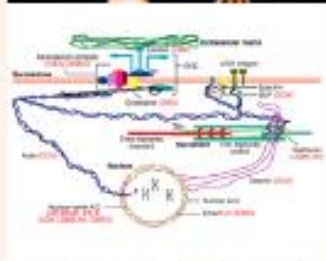
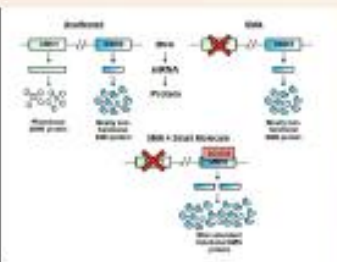


Enfermedades Musculares en la Infancia y Adolescencia(XIV)

Organizado por:



Servicio de Pediatría. B. García Cuartero. Jefe de Servicio

30 y 31 de Marzo de 2017

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

NOVEDADES EN EL TRATAMIENTO DE LA DISTROFIA MUSCULAR DE DUCHENNE

Marcos Madruga Garrido

Sección de Neuropediatría. HU Virgen del Rocío. sevilla

ÍNDICE



- INTRODUCCIÓN Y GENERALIDADES
- TRATAMIENTOS ACTUALES
- NOVEDADES TERAPÉUTICAS EN INVESTIGACIÓN
- NOVEDADES TERAPÉUTICAS APROBADAS

CURSO CLÍNICO

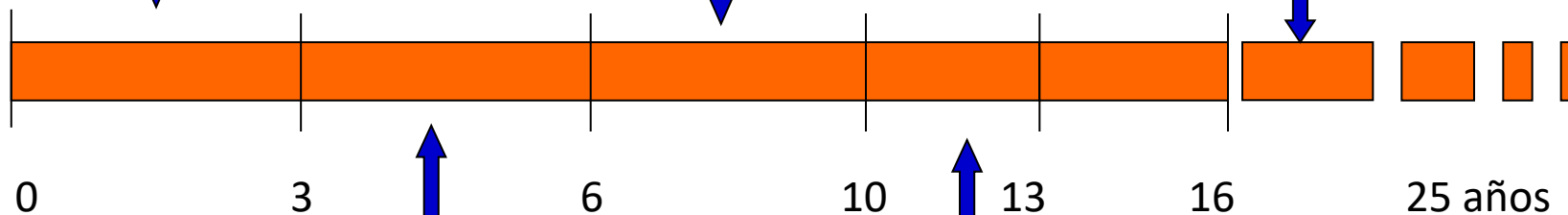


Fase preclínica

Fase ambulatoria tardía

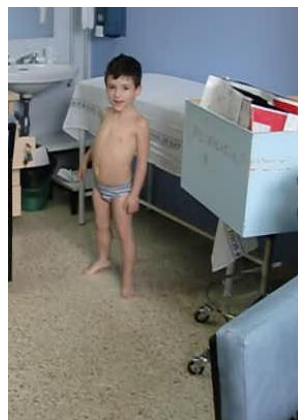


Fase no ambulatoria tardía

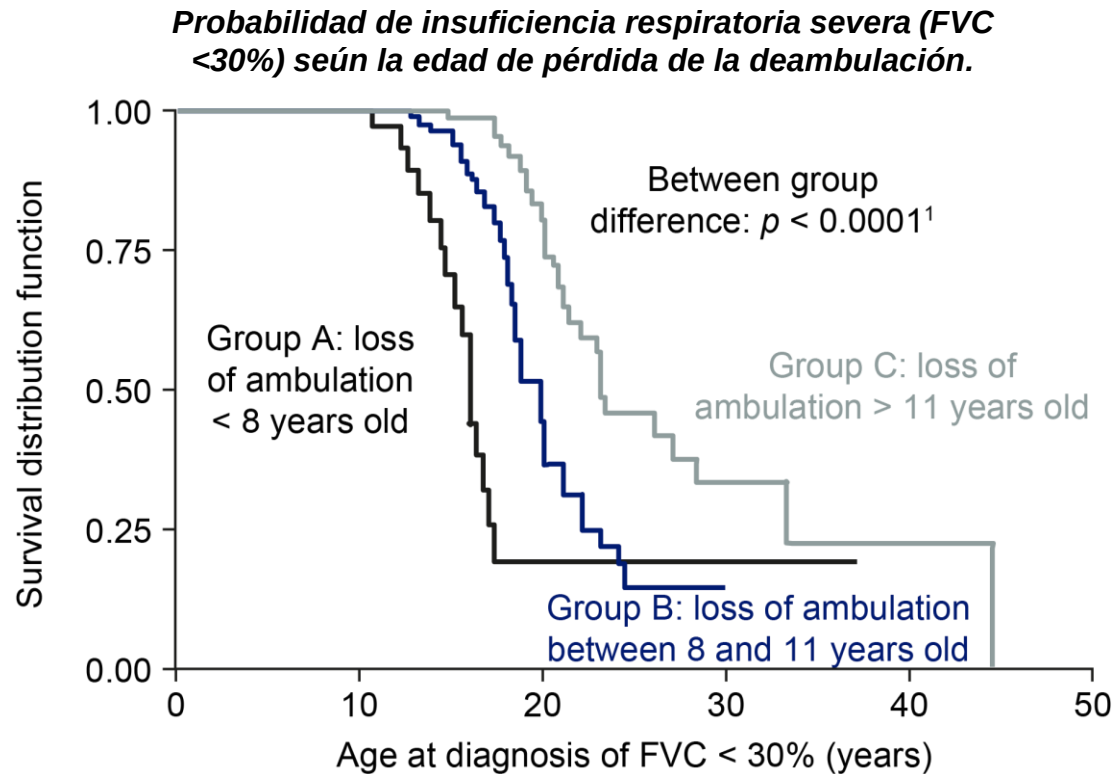


Fase ambulatoria temprana

Fase no ambulatoria temprana



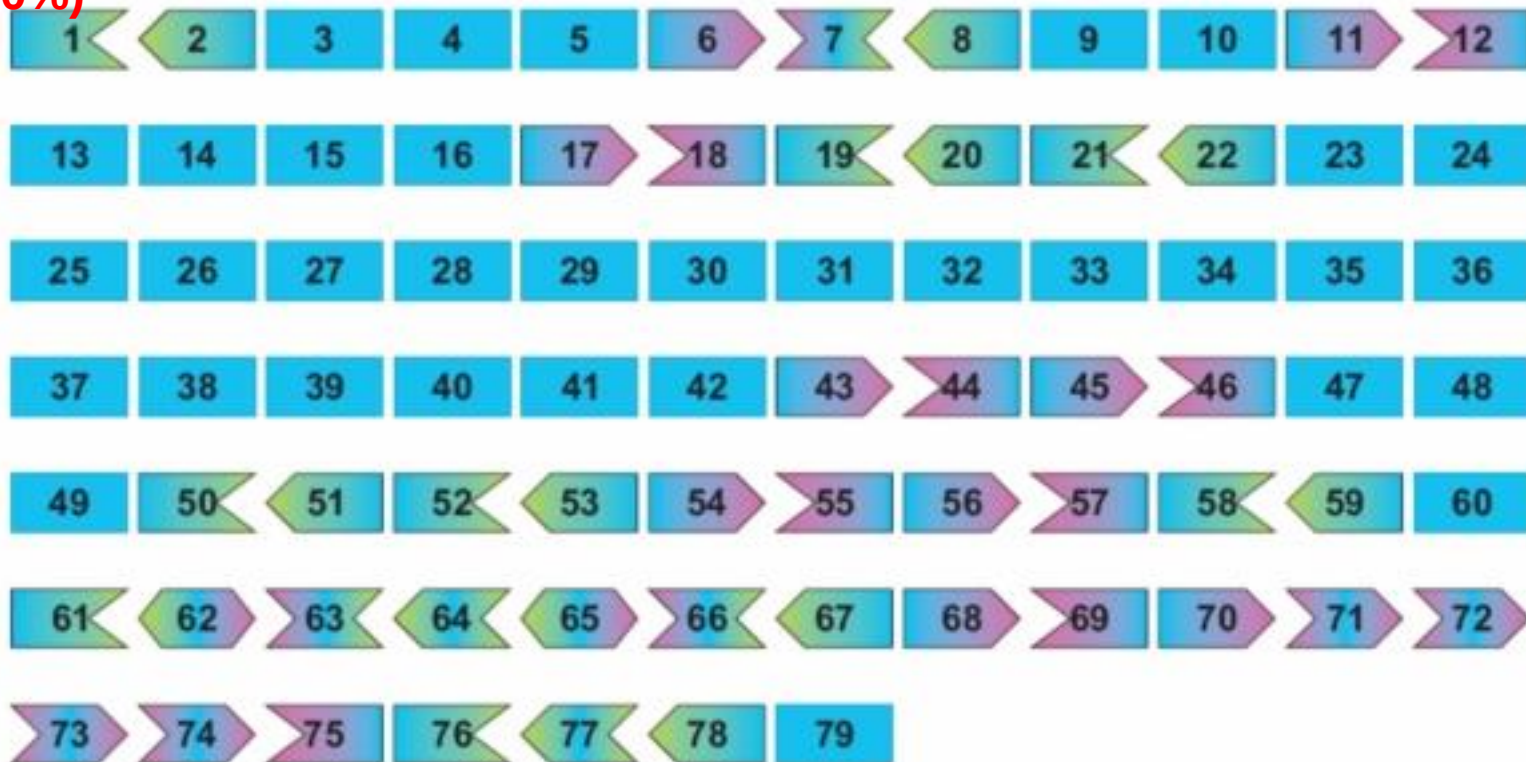
EVOLUCIÓN CLÍNICA



GEN DE LA DISTROFINA

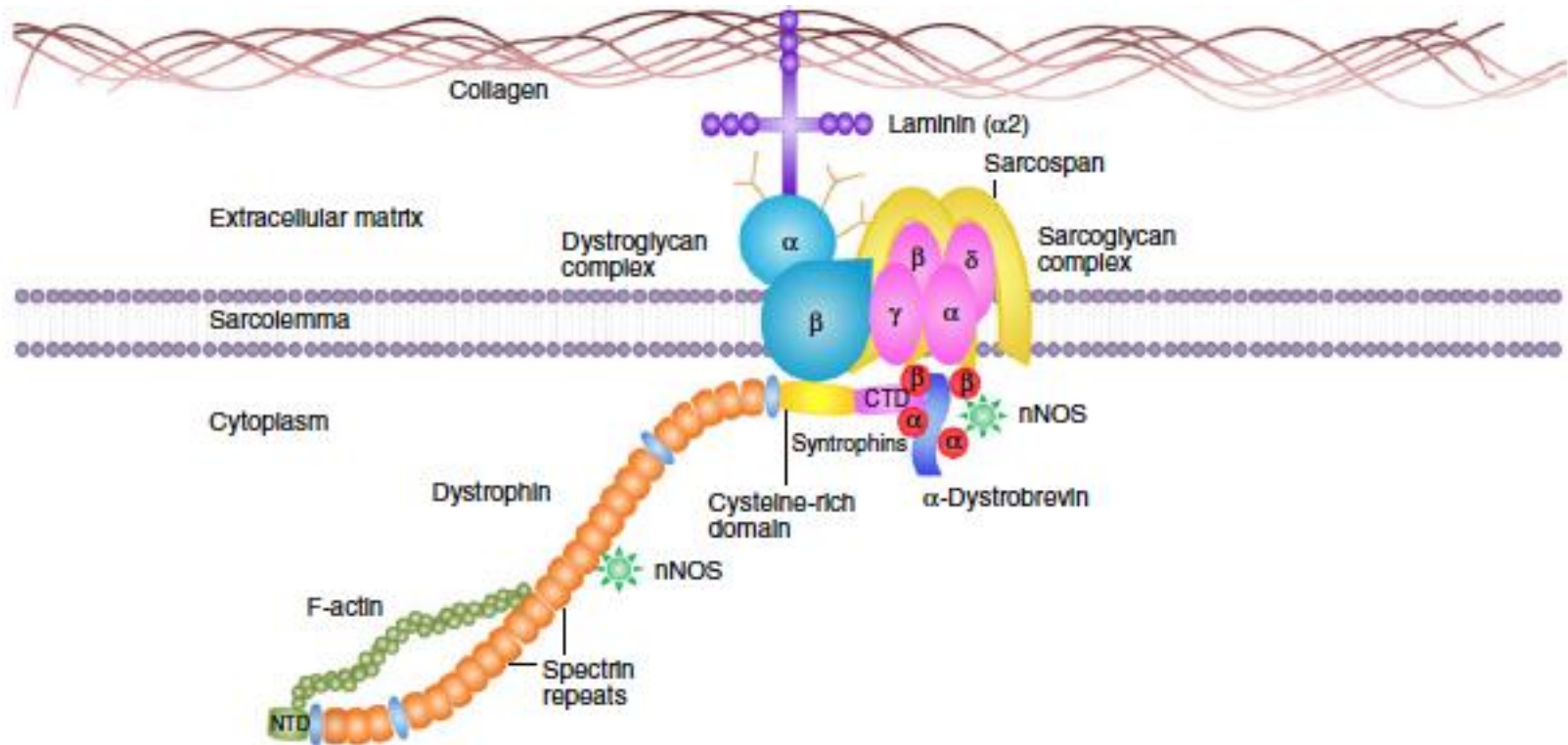
Delecciones (60-70%)

Duplicaciones (5-10%):

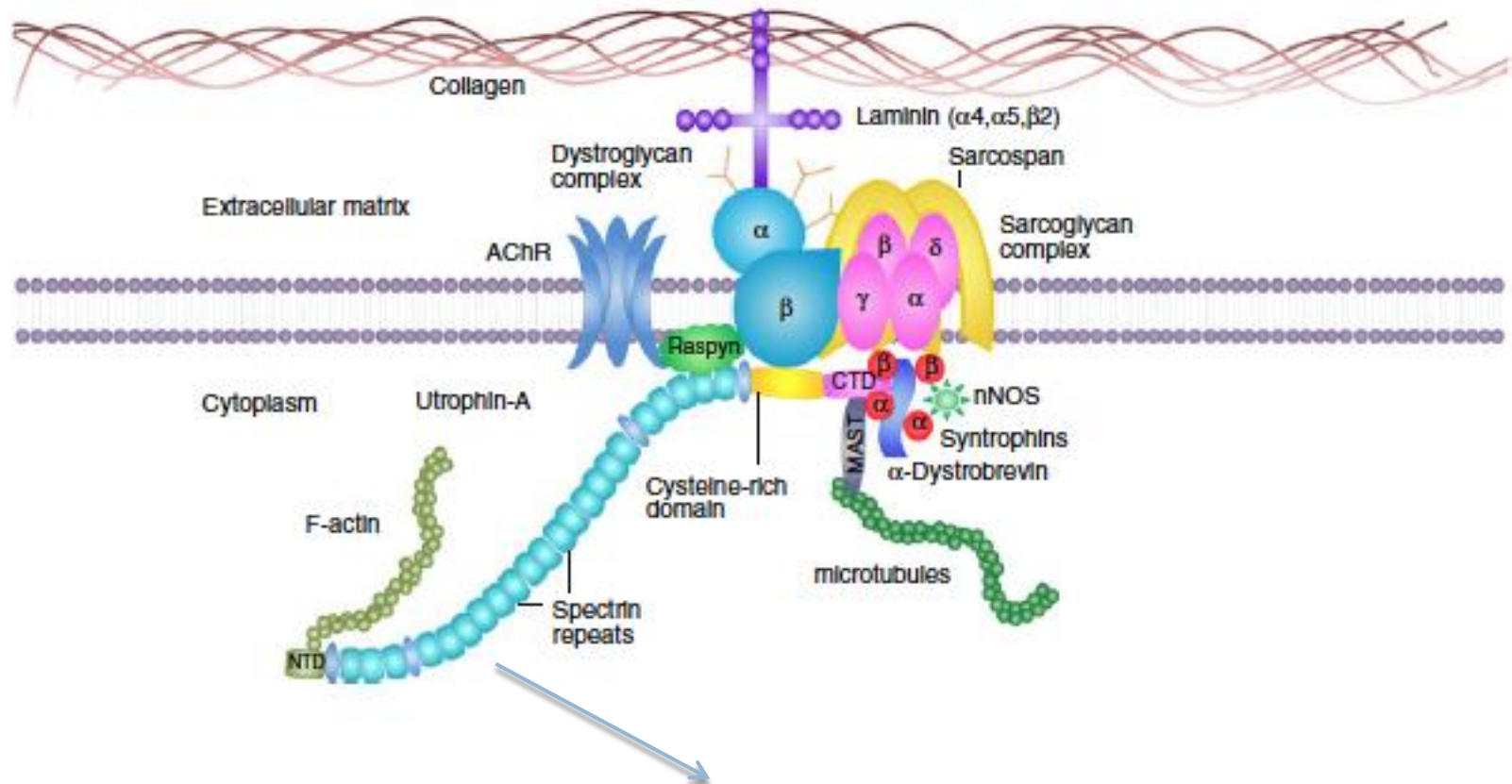


Mutaciones puntuales (20-30%)

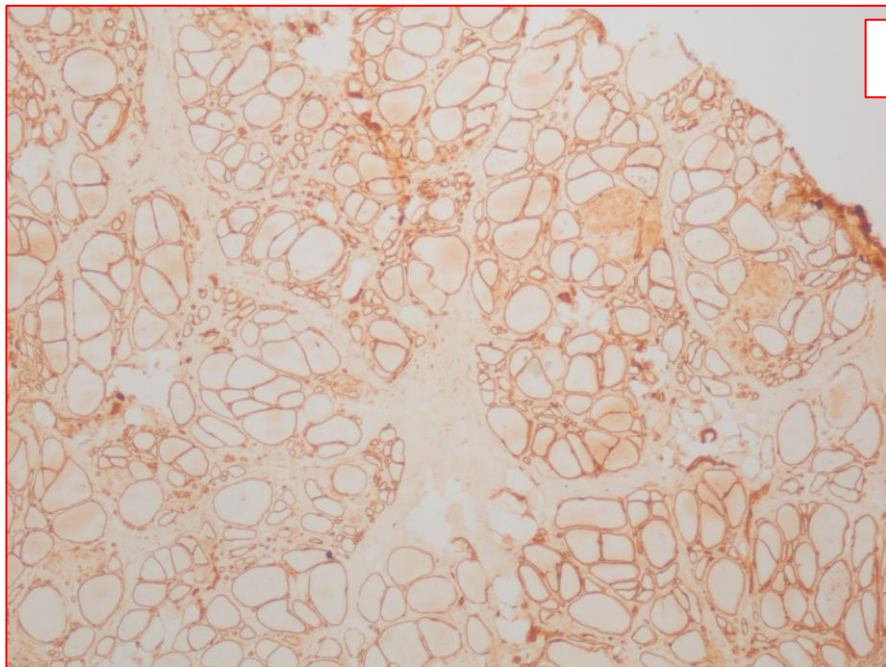
DISTROFIA MUSCULAR DE DUCHENNE



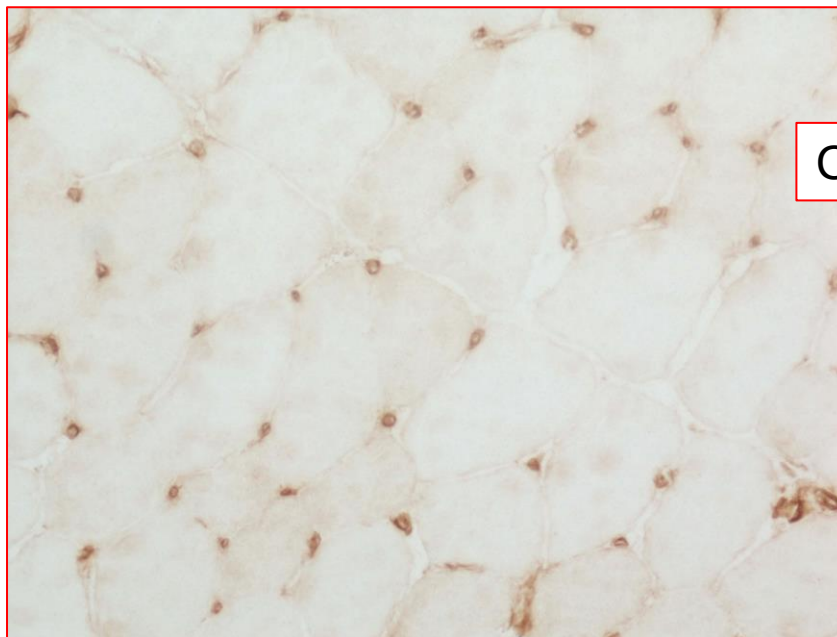
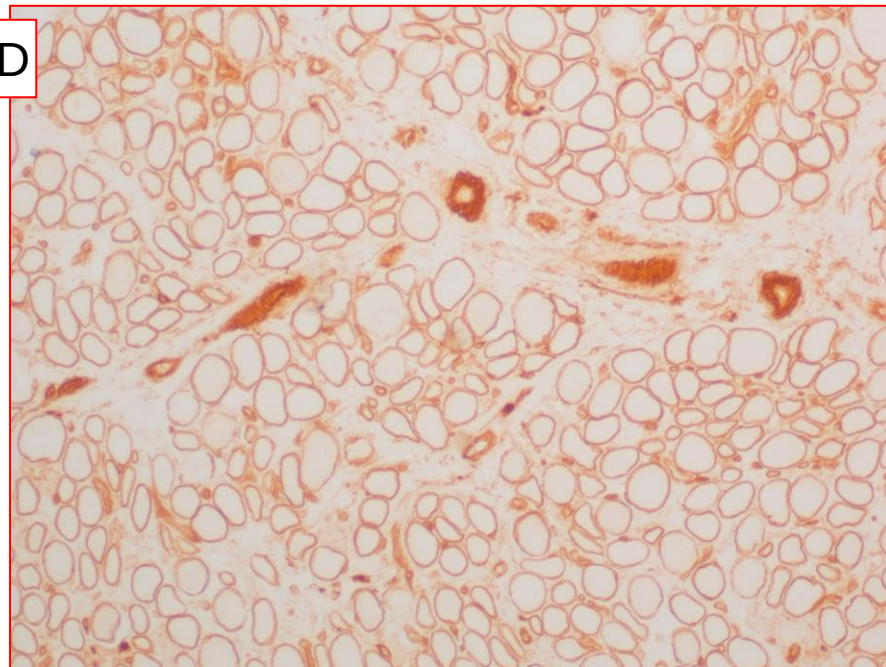
DISTROFIA MUSCULAR DE DUCHENNE



UTROFINA



DMD



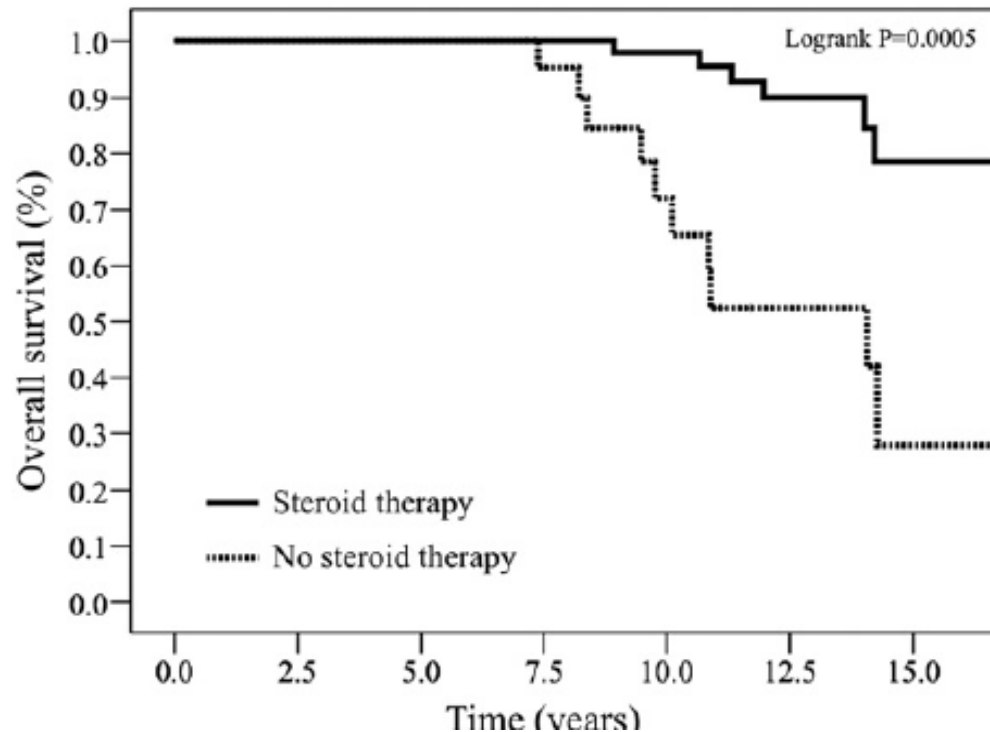
Control SANO

TERAPIAS ACTUALES

- Corticoides
 - ▣ Deflazacort (0, 90 mg/kg/día)
 - ▣ Prednisona (0,75 mg/kg/día)
- IECA (previo a signos)
- Manejo respiratorio
- Manejo dietético y nutricional
- Manejo de rehabilitador y fisioterapia
- Manejo traumatológico (escoliosis y deformidades articulares)
- Abordaje psicosocial
- Apoyo escolar

MANEJO MULTIDISCIPLINAR

Cambios en la evolución natural de DMD



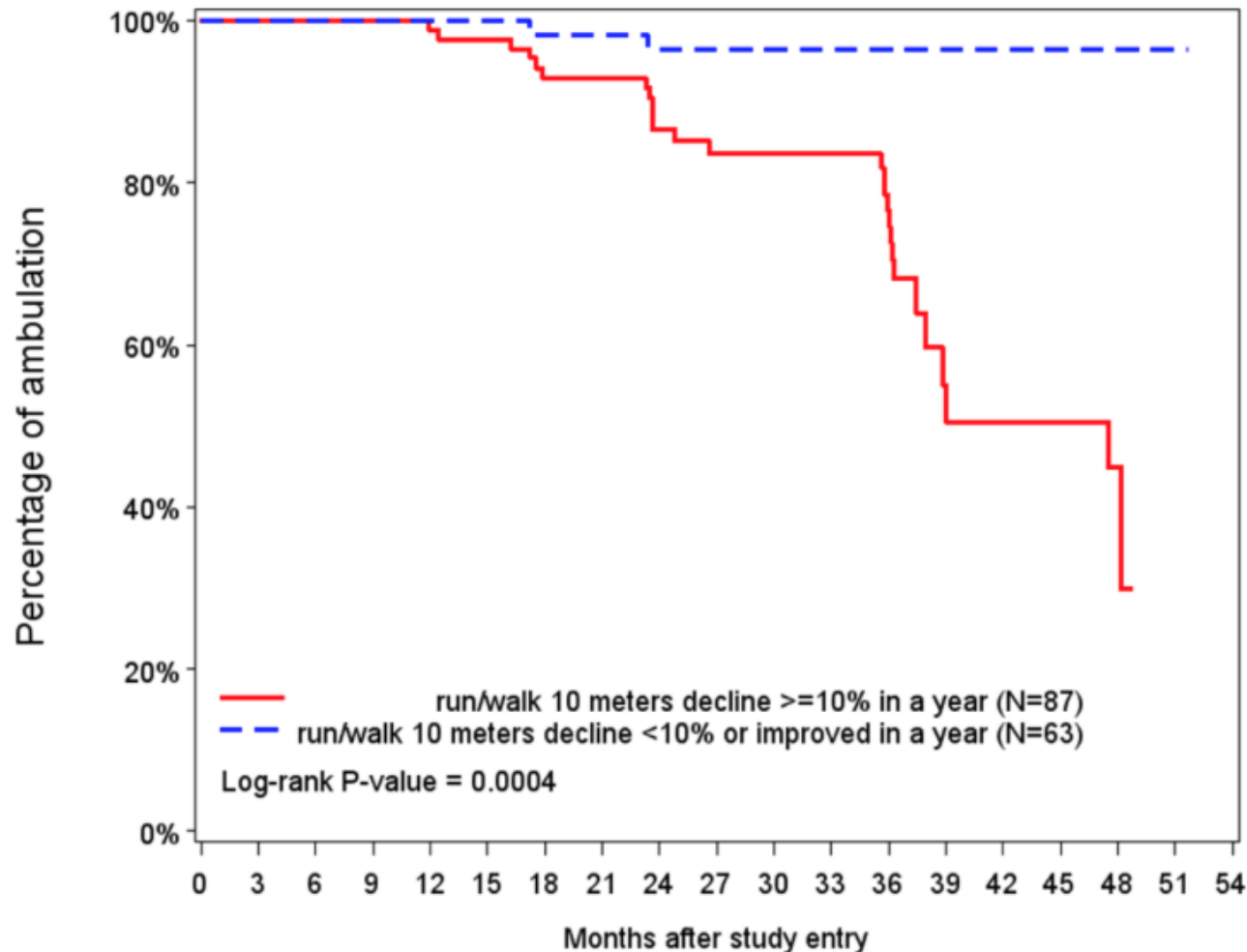
**Supervivencia 15 a: 78.6% con
Corticoides**

27.9% sin corticoides

Schram et al. *Journal of the American College of Cardiology*,
2013

Time to Event Analysis:

(< 10% decline versus $\geq 10\%$ decline in one year)



Cooperative International Neuromuscular Research Group
(CINRG) natural history study





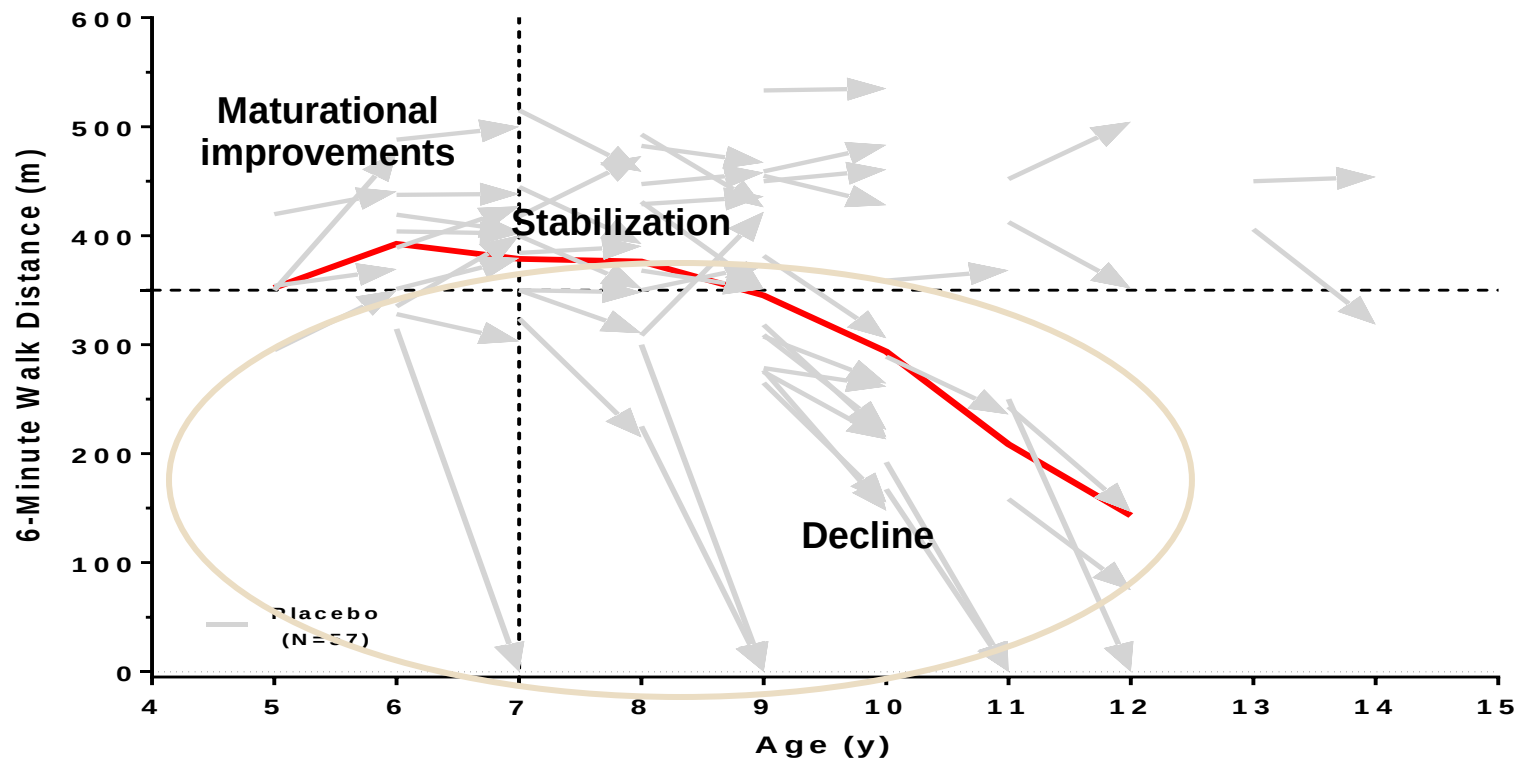
MÉTODOS DE EVALUACIÓN

Pruebas de valoración clínicas

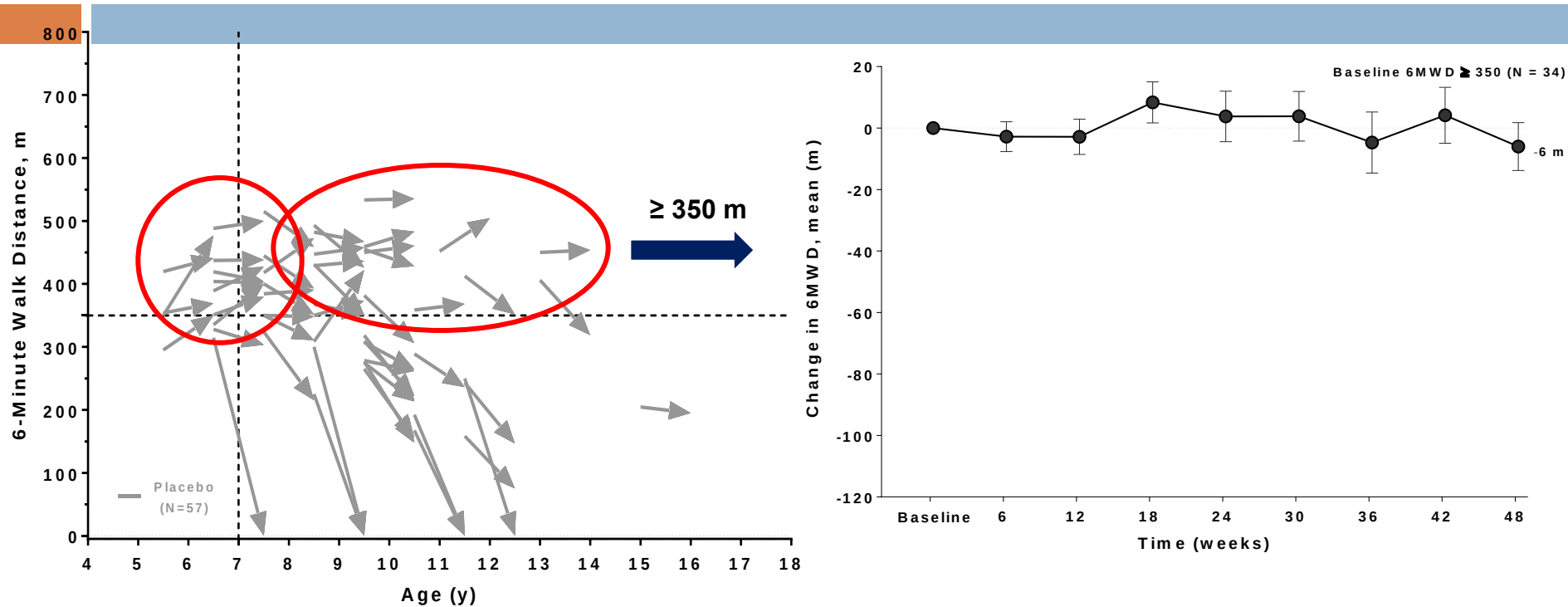
- **Las pruebas de función cronometradas:**
 - 10 m de marcha/carrera cronometrada
 - Maniobra Gowers cronometrada
 - Tiempo para subir/bajar 4 escalones
- **Prueba de marcha de 6 minutos (6MWT)**
- **Evaluación ambulatoria North Star**



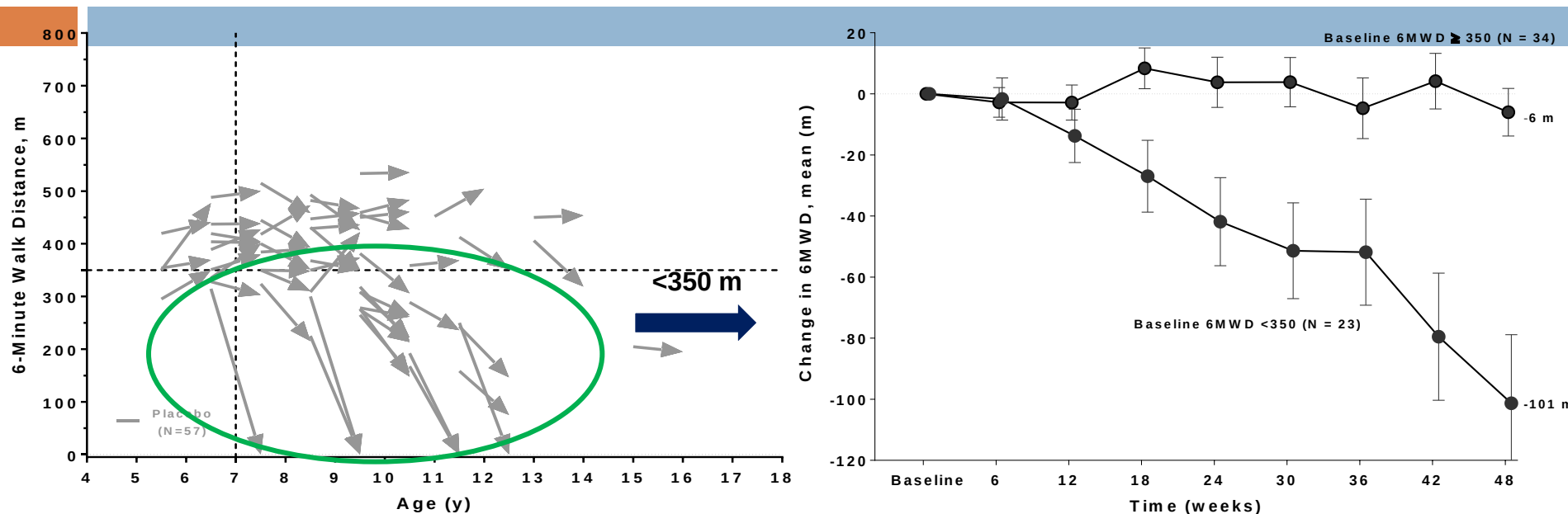
6MWD: OBSERVACIÓN DE HISTORIA NATURAL LONGITUDINAL TRAS 48 SEMANAS EN ESTUDIO MULTICÉNTRICO.



6MWD basal es un factor clave de la evolución en las siguientes 48 semanas



EL 6MWD BASAL ES UN FACTOR CLAVE EN LA DETERMINACIÓN DE EVOLUCIÓN DE LOS PACIENTES EN 48 SEMANAS

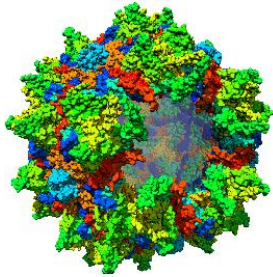


- Los pacientes con 6MWD basal >350 m mantenían resultados estables
 - Dificultad para demostrar efecto de tto en un estudio de 48 s
- Los pacientes con 6MWD basal <350 m mostraron un gran deterioro
 - Población más apropiada para demostrar efecto sobre deambulación en un estudio de 48 s



NOVEDADES TERAPÉUTICAS EN INVESTIGACIÓN

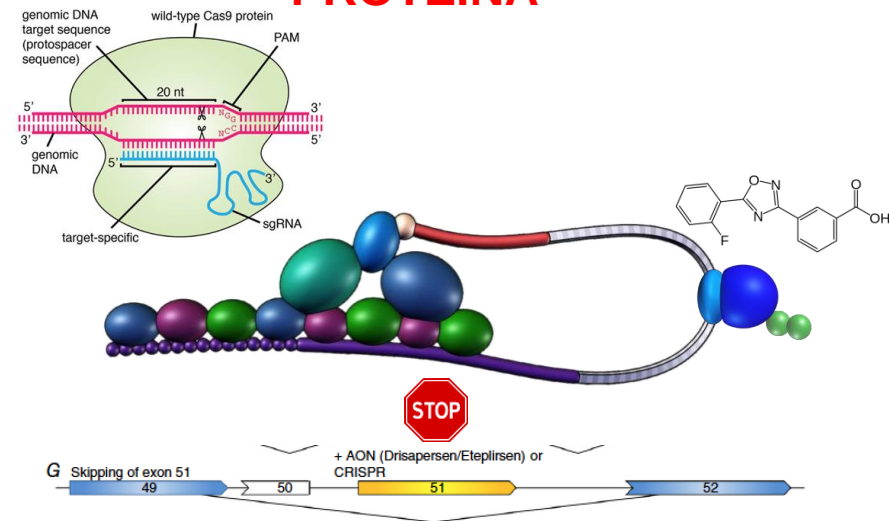
1. REEMPLAZAMIENTO DEL GEN



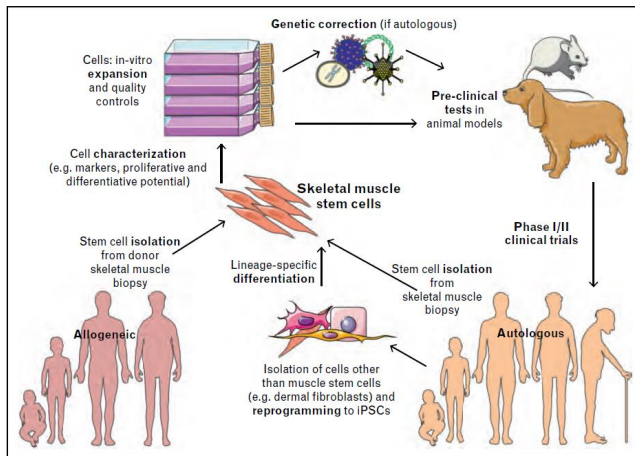
Mini-dystrophin



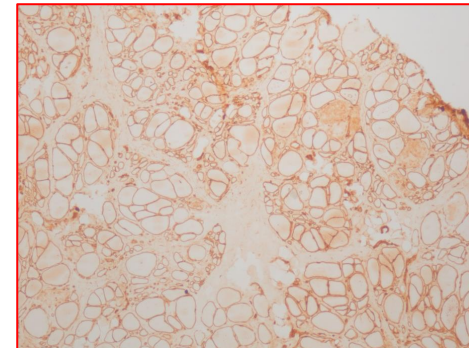
2. EDICIÓN GEN/REPARACIÓN PROTEÍNA



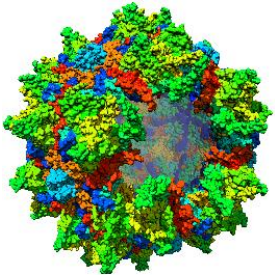
3. TERAPIA CELULAR



4. SOBREEXPRESIÓN DE OTRAS PROTEÍNAS Y OTRAS TERAPIAS



1. REEMPLAZAMIENTO DEL GEN

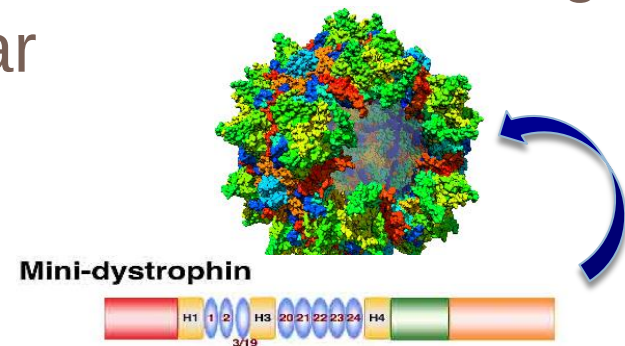


Mini-dystrophin

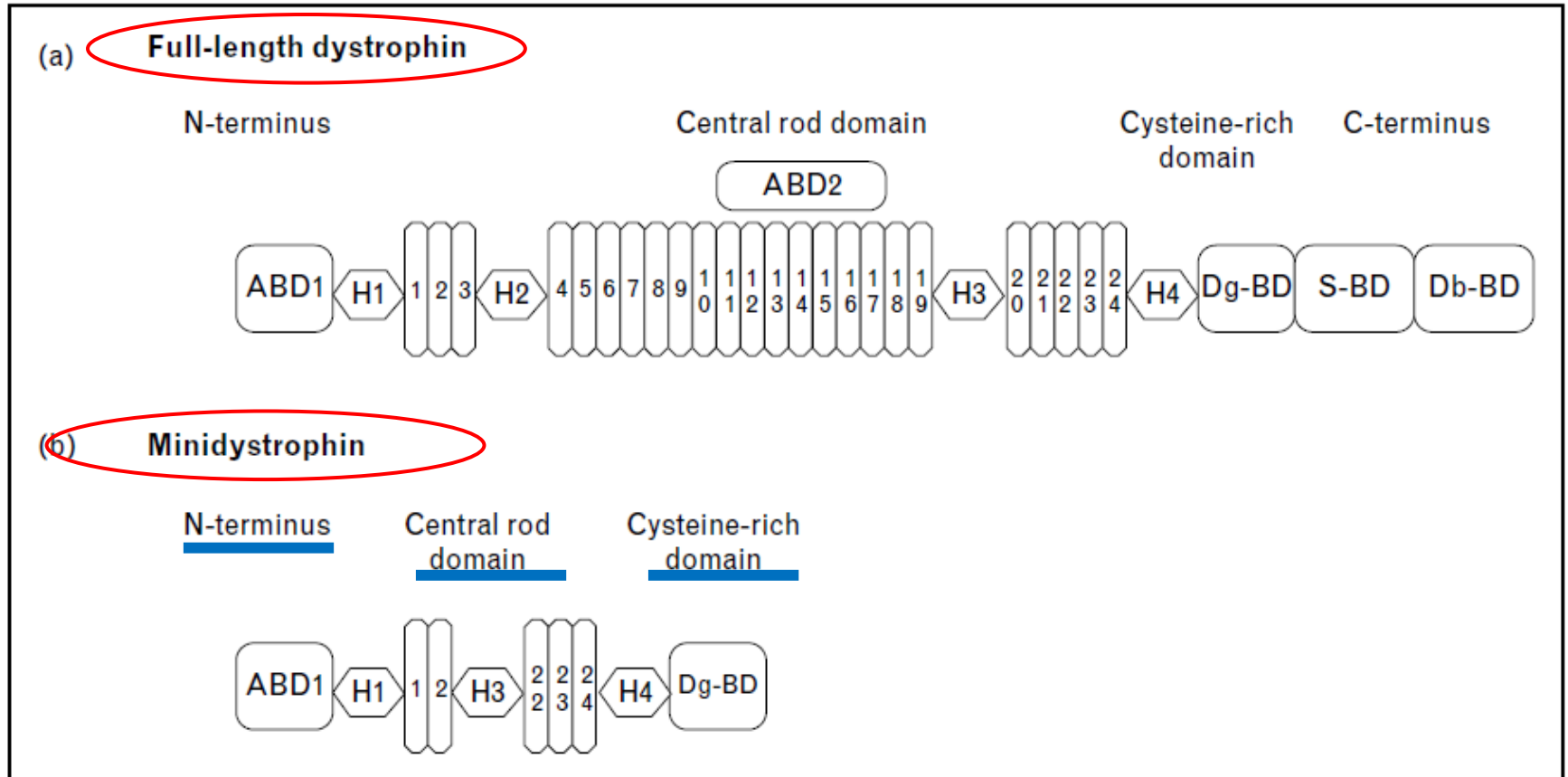


1. REEMPLAZAMIENTO DEL GEN DMD

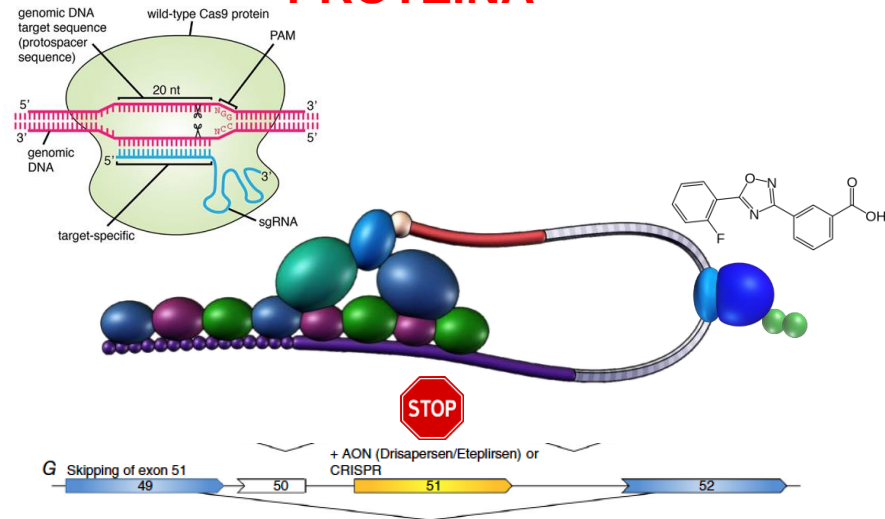
- **TERAPIA GÉNICA MEDIADA POR VECTORES VIRALES**
 - ▣ **Virus adenoasociados (AAV) recombinados.**
 - ▣ **Insertamos minidistrofina a través de virus**
 - ▣ Inconvenientes: respuesta inmune, duración efecto y efecto local insuficiente, tamaño del gen de la distrofina a vehicularizar
 - ▣ Dual y triple trans-splicing



1. REEMPLAZAMIENTO DEL GEN



2. EDICIÓN GEN/REPARACIÓN PROTEÍNA



2. EDICIÓN DEL GEN. REPARACIÓN DE PROTEÍNA

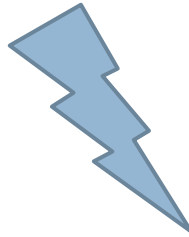
- **Traslational read-through**: suprimir mutaciones nonsense
 - ▣ PCT124 (ataluren). 13%
- **Exon skipping ó SALTO DEL EXÓN. Oligonucleótidos antisentido (AON)**
Resultados prometedores con drisapersen y eteplirsen
 - ▣ Específico de cada mutación: 14% exon 51
 - ▣ Pendiente Ensayo clínico exon skipping 45 /53

- **CRISPR/CAS9**

Muscle Nerve, 2013; 47:649–663
Curr Opin Neurol 2012, 25:588–596
F1000Research 2016, 1-7

ATALUREN

MUTACIÓN

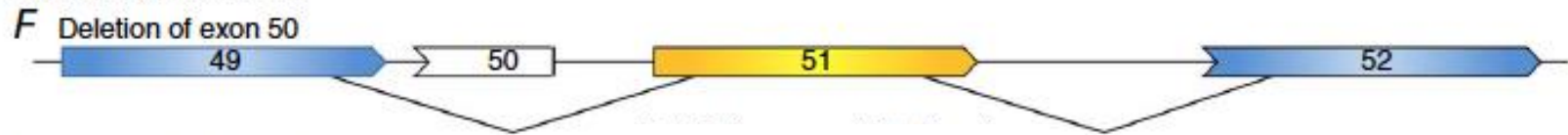


c Dystrophin-containing
nonsense mutation



SALTO DEL EXÓN

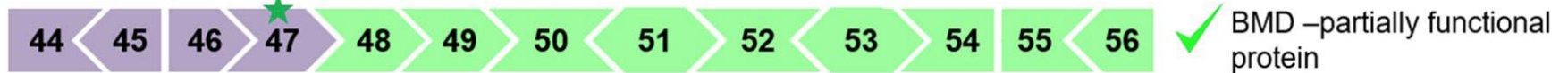
DMD and gene therapy



WT *DMD*



Missense mutation in exon 47



Nonsense mutation in exon 51



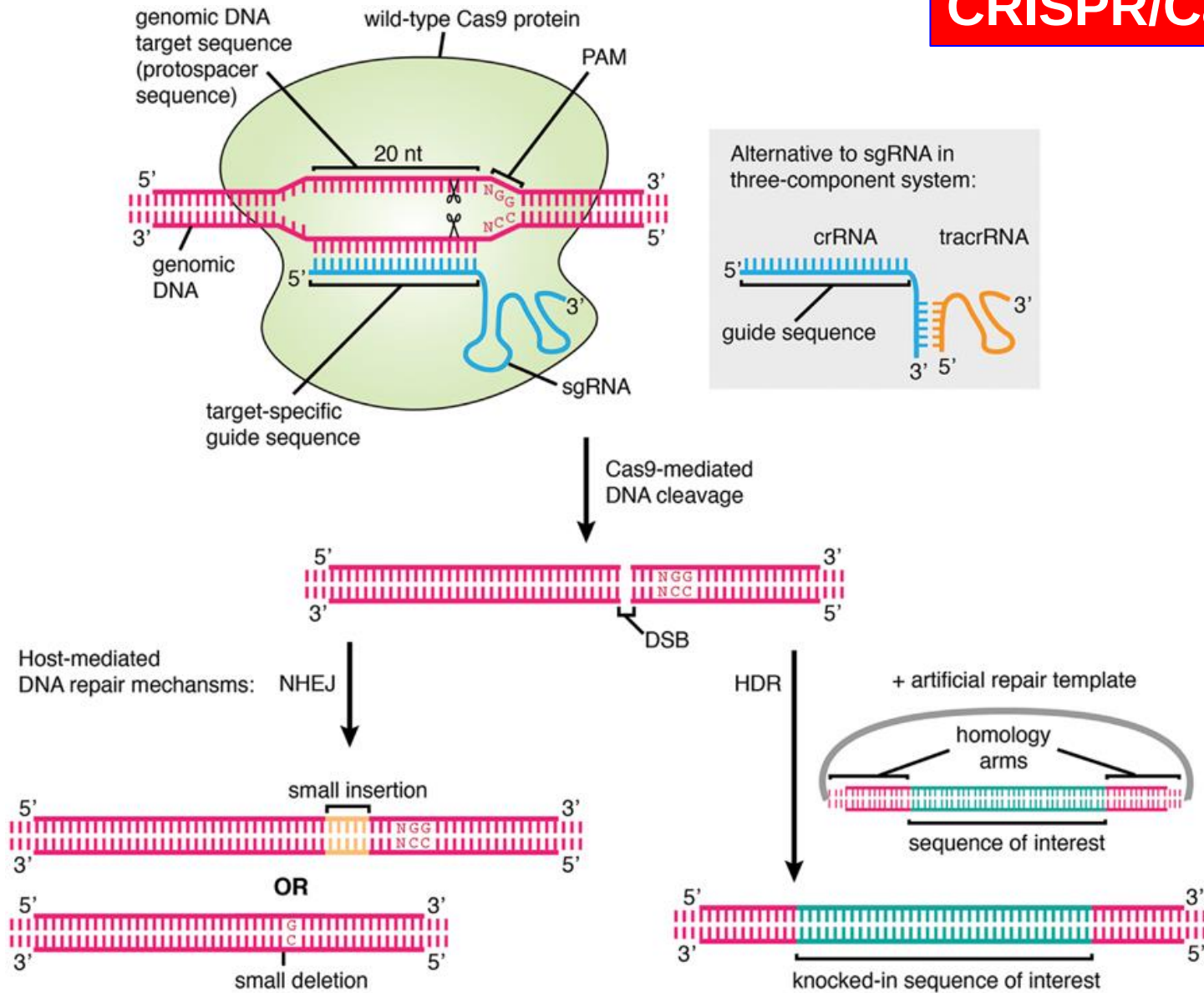
Deletion of exon 49



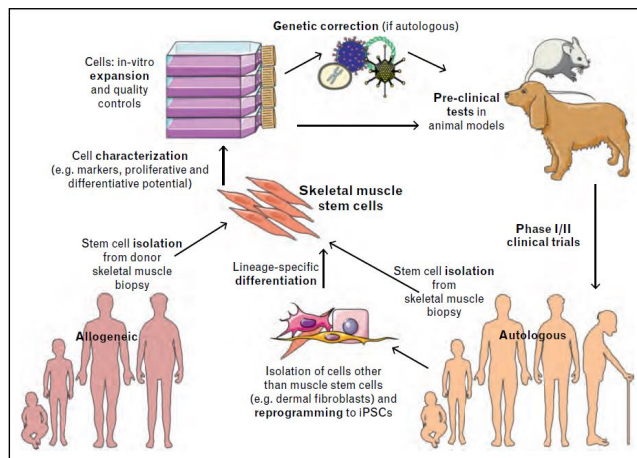
Deletion of exons 48-50



CRISPR/Ca

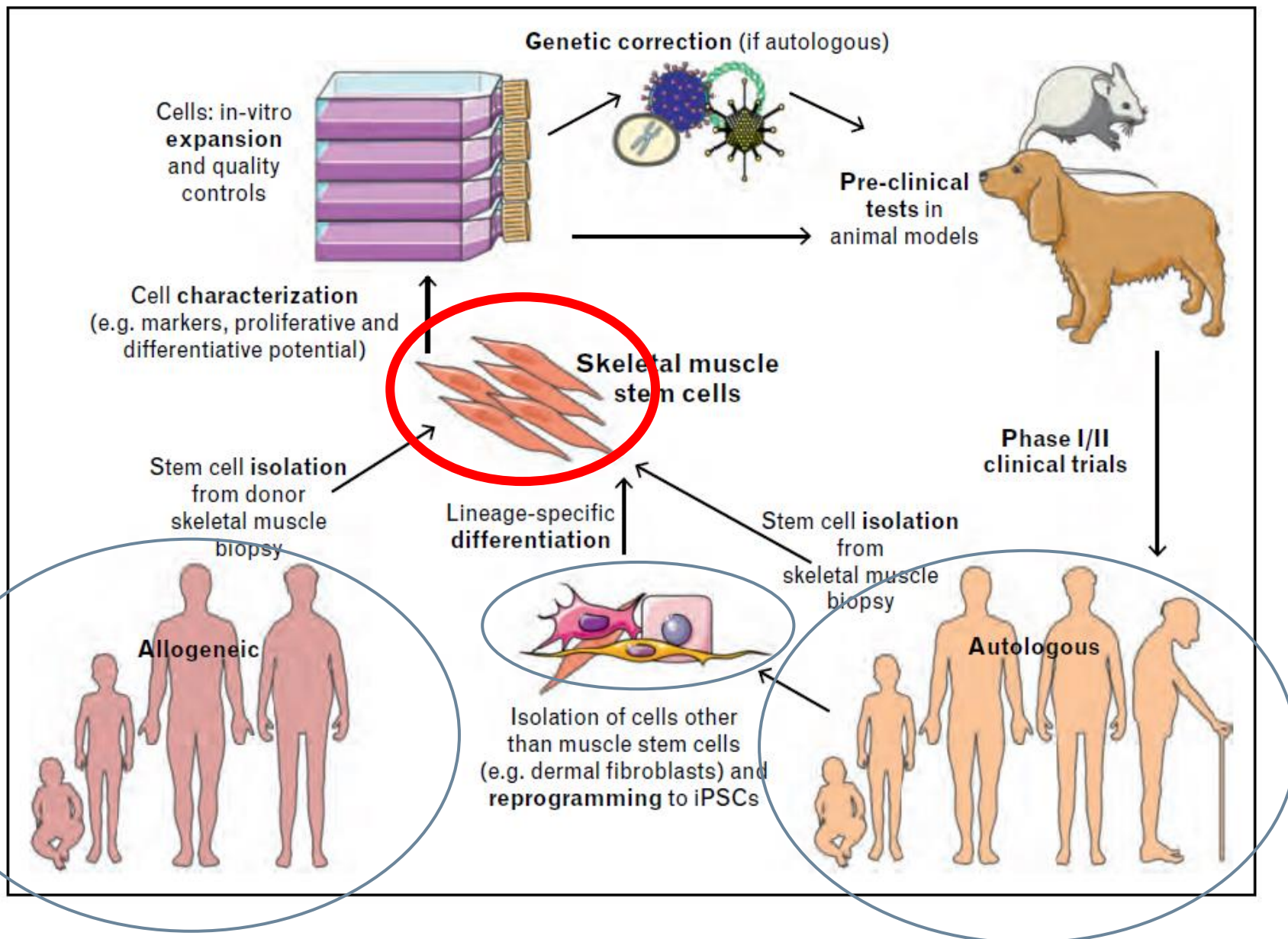


3. TERAPIA CELULAR

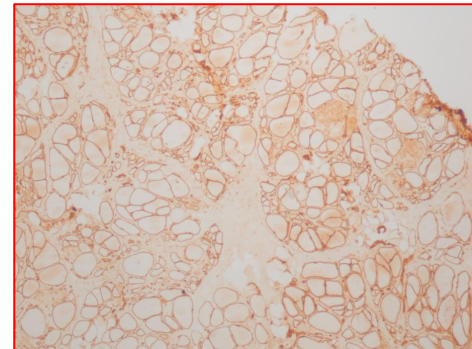


3. TERAPIA CELULAR

- Trasplante **autólogo** o alogénico
 - ▣ Trasplante de **células satélites y mioblastos** (local)
 - Principal célula madre del m. Esquelético
 - Problemas: respuesta inmune, pobre liberación sistémica y viabilidad de células trasplantadas



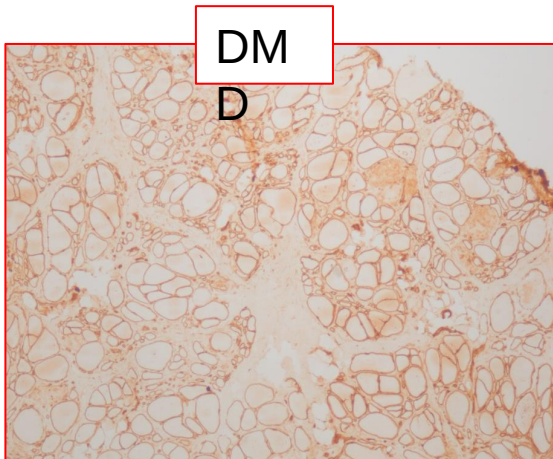
4. SOBREENPRESIÓN DE OTRAS PROTEÍNAS Y OTRAS TERAPIAS



4. SOBRE EXPRESIÓN DE OTRAS PROTEÍNAS

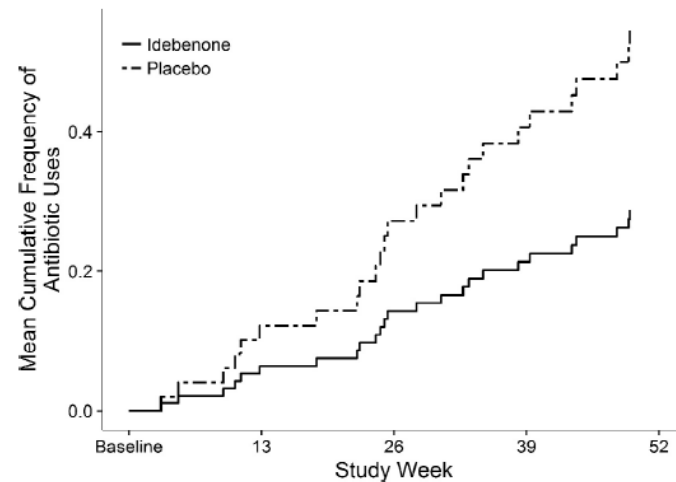
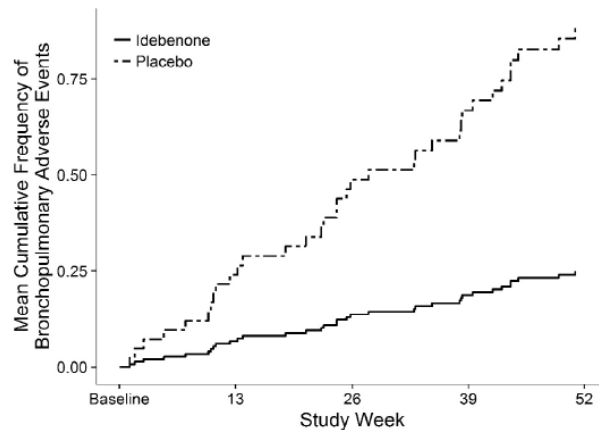
□ Utrofina

- ▣ Utrofina comparte 80% de secuencia del gen con distrofina y suple parte de su función
- ▣ Aumentando traducción (SMT C1100)



5. OTRAS

- **Inhibidores de Miostatina**
 - ▣ Miostatina: inhibe crecimiento muscular
- **VAMOROLONE**
- Antifibróticos (Losartán)
- **IDEBENONA**





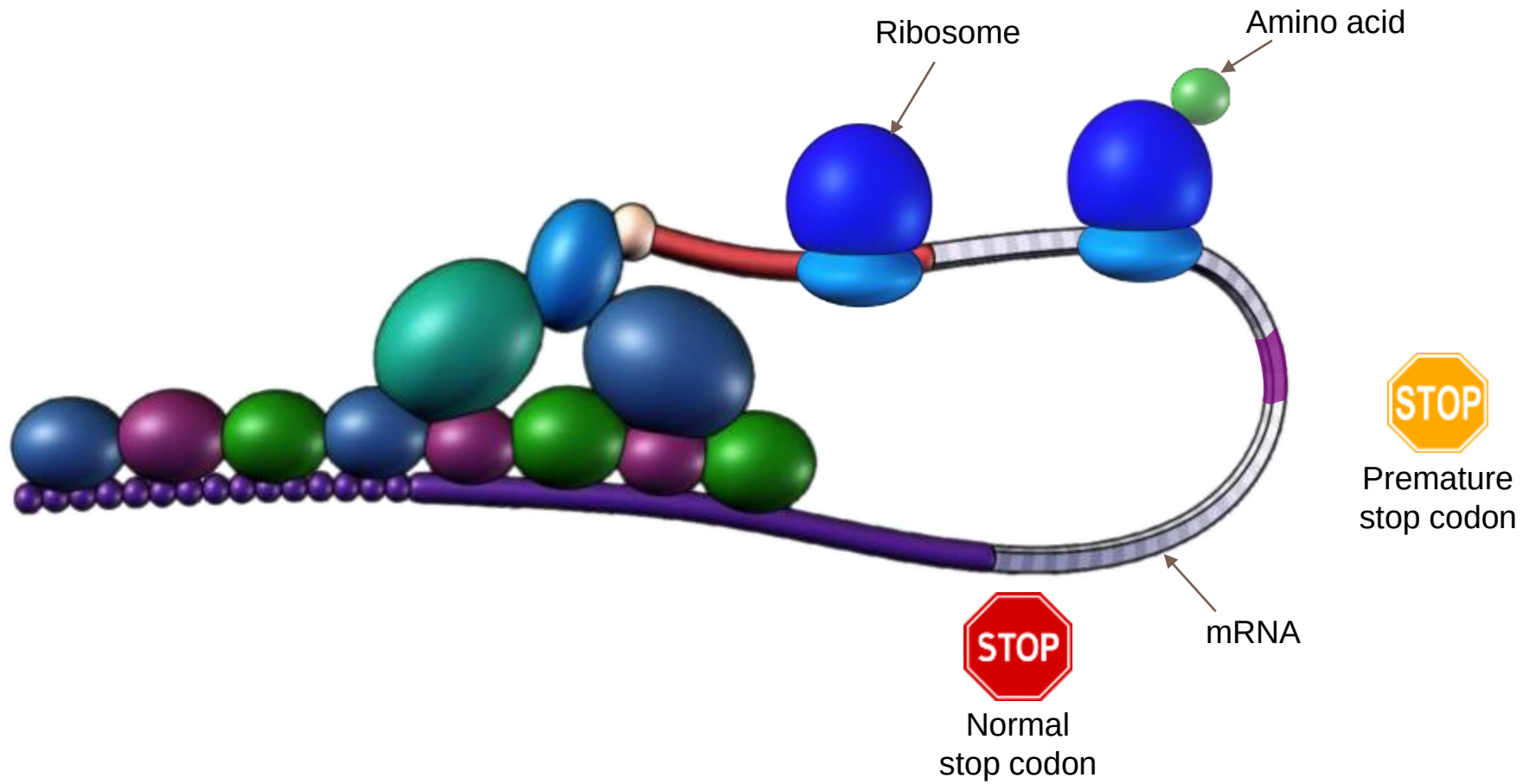
NOVEDADES TERAPÉUTICAS CON APROBACIÓN

NOVEDADES TERAPÉUTICAS CON APROBACIÓN

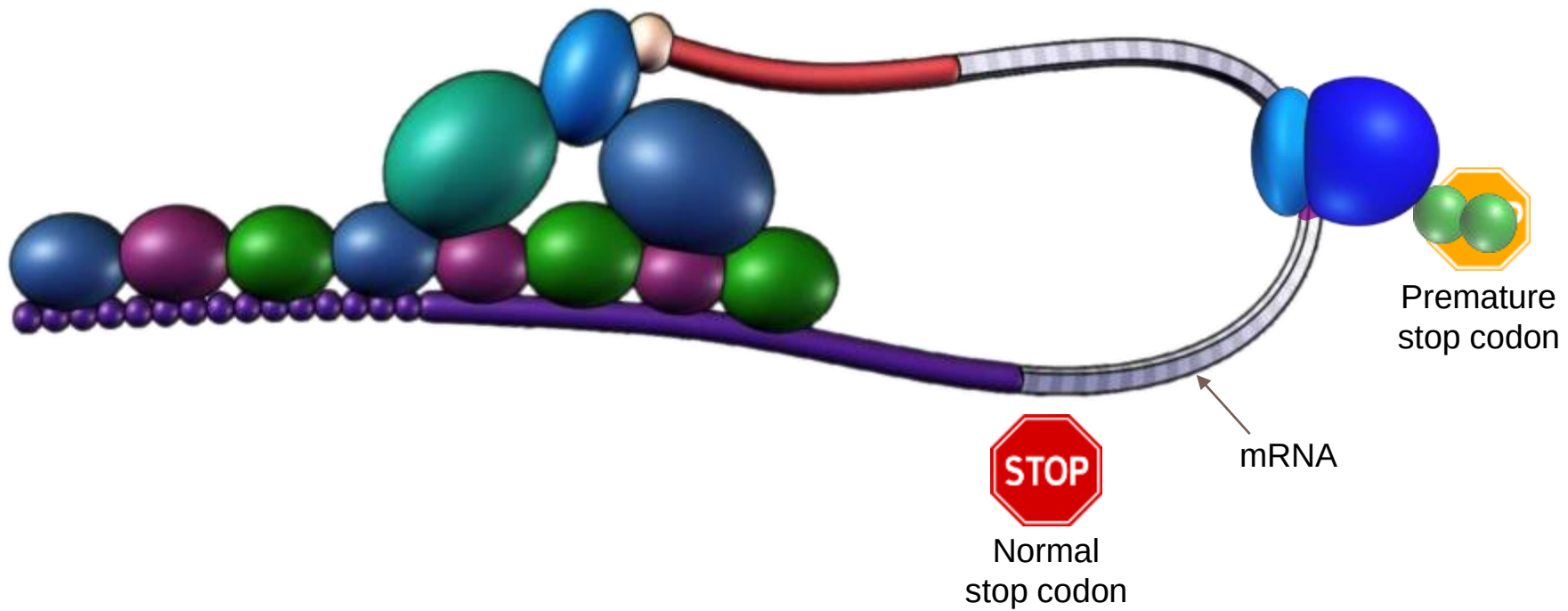
- ATALUREN
- ETEPLIRSEN



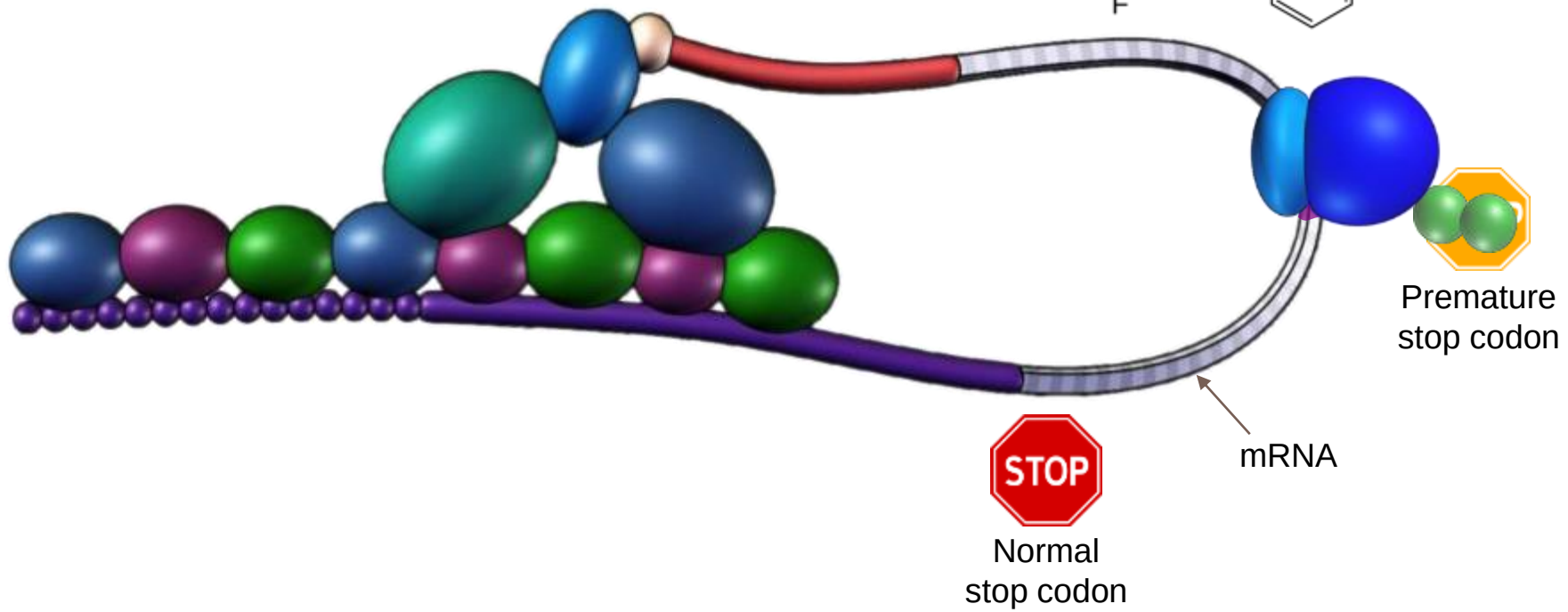
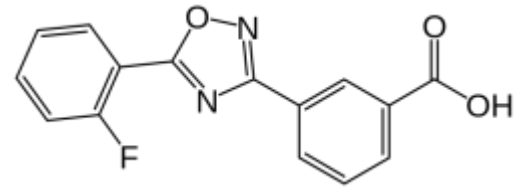
ATALUREN

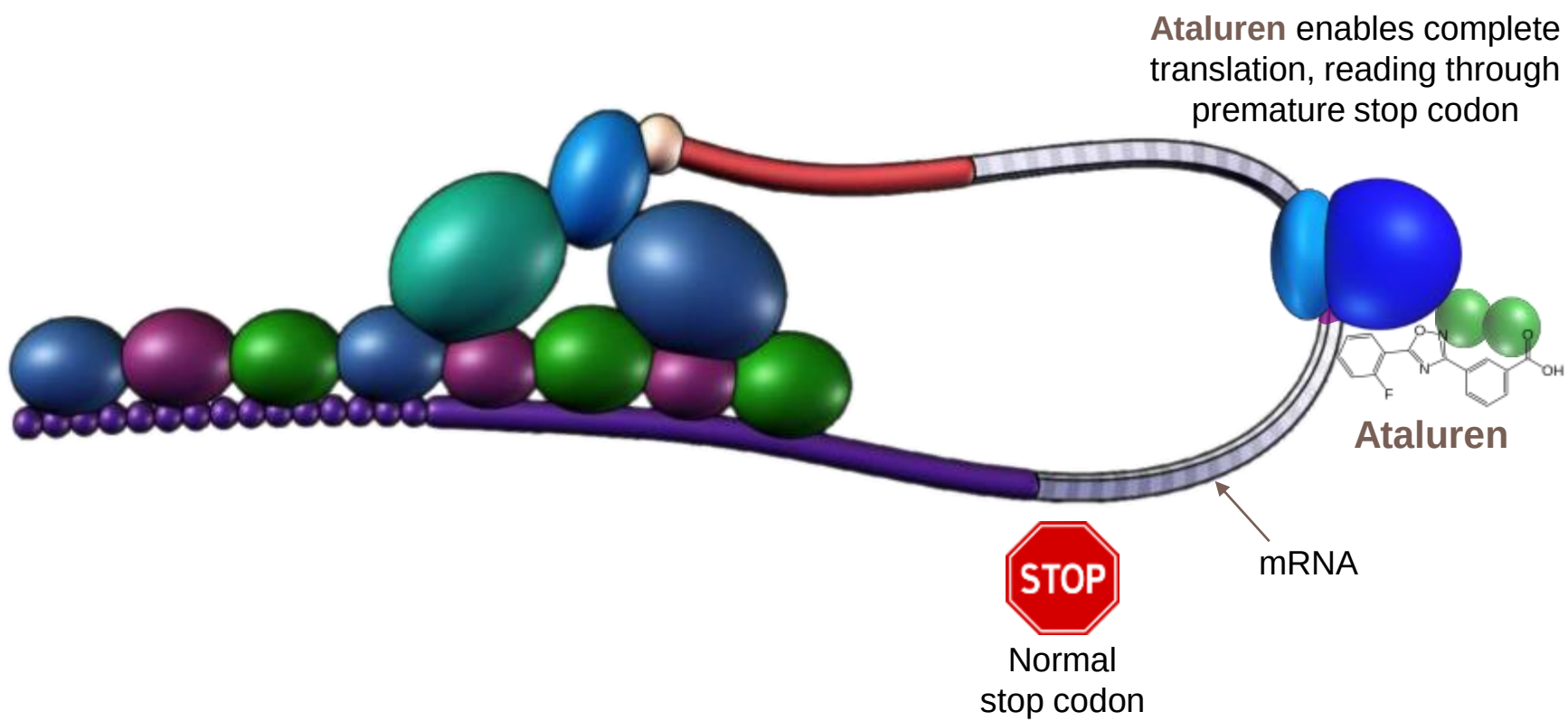


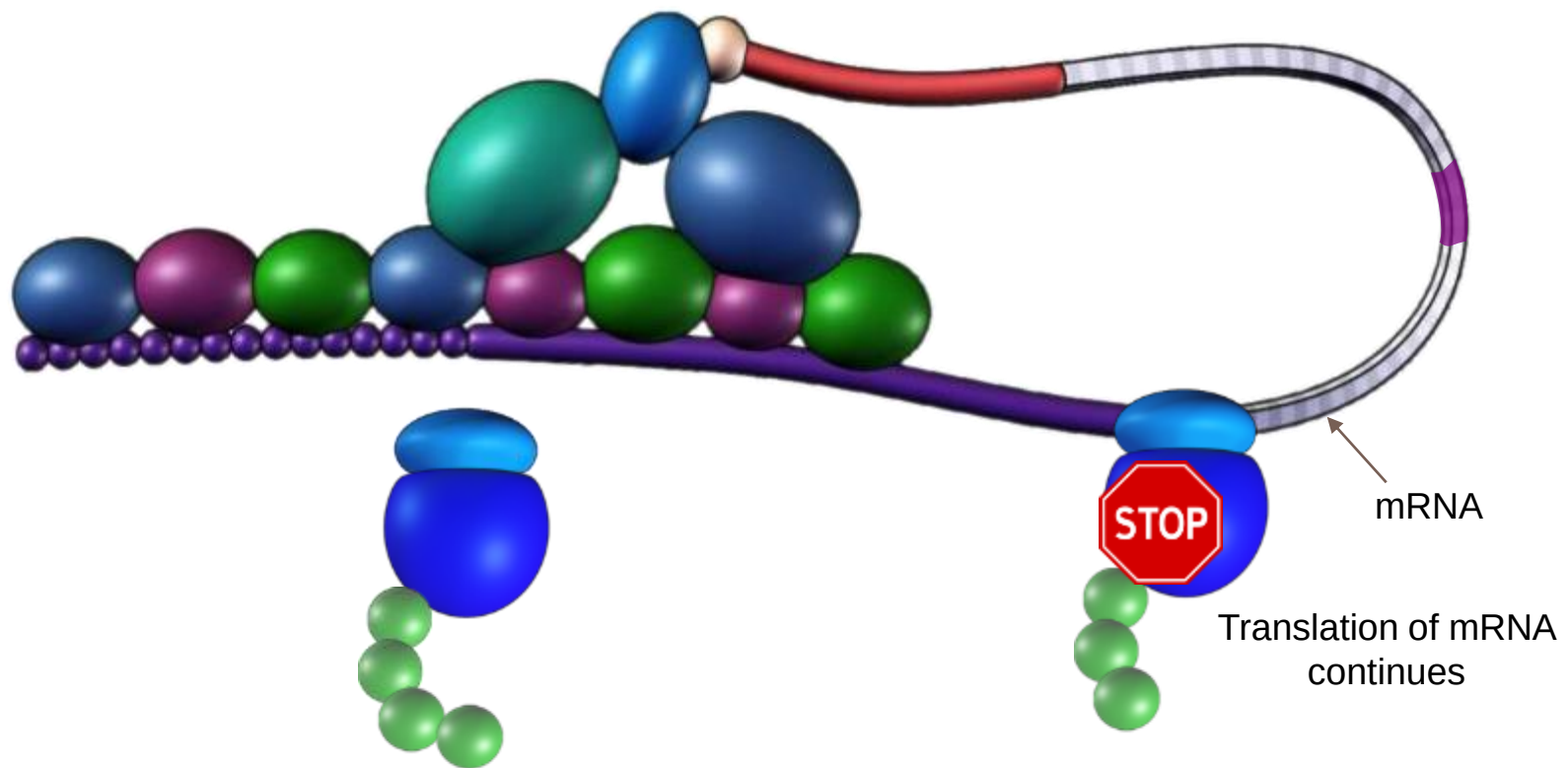
Premature stop codon
causes translation to stop
prematurely (e.g. in nmDMD)



Ataluren







Full length protein (e.g. dystrophin)
produced by complete
mRNA translation

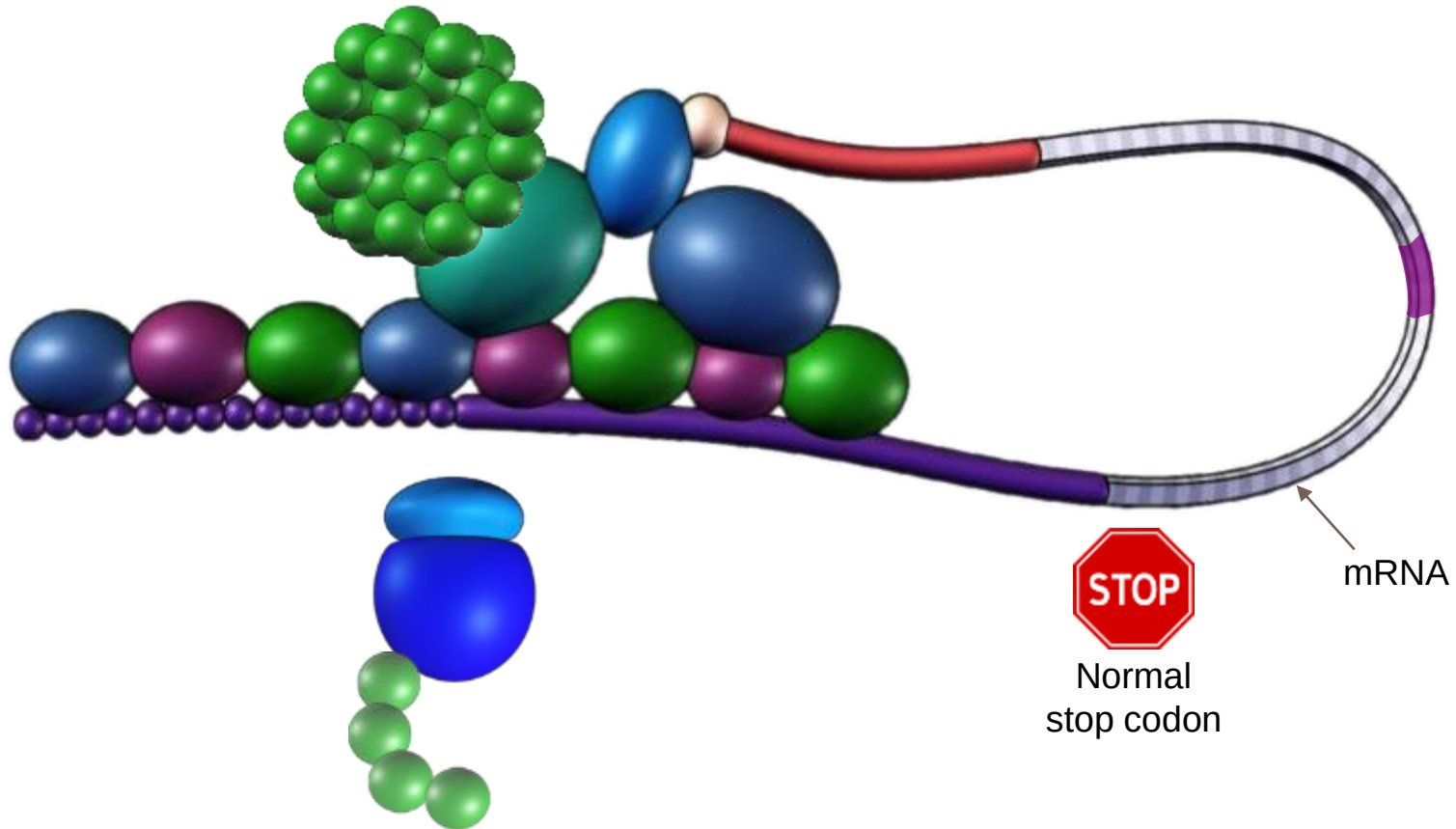


Table 1. Phase 2 and 3 Clinical Trials of Ataluren in nmDMD

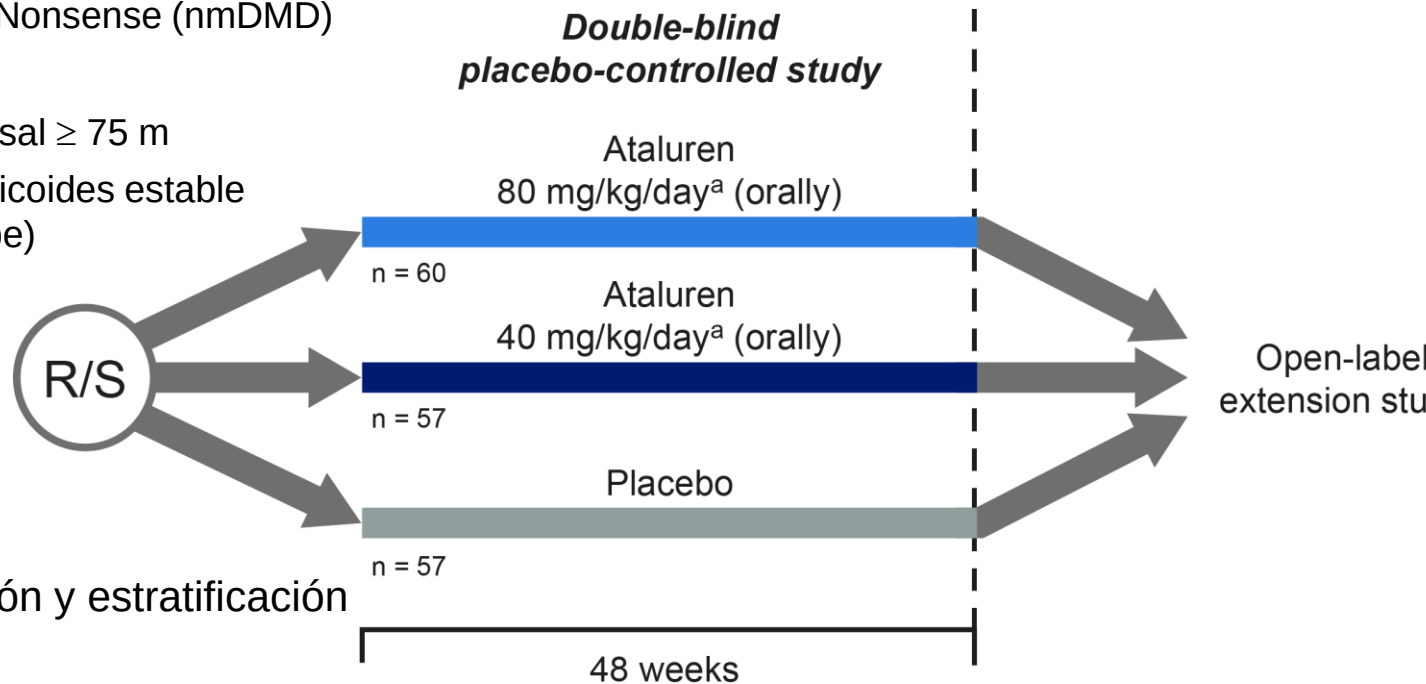
Study	No. of Sites Country	Start – Completion	Design/ Control	Route and Regimens	Treatment Duration	No of Patients (entered/ completed)	Age Range (years)
Phase 2a	3 USA	21 December 2005 – 3 May 2007	Open-label, dose- ranging	Oral, TID ataluren 4, 4, 8; 10, 10, 20; or 20, 20, 40 mg/kg	4 weeks	4, 4, 8 mg/kg: 6/6 10, 10, 20 mg/kg: 20/20 20, 20, 40 mg/kg: 12/12 Total: 38/38	5 – 17
Phase 2b ¹⁸	37 Australia, Canada, Europe, Israel, USA	28 February 2008 – 17 December 2009	Randomized, double-blind, placebo- controlled	Oral, TID placebo or ataluren 10, 10, 20 or 20, 20, 40 mg/kg	48 weeks	Placebo: 57/57 10, 10, 20 mg/kg: 57/57 20, 20, 40 mg/kg: 60/59 Total: 174/173	5 – 20
ACT DMD (phase 3)	54 Asia, Australia, Canada, Europe, Israel, South America, USA	26 March 2013 – 20 August 2015	Randomized, double-blind, placebo- controlled	Oral, TID placebo or ataluren 10, 10, 20 mg/kg	48 weeks	Placebo: 115/111 10, 10, 20 mg/kg: 115/110 Total: 230/221	7 – 14
ACT DMD extension*	55 Asia, Australia, Canada, Europe, South America, USA	20 March 2014 (ongoing)	Open-label extension study for patients who completed ACT DMD	Oral, TID ataluren 10, 10, 20 mg/kg	Median (range): 23.6 (0.3 to 71.3) weeks	199	7 – 15
Open-label extension – US*	15 USA	23 November 2010 (ongoing)	Open-label extension study for patients who completed previous studies	Oral, TID ataluren 10, 10, 20 mg/kg	Median (range) 222.5 (3.6 to 244.6) weeks	108	7 – 22*
Open-label extension – non-US*	21 Australia, Canada, Europe	25 May 2012 (ongoing)	Open-label extension study for patients who completed previous studies	Oral, TID ataluren 10, 10, 20 mg/kg	Median (range) 128.2 (16.3 to 166.1) weeks	94	9 – 21*

McDonald MC et al. An Overview of Clinical Trial Results in Nonsense Mutation Duchenne Muscular Dystrophy. Presented at the 5th International Congress of Myology, 14–18 march 2016, Lyon, France

Ataluren. Fase 2b

■ Criterios inclusión

- Mutación Nonsense (nmDMD)
- ≥ 5 años
- 6MWD basal ≥ 75 m
- Dosis corticoides estable (si lo recibe)

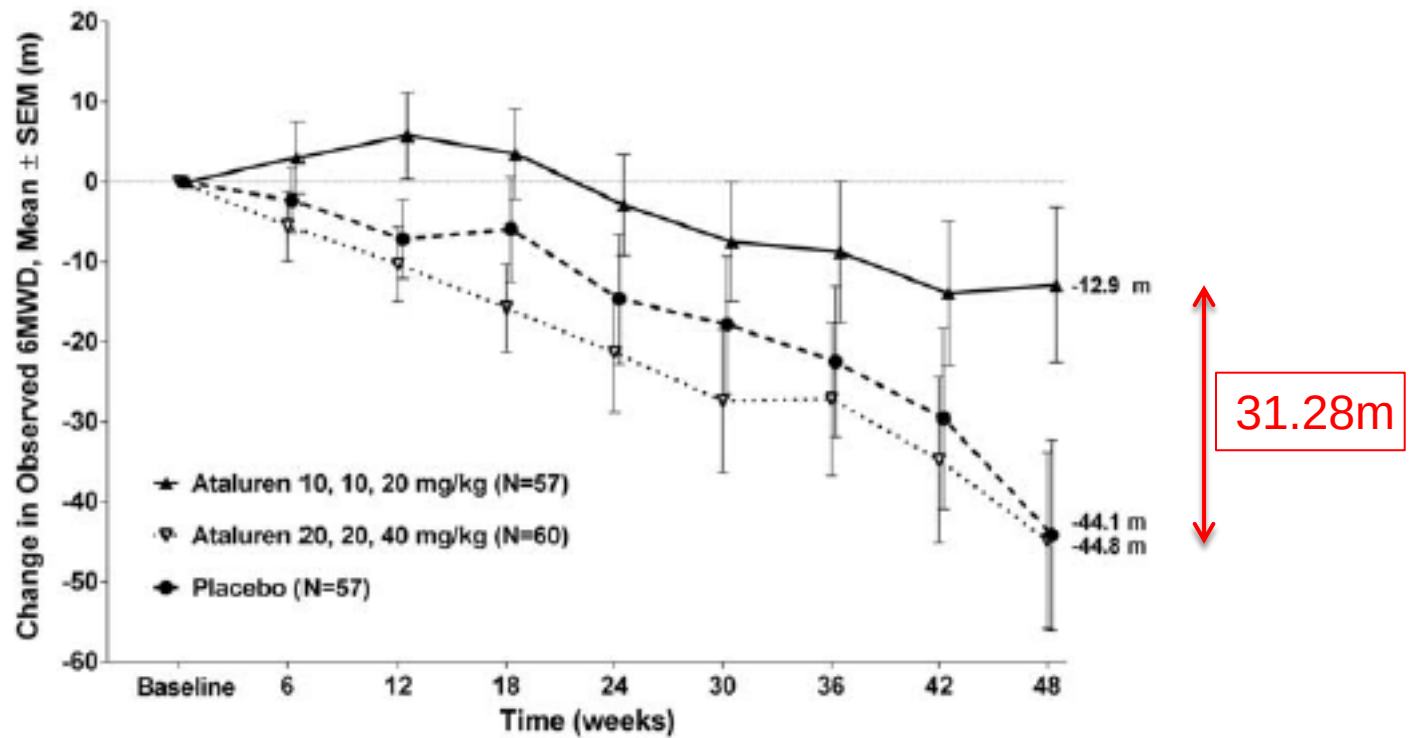


■ Aleatorización y estratificación

- Edad
- Uso de cortoides
- 6MWD basal

Primary endpoint

■ Change in 6MWD from baseline to 48 weeks



Bushby K et al. *Muscle Nerve* 50: 477–487, 2014

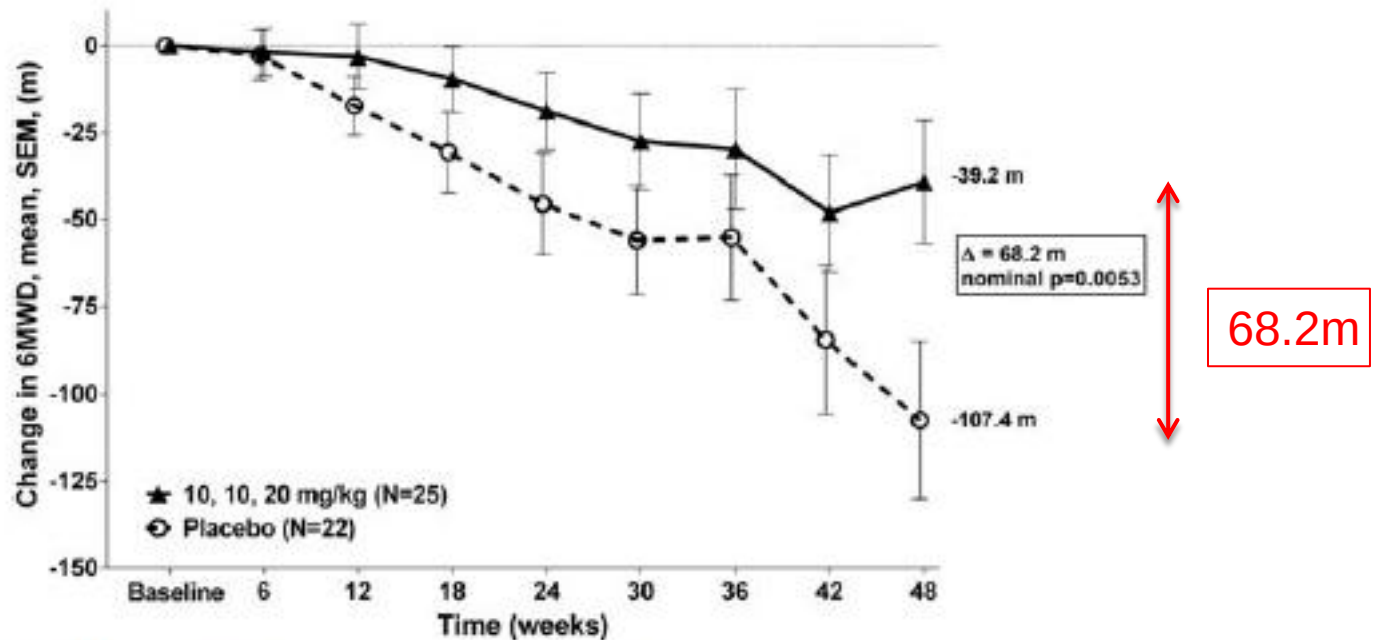
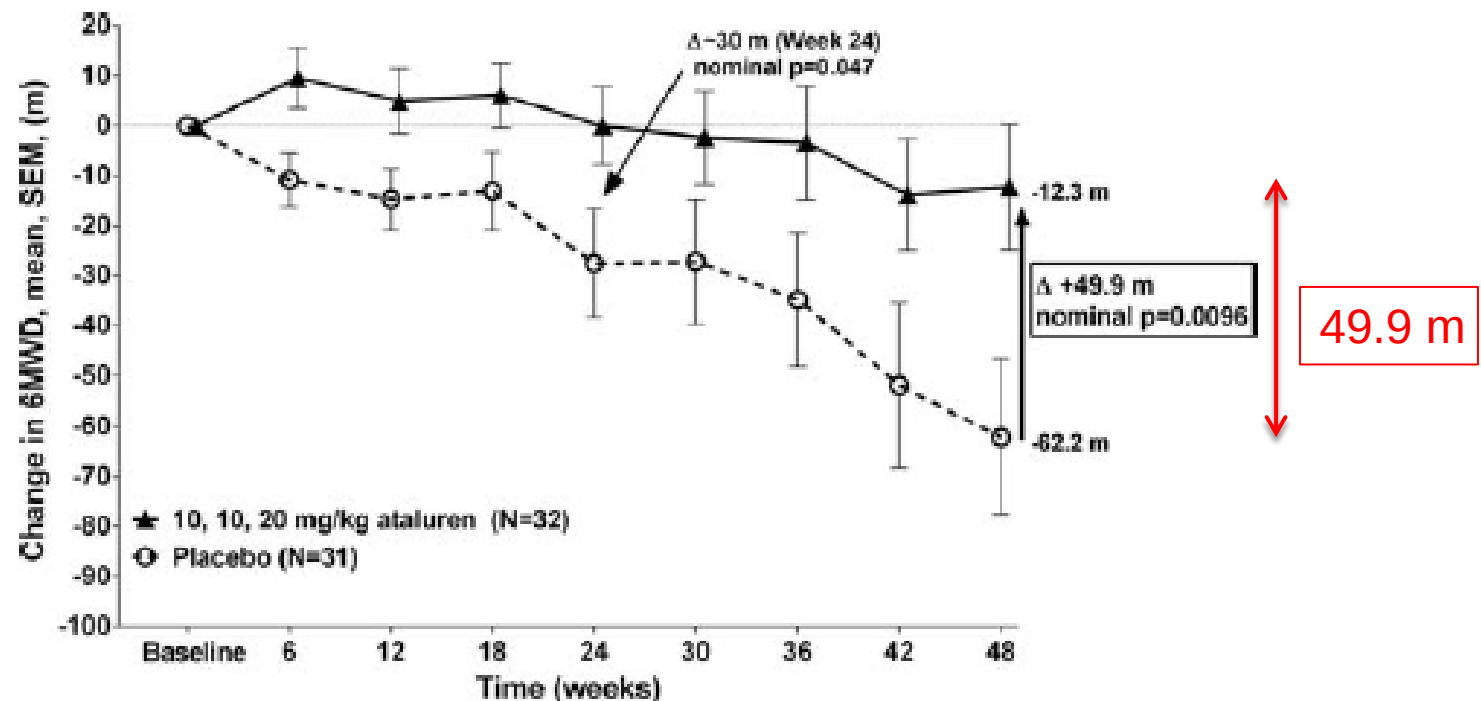


FIGURE 2. Mean change in 6MWD from baseline to week 48 in the < 350 meters 6MWD subgroup.

Subgrupo 6MWD > 150 m y < 80% previsto para edad y altura



*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.

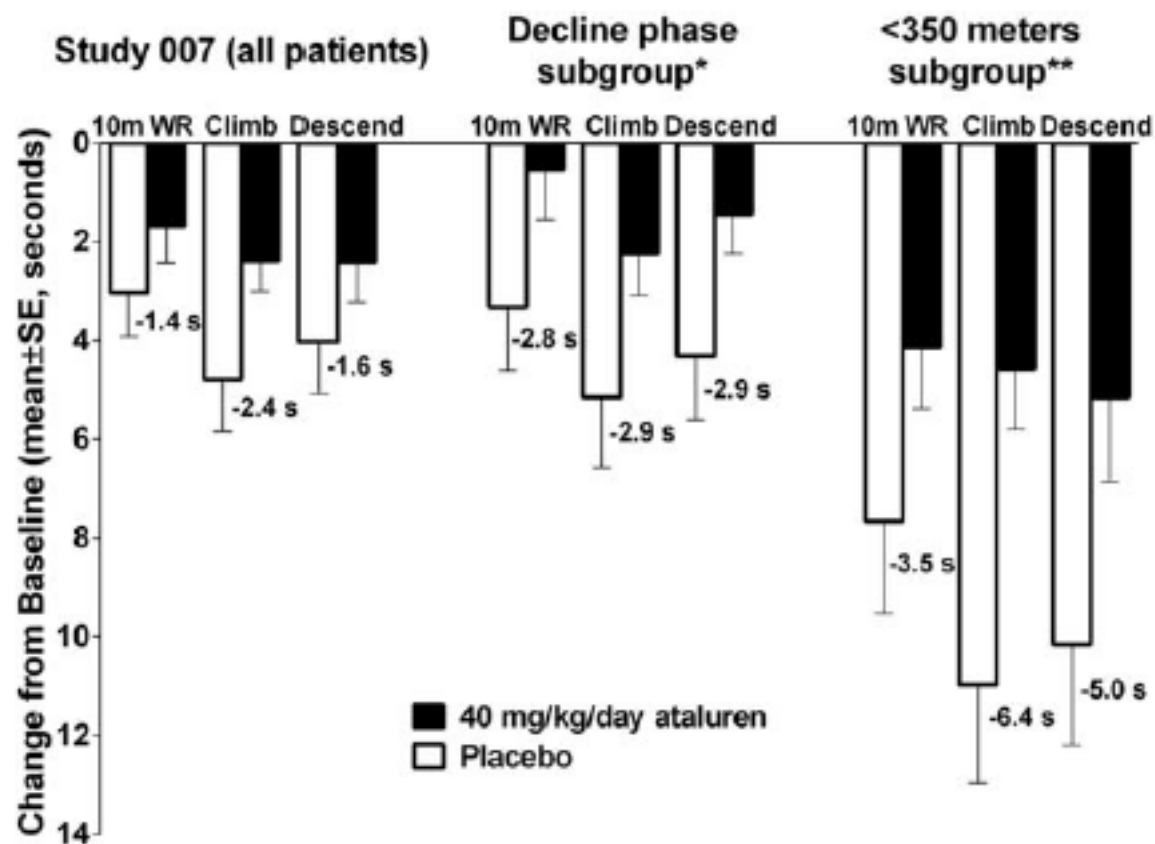
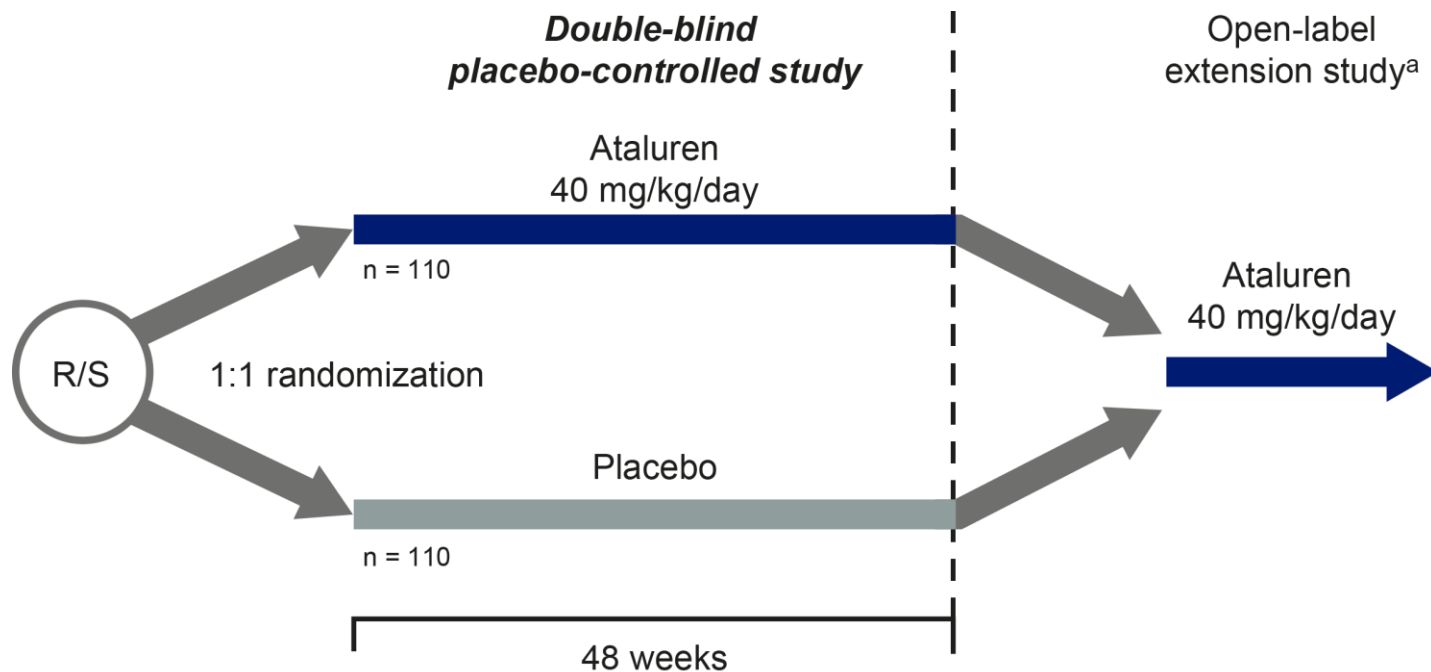


FIGURE 6. Timed function tests change from baseline to week 48 in Study 007 overall population versus decline-phase subgroup.

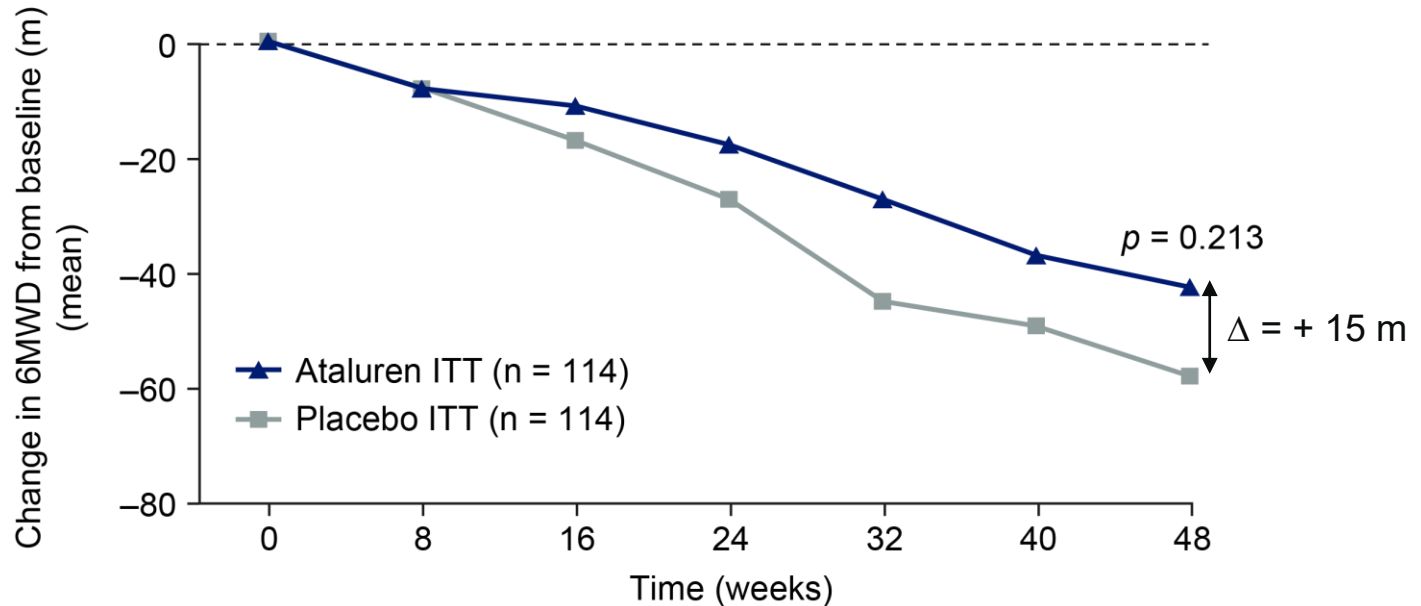
Ataluren Fase 3

■ Criterios de inclusión

- ≥ 7 and ≤ 16 años
- Uso de esteroides > 6 meses
- 6MWD ≥ 150 m y $\leq 80\%$ de estimado para edad y altura



6MWD

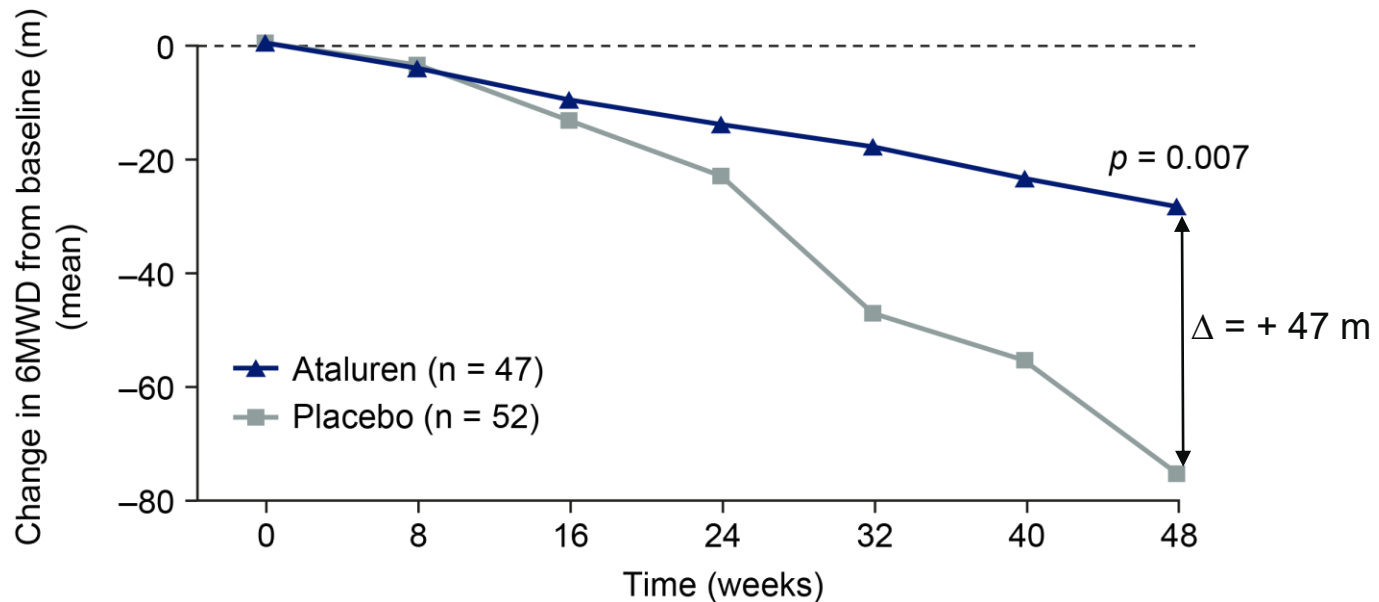


Mean (SD) change in 6MWD (m) from baseline to week 48	
Ataluren	-42.23 (84.99)
Placebo	-57.59 (98.76)

McDonald CM *et al.* Use of 6-minute walk distance (6MWD) across Duchenne muscular dystrophy (DMD) studies. Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

6MWD

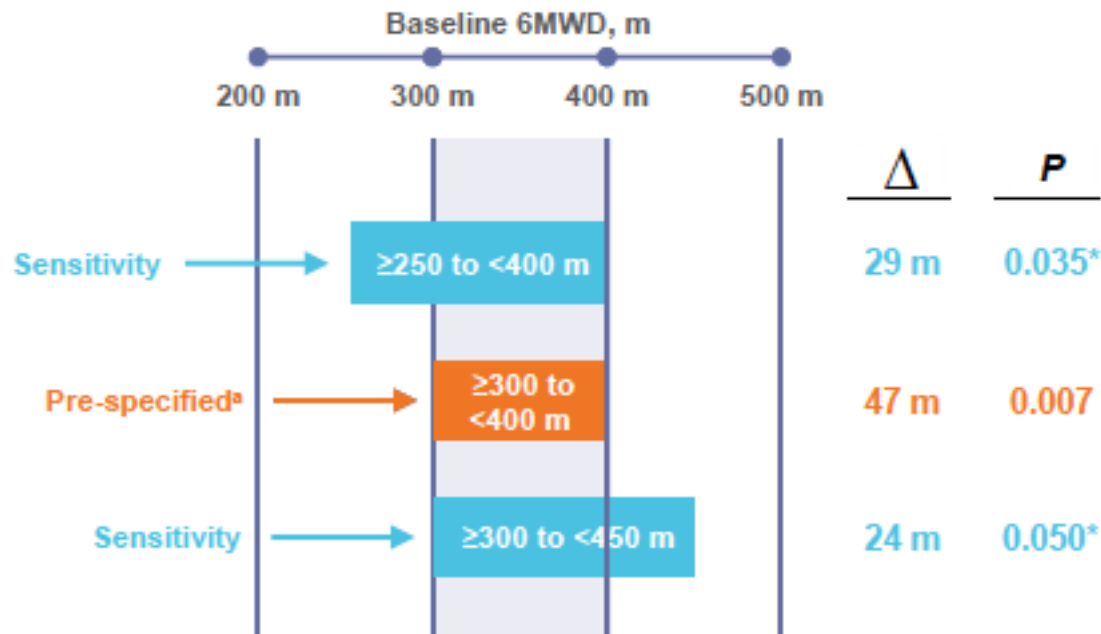
(subgrupo ≥ 300 to < 400 m basal)



Mean (SD) change in 6MWD (m) from baseline to week 48	
Ataluren	-28.32 (55.98)
Placebo	-75.48 (106.27)

McDonald CM *et al.* Use of 6-minute walk distance (6MWD) across Duchenne muscular dystrophy (DMD) studies. Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

Sensibilidad 6 MWD



McDonald CM *et al.* Use of 6-minute walk distance (6MWD) across Duchenne muscular dystrophy (DMD) studies. Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

Pruebas de función cronometrada

Figure 2A. Mean Change in Time to Run/Walk 10 Meters (ITT Population)

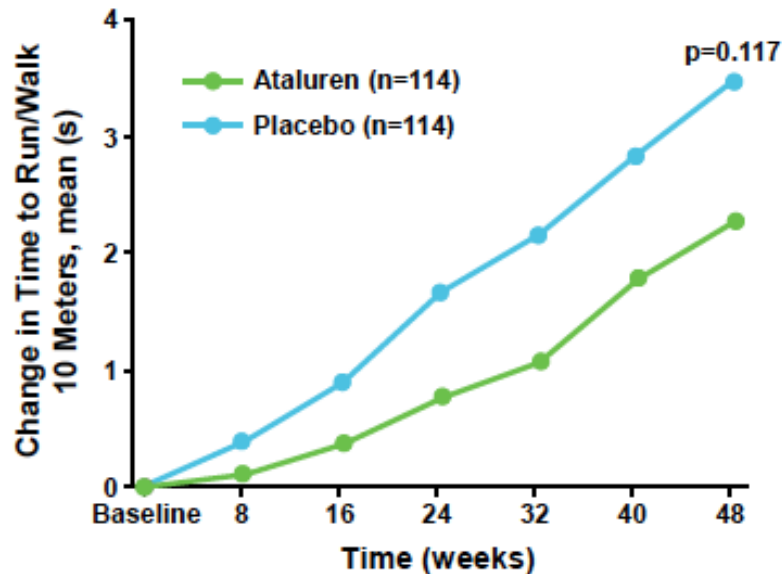
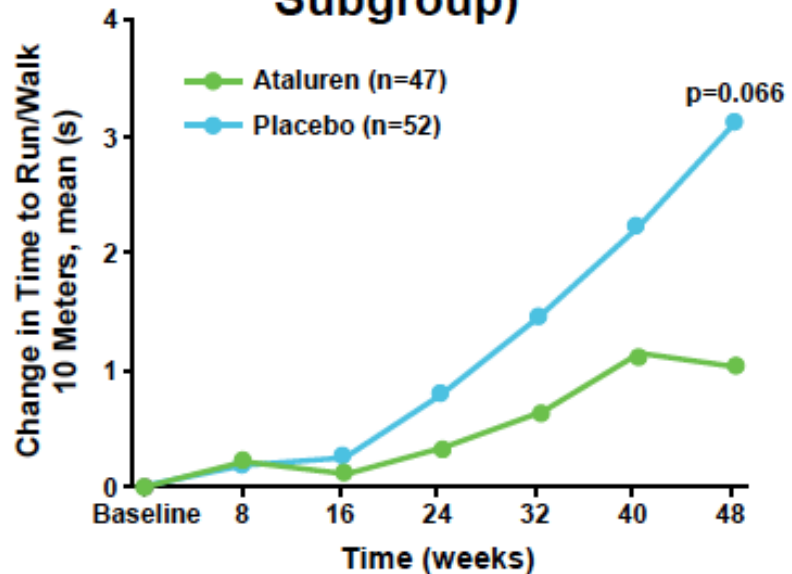


Figure 2B. Mean Change in Time to Run/Walk 10 Meters (Baseline 6MWD ≥ 300 to < 400 Meters Subgroup)



Goemans N. ACT DMD: Effect of Ataluren on Timed Function Tests in Nonsense Mutation Duchenne Muscular Dystrophy. Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

Pruebas de función cronometrada

Figure 3A. Mean Change in Time to Climb 4 Stairs (ITT Population)

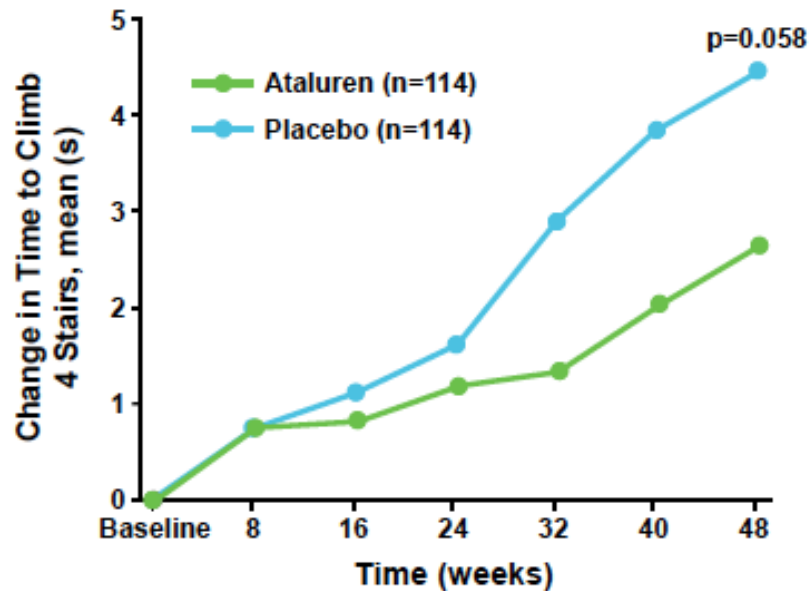
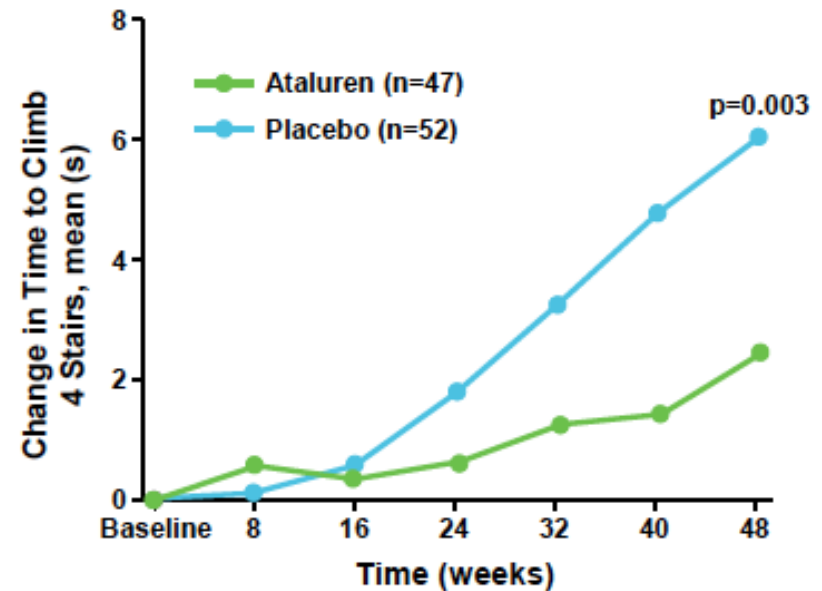


Figure 3B. Mean Change in Time to Climb 4 Stairs (Baseline 6MWD ≥ 300 to <400 Meters Subgroup)



Goemans N. ACT DMD: Effect of Ataluren on Timed Function Tests in Nonsense Mutation Duchenne Muscular Dystrophy. Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

Pruebas de función cronometrada

Figure 4A. Mean Change in Time to Descend 4 Stairs (ITT Population)

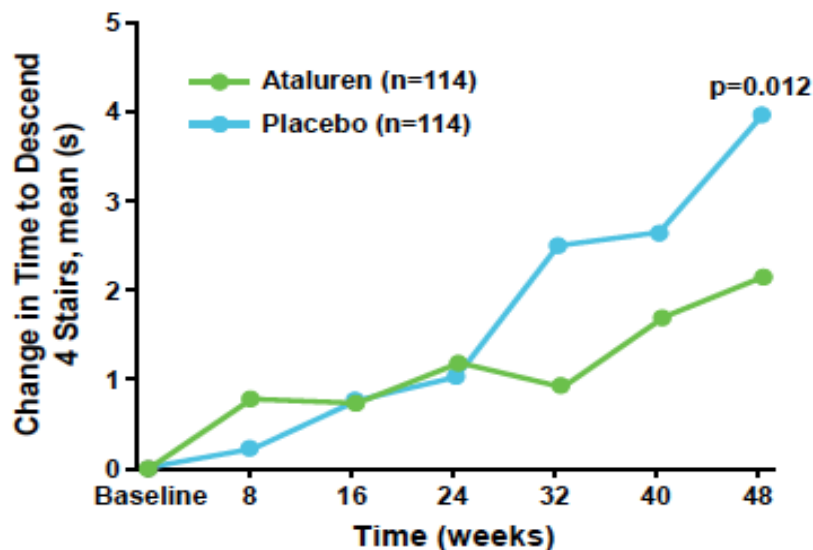
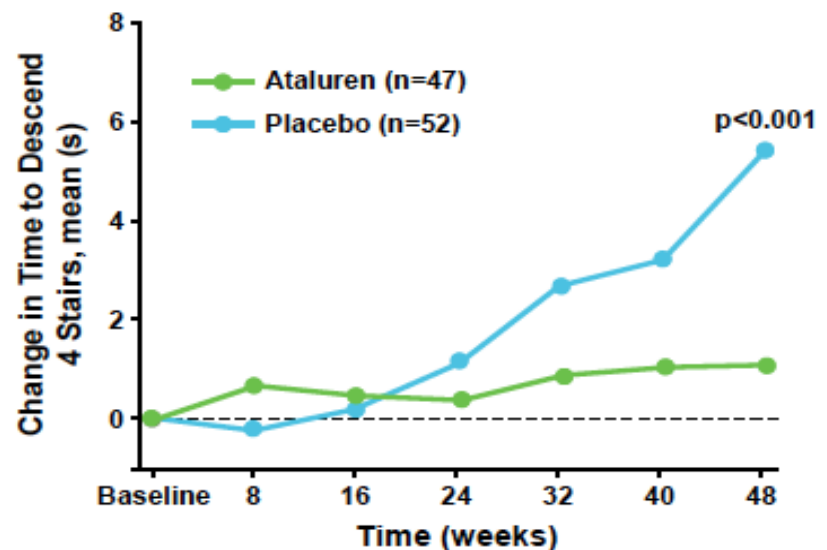


Figure 4B. Mean Change in Time to Descend 4 Stairs (Baseline 6MWD ≥ 300 to <400 Meters Subgroup)



Goemans N. ACT DMD: Effect of Ataluren on Timed Function Tests in Nonsense Mutation Duchenne Muscular Dystrophy. Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

Reacciones adversas frecuentes ($\geq 10\%$)

- Las reacciones adversas frecuentes son debidas a enfermedades comunes de la edad o a síntomas propios de DMD

AE n (%)	Placebo (n = 115)	Ataluren (n = 115)	Total (n = 230)
Vómitos	21 (18.3)	26 (22.6)	47 (20.4)
Nasofaringitis	22 (19.1)	24 (20.9)	46 (20.0)
Caídas	20 (17.4)	22 (19.1)	42 (18.3)
Cefalea	21 (18.3)	21 (18.3)	42 (18.3)
Tos	13 (11.3)	19 (16.5)	32 (13.9)
Diarrea	10 (8.7)	20 (17.4)	30 (13.0)
Fiebre	12 (10.4)	16 (13.9)	28 (12.2)
Dolor en miembros	14 (12.2)	10 (8.7)	24 (10.4)
Progresión de la enfermedad	14 (12.2)	9 (7.8)	23 (10.0)

AE, adverse event

Ataluren. Estado actual

- Aprobación condicional por EMA. Pte aprobación definitiva a los resultados finales del EC fase 3
- Uso compasivo en España.
 - ▣ MAYORES DE 5 AÑOS
 - ▣ DEAMBULANTES
 - ▣ MUTACIÓN NONSENSE GEN DMD

ETEPLIRSEN

- Exon skipping 51 (14%)
- Fase I/II N=19
 - ▣ Aumento de distrofina pero inconsistente
- Fase II N= 12 (30 ó 50 mg/kg/d ó placebo iv, semanal)
 - ▣ Mejoría en capacidad para caminar (50 mg/kg/d). $\Delta 87,4$ metros
 - ▣ Estabilización en función motora
 - ▣ Producción de distrofina de novo y restauración de DAC a las 24 (22,9%)y 48 semanas (51,7%)
 - ▣ 180 semanas (17,4%).
 - ▣ WB: 0.93% de valores normales vs 0,08% de no tratados
- Seguridad en ensayos clínicos y preclínicos
- Fase III. N=160 (30 mg/kg/día). En marcha hasta 2019

- Autorización FDA condicional de nuevos ensayos Sept 2016
- Aprobación por incremento de niveles de distrofina. Pte comprobar eficacia clínica.

Table 1 Information listing of all conducted, ongoing, and recruiting clinical trials on eteplirsen

ClinicalTrials.gov ID	Start month and year	Phase	Description	Participant profile, dosing scheme	Route	Status (month finished or estimated to finish)	Reference(s)
NCT00159250	October 2007	I/II	Single-blind, placebo-controlled, nonrandomized, dose-ranging study testing primarily for safety and tolerability, secondarily for efficacy of local treatment with eteplirsen	Seven patients, two cohort groups; one low-dose (0.09 mg) cohort of two patients, one high-dose (0.9 mg) cohort of five patients; patients all male, 10–16 years old at enrollment	Intramuscular	Complete (March 2009)	39
NCT00844597	January 2009	I/II	Open-label, non-placebo-controlled, nonrandomized, dose-ranging study testing primarily for safety and tolerability, secondarily for pharmacokinetics, efficacy of systemic treatment with eteplirsen	19 patients, six cohort groups; cohorts given either 0.5, 1, 2, 4, 10, or 20 mg/kg eteplirsen per week for at most 12 weeks; patients all male, 5–15 years old at enrollment	Intravenous	Complete (December 2010)	34
NCT01396239	July 2011	II	Double-blind, placebo-controlled, randomized, two-dose study testing for efficacy of systemic treatment with eteplirsen; safety, tolerability, pharmacokinetics also examined	12 patients, three cohort groups, four patients per cohort; cohorts given either 0 mg/kg (placebo group), 30 mg/kg, or 50 mg/kg eteplirsen per week for 24 weeks; patients all male, 7–13 years old at enrollment	Intravenous	Complete (June 2012)	35
NCT01540409	February 2012	II	Open-label, non-placebo-controlled, two-dose extension study of NCT01396239, testing for long-term efficacy, safety, and tolerability of systemic treatment with eteplirsen	Same profile as NCT01396239, except placebo cohort was converted to delayed eteplirsen-treated cohort; four patients in placebo cohort were split randomly into two subcohorts given either 30 mg/kg or 50 mg/kg eteplirsen per week; NCT01396239-treated patients continued to receive the same dose; treatment extended for an additional 212–236 weeks	Intravenous	Ongoing, not recruiting (September 2016)	27,35
NCT02255552	September 2014	III	Open-label, untreated-controlled, nonrandomized study testing for efficacy of systemic treatment with eteplirsen; results from this confirmatory study will be used for the final FDA-approval decision	160 patients projected, two cohort groups, 80 patients per cohort; cohorts will either be treated with 30 mg/kg eteplirsen per week or untreated; study to run for 96 weeks; male patients 7–16 years old eligible for study enrollment	Intravenous	Recruiting (May 2019)	23
NCT02286947	November 2014	II	Open-label, uncontrolled study testing primarily for safety, tolerability, secondarily for efficacy of systemic treatment with eteplirsen in advanced-stage DMD patients	20 patients projected (actual count not reported as of writing); all enrolled patients will be given 30 mg/kg eteplirsen per week for 96 weeks; male patients 7–21 years old eligible for study enrollment	Intravenous	Ongoing, not recruiting (September 2017)	NA
NCT02420379	May 2015	II	Open-label, controlled, nonrandomized study similar to NCT02286947, but for patients with early-stage DMD	40 patients projected, two cohort groups, 20 patients per cohort; one cohort will receive 30 mg/kg eteplirsen treatment per week; other cohort will consist of patients with mutations not amenable to eteplirsen treatment (observed only); study to run for 96 weeks; male patients 4–6 y/o eligible for study enrollment	Intravenous	Recruiting (February 2018)	NA

Conclusiones

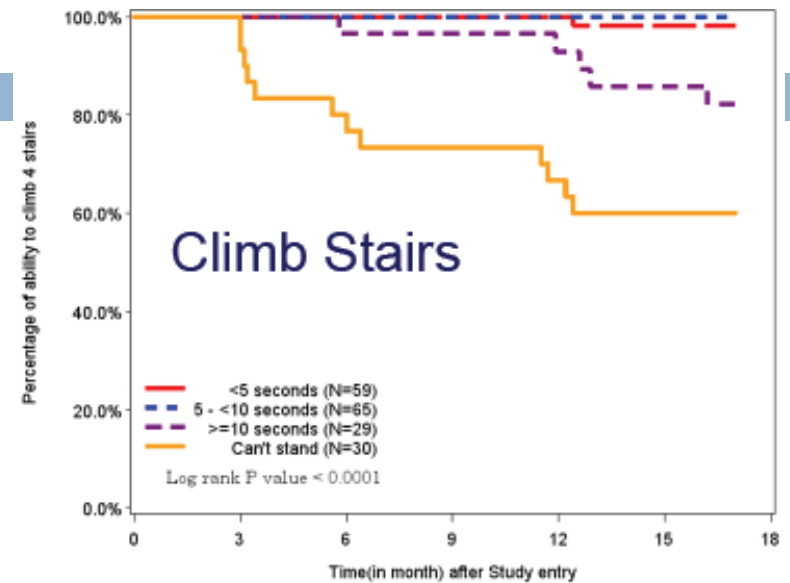
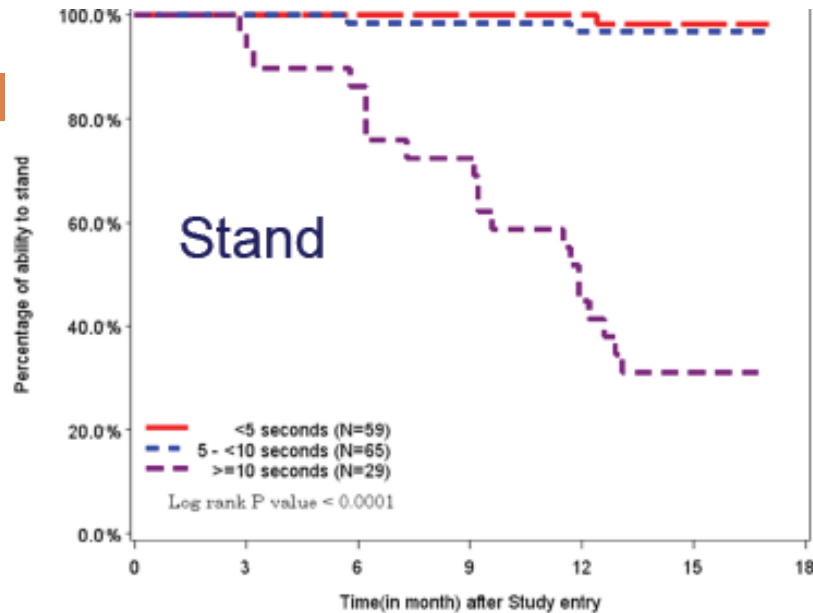
- DMD: enfermedad genética progresiva
- Tratamiento estándar (corticoides, IECAs...)
- Novedades terapéuticas en investigación, prometedoras
- **Ataluren** y eteplirsén son una realidad



Muchas
gracias

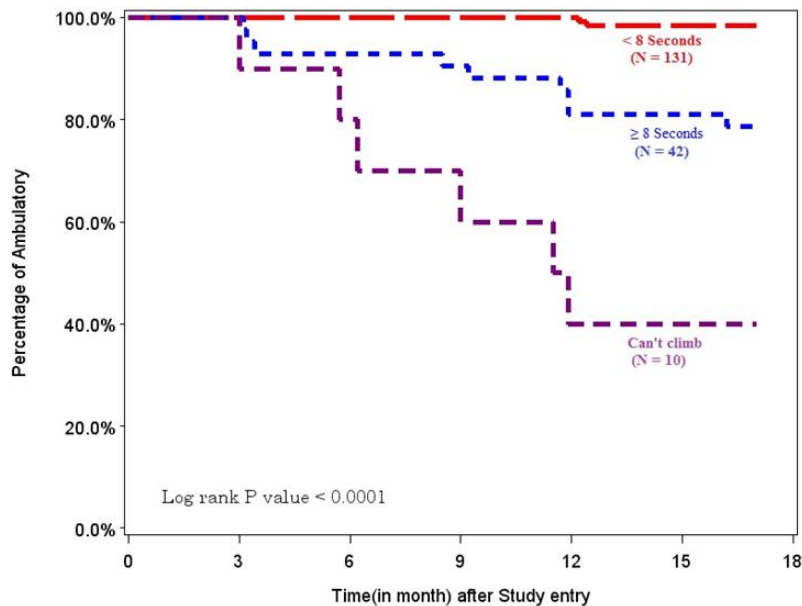
MM

Pruebas de función cronometradas (TFT)

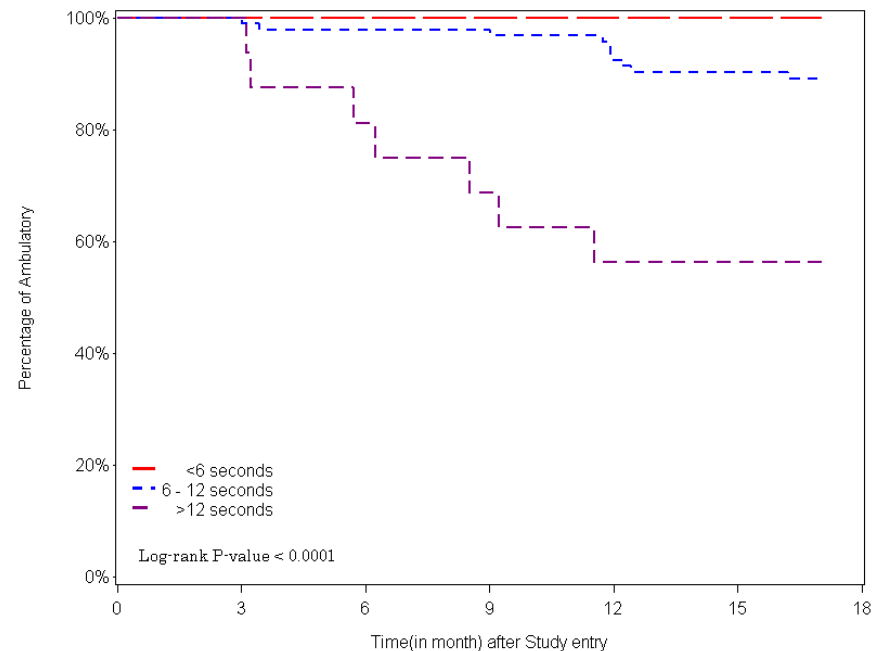


Tiempo en levantarse desde el suelo predice la pérdida de la capacidad de levantarse, subir escaleras y caminar de forma independiente en DMD

Tiempo en subir 4 escalones predice pérdida de deambulación



Riesgo de pérdida de deambulación en 12-18 m basado en test de marcha 10 m



A Full-length dystrophin



DRISAPERSEN

- Exon skipping 51
- FASE I: 17-35% restauración de distrofina con 1 inyección única im
- FASE II. Inyección sc semanal. N=12
 - ▣ Microalbuminuria y proteinuria
 - ▣ Leve aumento de expresión de distrofina
 - ▣ Mejoría 6MWT 35.2
- FASE II: N=53. Inyección semanal
 - ▣ Mejoría 6MWT en semana 25 y no en la 49
 - ▣ Leve mejora expresión de distrofina
- FASE III: N=186
 - ▣ No diferencias con placebo en 6MWT
- NO AUTORIZADO POR FDA

**Table 2. Meta-analysis of Phase 2* and Phase 3
Timed Function Test Study Results
(Ataluren n=146, Placebo n=145)**

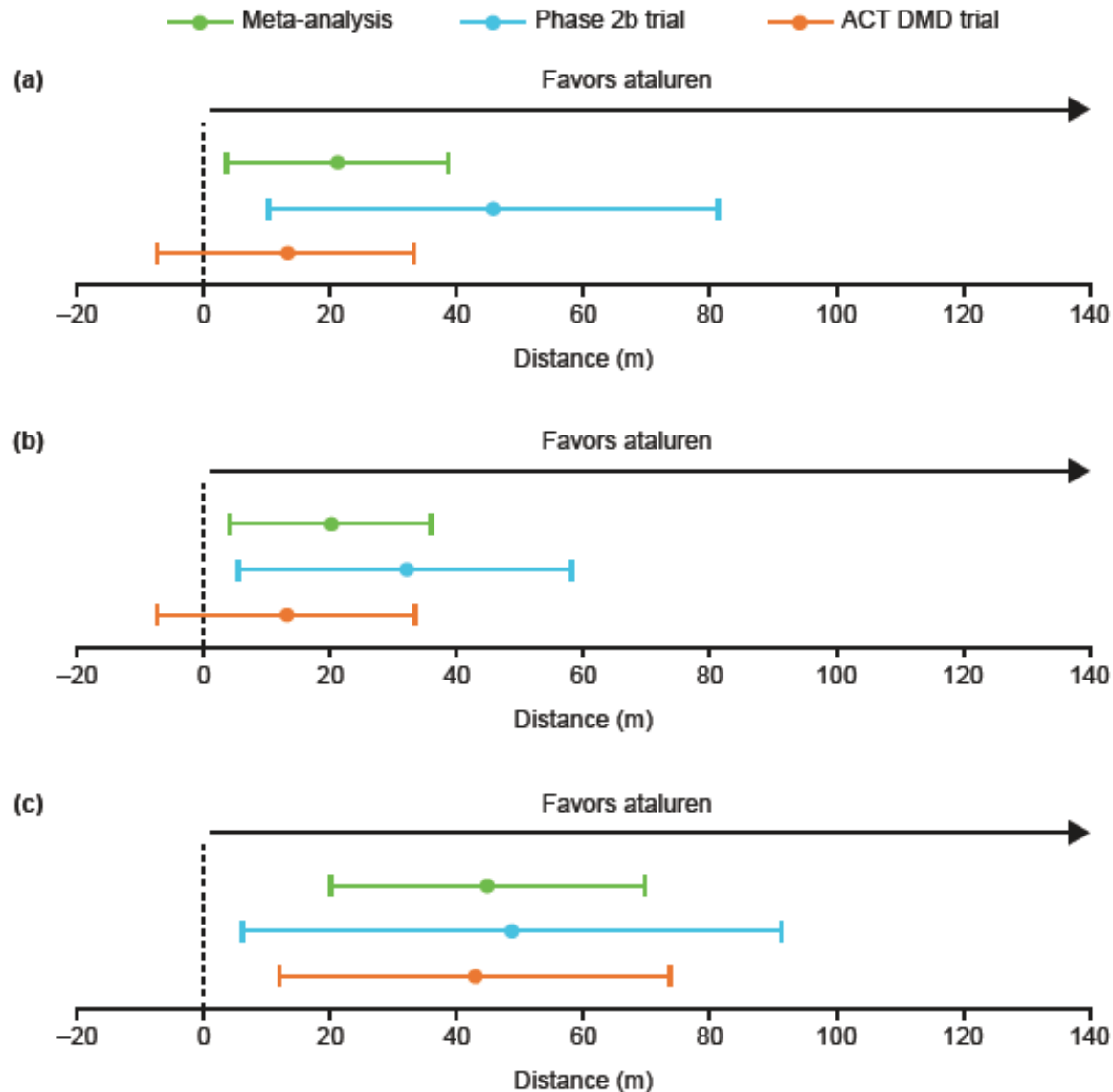
Change in time	Mean Δ	SE	P-value
To run/walk 10 meters, seconds	-1.4	0.608	0.025
To climb 4 stairs, seconds	-1.6	0.675	0.018
To descend 4 stairs, seconds	-2.0	0.712	0.004

Table 2. Risk of persistent 10% worsening in 6MWD in patients who received ataluren relative to placebo at week 48.

	Meta-analysis of patients meeting the ACT DMD entry criteria		Meta-analysis of the ITT# population		Meta-analysis of the ≥ 300 to <400 m 6MWD subgroup	
	Hazard ratio	<i>p</i> value	Hazard ratio	<i>p</i> value	Hazard ratio	<i>p</i> value
Risk of persistent 10% worsening in 6MWD	0.66	0.0232	0.67	0.0195	0.65	0.1082

Campbell C. **Meta-analyses of ataluren in patients with nonsense mutation Duchenne muscular dystrophy.** Poster presented at the 5th International Congress of Myology, 14–18 March 2016, Lyon, France

Figure 1. Mean difference in the change in 6MWD from baseline to week 48 between ataluren and placebo groups, as assessed by (a) meta-analysis of patients meeting the ACT DMD entry criteria, (b) meta-analysis of the ITT# population and (c) meta-analysis of the ≥ 300 to <400 m 6MWD subgroup.



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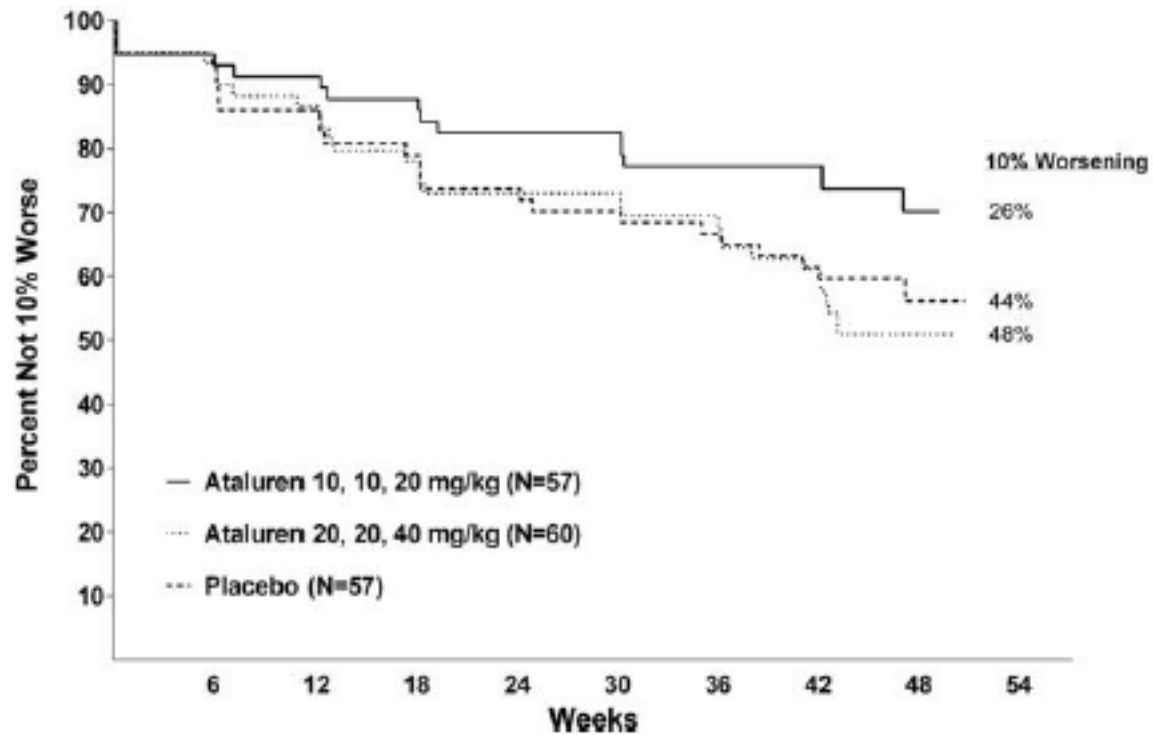
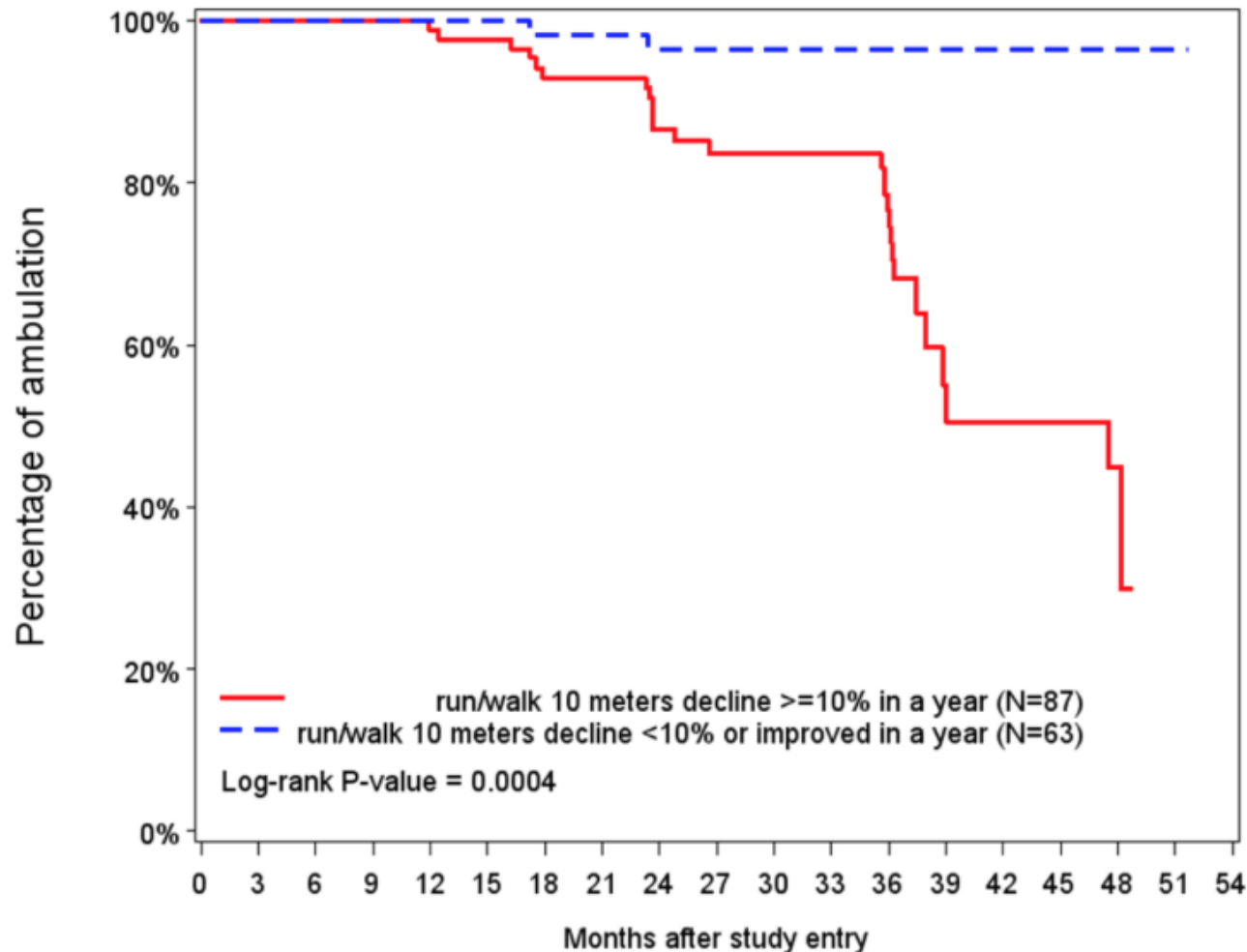


FIGURE 2. Time to persistent $\geq 10\%$ worsening in 6MWD.

Bushby K et al. *Muscle Nerve* 50: 477–487, 2014

Time to Event Analysis:

(< 10% decline versus $\geq 10\%$ decline in one year)



Cooperative International Neuromuscular Research Group
(CINRG) natural history study

