



SITUACIÓN ACTUAL DE LOS ENSAYOS CLÍNICOS EN LA ATROFIA MUSCULAR ESPINAL

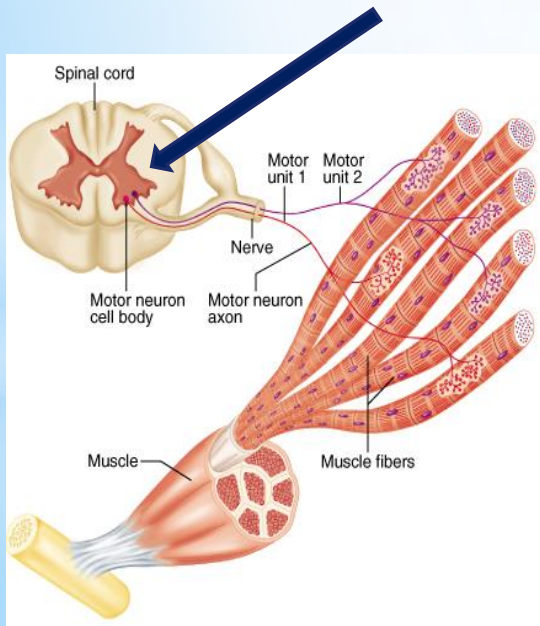
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Hospital Universitario Vall d'Hebron
Barcelona**

AME ES LA ENFERMEDAD GENÉTICA DE MAYOR MORTALIDAD EN LACTANTES Y NIÑOS

➤ Enfermedad neuromuscular severa caracterizada por:

- Pérdida de neuronas motoras de la médula espinal, atrofia muscular y pérdida de función motora
- Se estima que existen unos 30.000 pacientes en Europa, EEUU y Japón

Motoneurona



- La enfermedad está causada por la **pérdida o mutación del gen SMN1** (herencia autosómica recesiva, portador 1/50)
- La proteína SMN actúa regulando la biogénesis y el ensamblaje de snRNPs (alteración de splicing en un pequeño número de genes críticos)
- Los humanos tenemos un segundo gen, **SMN2**, que sufre una alteración de splicing y da lugar a una **proteína defectuosa** (~90%)
- Un número de copias variable de **SMN2** generalmente **se correlaciona con la severidad de la AME**, debido a la cantidad de proteína SMN residual efectiva

AME: Clasificación clínica/Pronóstico

Edad de inicio síntomas

TIPO 0 : Congénita

TIPO I : Werdnig-Hoffmann

TIPO II : Forma Intermedia

TIPO III : Kugelberg -Welander

TIPO IV : Adulto

0 m

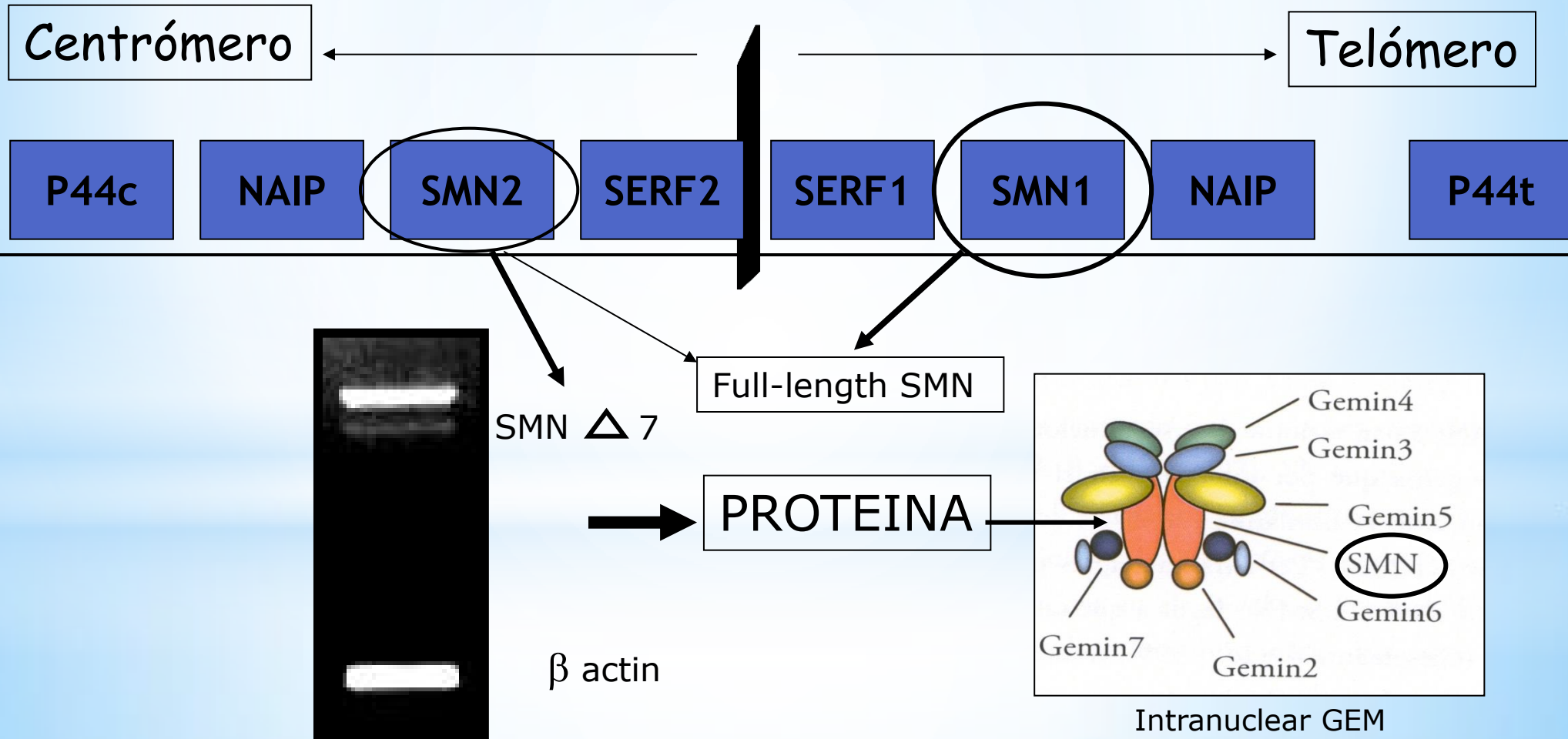
6 m

18 m

Type	Debut	The maximum motor function acquired	Life expectancy
0	prenatal	Requires ventilation support at birth	fatal without support
1	< 6 months	Does not sit Sits only with support	< 2 years
2	6 – 18 months	Sits independently Does not walk independently	10 – 40 years
3a	18 months - 3 years	Walks without support approximately 25 steps	indefinite
3b	> 3 years		
4	> 5 years	Walks normally	indefinite

SMN: SURVIVAL MOTORNEURON GENE

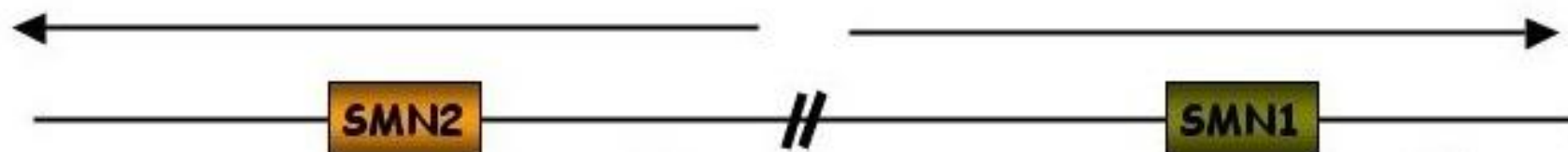
Gen duplicado e invertido (Cr 5 q11.2-13.3)



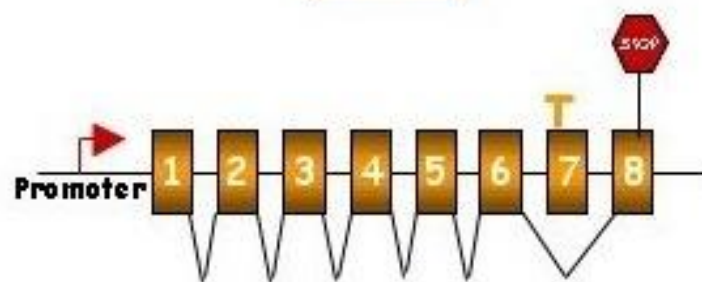
SMN2

SMN1

DNA (a)



RNA (b)



mRNA (c)



protein

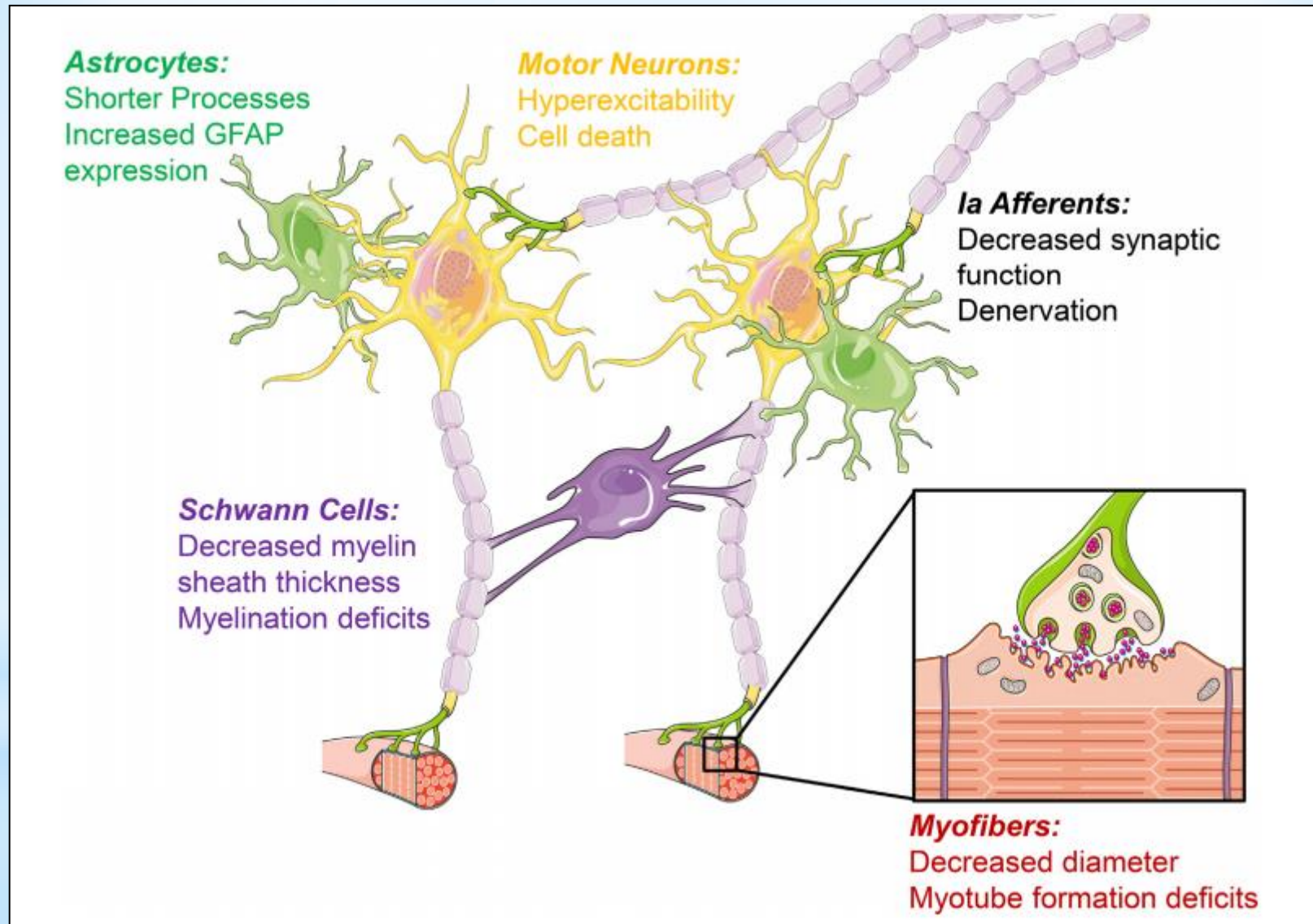


unfunctional
protein



functional
protein

TIPOS DE CÉLULAS IMPLICADAS EN LA SUPERVIVENCIA DE LAS MOTONEURONAS



Mecanismos candidatos y posibilidades terapéuticas para AME

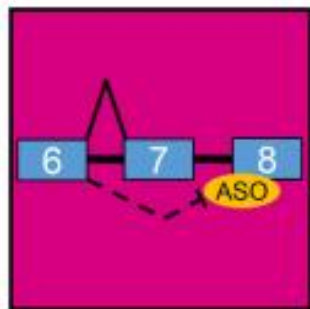
Treatment	Process	Models used	References
<i>Histone deacetylase inhibitors</i>			
Trichostatin A	Transcription	$\Delta 7$ SMA mice	[68,69]
Suberoylanilide hydroxamic acid	Transcription	Taiwanese mice	[80]
Sodium butyrate	Transcription	Taiwanese mice	[81]
Valproic acid	Transcription	Taiwanese mice	[90]
<i>Translation read-through compounds</i>			
G418 (geneticin)	Translation	$\Delta 7$ SMA mice	[65]
TC007	Translation	$\Delta 7$ SMA mice	[66,67]
<i>Quinazolines</i>			
RG3039	Transcription	$\Delta 7$ SMA mice	[63]
		Taiwanese mice	[79]
		2B	[79]
D156844	Transcription	$\Delta 7$ SMA mice	[64]
<i>Other small molecules that increase SMN2 expression</i>			
LDN-76070	Transcription	$\Delta 7$ SMA mice	[54]
Indoprofen	Splicing and/or translation	Line 89	[109]
<i>Antibiotics</i>			
Ceftriaxone	Cell signaling	$\Delta 7$ SMA mice	[60]
PTK-SMA1 (tetracycline-like)	Splicing	Taiwanese mice	[110]
<i>Signal transducing molecules</i>			
Sodium vanadate	Splicing	Taiwanese mice	[117]

Treatment	Process	Models used	References
<i>Neuroprotective compounds</i>			
BIP-135	Cell signaling	$\Delta 7$ SMA mice	[58]
N-Methyl-D-aspartic acid	Cell signaling	$\Delta 7$ SMA mice	[59]
Riluzole	Cell signaling	F7 or exon 7 floxed	[121]
<i>Polypeptides and proteins</i>			
Insulin-like growth factor 1	Cell signaling	$\Delta 7$ SMA mice	[57]
Follistatin	Cell signaling	$\Delta 7$ SMA mice	[61]
Prolactin	Transcription	$\Delta 7$ SMA mice	[62]
<i>Gene therapy and trans-splicing</i>			
SMN1 gene therapy	SMN-associated functions	$\Delta 7$ SMA mice	[70-75]
		Taiwanese mice	[82]
Trans-splicing	Splicing	$\Delta 7$ SMA mice	[133]
<i>Stem cell based therapy of SMA</i>			
Stem cell transplantation	SMN-associated functions	$\Delta 7$ SMA mice	[55,56]
<i>SMN-independent treatment strategies</i>			
Forced running	Multiple	$\Delta 7$ SMA mice	[148]
		Taiwanese mice	[78]
<i>ASO-based therapy</i>			
Antisense oligonucleotides	Splicing	$\Delta 7$ SMA mice	[50-53]
		Taiwanese mice	[76,77]

ESTRATEGIAS TERAPÉUTICAS EN AME

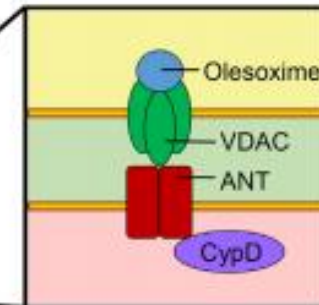
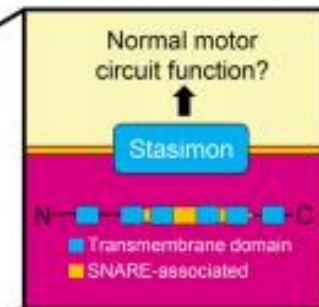
Antisense oligos or small molecules:

Promote exon 7 inclusion in SMN2



AAV vectors: Express full-length SMN

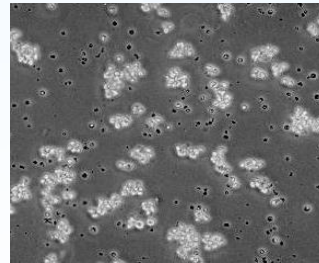
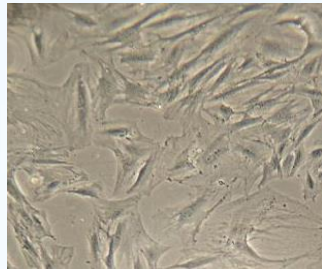
Targets downstream of SMN: Restore proteins lost due to splicing defect



Neuroprotective agents: Inhibit cell death; enhance regeneration

Estudios en células de pacientes en cultivo

*Fibroblastos (piel) y linfoblastos (sangre)



Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy

L. Brichth^{1,2}, Y. Hofmann¹, E. Hahnen³, F. A. Siebzehn¹, H. Raschke¹, I. Blumcke³, I. Y. Eyupoglu⁴ and B. Wirth^{1,2,*}

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Received May 8, 2003; Revised and Accepted July 25, 2003

Hydroxyurea Enhances SMN2 Gene Expression in Spinal Muscular Atrophy Cells

Susanna M. Grzeschik, PhD,¹ Madhuri Ganta, PhD,¹ Thomas W. Prior, PhD,² William D. Heavlin, PhD,³ and Ching H. Wang, MD, PhD¹

Phenylbutyrate increases SMN expression *in vitro*: relevance for treatment of spinal muscular atrophy

Catia Andreassi¹, Carla Angelozzi¹, Francesco D Tiziano¹, Tiziana Vitali¹, Eleonora De Vincenzi¹, Alma Boninsegna², Marcello Villanova³, Enrico Bertini⁴, Antonella Pini⁵, Giovanni Neri¹ and Christina Brahe^{*,1}

Downloaded from jmg.bmj.com on 2 June 2009

Short report

Salbutamol increases SMN mRNA and protein levels in spinal muscular atrophy cells

C Angelozzi, F Borgo, F D Tiziano, A Martella, G Neri, C Brahe

TRATAMIENTO CON CÉLULAS MADRE (MEDICINA REGENERATIVA)

El trasplante intratecal de células sanas de donante a la médula espinal de pacientes con AME podría compensar la degeneración de las motoneuronas endógenas

Dos estudios principales:

1. Células madre neurales de la médula espinal inyectadas en LCR aumentaron la supervivencia del ratón $\Delta 7$ SMA en un 39%
2. El trasplante intratecal de células madre neurales de células madre embrionarias aumentaron el número y el tamaño de las motoneuronas, mejoraron la inervación y aumentaron la supervivencia media del ratón $\Delta 7$ en un 64%
3. El trasplante de células satélite podría ser una buena estrategia como tratamiento coadyuvante (las células satélite de los pacientes con AME tiene una capacidad regenerativa disminuída). No hay evidencias preclínicas suficientes por el momento

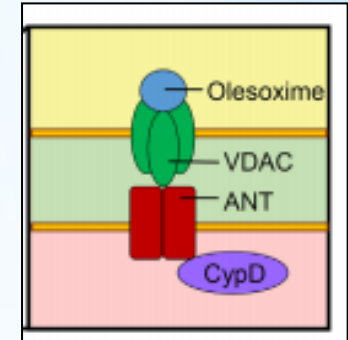
Son resultados **modestos pero prometedores**

Medicamentos que aumentan SMN2

- Se usaban para tratar otros problemas y enfermedades
- No estaba claro su efecto directo sobre las neuronas motoras
- Había mucha variabilidad individual en la respuesta: respondedores y no respondedores
- Los ensayos clínicos no han sido categóricos para decir que ha habido un beneficio claro para los pacientes

TRATAMIENTO CON COMPUESTOS NEUROPROTECTORES

Ensayo clínico fase 2/3 con OLESOXIME (TRO19622)



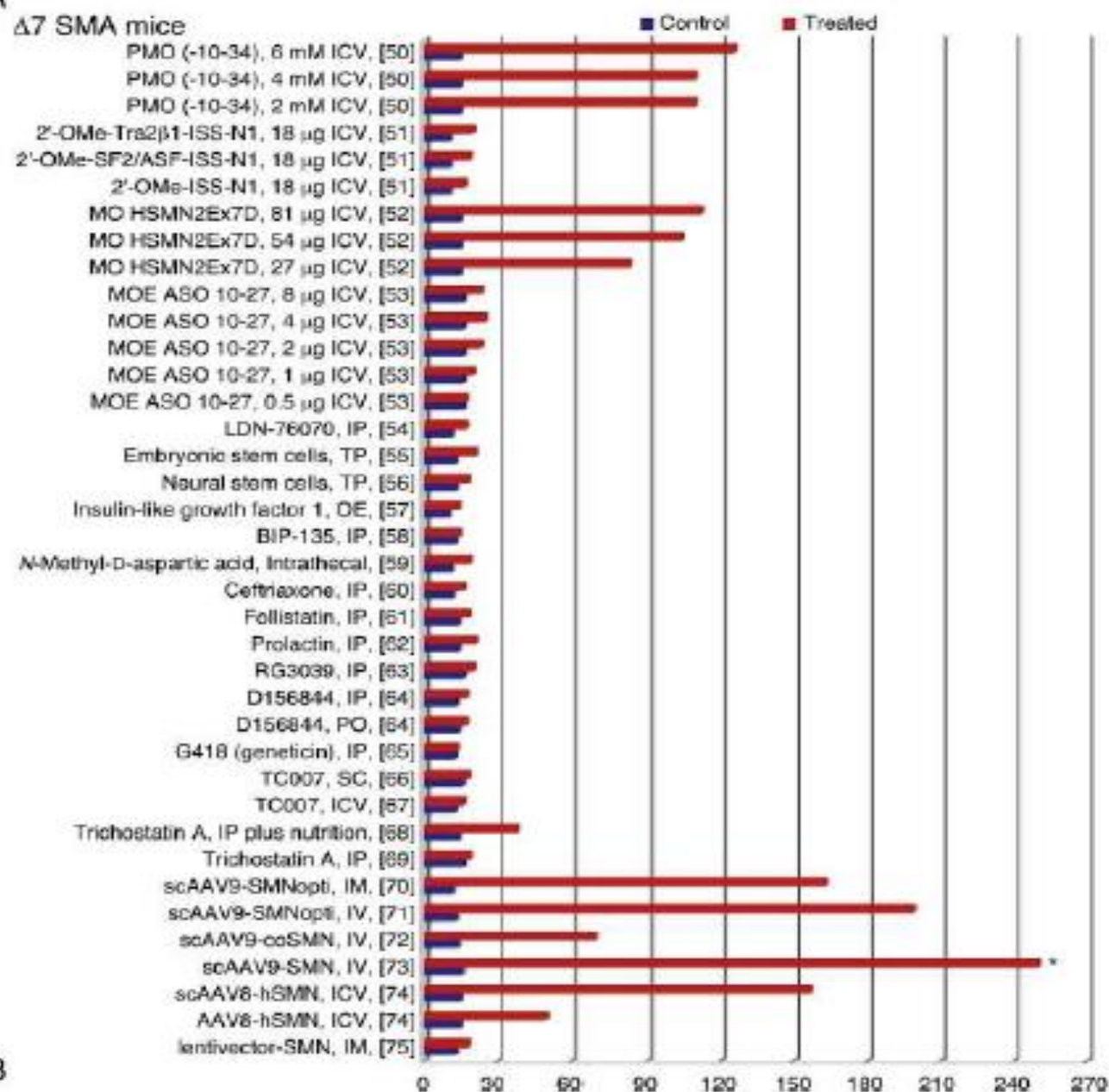
Olexosime se une a dos componentes del poro de transición de permeabilidad mitocondrial: VDAC (canal aniónico dependiente de voltaje) y TSPO (proteína translocadora) e impide la salida de citocromo C.

Su acción contribuiría en el bloqueo de la progresión (no curación)

165 pacientes, 22 centros en 7 países europeos

Demora de 2 años en la pérdida de función motora en pacientes con AME tipo II y tipo III no deambulantes

A

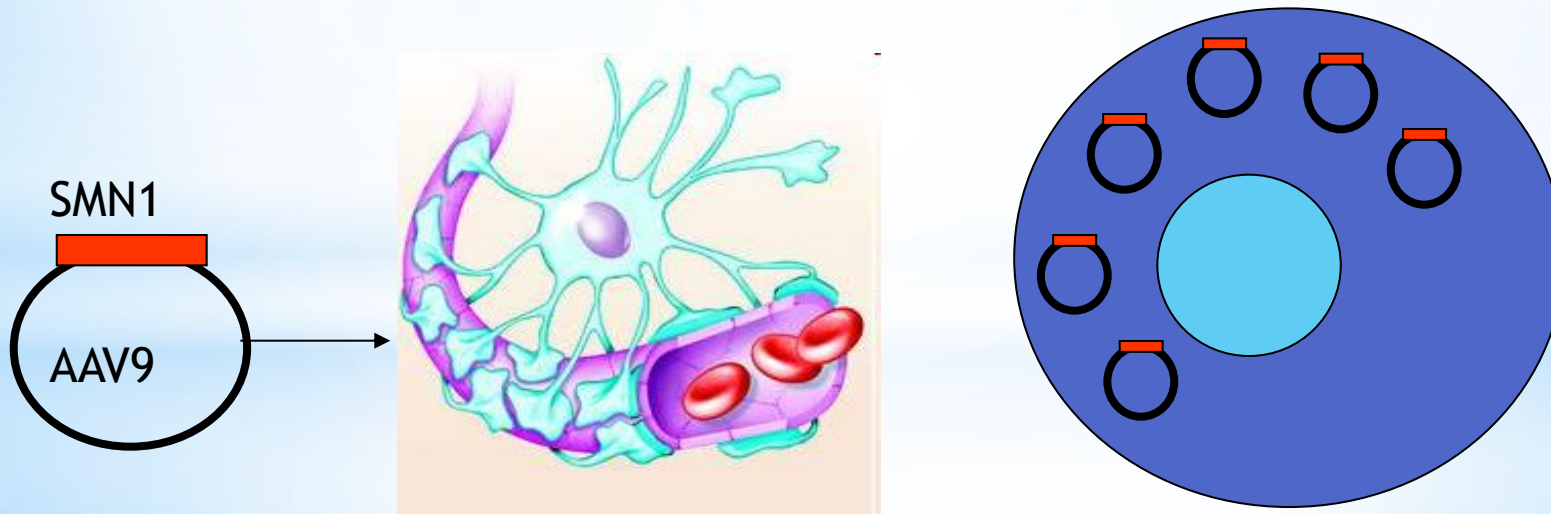
 $\Delta 7$ SMA mice

B

TERAPIA GÉNICA

- Solución permanente mediante la introducción e inserción del gen SMN1 completo o de la secuencia de cDNA en el genoma de pacientes con AME mediante vectores virales
- Proceso irreversible no exento de riesgos (problemas de inserción y/o sobreexpresión)

AAV9 que cruza la barrera hematoencefálica



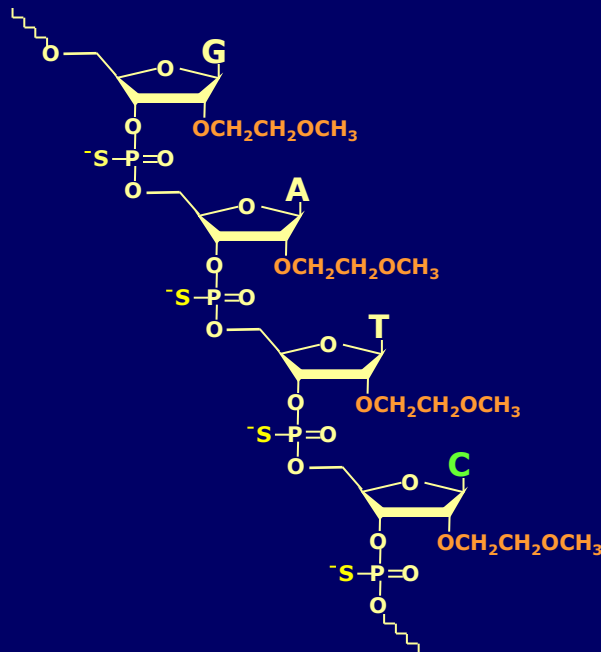
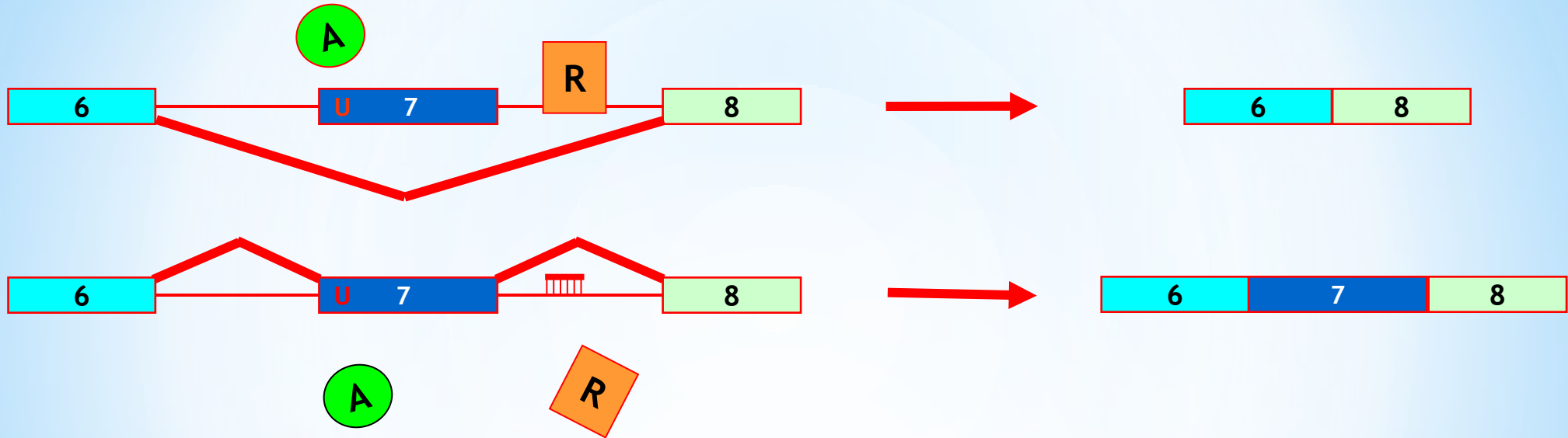
TERAPIA GÉNICA

- **Administración IV** del gen SMN1 humano entero al ratón $\Delta 7$ SMA, confirió alguna protección a las motoneuronas del tronco del encéfalo y aumento la esperanza de vida de 13 a 18 días -> resultado modesto pero significaba evidencia real de los beneficios terapéuticos (Azzouz 2004).
- **Administración ICV del gen** SMN1 (vector AAV9): aumento sustancial de la vida media del ratón $\Delta 7$ SMA (x10, de 15 a 150d) (Passini 2010)-> aumento de los niveles de SMN en el cerebro crucial para prolongar la vida de los pacientes !!
- Numerosos estudios de administración de SMN1 IV han demostrado resultados impresionantes en ratones sin embargo algunos no han sido tan buenos
- Precaución en la extrapolación de resultados de estudios pre-clínicos !!

RESULTADOS PROMETEDORES

BUENA ALTERNATIVA PARA PACIENTES DEMASIADO DEBILES PARA TOLERAR TRATAMIENTOS INVASIVOS REPETITIVOS

Método para aumentar la inclusión del exon 7



2'-O-(2-methoxyethyl) ribose

phosphorothioate

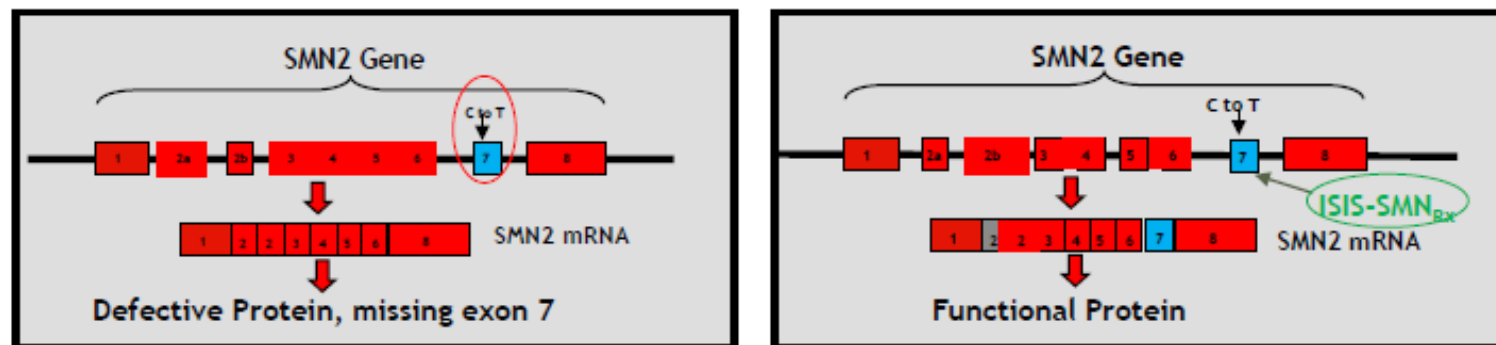
5-methyl cytosine



ISIS-SMNRx: Modulador de splicing de SMN2 cuya finalidad es aumentar la proteína SMN

Compuesto antisentido 2'-O-methoxyethyl modificado (MOE)

- Corrige la alteración de splicing de SMN2, dando lugar a la producción de una proteína entera y funcional en los modelos animales
- Su administración intratecal en los modelos murinos de AME leve y severa produce un beneficio fenotípico
- Tras su administración intratecal se distribuye ampliamente por la medula espinal en primates
- Tiene un tiempo de vida media larga en el SNC (>6 meses en modelos animales)



*(Hua et al., Genes Dev., 2010; Passini et al., Sci Transl Med, 2011; Hua et al., Nature, 2011)

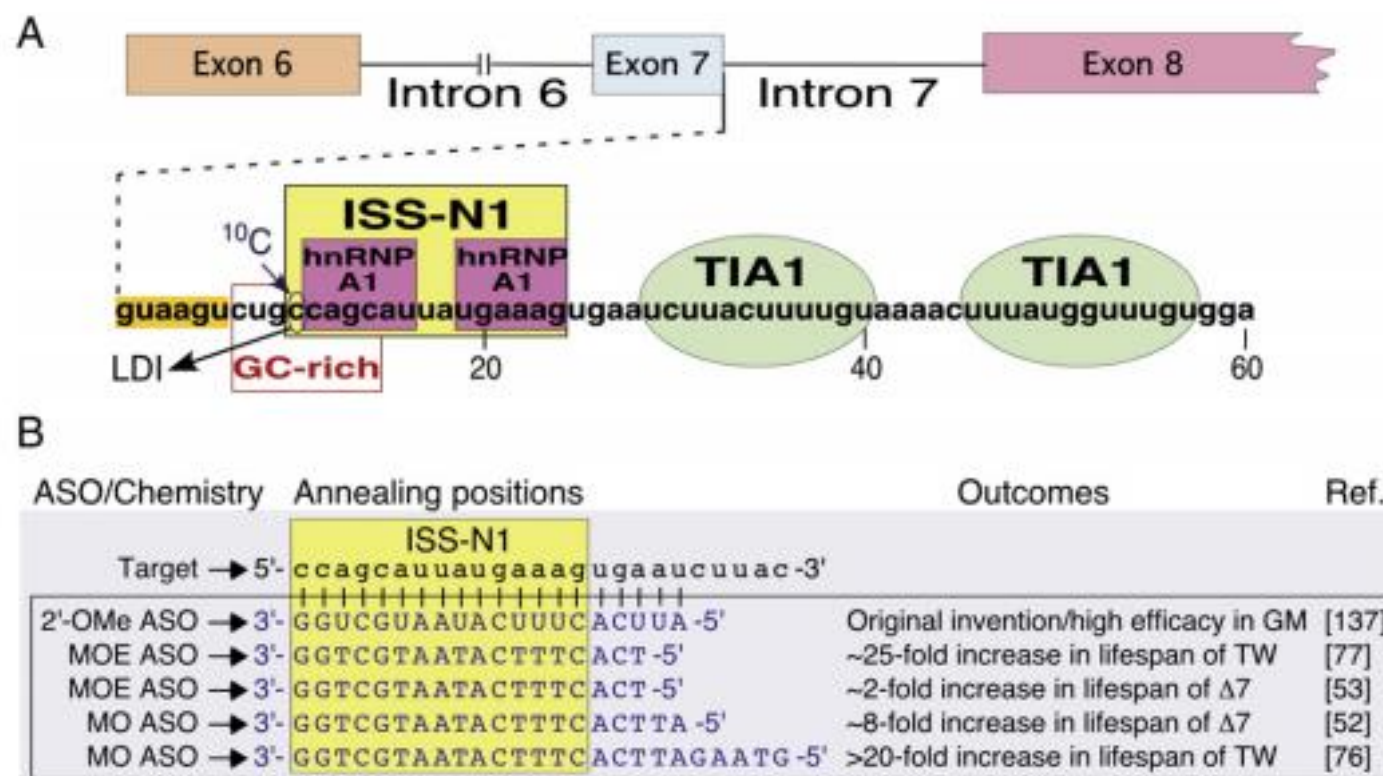
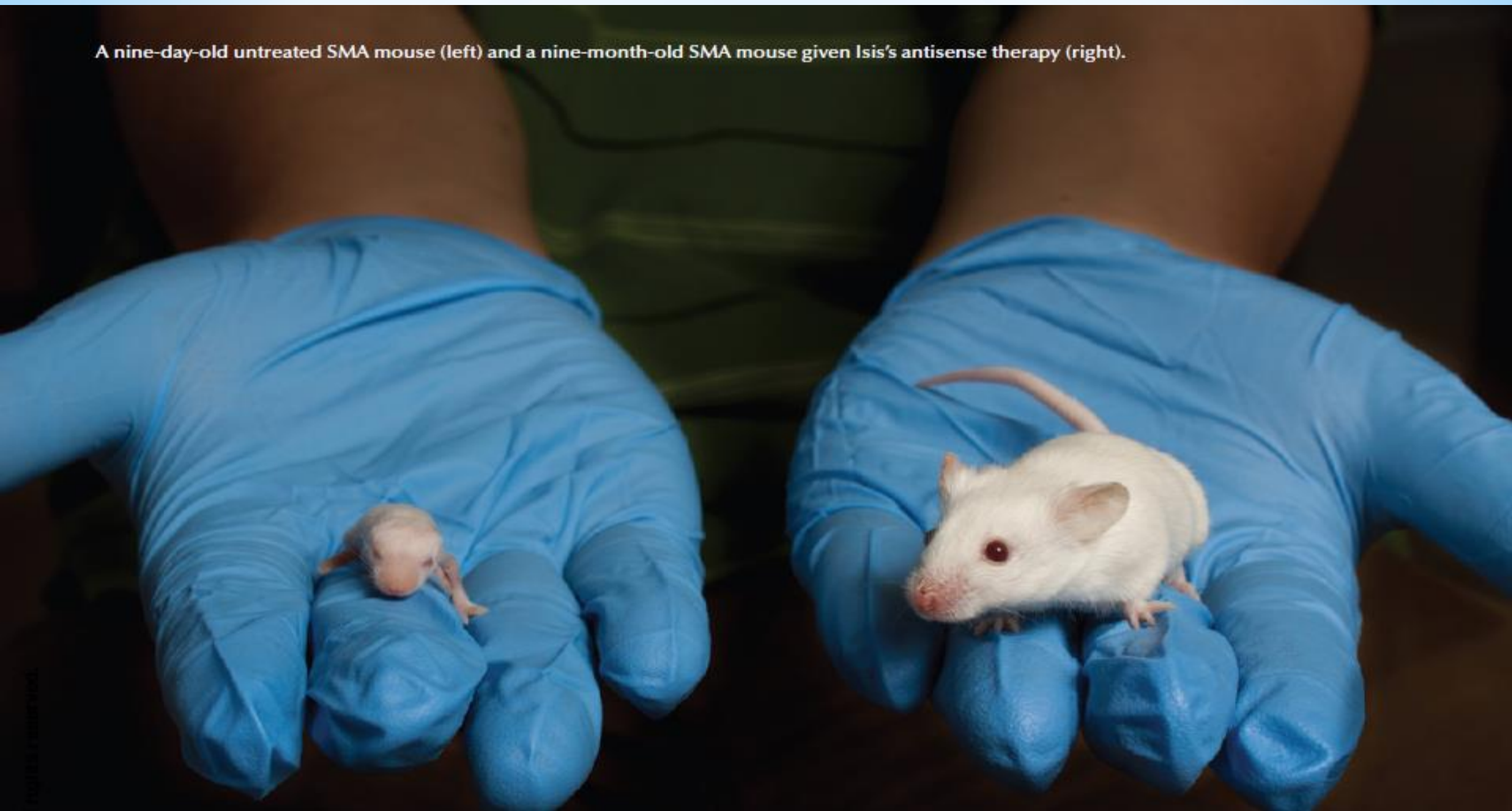


Fig. 2. ASO-mediated *SMN2* splicing correction as a therapy for SMA. (A) Diagrammatic representation of splicing cis-elements in *SMN2* intron 7. Numbering begins from the first position of intron 7. The negative cis-element ISS-N1 (yellow box) contains two hnRNP A1 binding sites (magenta boxes) and has emerged as a leading ASO target for splicing correction in SMA. Green ovals represent binding sites for TIA1, an enhancer of exon 7 splicing. (B) Representative ISS-N1-targeting ASOs tested in SMA mouse models. Intron 7 sequence is in lower caps and ASO sequences are in upper caps. The chemistry for each ASO is listed to the left of the sequence. The outcomes for studies in which the ASOs were tested are listed to the right of the sequence; references are denoted in brackets. Abbreviations: ASO, antisense oligonucleotide; ISS-N1, intronic splicing silencer N1; hnRNP A1, heterogeneous ribonucleoprotein A1; TIA1, T-cell restricted intracellular antigen 1; LDI, long-distance interaction; 2'-OMe, an ASO with phosphorothioate backbone and 2'-O-methyl modification; MOE, an ASO with phosphorothioate backbone and 2'-O-methoxyethyl modification; MO, morpholino; GM, SMA patient fibroblast cells (cell line GM03813); TW, Taiwanese SMA mouse model; Δ7, Δ7 SMA mouse model.

A nine-day-old untreated SMA mouse (left) and a nine-month-old SMA mouse given Isis's antisense therapy (right).

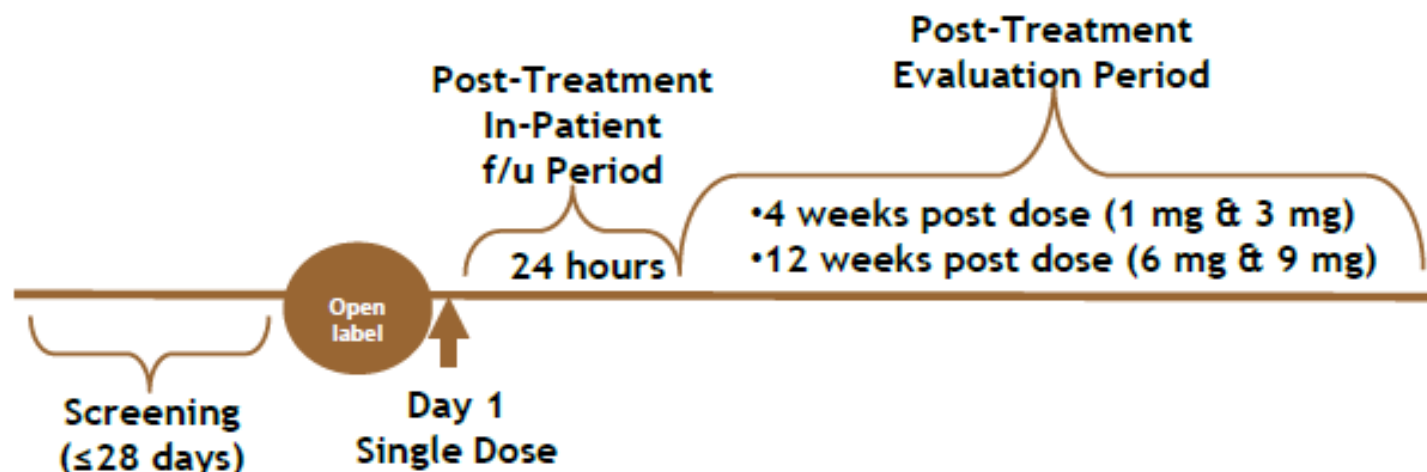


Phase 1 Open-label, Single-dose Study in Medically Stable SMA Patients 2-14 Years of Age

Objective: To evaluate the safety, tolerability, and pharmacokinetics of a single dose of ISIS-SMN_{Rx} administered intrathecally to patients with Spinal Muscular Atrophy

- Single dose given intrathecally as an LP bolus injection in male and female SMA patients 2-14 years old who are medically stable
- **Primary endpoints:**
 - Safety/tolerability
 - CSF and plasma drug level pharmacokinetics
- **Exploratory efficacy endpoints** included to gain experience with these endpoints

Cohorts	n
1 mg	6
3 mg	6
6 mg	6
9 mg	10



Phase 1 Open-label, Single-dose Study in Medically Stable SMA Patients 2-14 Years of Age

Objective: To evaluate the safety, tolerability, and pharmacokinetics of a single dose of ISIS-SMN_{Rx} administered intrathecally to patients with Spinal Muscular Atrophy

- **ISIS-SMN_{Rx} was well tolerated at all dose levels - no safety or tolerability concerns were identified**
- **The LP injection procedure was shown to be feasible in SMA children**
- **CSF and plasma drug concentrations were dose-dependant**
 - Observations were consistent with preclinical data, thus support infrequent administration (i.e. every 6-9 months)
- **Improvement in HFMSE scores observed at the highest dose level**
 - Interpret with caution due to open-label nature of the study and small number of subjects
- **Electrophysiology measurements in highest dose cohort at 3 months demonstrated increase in MUNE with stable CMAP**
- **Ongoing multiple-dose study with additional endpoints and longer follow-up will provide more data on safety and potential efficacy**
- **Controlled Phase 2/3 registration-enabling studies in infants and children with SMA are being planned**

ISIS 396443

FASE III en AME tipo I (111 pacientes) y AME tipo II-III (117 pacientes)

- * Estudio de fase 3 multicéntrico, doble-ciego, randomizado, controlado con placebo
- * Duración total de participación en el estudio es de 14-16 meses
- * Los sujetos se randomizan 2:1 para recibir dosis de 12 mg de ISIS 396443 o procedimiento placebo, respectivamente.
- * ISIS 396443 se administra los días 1, 15, 29 y 64 y dosis de mantenimiento a los 4 meses (día 183/302).

A Study to Assess the Efficacy and Safety of ISIS-SMN Rx in Infants With Spinal Muscular Atrophy

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2015 by Isis Pharmaceuticals

Sponsor:

Isis Pharmaceuticals

Information provided by (Responsible Party):

Isis Pharmaceuticals

ClinicalTrials.gov Identifier:

NCT02193074

First received: July 14, 2014

Last updated: March 18, 2015

Last verified: March 2015

[History of Changes](#)

Full Text View

Tabular View

No Study Results Posted

[Disclaimer](#)

[? How to Read a Study Record](#)

Purpose

This study will test the Clinical Efficacy and Safety of ISIS-SMN Rx in patients with infantile-onset **Spinal Muscular Atrophy**.

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Spinal Muscular Atrophy	Drug: ISIS-SMN Rx Procedure: Sham procedure	Phase 3

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Primary Purpose: Treatment

Official Title: A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients With Infantile-onset **Spinal Muscular Atrophy**



A PHASE 3 CLINICAL STUDY OF ISIS-SMN_β IN PATIENTS WITH INFANT-ONSET SPINAL MUSCULAR ATROPHY



Primary Outcome Measures:

- Time to death or permanent ventilation [Time Frame: Up to 13 months] [Designated as safety issue: No]

Secondary Outcome Measures:

- Change from baseline in CHOP INTEND [Time Frame: At 13 months] [Designated as safety issue: No]
- Change from baseline in motor milestones [Time Frame: At 13 months] [Designated as safety issue: No]
- Percent of subjects not requiring permanent ventilation [Time Frame: Up to 13 months] [Designated as safety issue: No]
- Survival rate [Time Frame: Up to 13 months] [Designated as safety issue: No]
- Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration [Time Frame: Up to 13 months] [Designated as safety issue: No]
- Time to death or permanent ventilation in the subgroups of subjects above the study median disease duration [Time Frame: Up to 13 months] [Designated as safety issue: No]

Estimated Enrollment: 111
Study Start Date: July 2014
Estimated Study Completion Date: July 2017
Estimated Primary Completion Date: June 2017 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: ISIS-SMN Rx Administered by intrathecal injection	Drug: ISIS-SMN Rx Administered by intrathecal injection Other Name: ISIS 396443
Sham Comparator: Sham procedure Small needle prick on the lower back at the location where the IT injection is normally made	Procedure: Sham procedure Small needle prick on the lower back at the location where the IT injection is normally made



Soy un **luchador**

[Inicio](#) [Acerca de este estudio de investigación](#) [Mi niño elegible?](#) [FAQ](#) [Enlaces](#) [Información de contacto del sitio](#) [Acerca de los estudios de investigación](#)

Estudio de investigación clínica sobre la atrofia muscular
espinal

ISIS-SMN_{Rx}
Infant Phase 3 Study

Criterios de elegibilidad:

- Tener 7 meses (210 días) de edad o menos en el momento de la selección
- Haber nacido entre las 37 y 42 semanas
- Tener diagnosticada atrofia muscular espinal (AME) y tener 2 copias de SMN2
- No tener un historial de enfermedades cerebrales ni medulares que puedan interferir con los procedimientos de punción lumbar, la circulación del LCR o las evaluaciones de seguridad necesarias para el estudio
- Ser capaz de seguir todos los procedimientos del estudio
- Residir a menos de 9 horas de viaje/trayecto por tierra mientras dure el estudio
- Cumplir otros criterios adicionales relacionados con el estudio

Detailed Description:

This is a Phase 3 multicenter, double-blind, randomized, sham-procedure controlled study of ISIS-SMN Rx in patients with infantile-onset SMA. Subjects will be randomized 2:1 to receive ISIS-SMN Rx or a sham procedure control, respectively.

 Eligibility

Ages Eligible for Study: up to 210 Days
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Be 7 months (210 days) of age or younger at screening
- Be born (gestational age) between 37 and 42 weeks
- Be medically diagnosed with spinal muscular atrophy (SMA)
- Have SMN2 Copy # of 2
- Body weight equal to or greater than 3rd percentile for age using appropriate country-specific guidelines
- Be able to follow all study procedures
- Reside within 9 hours ground travel each way, for the duration of the study
- Meet additional study-related criteria

Exclusion Criteria:

- Hypoxemia (O2 saturation awake less than 96% or O2 saturation asleep less than 96%, without ventilation support) during screening evaluation
- Meet additional study-related criteria



A PHASE 3 CLINICAL STUDY OF ISIS-SMN_{Rx} IN PATIENTS
WITH LATER-ONSET SPINAL MUSCULAR ATROPHY

Log in

ISIS-SMN_{Rx}

Childhood Phase 3 Study

[Home](#) [About This Research Study](#) [Is my child eligible](#) [FAQ](#) [Links](#) [Site Contact Info](#) [About Research Studies](#)

Spinal Muscular Atrophy Medical Research Study

If your child has been diagnosed with Spinal Muscular Atrophy (SMA), you face a number of tough decisions. And while you work to better understand the best medical options for your child, you are likely experiencing emotions like fear, confusion, anger, and sadness.

Because of the physical and emotional toll SMA can have on your life, it can seem like an endless battle, but you, and your child, are fighters.

Right now, treatments for SMA are limited, which leads many parents of SMA children to consider medical research studies. This research study is evaluating the safety and effectiveness of an investigational medication for children diagnosed with SMA.

If your child has been diagnosed with SMA and you are considering medical research as an option, [click here](#) to learn more about this study.

ISIS-SMN_{Rx}

Childhood Phase 3 Study

Is my child eligible?

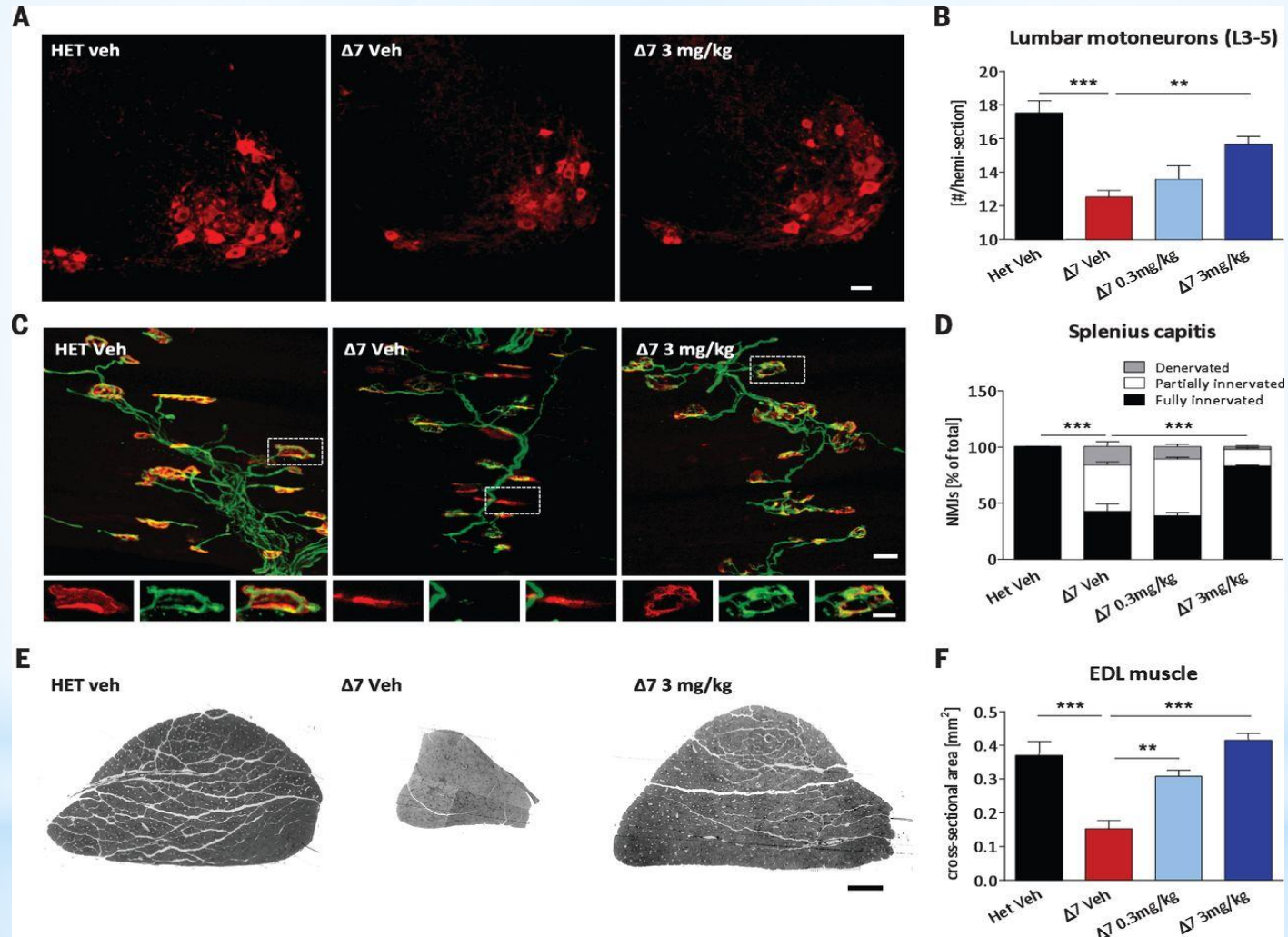
[Find out more](#)

Is My Child Eligible?

To qualify for this study, your child must:

- Be 2 to 12 years of age at screening
- Be medically diagnosed with spinal muscular atrophy (SMA)
- Have had onset of clinical signs and symptoms consistent with SMA at >6 months of age
- Be able to sit independently, but has never had the ability to walk independently
- Not have a medical need for ventilation for >6 hours during a 24 hour period, at screening
- Not have a medical need for a gastric feeding tube, where most feeds are given this way
- Not have severe contractures or severe scoliosis by X-ray examination at screening
- Not have been hospitalized for surgery (including scoliosis surgery), pulmonary event, or nutritional support within 2 months of screening or planned during the length of the study
- Not have an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period
- Not have a history of brain or spinal cord disease that would interfere with lumbar puncture procedures, CSF circulation, or safety assessments necessary for the study
- Not have an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Not have a history of bacterial meningitis
- Not have received this investigational medication in any previous clinical study
- Not have had a prior injury (e.g., upper or lower limb fracture) or surgical procedure which affects your child's ability to perform any of the outcome measure testing required in the protocol
- Not have been treated with another investigational drug, biological agent, or device within 1 month of screening
- Not have been treated with valproate or hydroxyurea within 3 months of screening
- Not have had gene therapy, antisense oligonucleotide therapy, or cell transplantation
- Be able to follow all study procedures
- Meet additional study-related criteria

SMN splicing modifiers prevent neuromuscular pathology in $\Delta 7$ mice. Animals were treated from P3 through P14 once daily with vehicle or SMN-C3 by intraperitoneal injection at 0.3 or 3 mg/kg.



Nikolai A. Naryshkin et al. Science 2014;345:688-693

A Study of RO6885247 in Adult and Pediatric Patients With Spinal Muscular Atrophy (MOONFISH)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified March 2015 by Hoffmann-La Roche

Sponsor:
Hoffmann-La Roche

Information provided by (Responsible Party):
Hoffmann-La Roche

ClinicalTrials.gov Identifier:
NCT02240355

First received: September 11, 2014
Last updated: March 23, 2015
Last verified: March 2015
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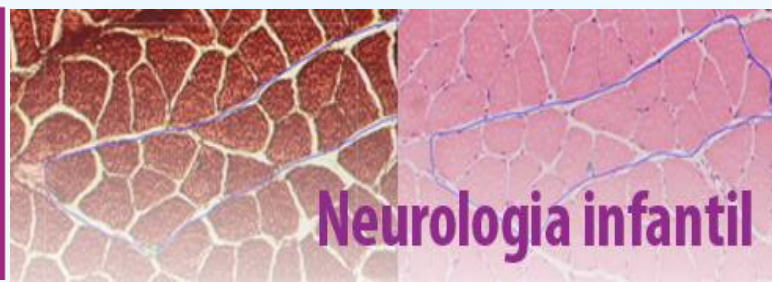
Purpose

This multicenter, randomized, double-blind, 12-week, placebo-controlled multiple dose study will investigate the safety and tolerability of RO6885247 in adult and pediatric patients with **spinal muscular atrophy** (SMA).

Condition	Intervention	Phase
Muscular Atrophy, Spinal	Drug: placebo Drug: RO6885247	Phase 1

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

Official Title: A Multicenter, Randomized, Double Blind, Placebo Controlled, Multiple Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO6885247 Following 12 Weeks of Treatment in Adult and Pediatric Patients With **Spinal Muscular Atrophy** (MOONFISH).



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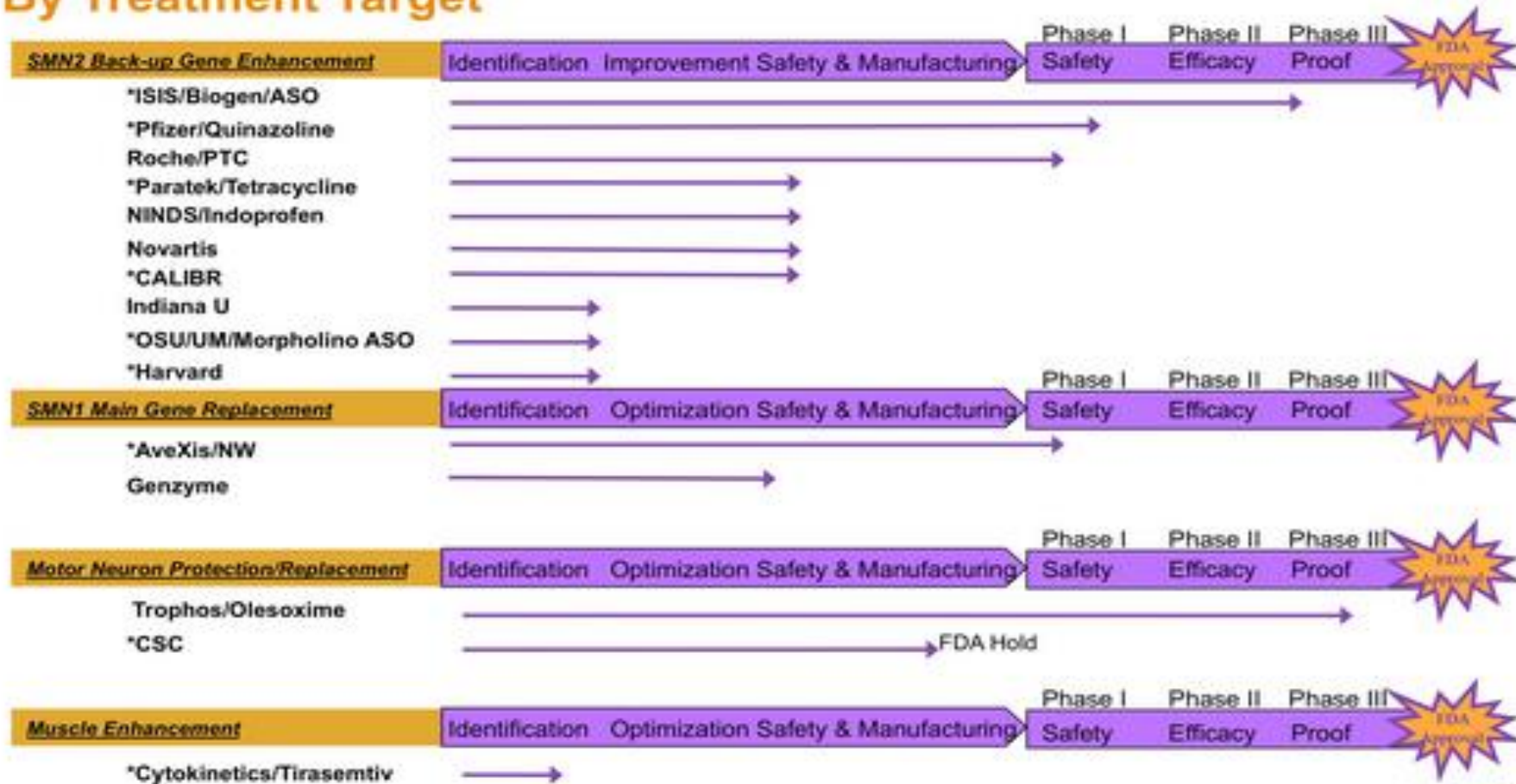
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SMA Drug Pipeline – June 2014

By Treatment Target



*Projects with Cure SMA Funding Involvement

cure
SMA

[Genetic and Rare Diseases Information Center](#) resources: [Spinal Muscular Atrophy](#) [Spinal Muscular Atrophy 1](#)

[U.S. FDA Resources](#)

Further study details as provided by Nationwide Children's Hospital:

Primary Outcome Measures:

- Safety Outcome Measure [Time Frame: 2 years] [Designated as safety issue: Yes]
Any one Grade III or higher treatment-related toxicity

Secondary Outcome Measures:

- Mortality [Time Frame: 2 years] [Designated as safety issue: No]
Time from birth to time of death
- Time-to-Event Outcome Measure [Time Frame: 2 years] [Designated as safety issue: No]
Time from birth to medically prescribed respiratory assistance required 16 hours per day or more.

Estimated Enrollment: 9
Study Start Date: April 2014
Estimated Study Completion Date: June 2017
Estimated Primary Completion Date: June 2017 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Cohort 1 Low dose: 6.7 X 10 ¹³ vg/kg of scAAV9.CB.SMN delivered one-time through a venous catheter inserted into a peripheral vein (n=3)	Biological: scAAV9.CB.SMN Self-complementary AAV9 carrying the SMN gene under the control of a hybrid CMV enhancer/chicken-β-actin promoter
Experimental: Cohort 2 High dose: 3.3 X 10 ¹⁴ vg/kg of scAAV9.CB.SMN delivered one-time through a venous catheter inserted into a peripheral vein (n=6)	Biological: scAAV9.CB.SMN Self-complementary AAV9 carrying the SMN gene under the control of a hybrid CMV enhancer/chicken-β-actin promoter

Short and Long Term Treatment With 4-AP in Ambulatory SMA Patients

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified January 2014 by Columbia University

Sponsor:

Columbia University

Information provided by (Responsible Party):

Claudia Chiriboga, Columbia University

ClinicalTrials.gov Identifier:

NCT01645787

First received: July 5, 2012

Last updated: January 27, 2014

Last verified: January 2014

[History of Changes](#)

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► Purpose

The purpose of this study is to assess whether 4-AP (Ampyra) improves walking ability and endurance in adult patients with SMA Type 3 compared to placebo and whether the duration of treatment affects outcome.

Condition	Intervention	Phase
Spinal Muscular Atrophy	Drug: 4-aminopyridine (dalfampridine, Ampyra) Drug: Placebo	Phase 2 Phase 3

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Crossover Assignment

Masking: Double Blind (Subject, Investigator, Outcomes Assessor)

Primary Purpose: Treatment

Official Title: Columbia SMA Project: 4-AP as a Potential SMA Therapeutic Agent and Biological Mechanisms of Action

An Open-label Study of LMI070 in Type 1 Spinal Muscular Atrophy (SMA)

This study is not yet open for participant recruitment. (see [Contacts and Locations](#))

Verified October 2014 by Novartis

Sponsor:

Novartis Pharmaceuticals

Information provided by (Responsible Party):

Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:

NCT02268552

First received: October 1, 2014

Last updated: October 15, 2014

Last verified: October 2014

[History of Changes](#)

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► Purpose

An open-label, multi-part, first-in-human study of oral LMI070 in infants with Type 1 **spinal muscular atrophy**. The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy after 13 weeks; and to estimate the Maximum Tolerated Dose (MTD) and optimal dosing regimen of orally administered LMI070 in patients with Type 1 SMA.

Condition	Intervention	Phase
Muscular Atrophy, Spinal [C10.668.475]	Drug: LMI070	Phase 2

Study Type: Interventional

Study Design: Endpoint Classification: Safety/Efficacy Study

Intervention Model: Single Group Assignment

Masking: Open Label

Primary Purpose: Treatment

Official Title: An Open-label Multi-part First-in-human Study of Oral LMI070 in Infants With Type 1 **Spinal Muscular Atrophy**



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Safety and Efficacy of Olesoxime (TRO19622) in 3-25 Years SMA Patients.

This study has been completed.

Sponsor:

Trophos

Collaborator:

Association Française contre les Myopathies (AFM), Paris

Information provided by (Responsible Party):

Trophos

ClinicalTrials.gov Identifier:

NCT01302600

First received: February 18, 2011

Last updated: October 18, 2013

Last verified: October 2013

[History of Changes](#)

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Purpose

Assess the efficacy and the safety of olesoxime in SMA type 2 or type 3 non ambulant patients aged 3-25 years

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Spinal Muscular Atrophy Type II Spinal Muscular Atrophy Type III Non Ambulant	Drug: Olesoxime Drug: Placebo	Phase 2

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Primary Purpose: Treatment

An Open-label Study of LMI070 in Type 1 Spinal Muscular Atrophy (SMA)

This study is not yet open for participant recruitment. (see [Contacts and Locations](#))

Verified October 2014 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT02268552

First received: October 1, 2014
Last updated: October 15, 2014
Last verified: October 2014
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How to Read a Study Record

Purpose

An open-label, multi-part, first-in-human study of oral LMI070 in infants with Type 1 **spinal muscular atrophy**. The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy after 13 weeks; and to estimate the Maximum Tolerated Dose (MTD) and optimal dosing regimen of orally administered LMI070 in patients with Type 1 SMA.

Condition	Intervention	Phase
Muscular Atrophy, Spinal [C10.668.475]	Drug: LMI070	Phase 2

Study Type: Interventional

Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-label Multi-part First-in-human Study of Oral LMI070 in Infants With Type 1 **Spinal Muscular Atrophy**