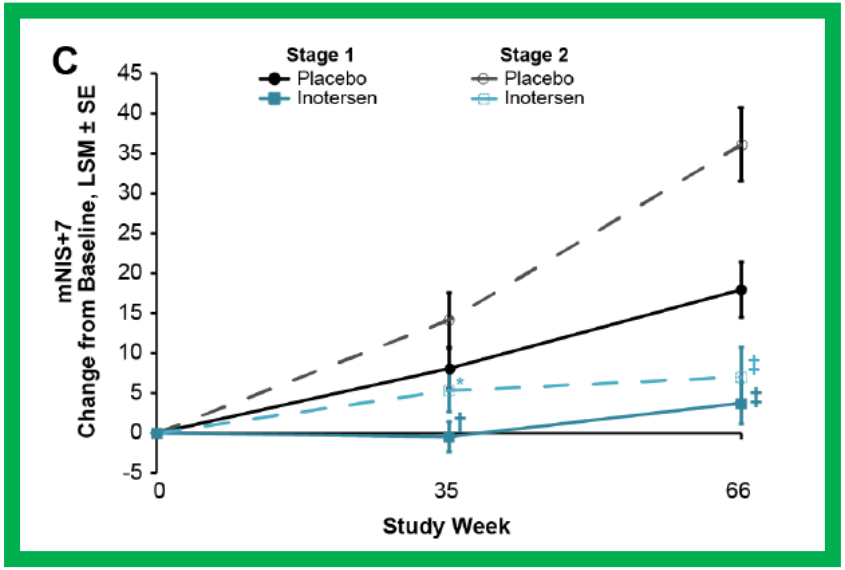




ORIGINAL ARTICLE

# Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

N Engl J Med 2018;379:22-31.



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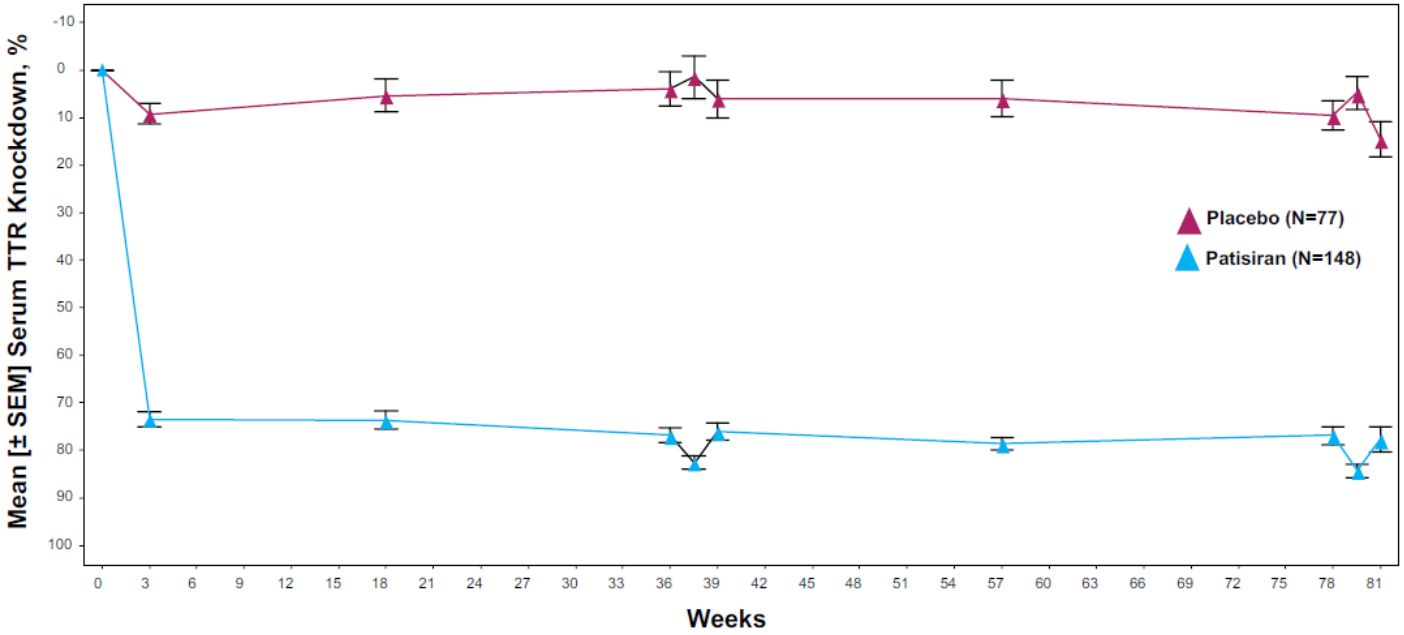
# Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

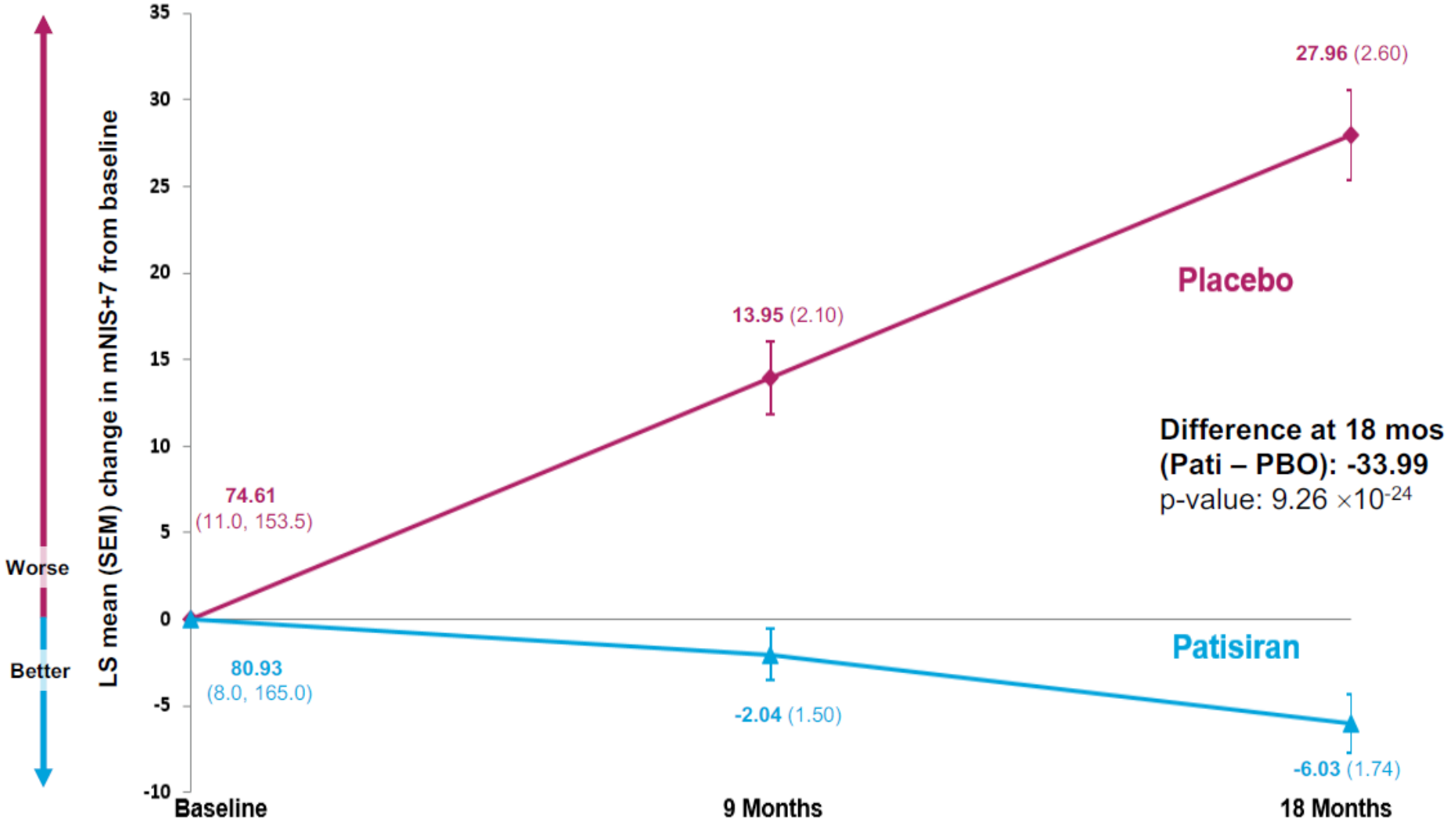
N Engl J Med 2018;379:11-21.

**87.8% mean max serum TTR reduction from baseline for patisiran over 18 months**



# Patisiran Phase 3 APOLLO Study Results

## mNIS+7: Change from Baseline



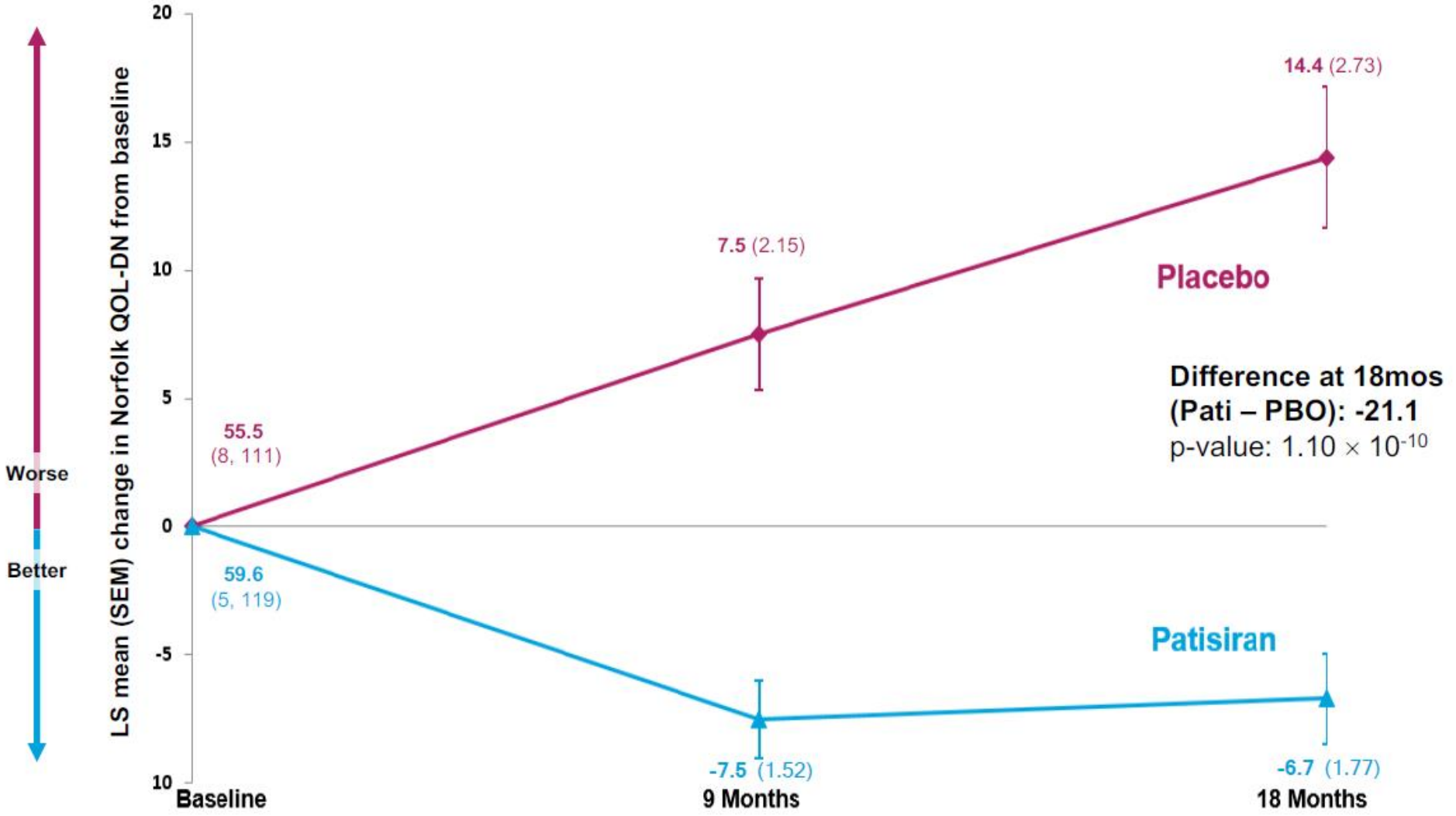



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
mNIS+7 reference range: 0-304 points

APOLLO

# Patisiran Phase 3 APOLLO Study Results

## Norfolk QOL-DN: Change from Baseline



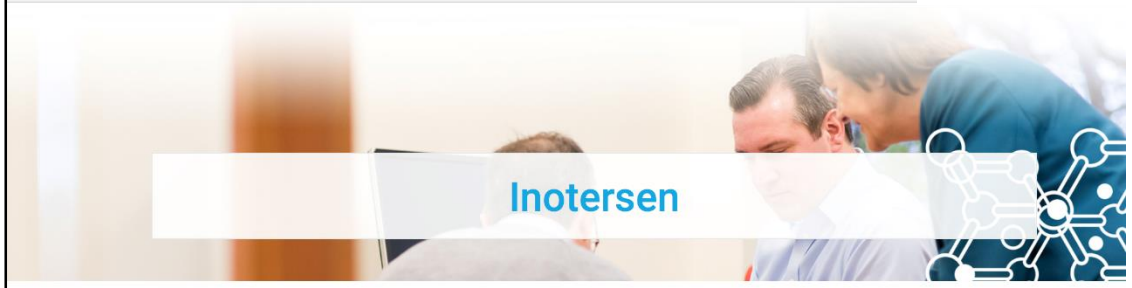



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
Norfolk QOL-DN reference range: -4 to 136

APOLLO

AKCEA THERAPEUTICS

IONIS PHARMACEUTICALS



# Inotersen

Inotersen is an antisense drug designed to reduce the production of transthyretin, or TTR protein, to treat hereditary ATTR amyloidosis (hATTR), a severe, rare and fatal genetic disease. In patients with hATTR, both the mutant and wild type (wt) TTR protein builds up as fibrils in tissues, such as the peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. As the TTR protein fibrils enlarge, more tissue damage occurs and the disease worsens, resulting in poor quality of life and eventually death.

## Expanded Access/Compassionate Use

An expanded access program (EAP) is available for eligible patients with hATTR. For more information, please visit this link.

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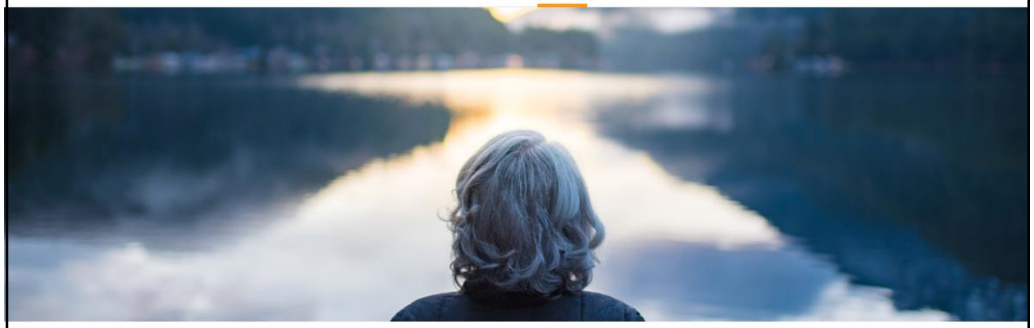

# EXPANDED **ACCESS PROGRAM**

## Expanded Access Program to Help Eligible Patients with hATTR Amyloidosis with Polyneuropathy Gain Access to Patisiran

# Alnylam Clinical Development Pipeline

## Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases
- CNS Diseases

| | | HUMAN POC[1] | BREAKTHROUGH DESIGNATION | EARLY STAGE *(IND or CTA Filed-Phase 2)* | LATE STAGE *(Phase 2-Phase 3)* | REGISTRATION/ COMMERCIAL[2] | COMMERCIAL RIGHTS |
|---|---|---|---|---|---|---|---|
| **Patisiran** | *Hereditary ATTR Amyloidosis* | ✓ | ✓ | | | ● | Global |
| **Givosiran** | *Acute Hepatic Porphyrias* | ✓ | ✓ | | ● | | Global |
| **Fitusiran** | *Hemophilia and Rare Bleeding Disorders* | ✓ | | | ● | | 15-30% Royalties |
| **Inclisiran** | *Hypercholesterolemia* | ✓ | | | ● | | Milestones & up to 20% Royalties |
| **ALN-TTRsc02** | *ATTR Amyloidosis* | ✓ | | ● | | | Global |
| **Lumasiran** | *Primary Hyperoxaluria Type 1* | ✓ | ✓ | ● | | | Global |
| **Cemdisiran** | *Complement-Mediated Diseases* | ✓ | | ● | | | Global |

[1]POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2]Includes marketing application submissions

As of May 2018


UOC di Neurologia e M.N.M
Università di Messina

Centro Clinico Nemo Sud
per le Malattie Neuromuscolari