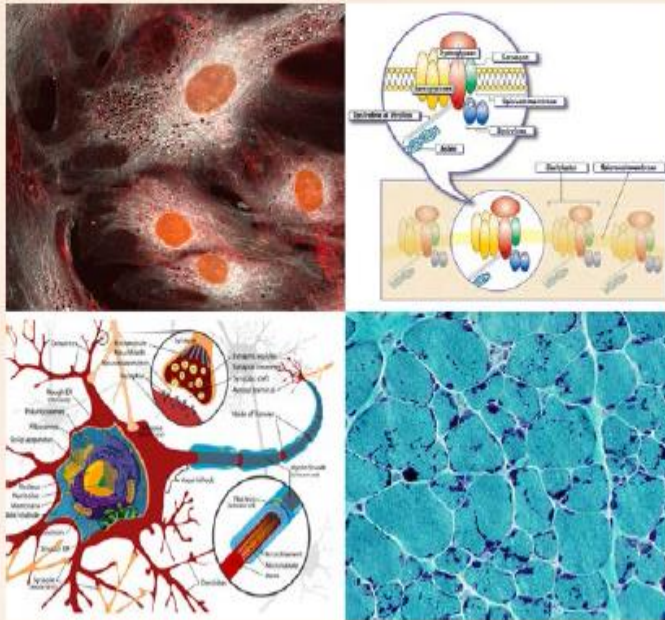


Enfermedades Musculares en la Infancia y Adolescencia (XII)



26 y 27 de Marzo de 2015

Salón de Actos. Planta 0 centro.
Hospital Universitario Ramón y Cajal

Situación actual de los ensayos clínicos en la distrofia muscular de Duchenne

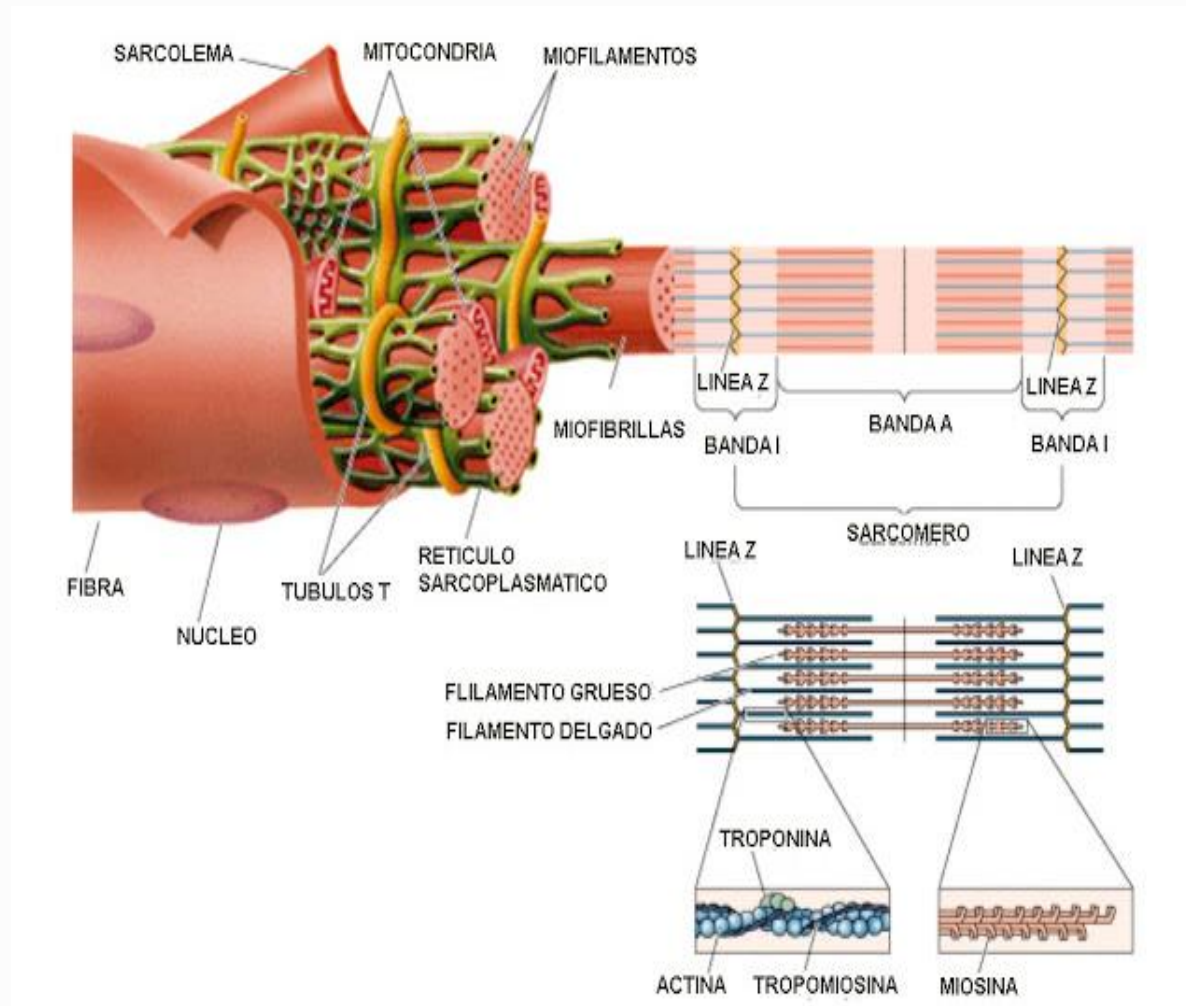
Dr. S. I. Pascual Pascual

Jefe de Sección

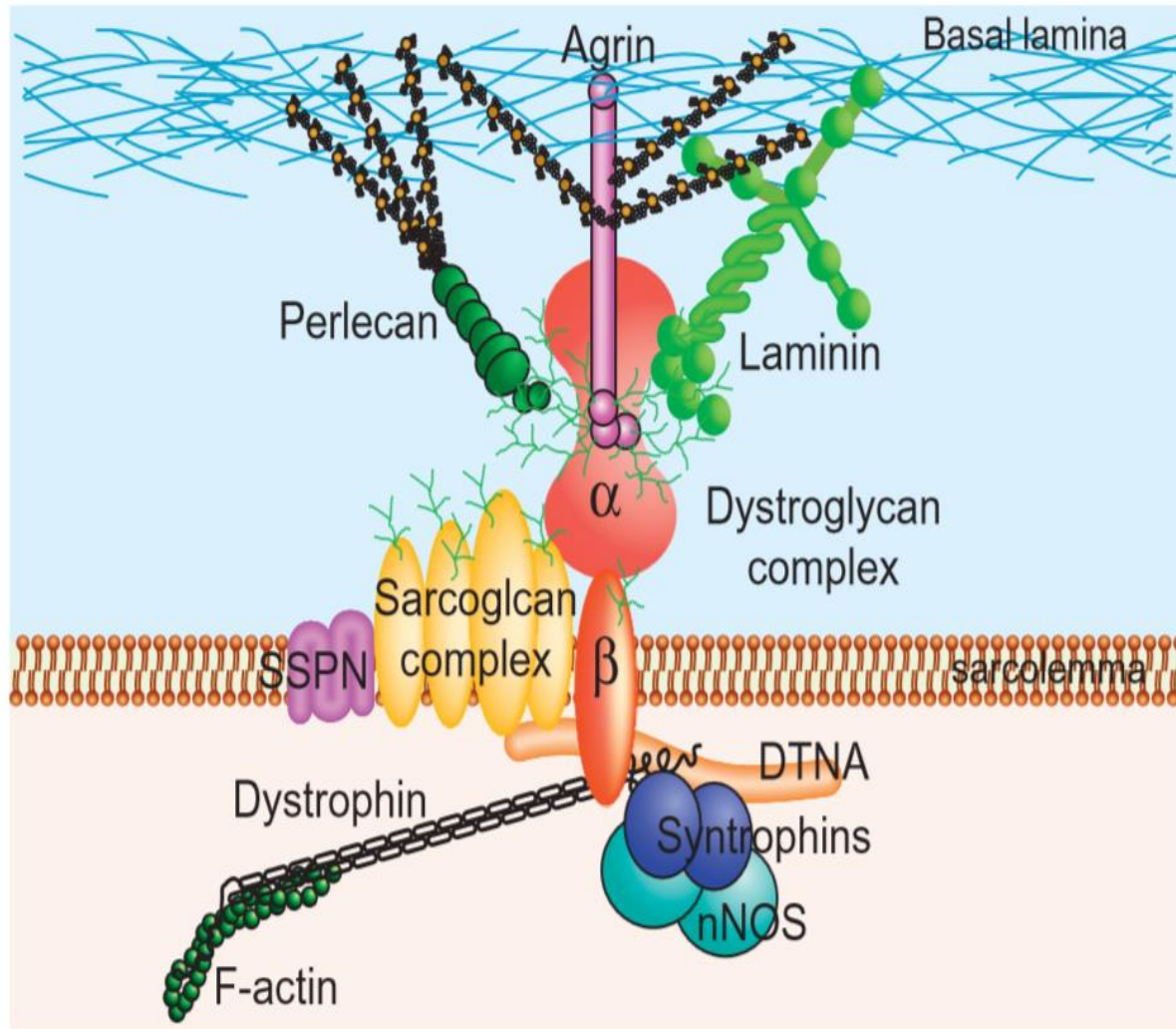
Servicio Neurología Pediátrica. H.U La Paz

Prof. Asociado U. Autónoma Madrid.

COMPLEJO DISTROFINA-GLICOPROTEÍNA



COMPLEJO DISTROFINA-GLICOPROTEÍNA

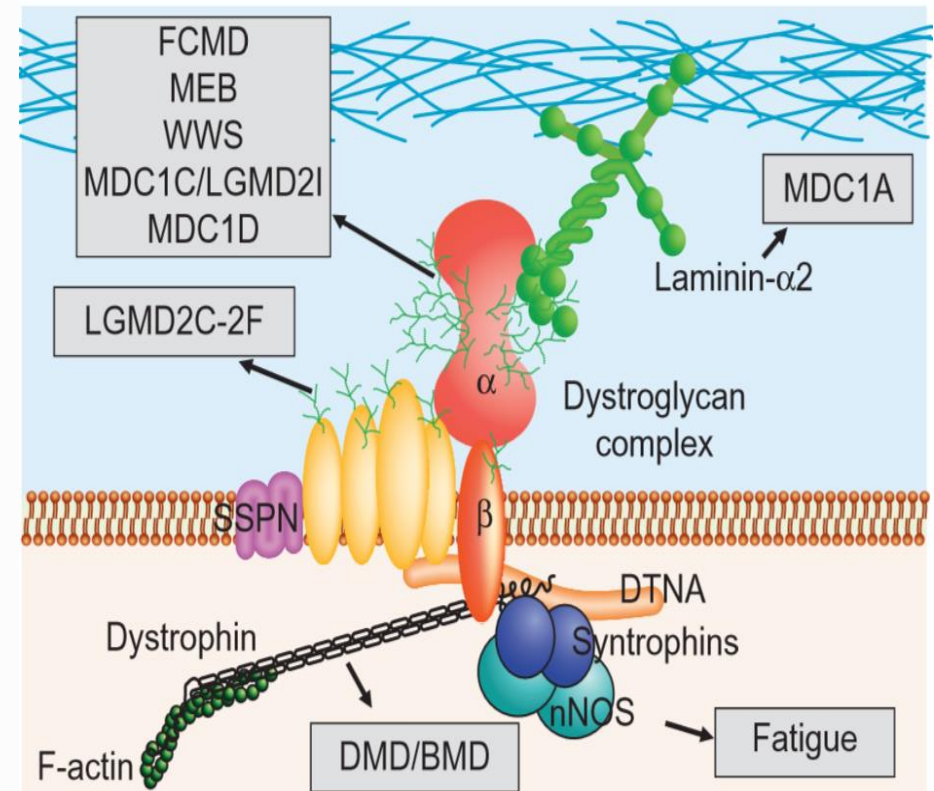


COMPLEJO DISTROFINA-GLICOPROTEÍNA

- Confiere estabilidad a la membrana muscular, protegiendo las fibras musculares del daño inducido por la contracción
- Sirve de andamiaje de moléculas de señalización, como nNOS:
 - En pacientes con DM de Duchenne o de Becker, se pierde nNOS
 - En pacientes con DM de cinturas asociadas a sarcoglicanos, se pierde nNOS
 - Pérdida de nNOS conlleva pérdida de atenuación de la vasoconstricción tras ejercicio, provocando contracción vascular e isquemia muscular funcional.
 - Fatiga exagerada al ejercicio moderado, edema.

COMPLEJO DISTROFINA-GLICOPROTEÍNA Y DMD

- La ausencia de distrofina en el músculo esquelético altera la integridad del complejo distrofina-glicoproteína y conlleva disminución en la expresión del resto de componentes
- Altera la unión entre la matriz extracelular y el citoesqueleto subsarcolémico
- En modelos animales, se comprueba que el papel del complejo es proteger el sarcolema

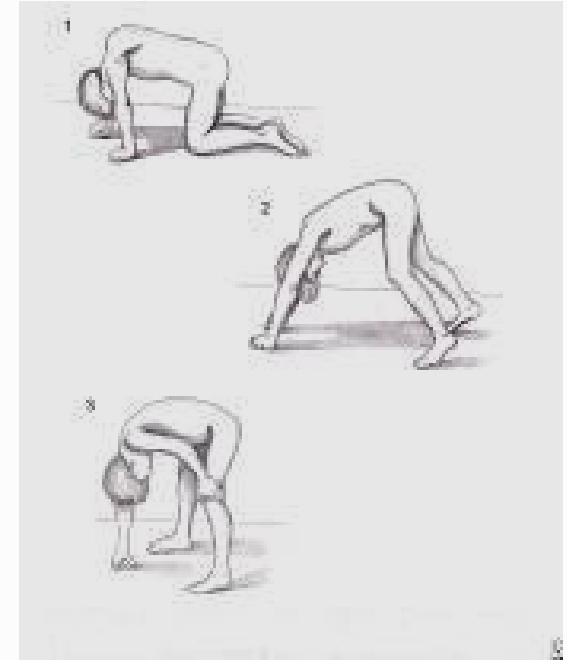
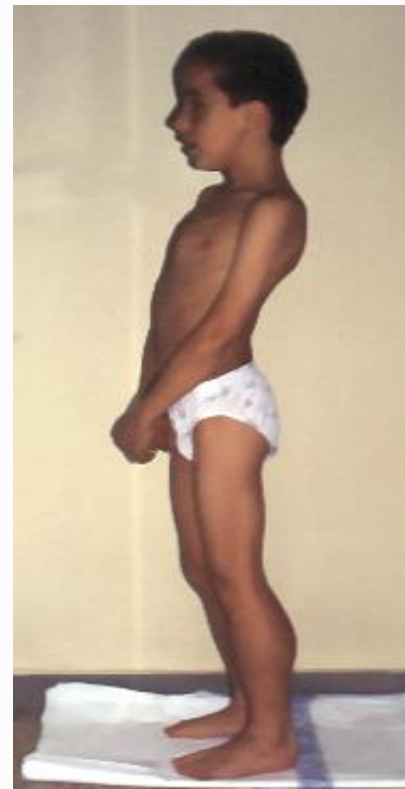


DISTROFINOPATIAS

- **Fenotipos:**

- DMD, (1/3.500 varones nacidos vivos).
- DMB, (1/18.000 a 1/31.000 varones nacidos vivos).
- Formas intermedias o “outliers” entre DMD y DMB.
- Otras distrofinopatías:
 - (XLDCM) Cardiomiopatía dilatada ligada cromosoma X.
 - Miopatía aislada del cuádriceps.
 - Mioglobinuria con calambres musculares.
 - Elevación asintomática de enzimas musculares.
 - Mujeres portadoras de DMD o DMB.

Distrofia muscular Duchenne



Ligada al X, recesiva

CPK x10-100

Debilidad desde 1-3 años, progresiva

Pérdida de marcha a los 10-12 años

Fallecimiento: 15-20 años.

Miocardopatía, frecuentemente leve

Inteligencia límite o Retraso Mental Leve

Madre portadora en 2/3, con:

Hiper-CK (no siempre)

Asintomática (95%)

Diferencia Duchenne-Becker

GEN DE LA DISTROFINA

MUTACIONES “OUT OF FRAME” O “IN-FRAME”

Mutaciones out of frame → reducción severa o ausencia de distrofina

DMD

Mutaciones in-frame → distrofina truncada, parcialmente funcional (DMB)

Esta hipótesis es cierta para el 90% de los casos

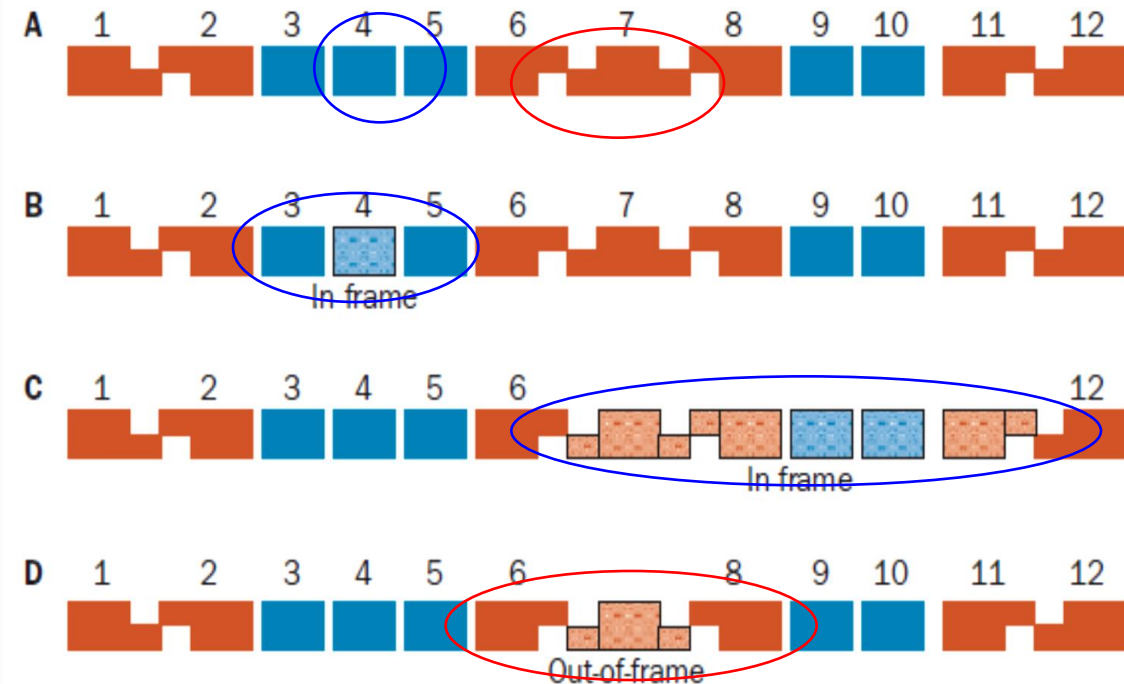
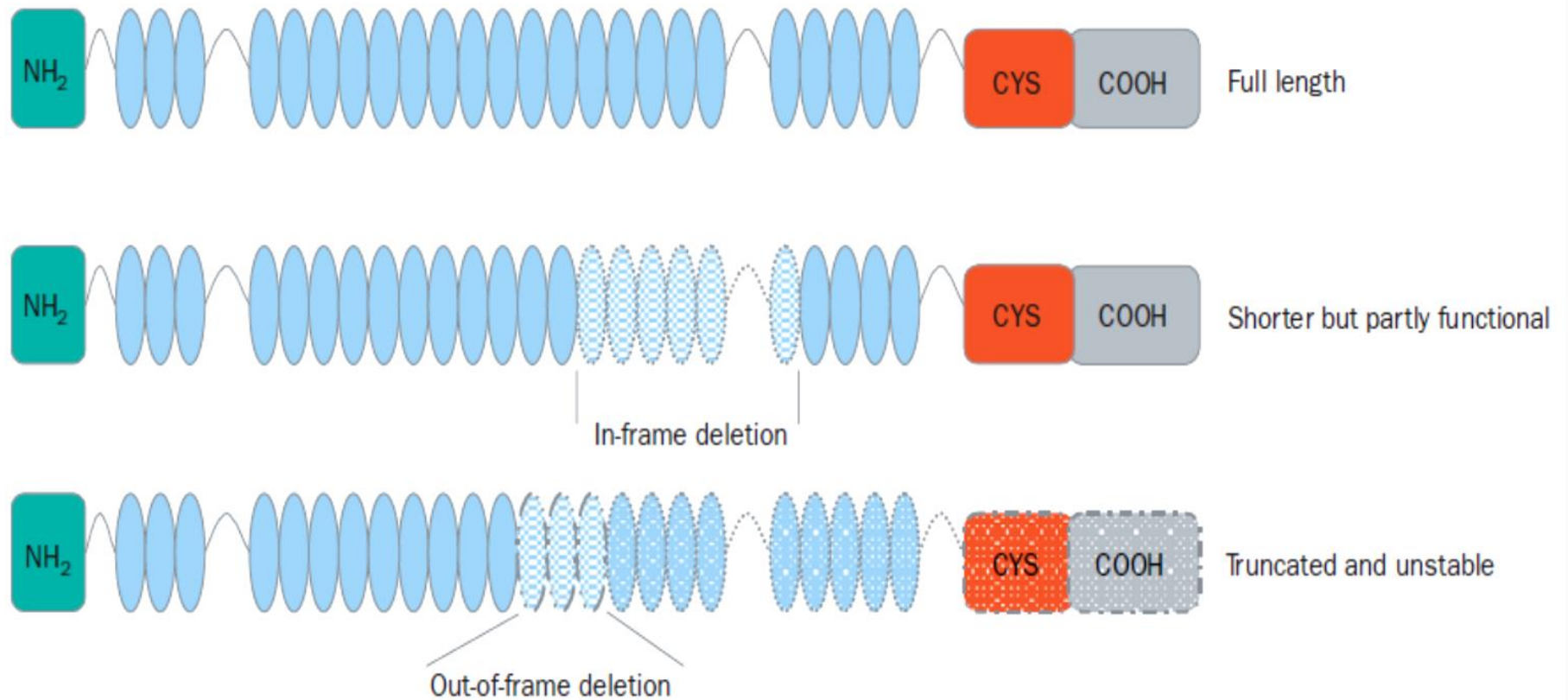


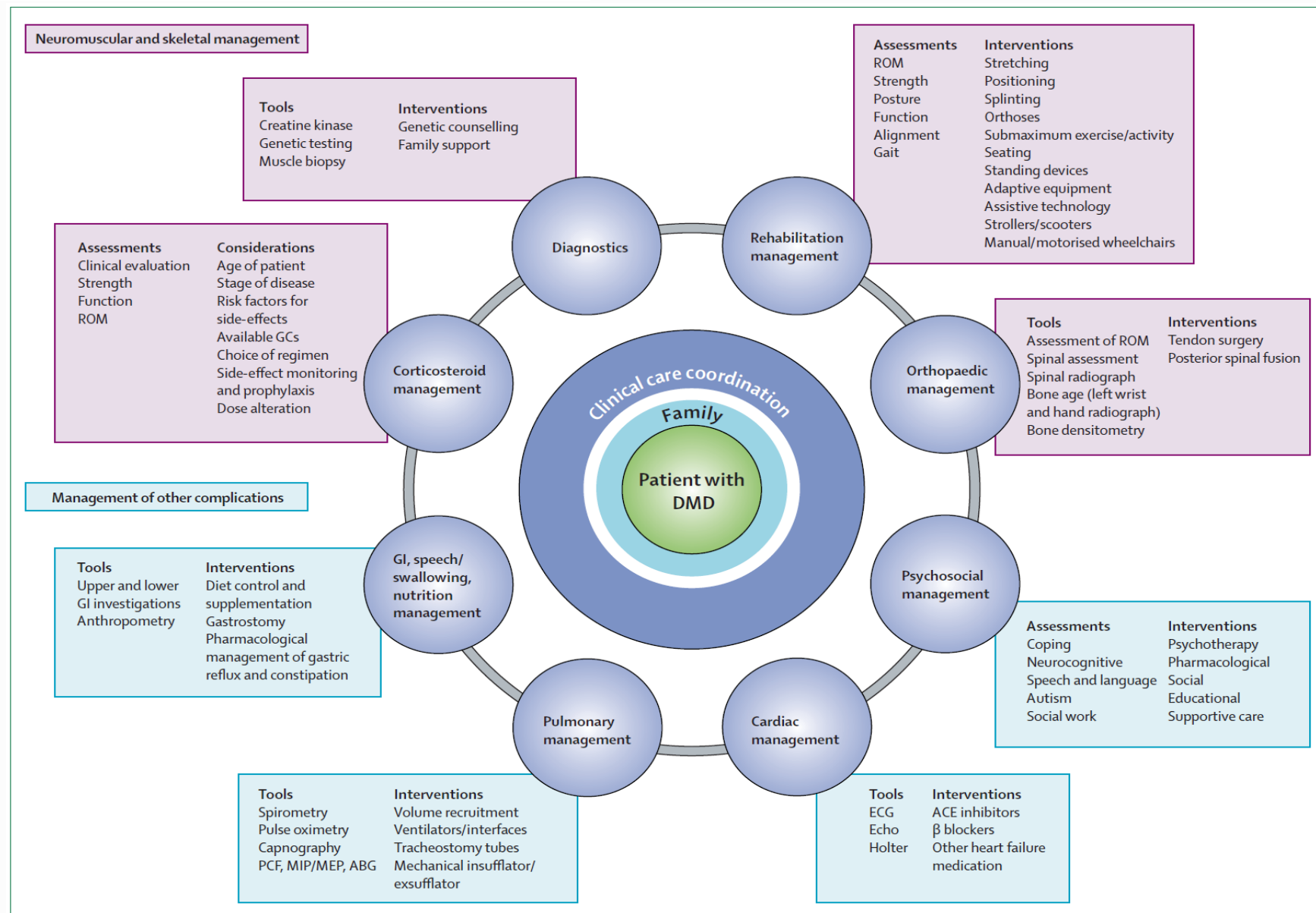
Figure 2. Effects of different genomic deletions on the reading frame of the dystrophin gene (A). The removal of exon 4 (B) and of exon 7-11 (C) maintains the open-reading frame. The deletion of exon 7 leads to the loss of the open-reading frame (D).

GEN DE LA DISTROFINA

MUTACIONES “OUT OF FRAME” O “IN-FRAME”



***Lancet Neurol* 2010; 9: 77–93**



Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management



Lancet Neurol 2010; 9: 77–93

Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula R Clemens, Linda Cripe, Ajay Kaul, Kathi Kinnett, Craig McDonald, Shree Pandya, James Poyosky, Frederic Shapiro, Jean Tomezsko, Carolyn Constantin, for the DMD Care Considerations Working Group*

CORTICOIDES

Starting GCs

Prednisone

0.75 mg/kg/day

First line unless pre-existing weight and/or behavioural issues favour deflazacort

Deflazacort

0.9 mg/kg/day

Consider as first line when pre-existing weight and/or behavioural issues

Age <2 years

Improving (typical): GC initiation not recommended

Plateau (uncommon): monitor closely

Decline (atypical): consider alternative diagnoses/concomitant pathology

Age 2–5 years

Improving: GC initiation not recommended

Plateau: GC initiation recommended

Decline: GC initiation highly recommended

Age ≥6 years

Improving (uncommon): consider BMD

Plateau: GC initiation highly recommended

Decline: GC initiation highly recommended

Non-ambulatory: refer to text

- Consider age, function (improving, plateau, declining), pre-existing risk factors, physician relationship with family
- Ensure immunisation schedule is complete before initiating GCs

DM DUCHENNE: EVOLUCION NATURAL

Long Term Natural History Data in Ambulant Boys with Duchenne Muscular Dystrophy: 36-Month Changes

Marika Pane^{1§}, Elena Stacy Mazzone^{1§}, Serena Sivo^{1§}, Maria Pia Sormani², Sonia Messina³, Adele D'Amico⁴, Adelina Carlesi⁴, Gianluca Vita³, Lavinia Fanelli¹, Angela Berardinelli⁵, Yvan Torrente⁶, Valentina Lanzillotta⁷, Emanuela Viggiano⁸, Paola D'Ambrosio⁸, Filippo Cavallaro³, Silvia Frosini⁹, Andrea Barp¹⁰, Serena Bonfiglio¹¹, Roberta Scalise¹, Roberto De Sanctis¹, Enrica Rolle¹², Alessandra Graziano¹, Francesca Magri⁶, Concetta Palermo¹, Francesca Rossi¹⁴, Maria Alice Donati¹³, Michele Sacchini¹³, Maria Teresa Arnoldi¹⁴, Giovanni Baranello¹⁴, Tiziana Mongini¹², Antonella Pini¹¹, Roberta Battini⁹, Elena Pegoraro¹⁰, Stefano Previtali¹⁵, Claudio Bruno⁷, Luisa Politano⁸, Giacomo P. Comi⁶, Enrico Bertini⁴, Eugenio Mercuri^{1*}

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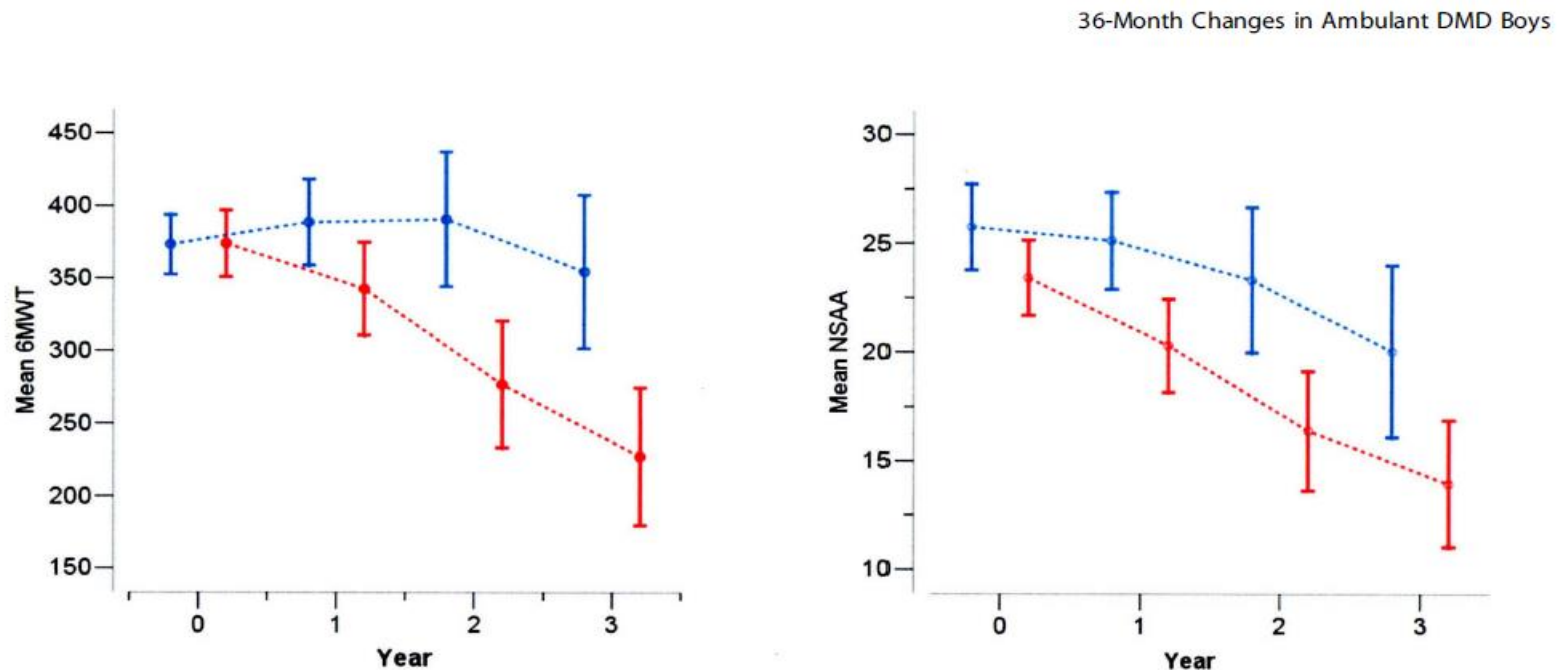


Figure 1. 6MWT (left pannel) and NSAA (right pannel) at baseline, 1, 2 and 3 years in DMD boys, below (red) and above (blu) the age of 7 years.

doi:10.1371/journal.pone.0108205.g001

Long Term Natural History Data in Ambulant Boys with Duchenne Muscular Dystrophy: 36-Month Changes

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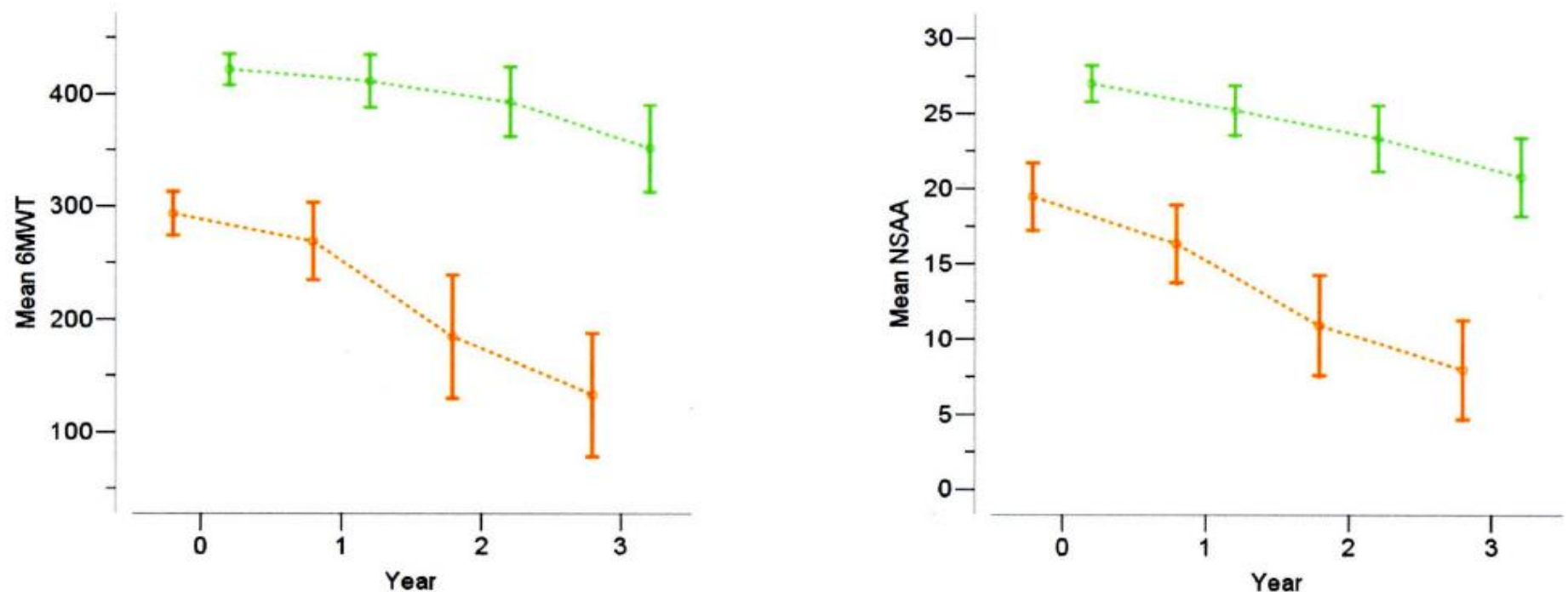


Figure 2. 6MWT (left pannel) and NSAA (right pannel) at baseline, 1, 2 and 3 years in DMD boys, below (green) and above (orange) 350 m of 6MWD.

Long Term Natural History Data in Ambulant Boys with Duchenne Muscular Dystrophy: 36-Month Changes

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36-Month Changes in Ambulant DMD Boys

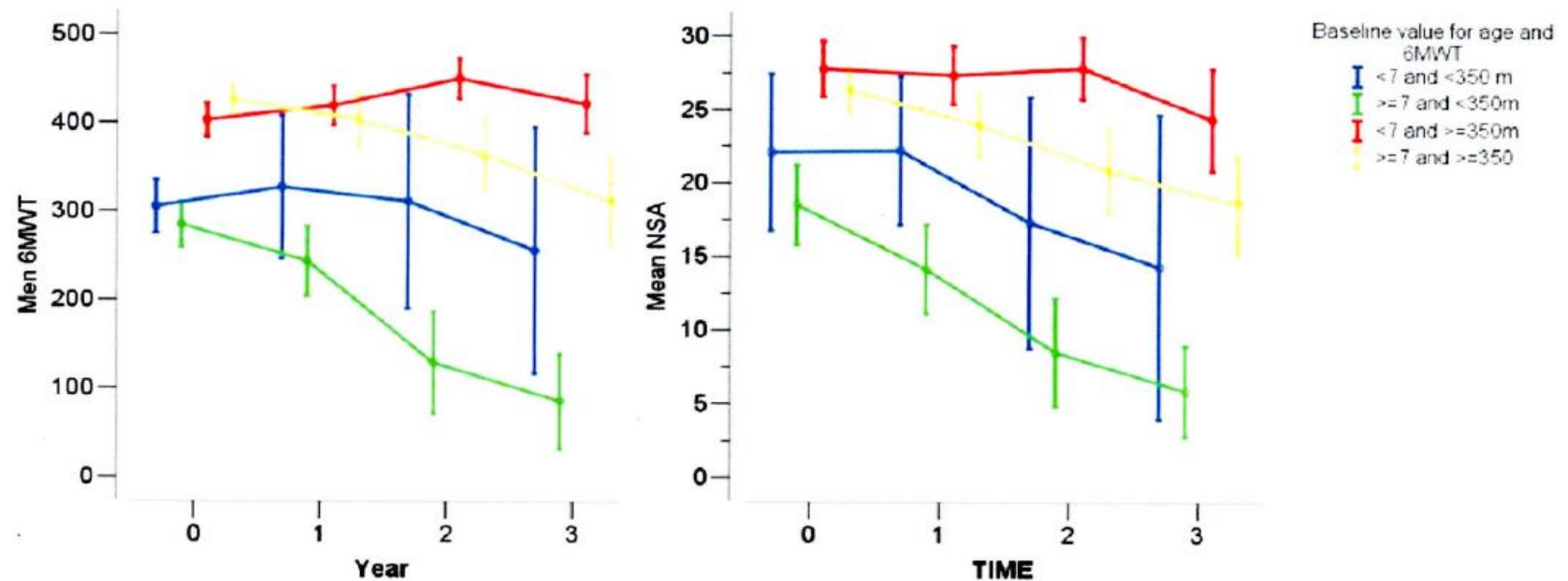


Figure 3. 6MWT (left pannel) and NSAA (right pannel) at baseline, 1, 2 and 3 years in DMD boys, subdivided according to a combination of age (below and above 7 years) and distance (below and above 350 m of 6MWT).

Long Term Natural History Data in Ambulant Boys with Duchenne Muscular Dystrophy: 36-Month Changes

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	Cambio 6MWT a 36 meses			Cambio NSAA a 36 meses	
ESTEROIDES	Metros	SD		Score	SD
Sin tratamiento	-216.8	84.9		-15.3	5.4
Intermitente (dias alternos o 10/10 dias)	-128.3	161		-10	8
Continuo	-75	129		-6.2	7.3

Functional changes in Duchenne muscular dystrophy

A 12-month longitudinal cohort study

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G. Vasco, MD*
M.P. Sormani, MD
Y. Torrente, MD
A. Berardinelli, MD
S. Messina, MD
A. D'Amico, MD
L. Doglio, MD
L. Politano, MD
F. Cavallaro, PT
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L. Bello, MD
S. Bonfiglio, MD
E. Zucchini, MD
R. De Sanctis, PT
M. Scutifero, PT

ABSTRACT

Objective: The aim of the study was to assess different outcome measures in a cohort of ambulant boys with Duchenne muscular dystrophy (DMD) over 12 months in order to establish the spectrum of possible changes in relation to age and steroid treatment.

Methods: The study is a longitudinal multicentric cohort study. A total of 106 ambulant patients with DMD were assessed using the 6-minute walk test (6MWT) and North Star Ambulatory Assessment (NSAA) at baseline and 12 months. Clinical data including age and steroid treatment were collected.

Results: During the 12 months of the study, we observed a mean decline of 25.8 meters in the 6MWT with a SD of 74.3 meters. On NSAA, the mean decline was 2.2 points with a SD of 3.7. Not all the boys with DMD in our cohort showed a decline over the 12 months, with young boys showing some improvement in their 6MWT and NSAA scores up to the age of 7. NSAA and the 6MWT had the highest correlation ($r = 0.52$, $p < 0.001$).

Conclusions: This study provides longitudinal data of NSAA and 6MWT over a 12-month period. These data can be useful when designing a clinical trial. *Neurology*® 2011;77:250-256

Table 3 Twelve-month change of the functional scales values according to age and steroid regimen

	Age, y			p Values (none/intermittent vs continuous steroids) for each measure
	≤7 (n = 35)	>7 (n = 71)	Total	
NSAA 12-month change				
Steroid regimen				
None or intermittent (n = 51)	−0.7 (3.8)	−3.7 (4.0)	−2.5 (4.1)	0.13
Continuous (n = 55)	0.7 (3.5)	−2.8 (2.8)	−1.8 (3.3)	
Total (n = 106)	−0.08 (3.7)	−3.2 (3.4)	−2.2 (3.7)	
p Values (age ≥7 vs >7) for NSAA	<0.001			
6MWT 12-month change				
Steroid regimen				
None or intermittent (n = 51)	−0.44 (73.7)	−66.4 (77.7)	−40.6 (82.2)	<0.001
Continuous (n = 55)	18.8 (48.2)	−23.6 (65.9)	−12.1 (64.1)	
Total (n = 106)	−7.8 (63.9)	−42.3 (73.9)	−25.8 (74.3)	
p Values (age ≥7 vs >7) for 6MWT	0.01			

Long Term Natural History Data in Ambulant Boys with Duchenne Muscular Dystrophy: 36-Month Changes

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En resumen, al estratificar hay que tener en cuenta:

- Edad: < 7 años y > 7 años
- 6MWT: > 350 y < 350 m
- Tratamiento con esteroides

Treatment of Duchenne muscular dystrophy with ciclosporin A: a randomised, double-blind, placebo-controlled multicentre trial



Janbernd Kirschner*, Joachim Schessl*, Ulrike Schara, Bernd Reitter, Georg M Stettner, Elke Hobbiebrunken, Ekkehard Wilichowski, Günther Bernert, Simone Weiss, Florian Stehling, Gert Wiegand, Wolfgang Müller-Felber, Simone Thiele, Ulrike Grieben, Maja von der Hagen, Jürg Lütschg, Claudia Schmoor, Gabriele Ihorst, Rudolf Korinthenberg

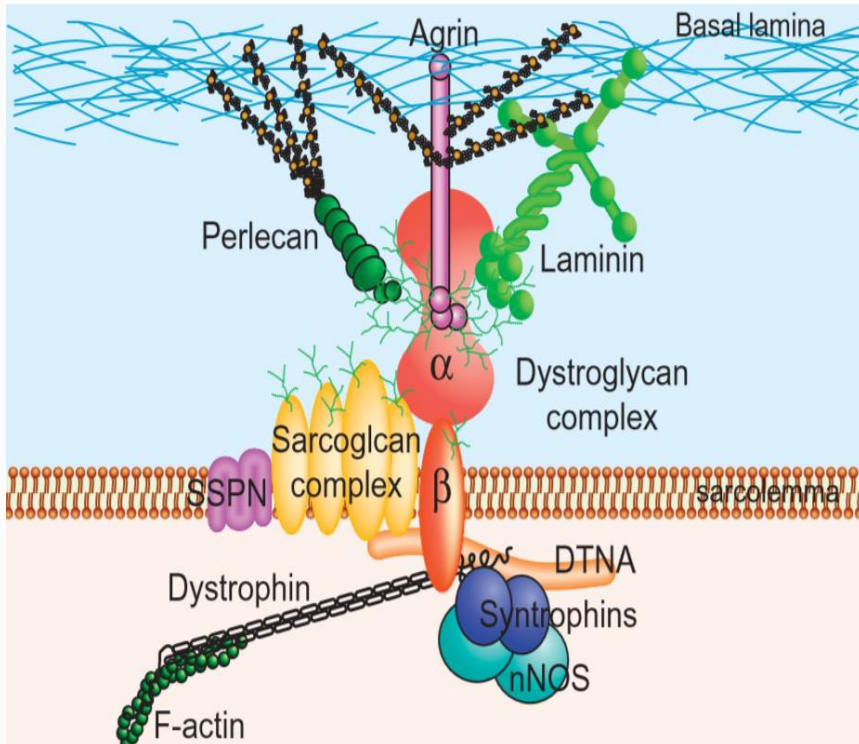
Methods Our study was a parallel-group, placebo-controlled, double-blind, multicentre trial at trial sites of the German muscular dystrophy network, MD-NET, over 36 months. Ambulant patients with Duchenne muscular dystrophy who were aged 5 years or older were randomly assigned to receive either ciclosporin A (3.5–4.0 mg/kg per day) or matching placebo. Allocation was done centrally with computer-generated random numbers. Patients and investigators were masked to the allocated treatment. After 3 months of treatment, both groups were also given intermittent prednisone for a further 12 months (0.75 mg/kg, alternating 10 days on with 10 days off). All patients who received at least one dose of study drug or placebo were included in the primary analysis. The primary outcome measure was manual muscle strength measured on the Medical Research Council (MRC) scale. This trial is registered with the German clinical trial register DRKS, number DRKS00000445.

Findings 77 patients were randomly assigned to the ciclosporin A group and 76 to the placebo group; 73 patients on ciclosporin A and 73 on placebo received at least one dose and were available for efficacy analyses. 3 months of treatment with ciclosporin A alone did not show any significant improvement in primary outcome measures (mean change in the proportion of a possible total MRC score [%MRC] was –2.6 [SD 6.0] for patients on ciclosporin A and –0.8 [4.9] for patients on placebo; adjusted group difference estimate –0.88, 97.5% CI –2.6 to 0.9; $p=0.26$). The combination of ciclosporin A with intermittent steroids was not better than intermittent steroids alone over 12 months (mean change in %MRC was 0.7 [7.1] for patients on ciclosporin A and –0.3 [7.9] for patients on placebo; adjusted group difference estimate –0.85, –3.6 to 1.9; $p=0.48$). Numbers of adverse events (75 in patients on ciclosporin A and 74 on placebo) and serious adverse events (four with ciclosporin A and four with placebo) did not differ significantly between groups.

Interpretation Ciclosporin A alone or in combination with intermittent prednisone does not improve muscle strength or functional abilities in ambulant boys with Duchenne muscular dystrophy, but is safe and well tolerated.

TADALAFILO

TADALAFILO



- En pacientes con DMD, la nNOS se encuentra en el citosol.
- Pérdida de respuestas hemodinámicas normales al ejercicio
- Incapacidad muscular para aumentar el flujo y la perfusión → Isquemia muscular
- La potenciación de la señalización de cGMP mediada por NO puede restaurar la respuesta hemodinámica normal

TADALAFILO

- Inhibidor selectivo reversible de la PDE5 específica del cGMP (que degrada el cGMP)
- Aprobado como Cialis® para tratamiento de disfunción eréctil y como Adcirca® para tratamiento de la hipertensión pulmonar
- La inhibición de PDE5 puede ejercer efectos favorables en la función muscular en la DM Duchenne
- En el modelo murino mdx de la DMD se consiguen mitigar características de la distrofia potenciando la señalización cGMP mediada por el NO :
 - Expresión transgénica de nNOS
 - Fármacos que aportan NO
 - Tratamientos con el precursor del NO (L-arginina)
 - Inhibición de PDE5

TADALAFILO

- Efectos en el modelo murino mdx de la inhibición de PDE5:
 - Reproduce los efectos asociados con la restauración de la nNOS en el sarcolema
 - Restaura la hemodinámica normal
 - Atenúa el daño y la necrosis muscular
 - Disminuye el edema muscular
 - Mejora la movilidad y deambulaci3n (INCORPORACI3N Y 6MWT)

Primary Role of Functional Ischemia, Quantitative Evidence for the Two-Hit Mechanism, and Phosphodiesterase-5 Inhibitor Therapy in Mouse Muscular Dystrophy

Akihiro Asai^{1,2}, Nita Sahani¹, Masao Kaneki¹, Yasuyoshi Ouchi², J. A. Jeevendra Martyn¹, Shingo Egusa Yasuhara^{1*}

1 Department of Anesthesiology and Critical Care, Shriners Hospital for Children, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, 2 Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

of a “two-hit” mechanism in the pathogenesis of this disease. **Conclusions/Significance.** Evidence was provided supporting the essential role of functional ischemia in contraction-induced myofiber damage in *mdx* mice. Furthermore, the first quantitative evidence for the “two-hit” mechanism in this disease was documented. Significantly, the vasoactive drug tadalafil, a phosphodiesterase 5 inhibitor, administered to *mdx* mice ameliorated muscle damage.

TADALAFILO

Primary Role of Functional Ischemia, Quantitative Evidence for the Two-Hit Mechanism, and Phosphodiesterase-5 Inhibitor Therapy in Mouse Muscular Dystrophy

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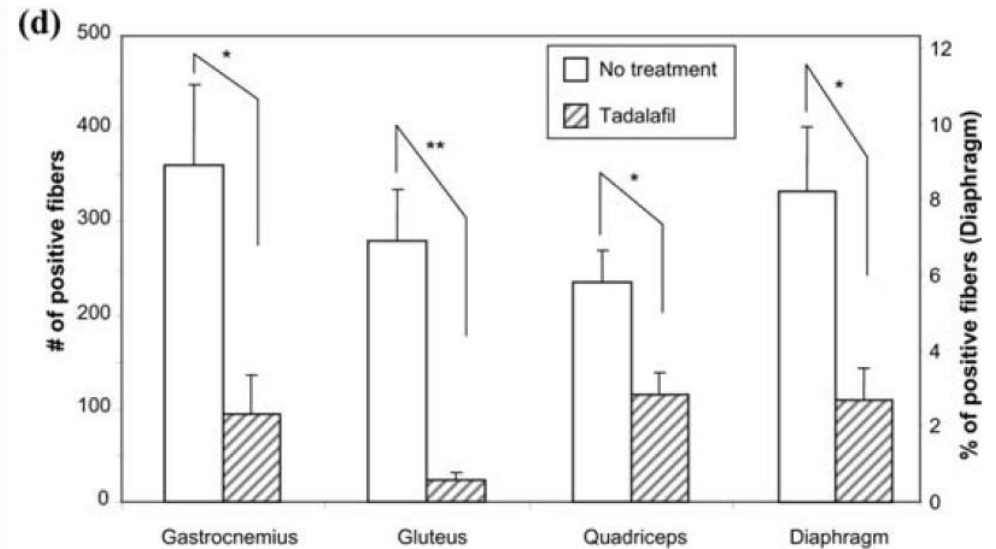
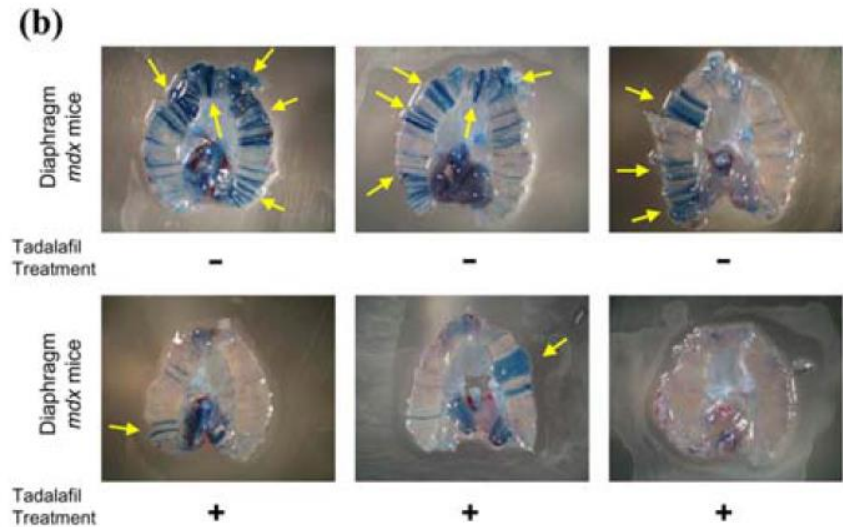


Figure 7. Evans Blue staining of the damaged fibers in the hindlimb and the diaphragm muscles of *mdx* mice (4 weeks old). (a&b) Six hours after the injection of Evans Blue dye, the extent of myofiber damage as indicated by blue staining was observed in the superficial hindlimb muscles (a) and the diaphragm (b). Three mice from each group are shown (a and b). Compare lateral and medial views of the stained fibers (arrows) in mice without (–) and with (+) tadalafil treatment (a). Mice without tadalafil treatment (–) show extensive blue staining (arrows in a and b). Tadalafil treatment (+)

TADALAFILO

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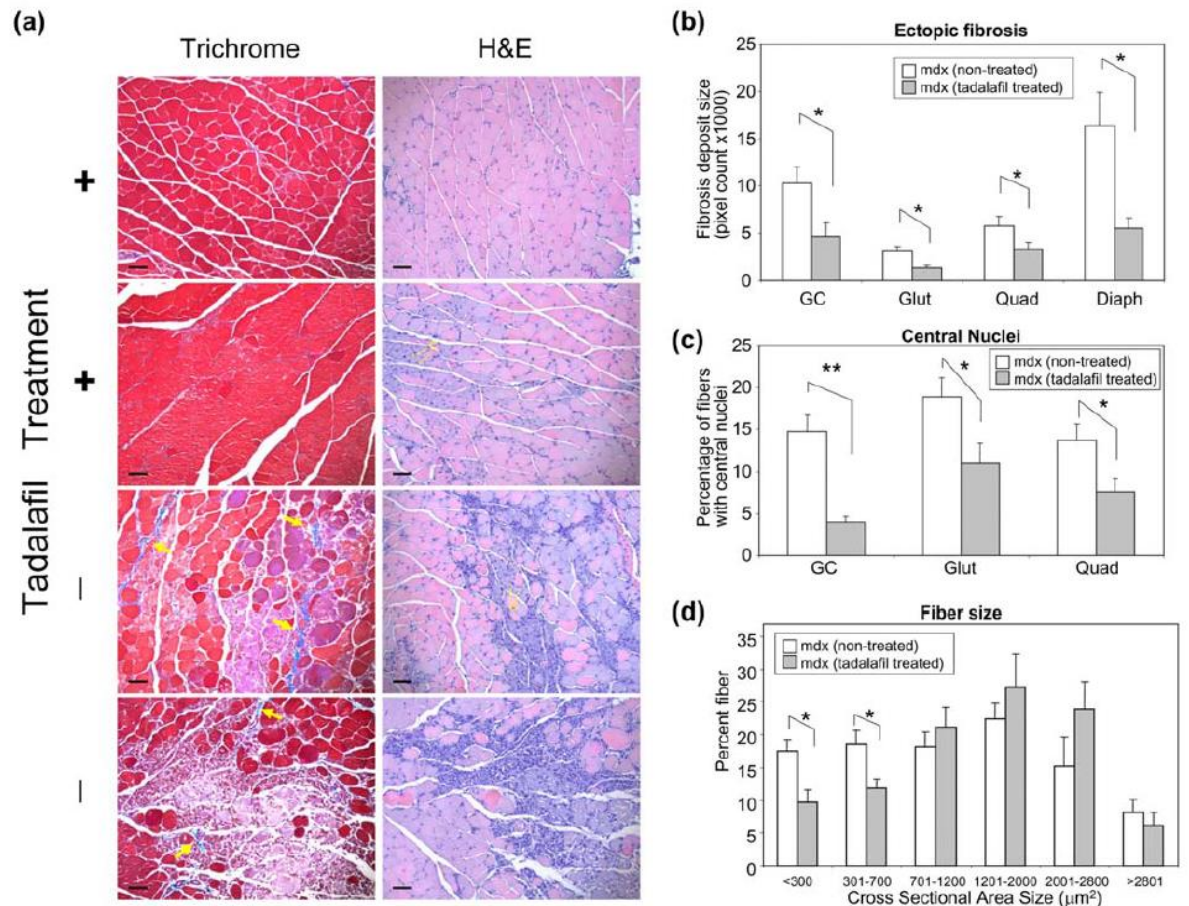


Figure 8. Evaluation of the efficacy of tadalafil by conventional histology. (a) Two images from different animals in tadalafil-treated and non-treated groups are presented for trichrome staining of gastrocnemius muscles (left panels); Ectopic fibrosis in extensively damaged areas was

Tadalafil alleviates muscle ischemia in patients with Becker muscular dystrophy

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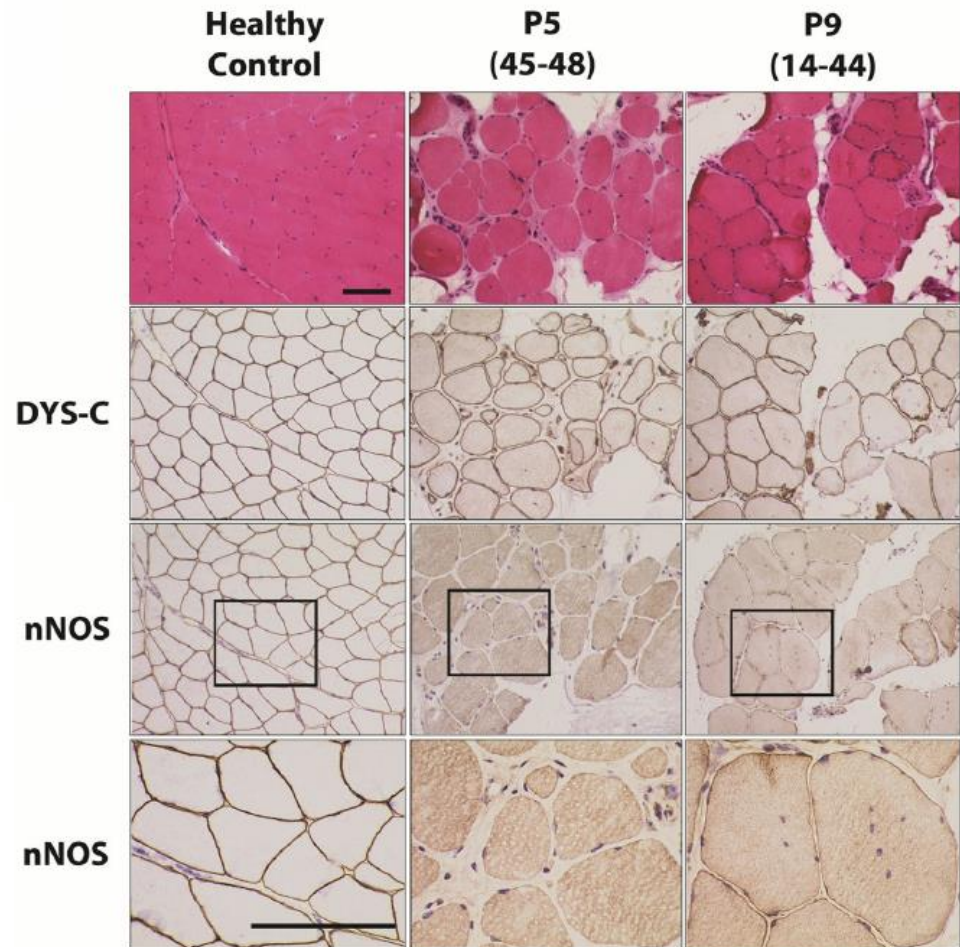
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Abstract

Becker muscular dystrophy (BMD) is a progressive X-linked muscle wasting disease for which there is no treatment. Like Duchenne muscular dystrophy (DMD), BMD is caused by mutations in the gene encoding dystrophin, a structural cytoskeletal protein that also targets other proteins to the muscle sarcolemma. Among these is neuronal **nitric oxide synthase (nNOS μ)**, which requires certain spectrin-like repeats in dystrophin's rod domain and the adaptor protein α -syntrophin to be targeted to the sarcolemma. **When healthy skeletal muscle is subjected to exercise, sarcolemmal nNOS μ -derived nitric oxide (NO) attenuates local α -adrenergic vasoconstriction thereby optimizing perfusion of muscle.** We found previously that this protective mechanism is defective—causing functional muscle ischemia—in dystrophin-deficient muscles of the *mdx* mouse (a model of DMD) and of children with DMD, in whom nNOS μ is mislocalized to the cytosol instead of the sarcolemma. **Here, we report that this protective mechanism also is defective in men with BMD in whom the most common dystrophin mutations disrupt sarcolemmal targeting of nNOS μ .** In these men, the vasoconstrictor response, measured as a decrease in muscle oxygenation, to reflex sympathetic activation is not appropriately attenuated during exercise of the dystrophic muscles. **In a randomized placebo-controlled cross-over trial, we show that functional muscle ischemia is alleviated and normal blood flow regulation fully restored in the muscles of men with BMD by boosting NO-cGMP signaling with a single dose of the drug tadalafil, a phosphodiesterase (PDE5A) inhibitor.** These results further support an essential role for

immunohistochemistry of muscle biopsies from BMD patients. Muscle biopsy sections stained with haematoxylin and eosin (upper panel) from patient P5 (deletion of exons 45–48) and patient P9 (deletion of exons 14–44) show typical dystrophic hallmarks including variation in muscle fiber size, internal nuclei, fibrosis, and increase in fat tissue. Staining for dystrophin C-terminus (DYS-C) is present in muscle from both P5 and P9. Cytoplasmic staining for nNOS is evident in both P5 and P9 but not in control muscle. Sarcolemmal nNOS labeling is present in P9 but not detected in P5. Bottom panel shows higher magnification of fields enclosed in rectangles. Scale bars are 100 μ m.



PDE5 inhibition alleviates functional muscle ischemia in boys with Duchenne muscular dystrophy



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ABSTRACT

Objective: To determine whether phosphodiesterase type 5 (PDE5) inhibition can alleviate exercise-induced skeletal muscle ischemia in boys with Duchenne muscular dystrophy (DMD).

Methods: In 10 boys with DMD and 10 healthy age-matched male controls, we assessed exercise-induced attenuation of reflex sympathetic vasoconstriction, i.e., functional sympatholysis, a protective mechanism that matches oxygen delivery to metabolic demand. Reflex vasoconstriction was induced by simulated orthostatic stress, measured as the decrease in forearm muscle oxygenation with near-infrared spectroscopy, and performed when the forearm muscles were rested or lightly exercised with rhythmic handgrip exercise. Then, the patients underwent an open-label, dose-escalation, crossover trial with single oral doses of tadalafil or sildenafil.

Results: The major new findings are 2-fold: first, sympatholysis is impaired in boys with DMD—producing functional muscle ischemia—despite contemporary background therapy with corticosteroids alone or in combination with cardioprotective medication. Second, PDE5 inhibition with standard clinical doses of either tadalafil or sildenafil alleviates this ischemia in a dose-dependent manner. Furthermore, PDE5 inhibition also normalizes the exercise-induced increase in skeletal muscle blood flow (measured by Doppler ultrasound), which is markedly blunted in boys with DMD.

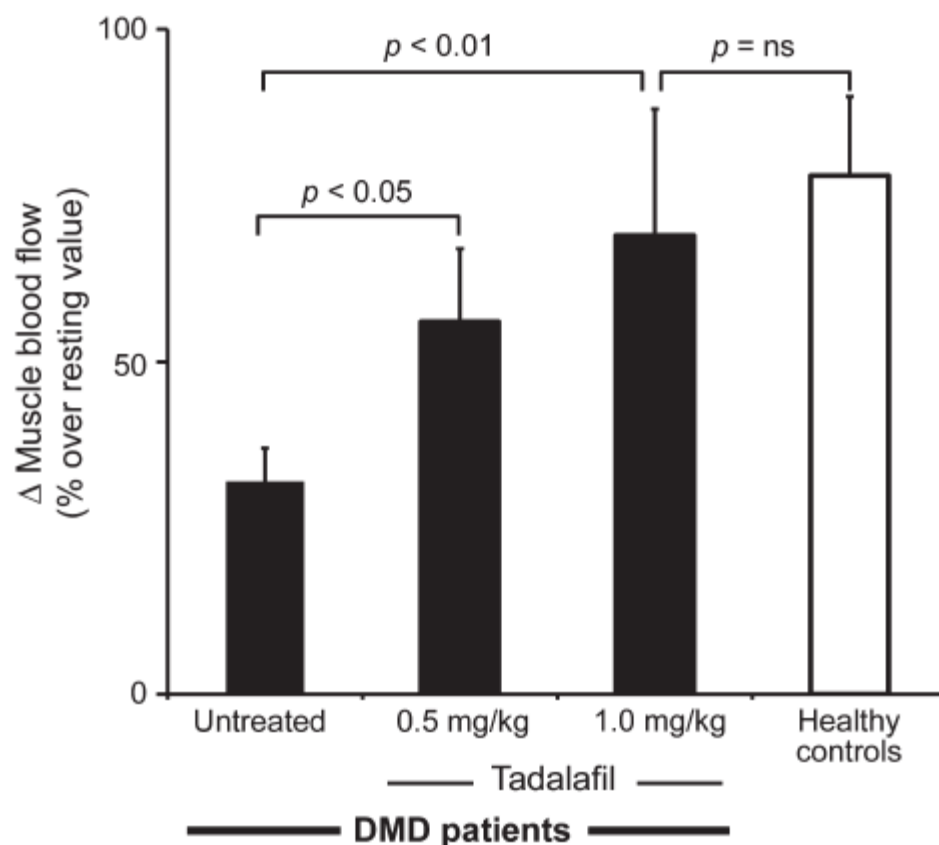
Conclusions: These data provide in-human proof of concept for PDE5 inhibition as a putative new therapeutic strategy for DMD.

Classification of evidence: This study provides Class IV evidence that in patients with DMD, PDE5 inhibition restores functional sympatholysis. *Neurology*® 2014;82:2085–2091

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Figure 3 Postexercise hyperemia is impaired in DMD and rescued by tadalafil



Exercise-induced change in skeletal muscle blood flow, from rest to postexercise, in 10 patients with Duchenne muscular dystrophy (DMD) and 10 healthy controls. Data expressed as mean $\pm$ SEM. ns = not significant.

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a putative new

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TADALAFILO

- Efectos en DMD y DMB:
 - Estudio en 20 pacientes con DMB, aleatorizado controlado con placebo VS una dosis de Tadalafilo 20mg: mitigó la isquemia muscular y restauró la regulación del flujo sanguíneo.
Sci Transl Med. 2012 November 28; 4(162): 162ra155. doi:10.1126/scitranslmed.3004327
 - Dosis únicas de Tadalafilo en niños con DMD restauran la respuesta hemodinámica normal.
- Cuestión: ¿supondrá un beneficio clínico?
- Seguridad:
 - Efectos adversos frecuentes: cefalea, dispepsia, congestión, dorsalgia, mialgia, rubor.

TADALAFILO: ENSAYO CLÍNICO H6D-MC-LVJJ

- **OBJETIVO PRINCIPAL:**

Si tadalafilo reduce el deterioro de la capacidad ambulatoria, medido según el 6MWD, en comparación con pacientes tratados con placebo

- **OBJETIVOS SECUNDARIOS:**

Si asocia menor disminución de la puntuación escala North Star

Si reduce el deterioro en pruebas funcionales cronometradas

Si prolonga el tiempo hasta que se observa un empeoramiento del 10% en 6MWD y NSAA

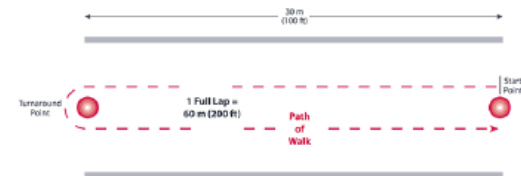
Si reduce el deterioro de la calidad de vida

Caracterizar la farmacocinética y seguridad

TADALAFILO: ENSAYO CLÍNICO H6D-MC-LVJJ

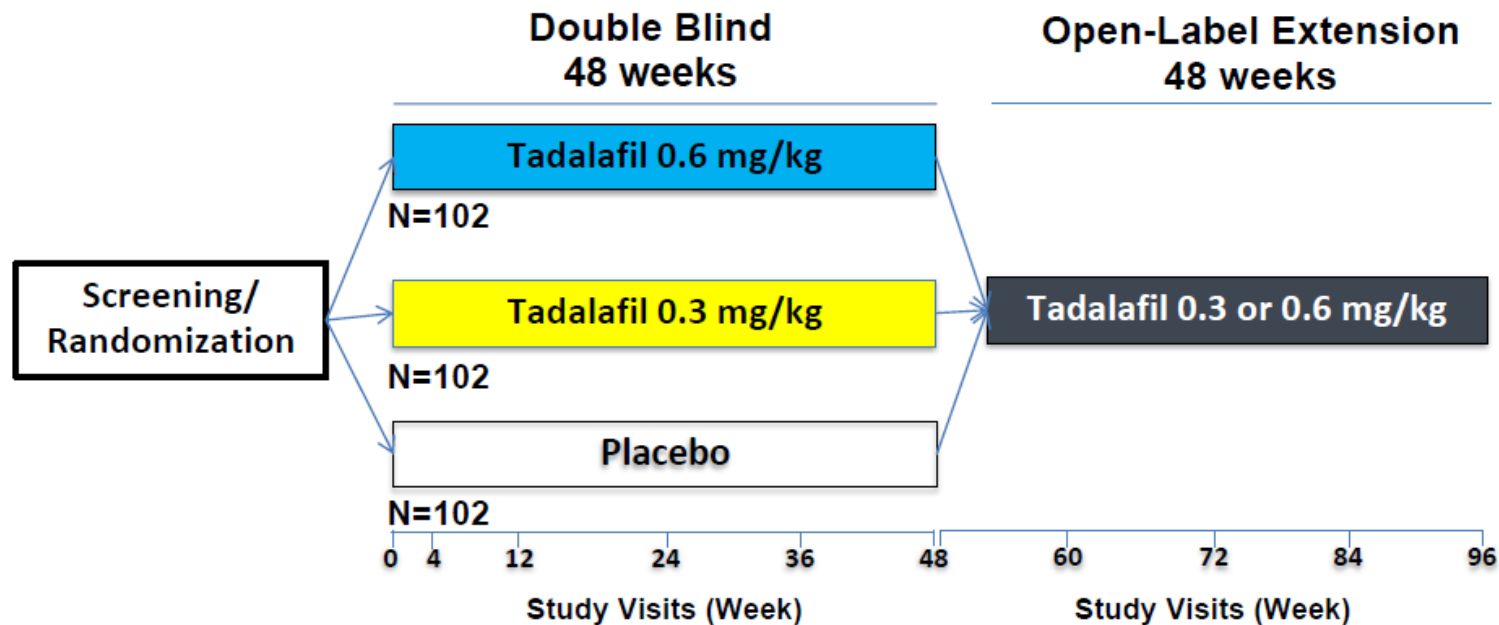
Efficacy Measures – Functional Assessments

- **Primary – 6 Minute Walk Test**
- **Secondary**
 - North Star Ambulatory Assessment (NSAA)
 - Timed-function tests + grading:
 - Supine-to-standing (with NSAA)
 - 10 meter walk/run (with NSAA)
 - 4-stair climb and descend
- **Exploratory**
 - Performance of the Upper Limb (PUL) Scale



TADALAFILO: ENSAYO CLÍNICO H6D-MC-LVJJ

Study Design Overview



- Global, multicenter, phase 3 trial (14 countries, ~55 sites)
- Enrollment: 306 boys with DMD
- 90% power to detect a placebo-adjusted difference of 30 meters in changes in 6MWD for each tadalafil dose group

TADALAFILO: ENSAYO CLÍNICO H6D-MC-LVJJ

LVJJ Dose Rationale

Single doses that restored normal skeletal muscle blood flow responses to exercise

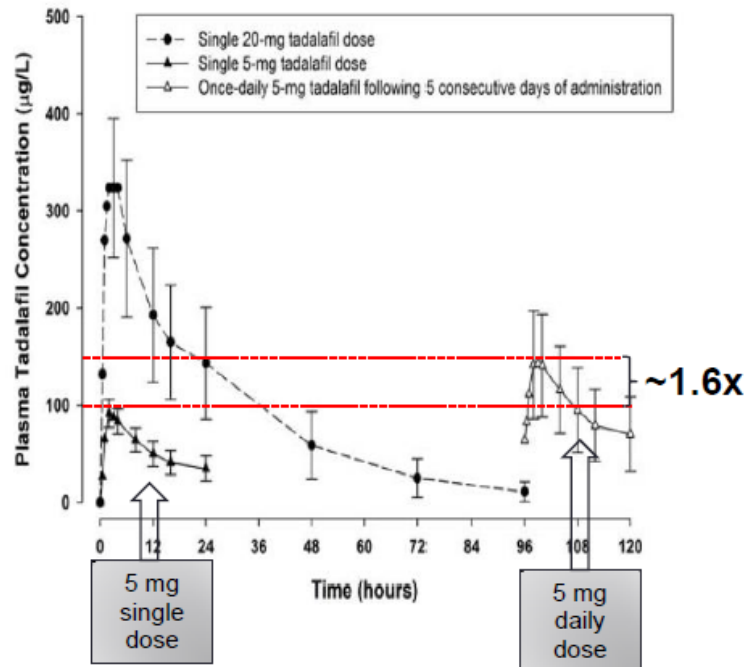
0.5 mg/kg

1.0 mg/kg

Daily doses to achieve comparable steady-state plasma levels

0.3 mg/kg

0.6 mg/kg



TADALAFILO: ENSAYO CLÍNICO H6D-MC-LVJJ

- CRITERIOS DE INCLUSIÓN:
 - Varón diagnosticado de DMD (clínica + genética o biopsia muscular)
 - De 7 a 14 años
 - Tratamiento estable con corticoides
 - Ambulante: 200-400 metros en 6MWD
 - Diferencia menor del 20% en la distancia de 6MWD en 2 ocasiones previo a la randomización
 - FEV > 50% por ecocardiograma

TADALAFILO: ENSAYO CLÍNICO H6D-MC-LVJJ

- CRITERIOS DE EXCLUSIÓN:

- Cirugía que afecte la fuerza muscular en los 3 meses previos
- Daño en EEII que no permita realizar 6MWT
- Problema conductual/cognitivo que impida realizar 6MWT
- Medicación que afecte la fuerza muscular o arginina, los 3 meses previos
- Ensayo previo 3 meses antes, o ensayo terapia génica
- Medicaciones concomitantes (Nitratos, GH...)
- Arritmia o insuficiencia cardíaca clase III o IV de la NYHA

TRATAMIENTOS ESPECIFICOS DE DISTROFINA

Posibilidades terapéuticas específicas en la DMD

1. **Reemplazar el gen de la distrofina**

1. Terapia génica: insertar el gen en las células musculares (Transferencia)
2. Terapia celular: insertar células madre con potencial para regenerar el músculo y que expresen la distrofina

2. **Restaurar la producción de distrofina**

1. **Alterando el procesamiento del RNAm para producir una distrofina funcional: Salto de exón.**
2. **Alterando los mecanismos de transferencia del RNAm**
Lectura a través de stop-codón prematuro: PTC 124

3. **Inducir la producción de proteínas endógenas similares a la distrofina:** utrofina

Transferencias génicas mediadas por virus.

Principales Problemas:

1.- El tamaño del gen

Capacidad portadora de *virus adenoasociados*: 4,5 kb.

Se han desarrollado microdistrofinas genes de hasta 4 kb que consiguen grados variables de éxito en el ratón mdx, permitiendo entrever resultados futuros.

Townsend et al. Mol Ther 2007;15:1086–1092..

Wang et al. Mol Ther 2007;15:1160–1166.

Gregorevic et al. Mol Ther 2008;66:657–664.

McNeil et al. Muscle Nerve (2010);41: 740–745.

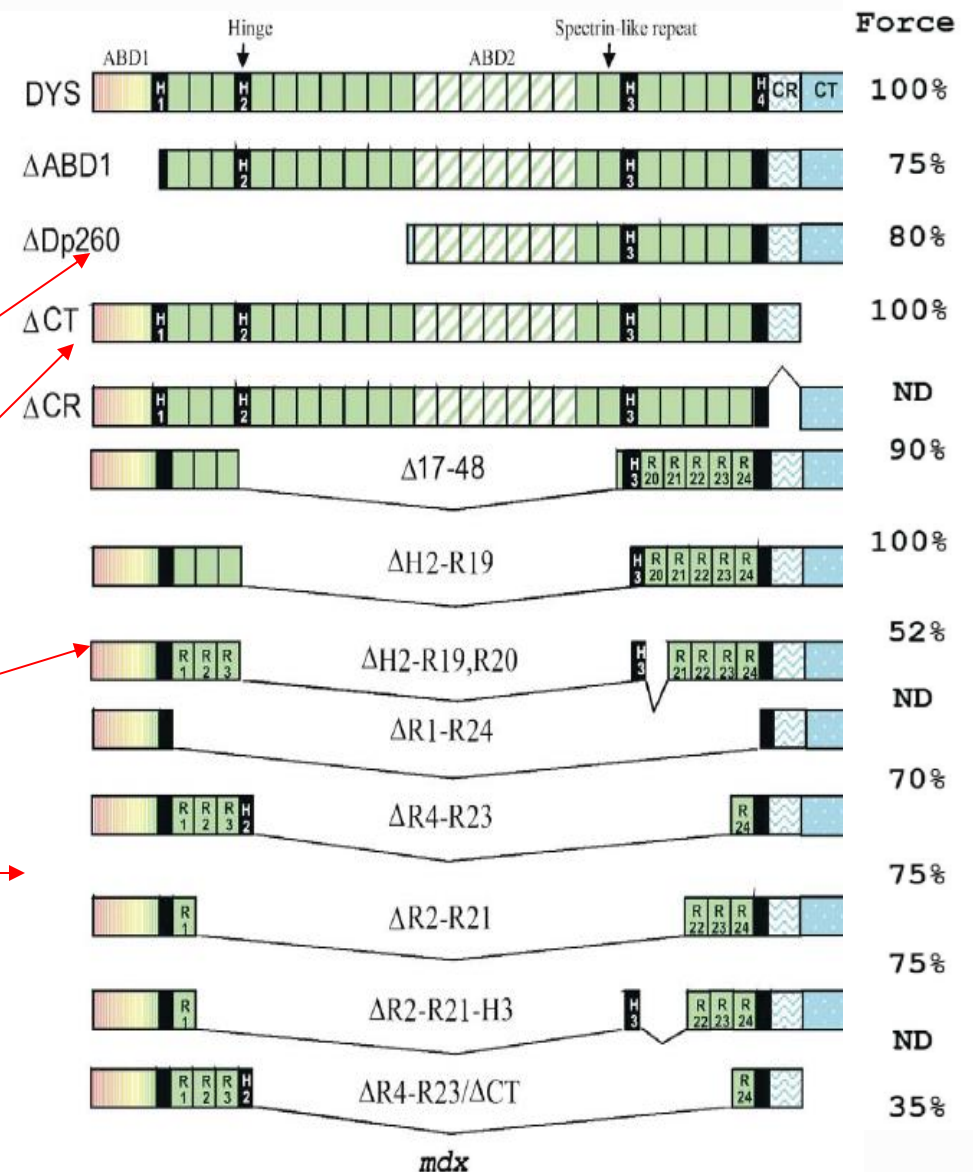
Ya hay algunos ensayos en marcha (<http://www.clinicaltrials.gov>).

Fase I.- Safety Study of Mini-dystrophin Gene to Treat Duchenne Muscular Dystrophy NCT00428935
J Child Neurol 2010; 25:1149-1157

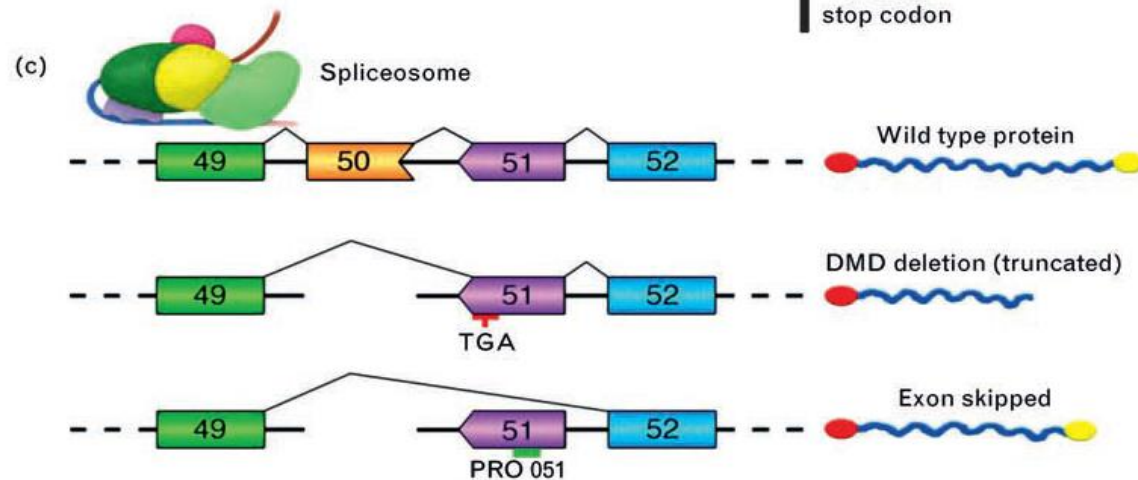
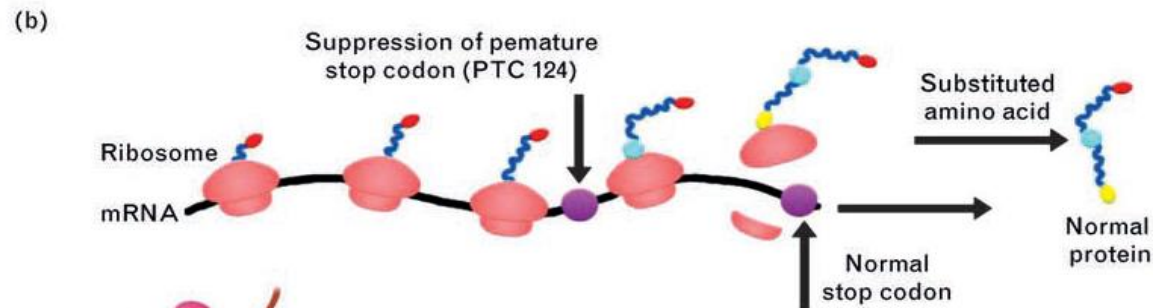
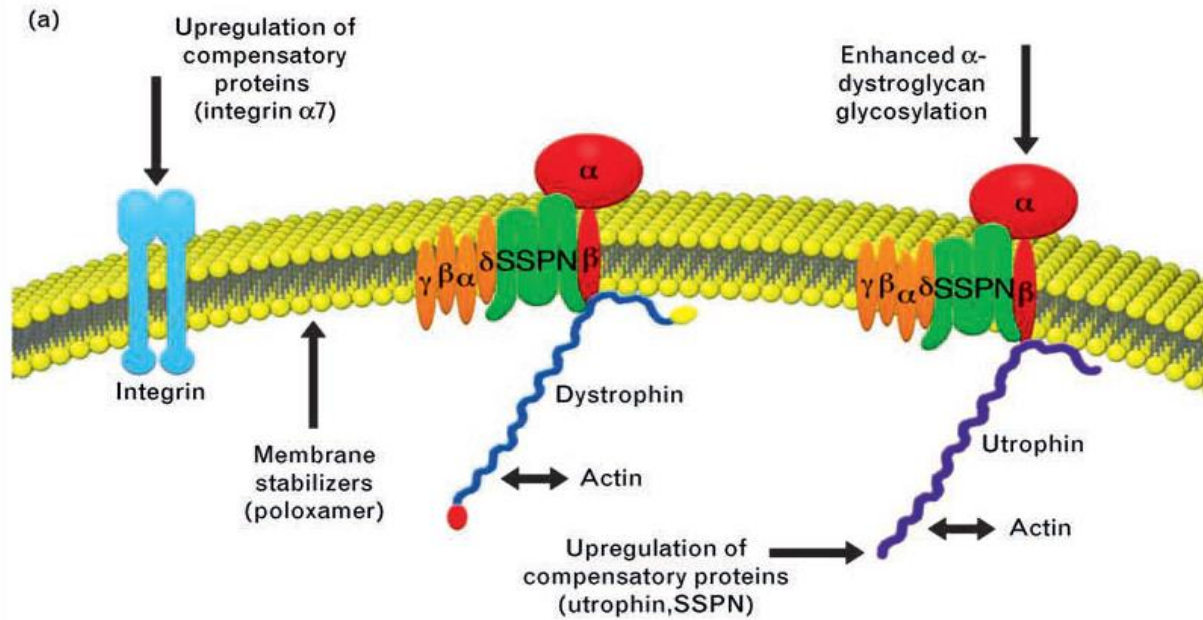
2.- la respuesta inmunológica del huésped al vector introducido.

La distrofina está formada por varios dominios y mantiene una alta funcionalidad cuando diversas partes de estos se suprimen. [Nature 1990,343:180-182](#)

- Modelos de ratones mdx con diferentes deleciones en los 4 dominios de la distrofina:
 - Pérdida del dominio N-terminal se asocia con **pérdida de función moderada**
 - El grupo C-terminal no es indispensable
 - la deleción del dominio rico en cisteína, causa un **fenotipo severo**.
 - La estructura central “rod” puede ser ampliamente reducida, **con fenotipo leve**



[Neuromusc Dis 2002;12\(supl 1\):s23-s29](#)



Emerging genetic therapies to treat Duchenne muscular dystrophy

Nelson et al

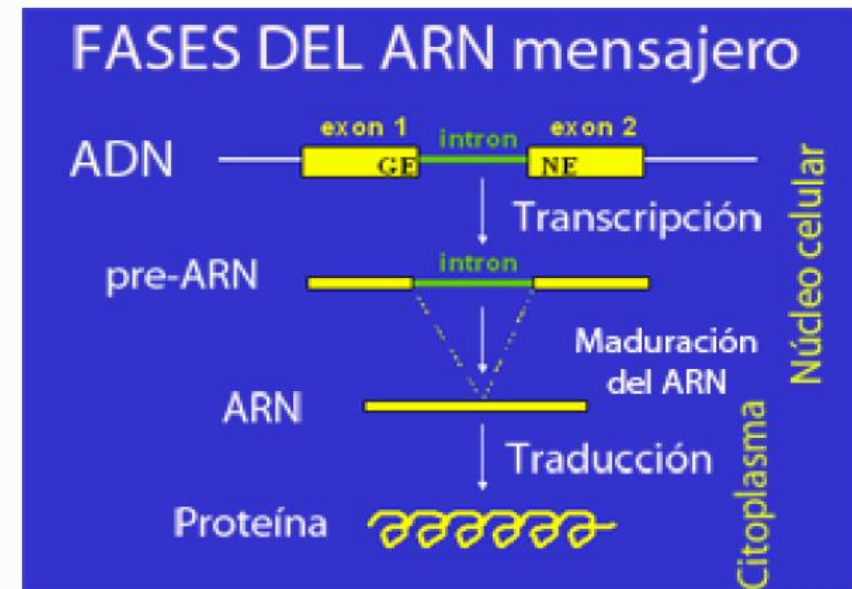
Current Opinion in Neurology 2009, 22:532–538

TERAPIAS DIRIGIDAS AL ARN

TERAPIAS DIRIGIDAS AL ARN

15% de todos los cambios de ADN implicados en enfermedades humanas causan alguna forma de **alteración del ensamblaje del ARN (*splicing*)**

*Un splicing anormal puede estar causado por cambios de ADN exonicos o intronicos que pueden excluir a un exon y activar *splicing* alternativos en el intron que **Incluyan** secuencias intronicas, **excluyan** secuencias exonicas o generen transcritos anormales.*



Hastings ML, Krainer AR. Curr Opin Cell Biol 2001; 13: 302-9.
Wilton SD, Fletcher S. Curr Gene Ther 2011; 11: 259-75.

Modificaciones del splicing:

excluir,

incluir o

cambiar exones en el ARNm mutado.

Sólo da resultado en algunas mutaciones genéticas :

- **exclusión de exones** (skipping) → si la proteína truncada resultante mantiene suficiente funcionalidad
- **inclusión de exones** será útil en aquellas mutaciones que conducen a delecciones del mRNA.

Hastings ML, Krainer AR. Curr Opin Cell Biol 2001; 13: 302-9.

Wilton SD, Fletcher S. Curr Gene Ther 2011; 11: 259-75.

SALTO DE EXON

SALTO DE EXON mediante OLIGONUCLEÓTIDOS ANTISENTIDO (OAS)

Zamecnik y Stephenson en 1978 publicaron el uso de OAS como posible modo de modificación de la expresión de los genes

[Proc Natl Acad Sci USA 1978; 75: 280-4](#)

Posteriores transformaciones químicas los hicieron resistentes a su degradación por nucleasas.

Oligoribonucleótidos antisentido (OAS)

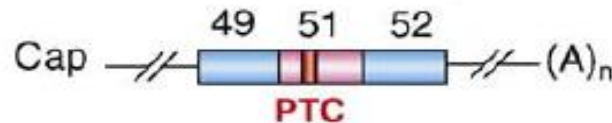
- RNA de 20-30 nucleótidos
- Se adhieren a su secuencia complementaria en el exón que se quiere suprimir, o en el intrón
- Interfieren con el ensamblaje de forma que el exón “diana” se “salta” en el RNAm.
- **Solo deben unirse a la secuencia complementaria de el exón diana** (no omisión en otros genes)

Deletion of exon 50

DMD pre-mRNA



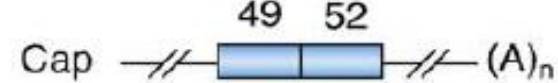
mRNA



protein



Truncated and unstable dystrophin: DMD phenotype



Shortened dystrophin: BMD-like phenotype

- restablece la pauta de lectura
- Se forma una proteína anómala, pero funcional
- Cambia mutación “Duchenne” en una mutación “Becker”.

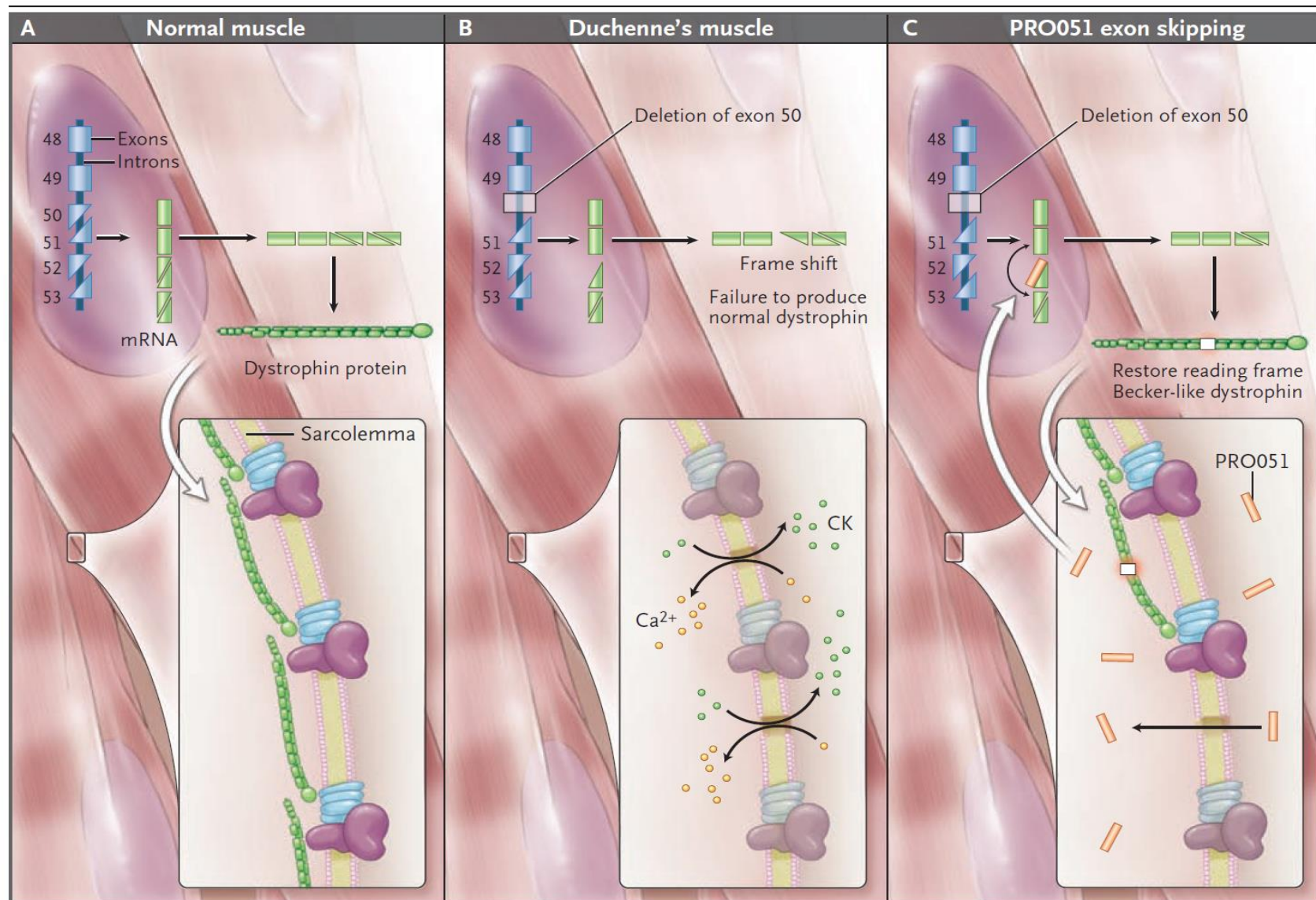


Figure 1. Mechanism of PRO051 in the Restoration of Dystrophin Expression through Exon Skipping.

La eficacia de los OAS esta influenciada por :

- la capacidad de liberación,
- de distribución sistémica y
- de persistencia celular, y
- Por el grado de especificidad de su unión a la diana.

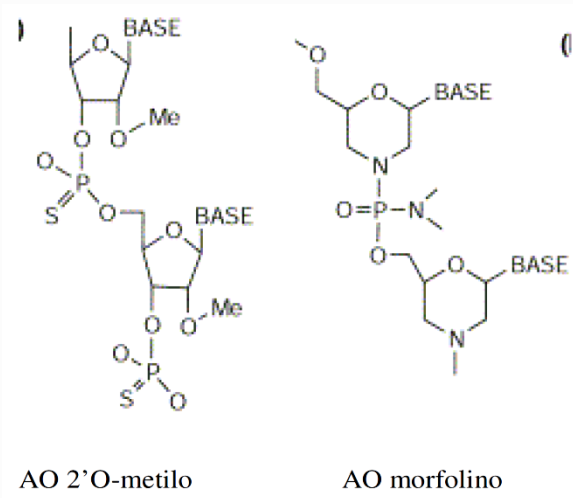
Wilton et al: Current Gene Therapy, 2011, 11, 259-275

Tipos de OAS usados:

los 2'O-metilo fosforotioato y los fosforodiamidato-morfolinos.

- El OAS 2'O-metilo : **PRO051/GSK2402968,**
- **Morfolino, AVI-4658,**

Ambos OAS se unen a la secuencia potenciadora del empalme exonica en el exon 51. Al bloquear la secuencia, se omite el exon 51 en el ARNm.



PRO051/GSK2402968
Morfolino, AVI-4658

UCUUUACGGUAGAAGGAACU
GAUCUUUACGGUAGAAGGAACUACAACCUC

El OAS 2'O-metilo restaura la producción de proteína en cultivo de células del ratón mdx

Mann et al: Proc Natl Acad Sci U S A 2001; 98: 42-7.

Con amplia distribución corporal, pero con resultado irregular en diferentes músculos y sin conseguir producción sustancial de distrofina en el miocardio

Lu et al Nat Med 2003; 9: 1009-14

Lu et al Proc Natl Acad Sci U S A 2005; 102: 198-203.

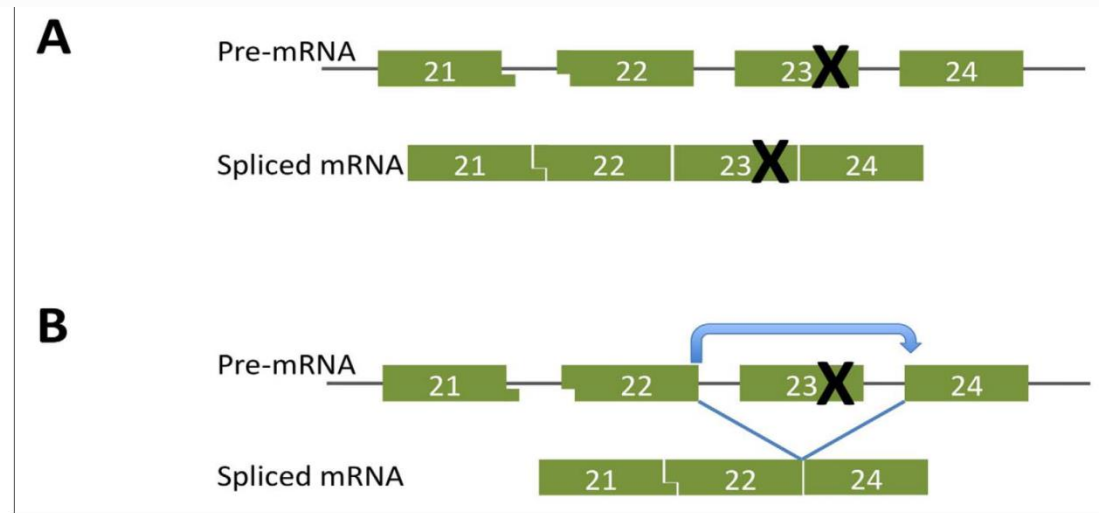


Figure 2. (A) The *mdx* mouse model of Duchenne muscular dystrophy is attributable to a nonsense mutation in exon 23 that blocks translation beyond this point. (B) Because exon 23 is not a frame-shifting exon, it can be skipped to generate a translatable transcript that produces dystrophin.

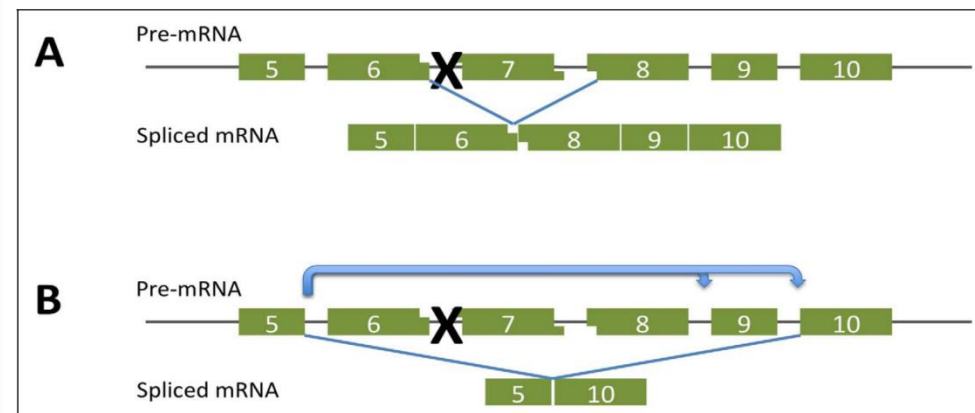
El OAS morfolino también activa la producción de distrofina en múltiples músculos **del ratón mdx**.

Alter et al. Nat Med 2006; 12: 175-7.

En el modelo canino, consigue formar distrofina nueva en proporción hasta del 50% en algunos músculos, que es funcionalmente útil. Un perro tratado se mantuvo sin deterioro a lo largo del tratamiento, a diferencia de lo observado en los perros no tratados



Yokota et al : Ann Neurol 2009; 65: 667-76.

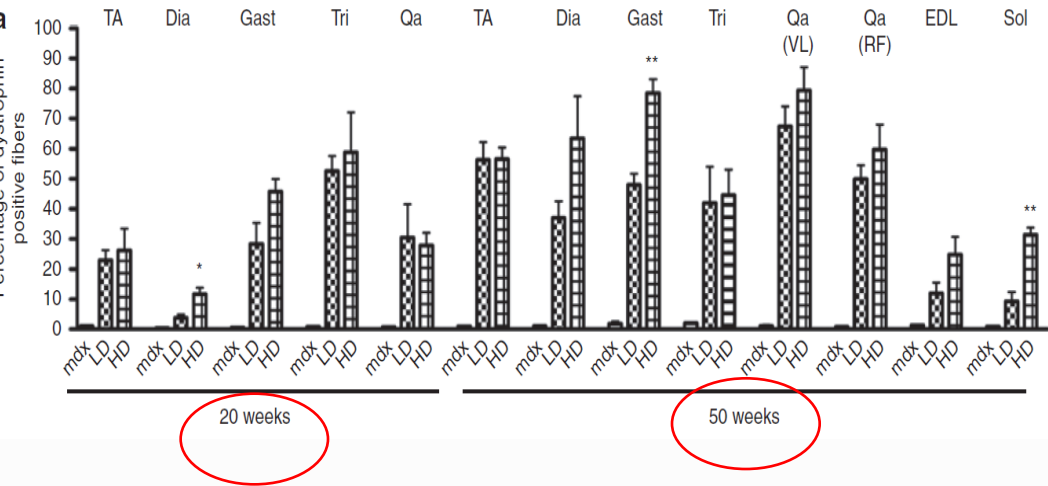


Chronic Systemic Therapy With Low-dose Morpholino Oligomers Ameliorates the Pathology and Normalizes Locomotor Behavior in *mdx* Mice

Alberto Malerba¹, Paul S Sharp², Ian R Graham¹, Virginia Arechavala-Gomez³, Keith Foster¹, Francesco Muntioni³, Dominic J Wells^{2,*} and George Dickson¹

¹School of Biological Sciences, Royal Holloway, University of London, Surrey, UK; ²Department of Cellular and Molecular Neuroscience,

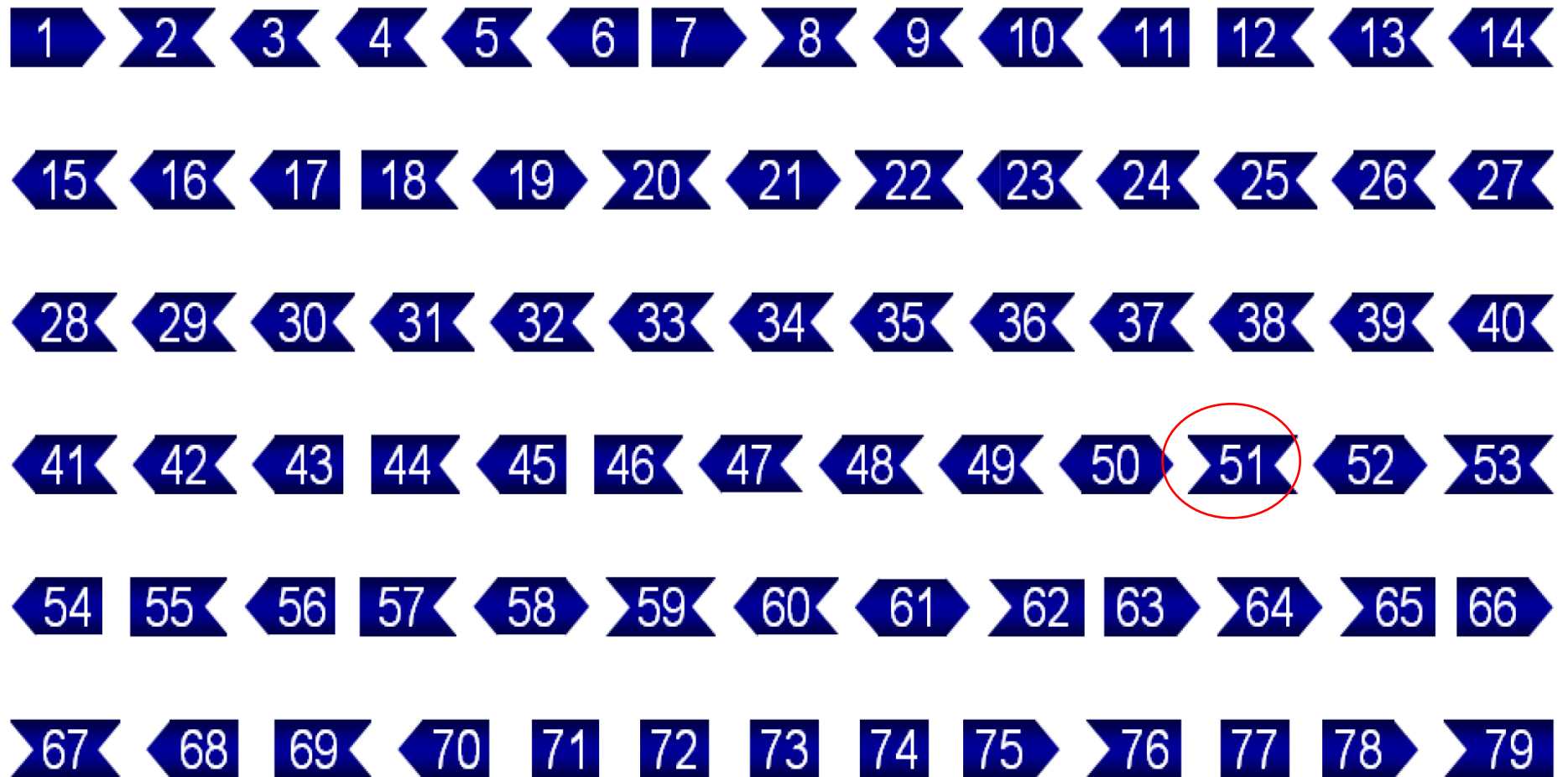
Molecular Therapy vol. 19 no. 2, 345–354 feb. 2011



The administration of antisense oligonucleotides (AOs) to skip one or more exons in mutated forms of the *DMD* gene and so restore the reading frame of the transcript is one of the most promising approaches to treat Duchenne muscular dystrophy (DMD). At present, preclinical studies demonstrating the efficacy and safety of long-term AO administration have not been conducted. Furthermore, it is essential to determine the minimal effective dose and frequency of administration. In this study, two different low doses (LDs) of phosphorodiamidate morpholino oligomer (PMO) designed to skip the mutated exon 23 in the *mdx* dystrophic mouse were administered for up to 12 months. Mice treated for 50 weeks showed a substantial dose-related amelioration of the pathology, particularly in the diaphragm. Moreover, the generalized physical activity was profoundly enhanced compared to untreated *mdx* mice showing that widespread, albeit partial, dystrophin expression restores the normal activity in *mdx* mice. Our results show for the first time that a chronic long-term administration of LDs of unmodified PMO, equivalent to doses in use in DMD boys, is safe, significantly ameliorates the muscular dystrophic phenotype and improves the activity of dystrophin-deficient mice, thus encouraging the further clinical translation of this approach in humans.

SALTO DE EXON 51:

Delección de los exones 45–50, 47–50, 48–50, 49–50, 50, 52 ó 52–63



Se han creado OAS para todos los exones de la DMD, cada uno con una estructura que bloquea solo el exon diana, sin afectar a ningún otro en los genes humanos.

En función de donde asienta la delección del gen *DMD*, *sera distinto el exon o exones a excluir.*

Las posibilidades teóricas de aplicación del salto de exon son del 64% de todos los pacientes con DMD

	Exon a ser omitido	% de todos los pacientes
	51	13.0
	45	8.1
	53	7.7
	44	6.2
	46	4.3
	52	4.1
	50	4.0
	43	3.8
		51.2%

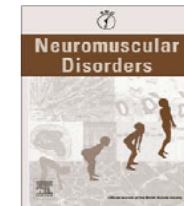
Aartsma-Rus A, et al: Muscle & Nerve 2006; 135-144.



Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd



Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human *DMD* gene: Implications for future clinical trials

Linda J. Popplewell^{a,1}, Carl Adkin^{b,1}, Virginia Arechavala-Gomez^a, Annemieke Aartsma-Rus^c, Christa L. de Winter^c, Steve D. Wilton^d, Jennifer E. Morgan^b, Francesco Muntoni^b, Ian R. Graham^a, George Dickson^{a,*}

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^cCenter for Human and Clinical Genetics, Leiden University Medical Center, PO Box 9600, 2300RC Leiden, The Netherlands

^dCentre for Neurological and Neuromuscular Disorders, Australian Neuromuscular Research Institute, University of Western Australia, Perth, WA 6009, Australia

A B S T R A C T

Duchenne muscular dystrophy (DMD) is caused by the lack of functional dystrophin protein, most commonly as a result of a range of out-of-frame mutations in the *DMD* gene. Modulation of pre-mRNA splicing with antisense oligonucleotides (AOs) to restore the reading frame has been demonstrated in vitro and in vivo, such that truncated but functional dystrophin is expressed. AO-induced skipping of exon 51 of the *DMD* gene, which could treat 13% of DMD patients, has now progressed to clinical trials. We describe here the methodical, cooperative comparison, in vitro (in DMD cells) and in vivo (in a transgenic mouse expressing human dystrophin), of 24 AOs of the phosphorodiamidate morpholino oligomer (PMO) chemistry designed to target exon 53 of the *DMD* gene, skipping of which could be potentially applicable to 8% of patients. A number of the PMOs tested should be considered worthy of development for clinical trial.

Doble omisión y multiomisión de exón

Muchos DMD necesitaran salto dos o más exones para restaurar el marco de lectura.

Se prevé que la omisión simultanea del 45 al 55 cambie una DMD por una DM Becker, leve, hasta en el 63% de los pacientes.

Se ha probado la omision de estos 11 exones en mioblastos de una persona sana y de dos pacientes con DMD, pero no se lograron mas que niveles bajos de distrofina, por lo que, en la actualidad, todavía no es clínicamente útil

[Bérout et al. Human Mutation 2007; 28; 196-202.](#)

Preclinical PK and PD Studies on 2'-O-Methyl-phosphorothioate RNA Antisense Oligonucleotides in the *mdx* Mouse Model

Hans Heemskerk¹, Christa de Winter¹, Petra van Kuik², Niki Heuvelmans², Patrizia Sabatelli^{3,4}, Paola Rimessi³, Paola Braghetta⁵, Gert-Jan B van Ommen¹, Sijf de Kimpe², Alessandra Ferlini³, Annemieke Aartsma-Rus¹ and Judith CT van Deutekom^{1,2}

¹Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; ²Prosensa Therapeutics B.V., Leiden, The Netherlands; ³Department of Experimental and Diagnostic Medicine, Section of Medical Genetics, University of Ferrara, Ferrara, Italy; ⁴IGM-CNR, Unit of Bologna c/o IOR, Bologna, Italy; ⁵Department of Histology, Microbiology, and Medical Biotechnology, University of Padova, Padova, Italy

Molecular Therapy, 2010;18:1210–1217

studies in mice. The results demonstrate that the levels of oligonucleotides in dystrophin-deficient muscle fibers are much higher than in healthy fibers, leading to higher exon-skipping levels. Oligonucleotide levels and half-life differed for specific muscle groups, with heart muscle showing the lowest levels but longest half-life (~46 days). Intravenous (i.v.), subcutaneous (s.c.), and intraperitoneal (i.p.) delivery methods were directly compared. For each method, exon-skipping and novel dystrophin expression were observed in all muscles, including arrector pili smooth muscle in skin biopsies. After i.v. administration, the oligonucleotide peak levels in plasma, liver, and kidney were higher than after s.c. or i.p. injections. However, as the bioavailability was similar, and the levels of oligonucleotide, exon-skipping, and dystrophin steadily accumulated overtime after s.c. administration, we selected this patient-convenient delivery method for future clinical study protocols.

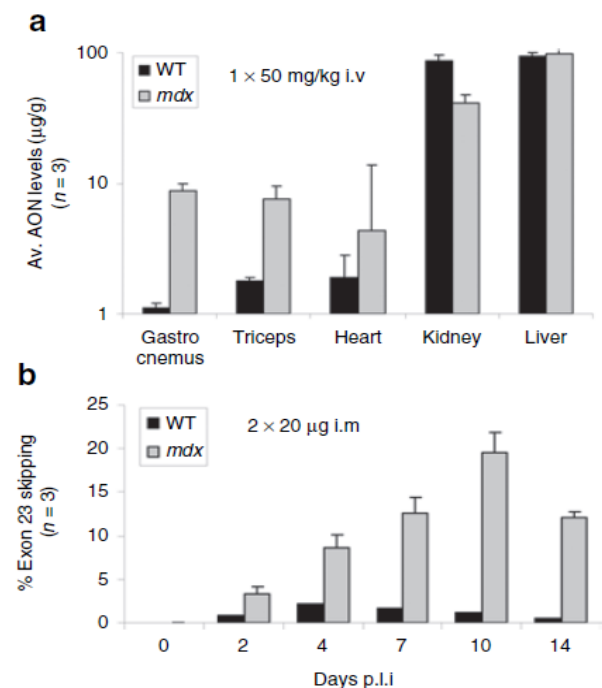


Figure 1 Enhanced levels of 2OMePS RNA AONs in dystrophic muscle. **(a)** Comparison of AON levels in skeletal muscles (gastrocnemius and triceps muscle), heart, kidney, and liver from wild-type (WT) versus *mdx* mice ($n = 3$), after a single intravenous (i.v.) injection of 50 mg/kg mouse exon 23-specific 2'-O-methyl-phosphorothioate antisense oligonucleotide (23AON). **(b)** Comparison of exon 23 skipping levels in gastrocnemius muscles from series of WT versus *mdx* mice ($n = 3$), at different time points (up to 14 days) after 2 intramuscular (i.m.) injections of 20 µg 23AON (with 24-hour interval).

Estudios realizados en humanos con DMD con OAS
PRO051/GSK2402968 (2'OMePS anti exon 51)

Local Dystrophin Restoration with Antisense Oligonucleotide PRO051

Judith C. van Deutekom, Ph.D., Anneke A. Janson, B.S., Ieke B. Ginjaar, Ph.D.,
Wendy S. Frankhuizen, B.S., Annemieke Aartsma-Rus, Ph.D.,
Mattie Bremmer-Bout, B.S., Johan T. den Dunnen, Ph.D., Klaas Koop, M.D.,
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Gerard J. Platenburg, M.Sc., Jan J. Verschuuren, M.D., Ph.D.,
and Gert-Jan B. van Ommen, Ph.D.

METHODS

Four patients, who were selected on the basis of their mutational status, muscle condition, and positive exon-skipping response to PRO051 in vitro, received a dose of 0.8 mg of PRO051 injected into the tibialis anterior muscle. A biopsy was performed 28 days later. Safety measures, composition of mRNA, and dystrophin expression were assessed.

RESULTS

PRO051 injection was not associated with clinically apparent adverse events. Each patient showed specific skipping of exon 51 and sarcolemmal dystrophin in 64 to 97% of myofibers. The amount of dystrophin in total protein extracts ranged from 3 to 12% of that found in the control specimen and from 17 to 35% of that of the control specimen in the quantitative ratio of dystrophin to laminin $\alpha 2$.

CONCLUSIONS

Intramuscular injection of antisense oligonucleotide PRO051 induced dystrophin synthesis in four patients with Duchenne's muscular dystrophy who had suitable mutations, suggesting that further studies might be feasible.

ORIGINAL ARTICLE

N Engl J Med 2011; 364: 1513-22.

Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy

Nathalie M. Goemans, M.D., Mar Tulinius, M.D., Ph.D.,
Johanna T. van den Akker, Ph.D., Brigitte E. Burm, Ph.D., Peter F. Ekhart,
Niki Heuvelmans, Tjadine Holling, Ph.D., Anneke A. Janson,
Gerard J. Platenburg, M.Sc., Jessica A. Sipkens, M.Sc., J.M. Ad Sitsen, M.D.,
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Gunnar Buyse, M.D., Ph.D., Niklas Darin, M.D., Ph.D.,
Jan J. Verschuuren, M.D., Ph.D., Giles V. Campion, M.D.,
Sjef J. de Kimpe, Ph.D., and Judith C. van Deutekom, Ph.D.

METHODS

We administered weekly abdominal subcutaneous injections of PRO051 for 5 weeks in 12 patients, with each of four possible doses (0.5, 2.0, 4.0, and 6.0 mg per kilogram of body weight) given to 3 patients. Changes in RNA splicing and protein levels in the tibialis anterior muscle were assessed at two time points. All patients subsequently entered a 12-week open-label extension phase, during which they all received PRO051 at a dose of 6.0 mg per kilogram per week. Safety, pharmacokinetics, serum creatine kinase levels, and muscle strength and function were assessed.

RESULTS

The most common adverse events were irritation at the administration site and, during the extension phase, mild and variable proteinuria and increased urinary α_1 -microglobulin levels; there were no serious adverse events. The mean terminal half-life of PRO051 in the circulation was 29 days. PRO051 induced detectable, specific exon-51 skipping at doses of 2.0 mg or more per kilogram. New dystrophin expression was observed between approximately 60% and 100% of muscle fibers in 10 of the 12 patients, as measured on post-treatment biopsy, which increased in a dose-dependent manner to up to 15.6% of the expression in healthy muscle. After the 12-week extension phase, there was a mean ($\pm$ SD) improvement of 35.2 ± 28.7 m (from the baseline of 384 ± 121 m) on the 6-minute walk test.

CONCLUSIONS

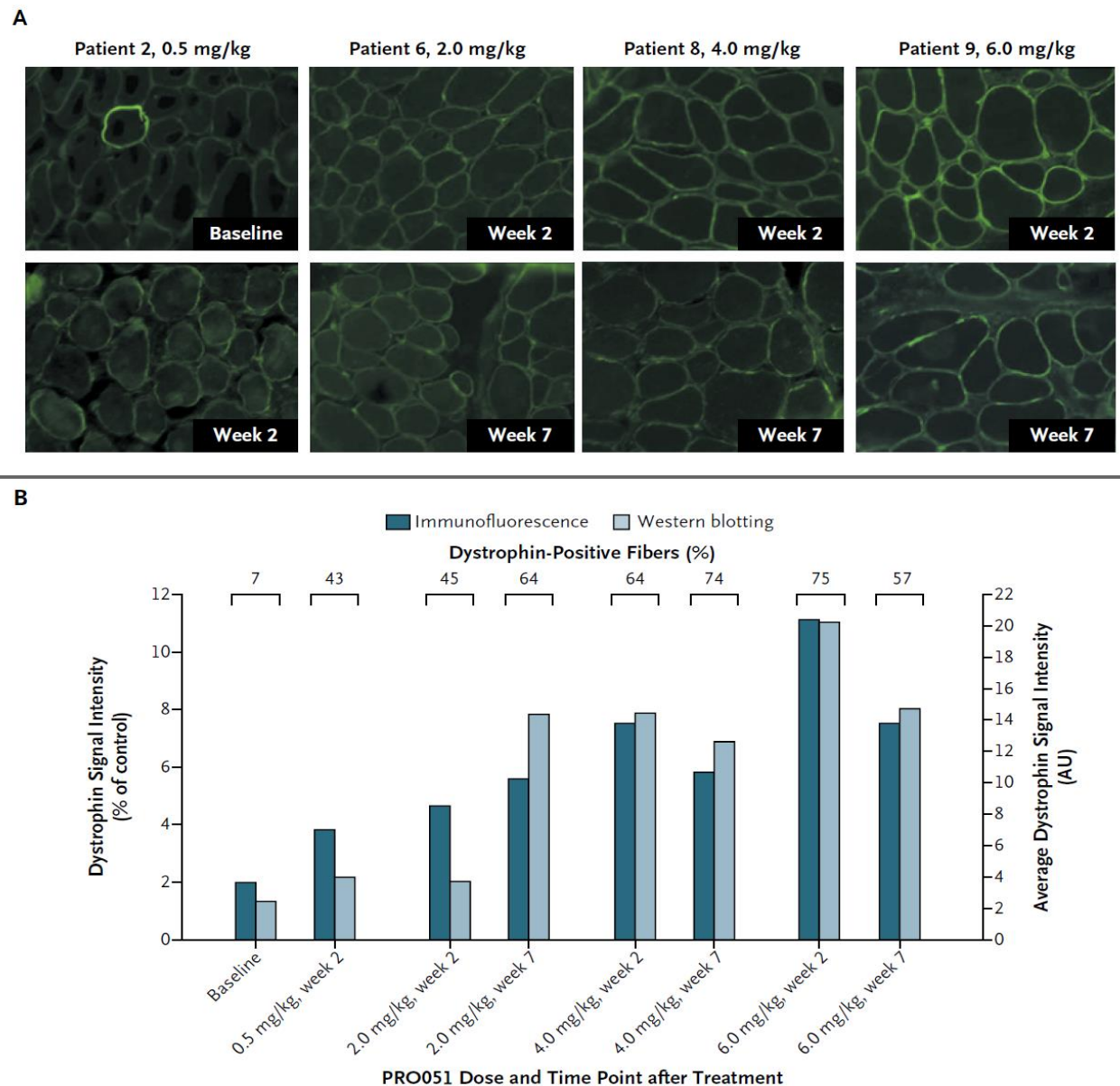
Systemically administered PRO051 showed dose-dependent molecular efficacy in patients with Duchenne's muscular dystrophy, with a modest improvement in the 6-minute walk test after 12 weeks of extended treatment. (Funded by Prosensa Therapeutics; Netherlands National Trial Register number, NTR1241.)

ORIGINAL ARTICLE

Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy

Nathalie M. Goemans, M.D., Mar Tulinius, M.D., Ph.D.,
 Johanna T. van den Akker, Ph.D., Brigitte E. Burm, Ph.D., Peter F. Ekhardt, M.Sc.,
 Niki Heuvelmans, Tjadine Holling, Ph.D., Anneke A. Janson,
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Systemic Administration of PRO051
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Sjef J. de Kimpe, Ph.D., and Judith C. van Deute

Table 2. Data from Muscle-Biopsy Analyses and the 6-Minute Walk Test, According to Dose and Weeks after Last Dose.*

Patient No.	Immunofluorescence Analysis						Western Blotting			6-Minute Walk Test		
	Baseline		2 Weeks		7 Weeks		Baseline	2 Weeks	7 Weeks	2 Weeks	13 Weeks	End of 12-Wk Extension Phase
	% positive fibers	mean signal intensity	% positive fibers	mean signal intensity	% positive fibers	mean signal intensity	dystrophin signal intensity				meters walked in 6 min vs. baseline distance	
0.5 mg/kg												
1	4	2.9	88	2.2	NT	NT	0.5	4.0	NT	-8	35	65
2	10	1.7	56	6.3	NT	NT	1.8	0.8	NT	-11	-69	69
3	NQ	1.4	20	3.0	NT	NT	5.1	7.2	NT	NA	NA	NA
2.0 mg/kg												
4	NT	NT	40	4.6	80	7.8	NT	5.4	8.6	-37	-86	NA
5	NT	NT	50	6.7	91	5.5	NT	2.8	23.5	-30	5	28
6	NT	NT	NQ	2.7	20	3.5	NT	3.0	11.0	7	11	21
4.0 mg/kg												
7	NT	NT	64	5.2	65	4.6	NT	7.4	11.4	11	31	66
8	NT	NT	76	15.6	85	9.2	NT	13.5	6.5	33	-46	16
9	NT	NT	51	1.8	71	3.7	NT	22.5	20.0	-11	19	50
6.0 mg/kg												
10	NT	NT	100	13.2	75	10.1	NT	28.5	22.5	39	-1	49
11	NT	NT	89	15.5	20	6.9	NT	19.6	9.5	-19	-38	-6
12	NT	NT	34	4.7	75	5.6	NT	12.6	12.2	-15	17	-6

* PRO051 was given for 5 weeks and then stopped for a period of 6 to 15 months, during which muscle-biopsy data were collected 2 weeks and 7 weeks after the last dose. The 6-minute walk test was performed 2 weeks and 13 weeks after the last dose. Treatment was then restarted for a 12-week period, at a dose of 6.0 mg per kilogram in all 12 patients. The 6-minute walk test was conducted once more, at the end of the extension period. Immunofluorescence analysis was performed on cross sections of muscle-biopsy specimens, with the percentage of positive fibers calculated for each cross section (in three to six images, depending on image size and quality), and the mean signal intensity reported relative to that of control samples (set at 100%). Western blotting was conducted with the use of total muscle-protein extracts, measuring dystrophin signal intensity relative to the average intensity of baseline samples. Baseline data for the 6-minute walk test are given in Table 1 in the Supplementary Appendix. NA denotes not assessed, NQ not quantifiable, and NT not tested.

ESTUDIOS CON PRO051/GSK2402968

16 sujetos con DMD en los dos estudios clínicos aludidos

Ensayos en marcha ([http:// www.clinicaltrials.gov](http://www.clinicaltrials.gov)):

DMD114044 fase III multicéntrico, randomizado, doble ciego, controlado con placebo (2/1), desde 2011. Dosis 6 mg/kg/sem.

Pretende reclutar 180 pacientes en Europa, Asia, Canadá y Sudamérica. Objet: Seguridad, farmacocinética y eficacia en niños ambulantes de 5 a 15 a.

DMD114876 fase II

Objet: evaluar dos dosis (3 mg/kg/ semana o bien 6 mg/kg/ semana, contra placebo) en niños con DMD.

DMD114117, fase II doble ciego, controlado con placebo

Objet: la eficacia de GSK2402968 en dos dosis (6 mg/kg/sem continuamente y otra de 6 mg/kg/semana intermitentemente), pretende reclutar 54 casos. **DMD114118**, evaluar **en niños con DMD no ambulantes** la farmacocinética y el efecto de PRO051/GSK2402968 en inyecciones subcutáneas de 6mg/kg/semana continua, 6mg/kg/semana intermitente en comparación con la evolución natural.

DMD144349, fase III, extensión abierta de de los **DMD114117** y **DMD114044**.

Comment Period Extended to 3/23/2015 for Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials

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Trial record **1 of 4** for: **duchenne AND drisapersen**

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Drisapersen Duchenne Muscular Dystrophy (DMD) Treatment Protocol

This study has been withdrawn prior to enrollment.

(Rights for the further development of drisapersen have been transferred to Prosensa. Therefore this study has been cancelled before enrollment.)

Sponsor:

GlaxoSmithKline

Information provided by (Responsible Party):

GlaxoSmithKline

ClinicalTrials.gov Identifier:

NCT01890798

First received: June 27, 2013

Last updated: March 20, 2014

Last verified: March 2014

[History of Changes](#)

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[Tabular View](#)

No Study Results Posted

[Disclaimer](#)

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No Study Results Posted on ClinicalTrials.gov for this Study

Terminación de la fase abierta del ensayo fase III Drisapersen de 186 pacientes tras el resultado de las 48 semanas DMD114044.

Goemans N, Campbell C, Kraus JE, et al. Drisapersen efficacy and safety in Duchenne muscular dystrophy: results of a phase III, randomized, double-blind, placebo-controlled trial (study DMD114044). World Muscle Society Congress; Asilomar, CA, USA; Oct 1–5, 2013.

Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study



Thomas Voit, Haluk Topaloglu, Volker Straub, Francesco Muntoni, Nicolas Deconinck, Giles Campion, Sjeff De Kimpe, Michelle Eagle, Michela Guglieri, Steve Hood, Lia Liefwaard, Afrodite Lourbakos, Allison Morgan, Joanna Nakielnny, Naashika Quarcoo, Valeria Ricotti, Katie Rolfe, Laurent Servais, Claire Wardell, Rosamund Wilson, Padraig Wright, John E Kraus

Summary

Background Duchenne muscular dystrophy is caused by dystrophin deficiency and muscle deterioration and preferentially affects boys. Antisense-oligonucleotide-induced exon skipping allows synthesis of partially functional dystrophin. We investigated the efficacy and safety of drisapersen, a 2'-O-methyl-phosphorothioate antisense oligonucleotide, given for 48 weeks.

Methods In this exploratory, double-blind, placebo-controlled study we recruited male patients (≥ 5 years of age; time to rise from floor ≤ 7 s) with Duchenne muscular dystrophy from 13 specialist centres in nine countries between Sept 1, 2010, and Sept 12, 2012. By use of a computer-generated randomisation sequence, we randomly allocated patients (2:2:1:1; block size of six; no stratification) to drisapersen 6 mg/kg or placebo, each given subcutaneously and either continuously (once weekly) or intermittently (nine doses over 10 weeks). The primary endpoint was change in 6-min walk distance (6MWD) at week 25 in patients in the intention-to-treat population for whom data were available. Safety assessments included renal, hepatic, and haematological monitoring and recording of adverse events. This trial is registered with ClinicalTrials.gov, number NCT01153932.

Findings We recruited 53 patients: 18 were given continuous drisapersen, 17 were given intermittent drisapersen, and 18 were given placebo (continuous and intermittent groups combined). At week 25, mean 6MWD had increased by 31.5 m (SE 9.8) from baseline for continuous drisapersen, with a mean difference in change from baseline of 35.09 m (95% CI 7.59 to 62.60; $p=0.014$) versus placebo. We recorded no difference in 6MWD changes from baseline between intermittent drisapersen (mean change -0.1 [SE 10.3]) and placebo (mean difference 3.51 m [-24.34 to 31.35]) at week 25. The most common adverse events in drisapersen-treated patients were injection-site reactions (14 patients given continuous drisapersen, 15 patients given intermittent drisapersen, and six given placebo) and renal events (13 for continuous drisapersen, 12 for intermittent drisapersen, and seven for placebo), most of which were subclinical proteinuria. None of the serious adverse events reported (one for continuous, two for intermittent, and two for placebo) resulted in withdrawal from the study.

Interpretation Continuous drisapersen resulted in some benefit in 6MWD versus placebo at week 25. The safety findings are similar to those from previous studies. Ambulation improvements in this young population with early-stage Duchenne muscular dystrophy are encouraging but need to be confirmed in larger studies.

Lancet Neurol 2014; 13: 987–96

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See [Comment](#) page 963

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Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study

Thomas Voit, Haluk Topaloglu, Volker Straub, Francesco Muntoni, Nicolas Deconinck, Giles Campion, Sjef J De Kimpe, Michelle Eagle, Michela Guglieri, Steve Hood, Lia Liefjaard, Afrodite Lourbakos, Allison Morgan, Joanna Nakielny, Naashika Quarcoo, Valeria Ricotti, Katie Rolfe, Laurent Servais, Claire Wardell, Rosamund Wilson, Padraig Wright, John E Kraus

	Placebo (combined; n=18)	Drisapersen 6 mg/kg continuous (n=18)	Drisapersen 6 mg/kg intermittent (n=17)
Baseline			
Number of patients	18	18	17
Mean (SD)	403.18 (45.13)	427.61 (70.05)	394.57 (66.95)
Week 25 (primary endpoint)			
Number of patients	16	16	15
Adjusted mean change (SE)	-3.6 (9.7)	31.5 (9.8)	-0.1 (10.3)
Adjusted mean difference vs placebo (95% CI)		35.09 (7.59 to 62.60)	3.51 (-24.34 to 31.35)
p value		0.014	0.801
Week 49 (secondary endpoint)			
Number of patients	17	18	15
Adjusted mean change (SE)	-24.7 (12.8)	11.2 (12.6)	2.4 (13.6)
Adjusted mean difference vs placebo (95% CI)		35.84 (-0.11 to 71.78)	27.08 (-9.83 to 63.99)
p value		0.051	0.147

Missing data for the 6-min walk distance (6MWD) in the primary analysis was a result of tight visit windows—ie, when a visit was attended 4 or more days early or late.

Table 2: Change from baseline in 6-min walk distance (intention-to-treat population, observed case data)

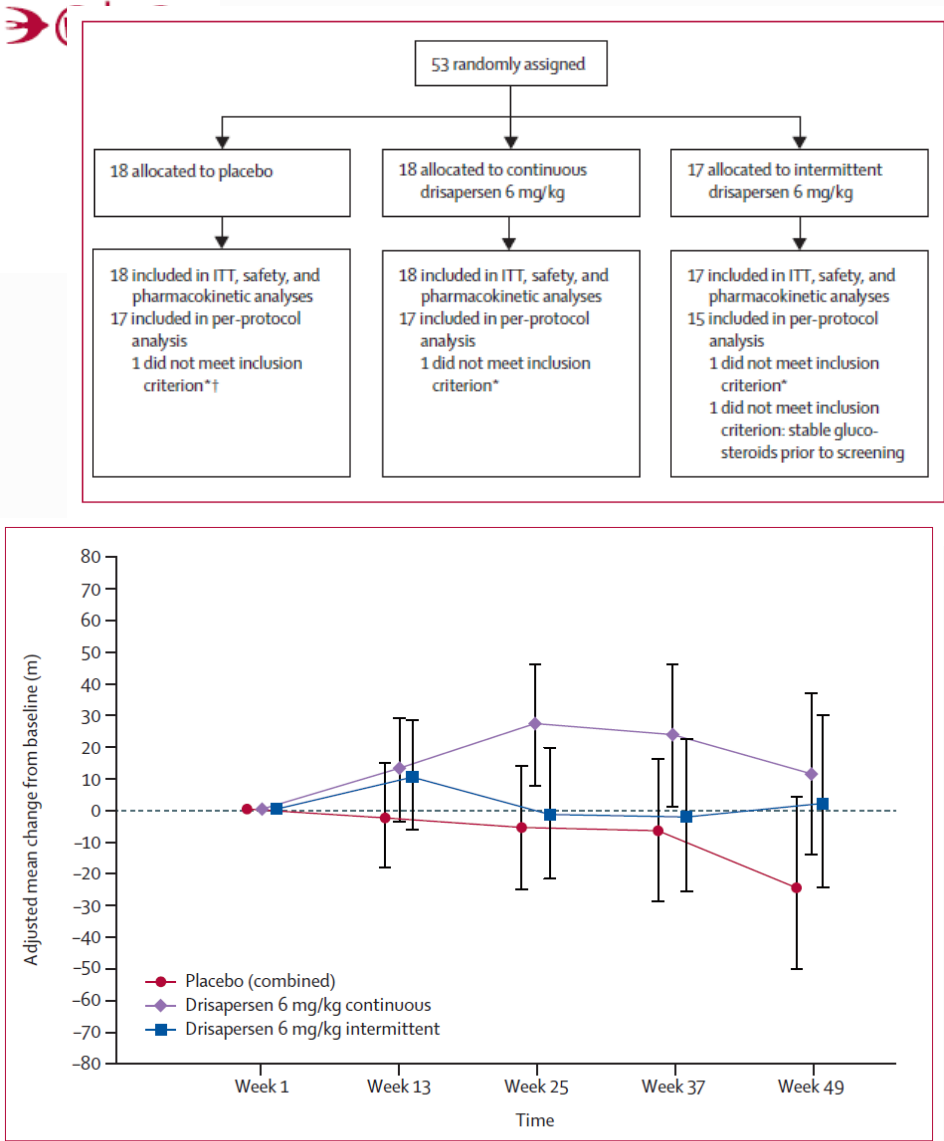


Figure 2: Change from baseline in 6-min walk distance at week 49, MMRM analysis (intention-to-treat population)

Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial

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Abstract

Duchenne muscular dystrophy (DMD) is a progressive, lethal neuromuscular disorder caused by the absence of dystrophin protein due to mutations of the dystrophin gene. Drisapersen is a 2'-O-methyl-phosphorothioate oligonucleotide designed to skip exon 51 in dystrophin pre-mRNA to restore the reading frame of the mRNA. This study assessed safety, tolerability, and pharmacokinetics of drisapersen after a single subcutaneous administration in non-ambulatory subjects. Eligible subjects were non-ambulant boys aged ≥ 9 years, in wheelchairs for ≥ 1 to ≤ 4 years, with a diagnosis of DMD resulting from a mutation correctable by drisapersen treatment. Four dose cohorts were planned (3, 6, 9 and 12 mg/kg), but study objectives were met with the 9 mg/kg dose. Less than proportional increase in exposure was demonstrated over the 3–9 mg/kg dose range, though post hoc analysis showed dose proportionality was more feasible over the 3–6 mg/kg range. Single doses of drisapersen at 3 and 6 mg/kg did not result in significant safety or tolerability concerns; however, at the 9 mg/kg dose, pyrexia and transient elevations in inflammatory parameters were seen. The maximum tolerated dose of 6 mg/kg drisapersen was identified for further characterization in multiple dose studies in the non-ambulant DMD

OAS P-Morfolino (AVI-4658) contra el exón 51

Estudio Fase I/II, 7 pacientes con DMD, intramuscular en el músculo EDB :

Fue seguro y produjo distrofina en el 44-79% de las fibras

Kinali et al, Lancet Neurology 2009;8:9118-28)

Estudio de fase I/II Cirak et al: Lancet 2011; 378: 595–605.

OAS P-Morfolino (AVI-4658) contra el exón 51

Tratamiento crónico, dosis acumuladas.
Seguridad a largo plazo?

Dosis tan bajas como cuatro inyecciones semanales de 5 mg/kg de P-morfolino induce expresión significativa de distrofina en el ratón mdx

Dosis de P-morfolino aplicadas durante un año son seguras en el ratón.
Restaura la producción de distrofina tanto a dosis de 5 mg/kg como a 50 mg/kg, y el ratón tratado consigue moverse como el animal sano.
Sin embargo, como muestran otros estudios, no se consigue expresión de distrofina en el músculo cardíaco

Malerba et al: *Hum Gene Ther* 2009; 20: 955–965.
Malerba et al: *Molecular Therapy* 2011; 19, 345–354.

Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study

Sebahattin Cirak*, Virginia Arechavala-Gomez*, Michela Guglieri, Lucy Feng, Silvia Torelli, Karen Anthony, Stephen Abbs, Maria Elena Garralda, John Bourke, Dominic J Wells, George Dickson, Matthew J A Wood, Steve D Wilton, Volker Straub, Ryszard Kole, Stephen B Shrewsbury, Caroline Sewry, Jennifer E Morgan, Kate Bushby, Francesco Muntoni

Lancet 2011; 378: 595–605

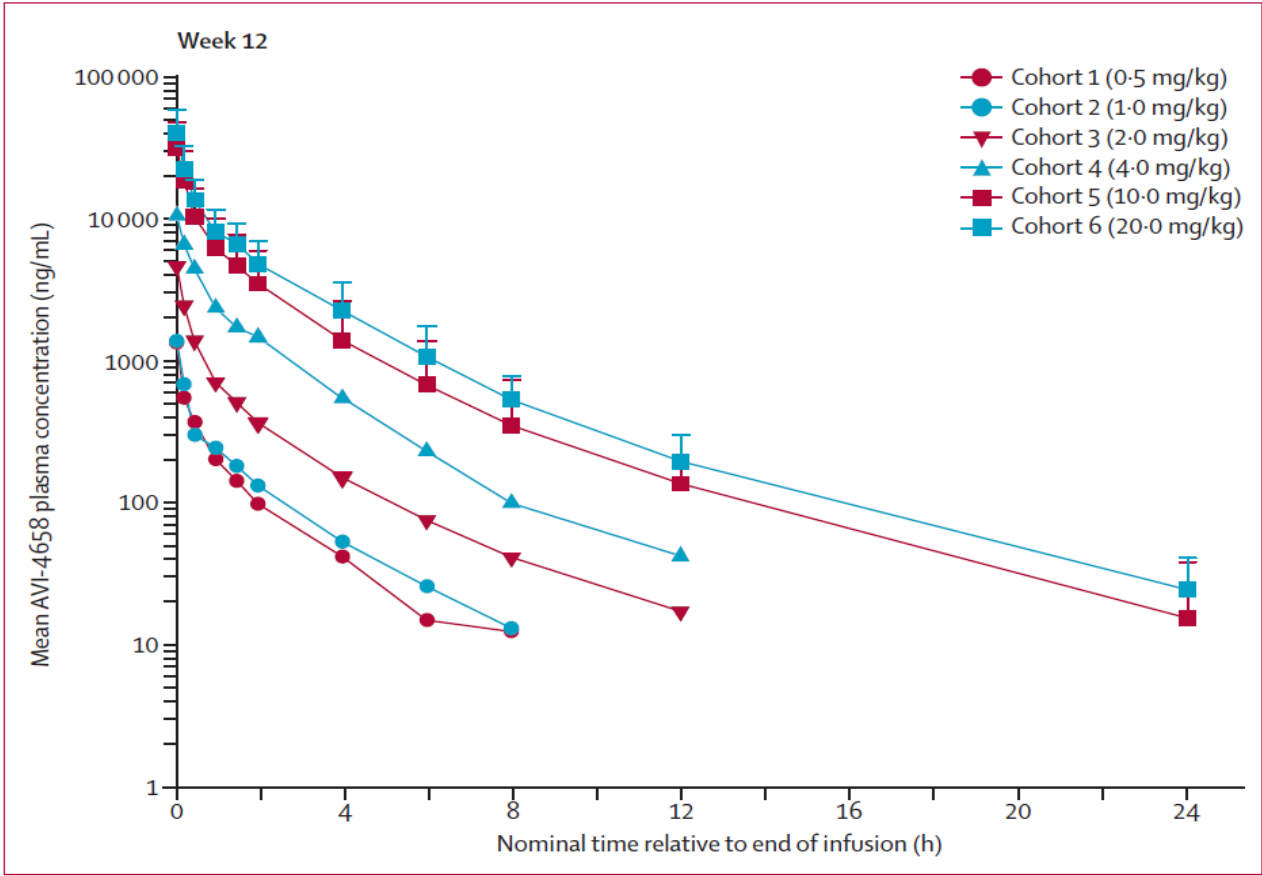


Figure 2: Plasma pharmacokinetics of AVI-4658
Mean plasma concentrations of AVI-4658 versus nominal elapsed time averaged across weeks 1, 6, and 12. Area under the curve (AUC) over 24 h accounted for greater than 95% of $AUC_{0-\infty}$ suggesting that most of the drug eliminated from the plasma was cleared within 24 h. AVI-4658 plasma exposure increased in a nearly proportional manner with dose for maximum concentration, AUC_{0-24h} and $AUC_{0-\infty}$. Error bars show SDs.

Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study

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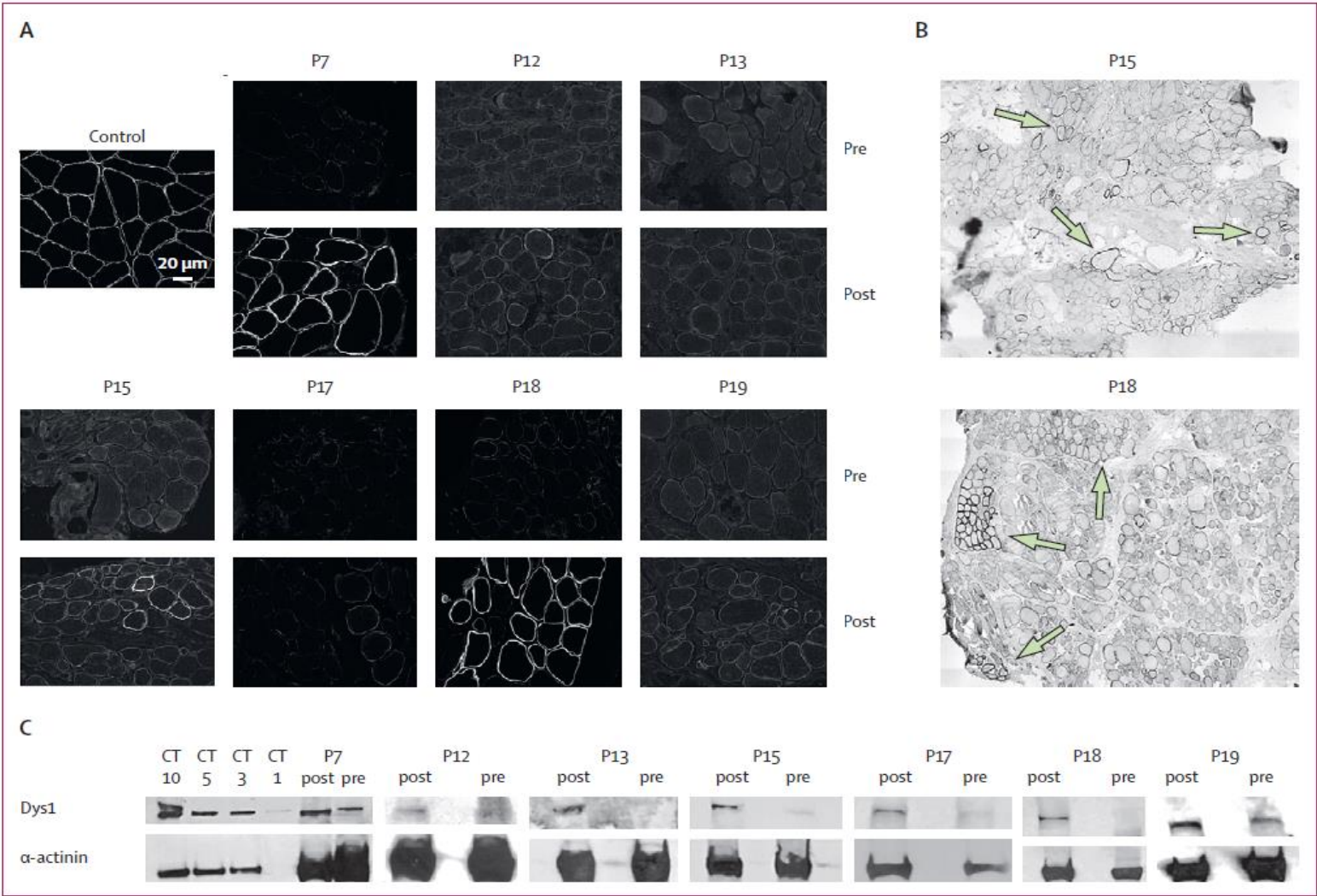


Figure 3: Dystrophin protein expression in the seven patients who responded to treatment
 (A) Transverse sections of treated (post) and untreated (pre) muscle specimens immunolabelled with MANDYS106 antibody. (B) Post-treatment biopsy samples from participants P15 and P18; low-magnification images showing widespread and patchy dystrophin expression (arrows). (C) Western blotting of pretreatment and post-treatment muscle biopsy samples with antidystrophin Dys1 (exon 26–30) and antisarcomeric α -actinin antibodies; an average of 150 μ g of total patient proteins was loaded per lane. CT= μ g control muscle extract.

Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study

Sebahattin Cirak, Virginia Arechavala-Gomez*, Michela Guglieri, Lucy Feng, Silvia Torelli, Karen Anthony, Stephen Abbs, Maria Elena Garralda, John Bourke, Dominic J Wells, George Dickson, Matthew J A Wood, Steve D Wilton, Volker Straub, Ryszard Kole, Stephen B Shrewsbury, Caroline Sewry, Jennifer E Morgan, Kate Bushby, Francesco Muntoni*

Estudio de fase I/II.

- 19 pacientes ambulantes con DMD
- Dosis de 0.5, 1.0, 2.0, 4.0, 10.0, y 20.0 mg/kg.
- Buena tolerancia, no se presentaron efectos adversos serios.
- Aumentó expresión de distrofina en relación directa con la dosis, en cantidad variable.
- 7 de los 19 pacientes respondieron al tratamiento,
- Los 3 pacientes con mayores respuestas alcanzaron 21%, 15%, y 55% de fibras distrofin positivas.

Eteplirsén for the Treatment of Duchenne Muscular Dystrophy

Jerry R. Mendell, MD,^{1,2,3,4} Louise R. Rodino-Klapac, PhD,^{1,4}
Zarife Sahenk, MD, PhD,^{1,2,3,4} Kandice Roush, RN,⁵ Loren Bird, RN,⁵
Linda P. Lowes, PhD,⁴ Lindsay Alfano, PT,⁴ Ann Maria Gomez, MD,^{1,4}
Sarah Lewis, HT, ASCP,^{1,4} Janaiah Kota, PhD,^{1,4} Vinod Malik, PhD,^{1,4}
Kim Shontz, BA, MS,^{1,4} Christopher M. Walker, PhD,^{1,4,6}
Kevin M. Flanigan, MD,^{1,2,3,4} Marco Corridore, MD,⁷ John R. Kean, MD,^{4,7}
Hugh D. Allen, MD,^{1,4} Chris Shilling, MS,^{1,3,4} Kathleen R. Melia, PhD,⁸
Peter Sazani, PhD,⁸ Jay B. Saoud, PhD,⁸ Edward M. Kaye, MD,⁸ and the
Eteplirsén Study Group

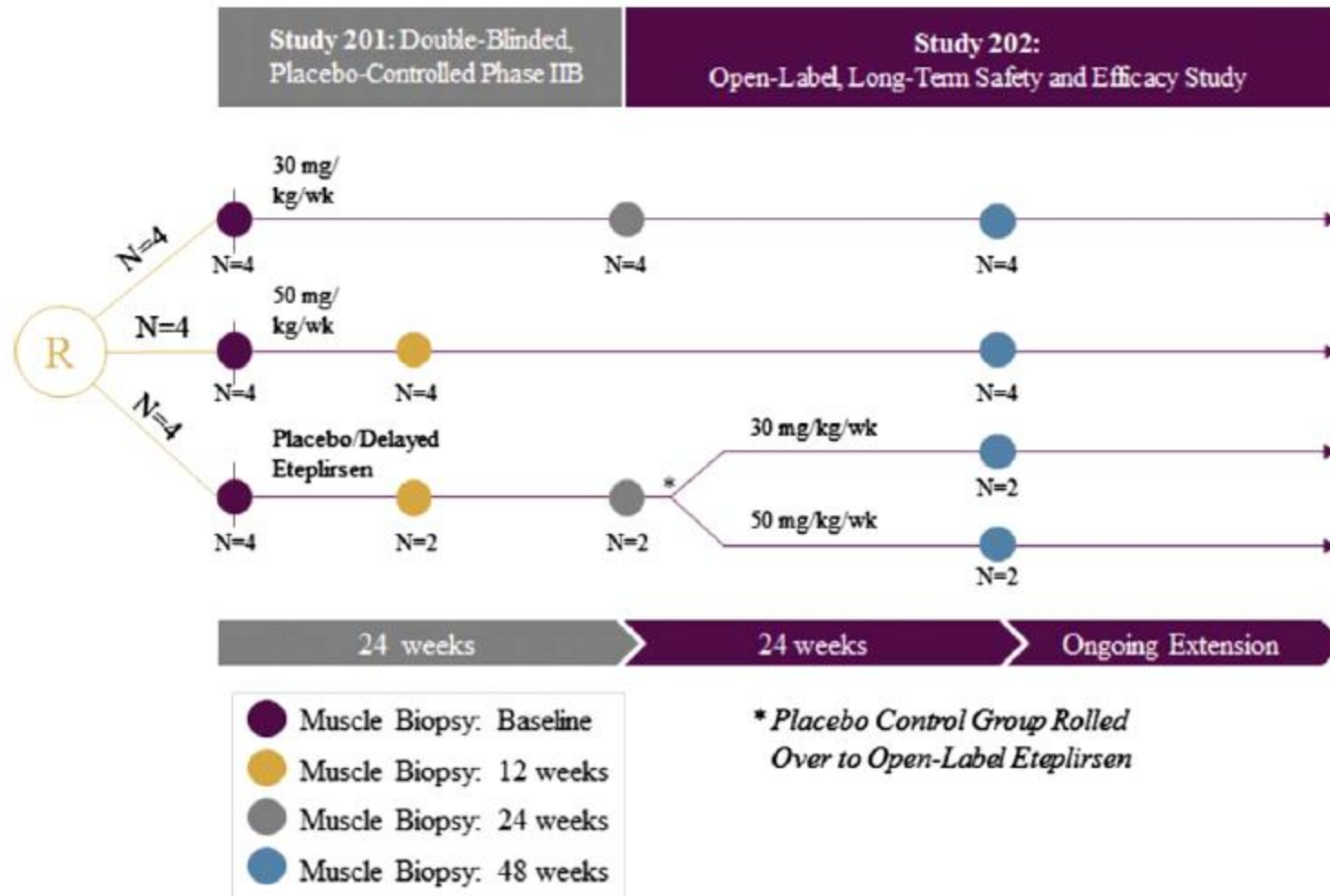
Objective: In prior open-label studies, eteplirsén, a phosphorodiamidate morpholino oligomer, enabled dystrophin production in Duchenne muscular dystrophy (DMD) with genetic mutations amenable to skipping exon 51. The present study used a double-blind placebo-controlled protocol to test eteplirsén's ability to induce dystrophin production and improve distance walked on the 6-minute walk test (6MWT).

Methods: DMD boys aged 7 to 13 years, with confirmed deletions correctable by skipping exon 51 and ability to walk 200 to 400 m on 6 MWT, were randomized to weekly intravenous infusions of 30 or 50 mg/kg/wk eteplirsén or placebo for 24 weeks ($n = 4/\text{group}$). Placebo patients switched to 30 or 50 mg/kg eteplirsén ($n = 2/\text{group}$) at week 25; treatment was open label thereafter. All patients had muscle biopsies at baseline and week 48. Efficacy included dystrophin-positive fibers and distance walked on the 6MWT.

Results: At week 24, the 30 mg/kg eteplirsén patients were biopsied, and percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma. Ambulation-evaluable eteplirsén-treated patients experienced a 67.3 m benefit compared to placebo/delayed patients ($p \leq 0.001$).

Interpretation: Eteplirsén restored dystrophin in the 30 and 50 mg/kg/wk cohorts, and in subsequently treated, placebo-controlled subjects. Duration, more than dose, accounted for dystrophin production, also resulting in ambulation stability. No severe adverse events were encountered.

Eteplirsén for the Treatment of Duchenne Muscular Dystrophy



...ation stability. NO SEVERE ADVERSE EVENTS WERE ENCOUNTERED.

Eteplirsen for the Treatment of Duchenne Muscular Dystrophy

Jerry R. Mendell, MD,^{1,2,3,4} Louise R. Rodino-Klapac, PhD,^{1,4}
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Linda P. Lowes, PhD,⁴ Lindsay Alfano, PT,⁴ Ann Maria Gomez, MD,^{1,4}
Sarah Lewis, HT, ASCP,^{1,4} Janaiah Kota, PhD,^{1,4} Vinod Malik, PhD,^{1,4}

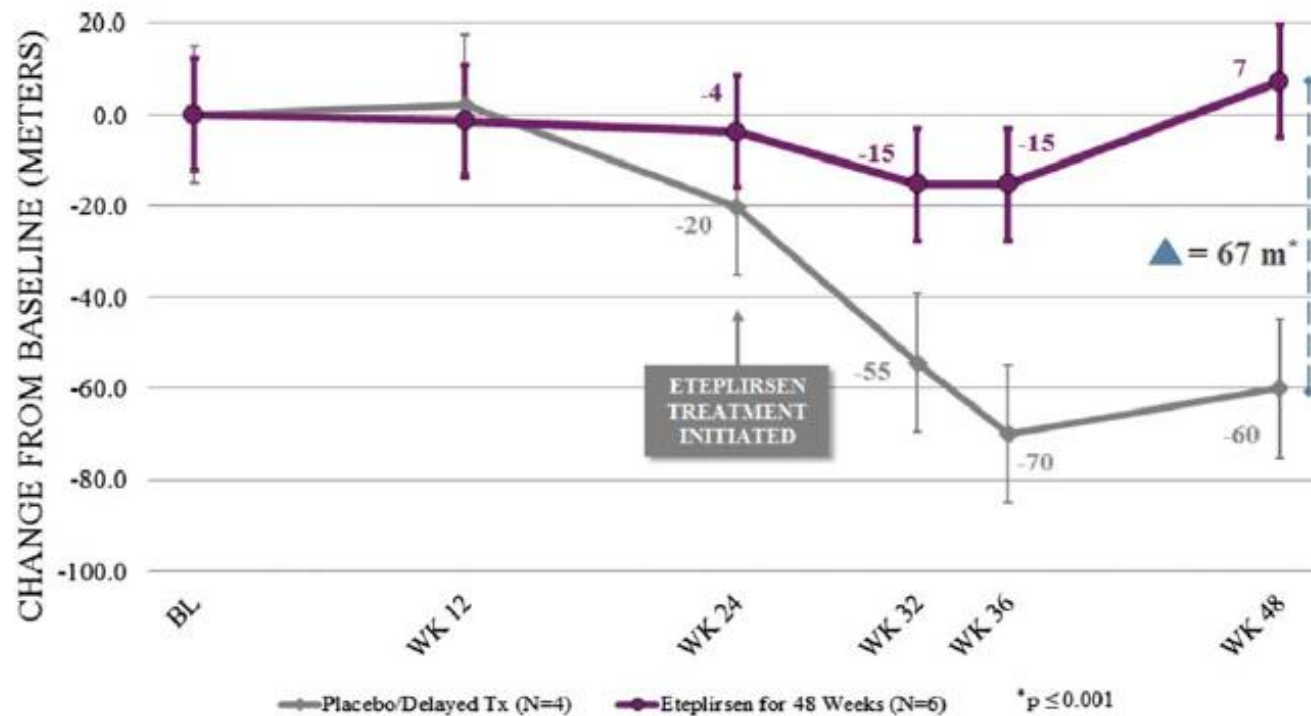


FIGURE 6: Functional efficacy of eteplirsen. The dark purple line shows the change from baseline (BL) in distance walked on the 6-minute walk test (6MWT) over time for the 6 evaluable patients who received eteplirsen from the start of Study 201 (the

Comparación entre ambos compuestos OAS

	Goemans and colleagues ⁵	Cirak and colleagues ⁶
Compound name	PRO051	AVI-4658
Chemistry	2'OMe	PMO
Administration method	Weekly subcutaneous injection	Weekly intravenous injection
Dose (mg/kg body weight)	0.5, 2, 4, and 6	0.5, 1, 2, 4, 10, and 20
Frequency of administration	5 weeks and extended 12 weeks	12 weeks
Total number of patients	12	19
Deletion exon(s) in patients	45–50, 48–50, 52	45–50, 47–50, 48–50, 49–50, 52
Maximum proportion of dystrophin-positive fibres	100% post-treatment	5% pretreatment, 55% post-treatment
Maximum dystrophin signal intensity to control muscles by immunofluorescence	15.6% post-treatment	11% pretreatment, 27% post-treatment
Maximum dystrophin protein level to control muscles by western blotting	Not available	5% pretreatment, 18% post-treatment
Serious adverse events	None	None
Cirak and colleagues⁶ calculated the success rate after subtracting the endogenous background level for each patient using a pretreatment biopsy, whereas Goemans and colleagues did not.⁵		
Table: Comparison of exon 51-skipping therapies using systemic antisense oligonucleotides		

Otros exones OAS- Prosensa

Drisapersen PRO044 PRO045 PRO053 Pre-Clinical Portfolio PRO052 and PRO055 PRO135 PRO289 Discovery Portfolio PROSPECT IP Portfolio	Indication	Compound	Discovery	Pre-clinical	Phase I/II	Phase III
	Duchenne Muscular Dystrophy (DMD)	Drisapersen	13% of DMD patients			
		PRO044	6% of DMD patients			
		PRO045	8% of DMD patients			
		PRO053	8% of DMD patients			
		PRO052	4% of DMD patients			
		PRO055	2% of DMD patients			
		PROSPECT	13% of DMD patients			
	Myotonic Dystrophy (DM1)	PRO135				
	Huntington's Disease (HD)	PRO289				

CONCLUSIONES

- El tratamiento de salto de exón con OAS es moderadamente prometedor en la DMD,
- Tanto con 2 oxi metilos como con P-morfolinos.
- No constituye la curación de la enfermedad sino una disminución de la gravedad.
- Tenemos resultados a corto plazo en la omisión del exón 51, que es aplicable al 13% de los pacientes con DMD.
- Clínicamente la mejora es ligera. Menor que la que esperábamos.
- No se consigue producir distrofina cardiaca.
- ¿enlentecen o estabilizan la evolución de la DMD o pueden conseguir algún grado de recuperación de la pérdida muscular?

CONCLUSIONES

- Formación muy variable de distrofina en unas fibras y otras
- Posible influencia del tipo de músculo, del avance de la enfermedad.
- En estudio los modos más eficientes de difusión y penetración en todos los músculos.
- Eliminación de la toxicidad a largo plazo.
- Posibles nuevos portadores con baja respuesta inmunológica y una mayor biodistribución.

Modulación de la translación del RNA (a nivel de los codones de terminación prematura – premature Termination Codon o PTC).

Probada en varias enfermedades:

Neuromusculares: DMD, AME

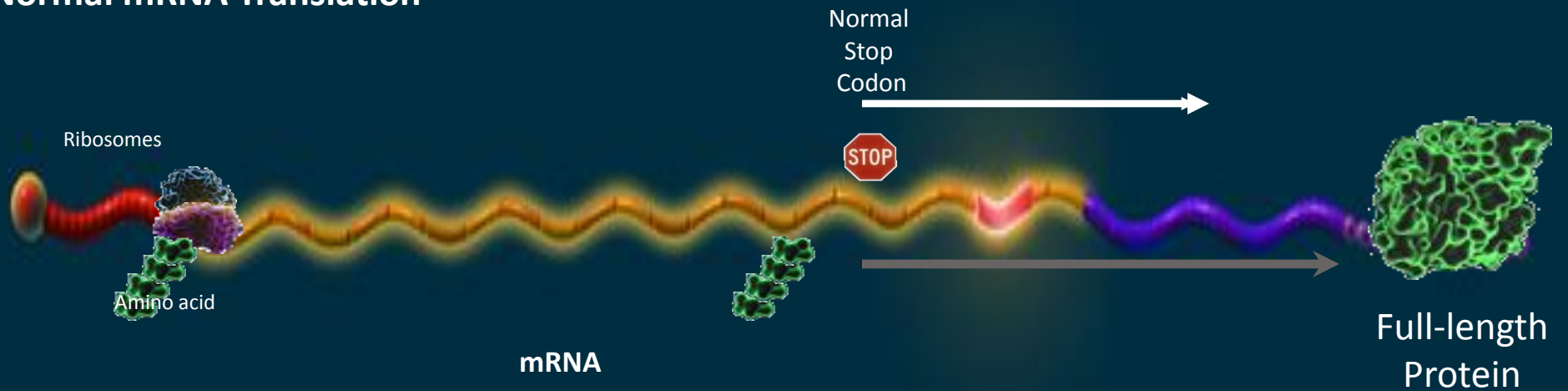
DMD: 13% a 15 % de los pacientes con DMD tienen una mutación sin sentido en el gen. Que induce una mutación de parada prematura - TGA, TAG, o TAA – en uno de los exones del gen de la distrofina.

Este tipo de tratamiento se ha logrado con
antibióticos
y con **PTC124 (Ataluren, Translarna ®)**

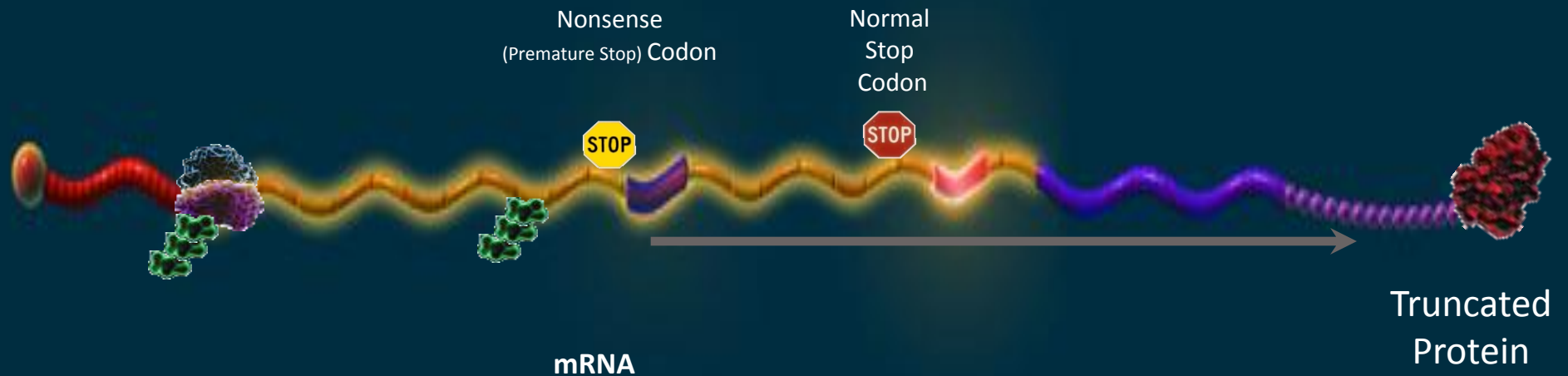
Welch EM, Barton ER, Zhuo J et al.: PTC124 targets genetic disorders caused by nonsense mutations. Nature 2007; 447, 87–91.

NORMAL FLOW OF GENETIC INFORMATION RESULTS IN FULL-LENGTH PROTEIN PRODUCTION

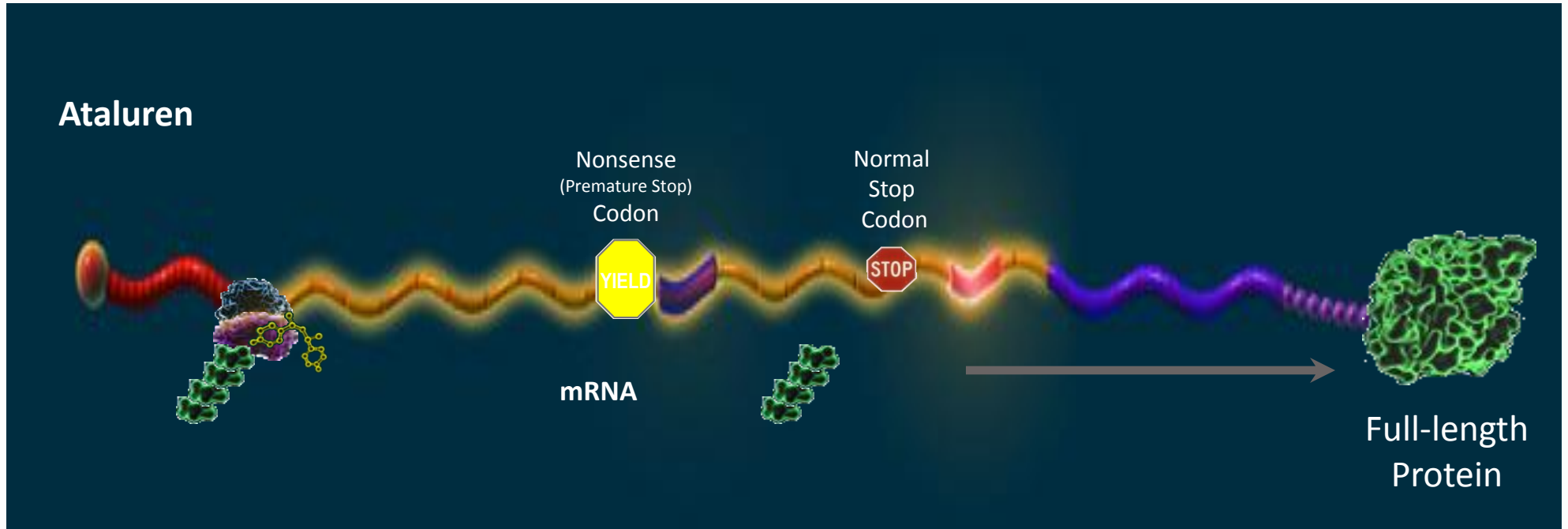
Normal mRNA Translation



NONSENSE MUTATION HALTS THE FLOW OF GENETIC INFORMATION AND RESULTS IN TRUNCATED PROTEIN PRODUCTION



OVERCOME NONSENSE MUTATIONS



- *A nonsense mutation must be present for Ataluren to be active*
- *Gene sequencing is necessary for patient selection*

LECTURA A TRAVES DE CODON-STOP

1.- Aminoglucósidos y negamicina

Se ligan al RNA ribosomal 18S e interfieren con la parada de la traslación. Permitiendo continuar la lectura a nivel de los PTCs.

-La eficiencia depende del tipo de codón de terminación prematura (PTC). El más eficiente es el UGA, seguido por el UAG y por ultimo del UAA.

La **gentamicina** fue el primero en utilizarse:

Restaura 10-20% de distrofina en el modelo murino de DMD tras inyectarla SC.

Pero:

No tienen especificidad por los PTCs,

Nefro y ototoxicidad.

Negamicina, antibiotico dipéptidico que también altera la translación

Incrementar los niveles de distrofina al 10% en musculo estriado y cardiaco (ratón mdx) Sin toxicidad.

No especificidad hacia los PTC.

[Wagner KR](#), [Hamed S](#), [Hadley DW](#), et al: Gentamicin treatment of Duchenne and Becker muscular dystrophy due to nonsense mutations. Ann. Neurol.2001;49, 706–711

[Barton-Davis ER](#), [Cordier L](#), [Shoturma DI](#), et al: Aminoglycoside antibiotics restore dystrophin function to skeletal muscles of mdx mice. J. Clin. Invest.1999;104, 375–381.

[Arakawa M](#), [Shiozuka M](#), [Nakayama Y](#), et al: Negamycin restores dystrophin expression in skeletal and cardiac muscles of mdx mice. J. Biochem. 2003;134, 751–758.

LECTURA A TRAVES DE CODON-STOP

2.- PTC124 (Ataluren®)

Similitud estructural con los aminoglucósidos.

Permite restaurar la lectura a nivel de los PTCs sin afectar a la terminación normal de la lectura de los genes.

Usado por vía oral o intraperitoneal

Incrementar la distrofina hasta 20-25% de lo normal en músculos en el ratón mdx.

Se ha comprobado la seguridad del PTC124 oral en voluntarios sanos (fase I).

Tras ello,
se realizó un **ensayo fase IIb (NCT00592553)** doble ciego, controlado contra placebo, para evaluar la seguridad y eficacia de dos dosis, 40 y 80 mg diarios, vía oral durante 48 semanas.
N= 174, ambulatorios mayores de 5 años en 37 centros.

Welch, E.M. et al. (2007) PTC124 targets genetic disorders caused by nonsense mutations. *Nature* 447, 87–91.

Hirawat S et al: Safety, tolerability, and pharmacokinetics of PTC124, a nonaminoglycoside nonsense mutation suppressor, following single- and multiple-dose administration to healthy male and female adult volunteers. *J. Clin. Pharmacol.* 2007;47, 430–444.

Finkel RS: Read-Through Strategies for Suppression of Nonsense Mutations in Duchenne/Becker Muscular Dystrophy: Aminoglycosides and Ataluren (PTC124). *Journal of Child Neurology* 25(9) 1158-1164

Results of a Phase 2b, Dose-Ranging Study of Ataluren (PTC124®) in Nonsense Mutation Duchenne/Becker Muscular Dystrophy (nmDBMD)

R Finkel¹, B Wong², K Bushby³, A Reha⁴, GL Elfring⁴, LL Miller⁴, J Babiak⁴, MA Morsy⁴, S Peltz⁴, E Welch⁴, L Atkinson⁴
for the Ataluren DBMD Steering Committee and Study Group

¹Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; ²Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA;

³Institute of Human Genetics, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK; ⁴PTC Therapeutics, South Plainfield, New Jersey, USA

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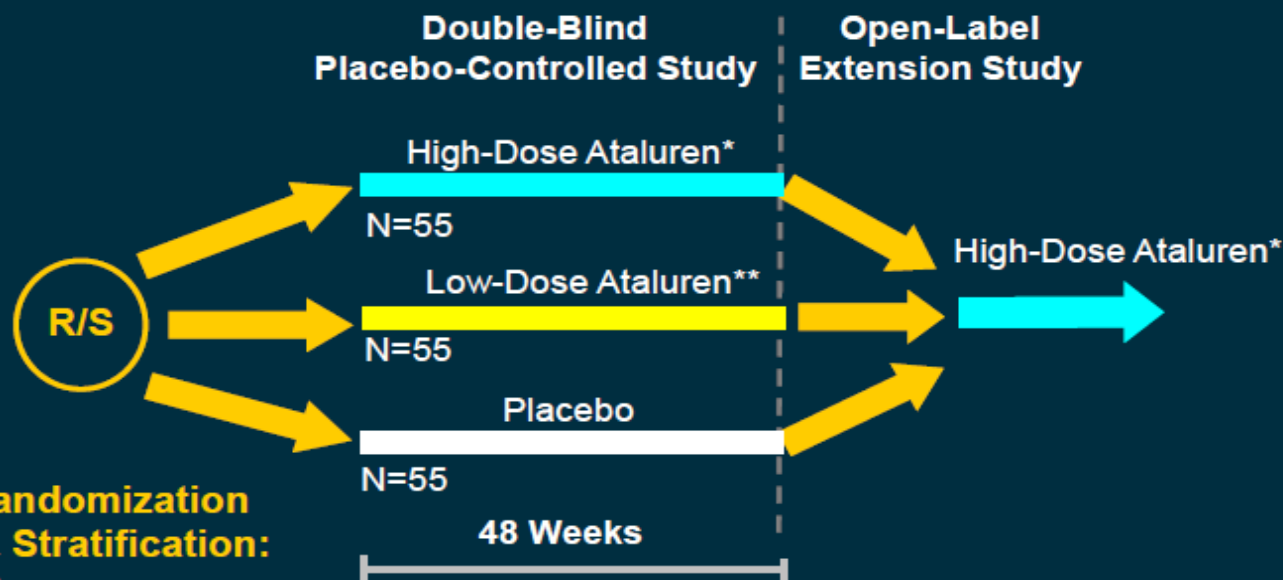
2. A Phase 2b Randomized, Placebo-controlled Study was Designed to Evaluate Ataluren Safety and Efficacy in nmDBMD

Eligibility Criteria:

- DBMD
- Nonsense mutation
- Males ≥ 5 years
- Able to walk ≥ 75 m
- Stable corticosteroid (if receiving)

Randomization & Stratification:

- Age
- Corticosteroid use
- Baseline 6MWD



Primary Outcome Measure

- 6-minute walk distance (6MWD)

* High-dose ataluren = 20 mg/kg (morning), 20 mg/kg (midday), 40 mg/kg (evening)

** Low-dose ataluren = 10 mg/kg (morning), 10 mg/kg (midday), 20 mg/kg (evening)

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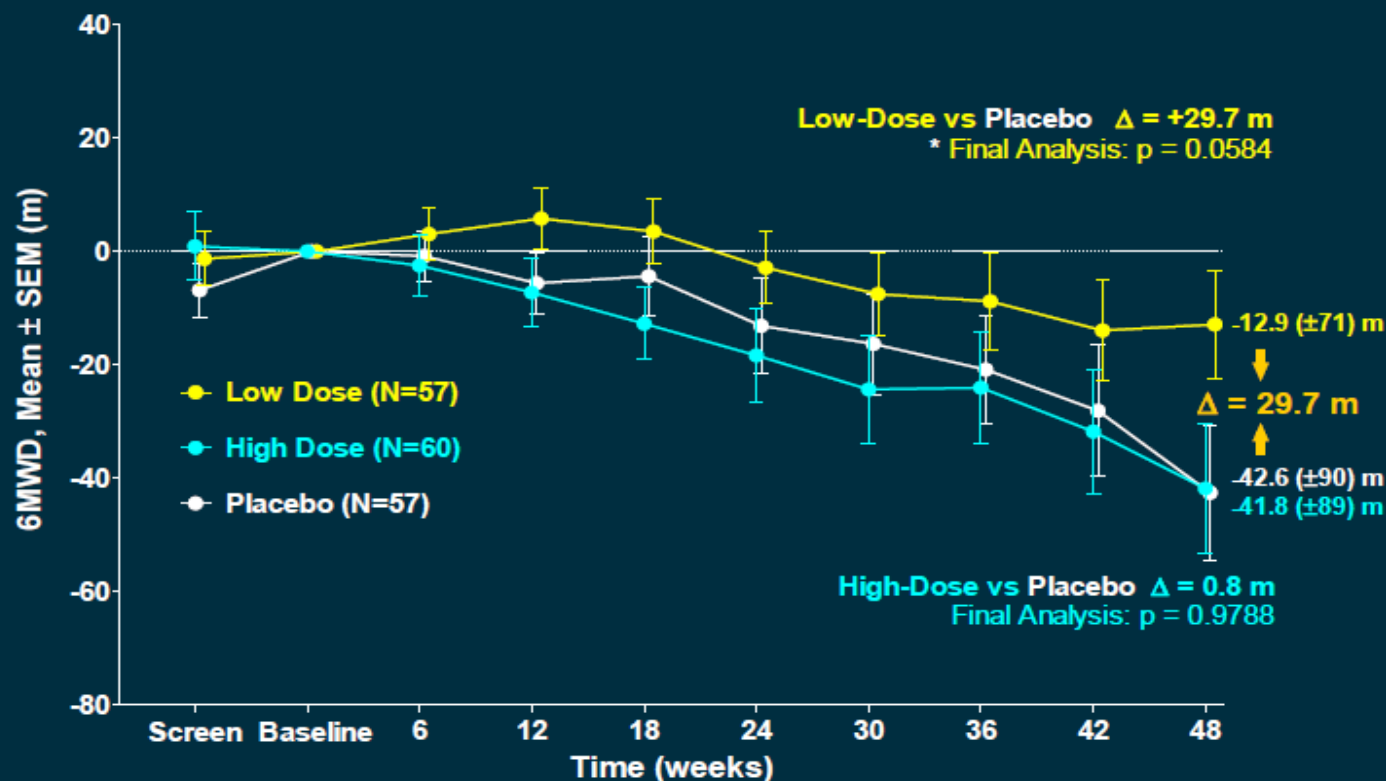
R Finkel¹, B Wong², K Bushby³, A Reha⁴, GL Elfring⁴, LL Miller⁴, J Babiak⁴, MA Morsy⁴, S Peltz⁴, E Welch⁴, L Atkinson⁴
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5. Low-Dose Ataluren Slows Loss of Walking Ability Compared to Placebo



* Final analysis was a correction of the pre-specified analysis

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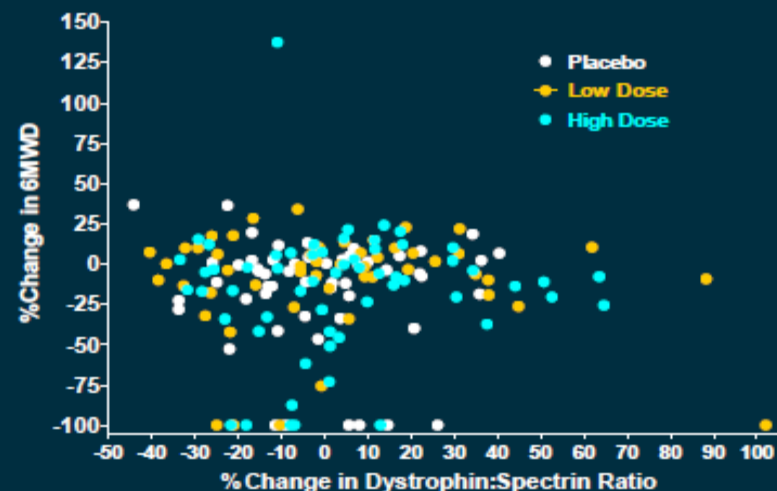
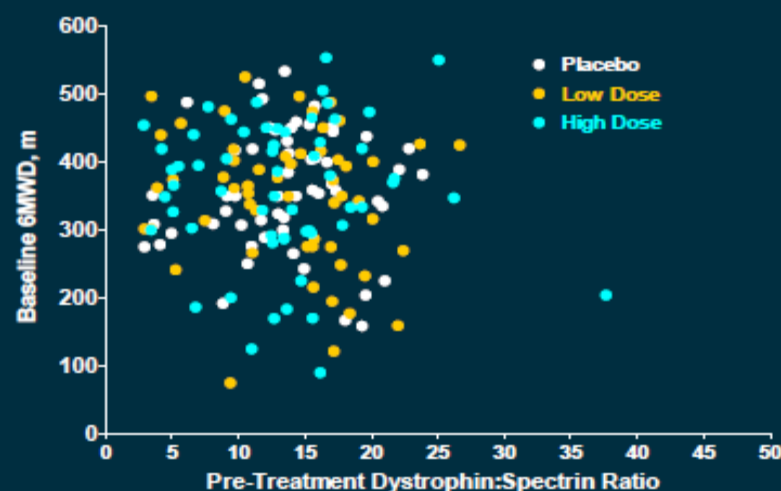
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11. Muscle Dystrophin Expression

Study 007 muscle dystrophin expression quantification was compromised by technical limitations of the method (eg, low sensitivity), poor sample quality due to procedural complexity, and high variability in disease pathology. Due in part to technical issues of the assay, no relationship could be established between 6MWD – a measure of clinical benefit – and dystrophin expression (Figure 1).

Figure 1: No Correlation between 6MWD and Dystrophin: Spectrin Ratio – Study 007



Low-dose ataluren = 10, 10, 20 mg/kg TID; High-dose ataluren = 20, 20, 40 mg/kg TID
Abbreviations: 6MWD = 6-minute walk distance, TID = 3 times per day

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13. Conclusions – Therapeutic Concept, Study Design, and Safety

Efficacy

- Relative to placebo, the low-dose ataluren arm showed:
 - A clinically meaningful difference in change in 6MWD (+ 30 meters, 8%)
 - Trials in other diseases using 6MWD have shown a 28-44 meter (8-11%) range
 - Longer time to 10% worsening in 6MWD
 - Positive trends in timed function tests
- Variability in 6MWD was higher than anticipated
- The high-dose ataluren arm did not show a treatment benefit vs placebo
- In this study, muscle dystrophin expression had no utility as a biomarker for either disease natural history or clinical benefit

Safety

- Ataluren was well-tolerated at both dose levels
- Adverse event profiles in ataluren-treated patients were similar to those in placebo-treated patients

ATALUREN TREATMENT OF PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

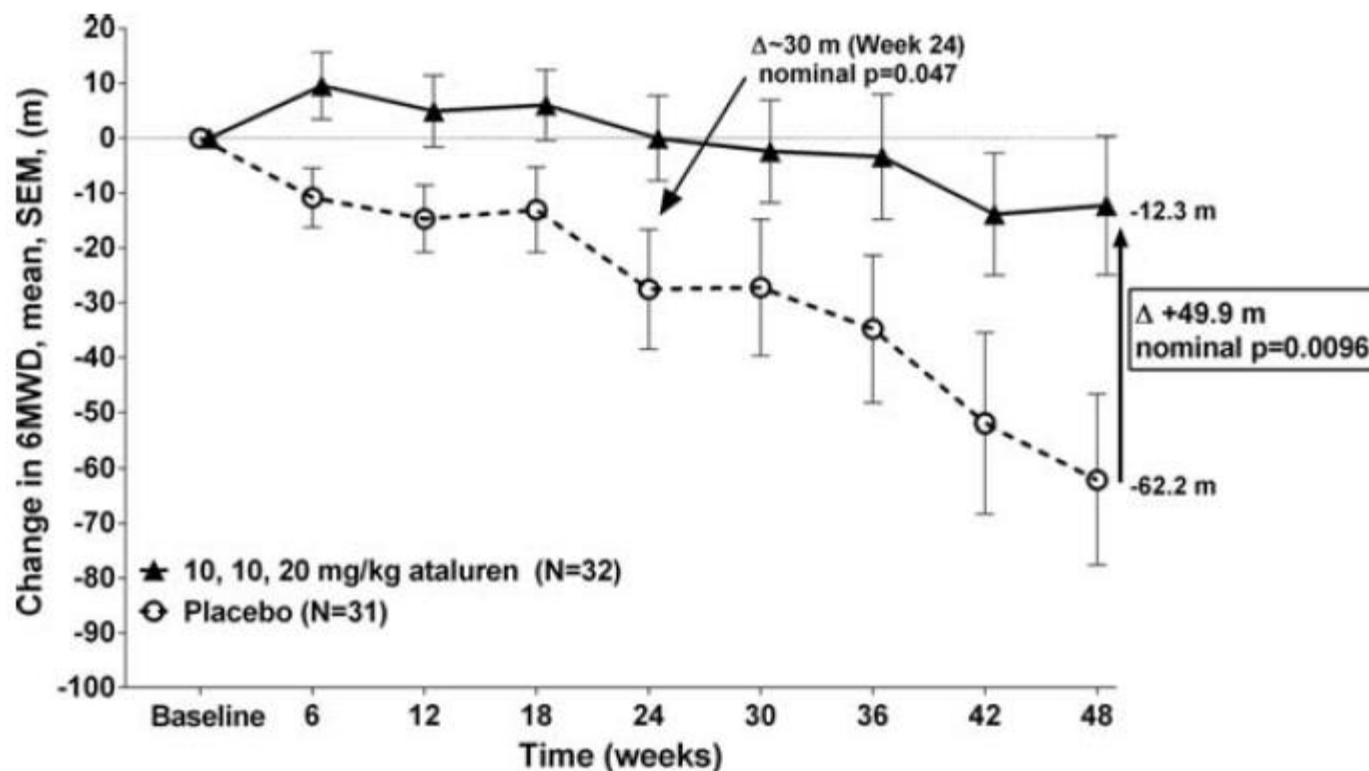
KATHARINE BUSHBY, MD,^{1*} RICHARD FINKEL, MD,^{2*} BRENDA WONG, MD,³ RICHARD BAROHN, MD,⁴
CRAIG CAMPBELL, MD,⁵ GIACOMO P. COMI, MD,⁶ ANNE M. CONNOLLY, MD,⁷ JOHN W. DAY, MD, PhD,⁸
KEVIN M. FLANIGAN,
ROS QUINLIVAN, MD,
MAR TULINIUS, MD, F
RICHARD T. ABRESC
EDUARD GAPPMAIER
GARY L. ELFRING, M
STUART W. PELTZ, PI

ABSTRACT: *Introduction:* Dystrophinopathy is a rare, severe muscle disorder, and nonsense mutations are found in 13% of cases. Ataluren was developed to enable ribosomal readthrough of premature stop codons in nonsense mutation (nm) genetic disorders. *Methods:* Randomized, double-blind, placebo-controlled study; males ≥ 5 years with nm-dystrophinopathy received study drug orally 3 times daily, ataluren 10, 10, 20 mg/kg ($N=57$); ataluren 20, 20, 40 mg/kg ($N=60$); or placebo ($N=57$) for 48 weeks. The primary endpoint was change in 6-Minute Walk Distance (6MWD) at Week 48. *Results:* Ataluren was generally well tolerated. The primary endpoint favored ataluren 10, 10, 20 mg/kg versus placebo; the week 48 6MWD $\Delta = 31.3$ meters, *post hoc* $P=0.056$. Secondary endpoints (timed function tests) showed meaningful differences between ataluren 10, 10, 20 mg/kg, and placebo. *Conclusions:* As the first investigational new drug targeting the underlying cause of nm-dystrophinopathy, ataluren offers promise as a treatment for this orphan genetic disorder with high unmet medical need.

Analisis de un subgrupo de pacientes

ATALUREN TREATMENT OF PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

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*Patients on corticosteroids, between 7 and 16 years of age, with baseline 6MWD ≥ 150 m and $\leq 80\%$ of predicted

FIGURE 4. Mean change in 6MWD from baseline to week 48 in the decline-phase subgroup.



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agencia española de
medicamentos y
productos sanitarios

INFORME DE POSICIONAMIENTO TERAPÉUTICO PT/V1/XXXX2014

Informe de Posicionamiento Terapéutico de Ataluren (Translarna[®])

Ataluren ha sido autorizado de manera condicional a la espera de los resultados de un estudio actualmente en curso que valide los resultados obtenidos en el subgrupo de pacientes que se encuentran en la fase de declive de la capacidad de deambulación. Por todo lo anteriormente expuesto, no podría recomendarse el uso de ataluren hasta disponer de los datos de este estudio.

No hay datos sobre el efecto de este medicamento en fases más avanzadas de la enfermedad.

CONCLUSIONES

➤ NEGATIVA:

Los efectos en el paciente a corto plazo son muy modestos, menores que los observados con los corticoides.

➤ POSITIVA:

Hay avances notables en desarrollo de nuevas formas de tratamientos:

 Específicas de la mutación, y
 Válidas para cualquier mutación

MUCHAS GRACIAS

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