Hospital Universitario Ramón y Cajal

SaludMadrid

UNIVERSIDAD DE ALCALÁ

Enfermedades Musculares
en la
Infancia y Adolescencia(XIV)

Organizado por:

instituto ramón y cajal de investigación sanitaria irycis

Resultados de los ensayos clínicos con *Nusinersen* en AME tipo I.

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Servicio Neurologia Pediatrica
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DECLARACIÓN DE CONFLICTO DE INTERESES

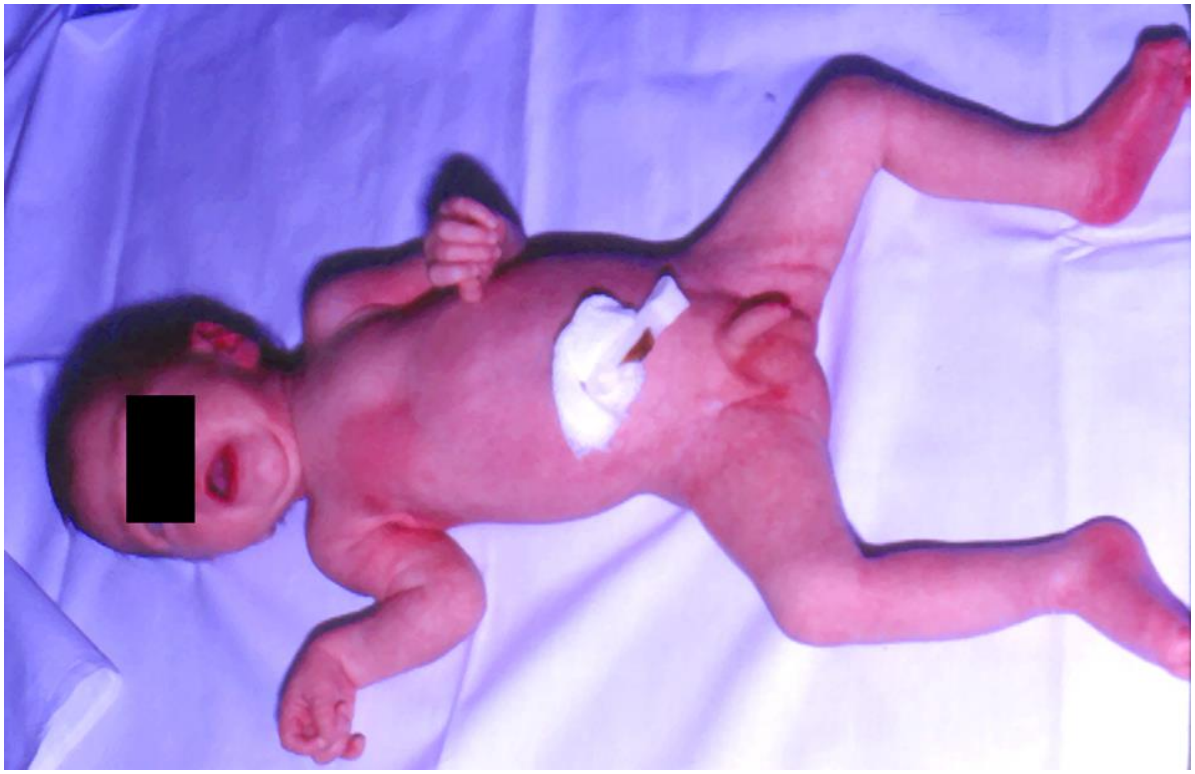
La intervención que presento **NO ha sido financiada**, total o parcialmente, por ninguna empresa con intereses económicos en los productos, equipos o similares citados en la misma.

El ponente participa en dos ensayos fase III IONIS en AME-I (nusinersen).

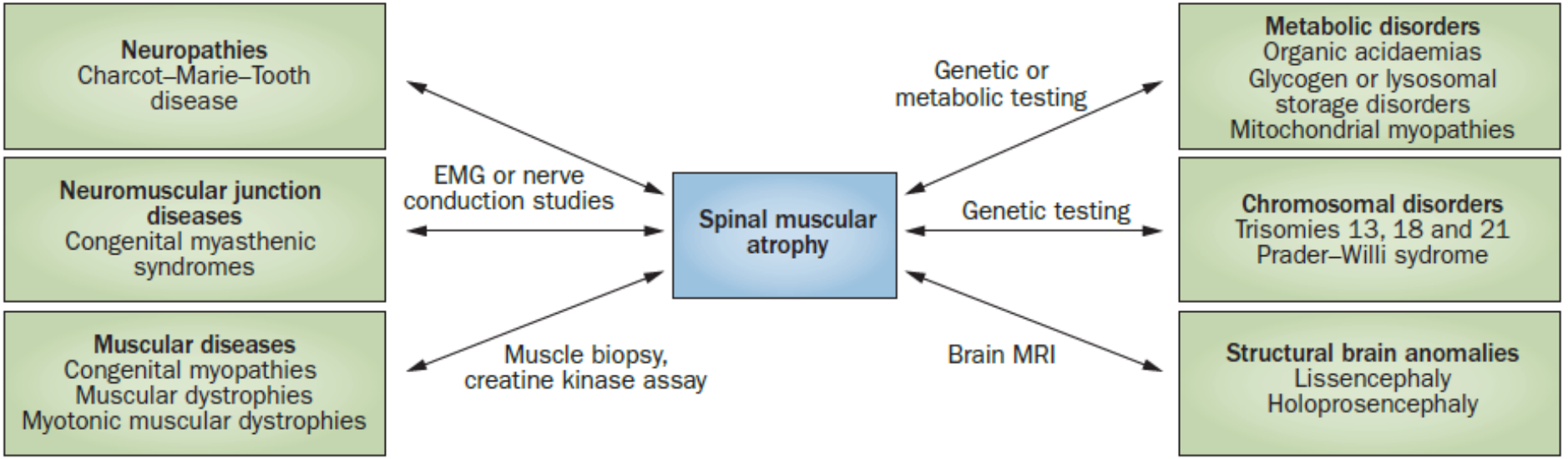
Atrofia muscular espinal

Descrita en 1891 por Werdnig y 1893 por Hoffmann.

1995.-Defecto genético en 5q11.2-q13.3 (SMN), Lefebvre et al.



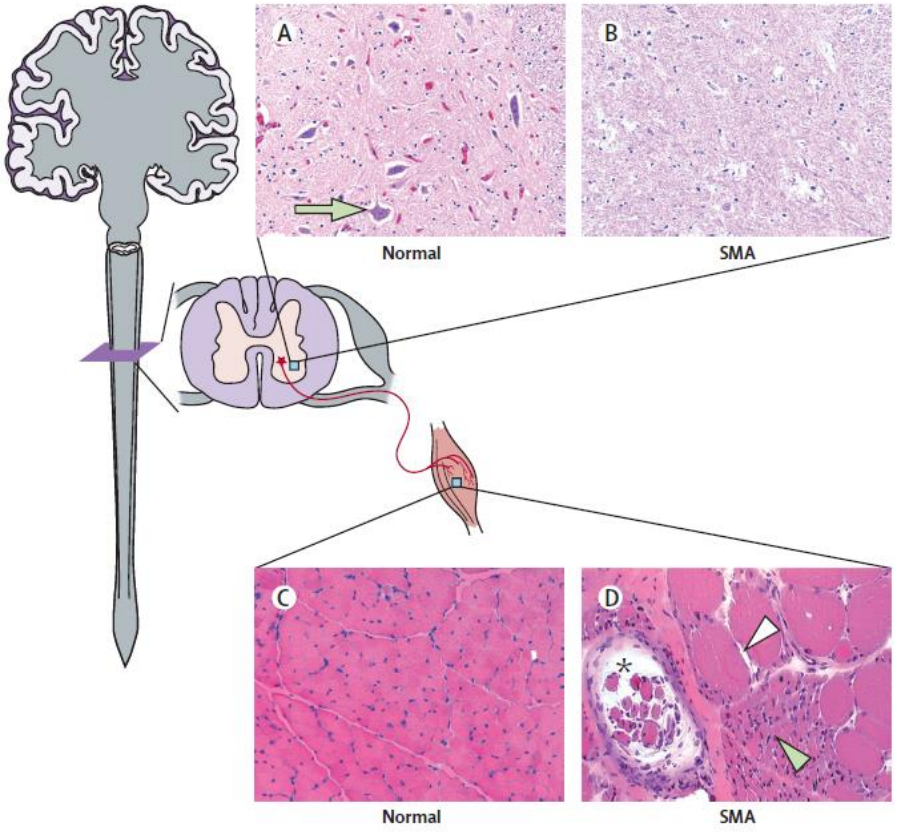
AME. Diagnóstico diferencial



Atrofia Muscular Espinal

INCIDENCIA

1/ 6,000 a 10,000 NACIDOS VIVOS.
Frecuencia de portadores del gen:
1/40-1/60



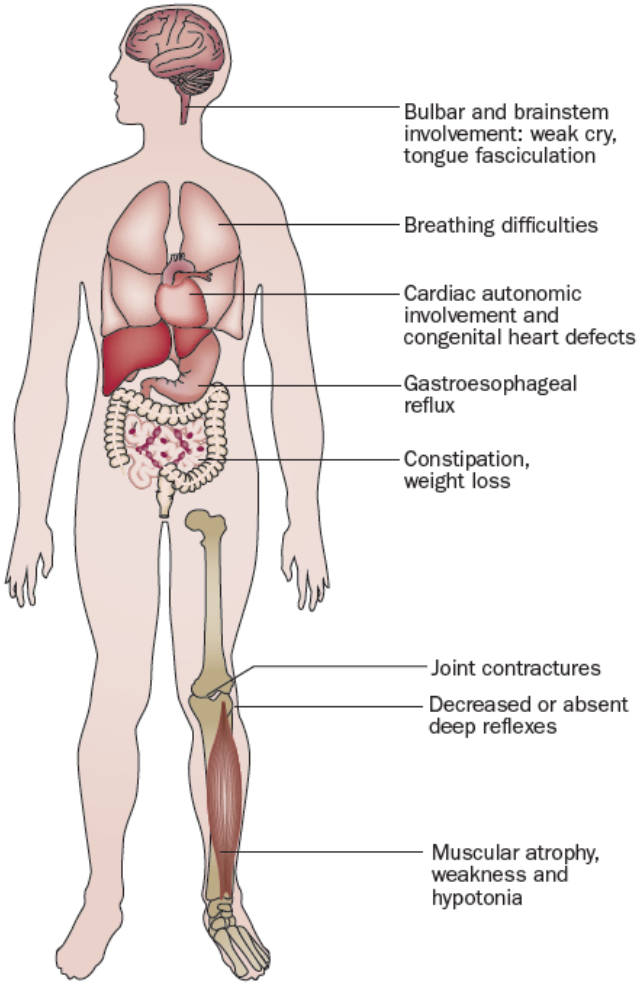
ATROFIA MUSCULAR ESPINAL Clasificación

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2·1 to 2·9
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	..

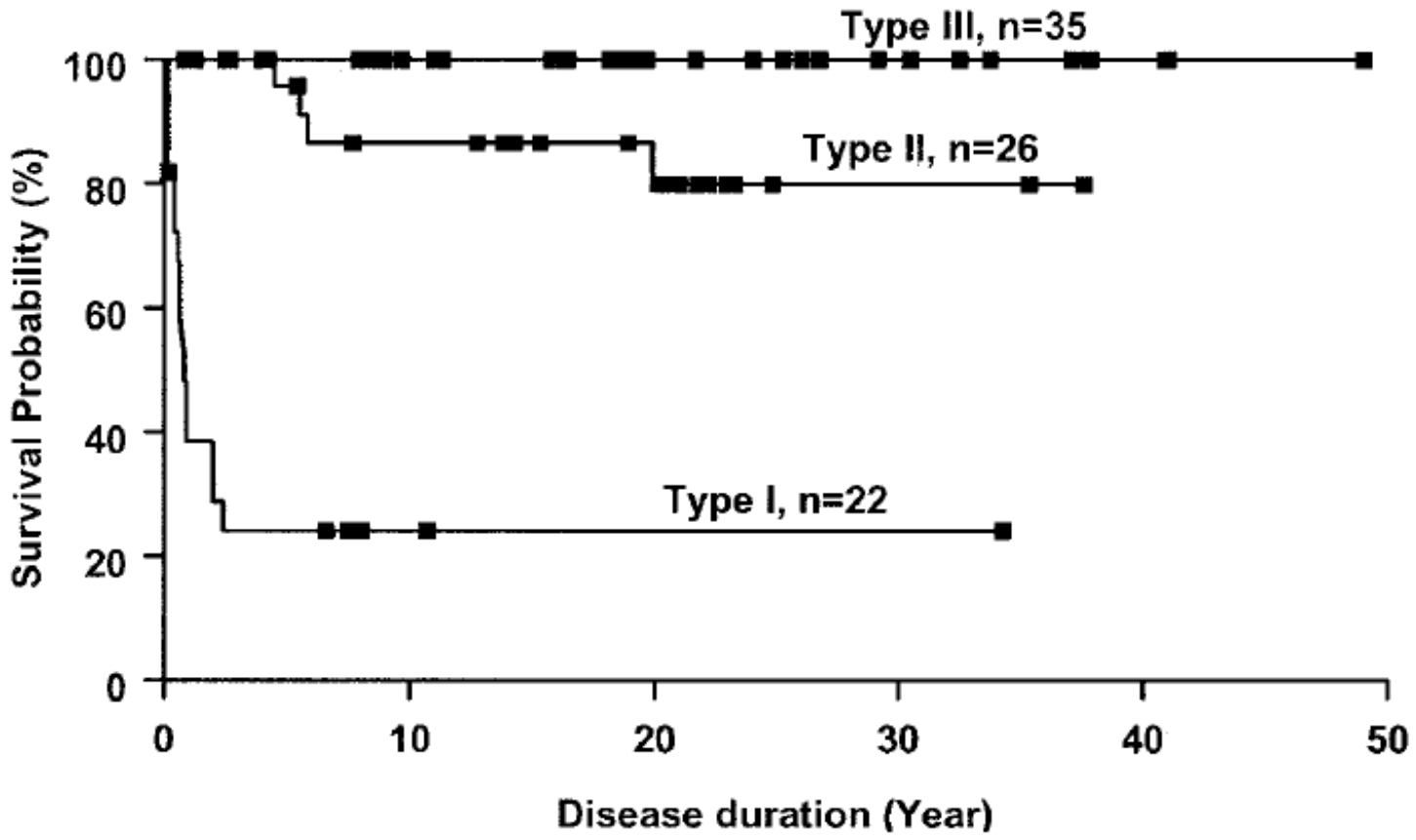
Lancet Neurol 2012; 11: 443–52

AME tipo 1 o Werdnig-Hoffmann

- Forma clínica más frecuente (50% de los casos)
- Inicio, 0-6 meses
- Hipotonía y debilidad generalizada: tronco y miembros, más de MMII, más proximal
- Grave afectación de músculos intercostales
- La cara no está afectada, o mínimamente
- ROT siempre abolidos, no deficit sensitivo
- Contracturas leves, frecuente en rodilla, raro en codo
- Fasciculaciones linguales
- Temblor postural en dedos (ocasional)
- Funciones cerebrales, e inteligencia normal
- Muerte por infecciones respiratorias recurrentes generalmente antes de los 2 años



Supervivencia AME con tratamiento paliativo



Pediatrics 2004;114;e548-e553

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 26 (2016) 754–759

www.elsevier.com/locate/nmd

Developmental milestones in type I spinal muscular atrophy

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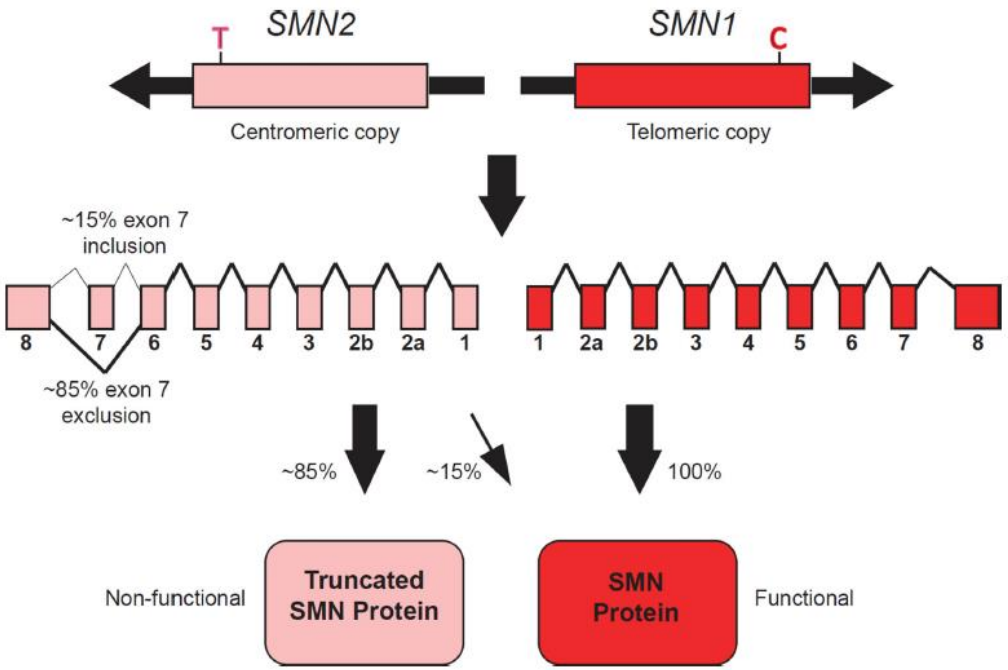
Abstract

The aim of this retrospective multicentric study was to assess developmental milestones longitudinally in type I SMA infants using the Hammersmith Infant Neurological Examination. Thirty-three type I SMA infants, who classically do not achieve the ability to sit unsupported, were included in the study. Our results confirmed that all patients had a score of 0 out of a scale of 4 on items assessing sitting, rolling, crawling, standing or walking. A score of more than 0 was only achieved in three items: head control (n = 13), kicking (n = 15) and hand grasp (n = 18). In these items, the maximal score achieved was 1 out of a scale of 4, indicating only partial achievement of the milestone. Infants with symptom onset after 6 months of age had longer preservation of a score of 1 when compared to those with onset before 6 months of age. Our results suggest that even when current standards of care are applied, developmental milestones are rarely even partially achieved as part of natural history in type I SMA infants. No infants in this study achieved a major milestone such as rolling over, or sitting independently, which would therefore represent robust outcomes in future interventional trials.

Genética AME



- Causa del 95%:

Delección homozigosis del gen SMN1 del cromosoma 5q

- **Existe gen homólogo, SMN2.**

Difiere en 11 nucleótidos de SMN1, 1 de ellos en el exón 7

- Splicing diferente:
  - SMN1 contiene el exón 7,
  - SMN2 no contiene exón 7

AME

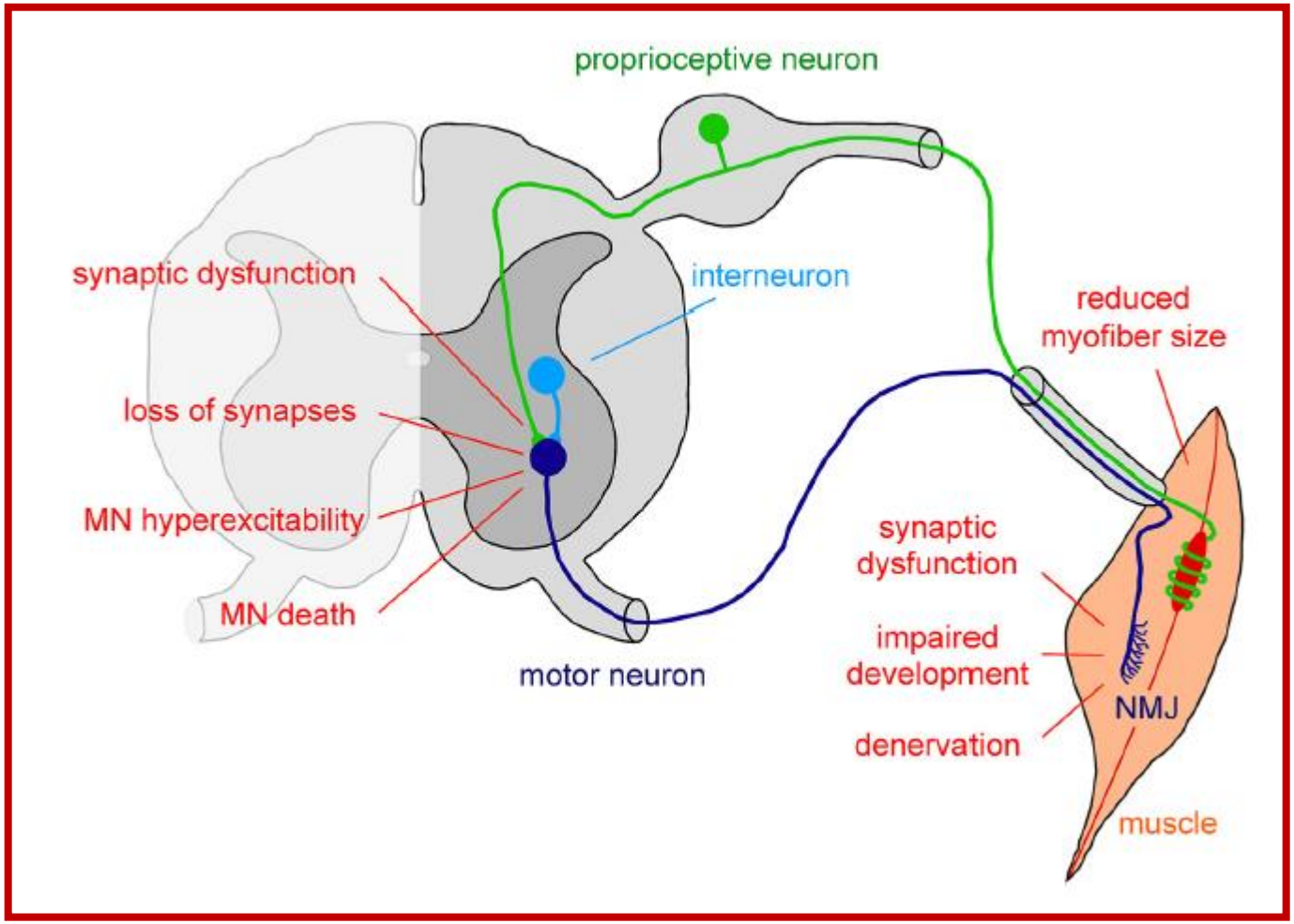
- Pérdida de motoneuronas
- Denervación en la unión neuromuscular (el cambio más precoz).

PNAS, 2016;113:10962–10967

La expresión de SMN se encuentra en todas las células, su defecto causa también alteraciones en el sistema vascular y esquelético.

SMN tambien está implicado en funciones celulares generales incluyendo biogénesis de pequeñas proteinas ribonucleares en el núcleo (snRNP) y metabolismo de glucosa

Alteraciones producidas por el defecto de SMN en el ratón



Tisdale and Pellizzoni, J. Neurosci. 2015;35:8691-8700

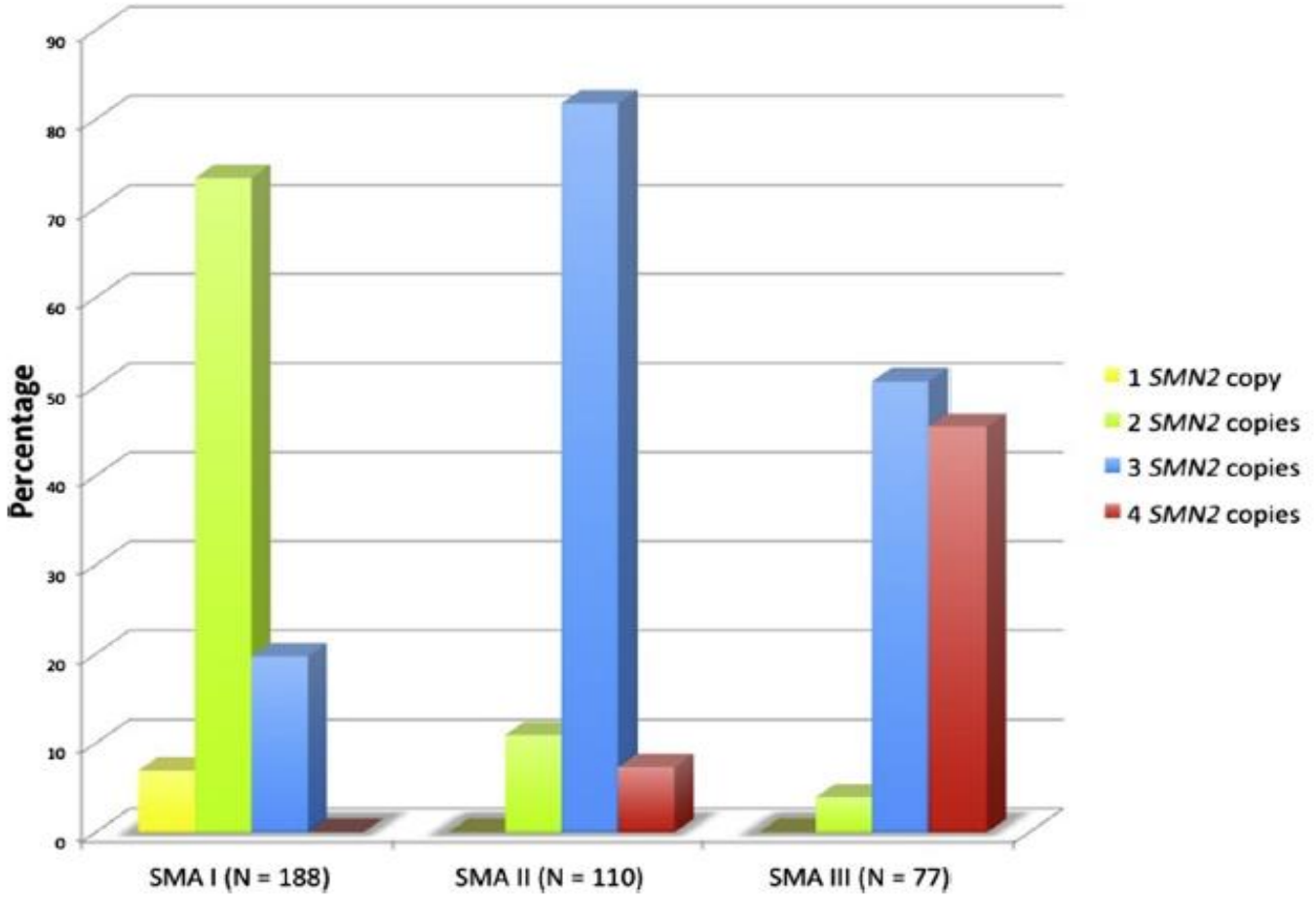
Genética AME

Table 3
Genetic diagnostic testing in spinal muscular atrophy

Type of Mutation	Test Applied	Mutation Detection Rate
Homozygous deletion of exon 7[a]	*SMN1* Targeted mutation analysis PCR/restriction enzyme analysis or MLPA methodologies	~95%–98%
Compound heterozygosity (deletion of *SMN1* exon 7 [allele 1] and an intragenic mutation of *SMN1*[b] [allele 2])	Targeted mutation analysis combined with *SMN1* gene sequence analysis[c]	2%–5%
SMN2 copy number[d]	Quantitative PCR analysis and other methodologies[e]	N/A

[a] Testing for exon 8 deletion is not necessary.
[b] Small intragenic deletions/insertions and nonsense, missense, and splice site mutations.
[c] Whole-gene deletions/duplications are not detected.
[d] *SMN2* copy number ranges from 0 to 5.
[e] MLPA, long-range PCR, CMA that includes the *SMN1*, *SMN2* chromosomal segment.
Adapted from Markowitz JA, Singh P, Darras BT. Spinal muscular atrophy: a clinical and research update. Pediatr Neurol 2012;46:5; with permission.

COPIAS del gen complementario SMN2



AME I: 1-2 (3) COPIAS
AME II.- 2-3 COPIAS
AME III.- 3-4 ó más COPIAS

Am J Hum Genet 2002;70:363

El pronóstico de gravedad en base al nº de copias de SMN2 es solo relativamente fiable

MANEJO Y TRATAMIENTOS DE LA AME

	Pulmonary		Gastrointestinal and nutritional		Orthopaedic and rehabilitation	
	Assessment and monitoring	Assistance and intervention	Assessment and monitoring	Assistance and intervention	Assessment and monitoring	Assistance and intervention
Non-sitters	Assessment of cough effectiveness; respiratory muscle function tests; overnight oximetry; standard oximetry	Airway clearance; cough assistance; chest physiotherapy; nocturnal non-invasive ventilation (if nocturnal ventilatory failure); non-invasive ventilation (if daytime ventilatory failure)	Assessment of feeding (speech or occupational therapist); videofluoroscopy (if indicated); search for signs of reflux	Gastrostomy (if aspiration or poor efficiency of feeding); Nissen fundoplication (if appropriate)	Physical and occupational therapy assessment (posture, contractures); hip and spine radiography; bone health	Equipment and devices for posture; splinting to preserve range of motion should be considered; no consensus on orthosis or surgery in scoliosis
Sitters and ambulant patients	Assessment of cough effectiveness; respiratory muscle function tests; forced vital capacity (patients >5 years); overnight oximetry	Airway clearance; cough assistance; chest physiotherapy; nocturnal non-invasive ventilation (if sleep-disorder breathing); immunisation and respiratory syncytial virus prophylaxis (when appropriate)	Assessment of feeding (speech or occupational therapist); videofluoroscopy (if indicated); search for signs of reflux	Optimise caloric intake with supplements (if not adequate intake but safe swallowing); gastrostomy (only if aspiration or poor efficiency of feeding after calories supplemented orally); medical management (when appropriate)	Physical and occupational therapy assessment (posture, contractures, strength); assessment of power and manual mobility	Contracture management and exercise; orthoses

Wang et al:Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol 2007,22:1027-1049.

Lancet Neurol 2012; 11: 443–52

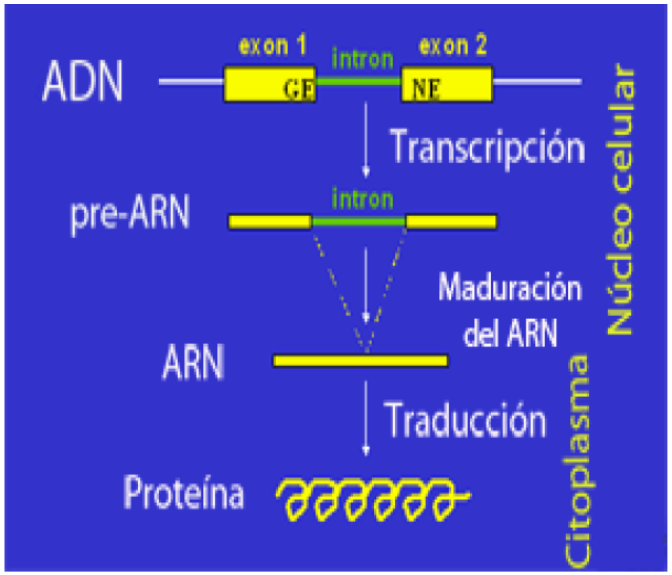
Nuevos tratamientos de AME

TRATAMIENTOS ESPECIFICOS DE AME

- **Pequeñas moléculas**
  que incrementan la expresión de la proteina SMN
- **Sobre RNA para mejorar la transcripcion SMN2**
  Oligonucleótidos (intratecal, o sistémico)

- **Tratamiento genético, sobre SMN1**
  vector virus adenoasociado (scAAV9 ..)
  Aumentan de 16 a 400 dias la supervivencia del raton SMA
  Cronodependiente (efectivo en el ratón en 1º dia, no efectivo en 10ª día)

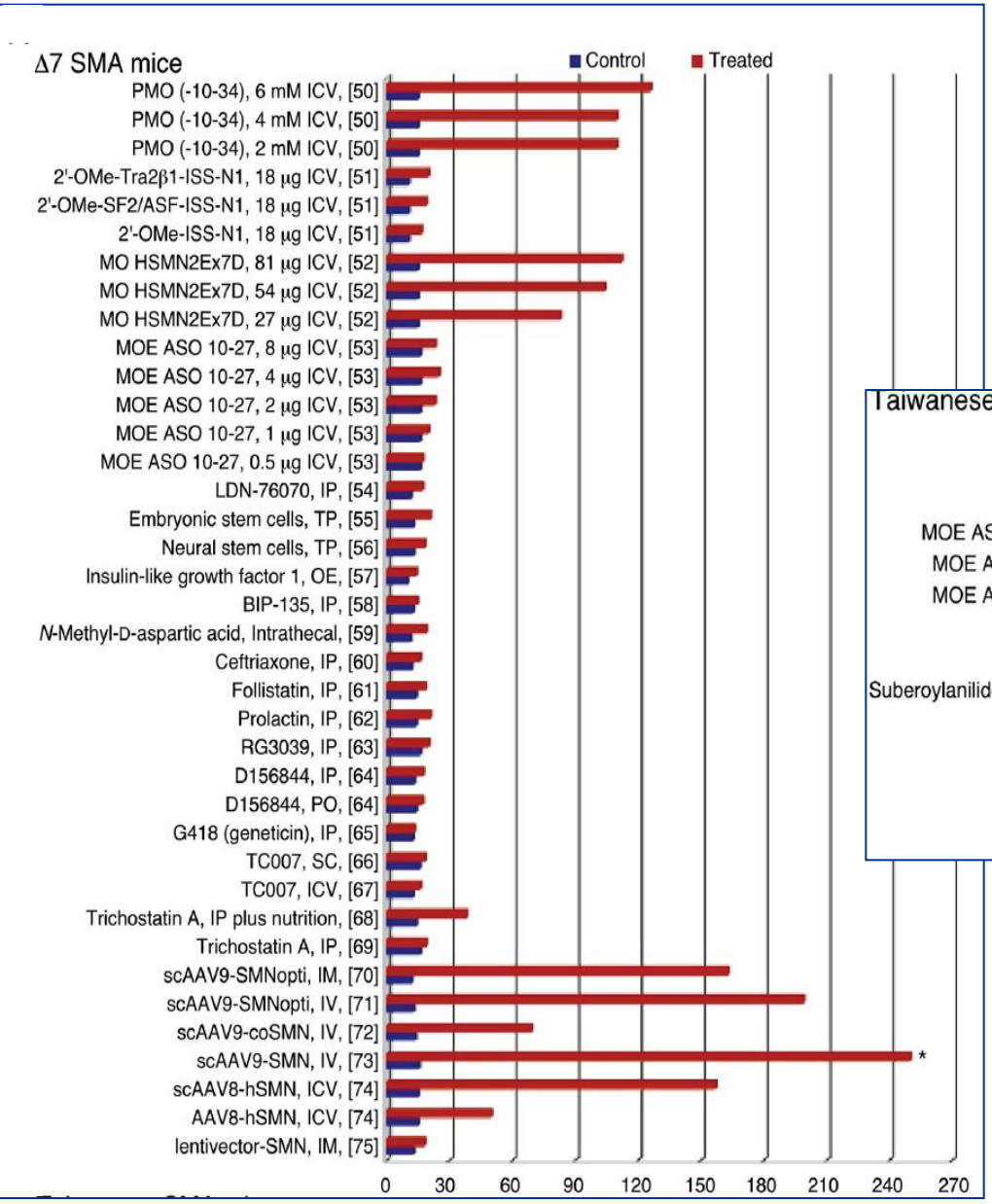
AME.- TRATAMIENTOS FARMACOLÓGICOS DE ACUERDO AL OBJETIVO PATOGÉNICO

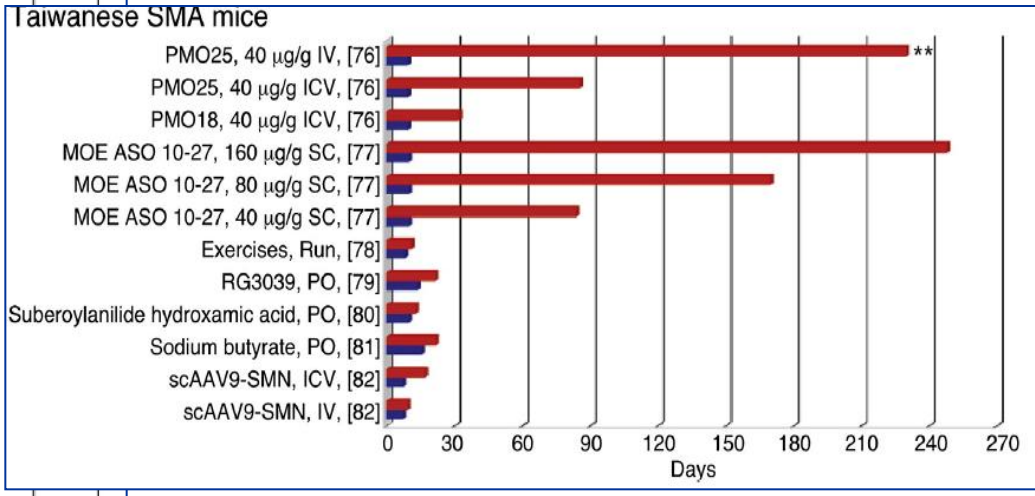


	Therapeutic targets	Therapeutic approaches	Trials completed or ongoing
SMN1 gene mutation	Replacement of *SMN1*	Gene replacement therapy	..
Alternative splicing of *SMN2* RNA	Inclusion of exon 7	Antisense oligonucleotides (new drugs developed by PTC Therapeutics, tetracycline)	New drugs developed by ISIS Pharmaceuticals
Decreased full-length SMN transcript	Increased amounts of SMN transcript	Histone deacetylase inhibitors, quinazolones, RG3039, aminoglycerides, albuterol, prolactin	Phenylbutyrate (randomised controlled trial)[52,53] Valproate (randomised controlled trial)[46,56,58] Hydroxyurea (randomised controlled trial)[59] Albuterol (open-label and ongoing randomised controlled trial)[54,60]
SMN protein deficiency	Stabilisation of SMN protein	Indoprofen, proteasome inhibitors, polyphenols	..
Loss of motor neurons	Neuroprotection	Neurotrophic factors	Gabapentin (randomised controlled trial)[61] Riluzole (open-label)[62] Olesoxime (TRO19622)
	Cell therapy	Stem cells	..
Clinical symptoms	..	..	..

Lancet Neurol 2012; 11: 443–52

AME.- EFICACIA EN MODELOS DEL RATON SMA





Biochim Biophys Acta,2013:27;1832(12):2180-2190.

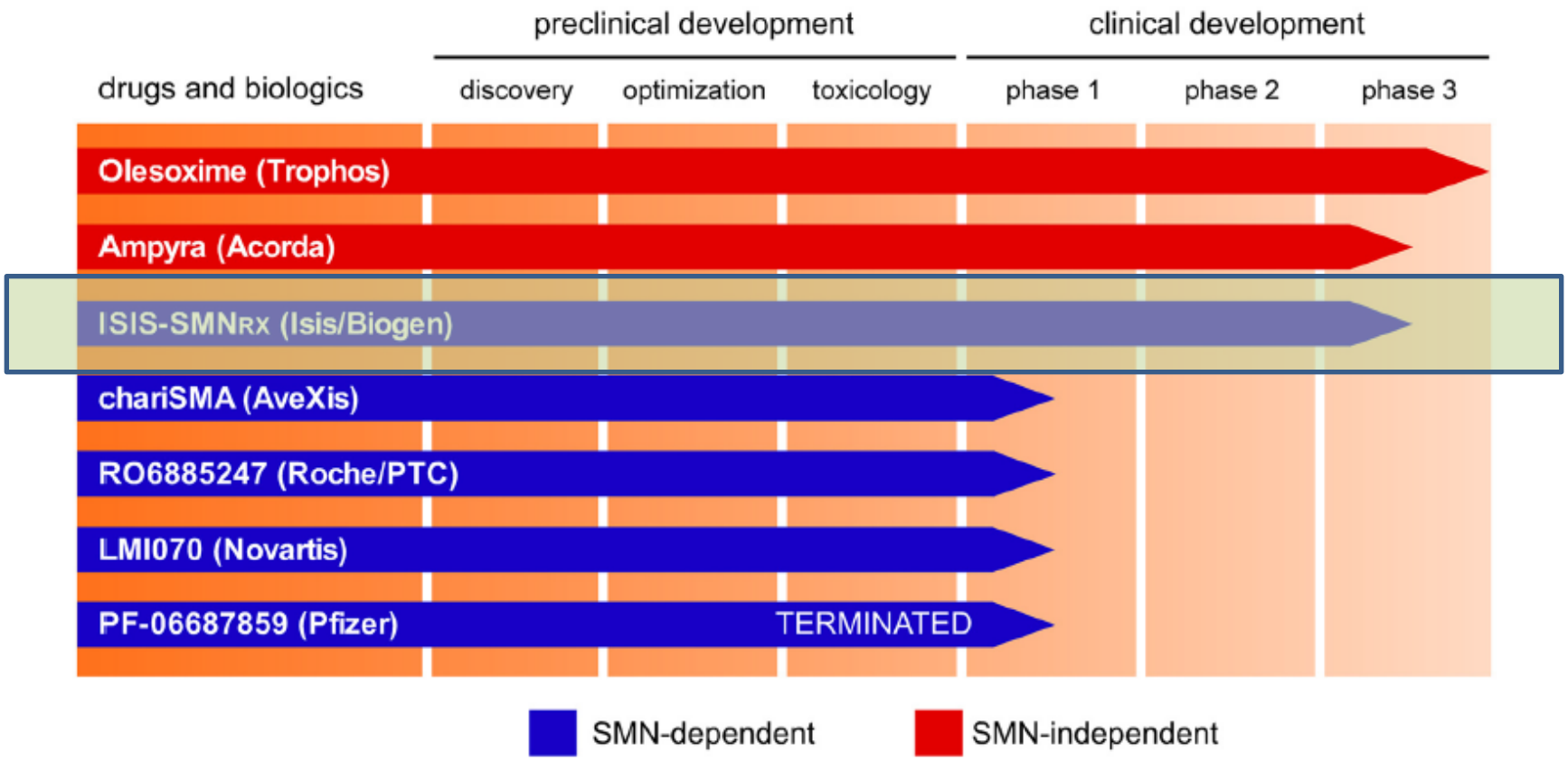
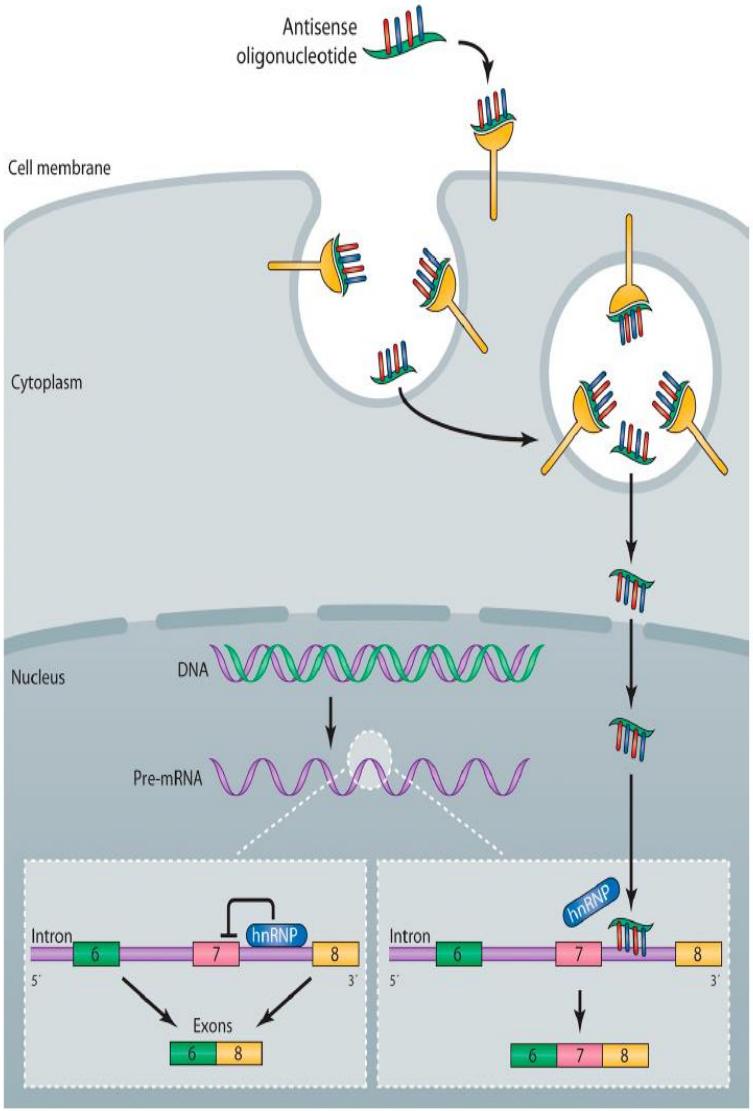


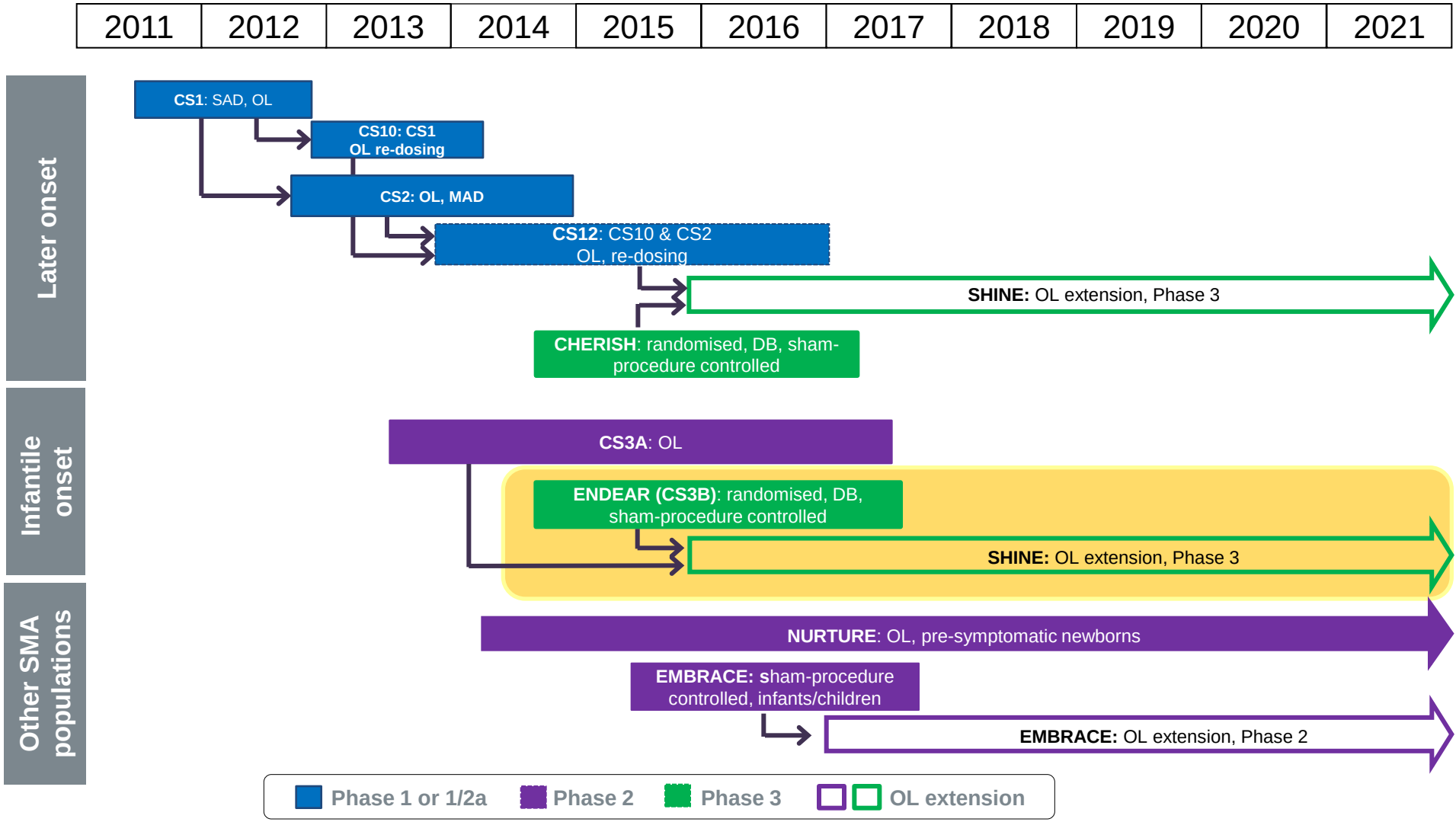
Figure 3. Candidate SMA therapeutics and their progress through the clinical development pipeline. The chart summarizes the current status of the most advanced programs in SMA therapeutic development based on publicly available information. Small molecules and biologics listed with blue bars aim to increase the functional levels of SMN, and those denoted with red bars act by improving motor system function through SMN-independent mechanisms.

Mecanismo de acción: ISIS 396443 nusinersen



- Oligonucleótido antisentido
- 18 nucleótidos
- Se une a secuencia específica del transcrito de SMN2
- Promueve la inclusión del exón 7 al mRNA
- mRNA con exón 7 → proteína completa

Nusinersen Clinical Development Program



DB = double-blind; OL = open-label; MAD = multiple ascending dose; SAD = single ascending dose.

Experiencia preclínica ISIS 396443 nusinersen

- **Fibroblastos:** más del 90% de proteína completa
- **Ratones SMA**: proteína completa en tejidos periféricos en la administración sistémica, y en SN al inyectarlo intraventicular. Más del 90% de proteína completa.
- **Ratones con forma grave SMA**: mejora de peso, fuerza muscular y coordinación motora.
- **Monos:** distribución extensa en SNC tras administración intratecal.

Experiencia clínica
nusinersen

- **Fase 1:** dosis ascendentes en pacientes de 2-14 años.

  Dosis 1, 3, 6, 9 mg

  Sin efectos secundarios serios

  Efectos secundarios leves-moderados no dependientes de dosis

Results from a phase 1 study of nusinersen (ISIS-SMN_{Rx}) in children with spinal muscular atrophy

OPEN

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Kathryn J. Swoboda, MD
Basil T. Darras, MD
Susan T. Iannaccone, MD
Jacqueline Montes, PT, EdD
Darryl C. De Vivo, MD
Daniel A. Norris, PhD
C. Frank Bennett, PhD
Kathie M. Bishop, PhD

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ABSTRACT

Objective: To examine safety, tolerability, pharmacokinetics, and preliminary clinical efficacy of intrathecal nusinersen (previously ISIS-SMN_{Rx}), an antisense oligonucleotide designed to alter splicing of *SMN2* mRNA, in patients with childhood spinal muscular atrophy (SMA).

Methods: Nusinersen was delivered by intrathecal injection to medically stable patients with type 2 and type 3 SMA aged 2–14 years in an open-label phase 1 study and its long-term extension. Four ascending single-dose levels (1, 3, 6, and 9 mg) were examined in cohorts of 6–10 participants. Participants were monitored for safety and tolerability, and CSF and plasma pharmacokinetics were measured. Exploratory efficacy endpoints included the Hammersmith Functional Motor Scale Expanded (HFMSE) and Pediatric Quality of Life Inventory.

Results: A total of 28 participants enrolled in the study (n = 6 in first 3 dose cohorts; n = 10 in the 9-mg cohort). Intrathecal nusinersen was well-tolerated with no safety/tolerability concerns identified. Plasma and CSF drug levels were dose-dependent, consistent with preclinical data. Extended pharmacokinetics indicated a prolonged CSF drug half-life of 4–6 months after initial clearance. A significant increase in HFMSE scores was observed at the 9-mg dose at 3 months postdose (3.1 points; $p = 0.016$), which was further increased 9–14 months postdose (5.8 points; $p = 0.008$) during the extension study.

Conclusions: Results from this study support continued development of nusinersen for treatment of SMA.

Classification of evidence: This study provides Class IV evidence that in children with SMA, intrathecal nusinersen is not associated with safety or tolerability concerns. *Neurology*® 2016;86:1–8

ARTICLES

Results from (ISIS-SMN$_R$ muscular atr

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ABSTRACT

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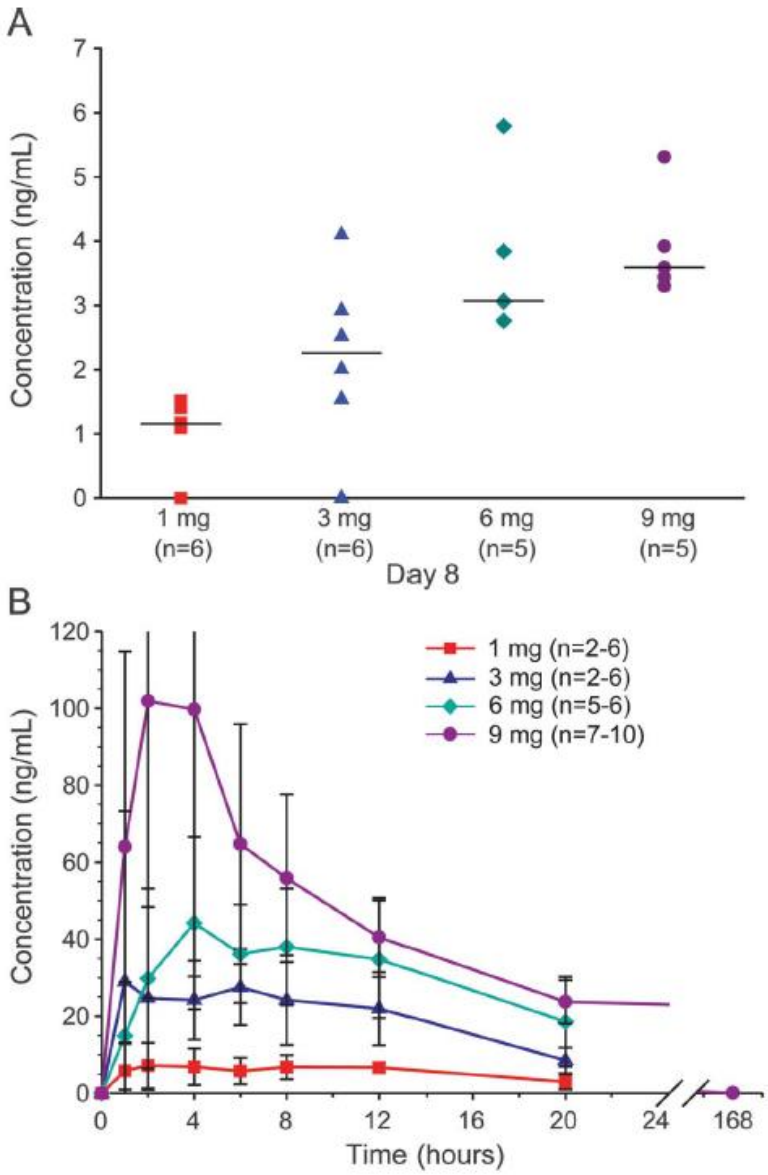
Methods: Nusinersen was 2 and type 3 SMA aged 2- Four ascending single-dos ipants. Participants were kinetics were measured. E Motor Scale Expanded (HF

Results: A total of 28 partic 9-mg cohort). Intrathecal n tified. Plasma and CSF Extended pharmacokinetic clearance. A significant inc postdose (3.1 points; p = points; $p = 0.008$) during

Conclusions: Results from of SMA.

Classification of evidence: T cal nusinersen is not associ

Figure 2 CSF and plasma concentrations of nusinersen



Measured nusinersen concentrations for each dose group are shown. (A) CSF at 7 days postdose. (B) Plasma over 24 hours (all groups) or 7 days (6- and 9-mg groups) postdose (mean ± SEM). As anticipated, plasma levels were below the limit of detection of the assay at day 8 postdose.

Original Article

Journal of Child Neurology
1-8

DOI: 10.1177/0883073815627882
jcn.sagepub.com
SAGE

Intrathecal Injections in Children With Spinal Muscular Atrophy: Nusinersen Clinical Trial Experience

Manon Haché, MD[1], Kathryn J. Swoboda, MD[2], Navil Sethna, MD, FAAP[3], Alan Farrow-Gillespie, MD[4], Alexander Khandji, MD[5], Shuting Xia, MS[6], and Kathie M. Bishop, PhD[6]

Abstract

Nusinersen (ISIS-SMN_{Rx} or ISIS 396443) is an antisense oligonucleotide drug administered intrathecally to treat spinal muscular atrophy. We summarize lumbar puncture experience in children with spinal muscular atrophy during a phase 1 open-label study of nusinersen and its extension. During the studies, 73 lumbar punctures were performed in 28 patients 2 to 14 years of age with type 2/3 spinal muscular atrophy. No complications occurred in 50 (68%) lumbar punctures; in 23 (32%) procedures, adverse events were attributed to lumbar puncture. Most common adverse events were headache (n = 9), back pain (n = 9), and post–lumbar puncture syndrome (n = 8). In a subgroup analysis, adverse events were more frequent in older children, children with type 3 spinal muscular atrophy, and with a 21- or 22-gauge needle compared to a 24-gauge needle or smaller. Lumbar punctures were successfully performed in children with spinal muscular atrophy; lumbar puncture–related adverse event frequency was similar to that previously reported in children.

Experiencia clínica nusinersen

Fase 2, SMA I

dosis de 6 y 12 mg

Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study

Richard S Finkel, Claudia A Chiriboga, Jiri Vajsar, John W Day, Jacqueline Montes, Darryl C De Vivo, Mason Yamashita, Frank Rigo, Gene Hung, Eugene Schneider, Daniel A Norris, Shuting Xia, C Frank Bennett, Kathie M Bishop

www.thelancet.com **Published online December 6, 2016**

Summary

Background Nusinersen is a 2′-*O*-methoxyethyl phosphorothioate-modified antisense drug being developed to treat spinal muscular atrophy. Nusinersen is specifically designed to alter splicing of *SMN2* pre-mRNA and thus increase the amount of functional survival motor neuron (SMN) protein that is deficient in patients with spinal muscular atrophy.

Methods This open-label, phase 2, escalating dose clinical study assessed the safety and tolerability, pharmacokinetics, and clinical efficacy of multiple intrathecal doses of nusinersen (6 mg and 12 mg dose equivalents) in patients with infantile-onset spinal muscular atrophy. Eligible participants were of either gender aged between 3 weeks and 7 months old with onset of spinal muscular atrophy symptoms between 3 weeks and 6 months, who had *SMN1* homozygous gene deletion or mutation. Safety assessments included adverse events, physical and neurological examinations, vital signs, clinical laboratory tests, cerebrospinal fluid laboratory tests, and electrocardiographs. Clinical efficacy assessments included event free survival, and change from baseline of two assessments of motor function: the motor milestones portion of the Hammersmith Infant Neurological Exam—Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function test, and compound motor action potentials. Autopsy tissue was analysed for target engagement, drug concentrations, and pharmacological activity. HINE-2, CHOP-INTEND, and compound motor action potential were compared between baseline and last visit using the Wilcoxon signed-rank test. Age at death or permanent ventilation was compared with natural history using the log-rank test. The study is registered at ClinicalTrials.gov, number NCT01839656.

Findings 20 participants were enrolled between May 3, 2013, and July 9, 2014, and assessed through to an interim analysis done on Jan 26, 2016. All participants experienced adverse events, with 77 serious adverse events reported in 16 participants, all considered by study investigators not related or unlikely related to the study drug. In the 12 mg dose group, incremental achievements of motor milestones ($p<0·0001$), improvements in CHOP-INTEND motor function scores ($p=0·0013$), and increased compound muscle action potential amplitude of the ulnar nerve ($p=0·0103$) and peroneal nerve ($p<0·0001$), compared with baseline, were observed. Median age at death or permanent ventilation was not reached and the Kaplan-Meier survival curve diverged from a published natural history case series ($p=0·0014$). Analysis of autopsy tissue from patients exposed to nusinersen showed drug uptake into motor neurons throughout the spinal cord and neurons and other cell types in the brainstem and other brain regions, exposure at therapeutic concentrations, and increased *SMN2* mRNA exon 7 inclusion and SMN protein concentrations in the spinal cord.

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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(16)32390-X

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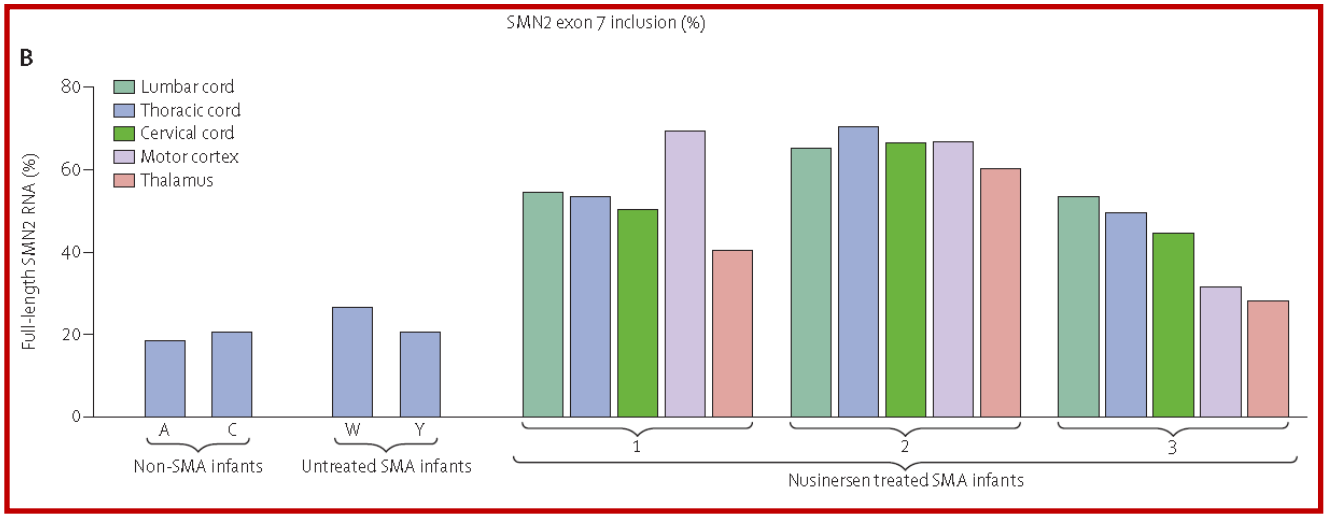
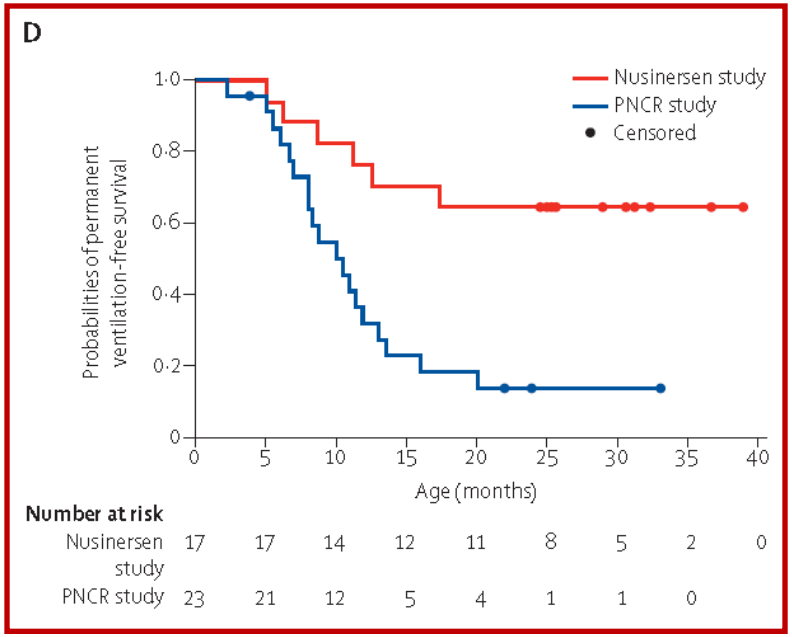
www.thelancet.com **Published online December 6, 2016**





Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study

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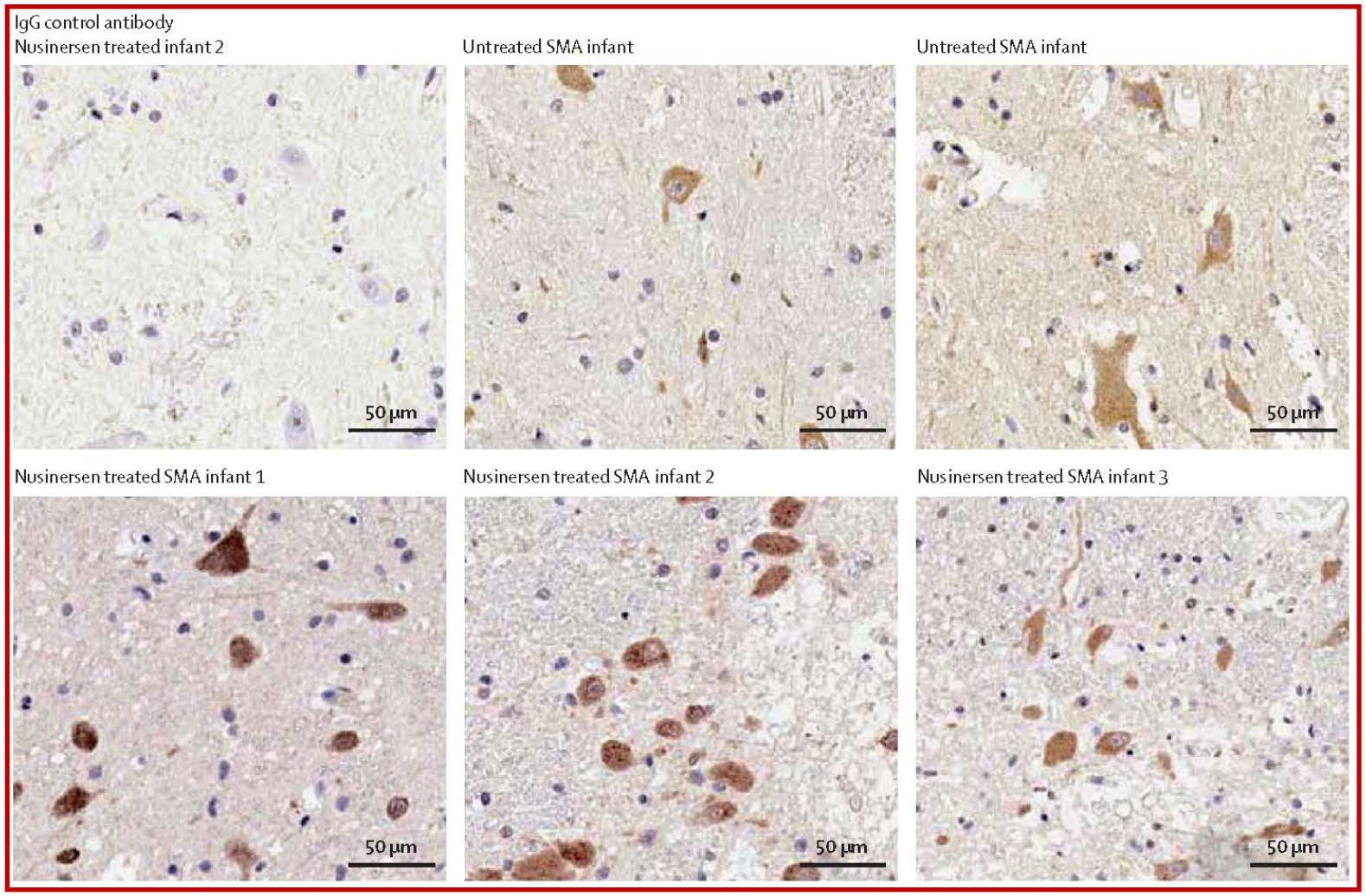

Proteina SMN (marrón) en neuronas de Médula torácica

Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study

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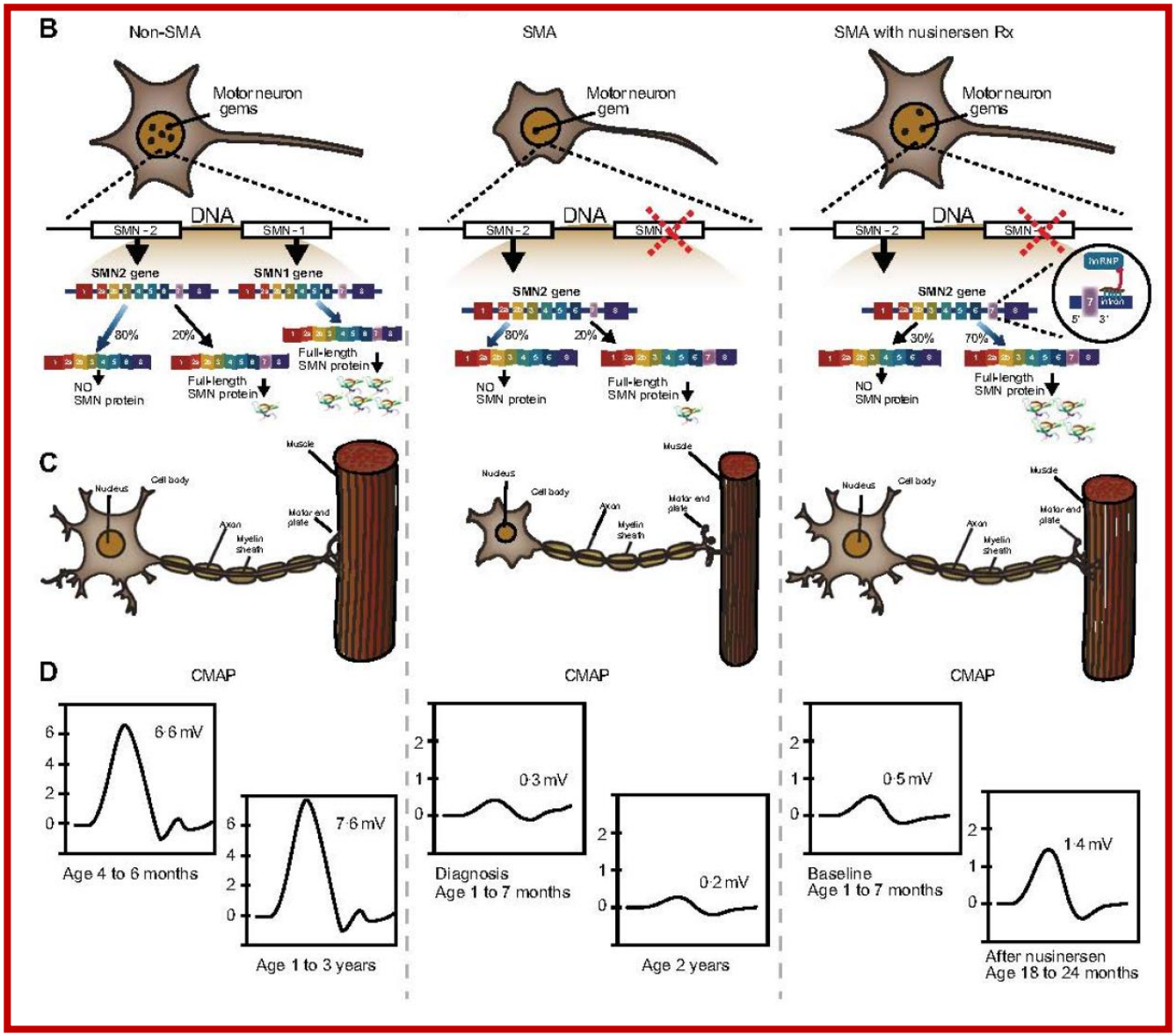


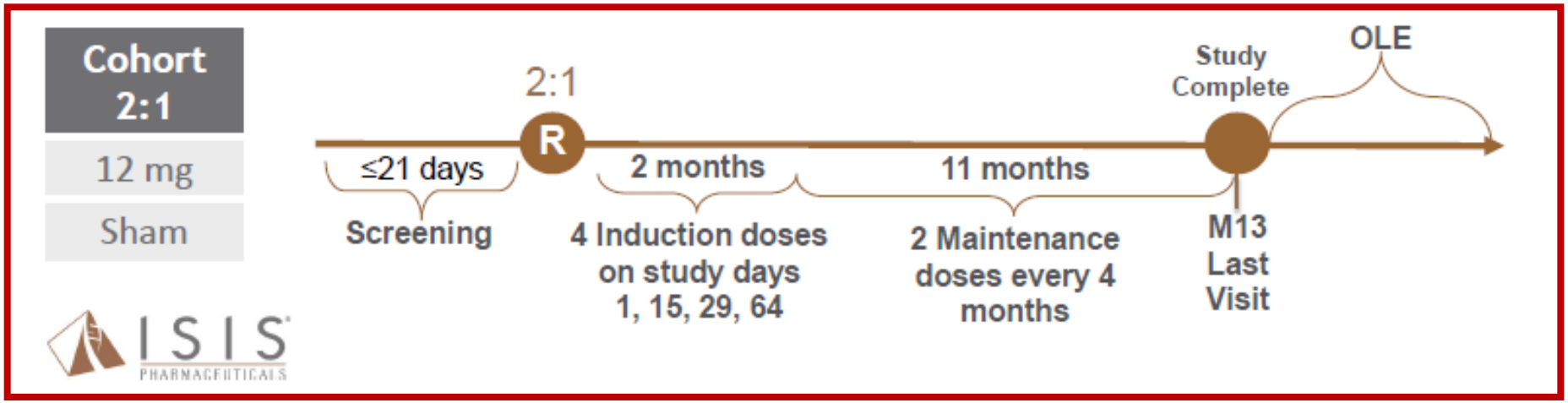
Estudio fase 3 (ENDEAR), randomizado, doble ciego, controlado con procedimiento placebo para evaluar la eficacia y seguridad del fármaco ISIS396443 administrado intratecal en pacientes con AME de tipo I.

España:
AME I.-H. Vall d´Hebron y H.U. La Paz

AME-II.- H. Sant Joan de Deu

Diseño del estudio

- Fase 3 multicéntrico, 13 meses de duración, 111 pacientes
- Randomizado con procedimiento simulado
- 2:1 fármaco/simulado
- Randomización en función de 2 grupos: duración de síntomas > o < 12 semanas
- Tras los 13 meses: estudio abierto, sin descubrir el ciego
- Primary endpoint: fallecimiento o ventilación > 16 horas /día, >21 días



Parámetros analizados

- Laboratorio
- Evaluación neurológica
- Farmacocinética
- CHOP-INTEND: Infant test for neuromuscular disease
- Hitos motores de Hammersmith (HINE)
- Estudio del CMAP
- Parámetros de crecimiento

Objetivos a analizar ENDEAR

- Primary endpoints
  - Proporción de respondedores (mejora en los hitos motores)
    - Test HINE después de 183 días de tratamiento[1]
    - Análisis preliminar de eficacia, cuando unos 80 niños han pasado el día 183
  - Supervivencia y libres de ventilación invasiva (traqueostomía) o sin necesitar soporte ventilatorio 16 horas diarias durante 3 semanas.

- Secondary endpoints
  - Mejora en CHOP INTEND
    - ≥4-point improvement from Baseline in total score from Day 183 onwards
  - Proporción de supervivientes
  - Proporción que no requieren ventilación permanente
  - CMAP

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; EAC = endpoint adjudication committee; HINE = Hammersmith Infant Neurological Exam; IES = interim efficacy set. [a]Primary analyses must reach statistical significance before inferential conclusions can be drawn from the remaining secondary and tertiary endpoints. 1. Haataja L, *et al*. *J Pediatr.* 1999;135(2 pt 1):153-161.

DEFINICION DE RESPONDEDORES escala HINE

Modified section 2 of the HINE

Motor function	Milestone progression score				
	0	1	2	3	4
Voluntary grasp	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick (supine)	No kicking	Kick horizontal, legs do not lift	Upward (vertical)	Touches leg	Touches toes
Head control	Unable to maintain upright	Wobbles	All the time upright		
Rolling	No rolling	Rolling to side	Prone to supine	Supine to prone	
Sitting	Cannot sit	Sit with support at hips	Props	Stable sit	Pivots (rotates)
Crawling	Does not lift head	On elbow	On outstretched hand	Crawling flat on abdomen	On hands and knees
Standing	Does not support weight	Supports weight	Stands with support	Stands unaided	
Walking	No walking	Bouncing	Cruising (walks holding on)	Walking independently	

Improvement

Improvement

Improvement: ≥2-point improvement in ability to kick (or maximal score), or ≥1-point improvement in any other milestone, excluding voluntary grasp

Worsening: ≥2-point worsening in ability to kick (or zero score), or ≥1-point worsening in any other milestone, excluding voluntary grasp

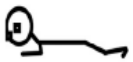
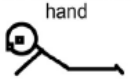
- **Motor milestone responder definition[a]:** more HINE categories with improvement than worsening
  - Participants who die or withdraw are counted as non-responders

Características de la población ENDEAR

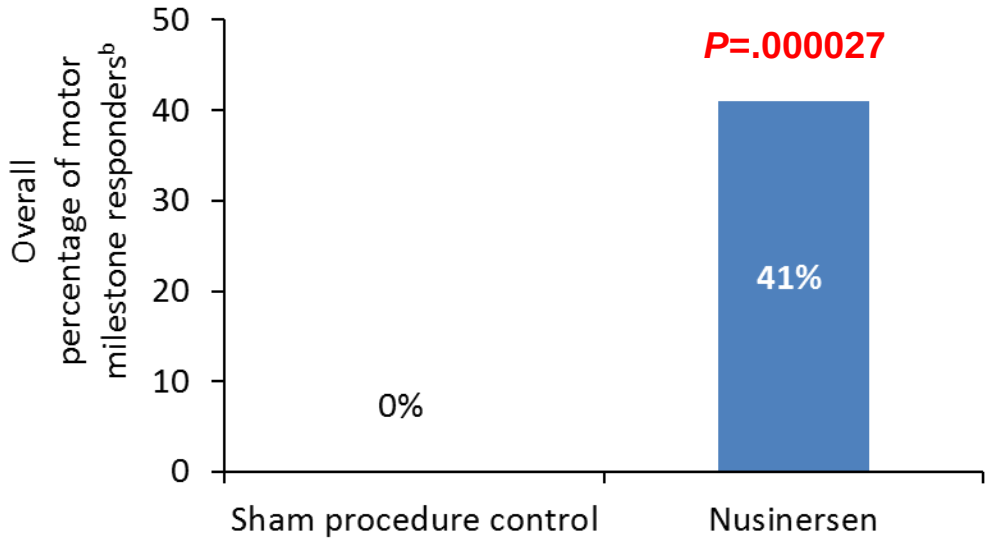
Characteristic	Sham procedure control n=41	Nusinersen n=80
Female, n (%)	24 **(59)**	43 **(54)**
Median age at first dose, d	205	165
Median age at symptom onset, wk	8.0	6.5
Median age at SMA diagnosis, wk	20.0	11.0
Median disease duration, wk	12.7	13.1
SMA symptoms, n (%)		
Hypotonia	41 **(100)**	80 **(100)**
Developmental motor delay	39 **(95)**	71 **(89)**
Paradoxical breathing	27 **(66)**	71 **(89)**
Pneumonia or respiratory symptoms	9 **(22)**	28 **(35)**
Limb weakness	41 **(100)**	79 **(99)**
Swallowing or feeding difficulties	12 **(29)**	41 **(51)**
Other	14 **(34)**	20 **(25)**
Participants requiring ventilation support, n (%)	6 **(15)**	21 **(26)**

Resultados SMA-1. ENDEAR (ISIS 396443)

- Análisis preliminar
  a los 6 meses
- Sham: 41 casos
- Tratados: 80 casos
- ANALISIS DE
  Hammesmith(HINE), s.2

Head control	Unable to maintain head upright normal up to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)  normal at 3m	Touches leg  normal at 4-5m	Touches toes  normal at 5-6m
Rolling	No rolling	Rolling to side (normal at 4m)	Prone to supine (normal at 6 m)	Supine to prone (normal at 6 m)	
Crawling or bottom shuffling	Does not lift head	On elbow  (normal at 3 m)	On outstretched hand  (normal at 4m)	Crawling flat on abdomen  (normal at 8m)	Crawling on hands and knees  (normal at 10m)
Standing	Does not support weight	Supports weight (normal at 4m)	Stands with support (normal at 7m)	Stands unaided (normal at 12m)	
Walking		Bouncing (normal at 6m)	Cruising (walks holding on) (normal at 12m)	Walking independently (normal by 15m)	

Mejora escala Hamersmith HINE
interim analysis

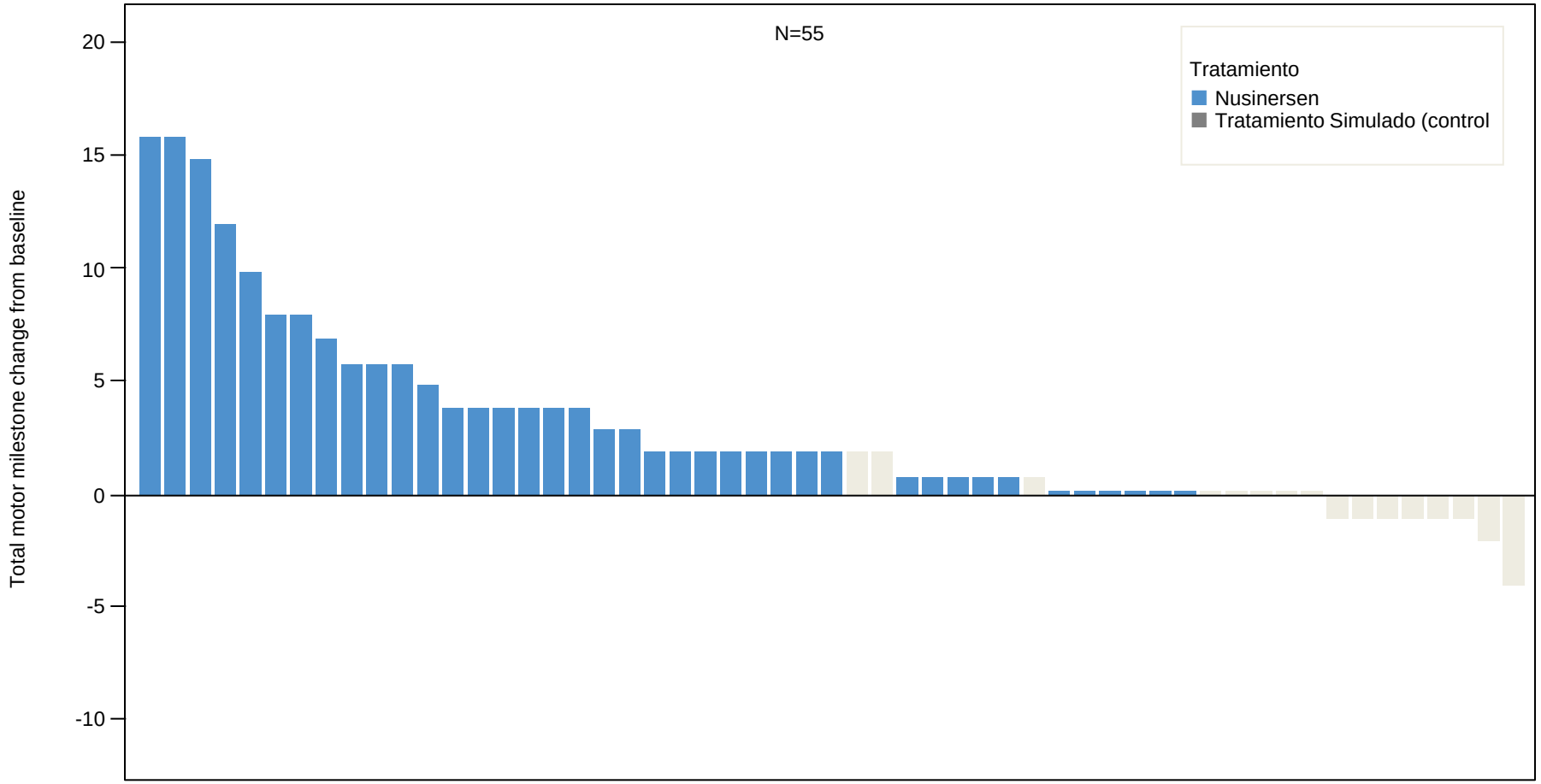


DECISION: Todos pasan a recibir el fármaco

APROBACION DEL USO COMPASIVO DEL FARMACO

Cambio total en la puntuacion HINE

- Los tratados con nusinersen tienen mayor beneficio que los controles



EVOLUCION NATURAL AME-I

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Developmental milestones in type I spinal muscular atrophy

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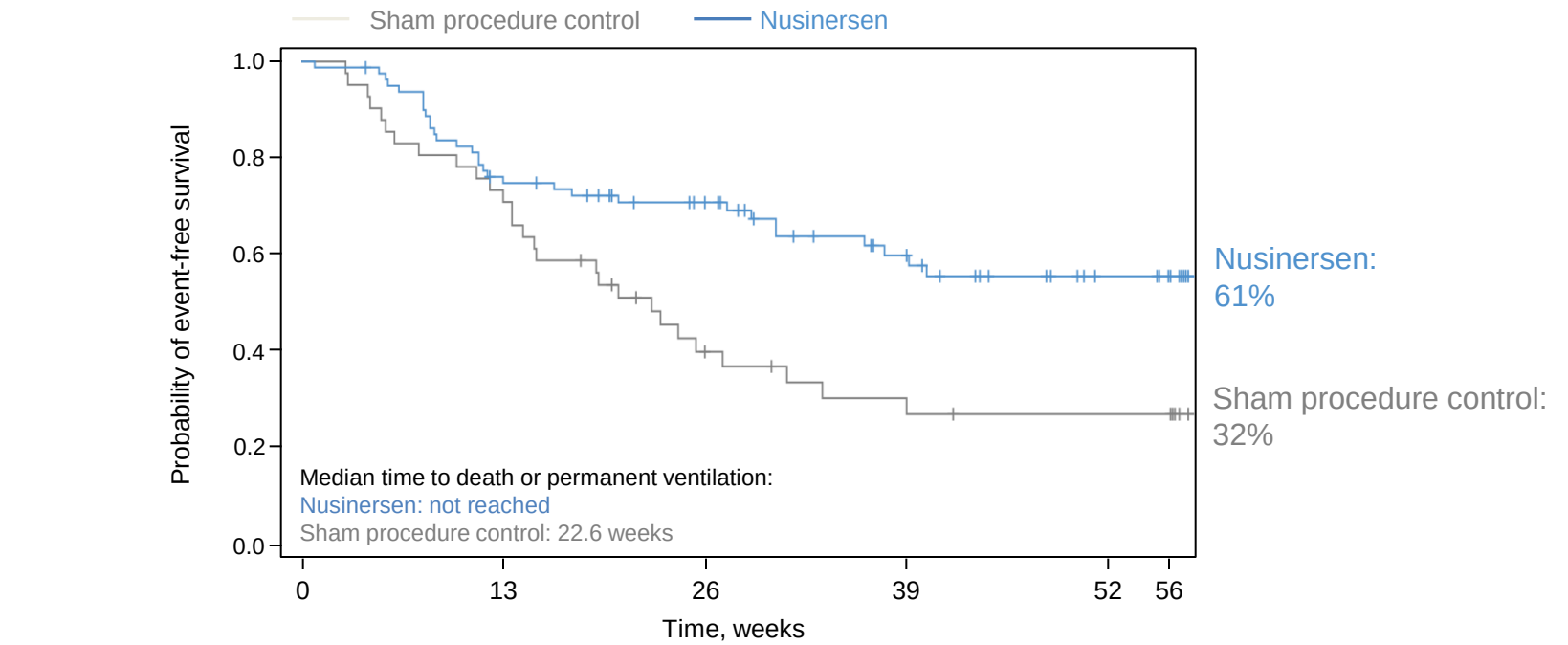
Abstract

The aim of this retrospective multicentric study was to assess developmental milestones longitudinally in type I SMA infants using the Hammersmith Infant Neurological Examination. Thirty-three type I SMA infants, who classically do not achieve the ability to sit unsupported, were included in the study. Our results confirmed that all patients had a score of 0 out of a scale of 4 on items assessing sitting, rolling, crawling, standing or walking. A score of more than 0 was only achieved in three items: head control (n = 13), kicking (n = 15) and hand grasp (n = 18). In these items, the maximal score achieved was 1 out of a scale of 4, indicating only partial achievement of the milestone. Infants with symptom onset after 6 months of age had longer preservation of a score of 1 when compared to those with onset before 6 months of age. Our results suggest that even when current standards of care are applied, developmental milestones are rarely even partially achieved as part of natural history in type I SMA infants. No infants in this study achieved a major milestone such as rolling over, or sitting independently, which would therefore represent robust outcomes in future interventional trials.

Resultados SMA-1. ENDEAR (ISIS 396443)

Supervivencia y sin ventlación permanente:

Diferencia Significativa (HR, 0.53; *P*=.0046)



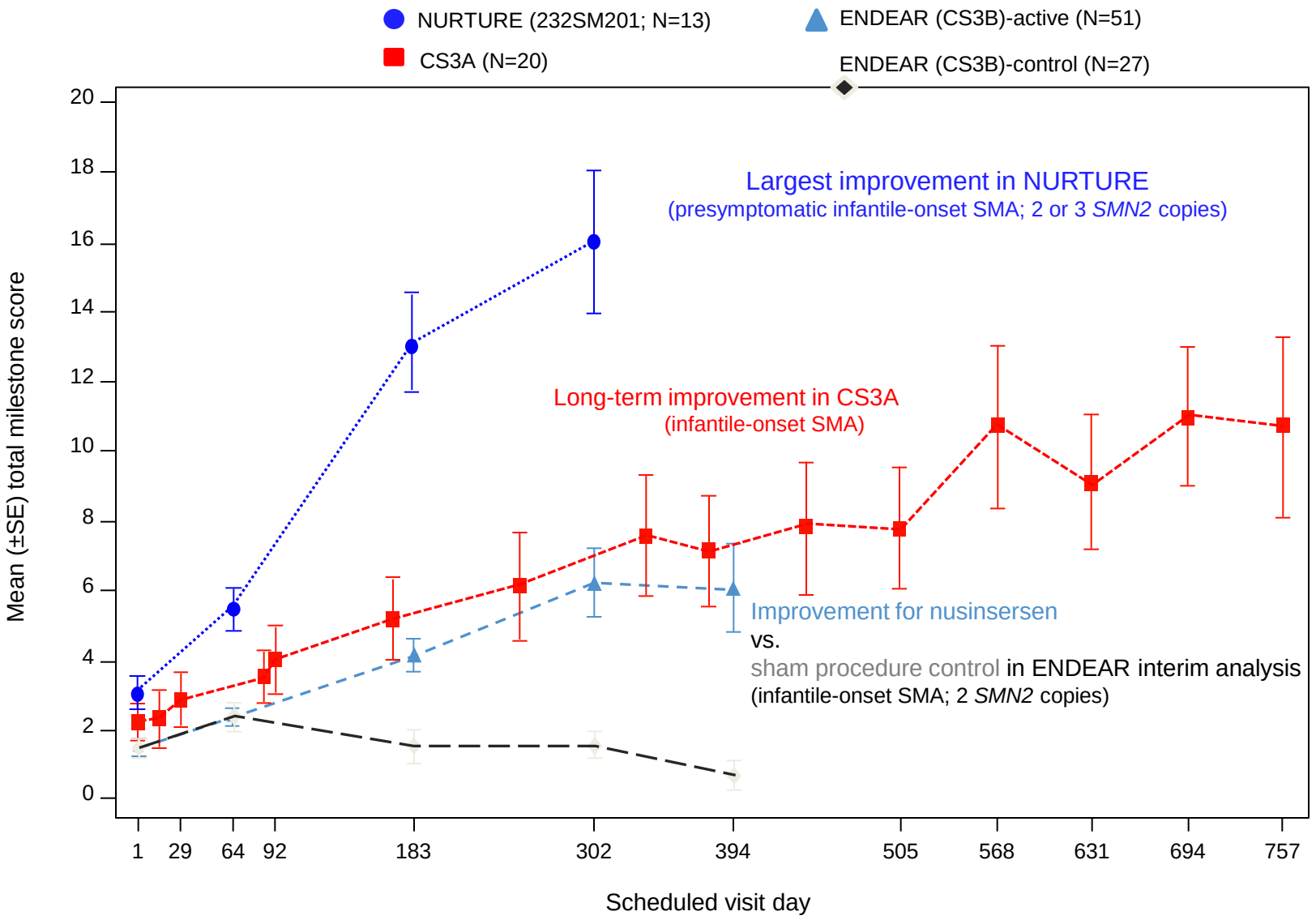
Outcome	Sham procedure control	Nusinersen
Death or permanent ventilation, n (%)	28 (68%)	31 (39%)
Alive and no permanent ventilation, n (%)	13 (32%)	49 (61%)

EFECTOS ADVERSOS.- FASE III ENDEAR (ISIS 396443)

- No EAs ni EAs importantes (serious) que se consideraran relacionados con el tratamiento por el investigador
- Todas las retiradas del tratamiento fueron por fallecimiento

AE, n (%)	Sham procedure control n=41	Nusinersen n=80
Any AE	40 **(98)**	77 **(96)**
AEs leading to discontinuation	16 **(39)**	13 **(16)**
Treatment-related AE[a]	0	0
Possibly treatment-related AE[a]	6 **(15)**	9 **(11)**
Severe AE	33 **(80)**	45 **(56)**
Serious AE	39 **(95)**	61 **(76)**
Serious AE with fatal outcome	16 **(39)**	13 **(16)**
Respiratory, thoracic and mediastinal disorders	12 **(29)**	7 **(9)**
Cardiac disorders	3 **(7)**	2 **(3)**
General disorders	1 **(2)**	2 **(3)**
Nervous system disorders	0	2 **(3)**

Cambio en la puntuación HINE en los estudios con nusinersen



CONCLUSION

Vemos un futuro más optimista en la AME

Es incluso más importante el diagnóstico precoz

Muchas gracias

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