Eteplirsen
NDA 206488

Peripheral and Central Nervous System
Drugs Advisory Committee
April 25, 2016

Introduction

Shamim Ruff
Sr. Vice President
Regulatory Affairs and Quality
Sarepta

Introduction

- DMD challenges: rare, heterogeneous, rapidly progressive
- Key findings
  - Eteplirsen unequivocally produces dystrophin
  - External control is valid, reliable, and reflective of DMD natural history
  - Eteplirsen-treated patients behave differently from natural history
    - Large magnitude of benefit on 6MWT and loss of ambulation (LOA)

DMD Disease Overview

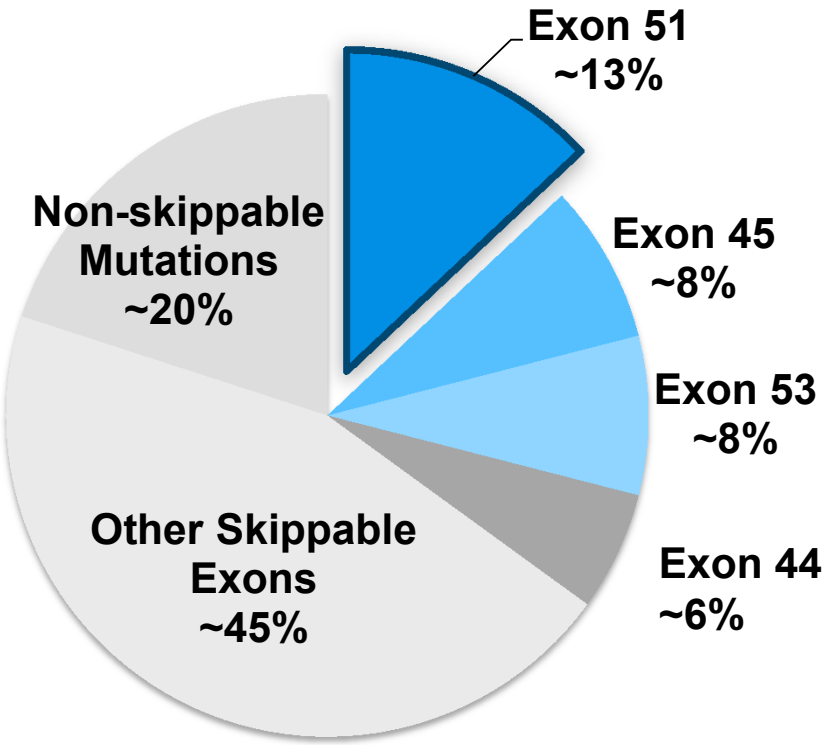
- Pediatric, X-linked, recessive neuromuscular disease
- Mutations in *DMD* gene prevent production of functional dystrophin protein
  - Vital for muscle structure, function and preservation
  - DMD is due to lack of functional dystrophin
- Progressive, debilitating and universally fatal
  - Loss of ambulation during adolescence
    - Leads to downstream complications
  - Premature death (mid-late 20s)
- No approved therapies in USA

Proposed Indication and Dosing for Eteplirsen

- **Proposed Indication:**
  - **Treatment of Duchenne muscular dystrophy in patients with a mutation of the *DMD* gene amenable to exon 51 skipping**
- **Proposed Dosing and Administration:**
  - **30 mg/kg weekly IV Infusion**

Eteplirsen Is Targeted to DMD Genotypes Amenable to Exon 51 Skipping

- US prevalence of DMD: 9,000 to 12,000 boys
- ~13% of DMD patients amenable to exon 51 skipping



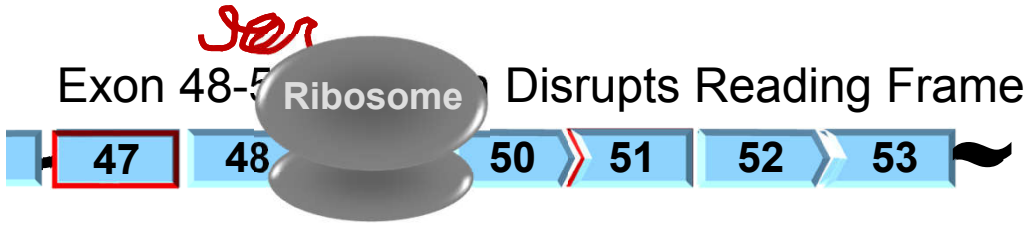
Source: *Aartsma-Rus, et al. Hum Mutat. 2009 Mar; 30(3):293-9.*

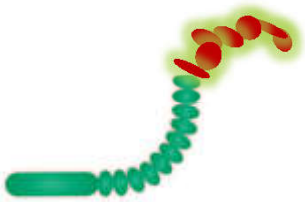
Eteplirsen Leads to Dystrophin Production in Exon 51 Amenable Boys

Normal Dystrophin mRNA

Normal Dystrophin Protein

Exon 48-5 Disrupts Reading Frame





Unstable/No Dystrophin Protein: DMD

Skipping Exon 51 Restores Reading Frame

Shortened Dystrophin Protein

How Did We Get Here?

- Data set: small, natural history control, 4 years
- Precedence for regulatory flexibility in rare diseases established
- More than a dozen meetings with FDA
- Early results precluded placebo-controlled study
- FDA defined pathway for NDA submission
  - April 2014: Request for natural history data
- The primary basis for effectiveness
  - Eteplirsen treated vs. untreated external control

FDA Extends NDA Review Time Due to Submission of 4-Year Data

- Dec 2015: FDA requested 4-year data
- Striking results at Year 4:
  - 162-meter benefit in 6MWT
  - 17% vs. 85% LOA by Kaplan-Meier analysis*
- Feb 2016: 3-month extension to PDUFA date
  - Due to submission of 4-year data

*Nominal log-rank *p*=0.011

Use of Accelerated Approval (AA) for Rare Diseases Encouraged by FDASIA

- FDASIA was signed into law in July of 2012
  - Broader use of AA beyond HIV/AIDS and oncology to rare diseases, such as DMD
  - Requires that FDA seek patient input during drug development and review
- AA allows for acceptable degree of uncertainty regarding anticipated benefit

NDA Submitted in Support of a "Sub-Part H" Application for Accelerated Approval

Characteristics	Accelerated Approval Section 506 (c)	Eteplirsen Pathway
Disease	Serious, life-threatening Severe or rare Lack of alternative treatments	Duchenne Muscular Dystrophy
Surrogate or "intermediate" clinical endpoint	*Reasonably* likely to predict clinical benefit	Dystrophin *and/or* 6MWT
Post-marketing (PM) studies	PM confirmatory trials required to verify and describe anticipated effect	Two confirmatory studies

What Constitutes Substantial Evidence of Effectiveness (CFR 314.126 (b))

- Intent: to reduce the chance of an "incorrect conclusion"
- Requirement for a large randomized placebo-controlled study not always essential
- Historical Controls recognized by FDA to be adequate and well-controlled
- Multiple examples of use of Historical Controls for rare and life-threatening diseases
  - Small sample size; use of Historical Controls
  - E.g. Myozyme, Cholbalm

FDA Issues: Week 180 Dystrophin Results

Issues	Sarepta's Position
Focus on Western blot (WB) results only • Discounted IHC	◆ No single definitive method ◆ Three complementary methods showed significant *de novo* dystrophin protein
Compared WB results to historical literature	◆ Historical literature semi-quantitative ◆ Fold increase over baseline by same assay more appropriate
0.9% by WB not clinically relevant	◆ Small amounts can have a clinical effect ◆ Unequivocal demonstration of dystrophin expression

FDA Issues: 6MWT Pathway

Issues	Sarepta's Position
Study 201 failed to show an advantage for eteplirsen vs. placebo for 6MWT at 24 weeks	◆ Primary 201 endpoint % dystrophin
Appropriateness of External Control as a comparator	◆ Predefined selection criteria ◆ Baseline comparability ◆ 4-year longitudinal data ◆ Standardized 6MWT protocol
Eteplirsen outcomes the same as natural history	◆ Compelling effect size ◆ Longitudinal outcomes different from natural history

Points To Consider

- **We know for certain that DMD boys, if left untreated, will progress in their disease, with a known risk of serious and fatal consequences**
  - **Given this, along with the production of *de novo* dystrophin protein**

    and
  - **The benefit seen on the 6MWT and the loss of ambulation,**

    Is the degree of uncertainty about whether the therapy will result in the anticipated clinical benefit acceptable for Accelerated Approval?

Presentation Agenda

Introduction	**Shamim Ruff, MSc** *Sr. Vice President, Regulatory Affairs and Quality, Sarepta*
Disease Background and Natural History	**Eugenio Mercuri, MD, PhD** *Professor of Pediatric Neurology* *Catholic University of the Sacred Heart, Rome*
Efficacy	**Edward M. Kaye, MD** *Chief Medical Officer (Interim CEO), Sarepta* *Pediatric Neurologist, Boston Children's Hospital*
Safety	**Helen Eliopoulos, MD** *Sr. Medical Director, Sarepta*
Clinical Perspective	**Jerry Mendell, MD** *Director, Center for Gene Therapy* *Professor of Pediatrics and Neurology,* *Nationwide Children's Hospital, Columbus, OH*
Concluding Remarks	**Edward M. Kaye, MD**

Additional Expert Advisors

Francesco Muntoni, MD Pediatric Neurologist Queen Square Centre for Neuromuscular Diseases (University College London Hospitals)	**Dystrophin Expert, Eteplirsen Investigator**
Stephen Wilton, PhD Foundation Chair in Molecular Therapy Centre for Comparative Genomics, Murdoch University, Australia	**Dystrophin Expert**
Bernard Kinane, MD Chief, Pediatric Pulmonary Unit Massachusetts General Hospital for Children	**Pulmonary Expert in DMD**
Craig M. McDonald, MD Professor and Chair, Department of Physical Medicine & Rehabilitation Director, Neuromuscular Disease Clinics University of California at Davis School of Medicine Study Chair, CINRG Duchenne Natural History Study	**DMD Natural History Expert**
Ping-Yu Liu, PhD Fred Hutchinson Cancer Research Center, Member Emeritus	**Statistician**

Received consulting fees and travel expenses covered by Sarepta.

Presentation By The Jett Foundation

Patient and Caregiver Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne

Christine McSherry
Executive Director
Jett Foundation

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Concluding Remarks	**Edward M. Kaye, MD**

Disease State and Natural History

Eugenio Mercuri, MD, PhD

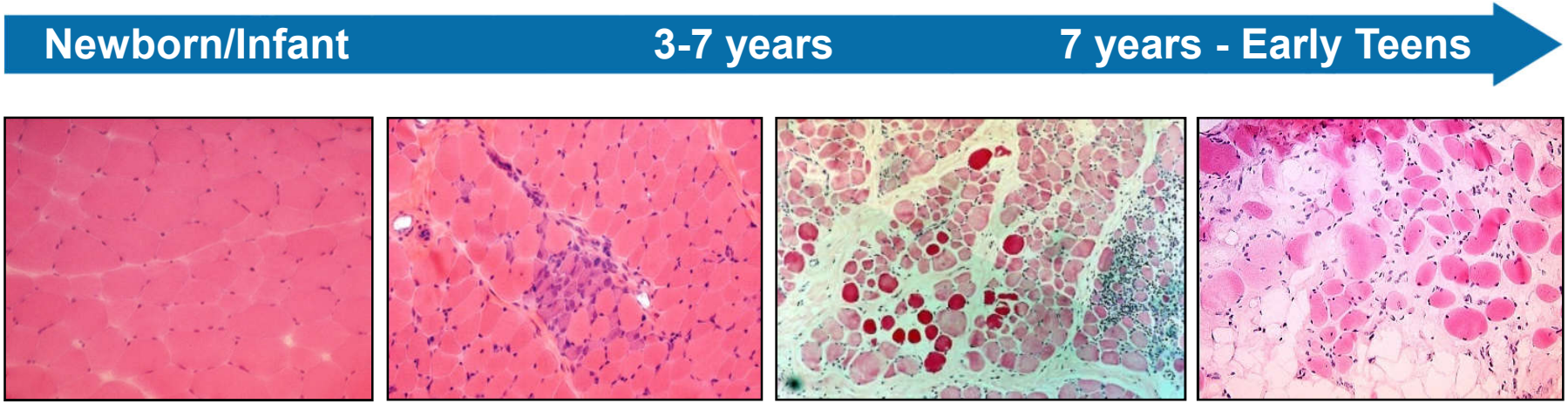
Professor of Pediatric Neurology

Catholic University of the Sacred Heart (Rome)

Role of Dystrophin in DMD

- **In healthy boys with normal dystrophin**
  - Dystrophin acts as a “molecular shock absorber” to protect muscle from damage during contraction
- **In DMD, absence of dystrophin leads to**
  - Progressive muscle damage and loss
  - Replacement of muscle with fibrotic tissue and fat
  - Progressive loss of muscle function

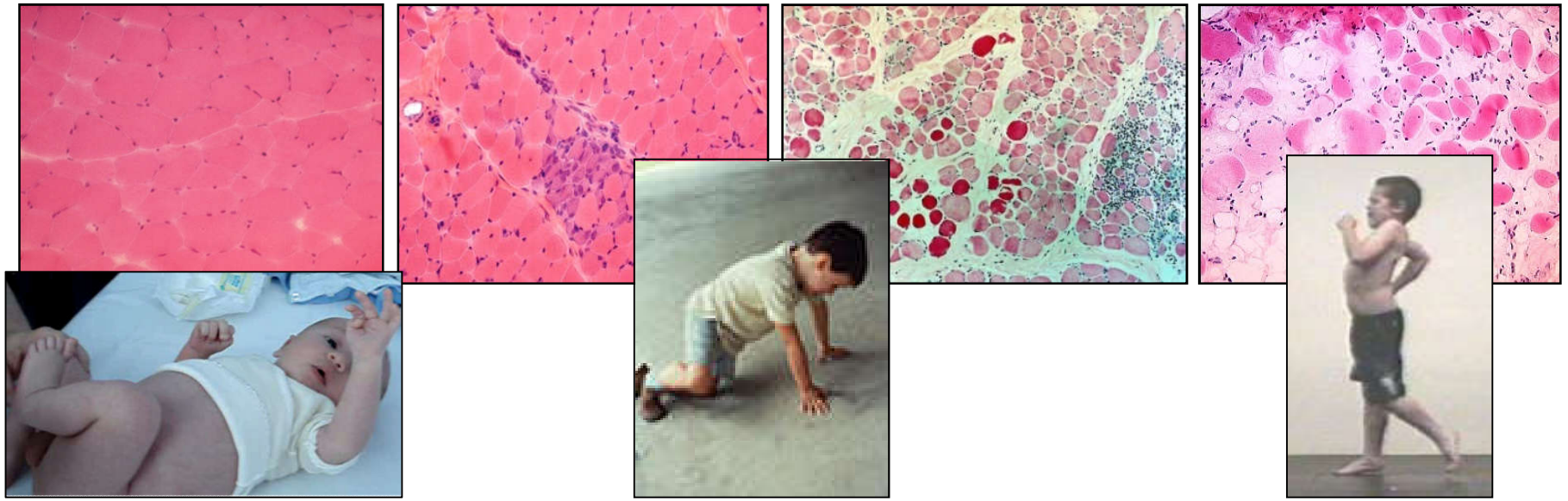
Absence of Dystrophin Leads to Muscle Loss and Replacement with Fat



Muscle biopsies showing progressive replacement by fibrotic tissue and fat

Predictable, Sequential Loss of Abilities

Newborn/Infant | **3-7 years** | **7 years - Early Teens**



- No obvious clinical manifestation
- Elevated CK

- Difficulty running, hopping followed by difficulty standing from supine and climbing stairs

- More rapid decline and loss of ambulation

Age at Loss of Ambulation in Steroid Treated DMD Consistent Across Countries

(Registry)	Mutations	N	Median Age+ (LOA)
Takeuchi 2013 (Japanese Remudy)	Any	245	11
Goemans 2013 (EU: Leuven NMD)	Any	65	12.6
Ricotti 2015 (EU: UK Northstar)	Any	513	13
Bello 2015 (Global: CINRG)	Any	252	13
Bello 2016 (*Neurology* in press) (Global: CINRG)	Exon 51*	33	12 95% CI (11.0-13.5)

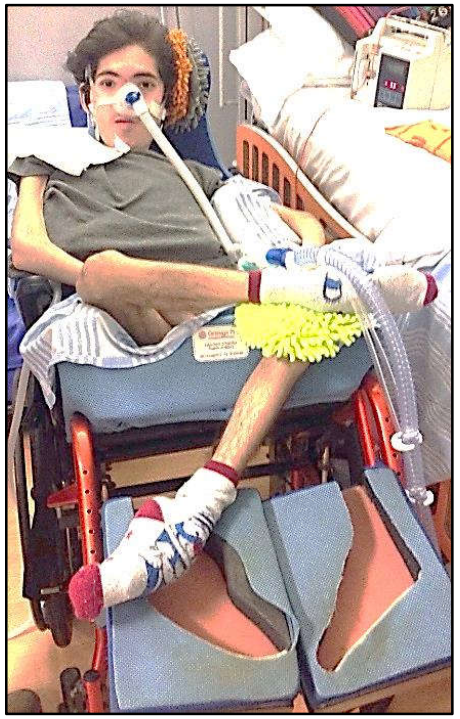
* Includes all exon 51 amenable pts tx with steroids ≥1 year, excluding 1 eteplirsen pt

+ Mean where indicated

Predictable, Sequential Loss of Abilities Continues Following Loss of Ambulation

Late Teens → **Early 20's**

- Decreasing upper limb function
- Respiratory impairment



- Declining pulmonary function
- Cardiac disease

Measuring Disease Progression

6MWT: Integrated Global Measure of Strength, Endurance and Cardiorespiratory Function

- Walk for six minutes on flat ground
  - 25-meter course marked by a cone at each end
- Modified for DMD population
  - 2 examiners
    - One records time and distance
    - One walks behind patient for safety
  - Standardized encouragement to maintain attention and limit bias

6MWT Highly Reliable Tool to Measure Progression in DMD

- Standardized administration of test
  - Conducted by experienced and trained physical therapists
  - Reproducible in a multi-centric setting
  - Highest test-retest reliability of the common DMD measures
- Most widely used measure in recent DMD clinical trials and natural history studies
- Correlation with other measures of disease progression

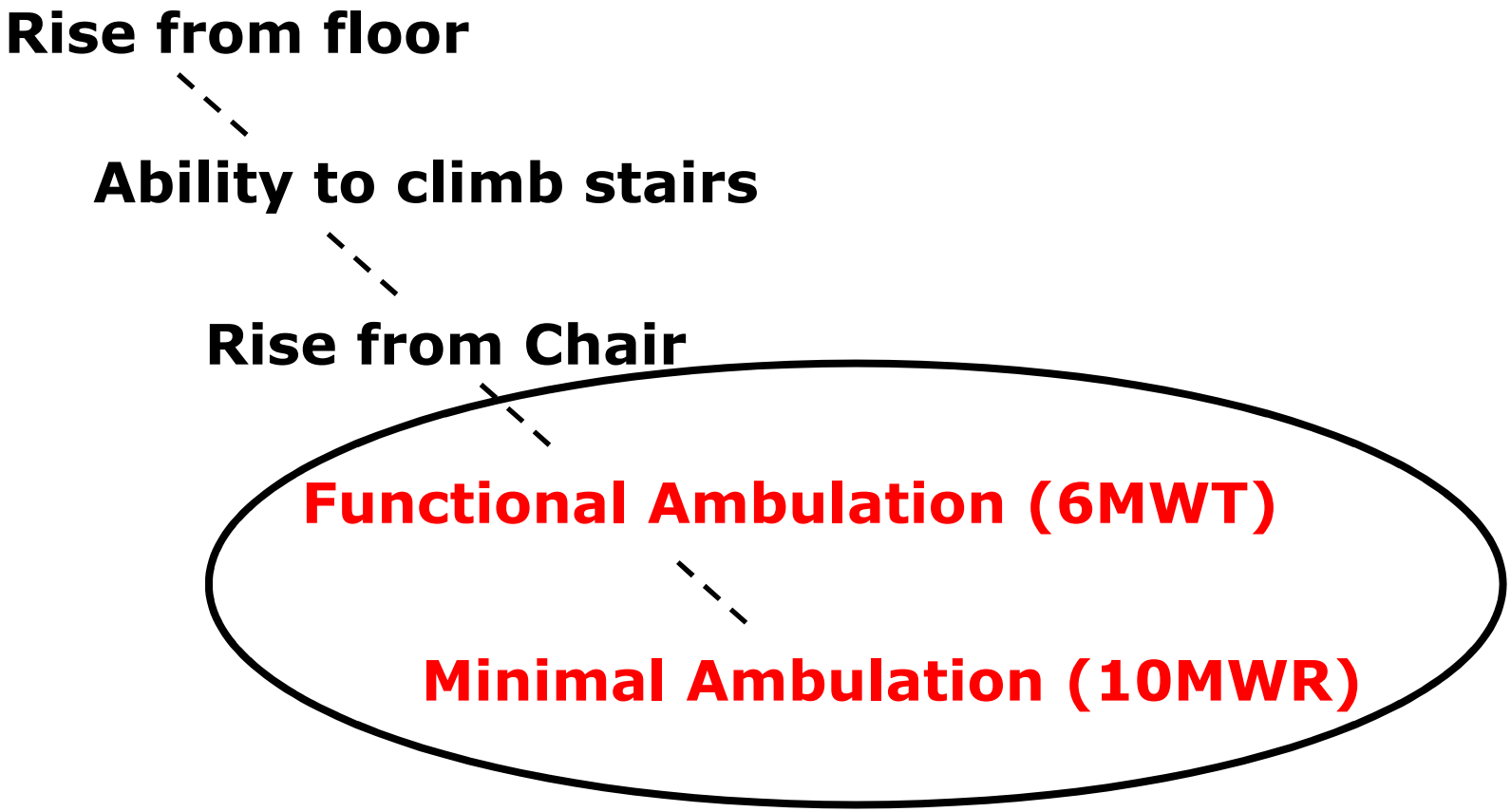
McDonald 2010, McDonald 2013, Mazzone 2011, Mercuri E, et al. 13th International Congress on Neuromuscular Diseases (ICNMD), July 5-10, 2014, Nice, France.

NSAA: Ordinal Scale of 17 Activities

#	Activity
1	Stand
2	Walk
3	Stand from chair
4/5	Stand on one leg (right/left)
6/7	Climb box step (right/left)
8/9	Descend box step (right/left)
10	Sit from supine
11	Rise from supine
12	Lift head from floor
13	Stand on heels
14	Jump
15/16	Hop on one leg (right/left)
17	10 meter run/walk

- Validated, reliable tool assessing Activities of Daily Living (ADL)
  - 17 items scored from 0, 1 or 2
  - Maximum total score of 34
- Order of items follows disease progression
- Younger boys on steroids are generally able to complete most items on the scale
- Progressive loss of abilities on the scale with increasing age
- Losing even one ability on the NSAA represents an irreversible loss of an ADL

Measuring Sequential Loss of Functional Ability in DMD



6MWT, 6-minute walk test.
Adapted from: McDonald CM. Natural History of DMD: What Is Clinically Meaningful? PPMD Webinar.

Loss of Ambulation Definition Varies

Publication (Registry)	Definition	Data Collection
Bello 2015 & 2016ǂ (Global: CINRG)	Patient-reported wheelchair: Confirmed when possible 10MWR	Prospective & Retrospective
Ciafaloni 2016 (U.S: MDSTARnet)	Full-time wheelchair or ambulation ceased (whichever earlier)	Prospective & Retrospective
Takeuchi 2013 (Japanese Remudy)	Unable to walk without support indoors	Retrospective
Pane 2014 (EU: Italian Telethon)	Inability to perform 6MWT; 6MWT=0	Prospective
Goemans 2013 (EU: Leuven NMD)	Inability to perform 6MWT; 6MWT=0	

ǂ *Neurology – in press. Data provided by CINRG (Dr. Craig McDonald).*

Natural History Data

Key Prognostic Factors Affecting Rate of Disease Progression

- Age
- Type of mutation
- 6MWT distance

6MWT Declines After Age 7

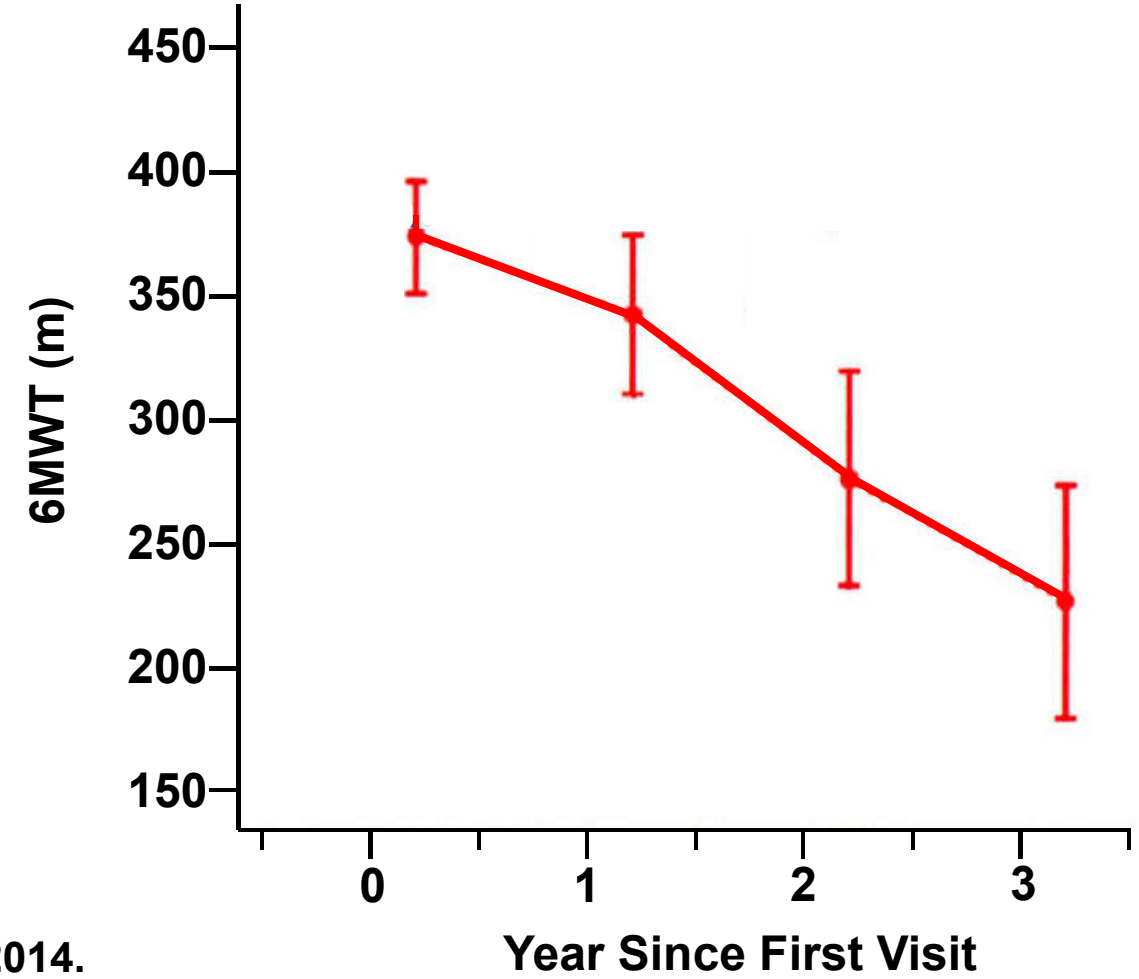
Age	Age Range, yrs	6MWT 12 Month Change (range)
≤7 years (N=80)	3.2 to 7	+27.37 (-95 to 175)
>7 years (N=111)	7.1 to 15	-37.25 (-325 to 102)

Useful for selecting inclusion criteria for a homogeneous, declining patient population

Pane, et al. 2014.

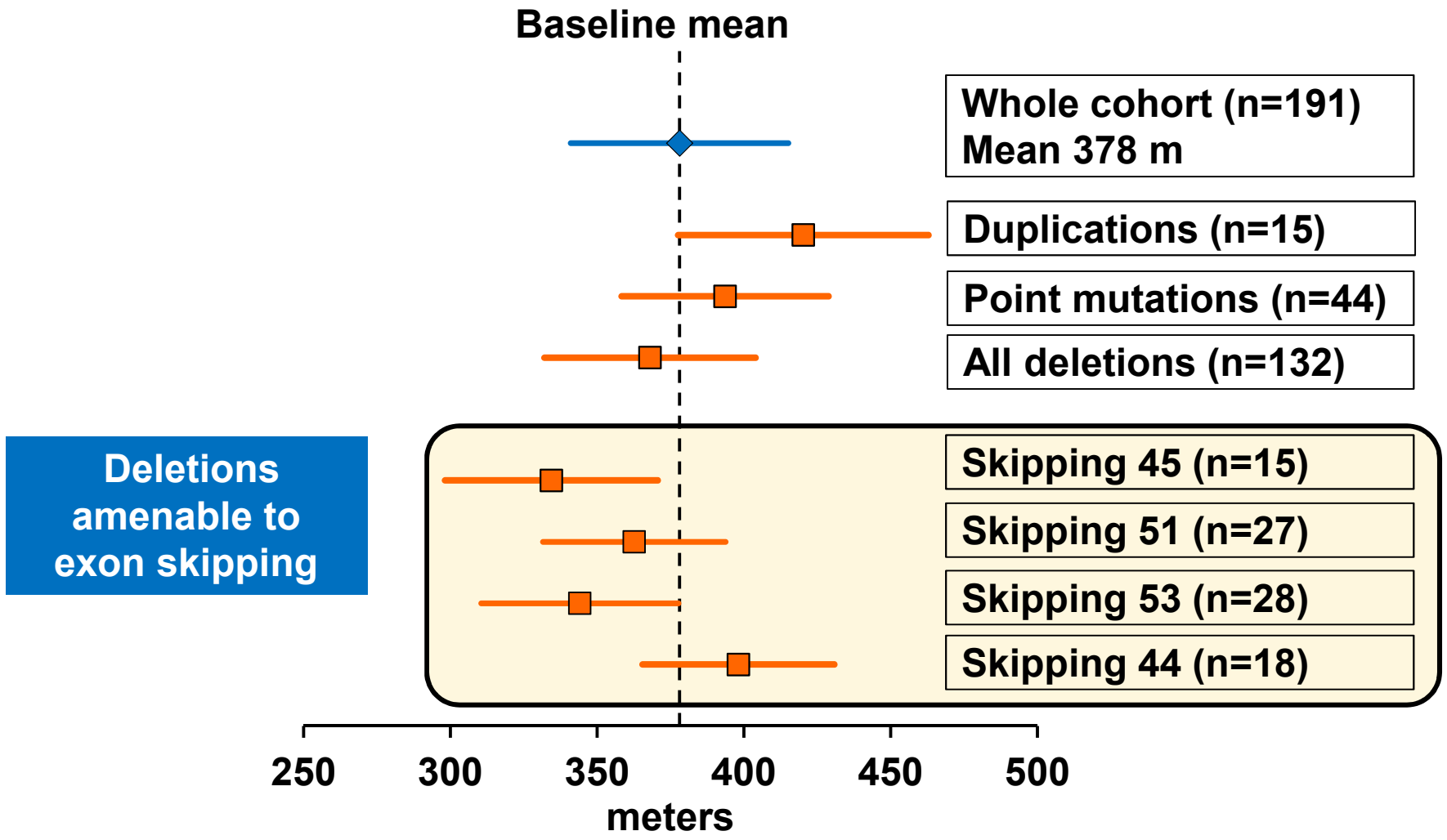
Progressive Decline in Ambulatory Ability After Age 7

- N=68, age at first visit 7-12.8 years



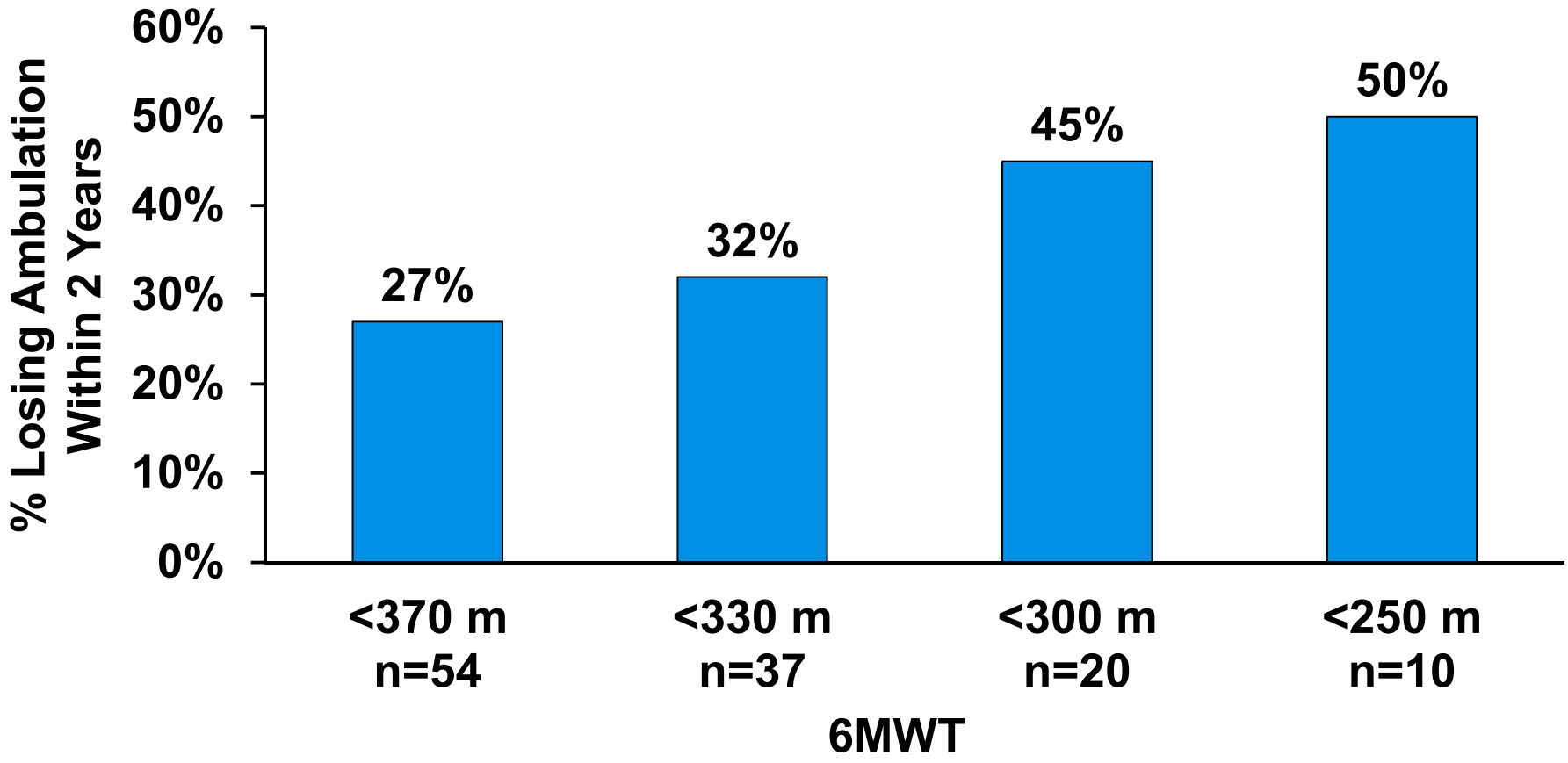
Pane et al, 2014.

Genetic Mutation Impacts 6MWT and Rate of Progression



Adapted from Pane M, et al. *PLOS One* 2014

Lower 6MWT Associated with Increased Risk of Losing Ambulation within 2 Years



Adapted from. Mazzone E, et al. *Plos One.* 2013; 24 Month Longitudinal Changes in Ambulant DMD Boys

Age at Loss of Ambulation Correlates to Age of Subsequent Disabilities

Age at Loss of Ambulation N=278	Age of Severe Respiratory Insufficiency Mean (+SD)	Age at Loss of Ability to Raise Hand to Mouth (self-feed) Mean (+SD)
< 8 years old	14.7 (1.89)	10.4 (1.36)
8-11 years old	18.1 (2.62)	12.1 (2.05)
>11 years old	22.1 (5.72)	14.4 (1.72)
Correlation	<0.0001	<0.0001

Humbertclaude, V. et al. *Eur J Paediatr Neurol*. 2012;16:149–160.

US and EU Harmonization of Standards of Care

- DMD Care Considerations Working Group
  - US CDC & EU TREAT-NMD collaboration and harmonization
- Published formal standards in 2009 that had already been utilized by US & EU DMD clinics for many years

Complication	Standard of Care
General decline	Steroids
Musculoskeletal	Physical therapy
Contractures, loss of balance, falls, fractures	Orthoses
Declining pulmonary function	Respiratory therapy, ventilation
Cardiomyopathy, cardiac arrhythmia	ACE inhibitors, β-blockers

Summary

- Improvements in standards of care have delayed disease progression, from time to loss of independent ambulation to respiratory failure and survival
- Despite these improvements in SOC, DMD remains a devastating, fatal disease
- Urgent, unmet need to find a treatment that may further slow down disease progression

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Concluding Remarks	**Edward M. Kaye, MD**

Efficacy

Edward M. Kaye, MD

Chief Medical Officer & CEO (Interim), Sarepta
Pediatric Neurologist, Boston Children's Hospital

Overview

- Development Rationale
- Clinical Development Program
- Pharmacodynamic Data
- External Control Search
- Efficacy: Eteplirsen vs. External Control
  - 6MWT
  - Loss of Ambulation
  - Supportive Clinical Endpoints
- Confirmatory Studies

Rationale for Eteplirsen Development

Dystrophinopathies

- Duchenne muscular dystrophy
  - Out of frame deletion
  - Little to no dystrophin
  - Severe phenotype
- Becker muscular dystrophy
  - In frame deletion
  - Internally shortened dystrophin
  - Generally mild phenotype
  - Published BMD levels range from 2% - 100%

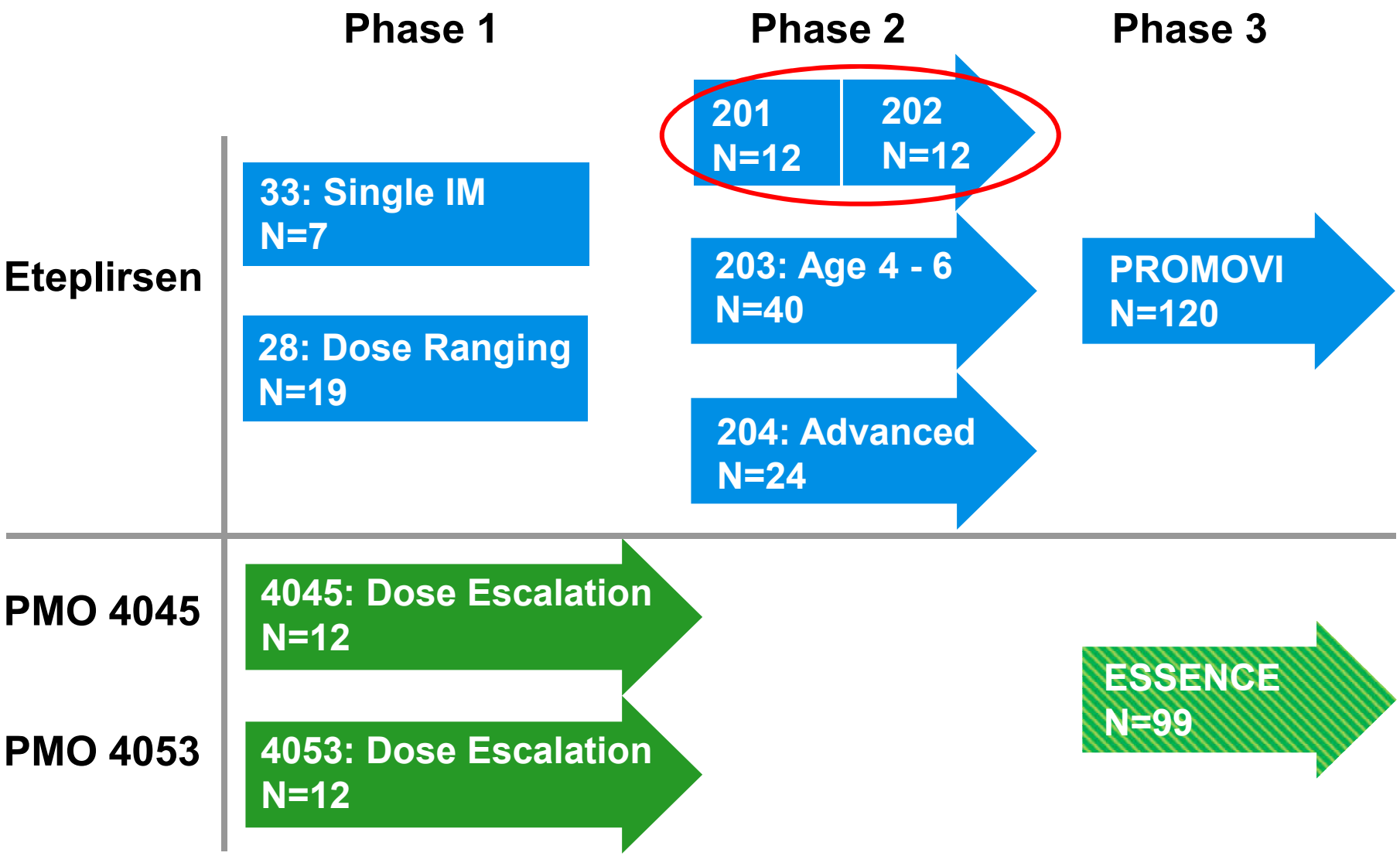
Small Amounts of Dystrophin are Clinically Meaningful

- Dystrophin threshold not established
- Low levels of dystrophin provide clinical benefit
  - DMD Exon 44 clinically milder phenotype[1-5]
- Increase from baseline most meaningful determination of treatment effect*

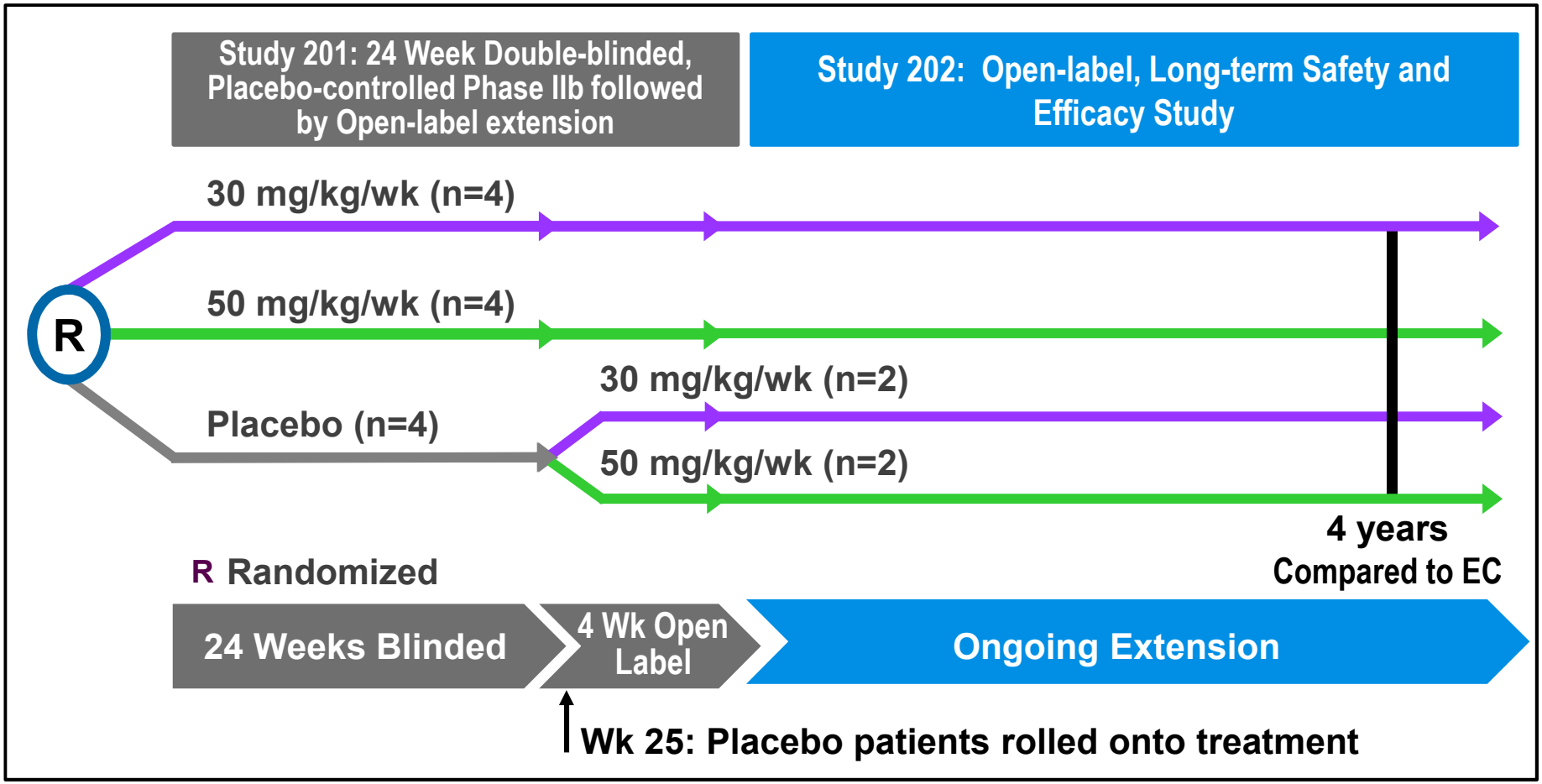
***FDA and NIH, Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data. March 20, 2015.**

1. Anthony. *JAMA Neurol* 2014; 2. Pane. *PLOS One* 2014; 3. Ricotti. *J Neurol Neurosurg Psychiatry* 2015; 4. van den Bergen. *J Neuromusc. Dis.* 2014;
5. Bello. *Neurology*, 2016 in press.

Sarepta's DMD Clinical Program



Pivotal 201/202 Study Design



Study 201/202 Key Enrollment Criteria

Prognostic Factors	Eteplirsen Enrollment Criteria
Mutation type	Exon 51 skipping amenable
Age	7-13
Steroid use	Steroid treated ≥24 weeks prior to entry & stable steroid treatment throughout
6MWT	180 – 440 m

Pivotal Study Endpoints

- **Study 201 Primary**
  - % Dystrophin Positive Fibers
- **Study 202 Primary Clinical**
  - 6MWT
- **Supportive**
  - RT-PCR / Dystrophin Assessment
  - NSAA
  - Rise from Supine

Pharmacodynamic Data

Multiple methods confirm de-novo dystrophin

Eteplirsen Mechanism of Action Confirmed by RT-PCR & Sequencing

- Exon skipping confirmed in all biopsied, eteplirsen-treated patients
- Shortened PCR product
- Sequencing confirms correct exon was skipped and demonstrates newly formed exon junction

Complementary Methods Required for Dystrophin Assessment

- Each assay measures different aspects of dystrophin

	Immunohistochemistry (IHC)	
Western Blot	Percent Dystrophin Positive Fibers (PDPF)	Dystrophin Intensity
• Quantification based on protein extraction from muscle tissue	• Localization of dystrophin to sarcolemma • Distribution	• Automated quantification of dystrophin at sarcolemma

Source: FDA and NIH, Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data. March 20, 2015.

24 Weeks Needed to Show Consistent Increase in Dystrophin

- Study 201 primary endpoint: increase in percent dystrophin positive fibers (PDPF)
  - No significant increase at 12 weeks (50 mg/kg)

Week 24 Multi-Rater PDPF (30 mg/kg)

Arm	Absolute Change from Baseline PDPF	Fold Increase	p-value
Eteplirsen, n=4	13.7%	2.0	0.007
Placebo, n=2	-0.39%	—	—

Fourth Biopsy (Week 180) Methods Developed in Consultation with FDA

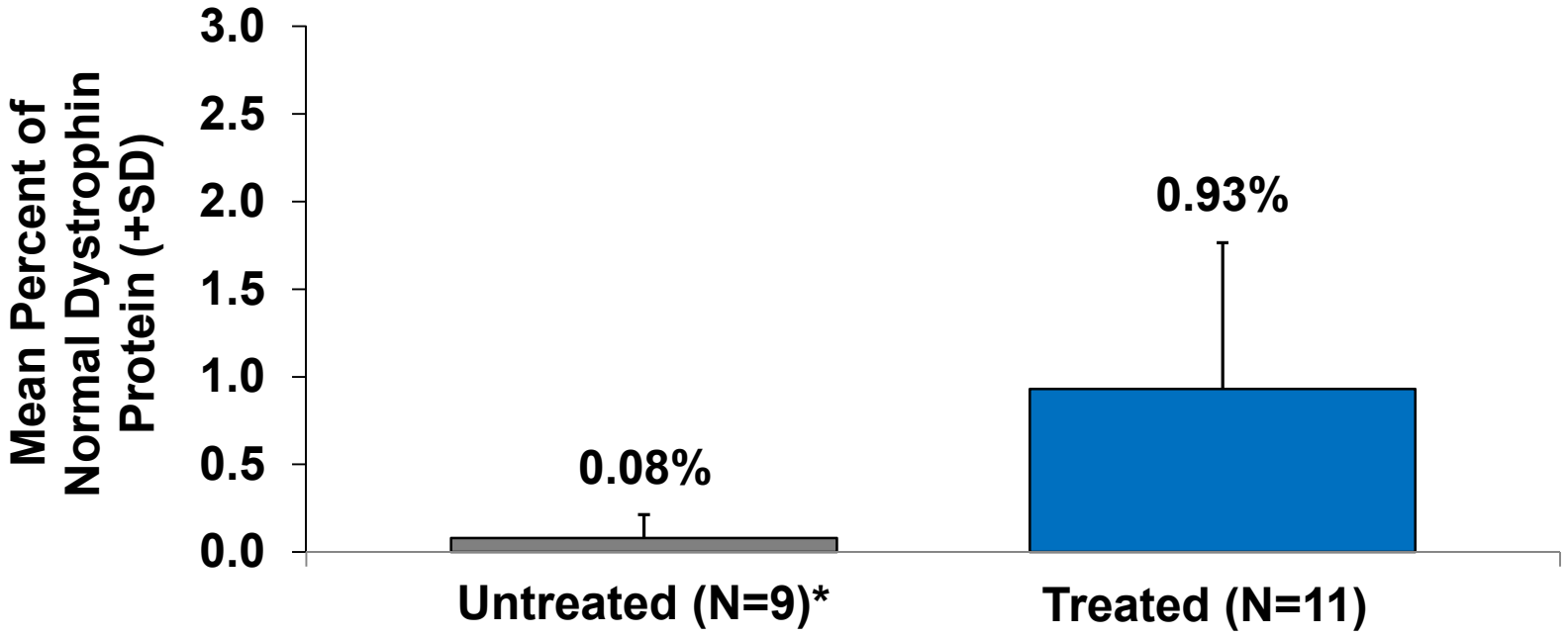
- Dystrophin increase measured relative to matched, untreated baseline samples
  - Study 201 (n=3)
  - Eteplirsen confirmatory study, PROMOVI (n=6)
    - First 6 patients with sufficient tissue
- Deltoid muscles primarily compared to biceps
- Samples blinded for treatment status and assay

Sarepta's Week 180 Western Blot Utilized the Most Advanced Methodology Available

- First quantitative dystrophin Western blot
  - 5 point calibration curve on each gel
  - Signal not saturated by overloading or overexposure
  - Samples randomized, blinded & run in duplicate
- Published Western blots not directly comparable
- Fold increase over baseline by same assay most accurate

Over 11 Fold Increase in Dystrophin by Western Blot (Week 180)

- 9 of 11 biopsied treated patients had a quantifiable dystrophin band



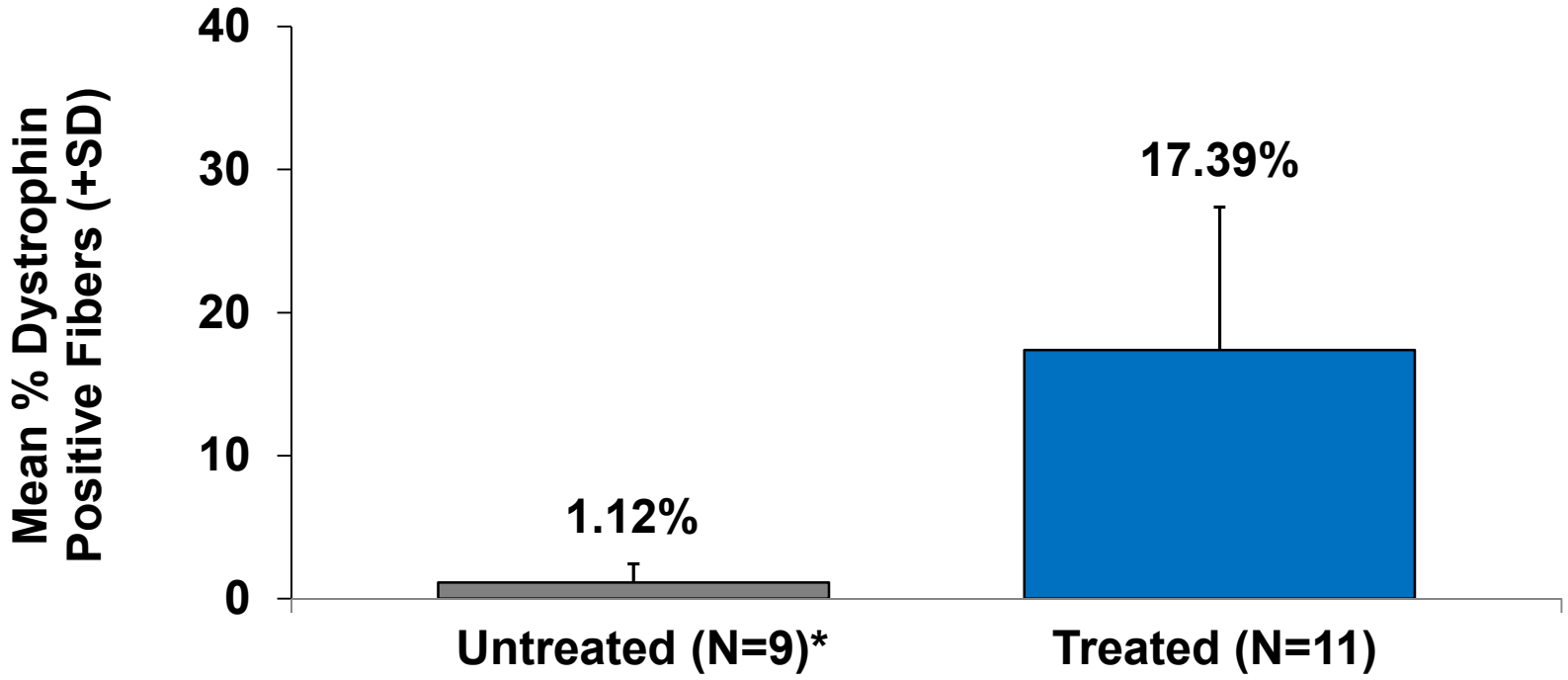
Absolute Difference of Means (Treated vs. Untreated)	Fold Increase	p-value
0.85%	11.6	0.007

*n=3 201/202 baseline + n=6 confirmatory study baseline

Rigorous Analysis of Percent Dystrophin Positive Fibers (PDPF)

- Only unenhanced images were used to score positive fibers
- Systematic, unbiased method to select images
- Pre-specified protocol to define positive fibers
  - Controlled viewing conditions
  - ≥30% membrane staining
  - All pathologists trained and tested on protocol
- High inter-rater reliability (Wk 180: 0.943)

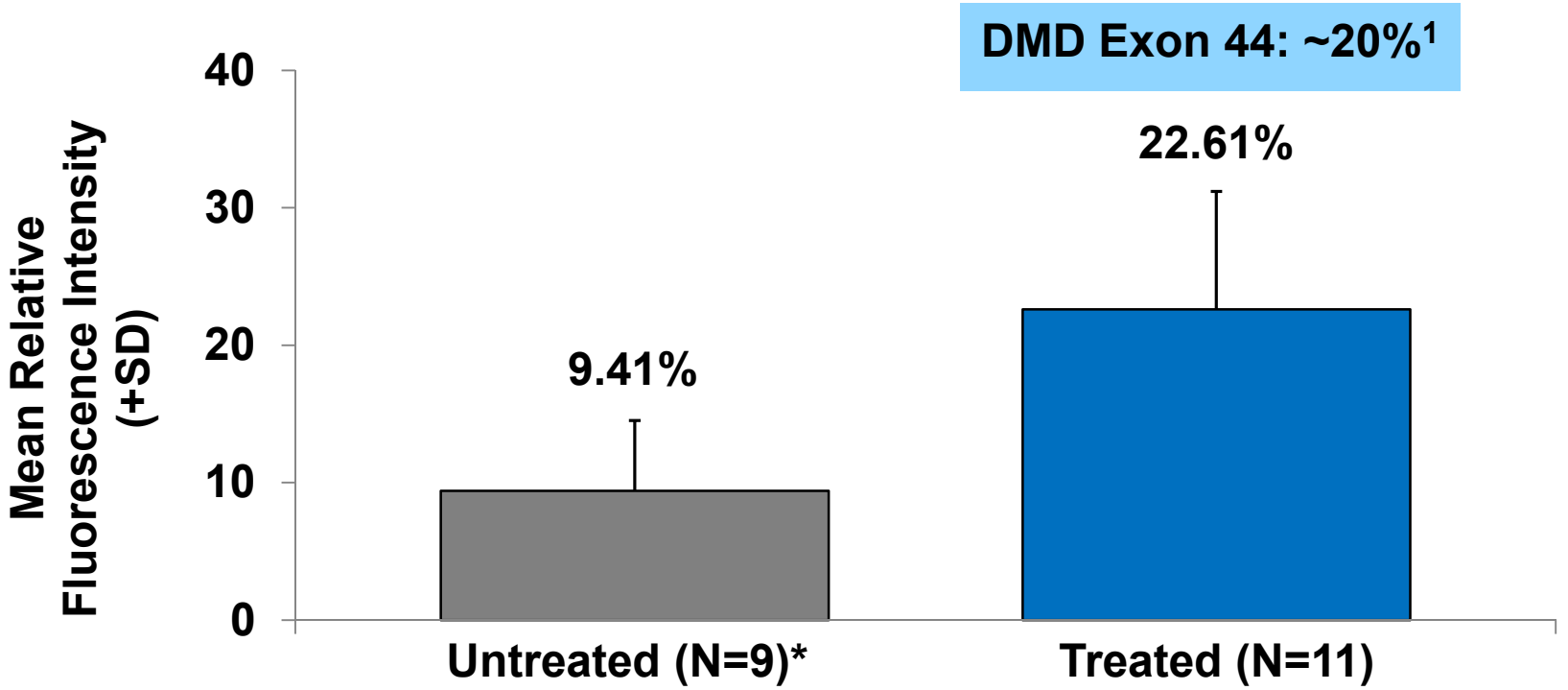
Over 15 Fold Increase in Dystrophin by Percent Dystrophin Positive Fibers (Week 180)



Pathologists	Absolute Difference of Mean PDPF (Treated vs. Untreated)	Fold Increase	p-value
Multi-rater (3)	16.27%	15.5	<0.001

*n=3 201/202 baseline + n=6 confirmatory study baseline

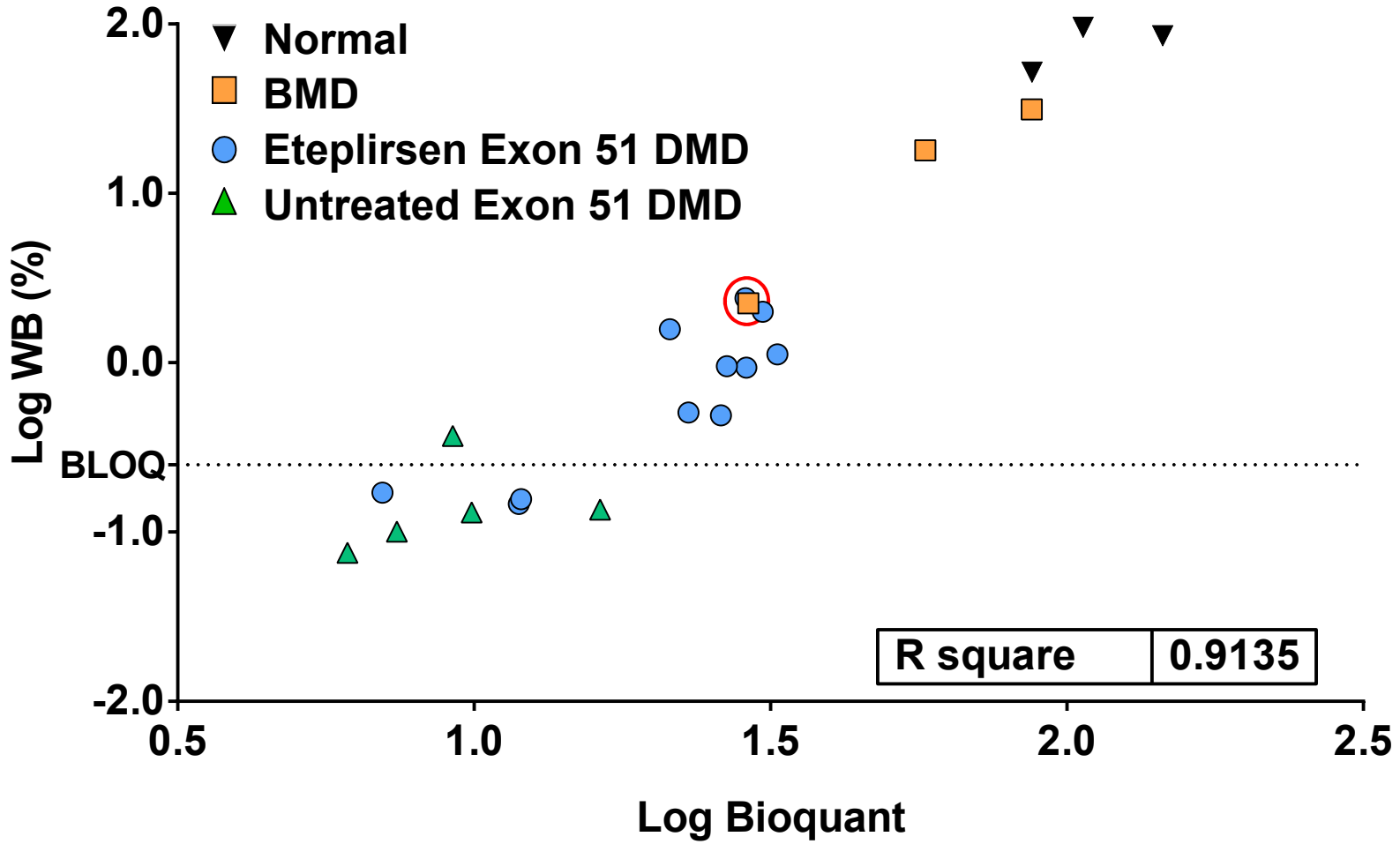
Over 2 Fold Increase in Dystrophin by Intensity (Week 180)



Absolute Difference of Mean Intensity (Treated vs. Untreated)	Fold Increase	p-value
13.20%	2.4	<0.001

*n=3 201/202 baseline + n=6 confirmatory study baseline, [1]Anthony JAMA Neurol 2014

Linear Relationship Between IHC Intensity and Western Blot (Week 180)



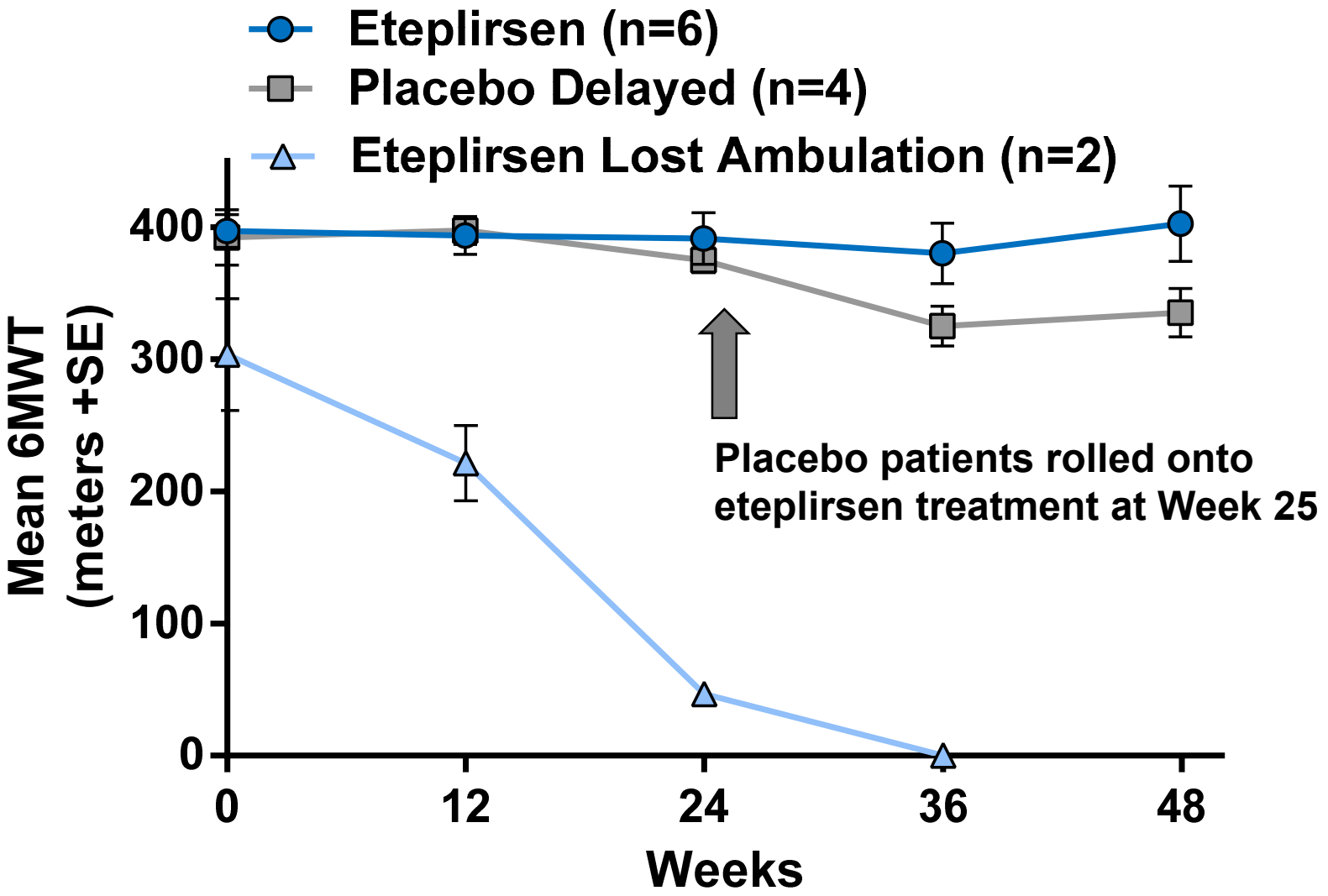
Consistent and Sustained Increases in Dystrophin by All Three Methods (Wk 180)

Method	Absolute Difference of Means (Treated vs. Untreated) (% of Normal)	Fold Increase	p-value
Western Blot	+0.85%	11.6	0.007
PDPF	+16.27%	15.5	<0.001
Intensity	+13.20%	2.4	<0.001

- Dystrophin functionality demonstrated by localization of dystrophin and associated proteins to sarcolemmal membrane

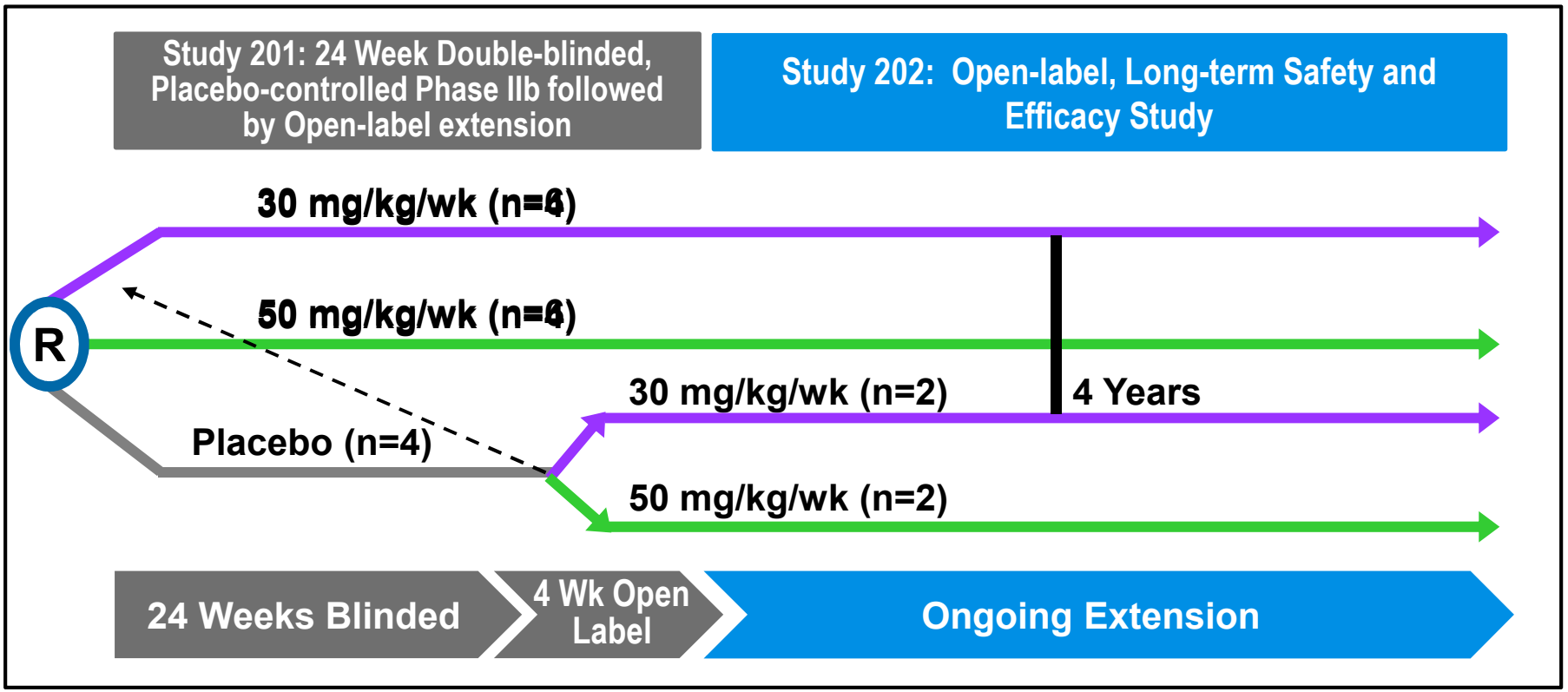
Early Clinical Results

Exploratory 6MWT Analysis Showed Limited but Encouraging Results at Week 48 (Study 201/202)



Patients Pooled from Day 1 of Eteplirsen for 4 Year Analysis (N=12)

- Placebo/delayed group T0=24 wks
- Dose groups pooled



External Control

Potential Biases Using External Controls

Potential Issue	Sarepta Position
Can include recognized and unrecognized prognostic factors	Key prognostic factors well understood and comparable
Selection of control group prior to comparative analyses	Filter criteria defined prior to selection (201 inclusion criteria)
Unpredictable disease course	Homogeneous group with highly predictable disease course
Lack of objective and standardized endpoint	Standardized 6MWT

Potential Biases Using External Controls

Potential Issue	Sarepta Position
Availability of patient-level data including baseline characteristics	4 year patient-level data including comparable baseline characteristics
Comparability of standards of care	Highly comparable standards of care
Tend to have worse outcomes	Consistent compared to CINRG, other databases & placebo arm
Dramatic treatment effect needed	Dramatic treatment effect on 6MWT and LOA

Search for DMD Natural History Data

- Sarepta consulted with external DMD experts and utilized findings from international consortiums
  - *International DMD Working Group 2011*
  - *Collaborative Trajectory Analysis Project*
- 12 external DMD databases identified with extensive clinical data
  - 2 databases met criteria
  - CINRG did not have long-term 6MWT data at the time

DMD Databases Identified are Contemporary with Eteplirsen

	Italian DMD Telethon N=97	Leuven Neuromuscular Research Center (LNMRC), Belgium N=89	Eteplirsen Pivotal Study N=12
Study Period	2008-present	2007-present	2011-present
Clinical Outcomes	6MWT & NSAA	6MWT	6MWT & NSAA

- Enrolled all eligible patients attending clinic
- Investigator initiated, published studies

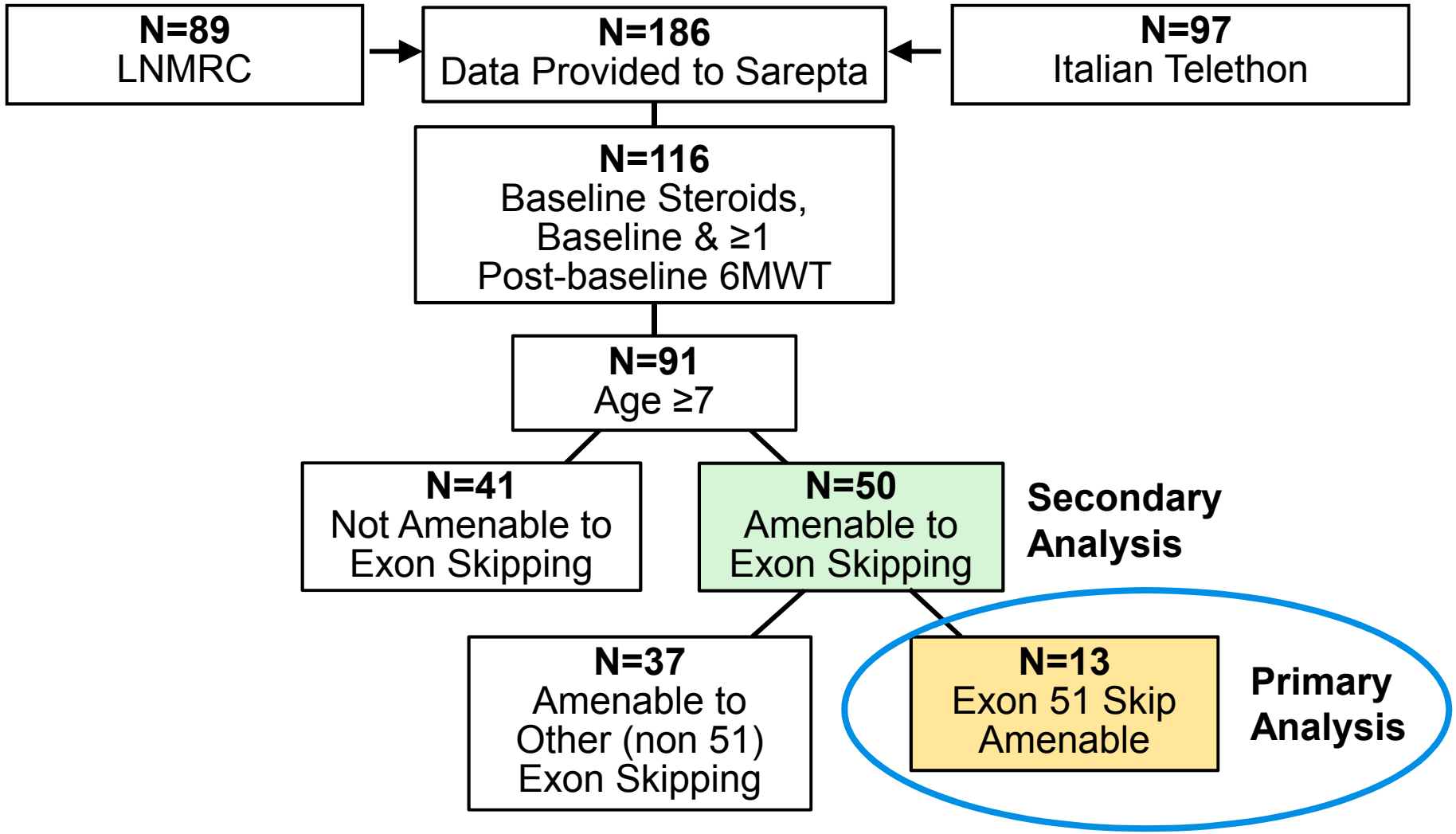
Database Patients Treated at Expert Neuromuscular Sites

- Patients treated according to international CDC/TREAT-NMD care standards from study start
  - Leading neuromuscular clinics
- Standardized assessment of 6MWT
  - Same protocol and script as eteplirsen trial
  - Same physical therapist training

Pre-Defined Filters for External Control Based on Enrollment Criteria

Filter	Eteplirsen Enrollment Criteria
Steroid use	Steroid treated ≥24 weeks prior to entry & stable steroid treatment throughout
Age	≥7 years old
Mutation type	Exon 51 skipping amenable

All Patients Meeting Criteria Were Included in External Control (EC)



Key Prognostic Factors Comparable at Baseline

Parameter	Eteplirsen Study 201/202 N=12	External Control: Exon 51 Skip Amenable N=13
Age, years		
Mean (SD)	9.4 (1.18)	9.5 (1.45)
Median	9.7	9.0
Min, Max	7.3, 11.0	7.3, 11.8
6MWT distance*, m		
Mean (SD)	363.2 (42.19)	357.6 (66.75)
Median	370	373
Min, Max	256, 416	200, 458
Deletion mutations represented:	45-50, 48-50, 49-50, 50, 52	45-50, 48-50, 49-50, 50, 52

*Day 1 values if tested more than once

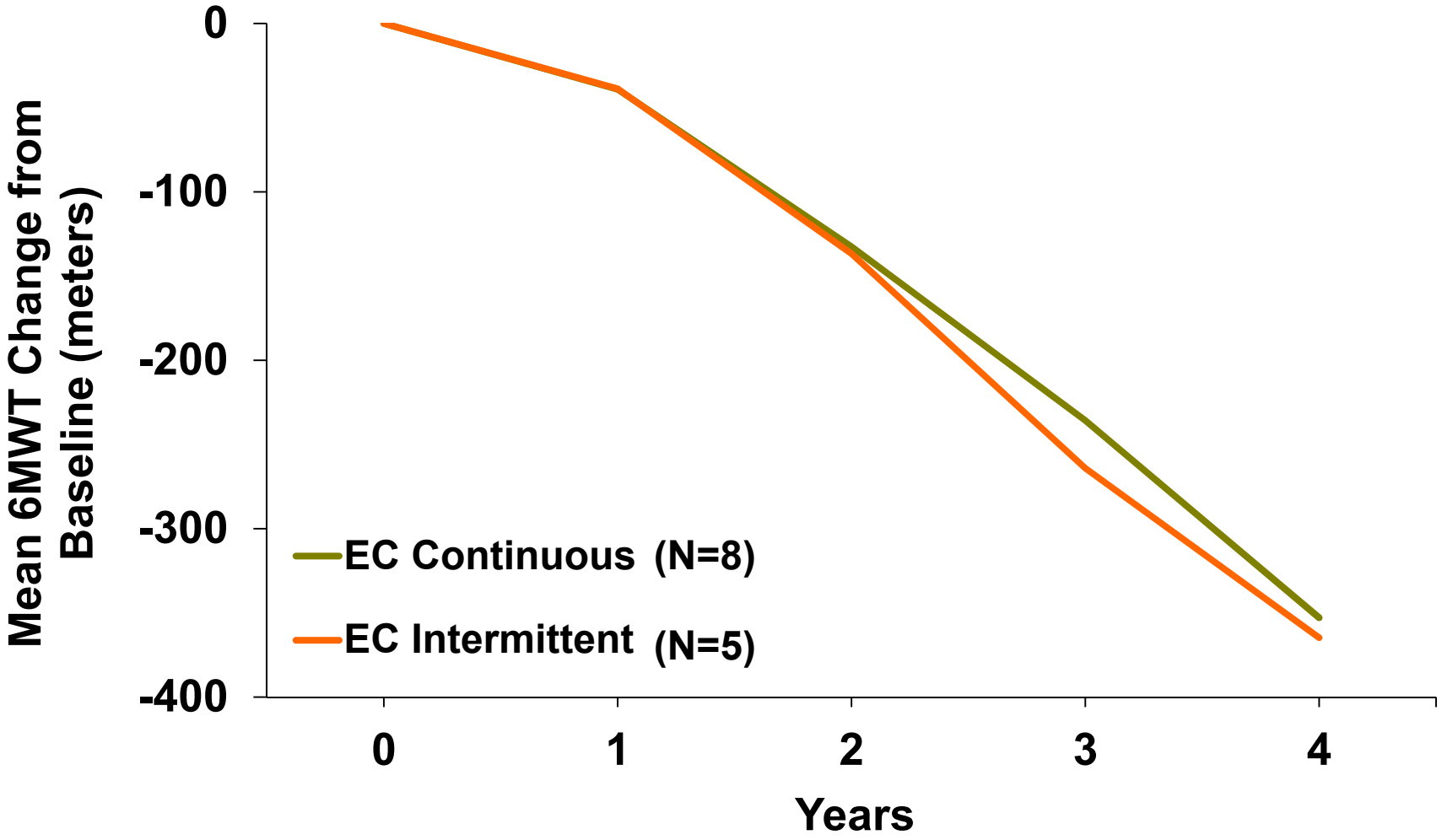
External Control Patients Received Intense Steroid Therapy

	Eteplirsen Study 201/202 N=12	External Control: Exon 51 Skip Amenable N=13
Deflazacort Prednisone	8 (67%) 4 (33%)	9 (69%) 4 (31%)
≥90% recommended dose	2 (17%)	9 (69%)

Minor Differences in Steroid Treatment Had Minimal Impact on 6MWT

	Eteplirsen Study 201/202 N=12	External Control: Exon 51 Skip Amenable N=13
Age at steroid start, years		
Mean (SD)	5.2 (1.09)	6.4 (2.19)
Median	5.5	6.0
Min, Max	3.5, 6.6	3.5, 10.7
Continuous	11 (92%)	8 (62%)
Intermittent	1 (8%)	5 (38%)

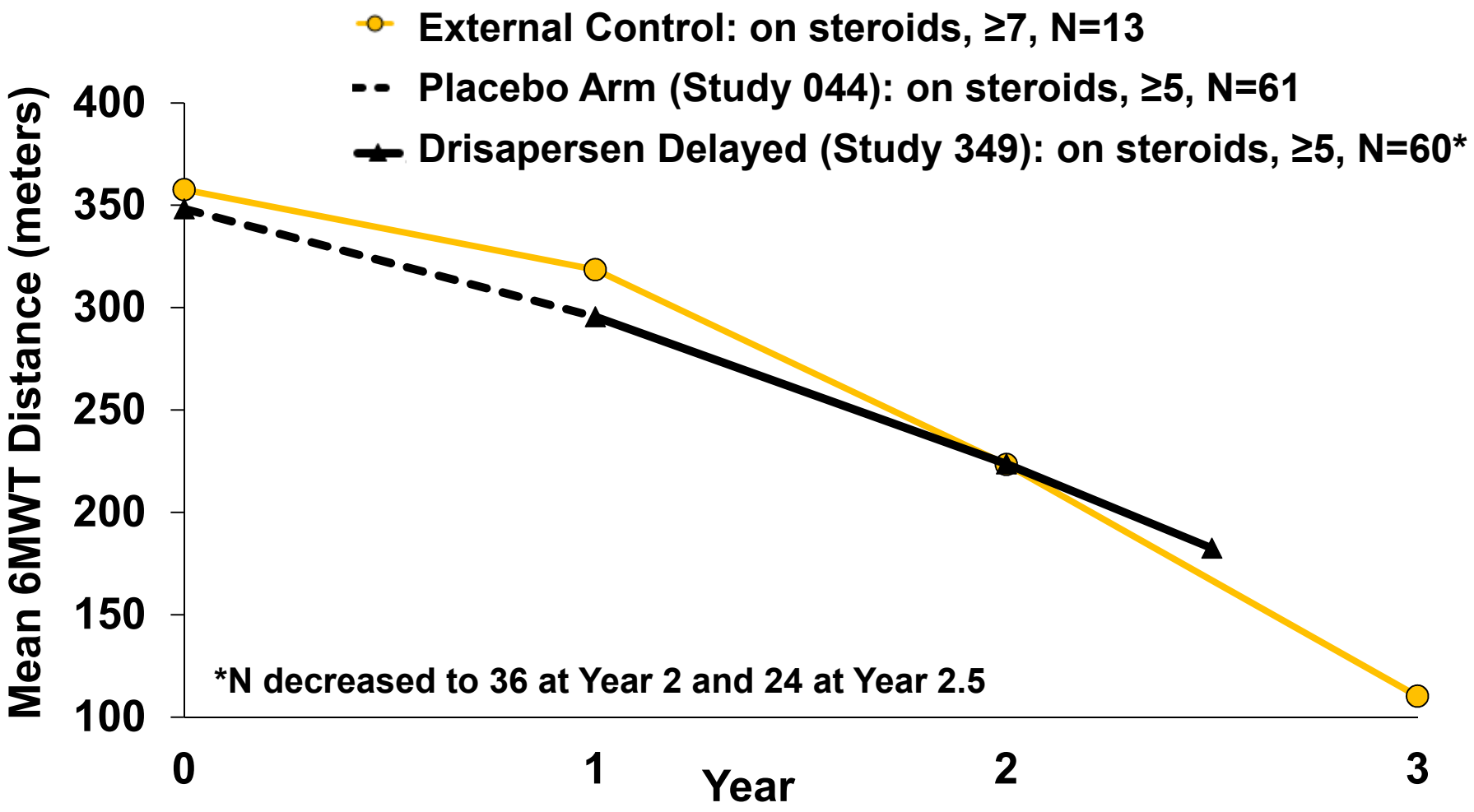
Steroid Regimen Does Not Significantly Impact External Control 6MWT



External Control Patients Received Higher Level of Physical Therapy Intervention

PT Intervention	Frequency (Days/wk or Usage)	Eteplirsen Study 201/202 N=12	External Control: Exon 51 Skip Amenable N=13
Physical Therapy Visits	4-6	2	5
	2-3	3	8
	≤1	5	0
	None	2	0
Night splints (Orthoses)	Used	11	11
	Not needed (TA<10°)	–	2
	Not used	1	–

External Control 6MWT Consistent with Exon 51 Patients from Randomized Drisapersen Trial



Data source: Biomarin advisory committee briefing document
Means for drisapersen are estimated from baseline and change from baseline

Clinical Results

Clarification of External Control Data

FDA Issue	Sarepta Response
Steroid regimen	3 patients with unknown regimens at NDA submission subsequently reported as continuous by investigator
2 patients entered interventional studies	6MWT obtained on these patients; overall results consistent
3 patients had positive 10MWR results yet 6MWT=0	Inability to execute 6MWT occurs first

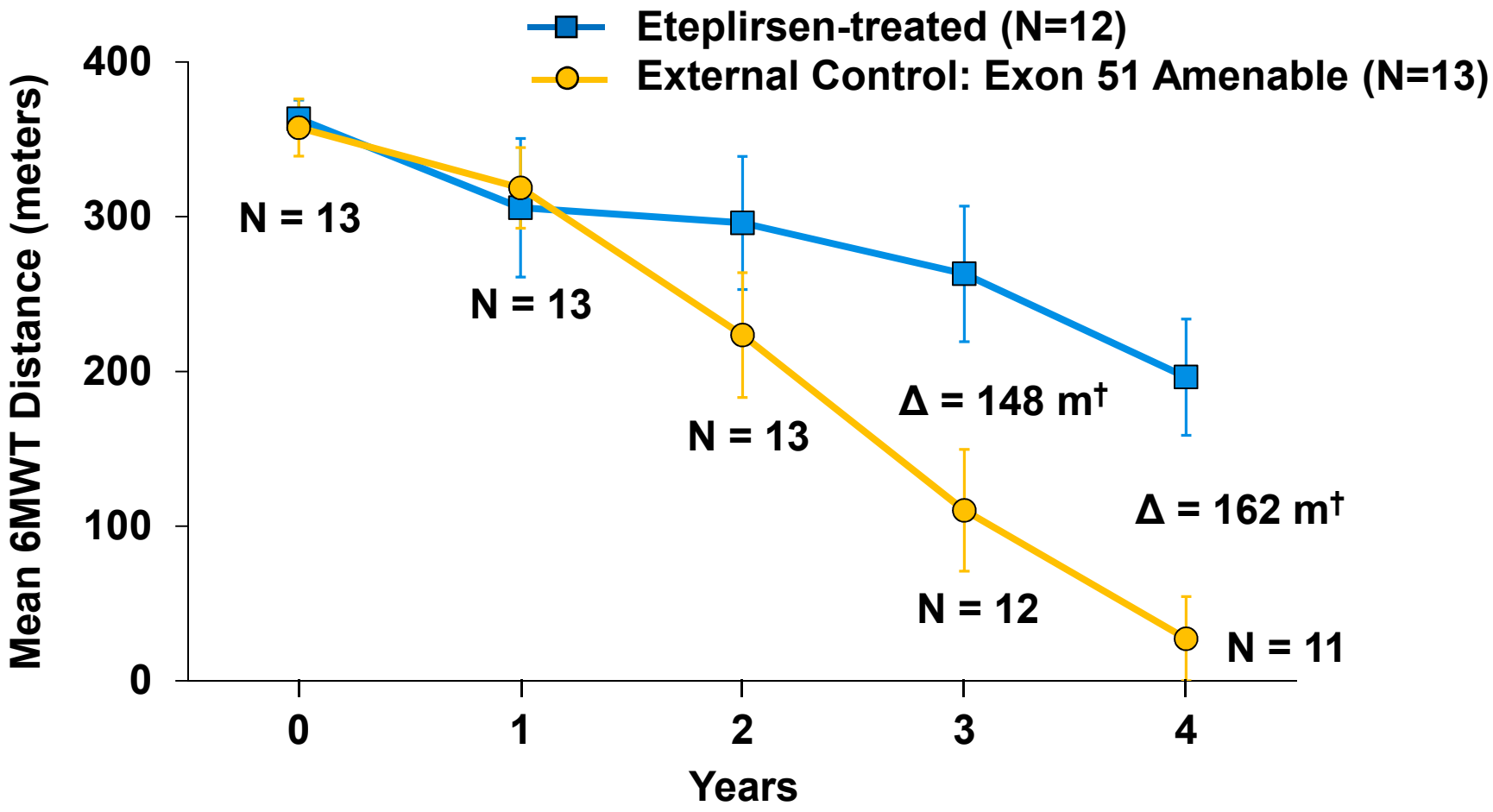
Clarification of Sarepta Analyses

FDA Issue	Sarepta Analyses
Eteplirsen patients had 2 opportunities to perform 6MWT	Day 1 measures for eteplirsen compared to single external control measure
2 external control patients with missing data were analyzed as “0” for NSAA	Correctly analyzed as missing data

Longitudinal External Control Data Available

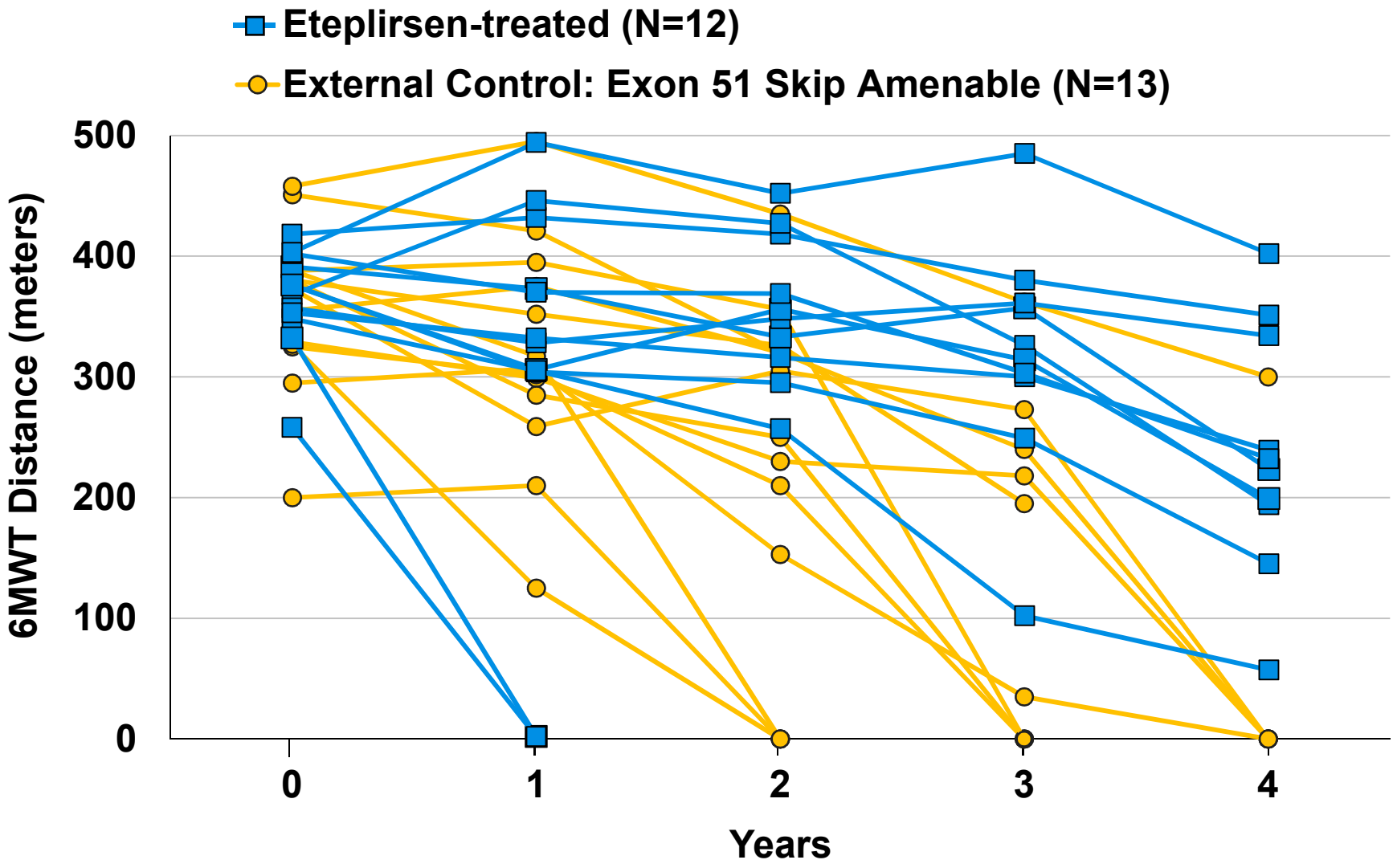
- 4 Year
  - 6MWT / LOA
- 3 Year
  - 6MWT / LOA
  - NSAA
  - Ability to Rise
- Treatment Expectation
  - Delay DMD disease progression

Eteplirsen Slows DMD Progression: 4 Year Analysis of 6MWT

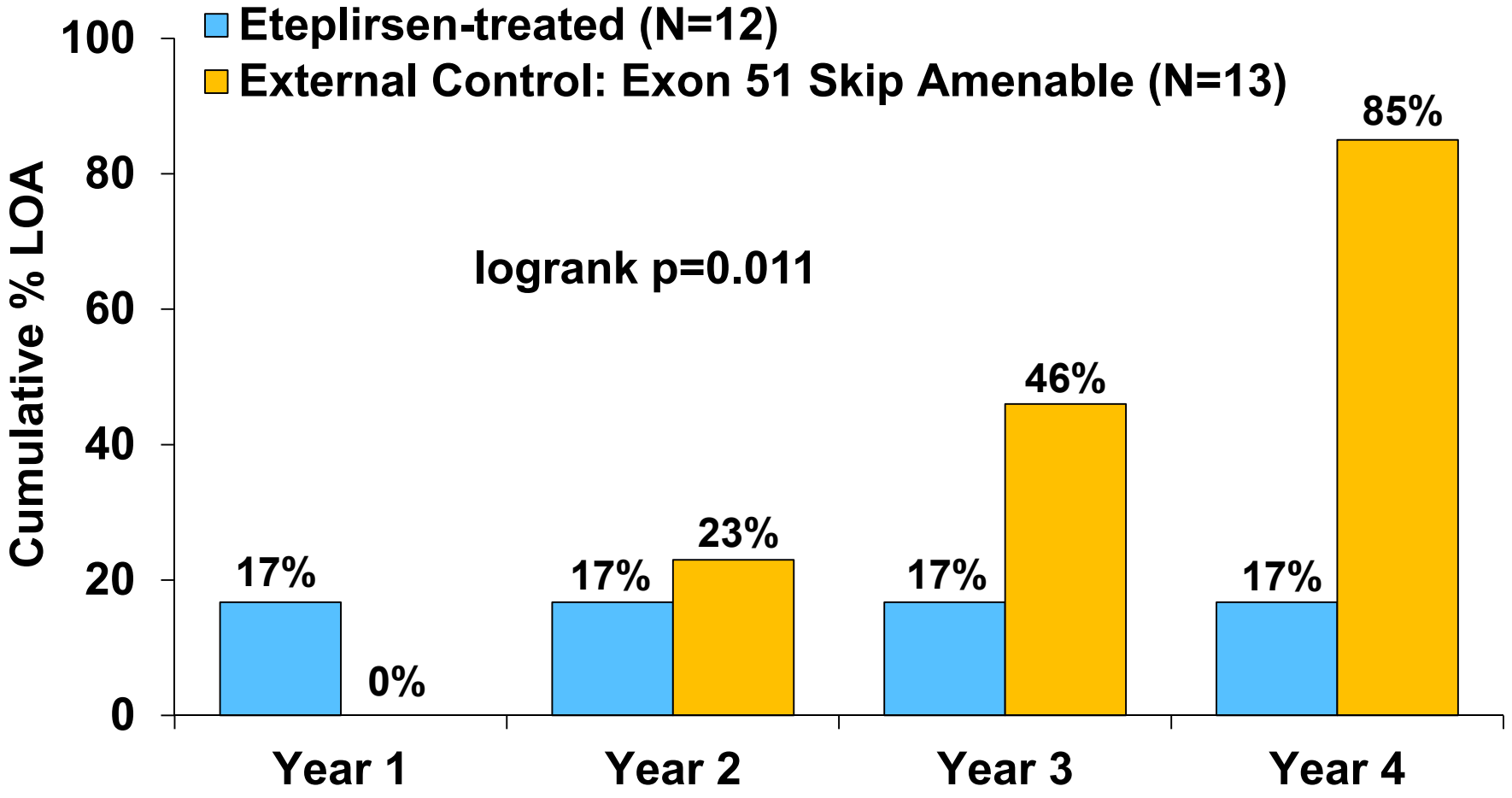


† Difference in mean change from baseline, Day 1 values used for eteplirsen
Patients who lost ambulation contributed a score of 0 to the mean
Individual time points missing: ECM2 Year 4, ECG3 Year 3 & 4

Individual 6MWT Progression Over 4 Years

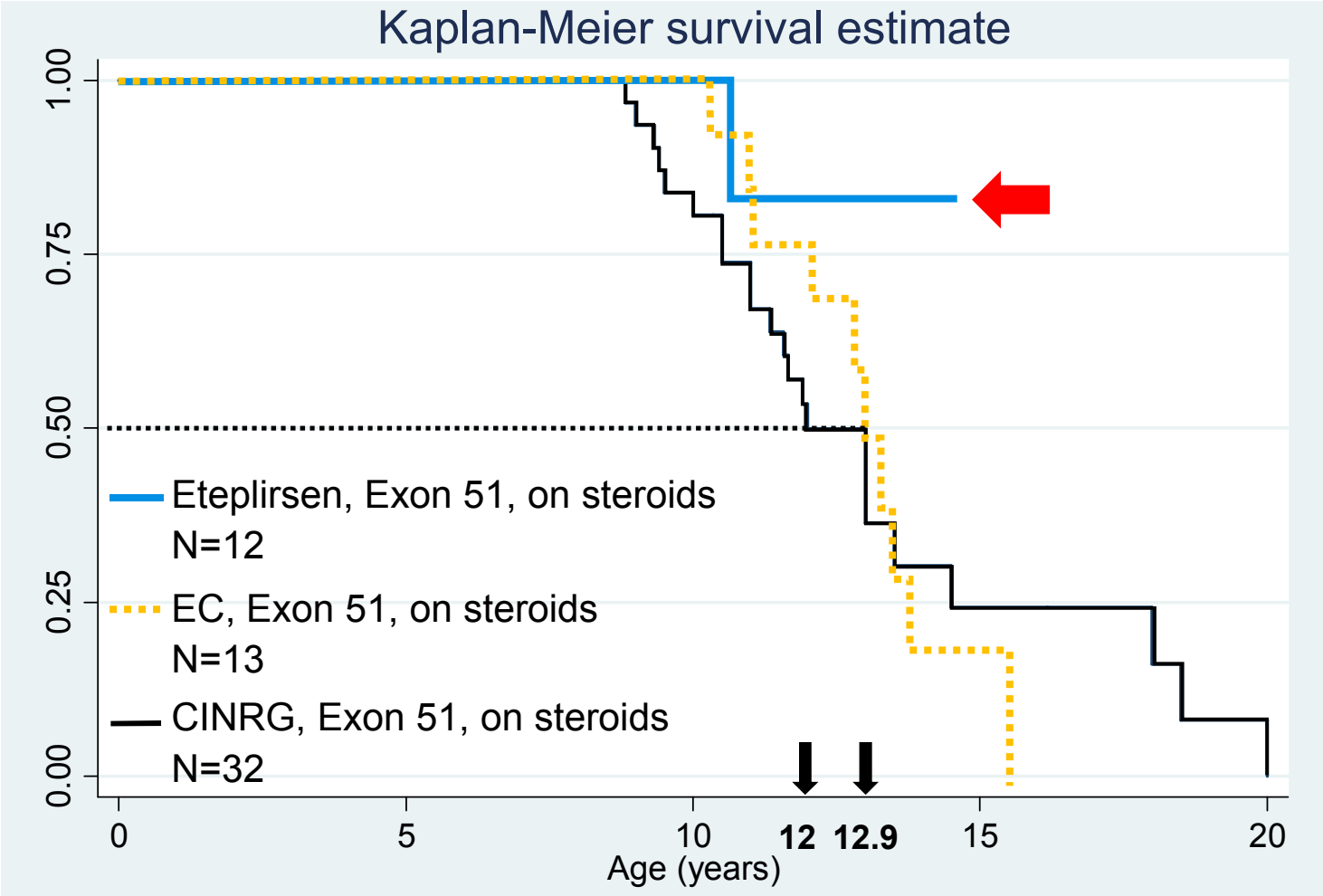


Eteplirsen Preserves Ambulation: 4 Year Kaplan-Meier Estimates



Individual time points missing: ECM2 Year 4, ECG3 Year 3 & 4

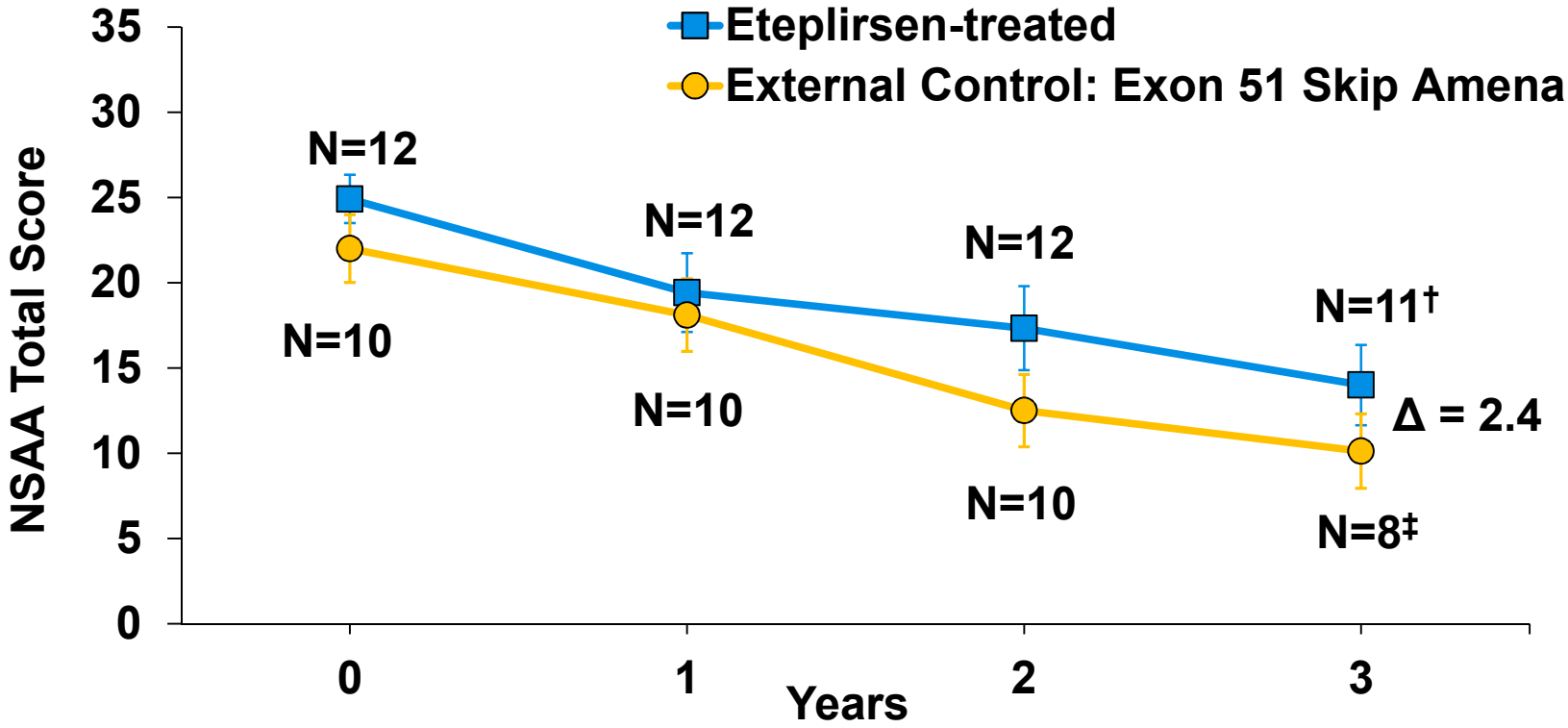
Eteplirsen Preserves Ambulation: Comparison to EC and CINRG Exon 51



CINRG Source: FDA briefing document referencing Bello. *Neurology,* 2016 in press.

Supportive Endpoints

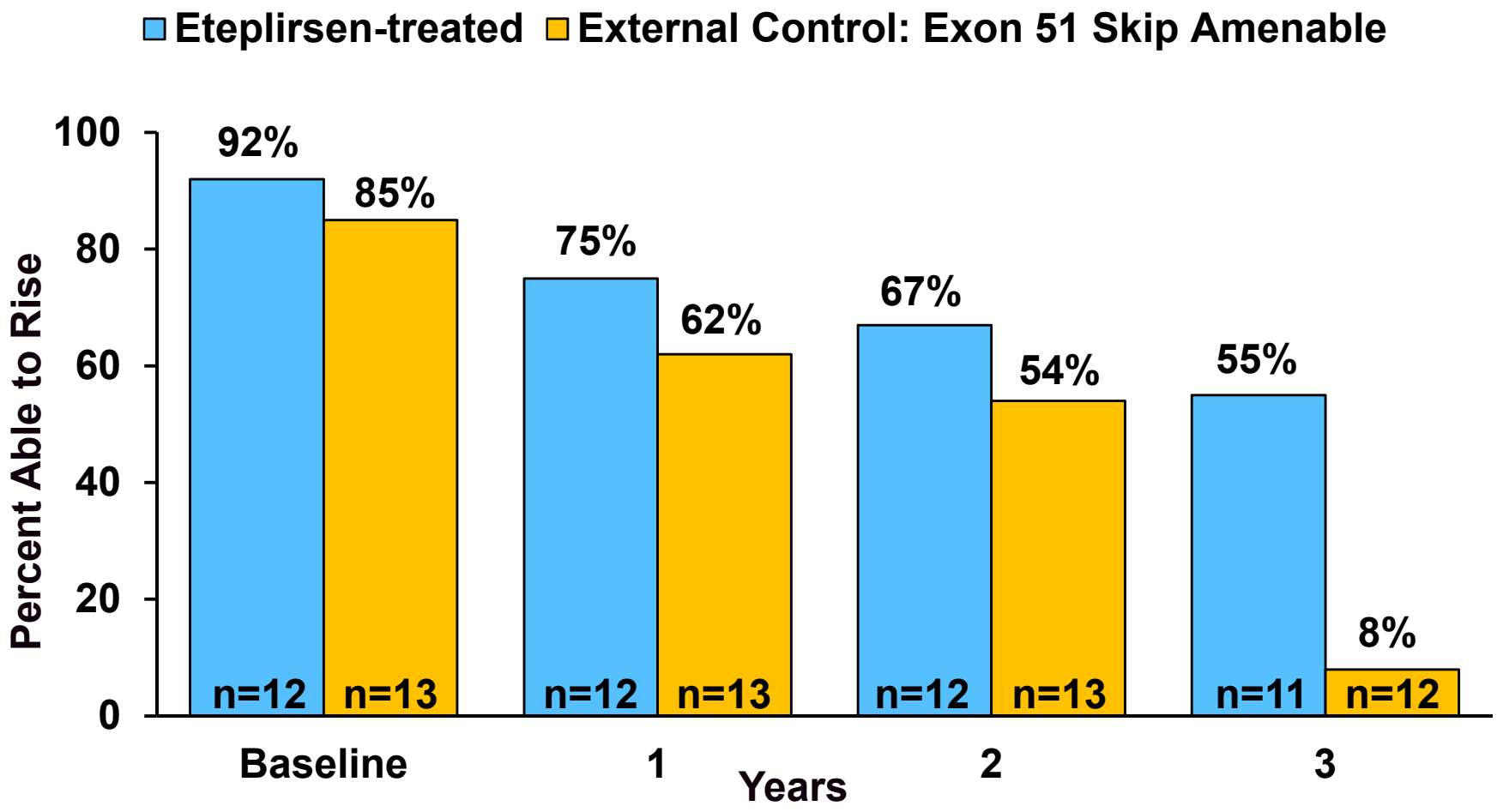
NSAA Directionally Consistent with 6MWT



	Baseline	Year 3	Mean Δ from BL
Eteplirsen	25	14	-11.3
External Control	22	10	-13.6

† 1 eteplirsen patient did not contribute data due to right knee pain
‡ 2 Italian Telethon patients had missing data

Ability to Rise Independently Over Time



Ability to rise independently defined as NSAA sub-score of 1 or 2; all patients had rise time measurements <30 seconds.

Efficacy Established by Multiple Endpoints

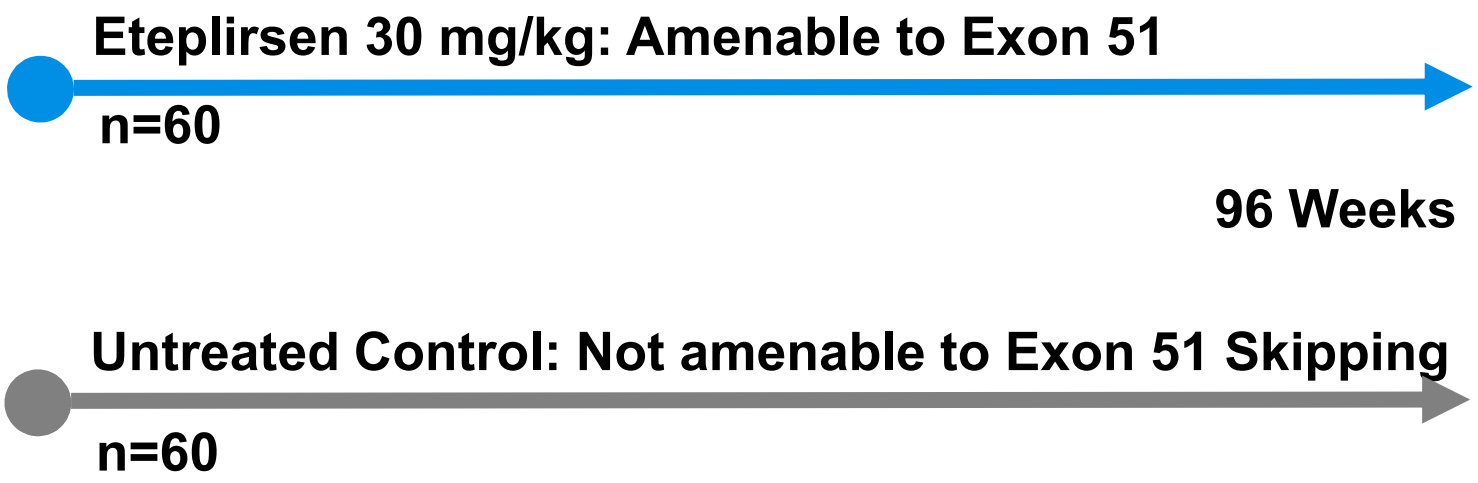
- First therapeutic to demonstrate unequivocal increase in dystrophin following treatment
- External control an appropriate comparator
  - Representative of other natural history databases
- Dramatic effect size on 6MWT and LOA
- Consistent support for eteplirsen benefit on other measures
  - NSAA, ability to rise from supine vs. external control

Confirmatory Studies

Confirmatory Study Approach

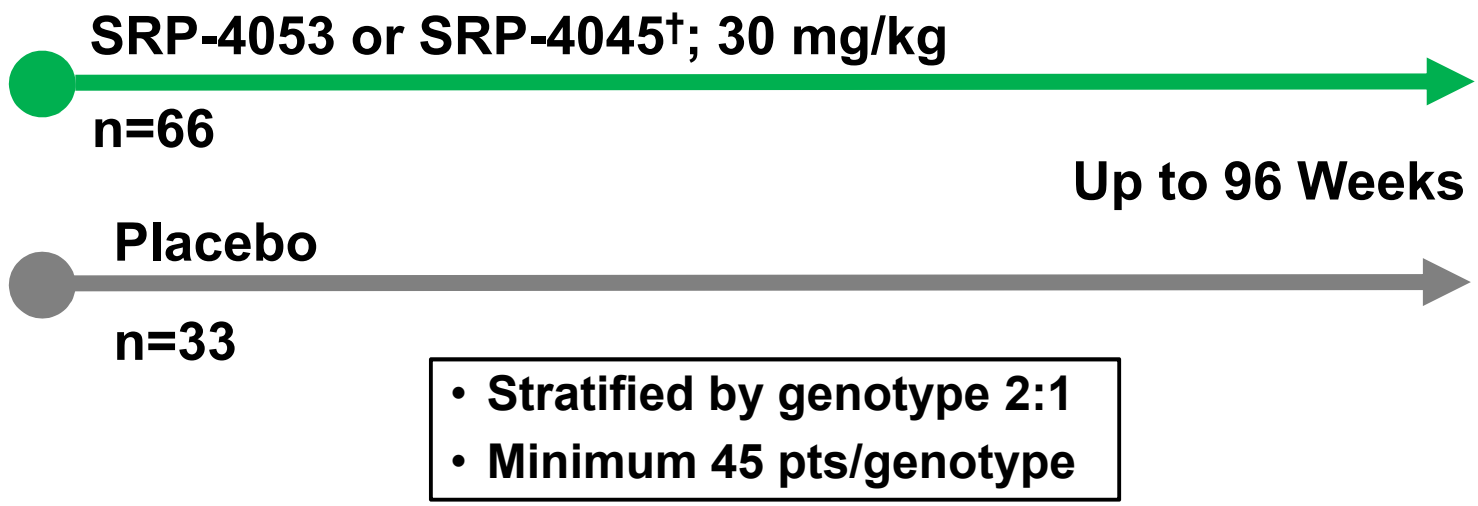
- Eteplirsen placebo-controlled study infeasible
- Flexible approach leveraging lessons learned
  - Longer study duration
  - Updated enrollment criteria
- Two Studies
  - PROMOVI: Eteplirsen vs. untreated (non exon 51)
  - ESSENCE: Other PMOs (exon 45 and exon 53)
    - Same chemical backbone and MOA as eteplirsen

PROMOVI: Open-Label Eteplirsen vs. Untreated Patients Amenable to Exon Skipping



Age	7-16
6MWT (m)	300-450
1º Clinical Endpoint	6MWT
Additional Endpoints	LOA, PFTs, NSAA, dystrophin
Enrollment Status	Underway

ESSENCE: Double-Blind, Placebo-Controlled Study of Two PMOs



Age	7-16
6MWT (m)	300-450
Mutation	Amenable to exon 45 or 53 Skipping
1º Clinical Endpoint	6MWT
Additional Endpoints	LOA, PFTs, NSAA, dystrophin

†*PMOs have same backbone chemistry; target different DMD nucleotide sequence.*

Presentation Agenda

Introduction	**Shamim Ruff, MSc** *Sr. Vice President, Regulatory Affairs and Quality, Sarepta*
Disease Background and Natural History	**Eugenio Mercuri, MD, PhD** *Professor of Pediatric Neurology* *Catholic University of the Sacred Heart, Rome*
Efficacy	**Edward M. Kaye, MD** *Chief Medical Officer (Interim CEO), Sarepta* *Pediatric Neurologist, Boston Children's Hospital*
Safety	**Helen Eliopoulos, MD** *Sr. Medical Director, Sarepta*
Clinical Perspective	**Jerry Mendell, MD** *Director, Center for Gene Therapy* *Professor of Pediatrics and Neurology,* *Nationwide Children's Hospital, Columbus, OH*
Concluding Remarks	**Edward M. Kaye, MD**

Safety

Helen Eliopoulos, MD

Senior Medical Director, Sarepta

Overview

- Nonclinical Safety Data
- Integrated Safety Analysis; All Eteplirsen Studies
  - Common Adverse Events
  - Serious Adverse Events
  - Severe Adverse Events
  - Adverse Events Leading to Discontinuation
  - Adverse Events of Special Interest

Nonclinical Data for Eteplirsen

- Eteplirsen is a PMO structurally and biologically distinct from other RNA analogs
- Kidney was identified as target organ for toxicity
- Class toxicities observed for other RNA analogs not seen with eteplirsen
- No findings of immune activation, thrombocytopenia, coagulopathy or vasculitis

Eteplirsen Integrated Safety, N=114[a] Originating from 7 Studies

Study	*Description*	Dose (mg/kg, IV)	N	
33	*Proof of principle*	≤0.9[b]	7	26 pts ≤20 mg/kg
28	*Dose ranging*	0.5 – 20	19	
201	*Pivotal*	30, 50	12	88 pts ≥30 mg/kg – 61 for ≥3 months – 12 for ~4 years
202				
PROMOVI	*Confirmatory*	30	48	
203	*Ages 4-6*	30	4	
204	*Advanced DMD*	30	24	

a) As of 14 August 2015
b) A single intramuscular dose was administered in Study 33.

Treatment-Emergent AEs in ≥10% of Patients
All Eteplirsen, N=114

Preferred Term	All Eteplirsen, N=114 n (%)
Headache	27 (24)
Back Pain	24 (21)
Vomiting	24 (21)
Cough	18 (16)
Pain in Extremity	17 (15)
Procedural Pain	16 (14)
Upper Respiratory Tract Infection	15 (13)
Arthralgia	14 (12)
Contusion	14 (12)
Excoriation	14 (12)
Nasopharyngitis	14 (12)
Oropharyngeal Pain	14 (12)
Nasal Congestion	13 (11)

Serious Treatment-Emergent AEs
All Eteplirsen, N=114

Event *Baseline Age*	Dose (mg/kg)	Description
Femur fracture *11 years*	30	Severe femur fracture following fall from wheelchair
Vomiting *9 years*	2	Post-operative vomiting following anesthesia; recovered the next day

- No deaths or life-threatening events

Discontinuation of Study Drug, N=1
All Eteplirsen, N=114

	IM, mg		IV, mg/kg			
AEs Leading to Discontinuation	0.09 & 0.9 N=7	≤4 N=11	10 N=4	20 N=4	30 N=82	50 N=6
Cardiomyopathy	0	1	0	0	0	0

- Cardiomyopathy (ECHO showed decreased LV fractional shortening)
- Investigator considered severe and possibly related to eteplirsen
- Independent cardiology review: normal LV ejection fraction

One additional case of mild cardiomyopathy (in patient with previous history) did not lead to discontinuation

Severe Treatment-Emergent AEs[a]
All Eteplirsen, N=114

Event *Baseline Age*	Dose (mg/kg)	Description
Incision site hemorrhage *7 years*	30	Incision from Port-a-Cath placement, bleeding after swimming; coagulation parameters normal
Nasal congestion *11 years*	30	Occurred 6 days after infusion; recovered and considered unrelated
Hemorrhoids *8 years*	50	Unrelated thumb-sized hemorrhoids
Back pain *8 years*	50	Back pain occurred after fall and resolved

a) Additional severe TEAEs discussed previously are cardiomyopathy, femur fracture, bone pain and balance disorder.

Adverse Events of Special Interest (AESI)

Treatment-Emergent Renal AEs
All Eteplirsen, N=114

Preferred Term	All Eteplirsen, N=114 n (%)
Total patients	16 (14)
Proteinuria / Protein urine	11 (10)
Dehydration	2 (2)
Blood creatinine increased	1 (1)
BUN increased	1 (1)
Blood urine present	1 (1)
Chromaturia	1 (1)
Crystalluria	1 (1)
Hypercalciuria	1 (1)
Urine analysis abnormal	1 (1)

Infusion Site Reactions in ≥2 Patients
All Eteplirsen IV, N=107

Preferred Term	All Eteplirsen IV, N=107 n (%)
Total Patients	24 (22)
Catheter site pain	10 (9)
Infusion site hematoma	7 (7)
Catheter site hematoma	4 (4)
Infusion site extravasation	4 (4)
Pyrexia	4 (4)
Infusion site pain	3 (3)

- Mild transient temperature elevation considered potential adverse drug reaction
- No serious or severe infusion site reactions

Potential Hypersensitivity Events in ≥2 Patients
All Eteplirsen, N=114

Preferred Term	All Eteplirsen, N=114 n (%)
Total Patients	27 (24)
Rash / Rash pruritic	11 (10)
Dermatitis contact	4 (4)
Erythema	3 (3)
Flushing	3 (3)
Papule	2 (2)
Pruritus	2 (2)
Rash papular	2 (2)
Seasonal allergy	2 (2)
Swelling / Lip swelling	2 (2)
Urticaria / Urticaria thermal	2 (2)

- Mild erythema and flushing considered potential adverse drug reactions
- No serious or severe potential hypersensitivity events

Other Adverse Events of Interest
All Eteplirsen, N=114

- No clinically relevant findings of:
  - Thrombocytopenia
  - Coagulopathy
  - Vasculitis
  - Severe cutaneous reactions
  - Hepatic toxicity

Summary: Eteplirsen Safety Profile

- No significant safety risks have been identified
- Most AEs are mild and consistent with population
- Low rate of discontinuations and serious events
- Eteplirsen safety profile will be monitored during trials, post-marketing surveillance, and a planned DMD registry

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Concluding Remarks	**Edward M. Kaye, MD**

Clinical Perspective

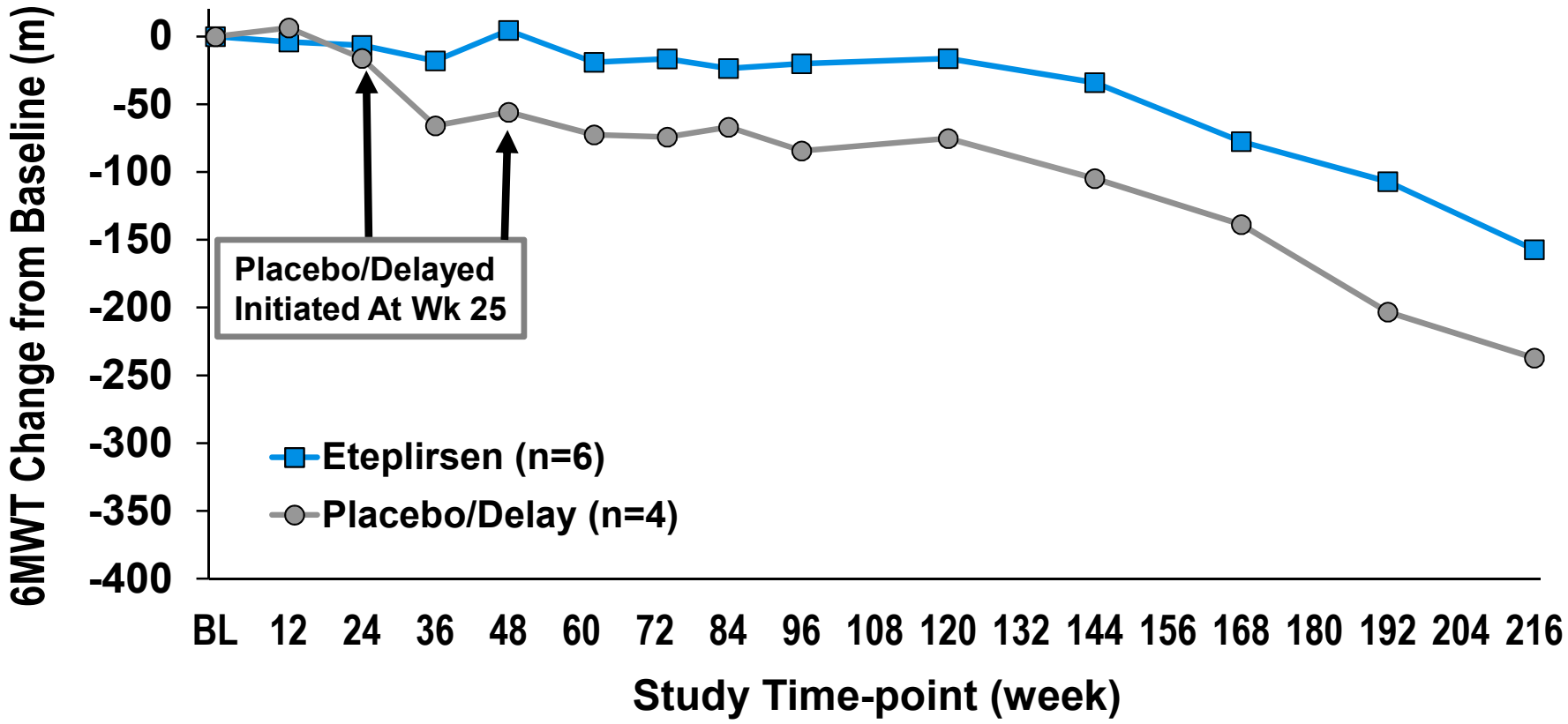
Jerry Mendell, MD
Curran-Peters Chair in Pediatric Research
Professor of Pediatrics and Neurology
Director, Center for Gene Therapy
Nationwide Children's Hospital
Columbus, OH

Context

- **Prolonged Ambulation**
  - **Median age at LOA in exon 51, steroid treated DMD is 12 years in CINRG database[1]**
  - **Avoid complications of wheelchair dependency**
- **Safety**
- **Consistency**

[1]Bello, 2016 (in press).

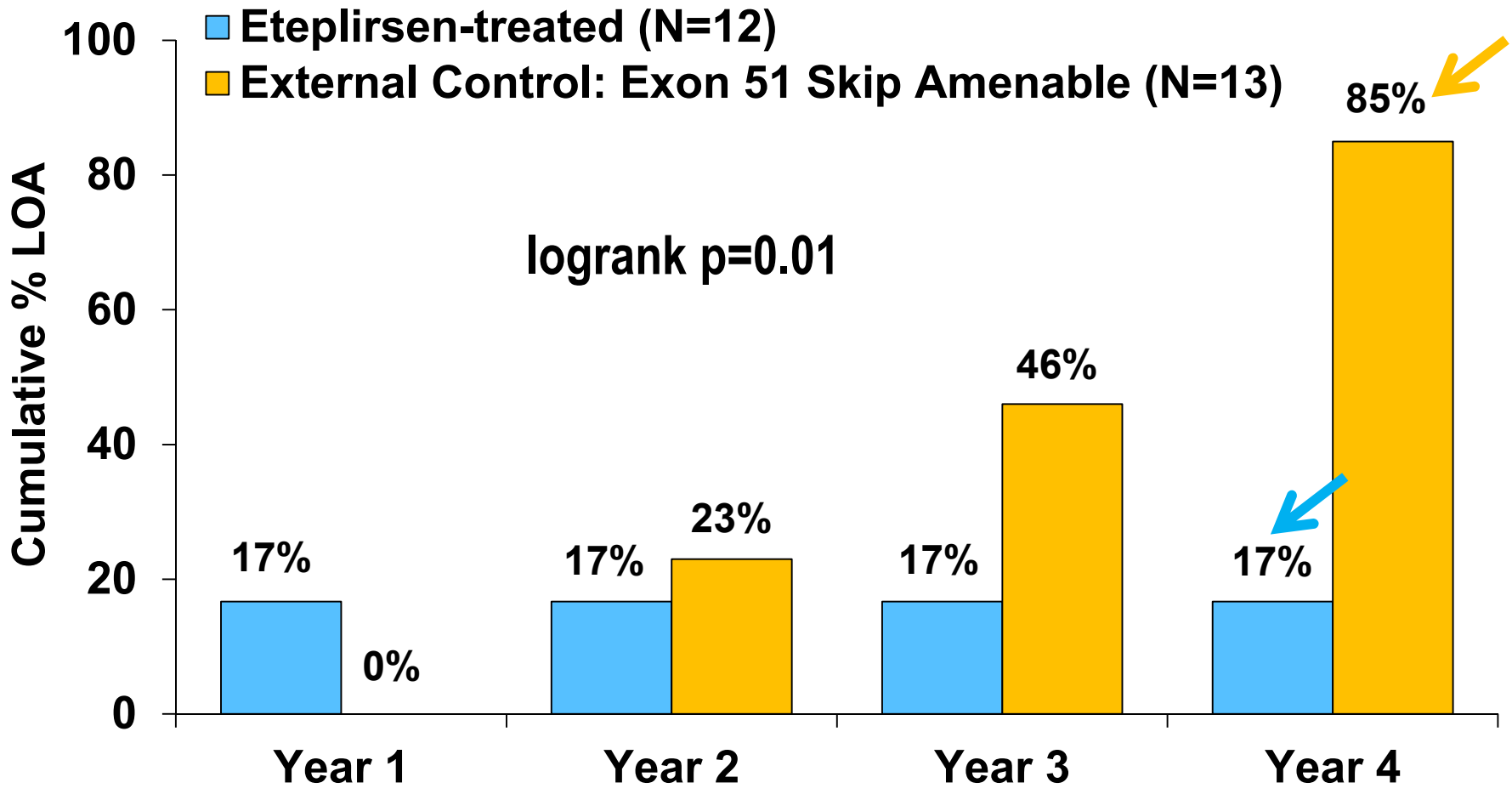
Long Term Stabilization of 6MWT with Eteplirsen (Completer Analysis*, N=10)



- **Delayed treatment (original placebo) patients never caught up**
- **Completer analysis does not include 2 patients with early LOA**

* Least Square Means Analysis. Data based on maximum 6MWT score when test repeated.

Eteplirsen Preserves Ambulation: 4 Year Kaplan-Meier Analysis of LOA



Eteplirsen-Treated Patient Pittsburgh Marathon, May 2, 2015*

* As of May 2, 2015 14.5 years of age.

Opportunity

- It’s a race against time
- Opportunity to change natural history of DMD
- Improve quality of life

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Concluding Remarks	**Edward M. Kaye, MD**

Concluding Remarks

Edward M. Kaye, MD

Key Voting Questions

Question	Sarepta's Position
Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen induces **production of dystrophin to a level that is reasonably likely to predict clinical benefit?**	Unequivocal increase in functional, de novo dystrophin by three complementary methods Presence of dystrophin is known to confer a clinical benefit

Key Voting Question (continued)

Question	Sarepta's Position
Were decisions to administer the **6-minute walk test** (vs. conclusions that the patient could no longer walk) **sufficiently objective and free of bias** and subjective decision-making by patients, their caregivers, and/or health care professionals **to allow for a valid comparison** between patients in Study 201/202 and an external control group?	Standardized 6MWT measurement Results consistent with other natural history databases

Key Voting Question (continued)

Question	Sarepta's Position
Do the clinical results of the single historically-controlled study (Study 201/202) provide **substantial evidence** (i.e., evidence from the adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy) **that eteplirsen is effective for the treatment of DMD?**	Dramatic 4-year effect on 6MWT and LOA

Eteplirsen
NDA 206488

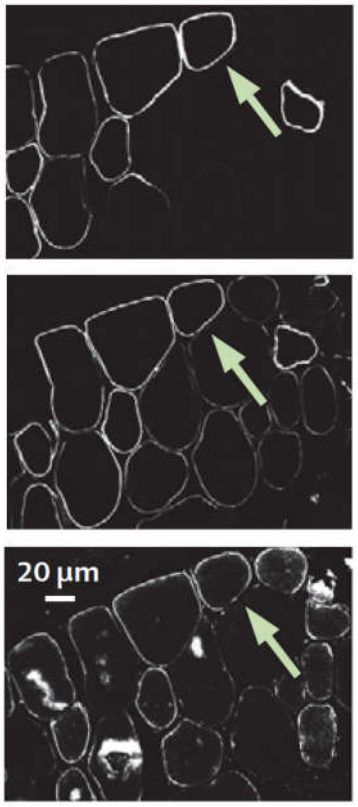
Peripheral and Central Nervous System
Drugs Advisory Committee
April 25, 2016

Sarepta Supporting Slides

DAPC Restoration Indicative of Dystrophin Functionality (Study 28)

- **Restoration of α-sarcoglycan and neuronal nitric oxide synthase (nNOS) to the membrane is indicative of dystrophin functionality**

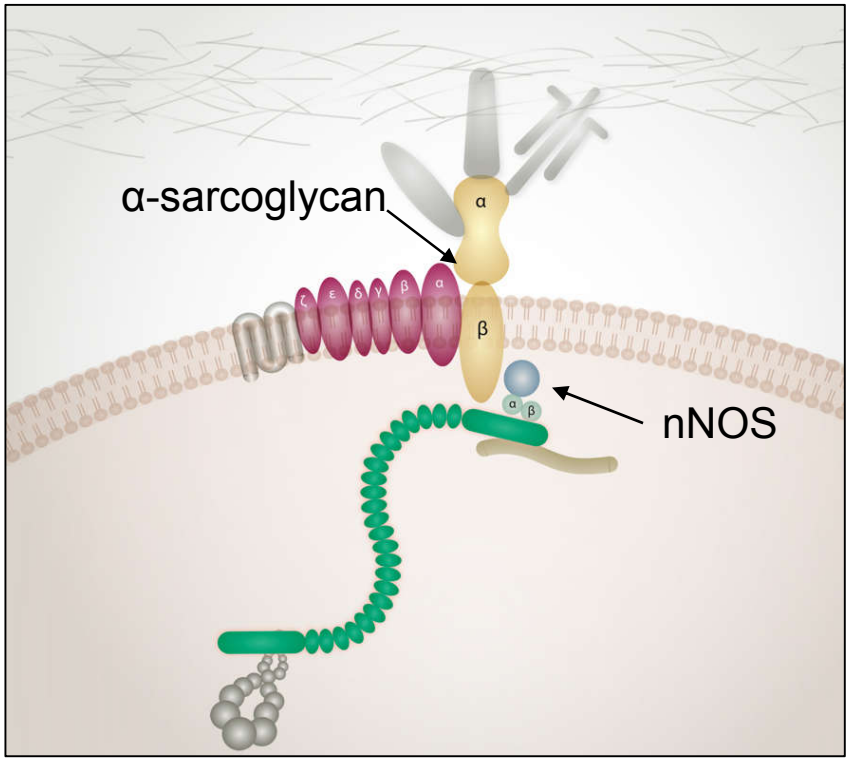
Patient 19
20 mg/kg



Dystrophin

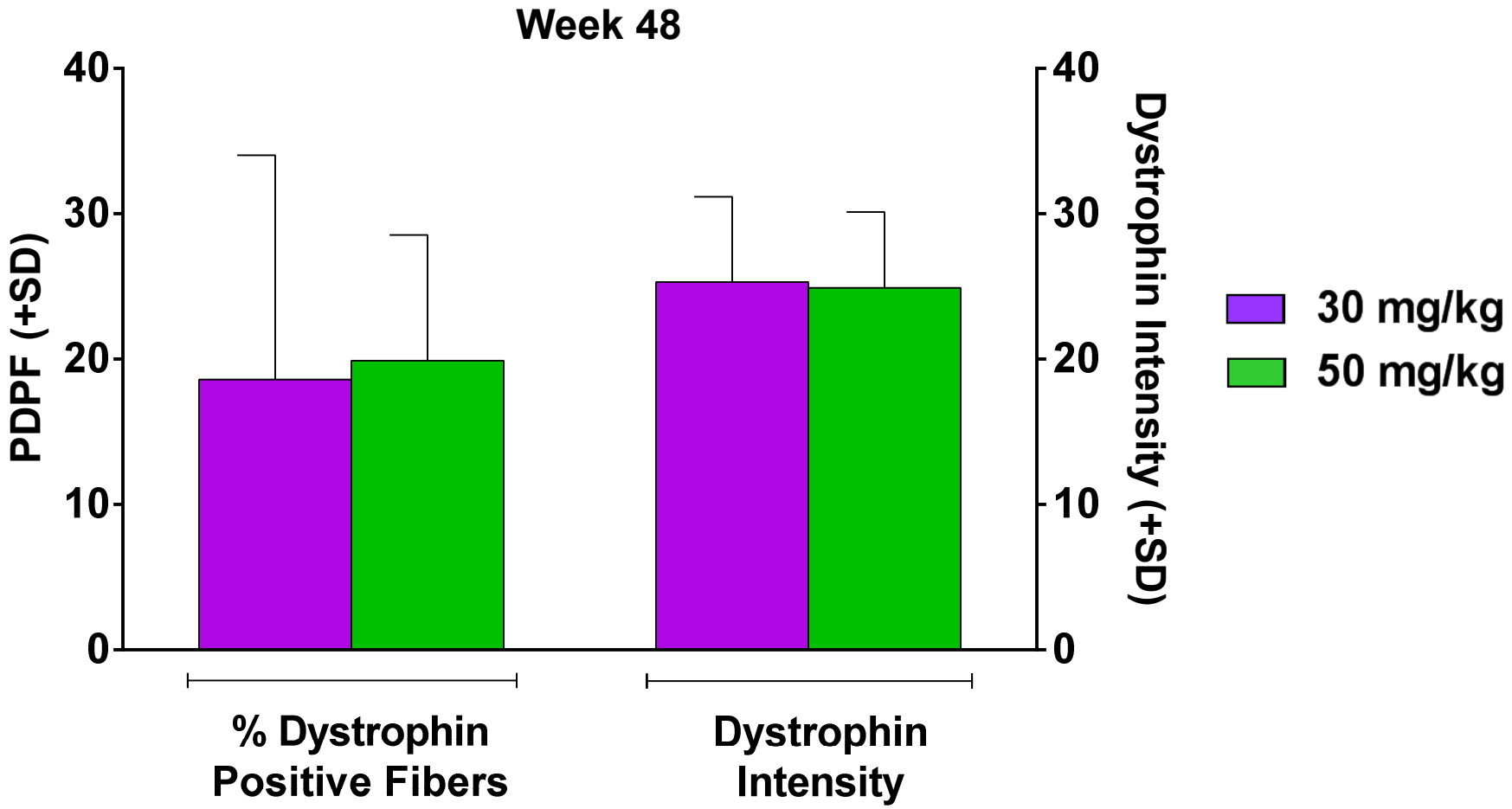
α-sarcoglycan

nNOS



Cirak, *Lancet* 2011

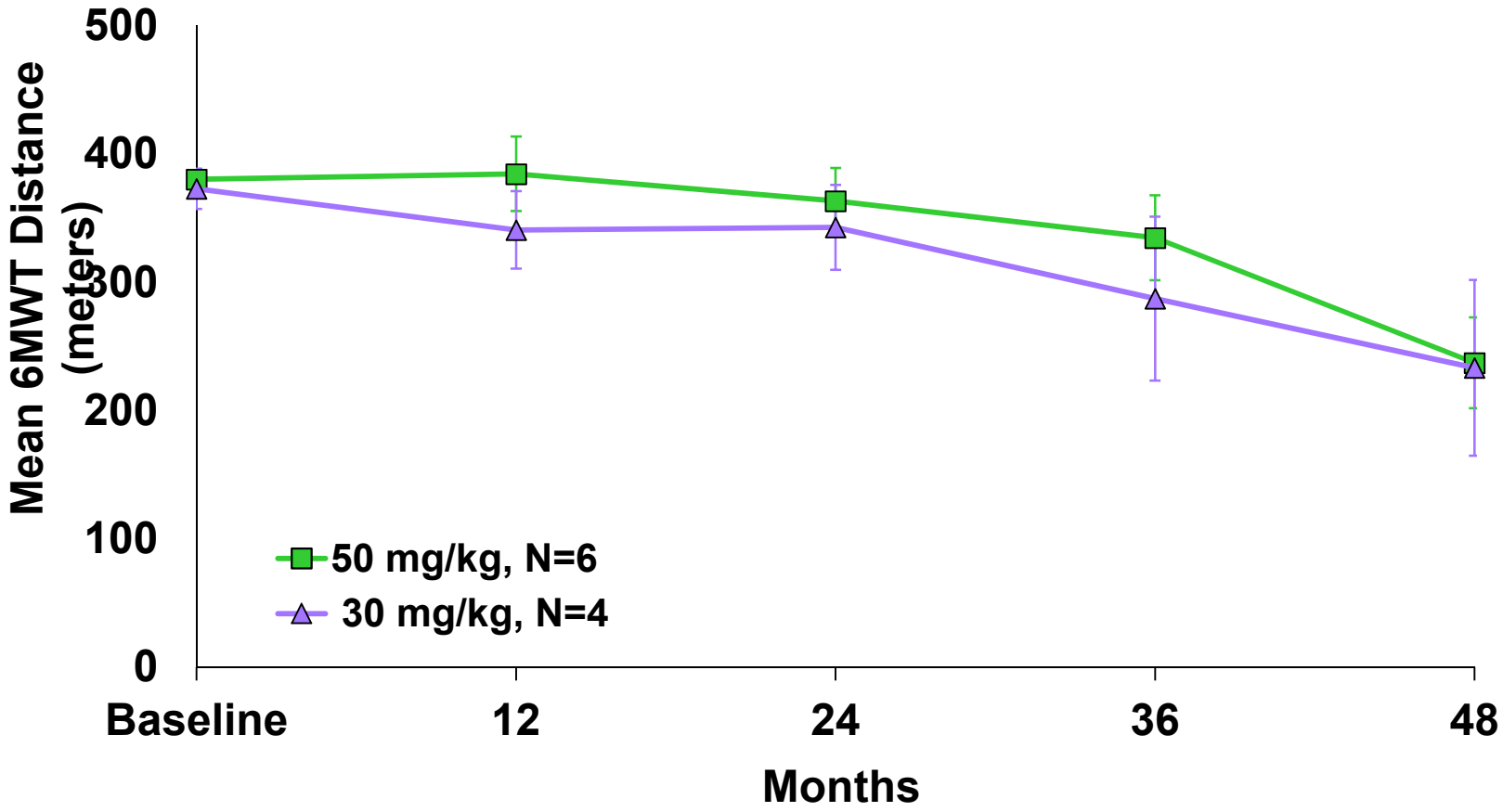
30 mg/kg and 50 mg/kg Resulted in Equivalent Dystrophin Response



Absolute Values
Each bar graph N=6;

Completer Analysis: 30 v 50 mg/kg
Study 201/202

- 30 vs 50 mg/kg groups do not differ on 6MWT when 2 boys with early LOA are removed from analysis



CINRG Definition of Loss of Ambulation

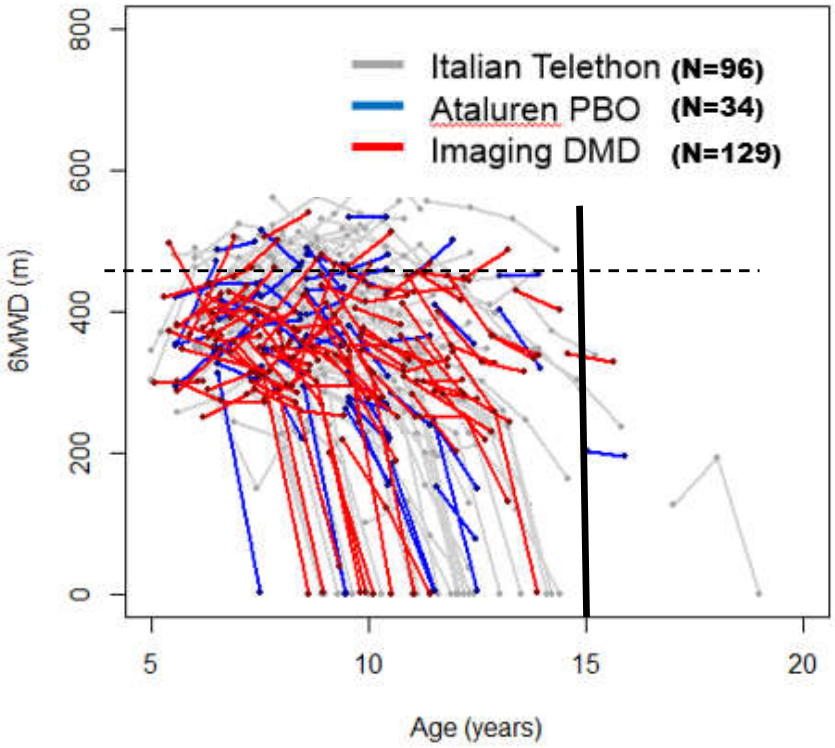
- Physician assessment (patient / parent report of full-time wheelchair use) on standard CRF

  (i.e. no independent household or minimal ambulation)

- Corroborated by loss of ability to perform the 10 meter run/walk test

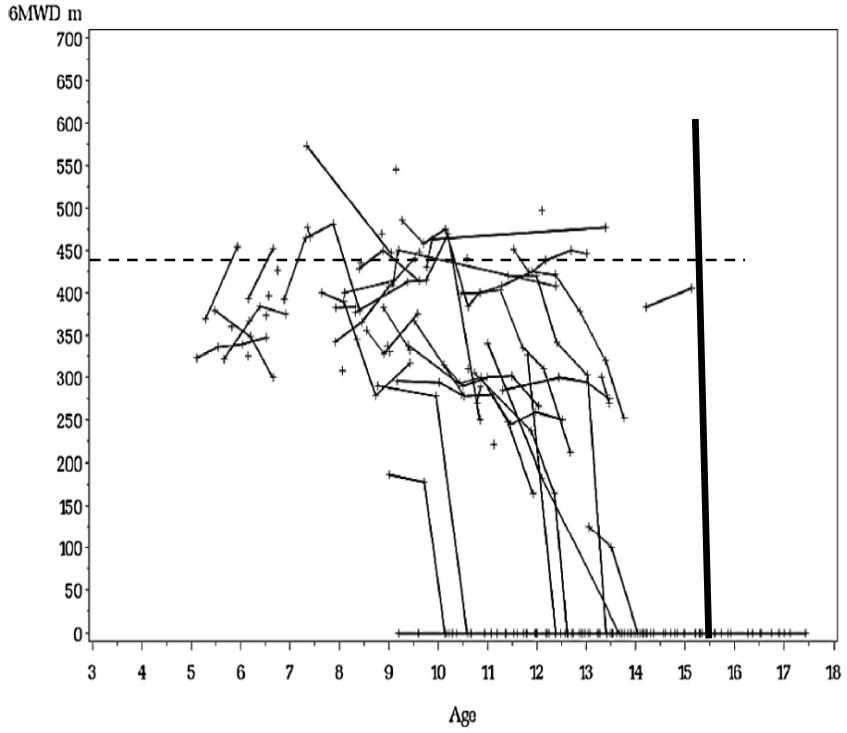
Worldwide DMD Literature: Available Patient Level 6MWT Data (N=324)

cData Courtesy: Trajectory Analysis Project (cTAP) (N=259)



>15 Years: 3% (~7/259) 6MWT >0

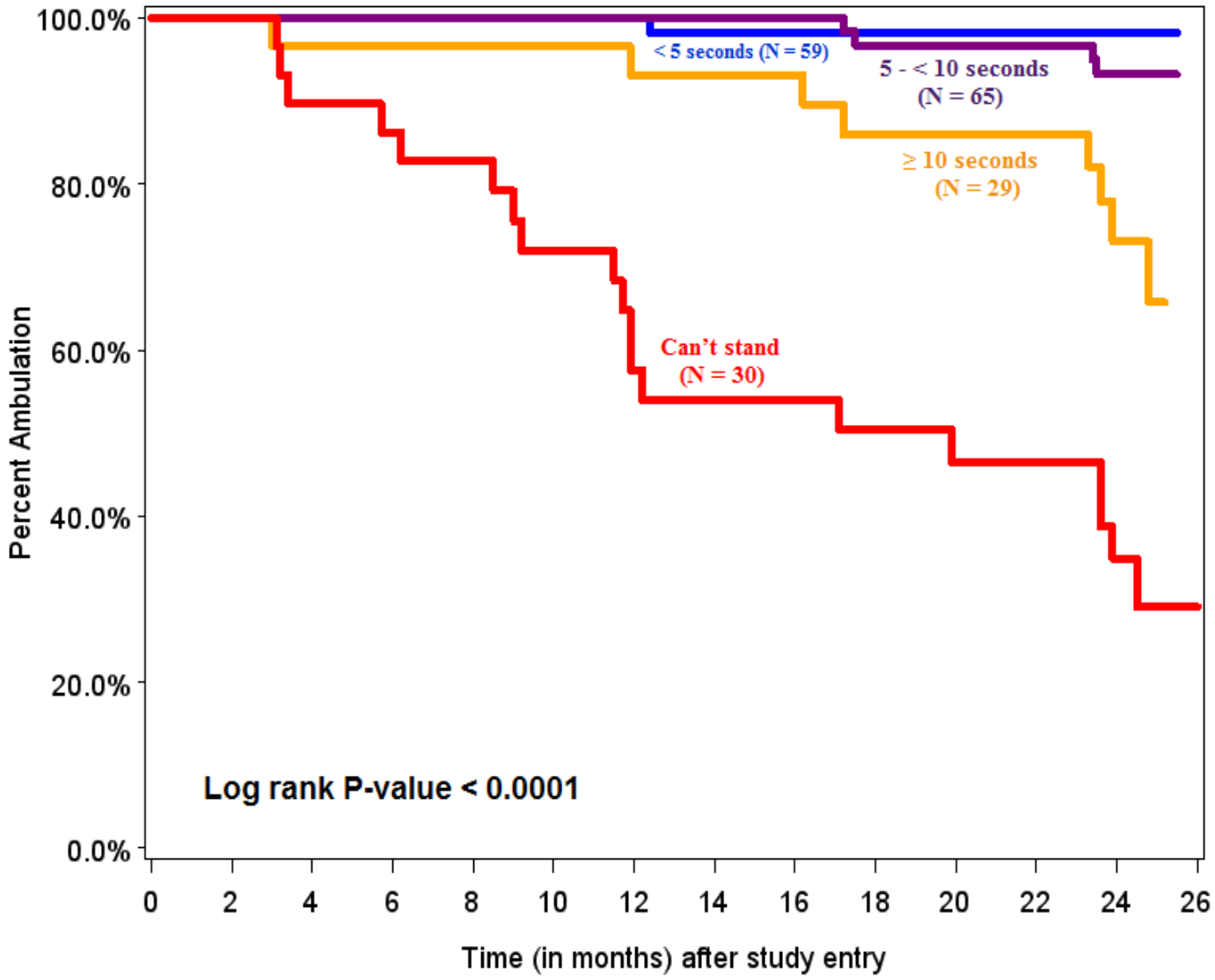
Goemans 2013 (N=65)



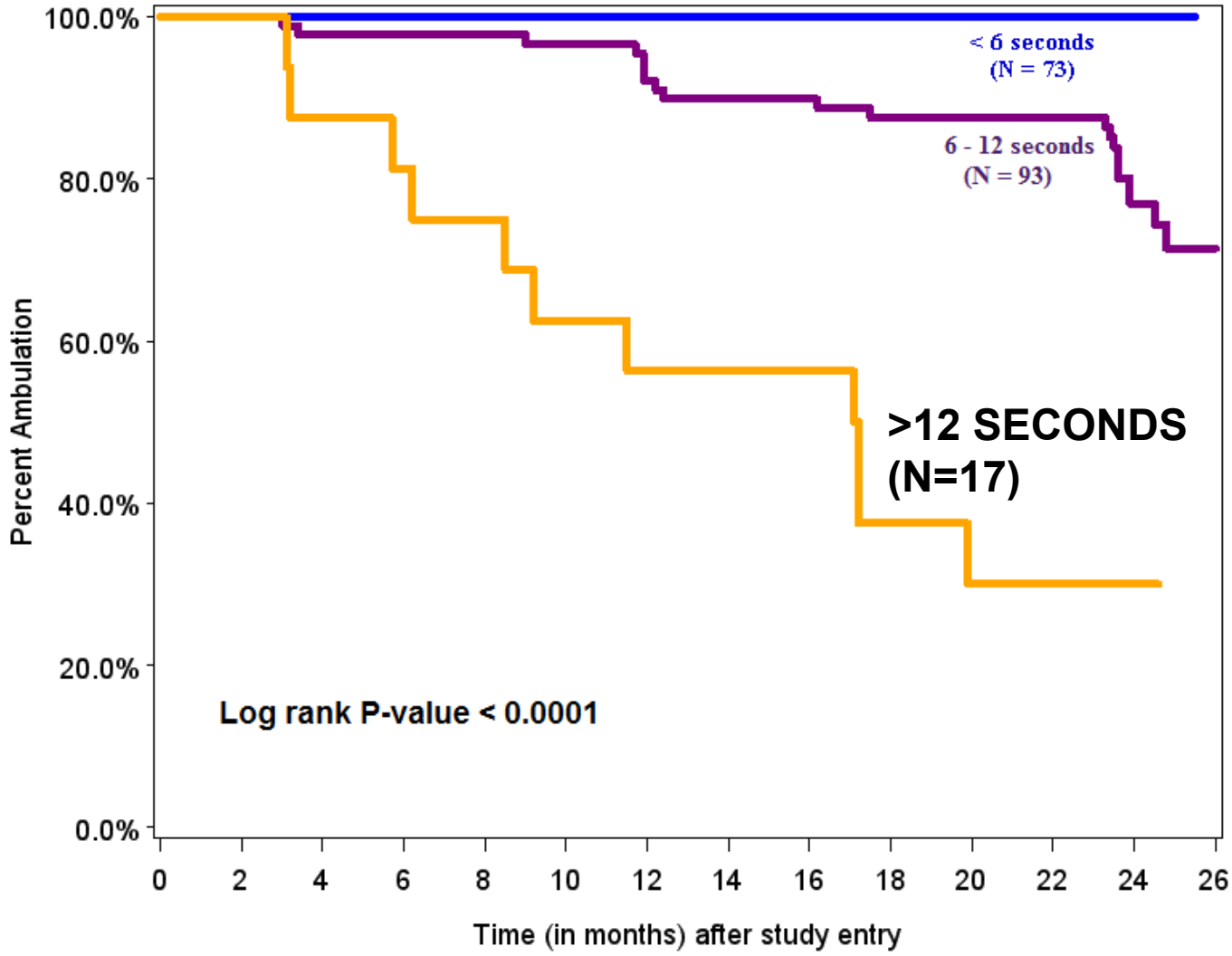
>15.5 Years: 0% (0/65) 6MWT >0

Prognostic: Prediction of Loss of Ambulation Using Baseline Time to Rise Ability

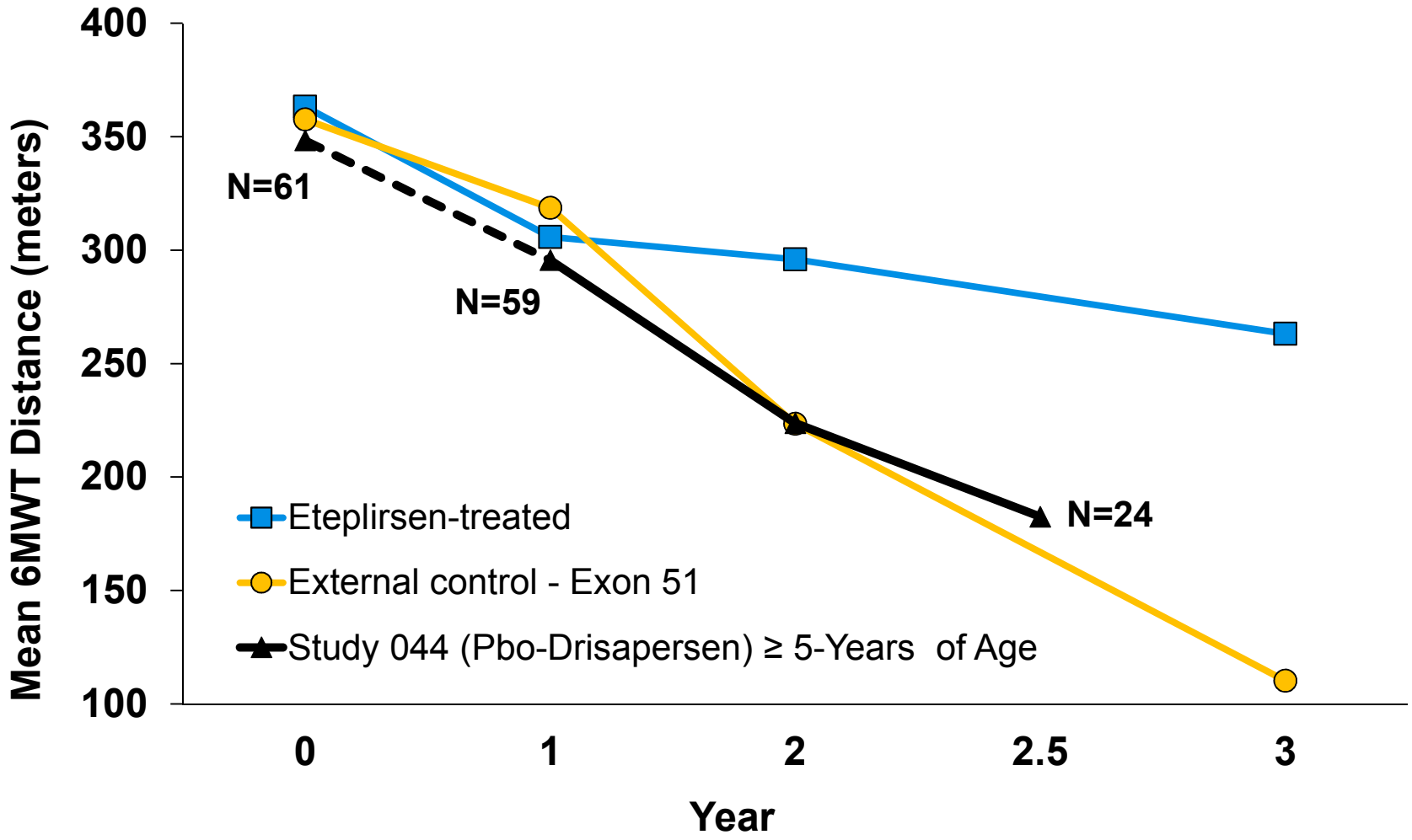
(CINRG data McDonald et al. *Neuromuscular Disorders*, 2013)



CINRG Data:
10 Meter Run/Walk Test Is Prognostic For Loss Of Ambulation



Eteplirsen Slows DMD Progression: 3 Year Analysis of 6MWT



Consistent Benefit Across Endpoints for Eteplirsen-treated Patients