UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

Intrathecal administration of Nusinersen in adult population: a real life safety assessment

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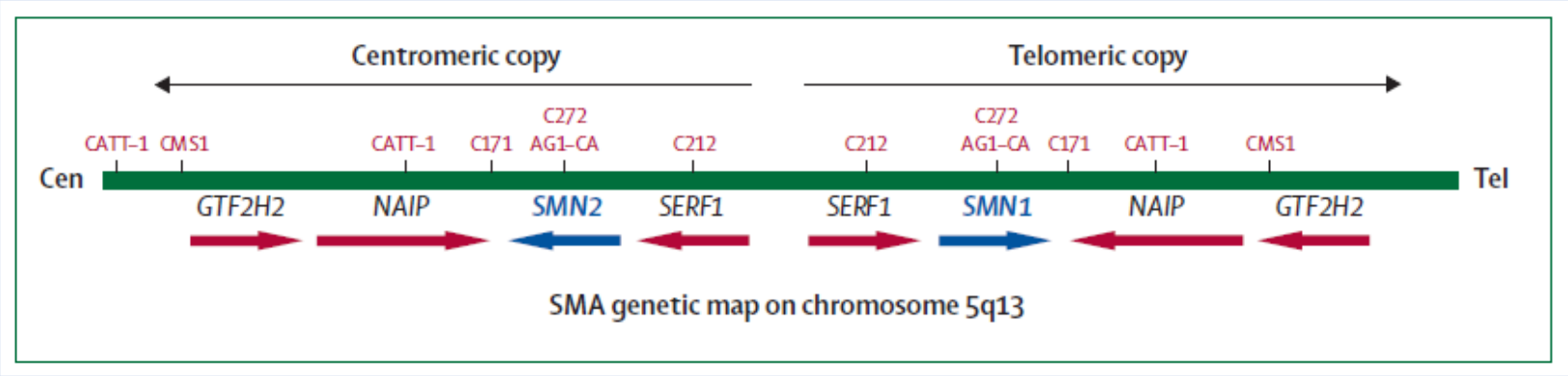
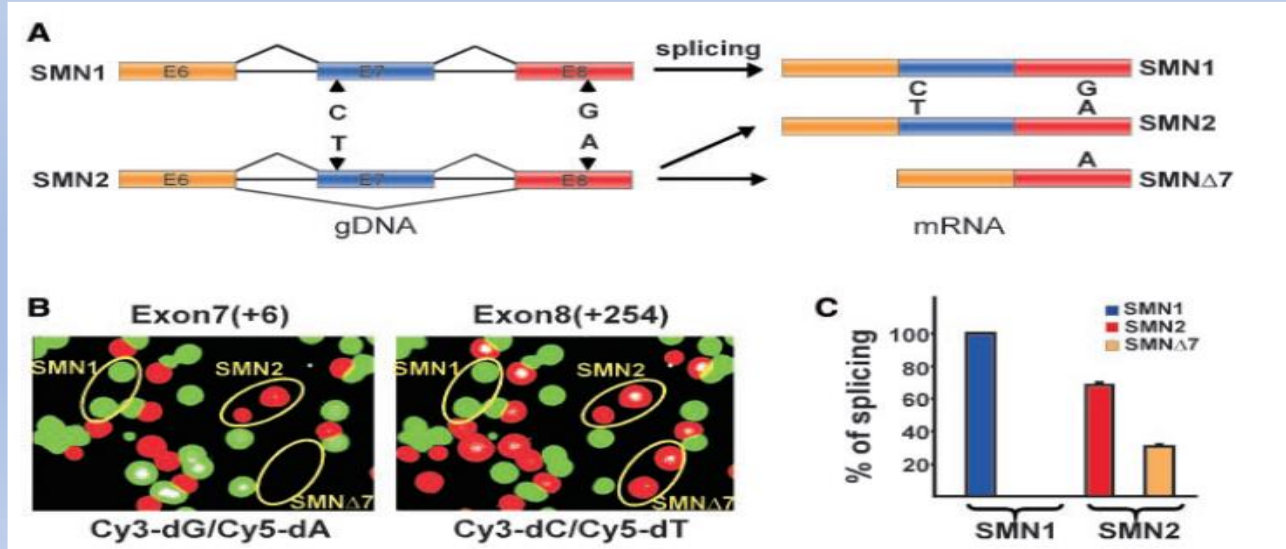
Sin SOCIETÀ ITALIANA DI NEUROLOGIA

Background

Spinal muscular atrophy (SMA) is a genetic and autosomal recessive motor neuron disorder clinically characterized by proximal spinal and bulbar muscle weakness and atrophy caused by degeneration of alpha motor neurons.

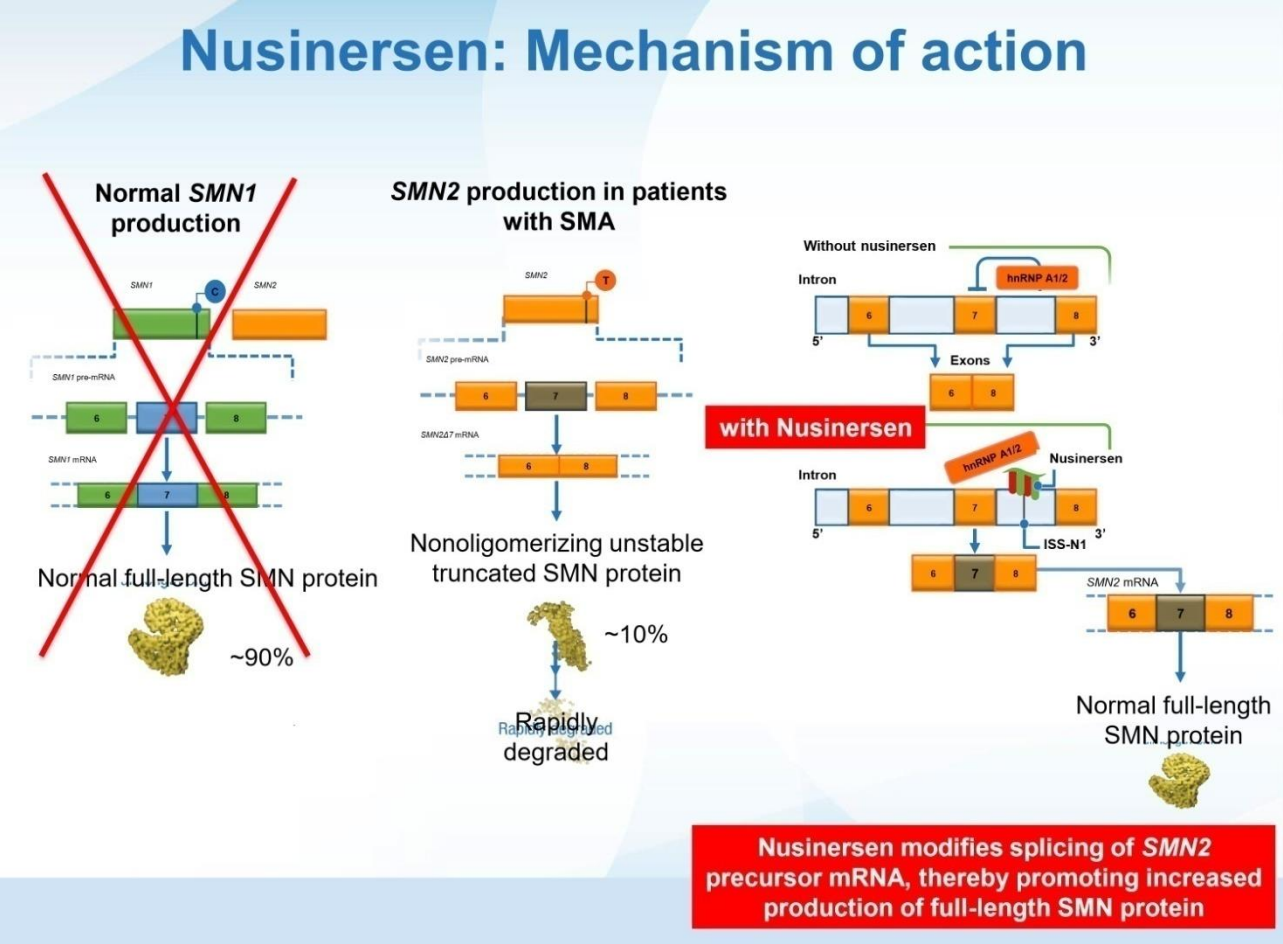


Lunn M. et al., Spinal Muscolar Atrophy, Lancet 2008, 371: 2120-2133



Zhu J. et al., Single molecule profiling of alternative pre-mRNA splicing, Science 2003, 301: 836-8

NUSINERSEN

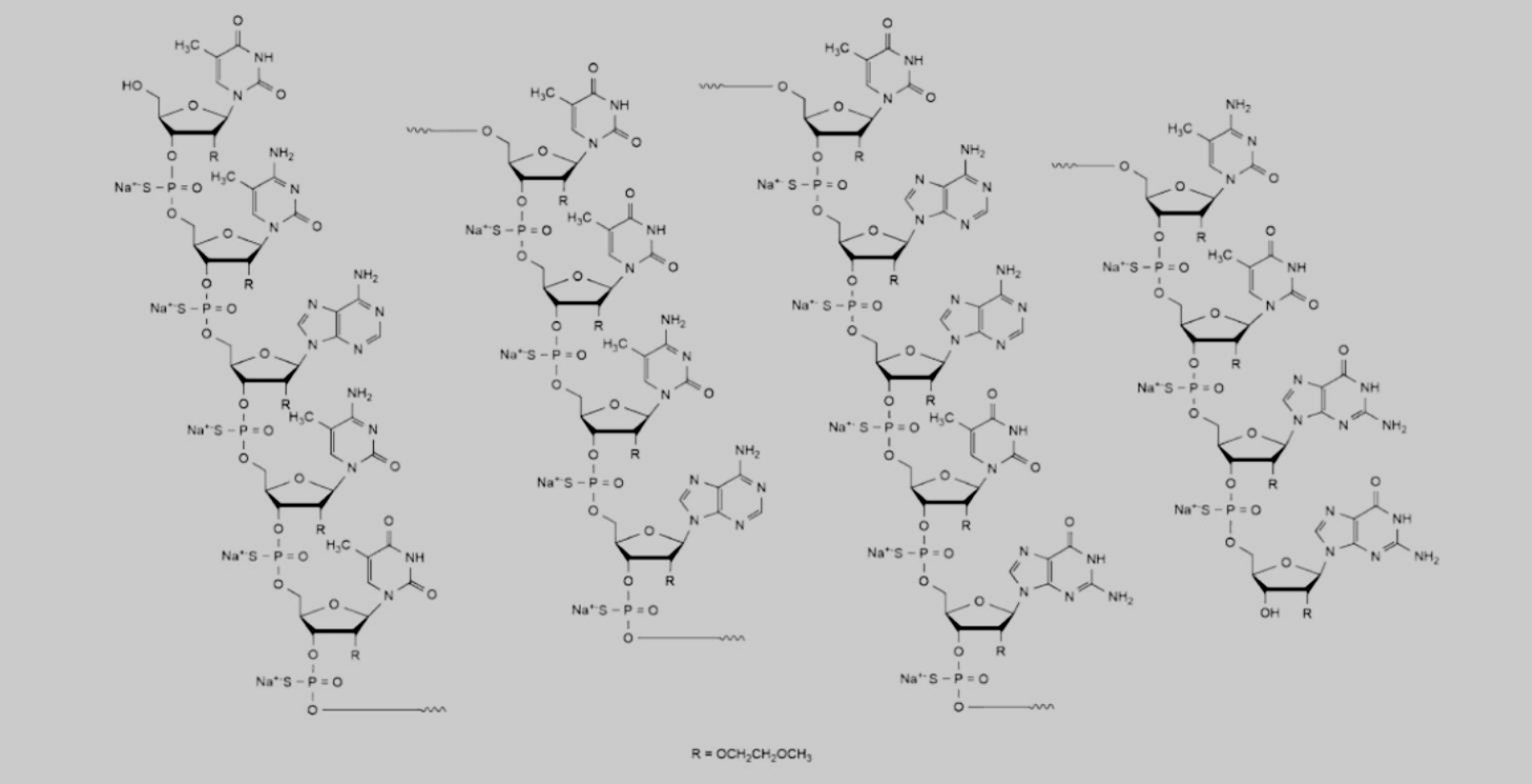


Pharmacodynamic properties

- An antisense oligonucleotide (ASO) which binds an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-mRNA and displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA that can be translated into the functional full length SMN protein.

NUSINERSEN

PHARMACEUTICAL FORM



Each 5 ml vial contains Nusinersen sodium equivalent to 12 mg nusinersen

NUSINERSEN

Clinical studies

Children with later-onset SMA, who received Nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group.

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*

ABSTRACT

BACKGROUND

Nusinersen is an antisense oligonucleotide drug that modulates pre–messenger RNA splicing of the survival motor neuron 2 (*SMN2*) gene. It has been developed for the treatment of spinal muscular atrophy (SMA).

METHODS

We conducted a multicenter, double-blind, sham-controlled, phase 3 trial of nusinersen in 126 children with SMA who had symptom onset after 6 months of age. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary end point was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at 15 months of treatment; HFMSE scores range from 0 to 66, with higher scores indicating better motor function. Secondary end points included the percentage of children with a clinically meaningful increase from baseline in the HFMSE score (≥3 points), an outcome that indicates improvement in at least two motor skills.

RESULTS

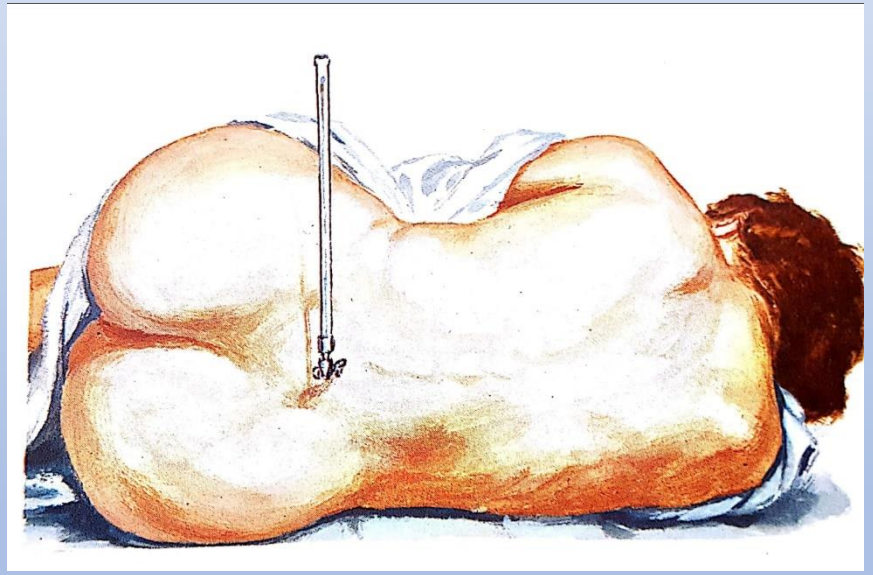
In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group (by 4.0 points)

Mercuri E. et al. Nusinersen versus sham control in later-onset spinal muscolar atrophy. N Eng J Med 2018, 378: 625-635»

NUSINERSEN

Dosage and method of administration

- Spinal lumbar puncture (LP)
- Remove a volume of CSF, equivalent to the volume of Nusinersen to be injected.
- Nusinersen is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle.
- Treatment should be **initiated as early as possible after diagnosis** with 4 loading doses on **days 0, 14, 28, 63.**
- A maintenance dose should be administered once **every 4 months thereafter**.



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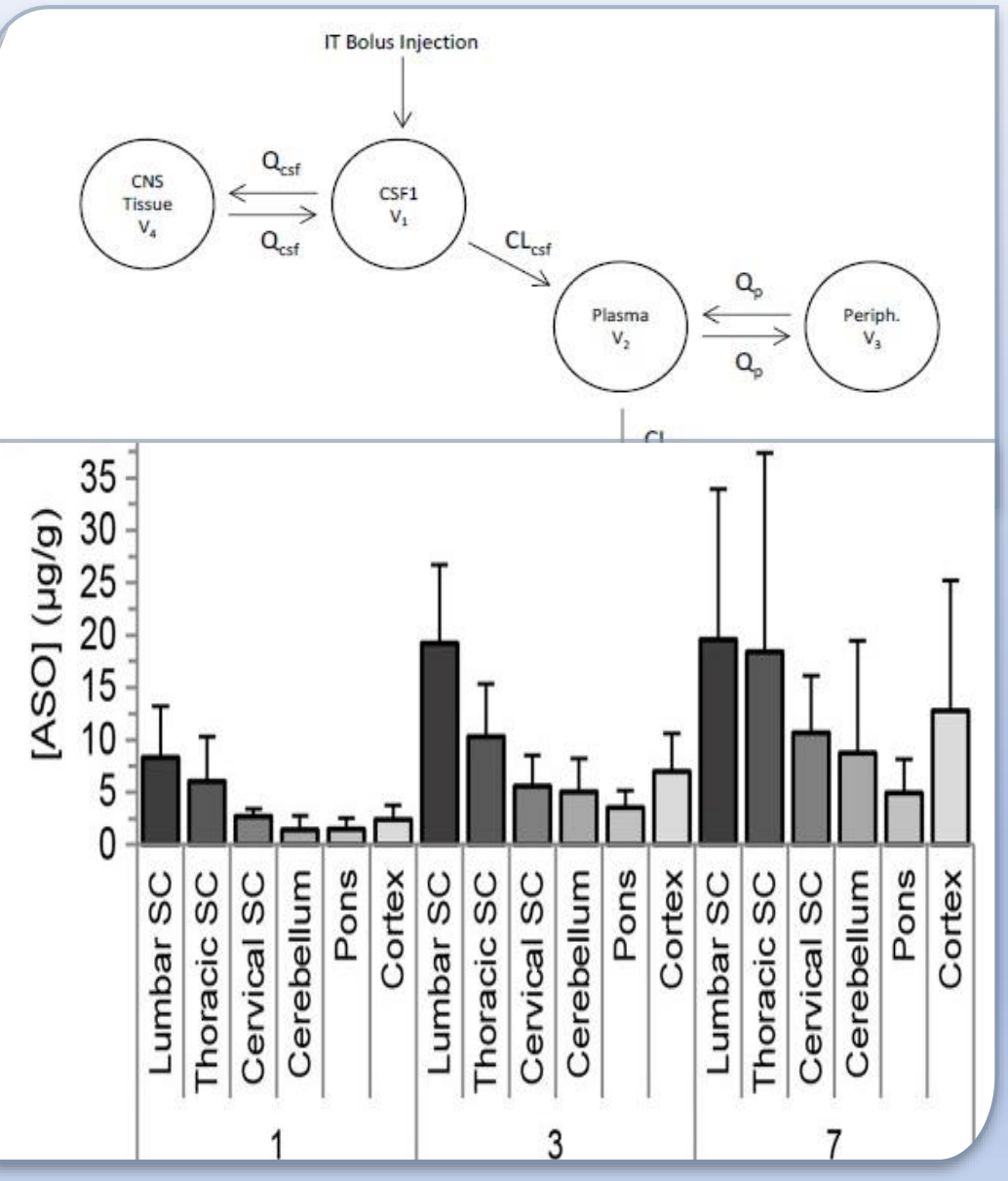
Pharmacokinetic



Tetracompartmental model: CSF and CNS tissue compartment, and two systemic compartments representing the plasma and periferical tissue.

- CLp represents the plasma clearance, CLcsf represents the CSF clearance.
- Qcsf and Qp represent the inter-compartmental clearances within the CSF and plasma, respectively.
- V1, V4, V2 and V3 represent the model-estimated apparent volumes.
- CSF: 135-177 days, Plasma: 85 days,
- Slow metabolism by exonuclease activity (N-1, 3')
- Excreted by the kidney as chain-shortened oligonucleotides,

Pharmacokinetics of Nusinersen in the CNS of non human primates after a single i.t. bolus injection. The amount of Nusinersen in various spinal cord and brain regions of each NHP was measured by ELISA

NUSINERSEN

- Contraindications:

  Hypersensitivity to the active substance or to any of the excipients

- Special warnings and precautions for use:

  Monitoring of laboratory parameters

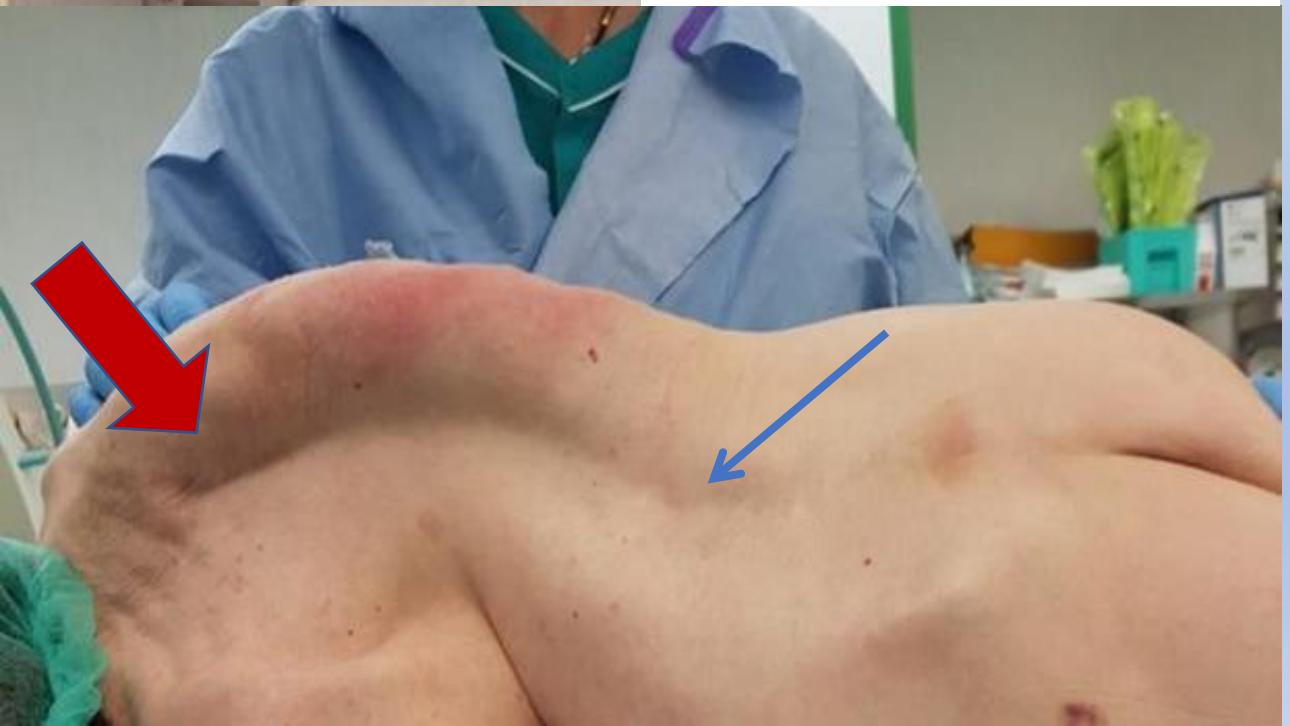
  - Platelet count
  - PT, aPTT
  - urine test with urinary protein dosage

MUST BE PERFORMED BEFORE EVERY I.T. ADMINISTRATION

PATIENTS

Eleven patients with SMA type 3, aged between 20–73 years, were recruited for treatment with Nusinersen. Two of them underwent to fusion surgery, 9 had severe scoliosis.

Age	SMN2 copies	Wheelchair	Scoliosis	Spinal fusion
41	2	Yes	Yes	no
38	4	Yes	No	no
43	4	No	Yes	no
20	3	No	No	no
72	3	Yes	Yes	no
52	3	Yes	Yes	Yes
45	3	Yes	Yes	no
38	3	Yes	Yes	no
52	3	Yes	Yes	no
44	3	Yes	Yes	no
65	3	Yes	Yes	No



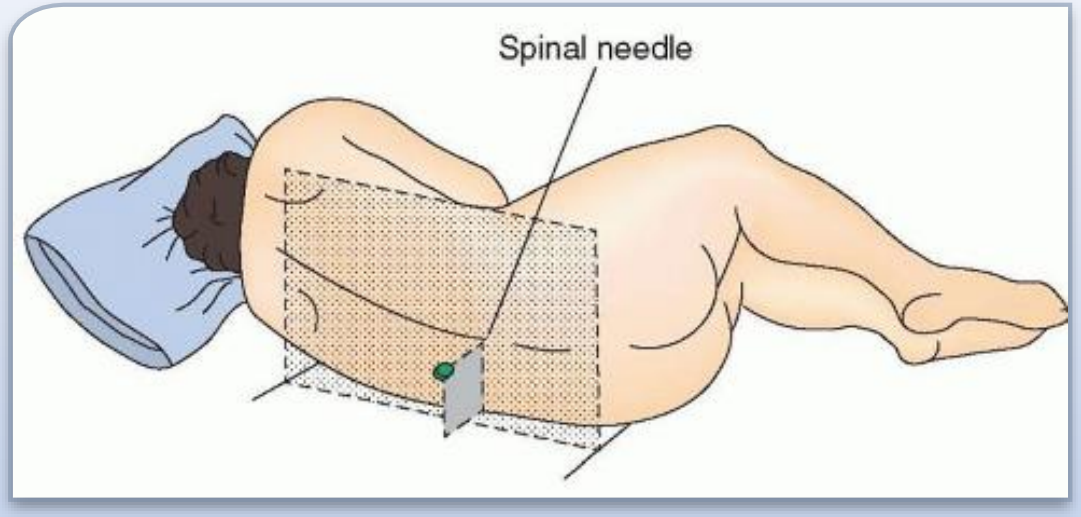
Critical issues

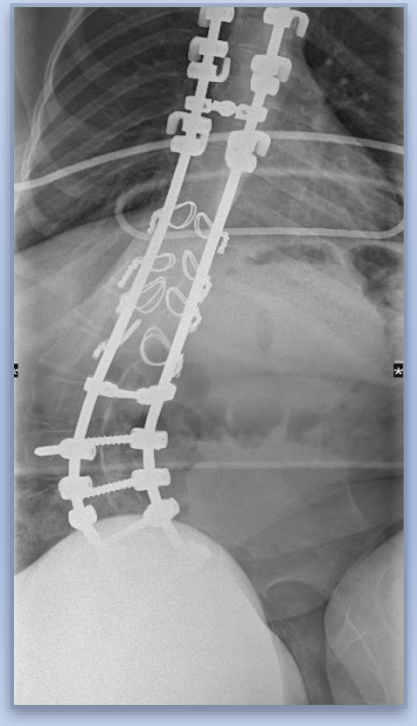
- LPs were performed with the intervention of anesthesiologist, under sterile conditions in lateral decubitus by using a 22-gauge needle .
- Vital signs were monitored during and after 24hours from procedures.
- CSF analyses and cultures were performed in all samples.

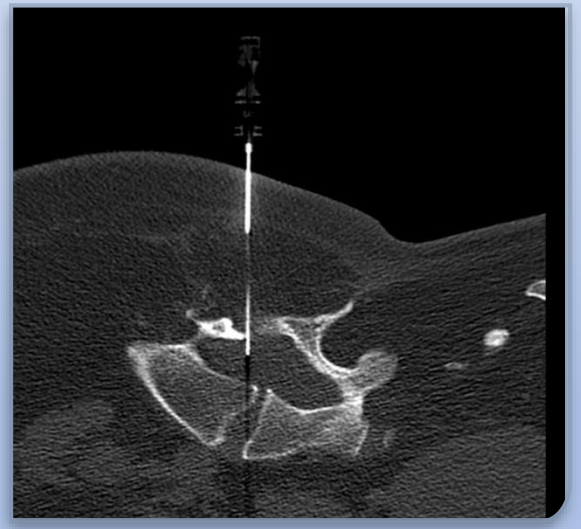
Results

The total number of LPs was 42

- 21 conventional
- 19 fluoroscopy-assisted
- 2 CT-guided LPs.
- 2 cannot be performed due to severe neuromyopathic scoliosis







Adverse events

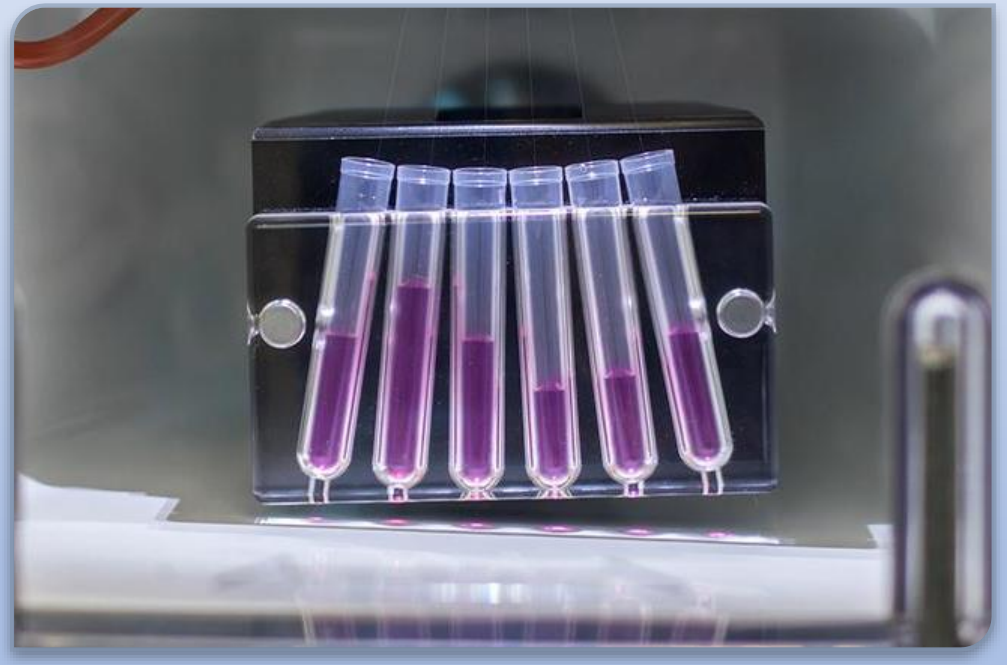
- No serious adverse events were reported.
- The most adverse events reported were headache, back pain and dizziness all of which are reported common complications of lumbar punctures.
- The side effects were all transient according to Common Terminology Criteria for Adverse Events (CTCAE).

Adverse Events
→ Headache (3/9 patients)
→ Dizziness(1/9 patients)
→ Back Pain (2/9 patients)
Nausea
Constipation
Upper respiratory infection

CSF findings

The CSF analysis did not show any signs of infection:

- Normal leukocytes count
- Normal CSF/serum Q glucose
- Only slight increase of CSF/Serum Q Albumin in 4 patients.
- CSF cultures were all negative.



Conclusions

- Only in two patients the procedure couldn’t be performed at baseline for severe spinal impairment.
- In all patients who started the treatment, the injection of Nusinersen was well-tolerated.
- Side effects were all mild, transient and related to lumbar puncture
- No patient stopped the treatment.
- A slight BBB damage was found in 4 patients, neither signs of infection
- An interdisciplinary cooperation between neurologists, anesthesiologists and neuroradiologists is mandatory.

«Ho tenuto una lezione di 20 minuti senza pause, senza affanno. La mia logopedista si commuoverà secondo me.» D.C.

«Sto sempre meglio. Riesco ad urlare perché i miei muscoli sono più forti, quindi è più bello litigare con mio padre. Parlo più limpidamente. Non ho più affanno, il mio viso è più tondo ed espressivo. Qui ringiovanisco, altro che Benjamin Button. Questo farmaco è divino. Sono felice. Vi voglio bene.» D.C.

«Ho sempre fatto la vita che volevo, nonostante stia seduto in carrozza da sempre. Ho fatto cose assurde, invidiabili. Ultimamente c'è stato sto farmaco, ed è stato come rinascere, perché mi consentirà di fare tutto ciò che già facevo e amavo per molto più tempo, dato che la mia malattia smetterà di peggiorare e addirittura migliorerò un po', come già sta accadendo.»


Thanks for your attention