Nuove terapie della SMA nell'adulto

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Centro Regionale Malattie del Motoneurone

ATROFIA MUSCOLARE SPINALE

Malattia degenerativa dei motoneuroni periferici, caratterizzata da progressiva debolezza e atrofia muscolare.

Sugarman EA, et al. Eur J Hum Genet 2012;20(1):27–32.

Incidenza 1/8,000 nati
Portatore 1/50
Malattia rara (in Italia circa 1000 casi)
Seconda patologia AR più frequente dell'infanzia dopo la fibrosi cistica

Studio retrospettivo, 165 pazienti **adulti**, 64F/101M

Maggi L et al. Adults with spinal muscular atrophy: a large-scale natural history study shows gender effect on disease. J Neurol Neurosurg Psychiatry. 2022 Oct 11

Effetto di genere rilevante sulla funzione motoria della SMA con **una maggiore gravità della malattia nei maschi, specialmente in età giovane-adulta.**

PATOLOGIA GENETICA

Mutazione scoperta nel 1995

98% dei casi da **delezione in omozigosi del gene SMN1 (Cr 5q13)** codificante per la proteina SMN (Survival Motor Neuron).

Genoma umano → 2 copie **SMN 1** (telomerico) e numero variabile del gene paralogo **SMN 2** (centromerico)

SMN2 differisce da **SMN** 1 per una C→T nella regione di splicing dell'esone 7 che riduce l'efficienza di splicing

↓

Esclusione dell'esone 7 in molti trascritti di mRNA prodotti dal gene **SMN2**

↓

Solo una minoranza di trascritti di mRNA di **SMN2** include l'esone 7 ed è in grado di produrre proteine normali.

Ruolo principale SMN → assemblaggio di piccoli complessi di proteine ribonucleari (SnRNP) necessari per lo splicing pre-mRNA

Espressa nel citoplasma e nel nucleo in tutti i tessuti somatici con quantità particolarmente **elevate nei motoneuroni del midollo spinale, soprattutto in epoca gestazionale e neonatale**.

Nella SMA la sopravvivenza del motoneurone diventa dipendente da una quantità insufficiente di proteina SMN che può essere prodotta solo dalle copie SMN2 di un individuo.

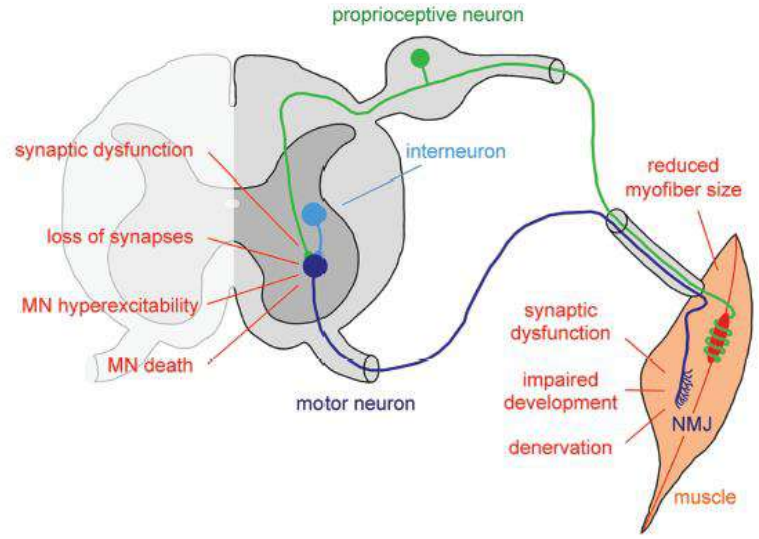


FIGURE 10-3
Inadequate SMN protein levels disrupt several interactions within the motor unit.

ATROFIA MUSCOLARE SPINALE

Indagine genetica → DIAGNOSI DI CERTEZZA
sensibilità 97%, specificità 100%

Il fenotipo della malattia è variabile.

Prima della disponibilità delle terapie per la SMA, la malattia era **classificata in gruppi in base all'età di insorgenza dei sintomi e alle tappe motorie raggiunte**.
Queste classificazioni, utili per la prognosi, sono ancora utilizzate per definire coorti in ambito di trial clinici.

SMA 5q: Classification (without treatment)

- Inheritance: Recessive
- SMN1 mutations: Bi-Allelic

More Severe

Less Severe

SMA Type	SMN2 Copies	SMA 5q %	Onset Age	Motor Milestone Achieved	Life Expectancy
0	1	< 1%	Birth	Never Sit	< 6 mo
1	2-3	55%	0 to 6 mo	Never Sit	8 to 24 mo
2	2-4	30%	6 to 18 mo	Sit	2 to 4 decades
3	3-5	10%	1.5 to 20 yrs	Walk	Normal
4	3-5	5%	Adult	Walk	Normal

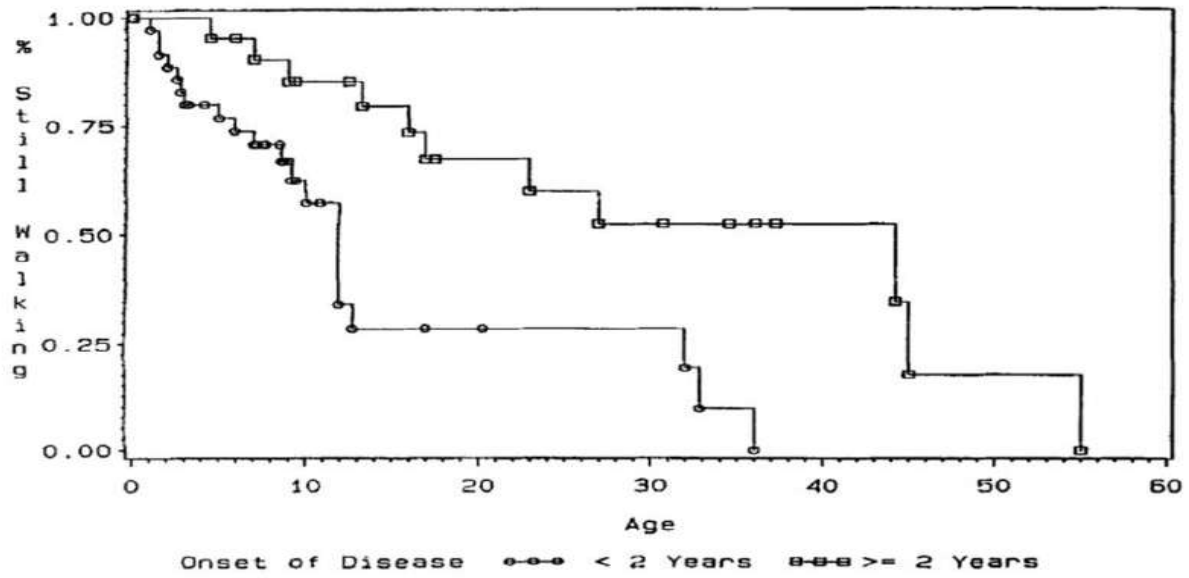
Il fenotipo clinico è influenzato dal numero di copie del gene SMN2 presenti.

B — % SMA type

SMN2 copy #	SMA I	SMA II	SMA III
1	7	0	0
2	73	11	4
3	20	82	51
4	0	7	45

SMA is a severe and progressive disease across all SMA subtypes regardless of age of symptom onset

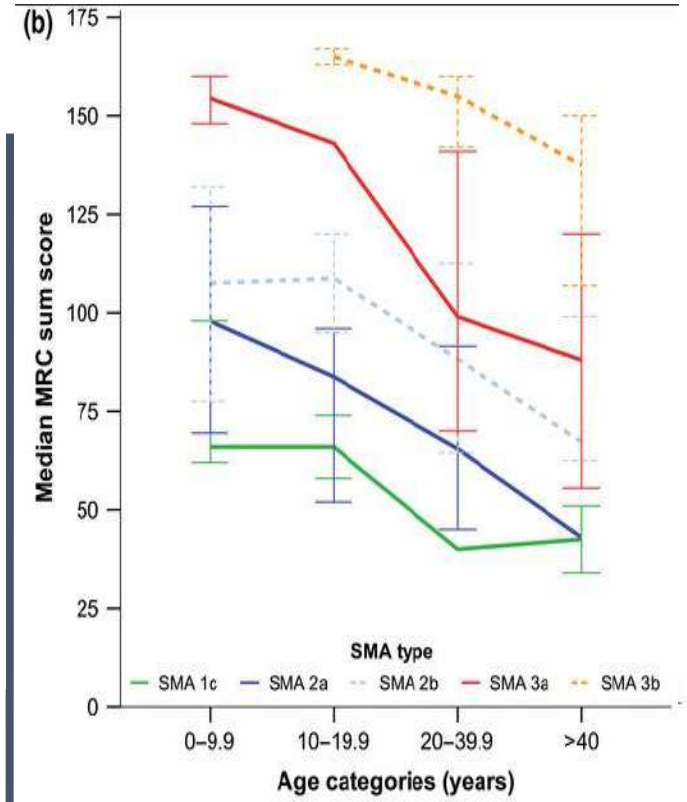
Percentage of patients still walking independently by age and age of onset subgroups

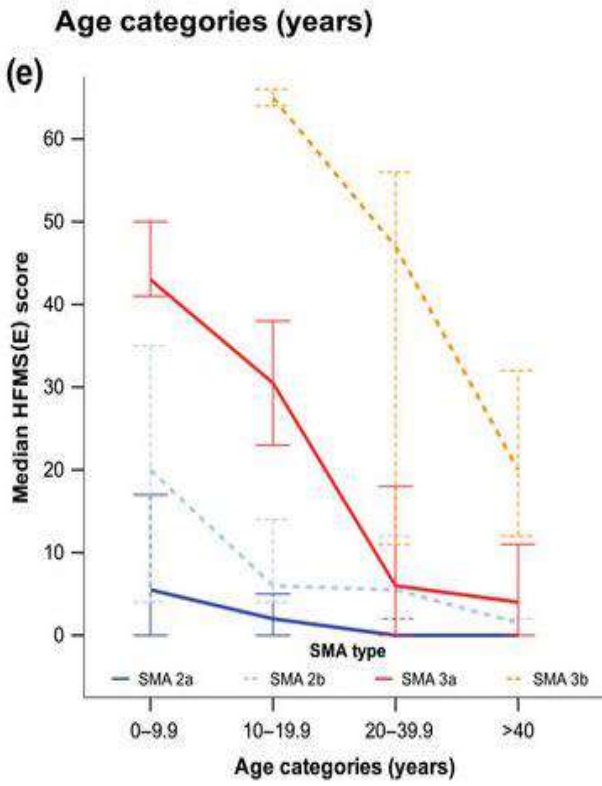


Russman BS et al. Neurology. 1996;47(4):973-6.

Age at which ambulation is lost is correlated with age of onset

The clinical course of disease is variable and age at which loss of ambulation occurs cannot be predicted





Wadman RI, et al. *Eur J Neurol*. 2018;25:512-518.

SMA Type II/III can have pronounced muscle deterioration in the 3rd decade and beyond 40 years of age

TERAPIE INNOVATIVE

Terapie ad oggi autorizzate in Italia

ADULTO → **NUSINERSEN** **(GU Serie Generale n.226 del 27-09-2017)**

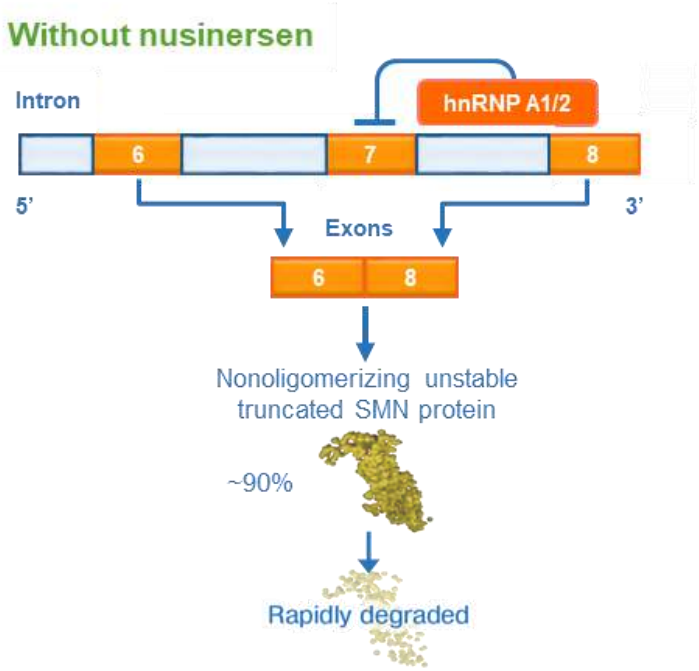
ONASEMNOGENE ABEPARVOVEC **(GU Serie Generale n.62 del 13-03-2021)**

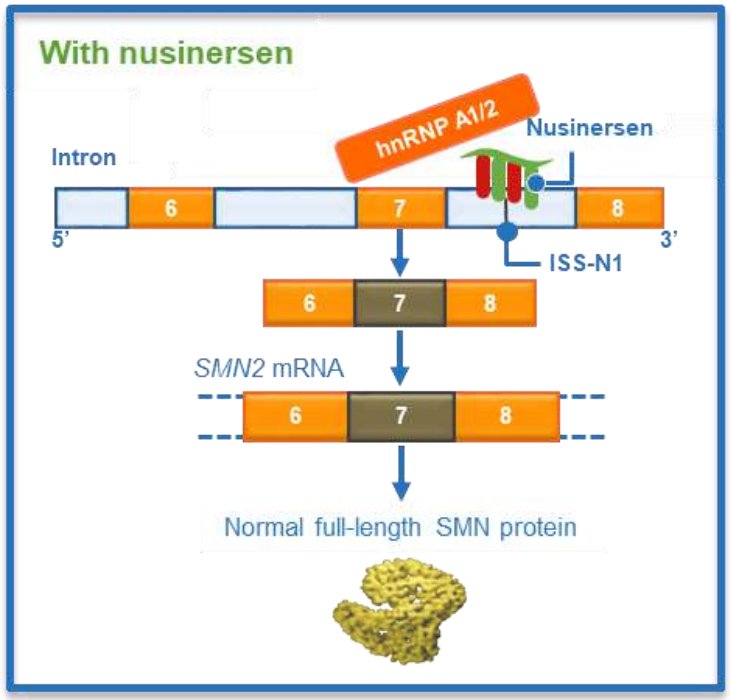
ADULTO → **RISDIPLAM** **(GU Serie Generale n.31 del 07-02- 2022)**

Nusinersen – Spinraza

Nusinersen is an antisense oligonucleotide (ASO).

It binds a splicing silencer region on SMN2 pre-mRNA, displacing a splicing repressor protein and boosting exon 7 inclusion in *SMN2* mRNA transcripts and production of full-length SMN protein.





Nusinersen – Spinraza

- Soluzione limpida e incolore.
- Nusinersen non attraversa la BEE.
- Somministrazione **intratecale**.

FIALE-USO INTRATECALE, 5ml/12 mg

Dose 1

Intervallo di 14 giorni

Dose 2

Intervallo di 14 giorni

Dose 3

Intervallo di 35 giorni

Dose 4

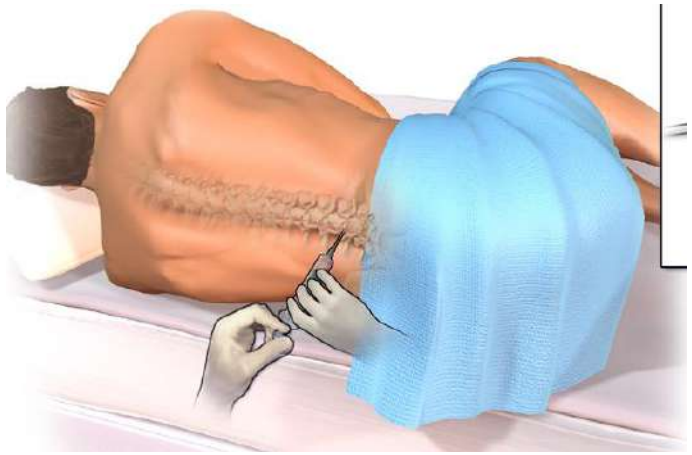
Dose di carico, 63 giorni

Intervallo di 4 mesi

Dose di mantenimento

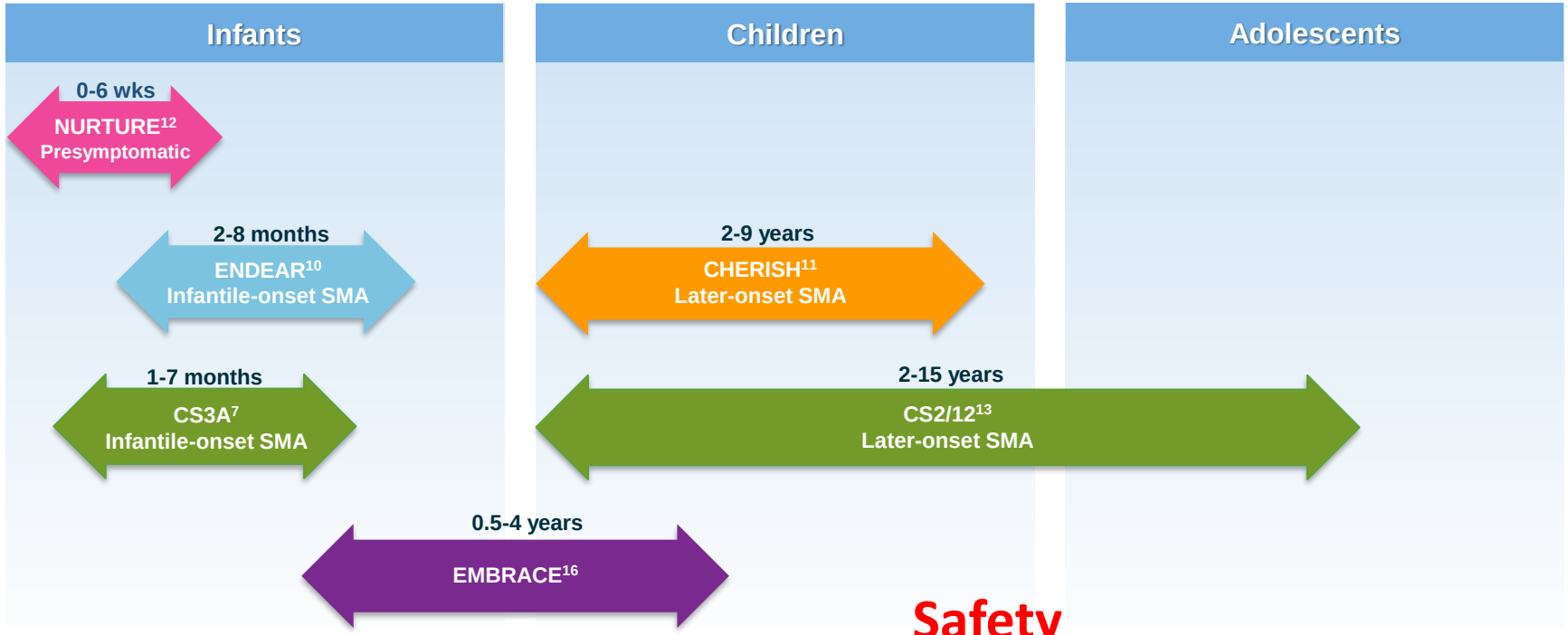
Intervallo di 4 mesi

Dose di mantenimento



Nusinersen – Spinraza

Clinical Development Program - Age range



Efficacy

- achievement of age-appropriate **motor milestones in presymptomatic individuals**
- increased event-free survival in infantile-onset SMA
- improved and maintained motor function in non-ambulatory and ambulatory individuals with later-onset SMA
- improved walking distance in ambulatory individuals with later-onset SMA

Safety

- Repeated lumbar punctures **well tolerated**
- Scoliosis and related surgery represent the **challenges for the wide application of this approach**
- Rare renal toxicity, bleeding for thrombocytopenia.
- Isolated cases of hydrocephalus (unclear)

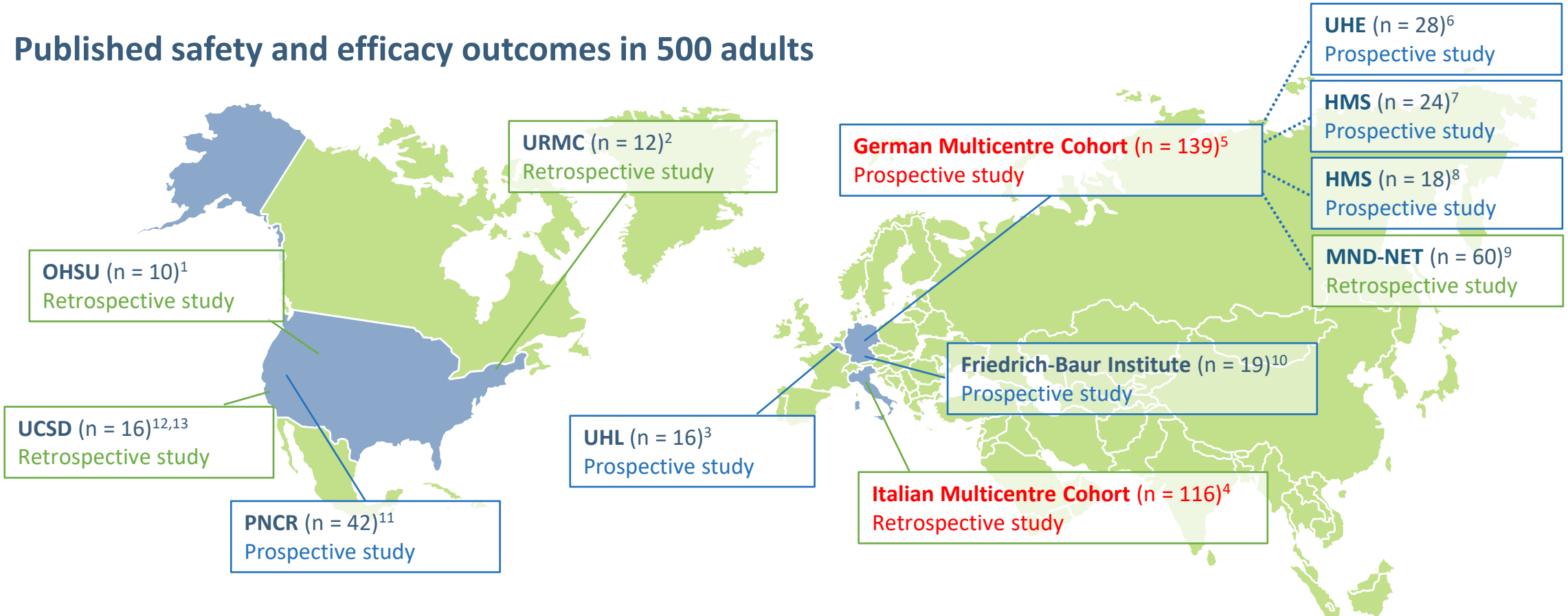
- **Evitare Nusinersen durante gravidanza e allattamento**
- Non osservati effetti su fertilitá (studi animali)

Nusinersen – Spinraza

Real world experience

5 years post registration, with over 11000 patients treated

Published safety and efficacy outcomes in 500 adults



Published manuscripts reporting on ≥ 10 adult patients were included. HMS, Hannover Medical School; OHSU, Oregon Health & Science University; MND-NET, German Network for Motoneuron DiseasesPNCR, Pediatric Neuromuscular Clinical Research Network; UCSD, University of California San Diego; UHE, University Hospital Essen; UHL, University Hospitals Leuven; URMC, University of Rochester Medical Center.

1. Moshe-Lilie O, et al. Neurology. 2020. 2020;28;95:e413-e416. 2. Veerapandiyan A, et al. Muscle Nerve. 2020;61:222-6. 3. De Wel D, et al. J Neurol. 2021;268:923-35. 4. Maggi L, et al. J Neurol Neurosurg Psychiatry. 2020;91:1166-74. 5. Hagenacker T, et al. Lancet Neurol. 2020;19:317-25. 6. Kizina K, et al. Sci Rep. 2020;10:11069. 7. Osmanovic A, et al. J Neurol. 2020;267:2398-407. 8. Binz C, et al. J Neurol. 2021;268:950-62. 9. Wurster CD, et al. Front Neurol. 2019;10:1179. 10. Walter MC, et al. J Neuromuscul Dis. 2019;6:453-45. 11. Duong T, et al. Neurol Clin Pract. 2021;10.1212/CPJ.0000000000001033. 12. Konersman CG, et al. J Neuromuscul Dis. 2021; 10.1016/j.nmd.2020.12.006. 13. Correspondence with Dr Konersman.

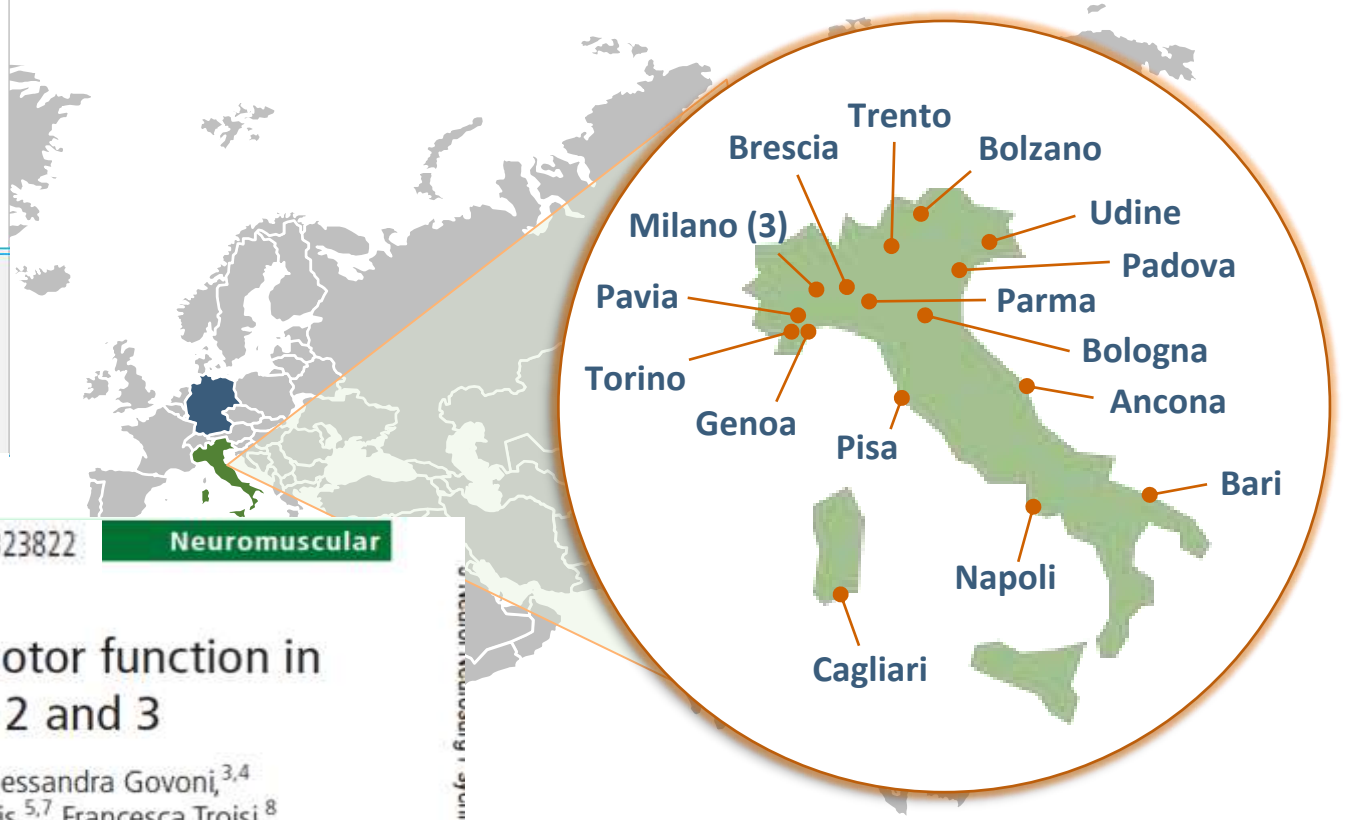
Nusinersen – Spinraza

The Italian Adult SMA Cohorts

Multicenter, observational studies to assess the safety and efficacy of nusinersen in adults with 5q SMA

	Age at Nusinersen Initiation Mean, years (range)	SMA Type 1 2 3	Ambulation Status
Italian[2,b] (n = 116)	34 (18–72)	11% / 89%	45% / 55%

HFMSE 22,5 (0-64); RULM 29 (0-37), 6MWT 322 (14-58)



J Neurol Neurosurg Psychiatry 2020;0:1–9. doi:10.1136/jnnp-2020-323822 Neuromuscular

ORIGINAL RESEARCH

Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3

Lorenzo Maggi ,[1] Luca Bello ,[2] Silvia Bonanno,[1] Alessandra Govoni,[3,4] Claudia Caponnetto,[5] Luigia Passamano,[6] Marina Grandis,[5,7] Francesca Trojsi,[8] Federica Cerri,[9] Manfredi Ferraro,[10] Virginia Bozzoni,[2] Luca Caumo,[2] Rachele Piras,[11] Raffaella Tanel,[12] Elena Saccani,[13] Megi Meneri,[3] Veria Vacchiano ,[14] Giulia Ricci,[4] Gianni Soraru' ,[2] Eustachio D'Errico,[15] Irene Tramacere,[16] Sara Bortolani,[10] Giovanni Pavesi,[17] Riccardo Zanin,[18] Mauro Silvestrini,[19,20] Luisa Politano,[6] Angelo Schenone,[5,7] Stefano Carlo Previtali ,[9] Angela Berardinelli,[21] Mara Turri,[22] Lorenzo Verriello,[23] Michela Coccia,[20] Renato Mantegazza,[1] Rocco Liguori,[14,24] Massimiliano Filosto ,[25,26] Gianni Marrosu,[27] Gabriele Siciliano,[4] Isabella Laura Simone,[15] Tiziana Mongini,[10] Giacomo Comi,[3,28] Elena Pegoraro[2]

Motor Function Changes

Maggi L, et al. J Neurol Neurosurg Psychiatry. 2020;91:1166-74.

	6 months			10 months			14 months		
	HFMSE	RULM	6MWT (m)	HFMSE	RULM	6MWT (m)	HFMSE	RULM	6MWT (m)
N	116	115	48	84	81	35	51	50	24
Mean score (SD)	27.83 (± 21.84)	25.54 (± 11.71)	323.19 (± 138.24)	29.73 (± 21.15)	26.59 (± 10.98)	317.98 (± 136.41)	31.88 (± 20.84)	27.62 (± 10.88)	329.08 (± 135.58)
Mean difference vs baseline (± SD)	**1.33 (± 2.29)**	**0.37 (± 1.97)**	**14.66 (± 27.57)**	**2.29 (± 2.75)**	**0.72 (± 2.07)**	**26.45 (± 34.6)**	**2.69 (± 2.92)**	**0.94 (± 2.13)**	**23.11 (± 51.2)**
p value	< 0.0001	0.038	0.0005	< 0.0001	0.0018	0.00019	< 0.0001	0.0038	0.016

SMA2 had no significant changes of median HFMSE and RULM between T0 and the following time points, although a **trend for improvement of RULM was observed.**

HFMSE changes were independently significant in SMA3 sitter and walker subgroups.

RULM in SMA3 significantly improved between T0 and T14 , with most of the benefit observed in sitters.

There was a nominally significant FVC% increase at T14 (median +7%; p=0.031) in the **SMA3 'walker' subgroup only**.

Overall Responders

Maggi L, et al. J Neurol Neurosurg Psychiatry. 2020;91:1166-74.

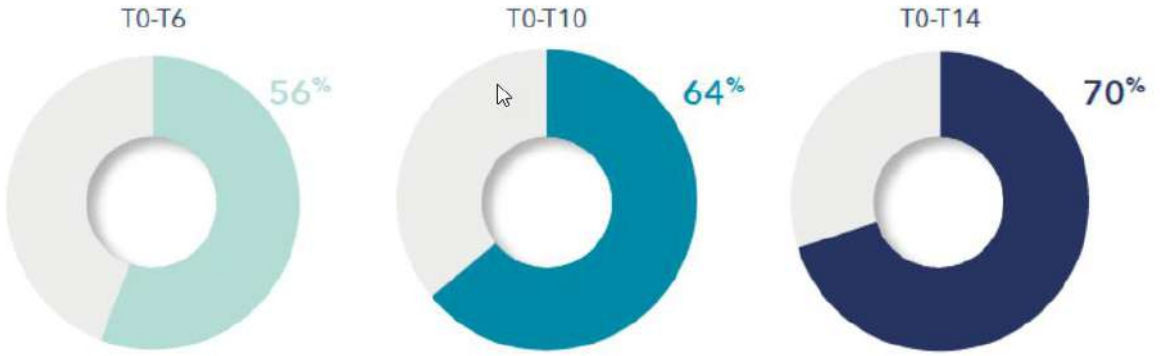
Clinically meaningful change:
HFMSE, 3 points; RULM, 2 points; 6MWT, 30m

Overall Responder:

A responder on at least one of the three outcome measures (HFMSE, RULM, 6MWT).

All Patients

6 months	10 months	14 months
56%	64%	70%
(61/116)	(53/84)	(35/51)



Nusinersen efficacy in adult SMA2 and SMA3 appears to be cumulative over time

In patients with extremely advanced disease, effects on residual motor function are less clear

Adverse Event : headache, lumbar pain, nausea

Nusinersen – Spinraza

The German Adult SMA Cohorts

Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study

Lancet Neurol 2020; 19: 317-25

Tim Hagenacker*, Claudia D Wurster*, René Günther*, Olivia Schreiber-Katz, Alma Osmanovic, Susanne Petri, Markus Weiler, Andreas Ziegler, Josua Kuttler, Jan C Koch, Ilka Schneider, Gilbert Wunderlich, Natalie Schloss, Helmar C Lehmann, Isabell Cordts, Marcus Deschauer, Paul Lingor, Christoph Kamm, Benjamin Stolte, Lena Pietruck, Andreas Totzeck, Kathrin Kizina, Christoph Mönninghoff, Otgonzul von Velsen, Claudia Ose, Heinz Reichmann, Michael Forsting, Astrid Pechmann†, Janbernd Kirschner†, Albert C Ludolph‡, Andreas Hermann, Christoph Kleinschnitz

Primary outcome → the **change in the total HFMSE score**, assessed at months 6,10, and 14, and based on pre–post comparisons

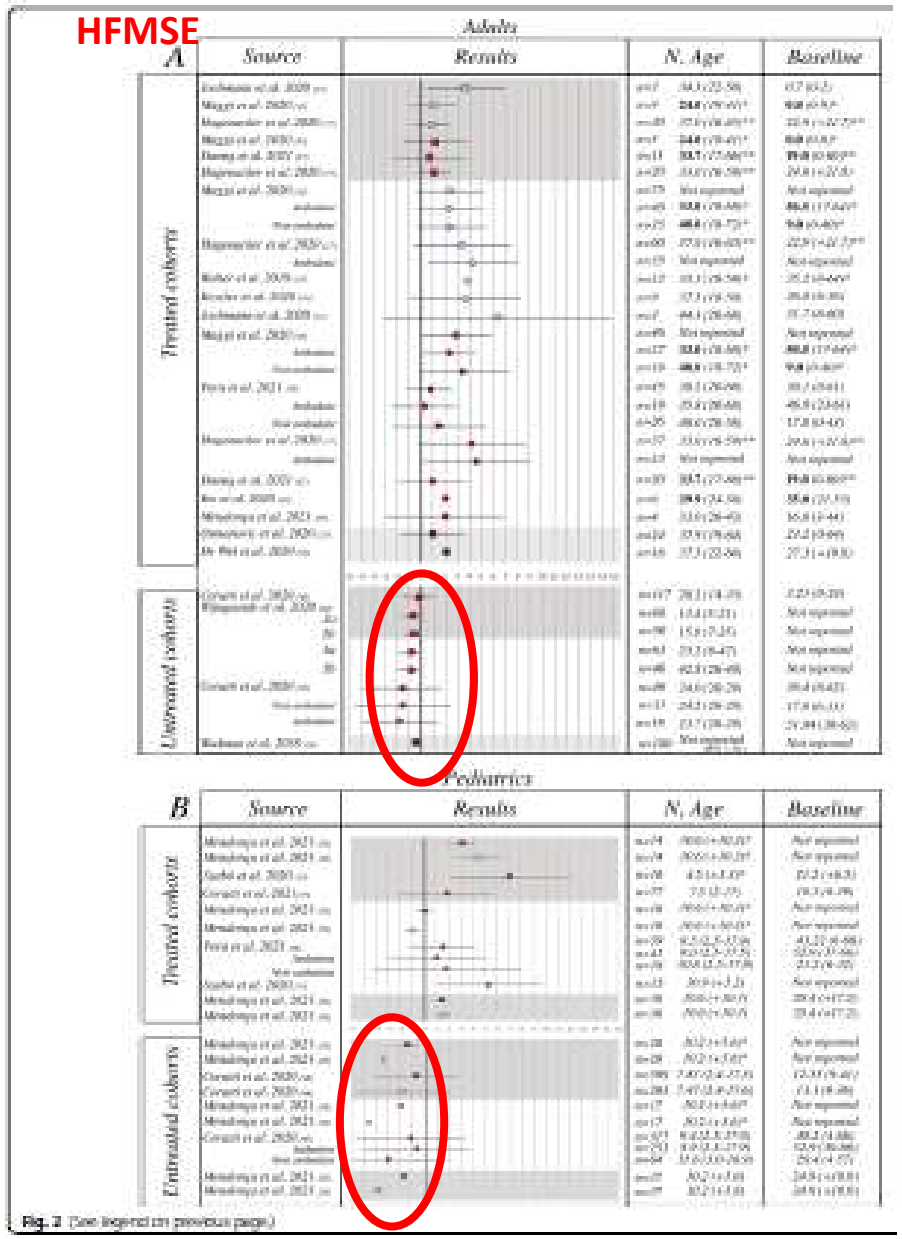
	6-month analysis				10-month analysis				14-month analysis			
	n	Mean score (SD)	Mean difference versus baseline (95% CI)	p value	n	Mean score (SD)	Mean difference versus baseline (95% CI)	p value	n	Mean score (SD)	Mean difference versus baseline (95% CI)	p value
HFMSE score	124	22·47 (22·41)	1·73 (1·05–2·41)	<0·0001	92	25·52 (22·97)	2·58 (1·76–3·39)	<0·0001	57	27·77 (23·47)	3·12 (2·06–4·19)	<0·0001
RULM score	120	21·53 (13·28)	0·66 (0·26–1·05)	0·0007	90	23·27 (12·46)	0·59 (0·15–1·03)	0·0014	58	23·95 (12·42)	1·09 (0·62–1·55)	<0·0001
6-minute walk test distance, m	47	366·8 (200·8)	22·1 (8·7–35·6)	0·0022	37	363·2 (224·2)	31·1 (15·2–47·1)	<0·0001	25	403·0 (225·7)	46·0 (25·4–66·6)	<0·0001

HFMSE=Hammersmith Functional Motor Scale Expanded. RULM=Revised Upper Limb Module.

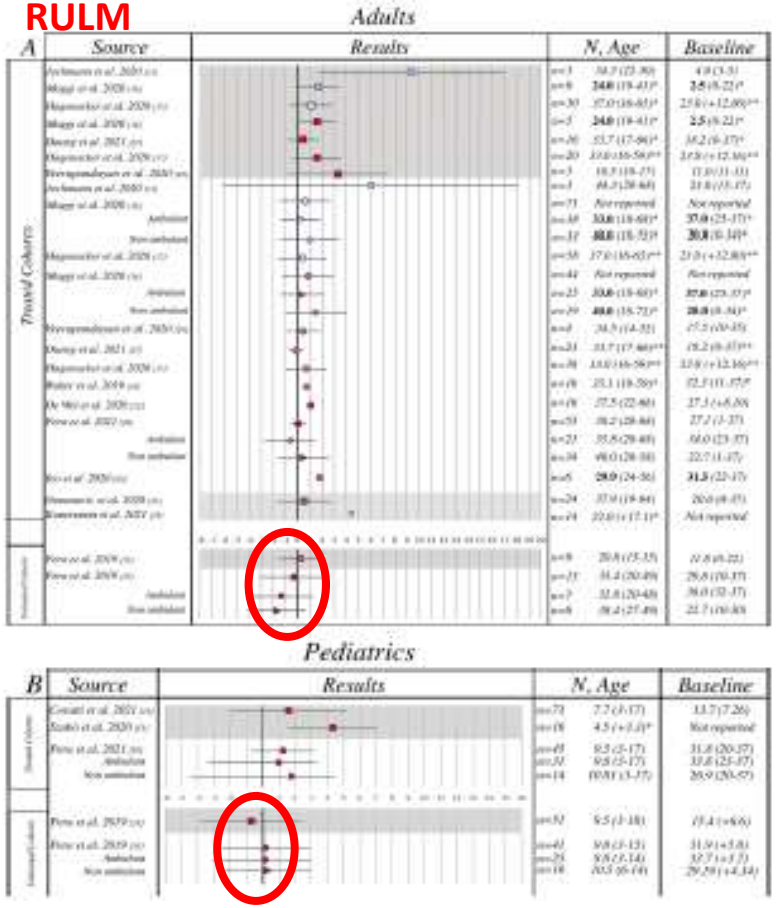
Table 2: Changes in HFMSE, RULM, and 6-minute walk test scores versus baseline

The most frequent **adverse effects** were **headache** (35% patients), **back pain** (22%), and **nausea** (11%).
No serious adverse events were reported.

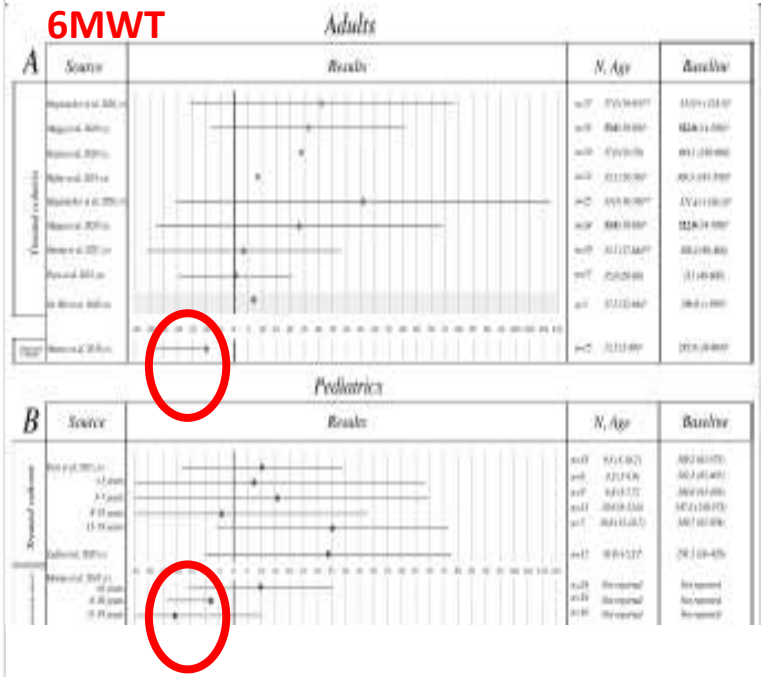
HFMSE



RULM



6MWT



Tutti gli studi hanno riportato nei pazienti trattati cambiamenti positivi in almeno una delle scale funzionali usate, mentre tutte le coorti non trattate hanno mostrato cambiamenti negativi

Journal of Neurology
https://doi.org/10.1007/s00415-021-10954-3

ORIGINAL COMMUNICATION

Quality of life assessment in adult spinal muscular atrophy patients treated with nusinersen

Silvia Bonanno[1] · Riccardo Zanin[2] · Luca Bello[3] · Irene Tramacere[4] · Virginia Bozzoni[3] · Luca Caumo[3] · Manfredi Ferraro[5] · Sara Bortolani[5] · Gianni Sorarù[3] · Mauro Silvestrini[6,7] · Veria Vacchiano[8,9] · Mara Turri[10] · Raffaella Tanel[11] · Rocco Liguori[8,9] · Michela Coccia[6] · Renato Emilio Mantegazza[1] · Tiziana Mongini[5] · Elena Pegoraro[3] · Lorenzo Maggi[1]

Received: 7 September 2021 / Revised: 15 December 2021 / Accepted: 23 December 2021

QoL was rated by the Individualized Neuromuscular Quality of Life (**INQoL**) questionnaire.

Motor function evaluation included
- Hammersmith Functional Motor Scale Expanded (**HFMSE**),
- The Revised Upper Limb Module (**RULM**),
- the 6 min walking test (**6MWT**).

INQoL scale, administered over **14 months** during nusinersen treatment, in **78 adult 5q-SMA patients**.

Patients reported a **meaningful improvement** in all the items of the questionnaire (**weakness, fatigue, activities independence, social relationship, emotions, global QoLscore**), **except** for the **muscle locking** and for the **pain**.

Nusinersen – Spinraza

Journal of Neurology
https://doi.org/10.1007/s00415-018-9124-0

Published online: 20 November 2018

ORIGINAL COMMUNICATION

Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients

Claudia D. Wurster[1] · Benedikt Winter[2] · Kurt Wollinsky[3] · Albert C. Ludolph[1] · Zeljko Uzelac[1] · Simon Witzel[1] · Michael Schocke[4] · Ralf Schneider[4] · Tugrul Kocak[5]

Received: 6 August 2018 / Revised: 10 November 2018 / Accepted: 13 November 2018

20 adolescent and adult SMA type 2 (9) and 3 (11)

Therapeutic Advances in Neurological Disorders *Original Research*

Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy

Ther Adv Neurol Disord
2018, Vol. 11: 1–9
DOI: 10.1177/
1756286418803244

Benjamin Stolte, Andreas Totzeck, Kathrin Kizina, Saskia Bolz, Lena Pietruck, Christoph Mönninghoff, Nika Guberina, Denise Oldenburg, Michael Forsting, Christoph Kleinschnitz and Tim Hagenacker

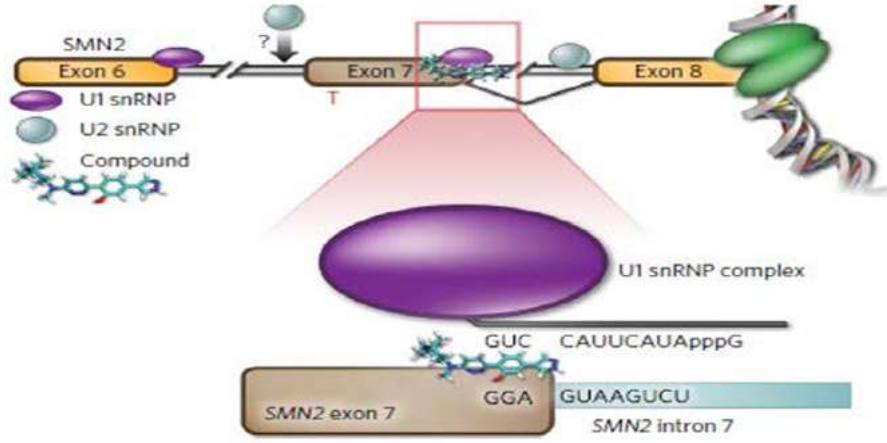
28 adult SMA patients (9 SMA 2 and 19 SMA 3) aged between 18–61 years

The intrathecal administration of nusinersen in adolescent and adult patients **is feasible and safe, even in patients with complex spinal anatomies and respiratory insufficiency**.

To guarantee the quality of the procedure, we recommend establishing an **experienced interdisciplinary team** consisting of neurologists /neuropediatricians, anesthesiologists, and/or neuroradiologists.

Risdiplam – Evrysdi

RNA splicing correctors → Promote inclusion of exon 7 in SMN2 mRNA, increasing levels of SMN protein.



Attraversa la BEE

STUDI REGISTRATIVI

SUNFISH, **Vs placebo,** to assess the **safety, tolerability and effectiveness** in patients with **SMA2 and SMA3**.

2 - 25 y.o.

FIREFISH open-label trial will assess the **effectiveness** in patients with **SMA1** (1–7 months old) with two copies of SMN2

JEWELFISH open label, **phase II study** in **adults and children with SMA2 or SMA3**, **who were previously treated with an SMN2-targeting therapy or Olesoxime**

6 mths-60 y.o.

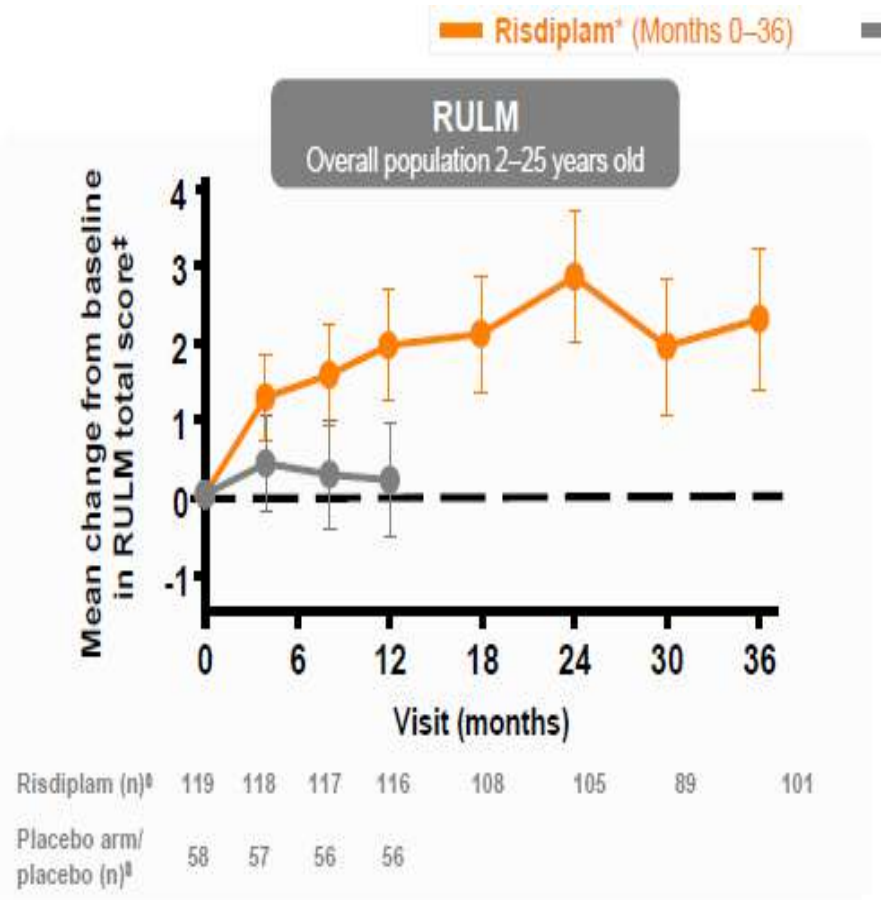
RAINBOWFISH Open-Label Study in **Infants** With Genetically Diagnosed and **Presymptomatic Spinal Muscular Atrophy.**

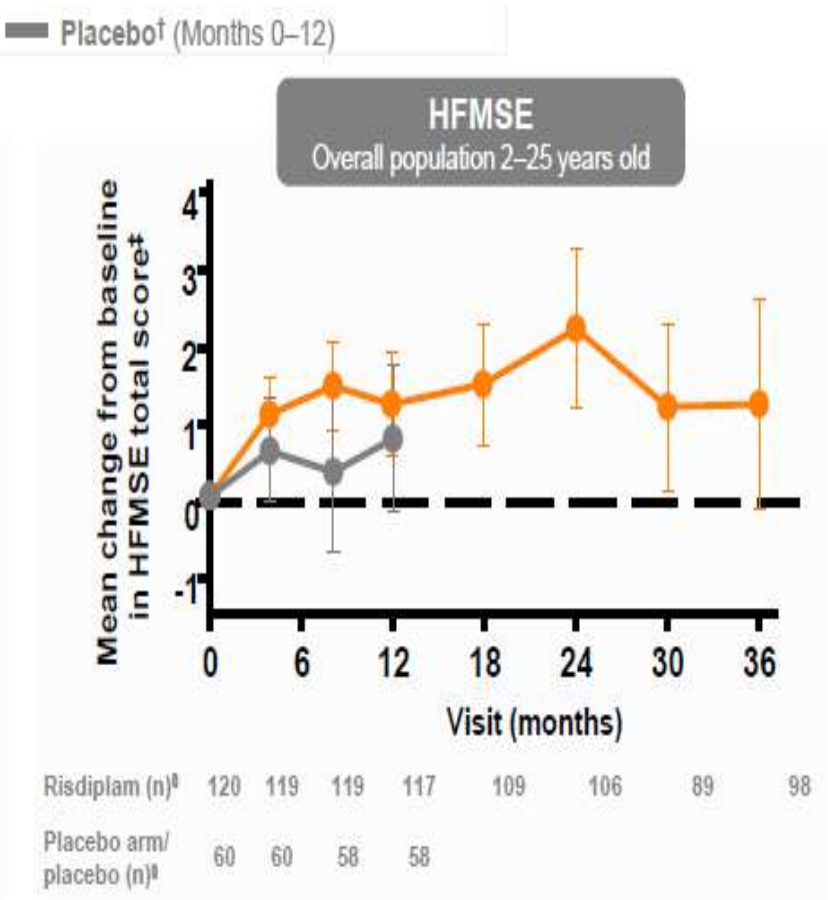
Risdiplam – Evrysdi

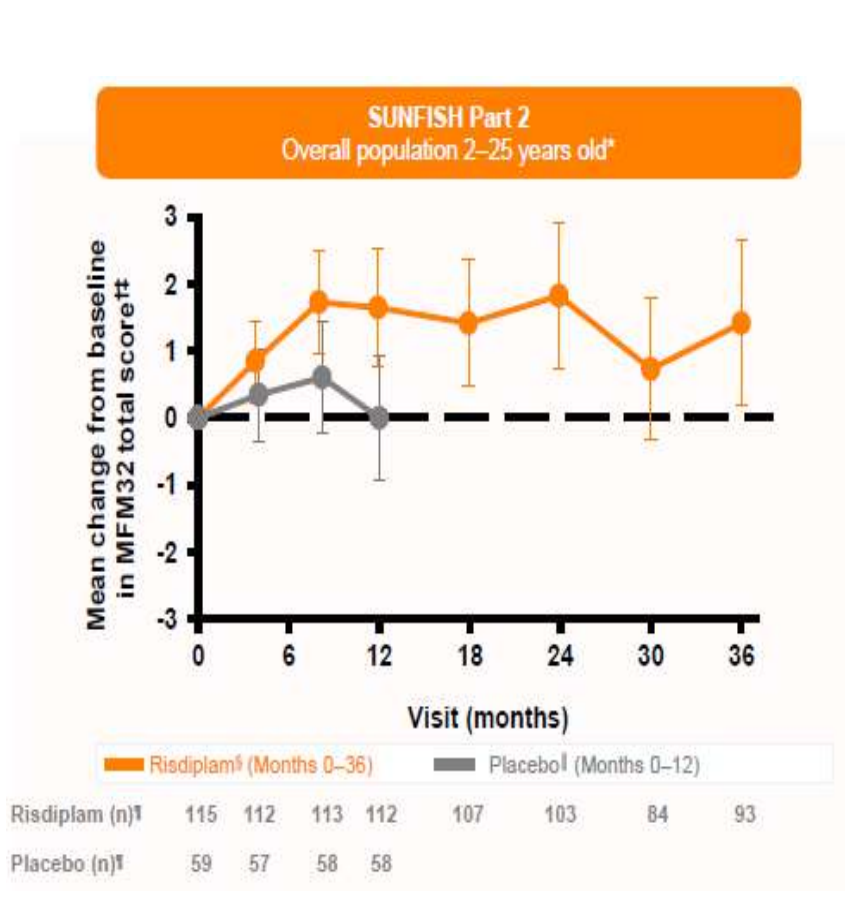
SUNFISH (NCT02908685) – studio registrativo, doppio cieco e vs placebo, **età 2 - 25 anni ,** SMA 2/3.

180 PAZIENTI, risdiplam (n=120) vs placebo (n=60)).
ENDPOINT PRIMARIO: funzione motoria in base al punteggio totale sulla scala (MFM-32) a 12 mesi vs placebo e per i successivi 24 mesi in estensione.

10 paz > 18 aa





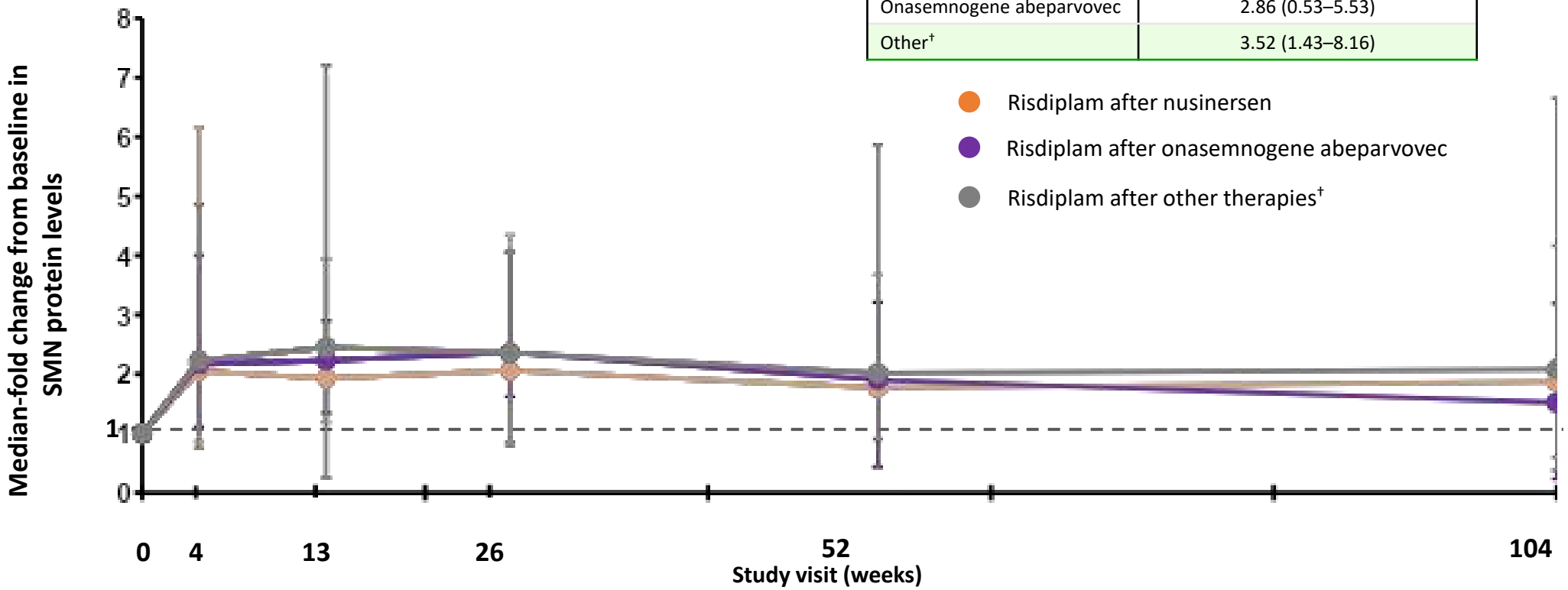


Risdiplam – Evrysdi

JEWELFISH ongoing, multicenter, open-label study,
Types 1–3 SMA with a wide range of ages (1–60 years), and disease severities.
Previously treated with nusinersen, olesoxime or other SMN2 splicing modifier, onasemnogene abeparvovec

All treatment groups showed rapid and sustained increases in SMN protein after 24 months of treatment with risdiplam

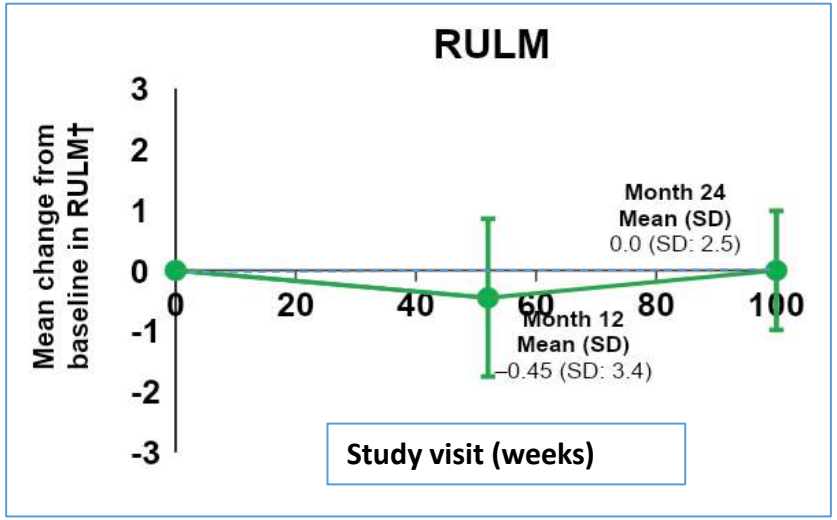
Previous treatment	Baseline median SMN protein in whole blood*; ng/mL (range)
Nusinersen	3.09 (1.01–6.91)
Onasemnogene abeparvovec	2.86 (0.53–5.53)
Other†	3.52 (1.43–8.16)

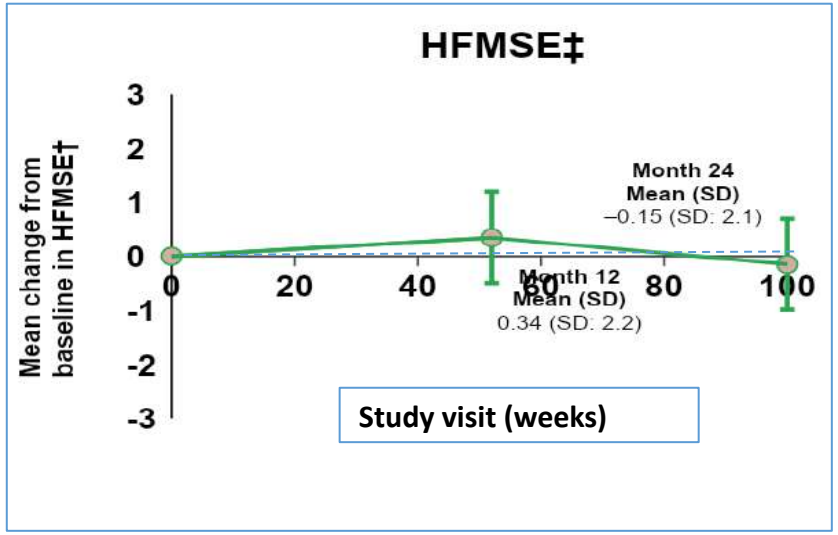


Risdiplam – Evrysdi

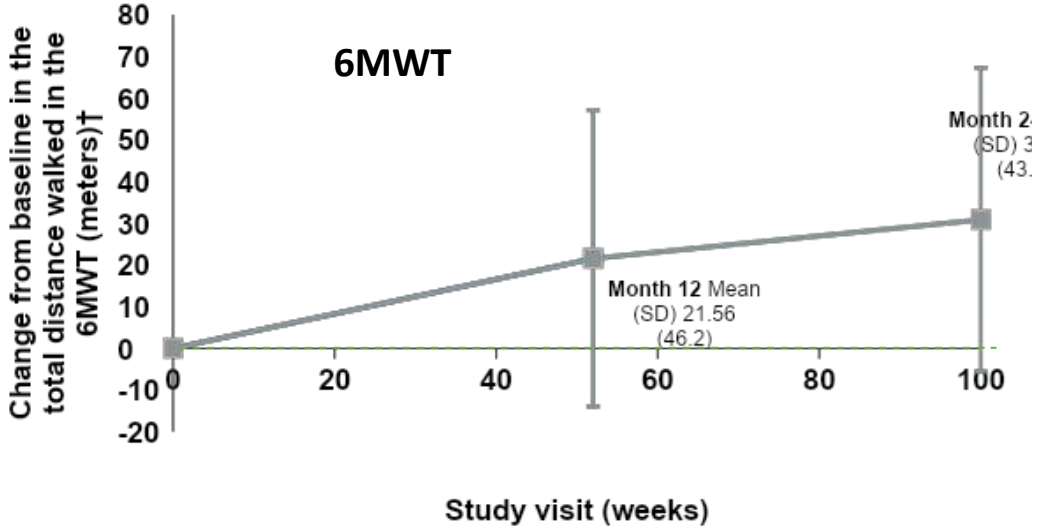
JEWELFISH

Motor function stabilization was observed after 24 months of treatment with risdiplam in pat aged 25-60 y.o.





Baseline characteristics	Patients aged 25–60 years (n=34)
Type 2, n (%)	13 (38)
Type 3, n (%)	21 (62)
HFMSE score <10, n (%)	22 (65)
Scoliosis, n (%)	
Yes	27 (79)
>40° curvature	13 (38)



13 ambulant patients, aged 11-19 y.o.

None of hem lost ability to walk

An increase in the 6MWT total distance walked was observed

In a natural history study, the mean rate of change from baseline in the total distance walked in the 6MWT was –20.8 meters per year in a similar age group (11–19 years of age)

. Montes J, et al. PLoS One. 2018; 13:e0199657

Risdiplam – Evrysdi

SAFETY

SUNFISH

JEWELFISH

There have been no treatment-related AEs leading to withdrawal or treatment discontinuation

Ophthalmologic monitoring has not shown any evidence in humans of the retinal findings seen in preclinical monkey studies

Hematologic parameters have remained stable over time and no drug-induced skin findings have been observed

SUNFISH Part 2 (N=179)*		Number of AEs per 100PY (95% CI)
Total PY at risk		495.8
AEs reported at a rate of ≥11 per 100PY	Headache	46.4 (40.6–52.8)
	Upper respiratory tract infection	24.8 (20.6–29.6)
	Nasopharyngitis	22.4 (18.4–27.0)
	Vomiting	18.8 (15.1–23.0)
	Pyrexia	18.4 (14.8–22.5)
	Cough	11.7 (8.9–15.1)
	Diarrhea	11.3 (8.5–14.7)
SAEs reported at a rate of ≥0.8 per 100PY	Pneumonia	5.2 (3.4–7.7)
	Gastritis	1.0 (0.3–2.4)
	Pyrexia	0.8 (0.2–2.1)
	Upper respiratory tract infection	0.8 (0.2–2.1)

Evitare Ridiplam durante gravidanza e allattamento

Potenziale tossicità embrio-fetale (studi animali)

Potenziali effetti sulla fertilità maschile, reversibili (studi animali)

Metodi contraccettivi

durante il trattamento e fino ad almeno 1 mese dopo l'ultima dose nelle donne, e 4 mesi dopo l'ultima dose negli uomini

Risdiplam

Flaconi 80 ml/60 mg (0,75 mg/ml)

Approved in more than 80 countries worldwide

Dose 2 mesi - 2 anni 0,20 mg/kg; ≥2 anni (<20 kg) 0,25 mg/kg; **≥20 kg 5 mg**
In USA < 2 mesi 0,15 mg/kg

Indicazioni → SMA 5q in pazienti a partire da 2 mesi di età, con una diagnosi clinica di SMA di tipo 1, tipo 2 o tipo 3 o aventi 1-4 copie di SMN2

La soluzione orale, una volta ricostituita, è stabile per 64 giorni.

Conservata in **frigorifero** (2 °C-8 °C), protetta dalla luce (al max 120 h a temperatura ambiente < 40°C.

Assunto per via orale una volta al giorno, dopo un pasto, all'incirca alla stessa ora ogni giorno.

Risdiplam può essere **somministrato attraverso SNG o PEG**.

Future treatment

Promotion of Muscle Growth targeting **enhancement of muscle cell growth**.

Myostatin is an endogenous protein that limits muscle cell growth.

SRK-015 (Apitegromab) is a highly selective inhibitor of the activation of latent myostatin.
TOPAZ trial - phase 2, SRK-015 + nusinersen, randomized, vs placebo. The 24-month results provide evidence of sizable motor function gains and improvement of QoL in SMA 2 and SMA 3 patients.

GYM329 An anti-latent myostatin sweeping antibody that eliminates latent myostatin from plasma and tissue.
MANATEE trial - randomized, vs placebo, to investigate the safety, tolerability, PK, PD and efficacy of GYM329 in combination with risdiplam in ambulant pediatric patients with SMA.

Enhancement of Muscle Function targeting **Improvement in the efficiency of muscle force generation**

Reldesemtiv is an activator of fast skeletal muscle troponin, which has demonstrated increased force of contraction in healthy subjects. ***Increases the sensitivity of the sarcomere to calcium, reducing fatigue***

Phase 2, randomized vs placebo, testing in patients with SMA1, SMA2, and SMA3 **demonstrated increased distance in the 6-MinuteWalk Test and improvement in respiratory function compared to controls.**
Safety good

Centro Regionale Malattie del Motoneurone
Clinica Neurologica Amaducci
Dipartimento di Scienze Mediche di Base, Neuroscienze e Organi di Senso,
Policlinico-Università di Bari _

Policlinico di Bari
Ospedale "Giovanni XXIII"

2015	8 paz
2018	16 paz
2022	32 paz

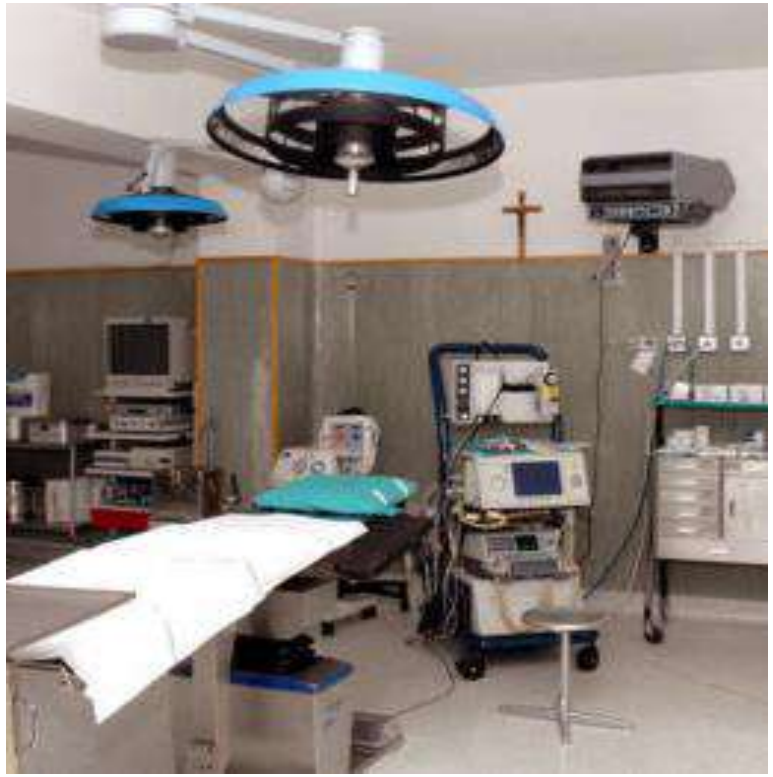
COLLABORAZIONI

UO Anestesia e Rianimazione Univ II
UO Medicina Fisica e Riabilitazione
Laboratorio Neurochimica
Pneumologia Universitaria
CNR Bari

Variabile	SMA (32 paz)
Età (anni)	41,6 (20-72)
Fasce d'età 20-30aa 30-40aa 40-50aa >50aa	8 6 11 7
Sesso (M/F)	17/15
SMA 1 / SMA 2/ SMA 3	1/17/14
Copie SMN 2 2 copie 3 copie 4 copie	9 18 5
Chirurgia Vertebrale	10/32
Scoliosi	28/32
Deambulante	9/32
Distribuzione regionale BA FG LE TA BR BAT FUORI REGIONE	 16 2 1 1 8 3 1

Nusinersen - Ottobre 2018

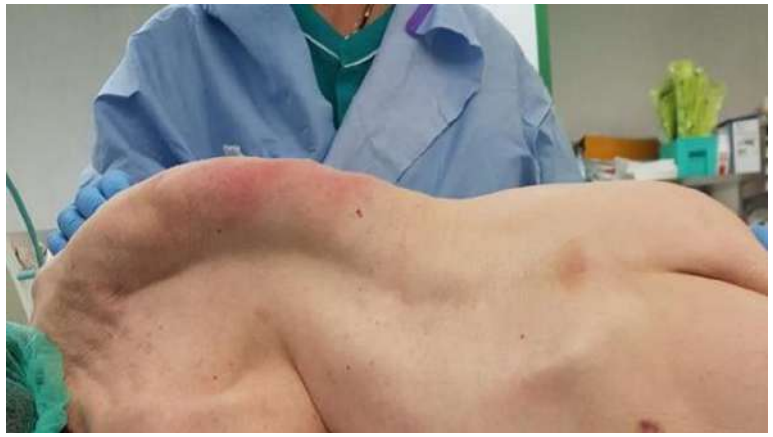
14 pazienti hanno accettato proposta terapeutica (8 M, 6 F)



Sede

Saletta operatoria della UO Anestesia e Rianimazione II

(dotata di fluoroscopio ed ecografo).



Operatore

Anestesista esperto in terapia del dolore e intratecale

Procedura: prelievo per caduta lenta (Ago spinale 22 G) di 5 ml di CSF e successiva somministrazione lenta (1-3 min) intratecale di Nusinersen.

3 pazienti (2 F, 1 M) mai avviato
(2 schiena difficile, 1 gravidanza)
4 pazienti (2 F, 2 M) sospeso
(schiena difficile)
7 pazienti (5 M, 2 F) in corso

11 pazienti, 7 M e 4 F
Età media 47,8 anni (19-72)
Walker/sitter 4/7
Chirurgia vertebrale 2 paz

5 **SMA-2** e 9 **SMA-3**

Copie di SMN 2
4 copie → 2 paz
3 copie → 8 paz
2 copie → 1 paz

HFMSE 21 (0-60)
RULM 20 (0-37)
6MWT 400 mt (248-463)

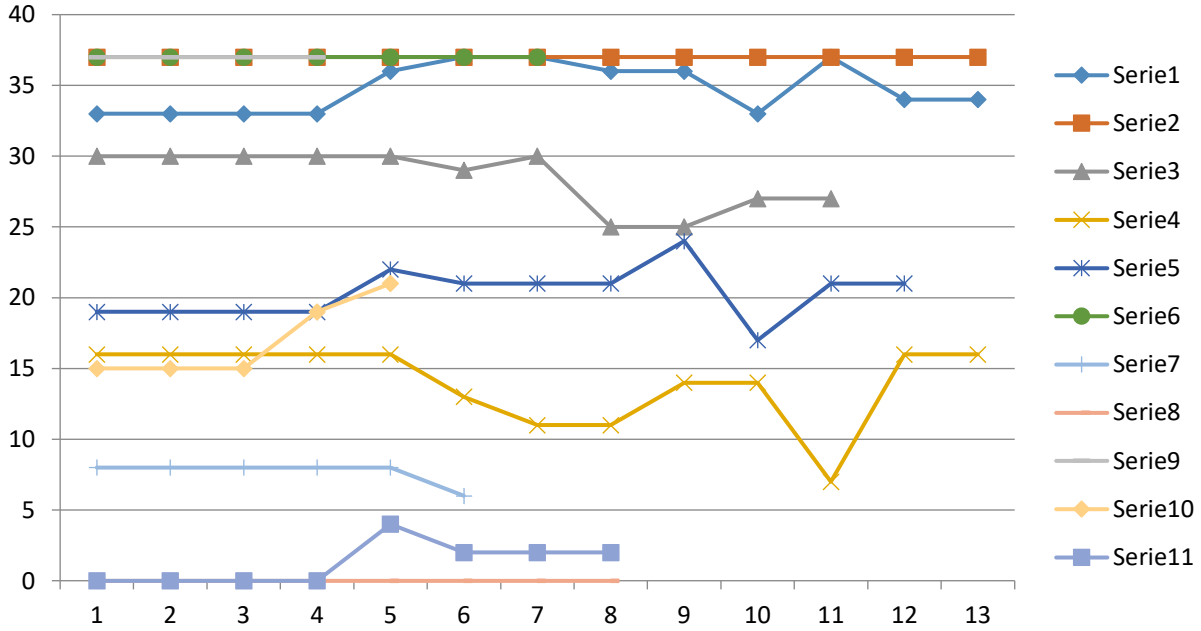
Follow up 5-48 mesi

Nusinersen

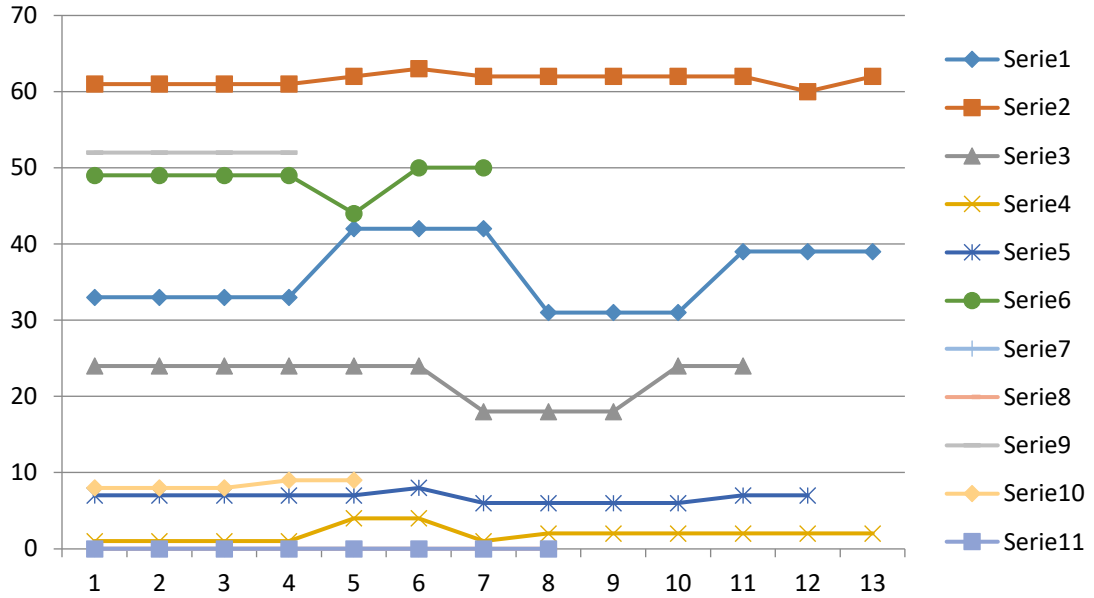
	Age yrs	SMN2 copies	SMA type	Walker/ Sitter	Scoliosis	Spinal fusion
13 somm	19	3	3	W	No	No
gravidanza	30	4	3	W	Yes	No
Schiena difficile, 8 s	36	3	2	S	Yes	Yes
12 somm	38	3	2	S	Yes	no
Schiena difficile, 5s	39	4	3	S	Yes	No
Schiena difficile	42	3	2	S	Yes	Yes
13 somm	42	2	3	S	Yes	No
13 somm	44	4	3	W	Yes	no
Schiena difficile, 6 s	46	3	2	S	Yes	no
Carico 4	48	3	3	W	Yes	no
11 somm	53	3	2	S	Yes	No
7 somm	57	3	3	W	Yes	No
Schiena difficile	68	3	3	S	Yes	no
Schiena difficile, 8s	72	3	3	S	yes	No

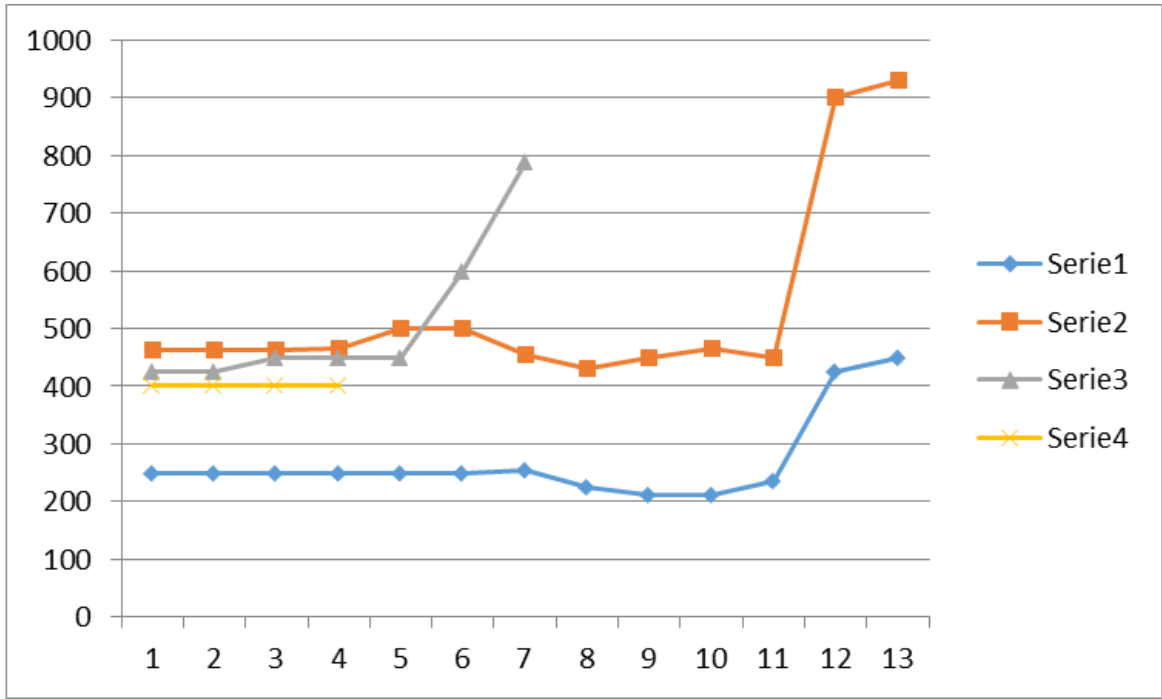
Nusinersen Efficacia

RULM stabile + 0,6 (-3 - +6)



HFMSE Miglioramento o stabilità +1 (0 - 6)





6MWT maggiore autonomia + 331 mt (+252 - +470)

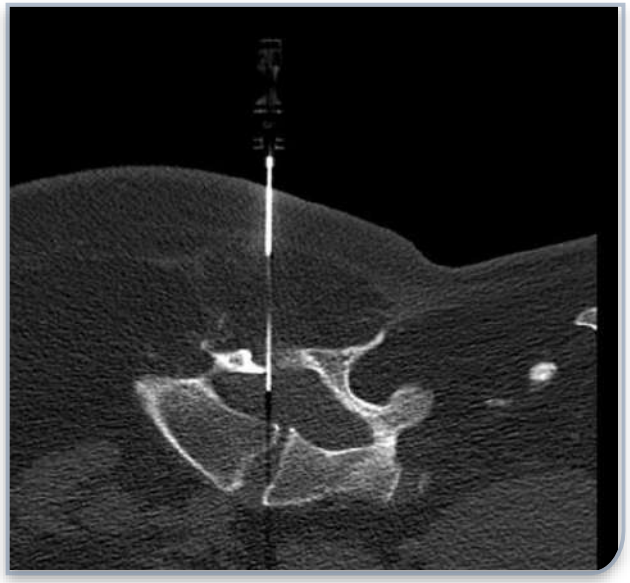
Nusinersen

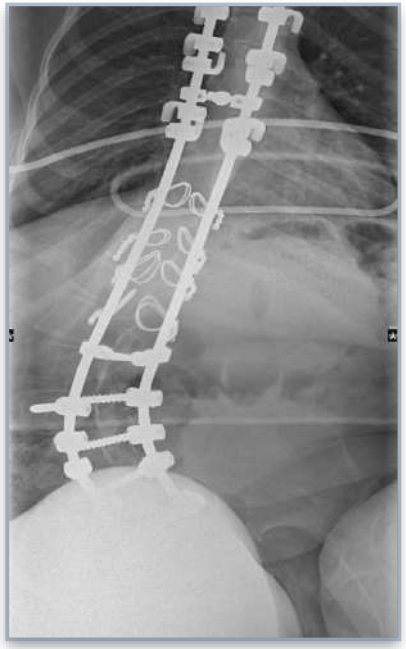
11 pazienti trattati

100 procedure 78 convenzionale

20 fluoroscopia

3 TC guidate.





SAFETY

Mai riportati eventi avversi seri

Gli effetti collaterali descritti sono stati nella maggior parte dei casi transitori (<24-48 ore).

Una paziente dolore lombare protratto

Eventi Avversi più comuni
Rachialgia (27/100)
Cefalea <24 h (15/100)
Vertigini < 24 h (5/100)

Analisi colturale del liquor eseguita durante ogni procedura → sempre negativa

Cerebrospinal Fluid and Clinical Profiles in Adult Type 2–3 Spinal Muscular Atrophy Patients Treated with Nusinersen: An 18-Month Single-Centre Experience

Giammarco Milella[1] · Alessandro Introna[1] · Eustachio D'Errico[1] · Angela Fraddosio[1] · Gaspare Scaglione[1] · Antonella Morea[1] · Maria Ucci[1] · Maddalena Ruggieri[2] · Mariangela Mastrapasqua[2] · Marisa Megna[3] · Filomena Puntillo[4] · Isabella Laura Simone[1]

Clin Drug Investig. 2021 Sep;41(9):775-784.

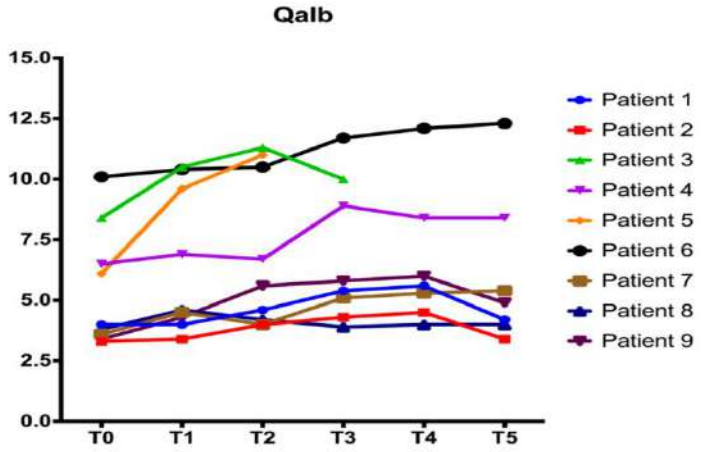
Accepted: 27 July 2021 / Published online: 13 August 2021

9 adult SMA2–3 and 12 control subjects without neurodegenerative disease.

CSF parameters, CSF NFl, CSF Tau and pTau, serum creatinine

- **Serum creatinine** levels were significantly lower in SMA patients than in control subjects, and significantly correlated with HFMSE and RULM at each time point.

- CSF/serum albumin ratio **(Qalb)** significantly increased from T0 to each time point, and it could be due to repeated lumbar puncture and to lumbar stenosis



- No significant differences in **routine CSF parameters** and **CSF markers of neurodegeneration** were found.

- **Markers of neurodegeneration** did not change during the follow-up and did not correlate with motor scores at baseline and at each timepoint→ **did not play a prognostic role in our cohort of adult SMA patients**.

CLINICAL RESEARCH SHORT REPORT

MUSCLE&NERVE WILEY

Is cerebrospinal fluid amyloid-β42 a promising biomarker of response to nusinersen in adult spinal muscular atrophy patients?

Muscle & Nerve. 2021;63:905-909.

Alessandro Introna MD[1] | Giammarco Milella MD[1] | Eustachio D'Errico MD, PhD[1] | Angela Fraddosio MD[1] | Gaspare Scaglione MD[1] | Maria Ucci MD[1] | Maddalena Ruggieri BSc[2] | Isabella Laura Simone MD[1]

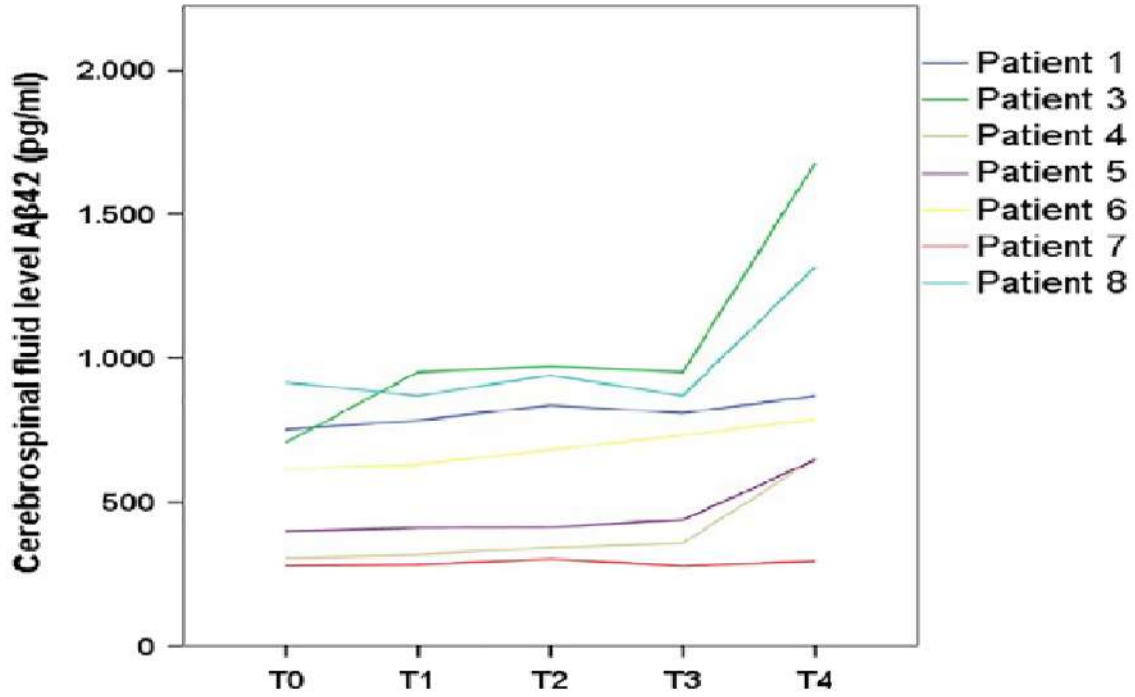


FIGURE 1 Cerebrospinal fluid levels of amyloid-β42 peptide over time [Color figure can be viewed at wileyonlinelibrary.com]

Results: CSF levels of Aβ42 increased from baseline to day 420 (95% confidence interval, $P = .018$), with a significant increase at days 180 and 420 compared with days 0 and 300, respectively (95% confidence interval, $P = .012$ and $P = .018$).

Discussion: The maintenance and promotion of wellness of residual motor neurons mediated by the restored level of SMN protein due to nusinersen could result in an increased level of amyloid peptides.

Risdiplam - Evrysdi

Gennaio 2021 **Farmacia AOU Policlinico**

Uso compassionevole: SMA-2, sitter, controindicazione nusinersen

6 pazienti (4 F, 2M), 3 pazienti in corso

Efficacia miglioramento clinico - 3 paz, 20 mesi **HFMSE +0,66 (0-2), RULM +6,6 (0-12)**

SAFETY 3 pazienti (2 F, 1 M) hanno sospeso per alvo diarroico dopo 7-8 mesi.

Maggio 2022 (post marketing) **Farmacie territoriali**

16 pazienti (9 F, 7 M) **9 SMA-3, 6 SMA-2, 1 SMA-1** **4 walkers, 12 sitters**

6 pz stabilizzazione vertebrale, 10 pazienti severa scoliosi

2 pazienti ex-Nusinersen

EFFICACIA in corso le rivalutazioni cliniche (HFMSE, RULM, 6MWT) a 6 mesi dall'avvio

provvisori (4 paz) HFMSE +1,5 (-2- + 4), RULM stazionario (-4 - +1)

SAFETY Nessun paziente ha sospeso trattamento. Non descritti effetti collaterali

19 pazienti (11F, 8M)

Età media 41,2 anni (21-71)

Walker/sitter 4/15

Chirurgia vertebrale 9 paz

1 **SMA-1**, 9 **SMA-2** e 9 **SMA-3**

Copie di SMN 2

4 copie → 2 paz

3 copie → 10 paz

2 copie → 7paz

Precedente Nusinersen 3 paz

HFMSE 11 (0-58)

RULM 16 (0-37)

6MWT 392 mt (210-533)

Take home message

Le terapie innovative, tanto in età pediatrica quanto in età adulta, stanno modificando la storia naturale di malattia → nuovi fenotipi di malattia

Nei pazienti deambulanti Nusinersen (studi post marketing) e Risdiplam (studi registrativi) hanno dimostrato un miglioramento delle performance motorie, cumulativo nel tempo.

Nei pazienti con abilità motorie più compromesse, una stazionarietà del quadro clinico può comunque essere considerato un valido obiettivo terapeutico.

Il profilo di sicurezza si è dimostrato valido anche nella "real world experience".

Sono necessari **ulteriori studi e periodi di osservazione più lunghi** al fine di comprendere al meglio le **potenzialità delle terapie innovative** e per individuare **algoritmi terapeutici specifici per i diversi fenotipi di malattia.**

- **differenti dosaggi in età adulta e pediatrica?**
- **Estensione a SMA 4 o SMN >4 ?**
- **Quando proporre shift terapeutico ?**
- **Associazioni di terapie?**

GRAZIE

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Clinica Neurologica Amaducci
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Policlinico-Università di Bari _

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Dott.ssa Maria Ucci, Dott.ssa Sarah Idrissi, Dott. Glauco Piccirilli, Dott. Alfredo Gabriele Nanni

Personale Infermieristico : ***Sig.ra Mitacchione Sig.ra De Tullio Sig.ra Lopez Sig. Citarelli***

Team Multidisciplinare ***(Prof.ssa Puntillo, Prof.ssa Resta, Dott.ssa Scacco, Prof.ssa Megna, Prof.ssa Ruggieri, Dott.ssa Liguori, Dott.ssa Giglio, Prof.ssa De Caro, Prof.ssa Fiorella, Dott.ssa Pierucci)***