Catabasis Investor Day

November 17, 2016
New York City

Corporate Overview

Jill Milne, PhD
Co-Founder & Chief Executive Officer

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including statements regarding our expectations and beliefs about our business, future financial and operating performance, clinical trial plans, product development plans and prospects. The words “believe”, “anticipate”, “plans,” “expect”, “could”, “should”, “will”, “would”, “may”, “intend” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements contained in this presentation and in remarks made during this presentation and the following Q&A session are subject to important risks and uncertainties that may cause actual events or results to differ materially from our current expectations and beliefs, including: uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of our product candidates; availability and timing of results from preclinical studies and clinical trials; whether interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; expectations for regulatory approvals to conduct trials or to market products; availability of funding sufficient for our foreseeable and unforeseeable operating expenses and capital expenditure requirements; other matters that could affect the availability or commercial potential of our product candidates; and general economic and market conditions. These and other risks are described under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, which is on file with the Securities and Exchange Commission, and in other filings that we may make with the Securities and Exchange Commission in the future.

In addition, the forward-looking statements included in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

Investor Day Agenda
8:30 – 11:30 am

Topic	Speaker
Welcome and Introduction	Jill Milne, PhD, Co-Founder & CEO
Corporate and Partnering Strategy	Rick Modi, MBA, CBO
Catabasis Pipeline	Andy Nichols, PhD, CSO
Edasalonexent (CAT-1004): Mechanistic Rationale and Preclinical Proof of Concept in DMD	H. Lee Sweeney, PhD University of Florida
Break (9:30am – 9:40am)	
Duchenne Muscular Dystrophy (DMD): Clinical Landscape and Natural History	Craig McDonald, MD University of California, Davis
Magnetic Resonance Imaging (MRI): Biomarker for Assessing Progression and Effects of Therapeutic Intervention in DMD	H. Lee Sweeney, PhD University of Florida
Edasalonexent: Clinical Overview and MoveDMD Trial	Joanne Donovan, MD, PhD CMO and SVP, Clinical Development
Q&A	All
Close	Jill Milne, PhD, Co-Founder & CEO

Welcome Attendees and External Speakers

- **Craig M. McDonald, MD**
  UC Davis NeuroNEXT Program Director
  University of California

  - Internationally recognized expert in DMD care and clinical trials
  - UC Davis NeuroNEXT Program Director
  - Chair of Cooperative International Neuromuscular Research Group (CINRG)
  - Author on multiple manuscripts and PI for multiple clinical trials for DMD

- **H. Lee Sweeney, PhD**
  UF Myology Institute Director
  University of Florida

  - Internationally recognized expert in DMD studies and MRI as a biomarker
  - Professor; Director; Myology Institute
  - Co-PI for ImagingDMD Group
  - Author on multiple manuscripts and PI for multiple preclinical and clinical studies for DMD

Catabasis Was Founded on a Simple Principle: To Do Things Differently

2008

An idea

- A unique technology
- Do drug discovery and development differently

Today, We Are Building a Robust Pipeline Based on Our Founding Principle

Today

A public clinical-stage company

- Robust clinical and preclinical pipeline
- Lead program: Phase 2 in Duchenne
- Talented team of 37 driven to make a difference

The Catabasis Vision Is to Be a Premier Rare Disease Company, to Make a Difference

Our goal

A premier rare disease company

- A different approach
- Therapies that work regardless of mutation type
- Therapies that work in multiple diseases

Since Founding the Company, We Have Been Executing Relentlessly on Our Strategic Plan

Set the foundation
Develop technology
Capitalize company
Attract leadership

Build the pipeline
Engineer conjugates
Move to clinic
Pursue partnerships

Benefit patients
Commercialize
Expand capabilities
Access new assets

2008
An Idea

Today
A public clinical-stage company

Our goal
A premier rare disease company

We Have an Experienced Leadership Team with a Strong Track Record of Success

Jill Milne, PhD
Co-Founder & CEO

Sirtris Pharmaceuticals (GSK)
Pfizer

Deirdre Cunnane, JD
General Counsel

Advanced Technology Ventures
Lightstone Ventures
BancBoston Ventures
BancBoston Capital

Joanne Donovan, MD, PhD
CMO & SVP, Clinical Development

Genzyme Corporation
GelTex
Harvard Medical School

Angelika Fretzen, PhD, MBA
SVP, Product Development

Ironwood Pharmaceuticals

Ted Hibben, MBA
SVP, Corporate Development

Ensemble Therapeutics
Cequent Pharmaceuticals (Marina)
Coley Pharmaceutical (Pfizer)
Centagenetix
Pericor
Ontogeny (Curis)
Marathon Biopharmaceuticals

Joe Johnston, MS, MBA
VP, Regulatory Affairs

Ionis Pharmaceuticals (previously Isis Pharmaceuticals)

Rick Modi, MBA
CBO

InterMune (Roche)
MedImmune (AstraZeneca)
Centocor (J&J)

Andrew Nichols, PhD
CSO

Merck
Zafgen
Millennium
SmithKline Beecham

We Have a Core Set of Internal Capabilities and a Values-Based Culture Focused on Execution

- **Our team**
  - 37 people, 19 with PhD
- **Capabilities**
  - Discovery to Clinical
  - G&A and business functions to support pipeline and public company status
- **SMART Linker drug discovery platform**
  - Enables engineering bi-functional molecules
- **Operating model**
  - Efficiency, ‘nimble-ness’
  - Strategic skills in-house, others outsourced
  - A values-based culture

We Have Made Significant Progress in the Last 18 Months

July 2015: Edasalonexent for DMD FDA Fast Track designation

Edasalonexent

Sept 2015: Edasalonexent for DMD FDA Rare Pediatric Disease designation

Edasalonexent

Oct 2015: Edasalonexent for DMD EC Orphan Medicinal Product designation

Edasalonexent

Jan 2016: Reported positive results for Phase 1 portion of MoveDMD trial showing safety, tolerability, adequate plasma exposure and target engagement

Edasalonexent

Feb 2016: Received grant from Muscular Dystrophy Association (MDA)

Edasalonexent

April 2016: Initiated Phase 2 portion of MoveDMD trial

Edasalonexent

July 2016: Initiated 36-week open-label extension of MoveDMD trial

Edasalonexent

September 2016: Announced joint research collaboration with Sarepta

Edasalonexent

June 2015 | July 2015 | Aug 2015 | Sept 2015 | Oct 2015 | Nov 2015 | Dec 2015 | Jan 2016 | Feb 2016 | March 2016 | April 2016 | May 2016 | June 2016 | July 2016 | Aug 2016 | Sept 2016 | Oct 2016

CAT-2000

June 2015: Reported positive Phase 1 results for CAT-2054 showing safety, tolerability and LDL-C effects

Corporate

Jan 2016: Published manuscript on technology in J. Med Chem

CAT-4001

Jan 2016: Received grant from Friedreich's Ataxia Research Alliance

Corporate

April 2016: Added to BoD: B. Adelman and M. Kishbauch and formed Science and Technology Committee

CAT-2000

May 2016: Reported positive preclinical results for CAT-2003 in NASH

CAT-2000

June 2016: Reported results for Phase 2a trial of CAT-2054 in hypercholest-erolemia

CAT-5571

October 2016: Reported positive preclinical results for CAT-5571 in CF

We Have Made Significant Progress in the Last 18 Months

Lead Program:
Edasalonexent in DMD

Edasalonexent

01.25.16 Catabasis Pharmaceuticals Announces Positive Top-Line Results from Part A of the MoveDMD Trial, a Phase 1 / 2 Trial of CAT-1004 for the Treatment of Duchenne Muscular Dystrophy

Edasalonexent

04.12.16 Catabasis Pharmaceuticals Initiates Part B of the MoveDMD Trial of CAT-1004 for the Treatment of Duchenne Muscular Dystrophy

Edasalonexent

07.07.16 Catabasis Pharmaceuticals Announces the Initiation of an Open-Label Extension for the MoveDMD® Trial Studying Edasalonexent (CAT-1004) in Duchenne Muscular

Edasalonexent

10.04.16 Catabasis Pharmaceuticals Completes Target Enrollment for Part B of the MoveDMD® Trial, a Phase 2 Trial of Edasalonexent (CAT-1004) for the Potential Treatment of Duchenne Muscular Dystrophy

June 2015	July 2015	Aug 2015	Sept 2015	Oct 2015	Nov 2015	Dec 2015	Jan 2016	Feb 2016	March 2016	April 2016	May 2016	June 2016	July 2016	Aug 2016	Sept 2016	Oct 2016

Building the Pipeline:
CAT-4001 in ALS or FA
CAT-5571 in CF

CAT-4001

01.19.16 FARA Announces Catabasis Pharmaceuticals as the Recipient of the Kyle Bryant Translational Research Award to Evaluate CAT-4001 as a Potential Therapy for Friedreich's Ataxia

CAT-5571

10.20.16 Catabasis Pharmaceuticals to Present CAT-5571, a Novel Activator of Autophagy, as a Potential Treatment for Cystic Fibrosis at the 30th Annual North American Cystic Fibrosis Conference

We Are Building a Robust Pipeline of Product Candidates in Rare Diseases

Product Candidate (Pathway)	Potential Indications	Discovery	Preclin	Phase 1	Phase 2	Phase 3
Edasalonexent CAT-1004 (NF-κB)	Duchenne muscular dystrophy					
Edasalonexent CAT-1004 (NF-κB)	Additional rare disease					
CAT-4001 (Nrf2/NF-κB)	Friedreich's ataxia Amyotrophic lateral sclerosis					
CAT-5571 (Autophagy)	Cystic fibrosis					

Our Value Proposition

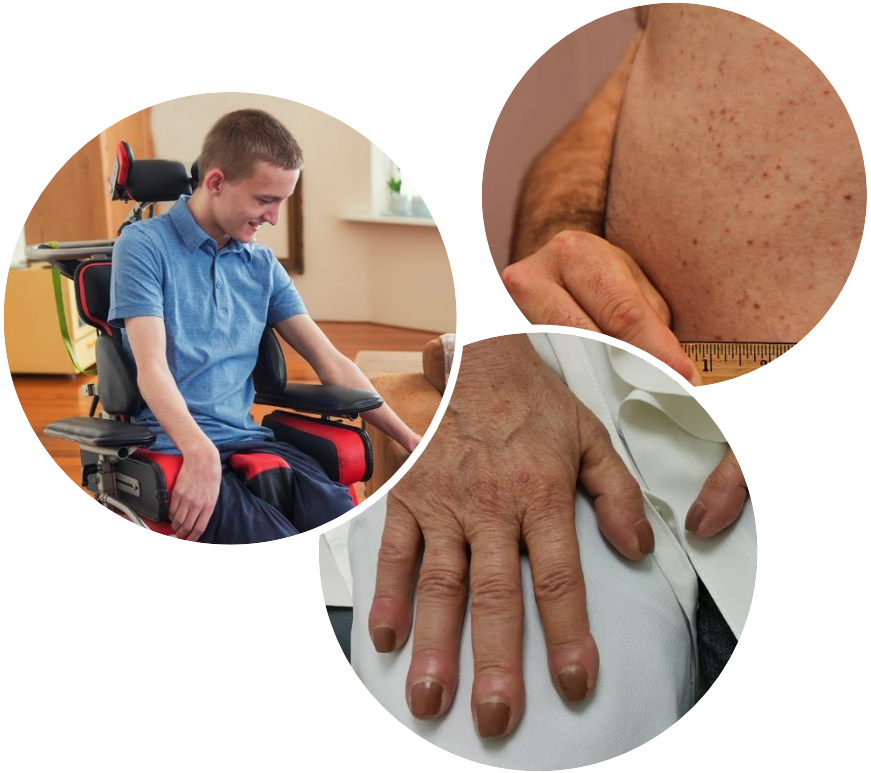
- **Building a premier rare disease company**
  - Experienced leadership team
  - Nimble and efficient organization with strong execution
  - Developing capabilities to take product candidates from idea to commercialization
- **Targeting rare diseases with a unique pathway approach**
  - Selecting central pathways implicated in multiple rare diseases
  - Simultaneously target multiple points in a disease pathway with SMART Linker Drug Discovery platform
- **Robust product pipeline of clinical and preclinical candidates**
  - Edasalonexent: Potential disease-modifying therapy for all DMD patients
  - Edasalonexent: Potential for additional rare disease indication
  - CAT-4001: Potential treatment of rare neurodegenerative diseases such as Friedreich's ataxia (FA) and amyotrophic lateral sclerosis (ALS)
  - CAT-5571: Potential treatment of cystic fibrosis and other rare diseases

Corporate and Partnering Strategy

Rick Modi
Chief Business Officer

Case for Rare Diseases
A Remarkable Patient Need

- **Significant unmet medical need**
  - 7,000 rare diseases
  - Only 5% have treatments
  - Affects 1 in 10 Americans; half are children
- **Efficient path to patients**
  - Relatively small trials
  - Favorable development and regulatory path
  - Potential to go to market on own



National Organization for Rare Disorders (NORD)

Case for Rare Diseases
The Catabasis Difference

Traditional Approach

- Pursue defined mutations as targets
- Target pathway at a singular point
- Molecules with no prior data

Implications

- Benefit subsets of patients in a disease
- One disease per molecule
- Price points reflective of patient subsets

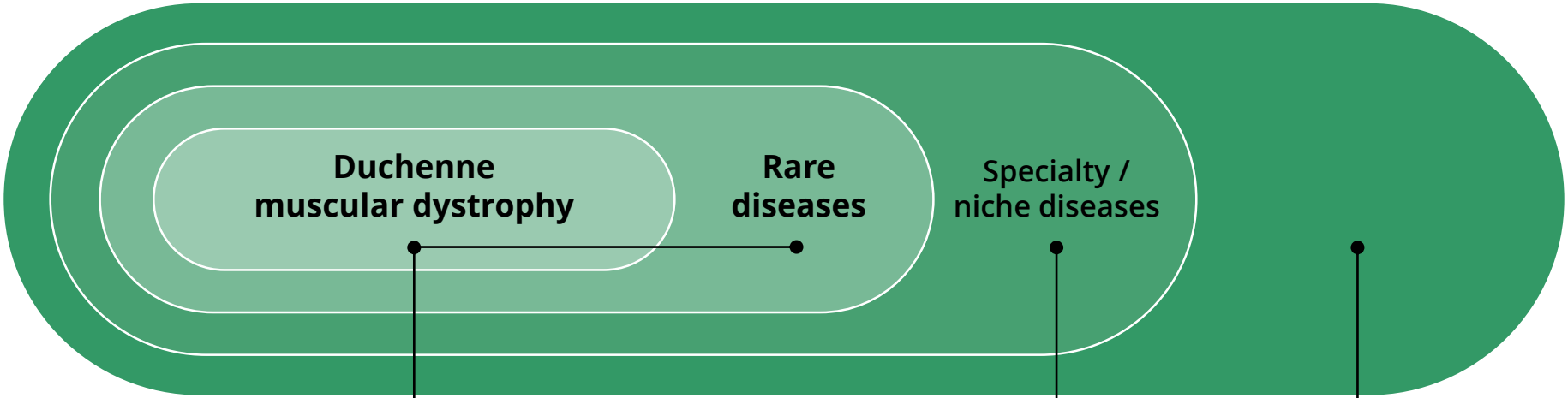
Catabasis Approach

- Rare diseases with multi-modal pathophysiology
- Pursue pathways in a bi-functional manner
- Pathways involved in multiple diseases
- Enhance known bioactives

Implications

- Benefit patients with a disease regardless of mutation type
- Multiple diseases per molecule
- Strong value proposition to payers

How We Select Our Programs
Disease Areas



Core disease areas:

- Duchenne muscular dystrophy
- Additional rare diseases e.g., ALS, FA, CF

Opportunistic

Non-rare diseases that are specialty diseases

Exclusion areas

Disease areas not in focus *e.g.,* diabetes

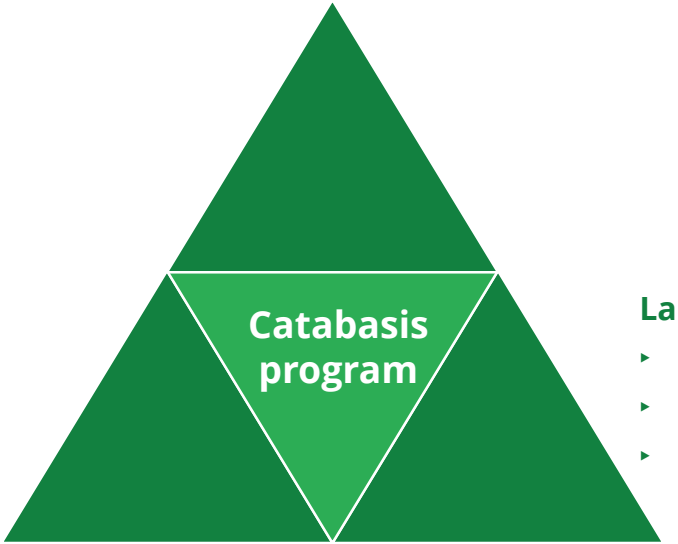
How We Select Our Programs
The Catabasis Criteria

Strong Scientific Rationale

- Central disease pathway
- Applicability to multiple diseases
- Ability to leverage technology

Favorable Development Path

- Early biomarker signal in clinic
- Supportive path to approval
- Favorable IND to NDA timeline



Large Patient Benefit

- Benefit thousands of patients
- Significant patient need
- Concentrated clinician base

Global Go-to-Market and Partnering Strategy
Reaching Patients Worldwide

Region	Considerations	Strategy
N. America	▸ Small, concentrated customer base ▸ Accounts for 40 – 50% of WW potential	▸ Develop and go-to-market on own
Europe, Japan, Lat-Am	▸ More complex regulatory, reimbursement and language environment ▸ Accounts for 30 – 50% of WW potential	▸ Preference to develop and go-to-market on own ▸ May pursue partnership for expertise and if terms are favorable
Rest of World	▸ Nascent infrastructure (notable exceptions exist)	▸ Generally via a partner / distributor

Global Go-to-Market and Partnering Strategy Leveraging Collaborations

Partnership Objectives

1. Access expertise and assets in diseases of focus
2. Monetize non-strategic assets and geographies
3. Realize value by leveraging technology

Key Activities

1. Pursue combinations for edasalonexent
2. Out-license non-strategic assets and geographies
3. Seek a platform deal

- **Efforts YTD in 2016 and anticipated for 2017:**
  - Announced joint research collaboration with SRPT for combination therapy approach in DMD (2016)
  - Multiple partnership opportunities: CAT-2000 series in NASH, ex-US rights for edasalonexent, technology application / preclinical programs

Strategy in Action
The Potential of Edasalonexent in Duchenne

- **Disease-modifying non-steroid oral therapy**
  - Intended for all patients, regardless of mutation type
  - Inhibit muscle degeneration, enhance regeneration
  - Benefits in skeletal muscle, diaphragm and heart
- **Potential foundational therapy**
  - Initiate upon diagnosis
  - Effective as monotherapy
  - May be complementary to dystrophin / utrophin upregulation approaches
- **Go-to-market and partnership strategy**
  - Go-to-market on own in US
  - Flexibility ex-US: on own or via partnership

Developing a potential NEW Standard of Care in Duchenne

Strategy in Action
Building an Edasalonexent Franchise Beyond Duchenne

Identified, screened and prioritized potential additional indications

- NF-κB-mediated muscle indications e.g., Becker muscular dystrophy, polymyositis
- NF-κB-mediated non-muscle indications e.g., IgA nephropathy, pulmonary arterial hypertension

All key Phase 1 gating milestones met to initiate Phase 2

- No safety signals and well tolerated
- Adequate exposure levels achieved
- Reduction in NF-κB activity shown

Pursue sequential Phase 2 development

- Finalize additional indication selection
- Intend to initiate Phase 2 trial in selected additional indication in Q4 2017 or Q1 2018

Strategy in Action
Building a Premier Rare Disease Pipeline

Product Candidate	Edasalonexent	CAT-4001	CAT-5571
Target	Bi-functional approach: targets NF-κB at two points	Bi-functional approach: targets NF-κB and Nrf2	Bi-functional approach: targets autophagy at two points
Lead Indication	DMD with 15,000 patients in US	FA with 6,000 patients or ALS with 30,000 patients in US	CF with 30,000 patients in US
Applicability	Multiple other diseases	Multiple other diseases	Multiple other diseases

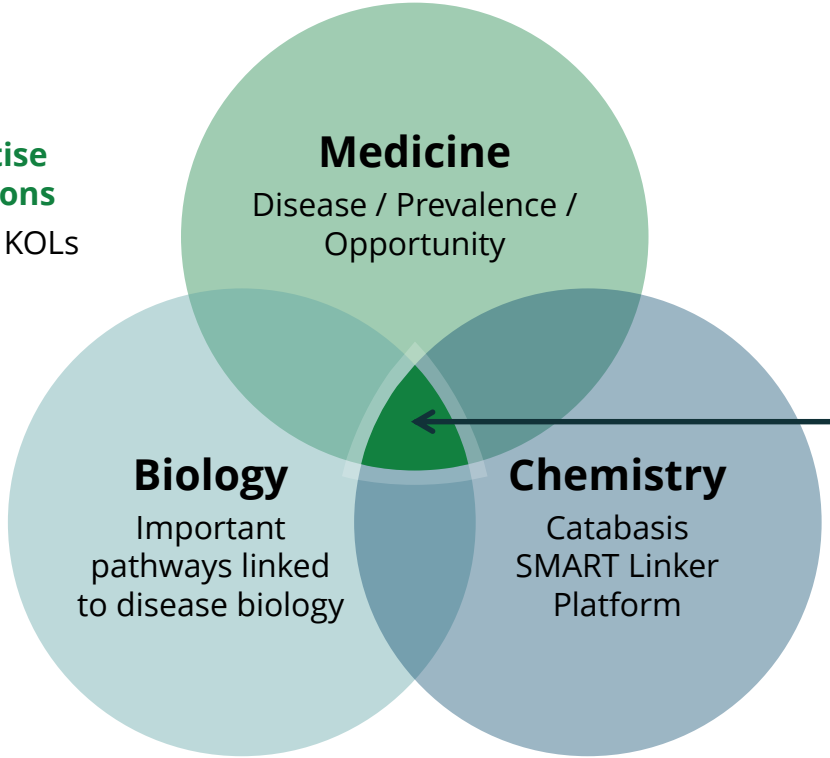
Catabasis Pipeline

Andy Nichols, PhD
Chief Scientific Officer

Building the Catabasis Pipeline: Utilizing the SMART Linker Platform

Clinical expertise in key indications

- Internal and KOLs



Expertise in key areas of biology

- Internal and collaborations

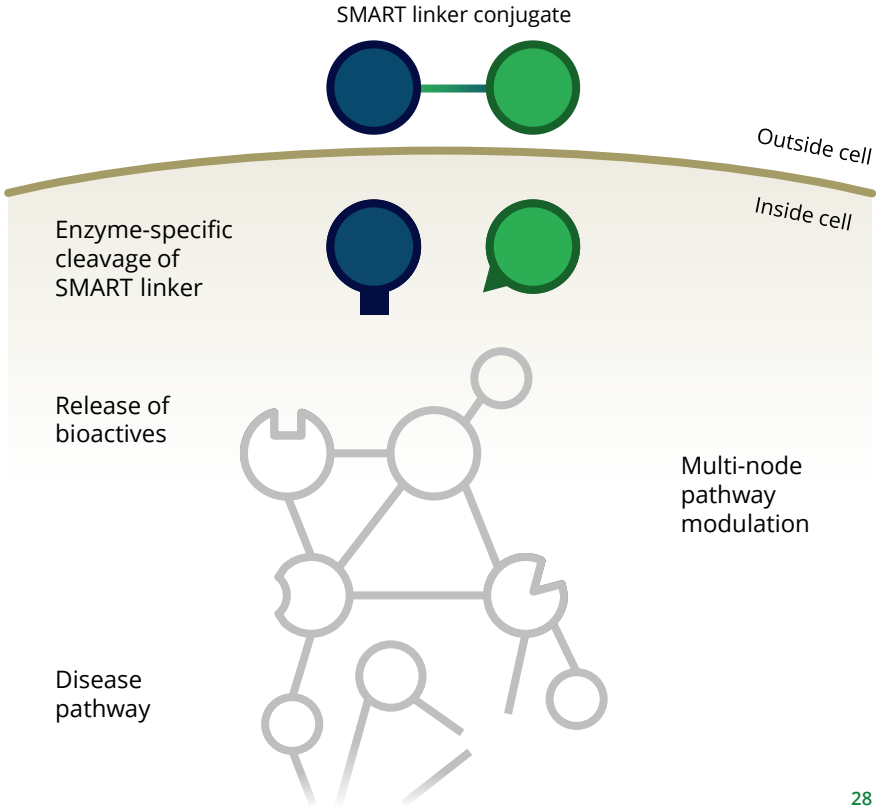
The Catabasis value proposition

Expertise in NCE discovery and development

- Internal and CROs

The Intersection of Pathway Biology and the SMART Linker Platform

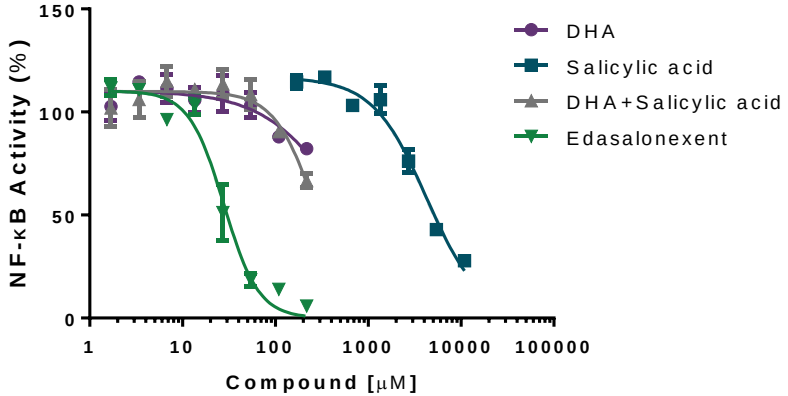
- **Conjugates engineered from a variety of proprietary, enzyme-cleavable small chemical linkers (“SMART linkers”)**
- **Pharmacophore linkage**
  - Inactivated bioactives
  - Uncleavable in gut & circulation
- **Cellular uptake by endocytosis**
  - Driven by linker and/or bioactive components
- **Intracellular hydrolysis of linker**
  - Intracellular enzyme access
- **Bioactives “reactivated” upon cleavage**
  - Freed to interact with intended targets



Biological Synergy Through the SMART Linker Platform

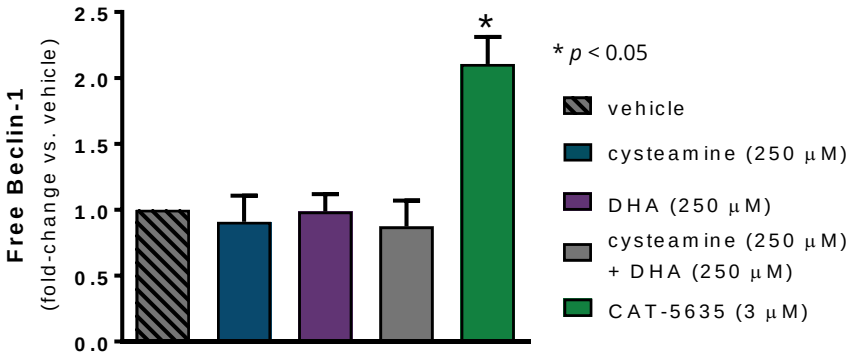
CAT-1000 Series
Synergy through multiple nodes in same pathway

- Synergistic inhibition of NF-κB



CAT-5000 Series
Synergy through multiple nodes in multiple pathways

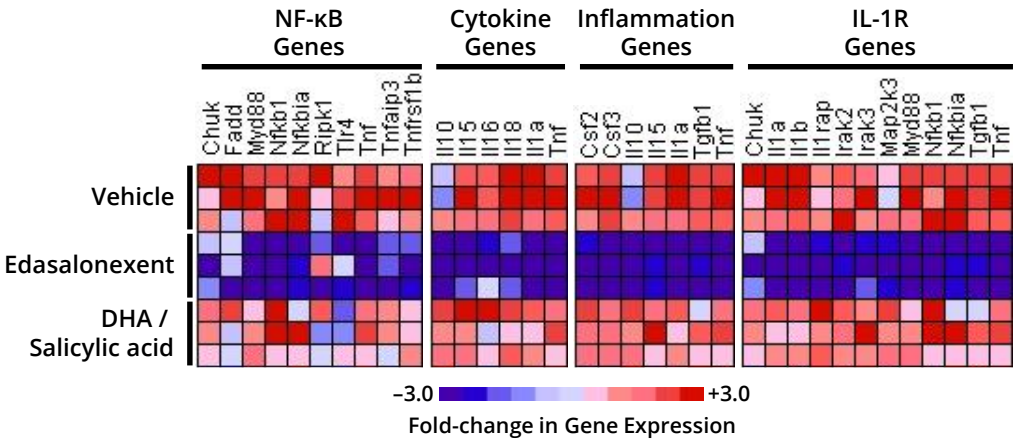
- Synergistic activation of autophagy



Edasalonexent Synergistically Inhibits NF-κB Activation as Compared to the Simple Combination of DHA and Salicylic Acid

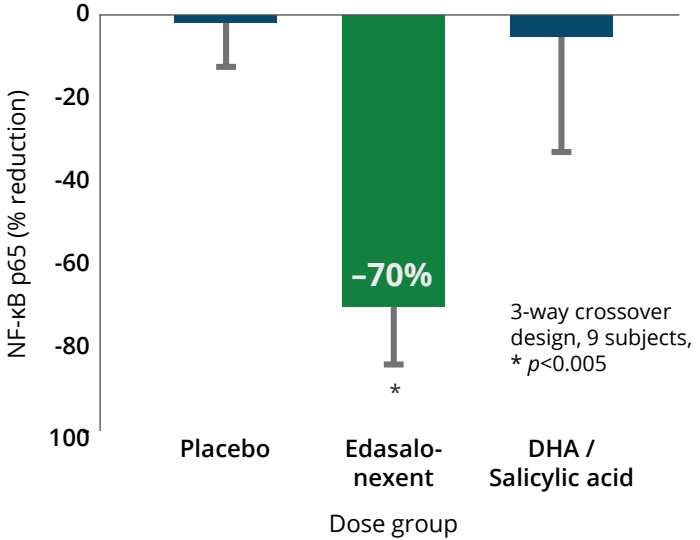
In Vitro Gene Set Analysis

Pathways Modulated in RAW Macrophages



LPS-stimulated NF-κB p65 DNA Binding Assay

Phase 1 Clinical Data Inhibition of Activated NF-κB



Edasalonexent

Inhibition of NF-κB for the Treatment of Duchenne Muscular Dystrophy and Additional NF-κB Mediated Diseases

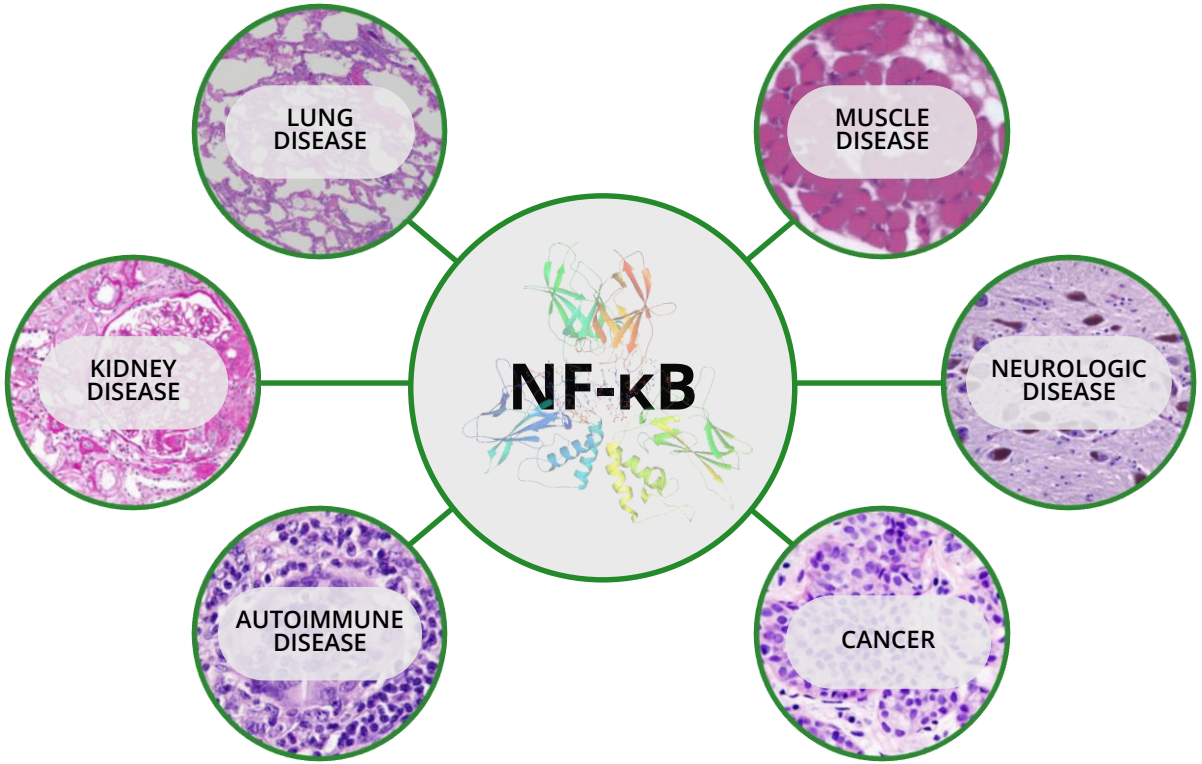
CAT-4001

Inhibition of NF-κB and Activation of Nrf2 to Reduce Neuroinflammation for the Treatment of Neurodegenerative Diseases

CAT-5571

Inhibition of Transglutaminase 2 and Activation of AMPK to Activate Autophagy for the Treatment of Cystic Fibrosis

A Focus on NF-κB: A Key Biological Node in Multiple Diseases



Pathogenic Role of Activated NF-κB in Muscle Diseases

Duchenne muscular dystrophy, Becker muscular dystrophy, polymyositis, others

Sarcolemma Function

β-Dystroglycan

Dystrophin

Actin

MMP-9

miRNA

Regeneration

Satellite Cell

Cyclin D1

Myoblasts

MyoD

Myotube

NF-κB

Inflammation + Fibrosis

Inflammation

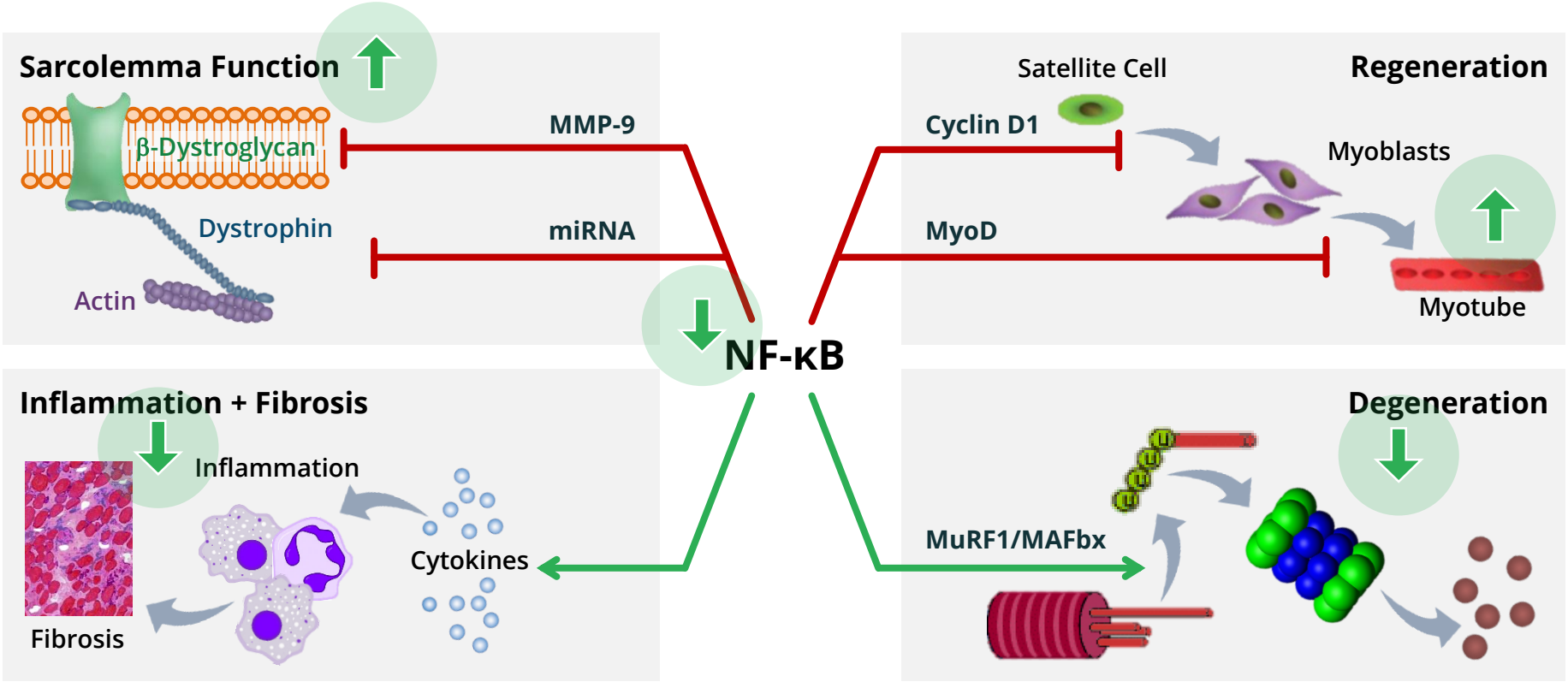
Cytokines

Fibrosis

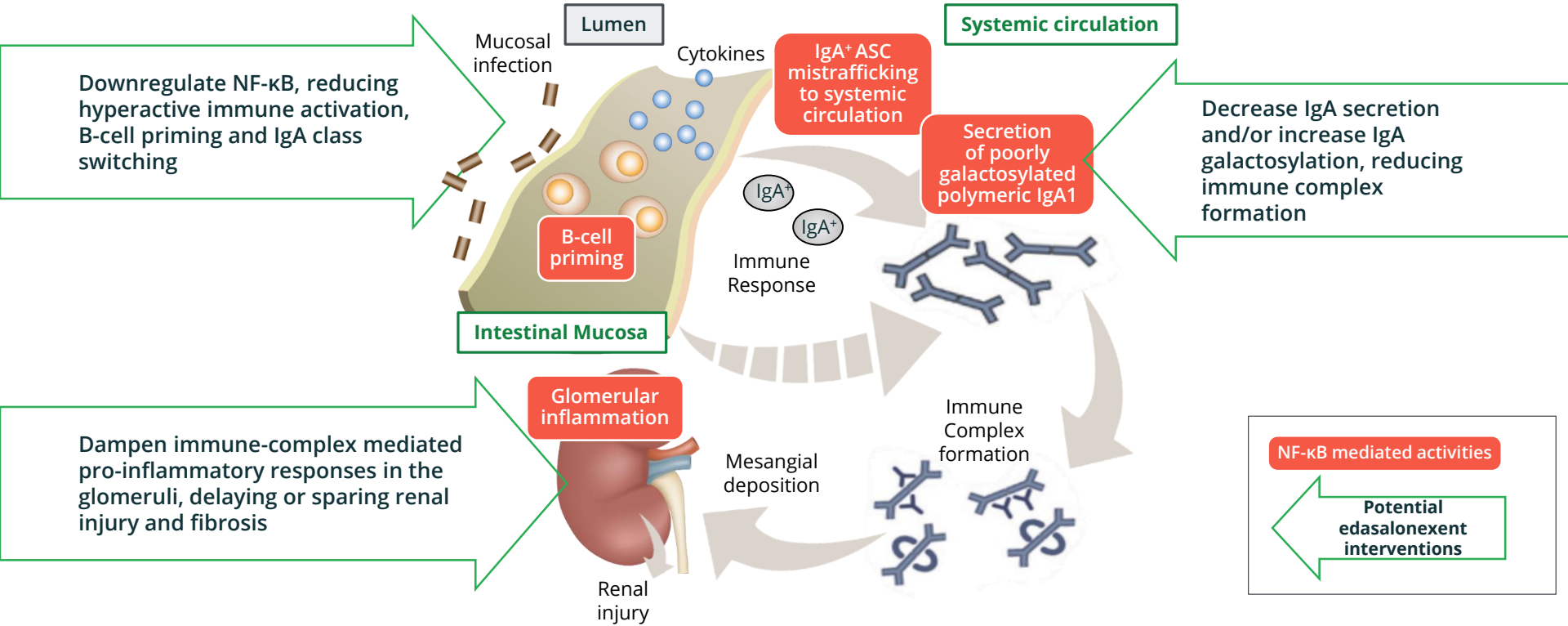
Degeneration

MuRF1/MAFbx

Edasalonexent Inhibits the Pathogenic Role of Activated NF-κB in Muscle Diseases



NF-κB in IgA Nephropathy



Edasalonexent

Inhibition of NF-κB for the Treatment of Duchenne Muscular Dystrophy and Additional NF-κB mediated Diseases

CAT-4001

Inhibition of NF-κB and Activation of Nrf2 to Reduce Neuroinflammation for the Treatment of Neurodegenerative Diseases

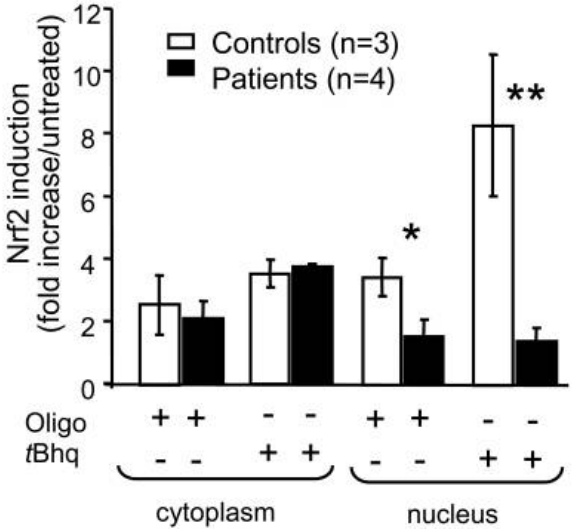
CAT-5571

Inhibition of Transglutaminase 2 and Activation of AMPK to Activate Autophagy for the Treatment of Cystic Fibrosis

Nrf2 and NF-κB: Key Modulators of Neuroinflammation

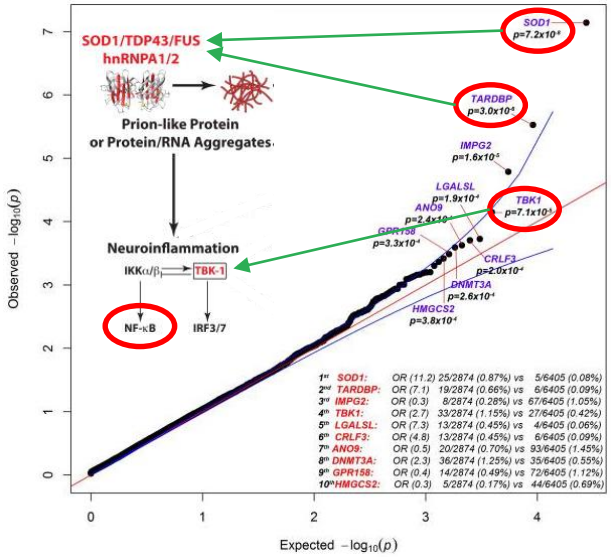
Insufficient Nrf2 activation is implicated in the pathophysiology of Friedreich's Ataxia

Nrf2 translocation to the nucleus is reduced in fibroblasts from people with Friedreich's ataxia



Modified from: Paupe et al, PLoSOne, 2009

NF-κB is a central pathway that is affected in ALS leading to motor neuron damage

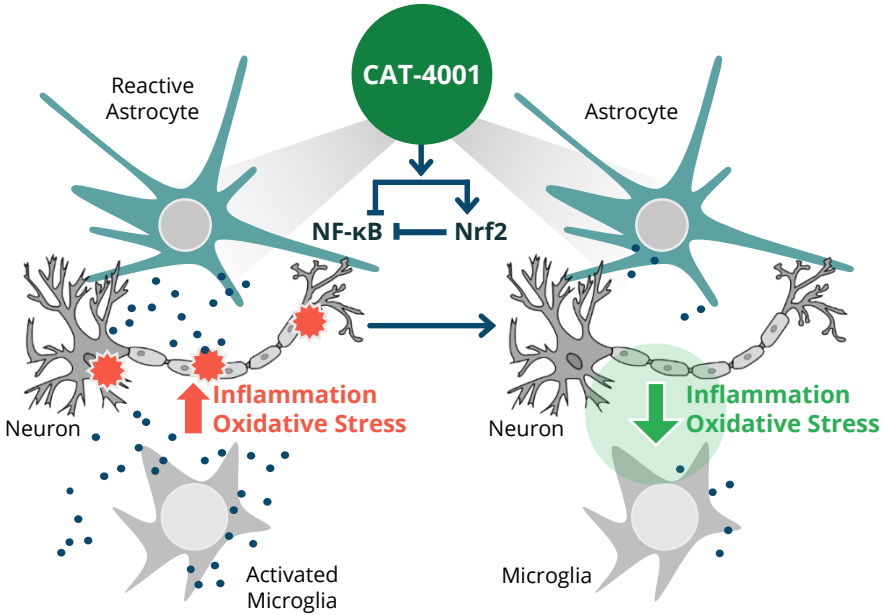


Mutations in several genes that lead to activation of NF-κB were identified in a GWAS study on people with ALS

Modified from: Cirulli et al, Science, 2015

CAT-4001

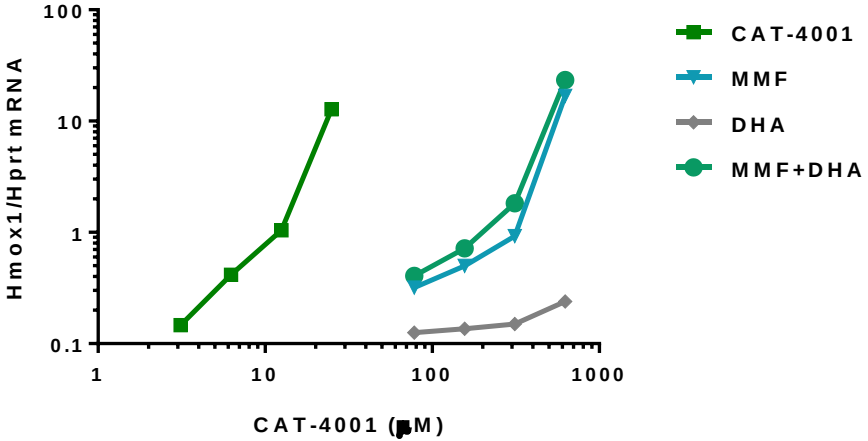
- **Friedreich's ataxia (FA)**
  - Debilitating life-shortening degenerative neuro-muscular disorder resulting in ataxia, fatigue, vision and other sensory impairment and potential scoliosis, heart disease and diabetes
  - Caused by a defect in the frataxin gene; neuroinflammation believed to be involved
  - CAT-4001 research in FA supported by a grant from the Friedreich's Ataxia Research Alliance



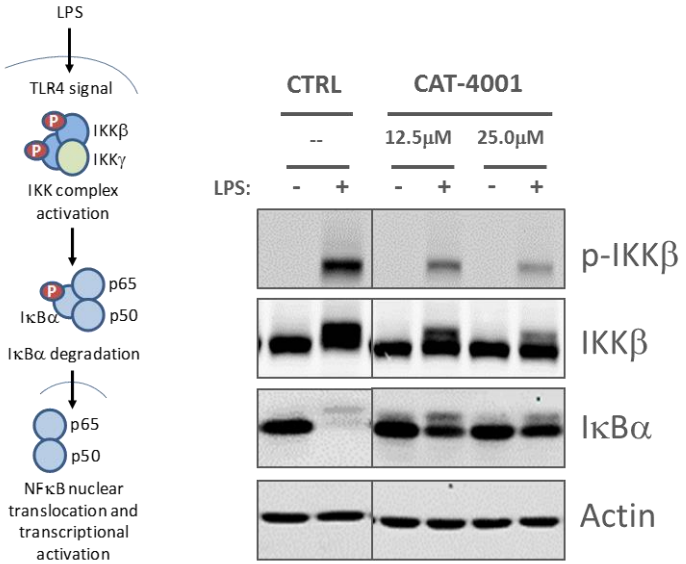
- **Amyotrophic lateral sclerosis (ALS)**
  - Progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord leading to muscle weakness, gradual loss of motor function and, eventually, death
  - Exact etiology unknown; NF-κB and neuroinflammation believed to be involved
  - Preclinical studies being conducted with ALS Therapy Development Institute

CAT-4001 Inhibits NF-κB and Activates Nrf2 *In Vitro*

Nrf2 Activation in THP-1 Cells



LPS-Stimulated THP-1 Human Monocytes

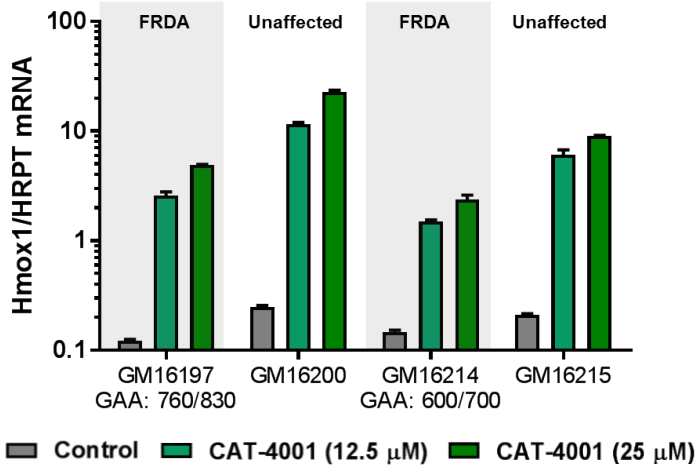


CAT-4001 **activates** Nrf2 with a greater potency than its component bioactives

CAT-4001 **inhibits** signaling events that activate NF-κB

CAT-4001 Inhibits NF-κB and Activates Nrf2 in Patient Cells

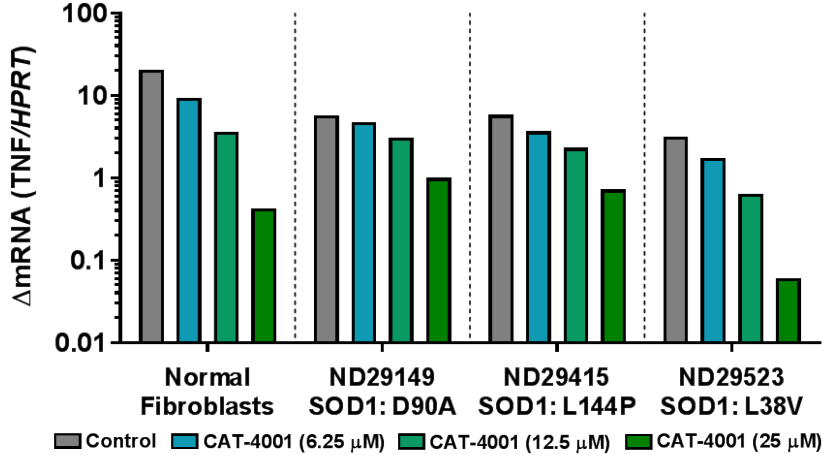
Nrf2 Activation in Cells from People with Friedreich's Ataxia



Data are mean ± SD of duplicate determinations
FRDA mutant (GM16197 and GM16214) or unaffected/het parent (GM16200 and GM16215) lymphoblastoid cell lines treated with CAT-4001 for 6hr

Nrf2 activation by CAT-4001 across different GAA-repeat lengths found in FRDA

NF-κB inhibition in LPS-stimulated Cells from People with ALS

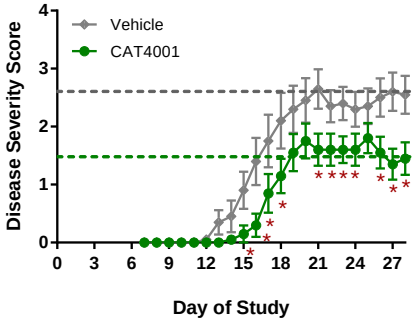


Fibroblasts from healthy volunteers or people with ALS were treated with CAT-4001 for 3h prior to stimulation with LPS for 2h

NF-κB inhibition by CAT-4001 across different SOD1 mutations found in ALS

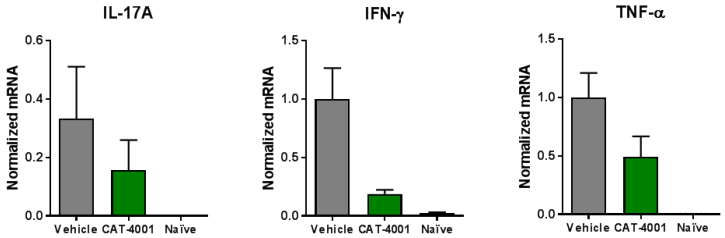
CAT-4001 Effects in *In Vivo* Models of Neuroinflammation

EAE Disease Progression

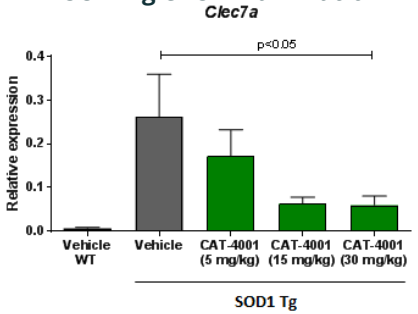


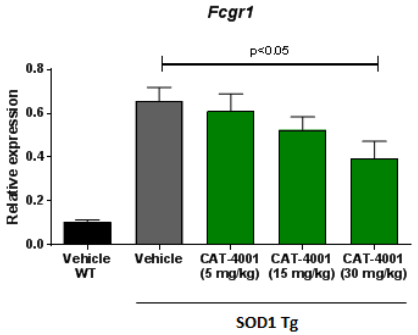
*p<0.05 severity score of CAT4001 300 mg/kg relative to vehicle

EAE CNS Inflammation



SOD1Tg CNS Inflammation





CAT-4001 reduces disease severity and CNS inflammation in the mouse EAE model of multiple sclerosis

CAT-4001 reduces CNS inflammation in the SOD1 Tg mouse model of ALS

Edasalonexent

Inhibition of NF-κB for the Treatment of Duchenne Muscular Dystrophy and Additional NF-κB mediated Diseases

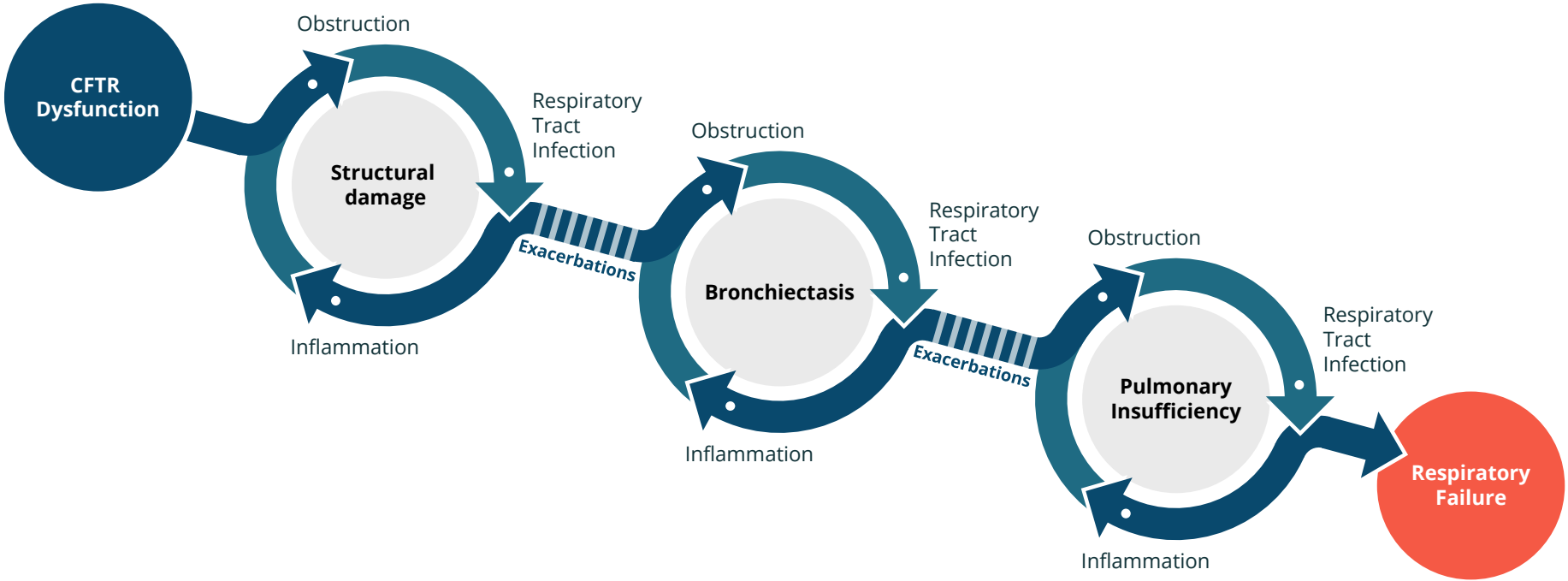
CAT-4001

Inhibition of NF-κB and Activation of Nrf2 to Reduce Neuroinflammation for the Treatment of Neurodegenerative Diseases

CAT-5571

Inhibition of Transglutaminase 2 and Activation of AMPK to Activate Autophagy for the Treatment of Cystic Fibrosis

CF Progression: The Infection, Inflammation, Obstruction Spiral



Autophagy

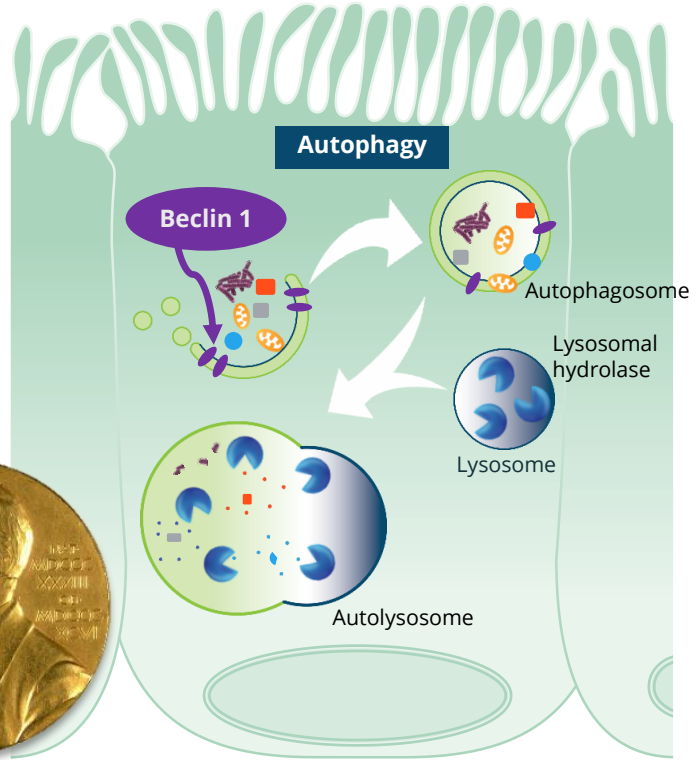
- **Endogenous mechanism for the orderly degradation and recycling of cellular components**
- **Involved in clearance of intracellular and phagocytosed pathogens**
- **Alterations in autophagy are thought to underlie the aging process and play a role in multiple diseases, including:**
  - Cystic fibrosis
  - Parkinson's disease
  - Huntington's disease
  - Amyotrophic lateral sclerosis
  - Systemic lupus erythematosus
  - Asthma
  - Paget's disease of bone
  - Various cancers


THE WALL STREET JOURNAL.

WORLD

Nobel Prize in Medicine Awarded to Japan's Yoshinori Ohsumi

Prize awarded for discoveries related to orderly degradation and recycling of cellular components

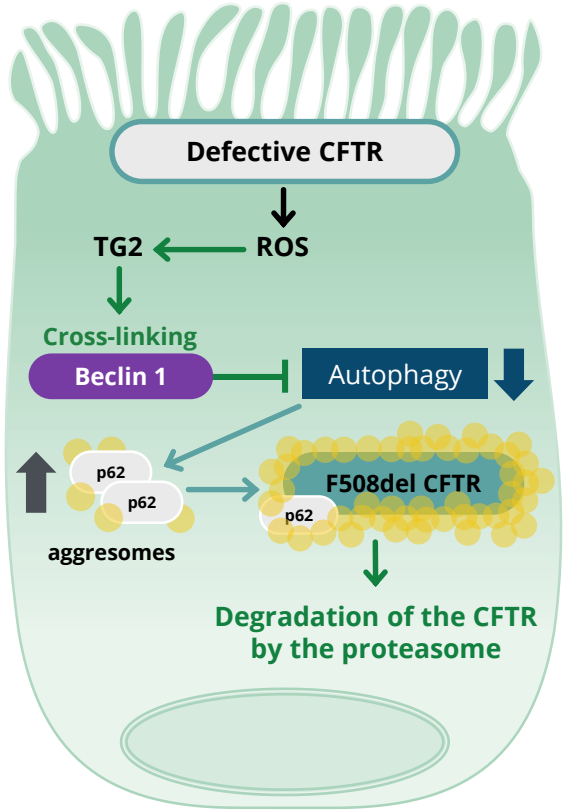


Autophagy: An Approach for the Treatment of CF

In CF, a defective CFTR induces an increase in the level of reactive oxygen species (ROS)

This triggers a cascade of biochemical events which causes the cross-linking of Beclin 1 by transglutaminase 2

Depressed autophagy causes an accumulation of the autophagy substrate p62, which traps the CFTR and prevents its trafficking to the cell surface

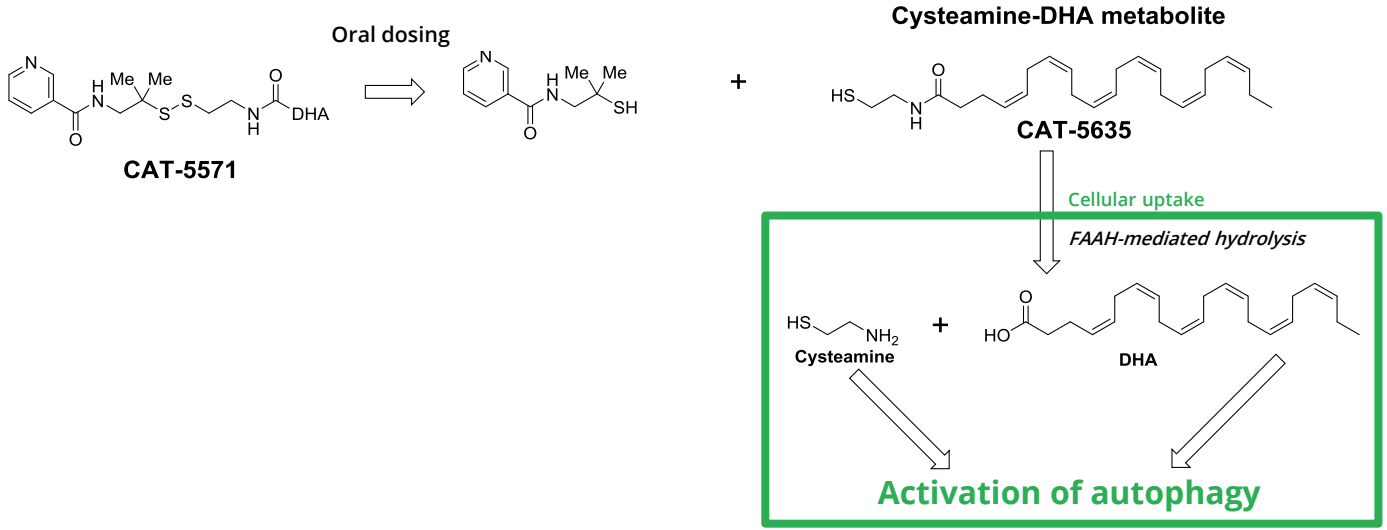


Hypothesis

CAT-5571 activates autophagy, which reduces p62 and allows the trafficking of the CFTR to the cell surface

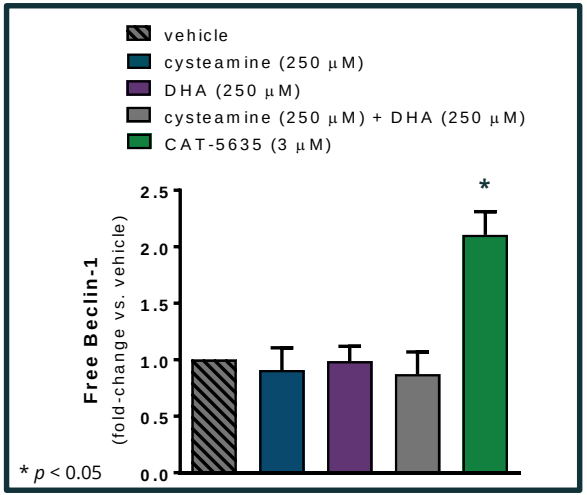
CAT-5571 Synergistically Activates Autophagy

- **Independent but intersecting pathways to modulate autophagy**
  - Cysteamine inhibits transglutaminase 2
  - DHA activates AMPK
- **Synergy allows the fatty acid cysteamine conjugate to activate autophagy at lower concentration than the individual components or a combination of the individual components**

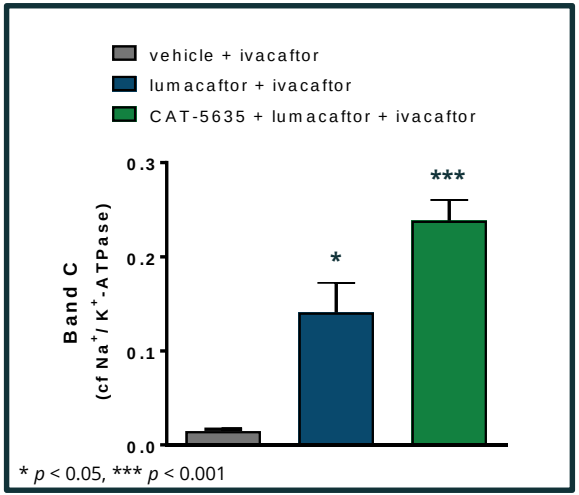


CAT-5571's Active Metabolite Activates Autophagy and Increases CFTR Function in Human F508del Cells

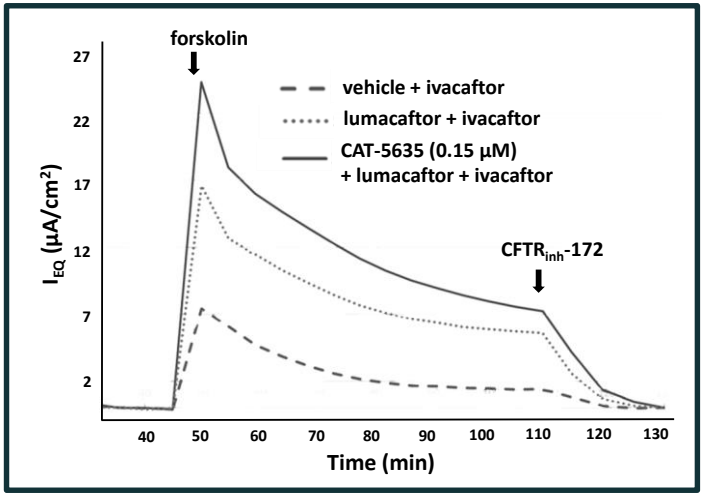
CAT-5571's active metabolite synergistically activates autophagy in homozygous F508del hBE cells



CAT-5571's active metabolite increases cell surface trafficking of CFTR homozygous F508del hBE cells

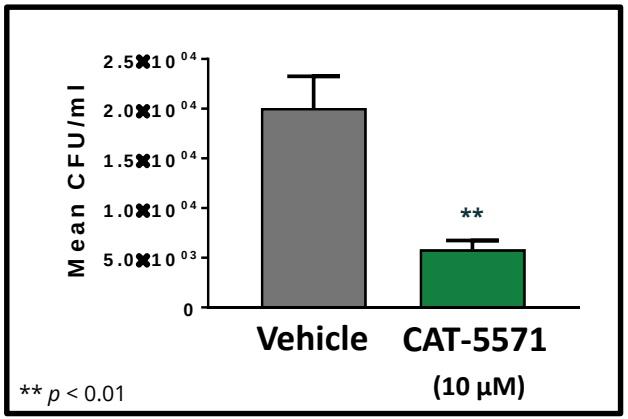


CAT-5571's active metabolite improves CFTR function in homozygous F508del hBE cells

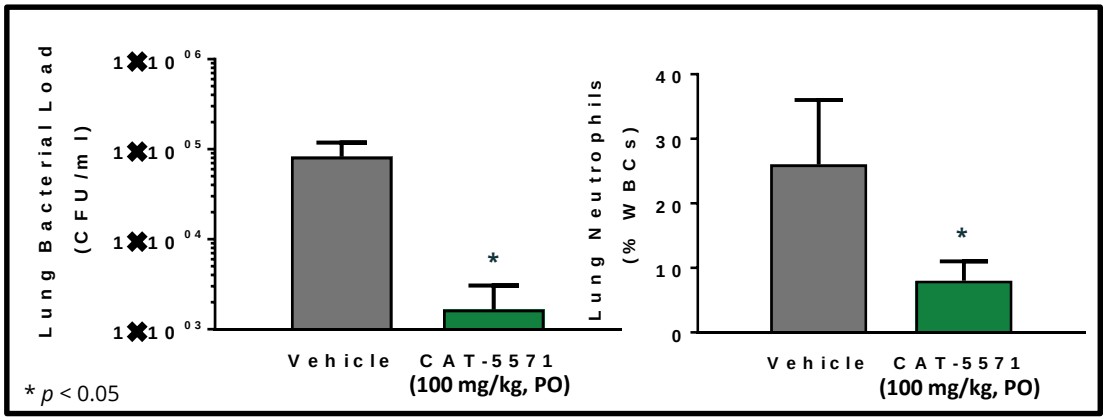


In Vitro and In Vivo Efficacy of CAT-5571: Activation of Autophagy and Bacterial Clearance

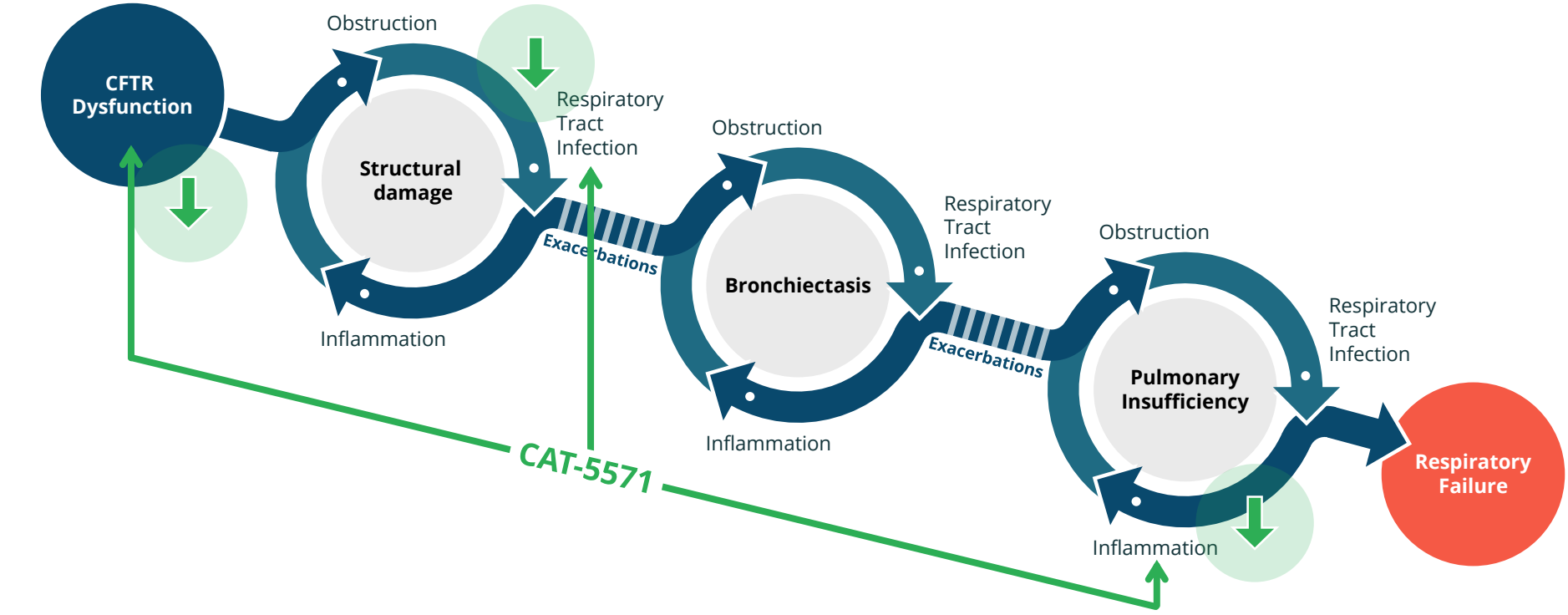
CAT-5571 reduces *P. aeruginosa* bacterial load in homozygous F508del hBE cells



CAT-5571 reduces pulmonary bacterial load and neutrophil infiltration in *P. aeruginosa* lung infection in CFTR Mice



CAT-5571: Breaking the Spiral of CF Progression



We Are Building a Robust Pipeline of Product Candidates in Rare Diseases

Product Candidate (Pathway)	Potential Indications	Discovery	Preclin	Ph 1	Ph 2	Ph 3
Edasalonexent CAT-1004 (NF-κB)	Duchenne muscular dystrophy					
Edasalonexent CAT-1004 (NF-κB)	Additional rare disease					
CAT-4001 (Nrf2/NF-κB)	Friedreich's ataxia ALS					
CAT-5571 (Autophagy)	Cystic fibrosis					

- **Ongoing preclinical research for CAT-4001 in FA and ALS in 2017**
- **Initiate Phase 1 trial for CAT-5571 in CF in Q4 2017 or Q1 2018**

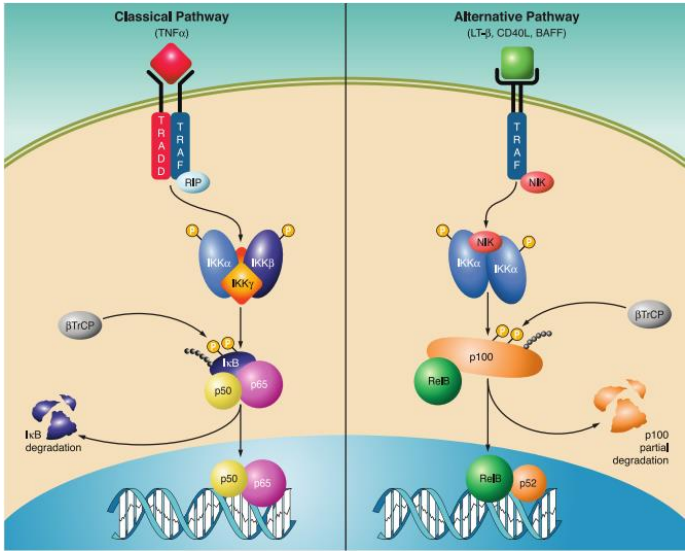
Edasalonexent (CAT-1004): Mechanistic Rationale and Preclinical Proof of Concept in DMD

H. Lee Sweeney, PhD
Director, UF Myology Institute
Department of Pharmacology & Therapeutics
College of Medicine
University of Florida

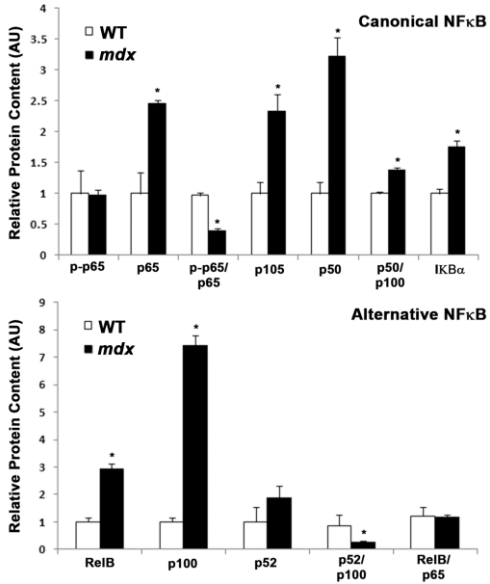
Disclosure

- **Conflict of interest: consultant for Catabasis Pharmaceuticals**

NF-κB Is Chronically Activated in DMD



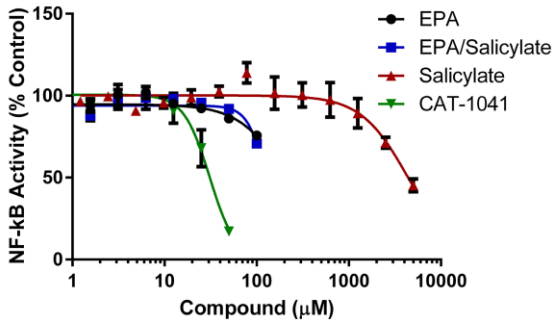
- **Activation of inflammatory genes**
- **Pro-survival system when transient**
- **Chronic activation in pathological conditions**

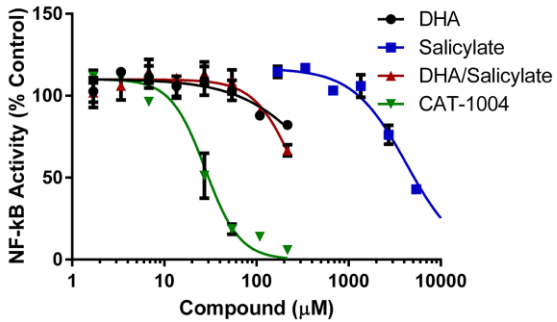


Components of classical (canonical) and alternative (non-canonical) pathways elevated in *mdx* muscle

Hammers et al., JCI Insights, in press

Edasalonexent (CAT-1004) and CAT-1041 are Novel Inhibitors of NF-κB

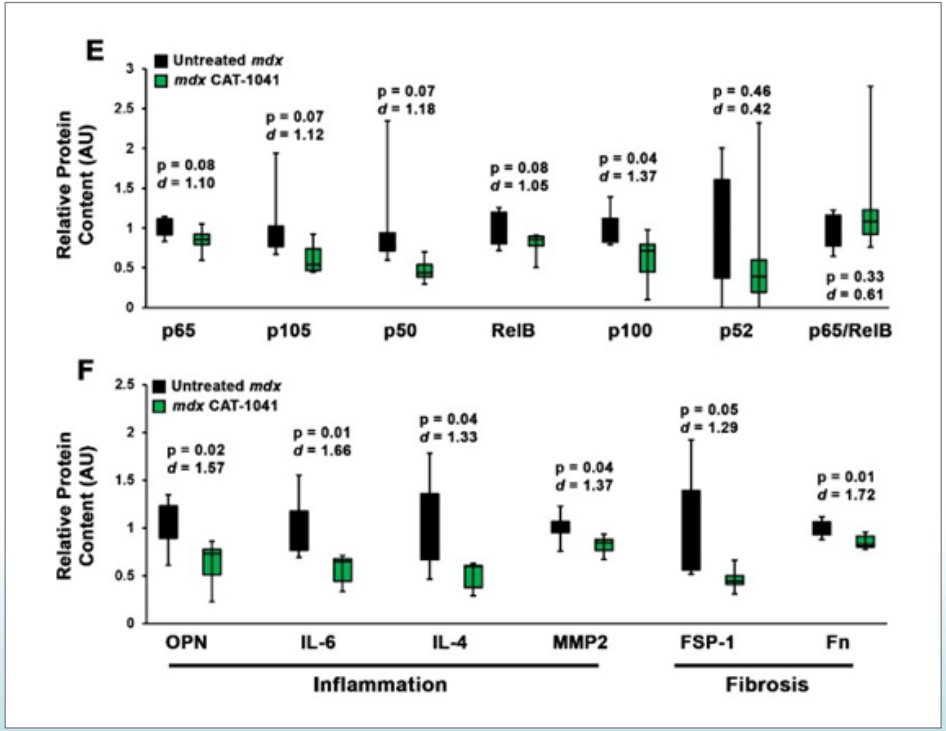




CAT-1041 was used in preclinical experiments as a proxy for CAT-1004, which was in Phase 1 trials

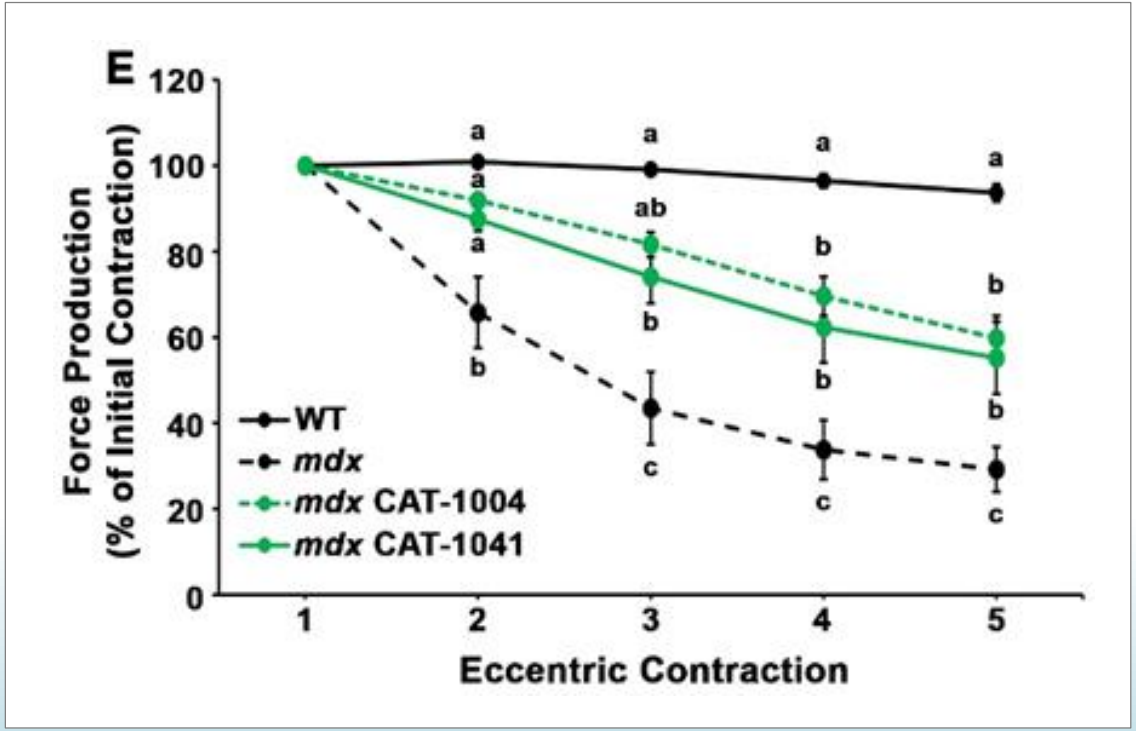
Hammers et al., JCI Insights, in press

Decreased NF-κB, Inflammation and Fibrosis with CAT-1041



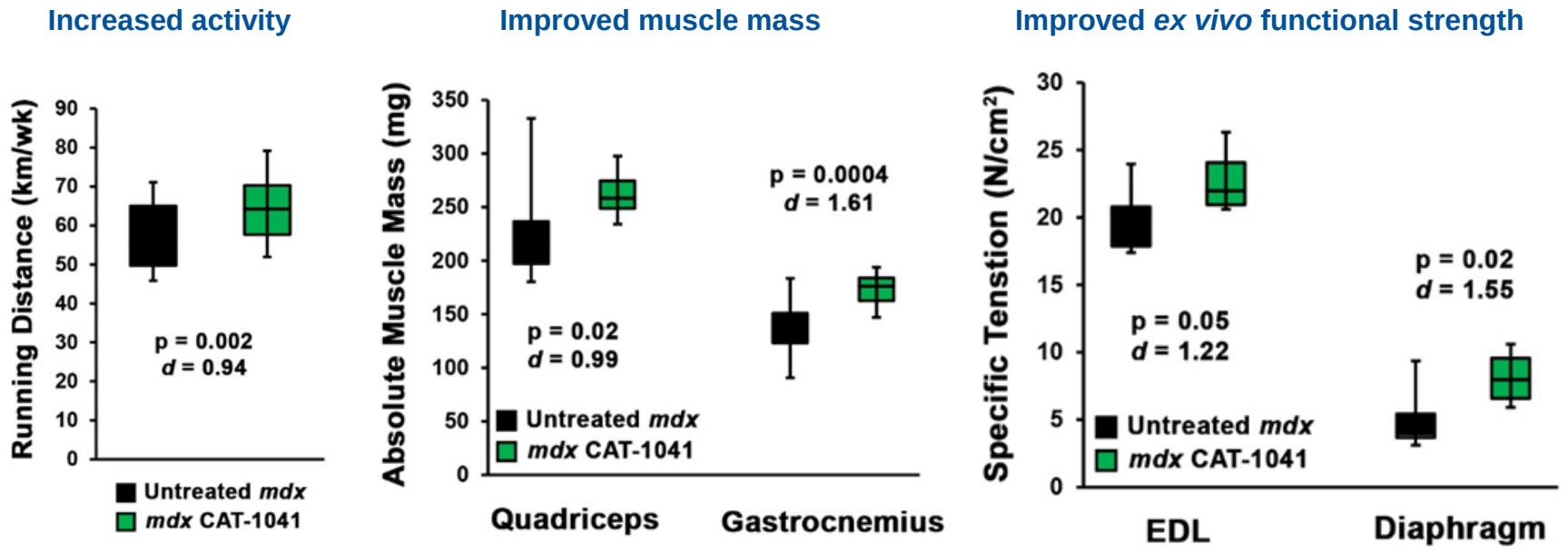
Hammers et al., JCI Insights, in press

CAT-1004 and CAT-1041 Afford Protection of *mdx* Muscle from Contraction-induced Injury



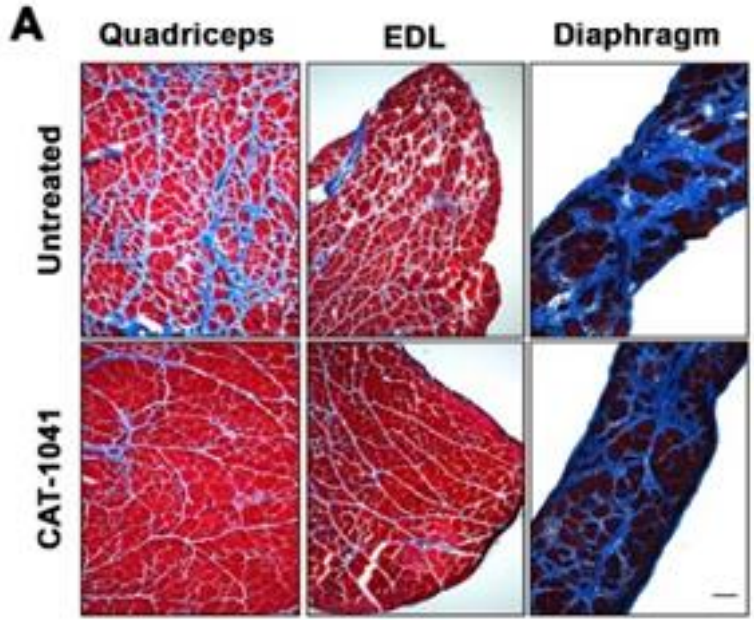
Hammers et al., JCI Insights, in press

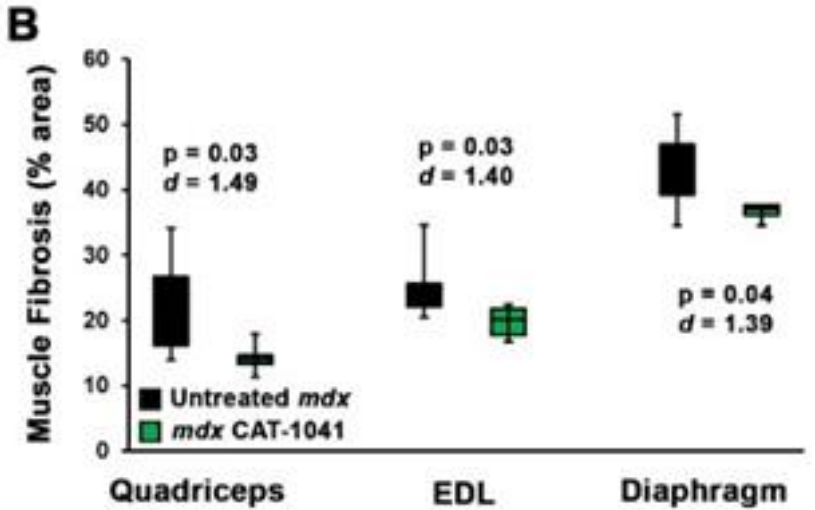
CAT-1041 Improves Exacerbated *mdx* Phenotype: Limb and Diaphragm



Hammers et al., JCI Insights, in press

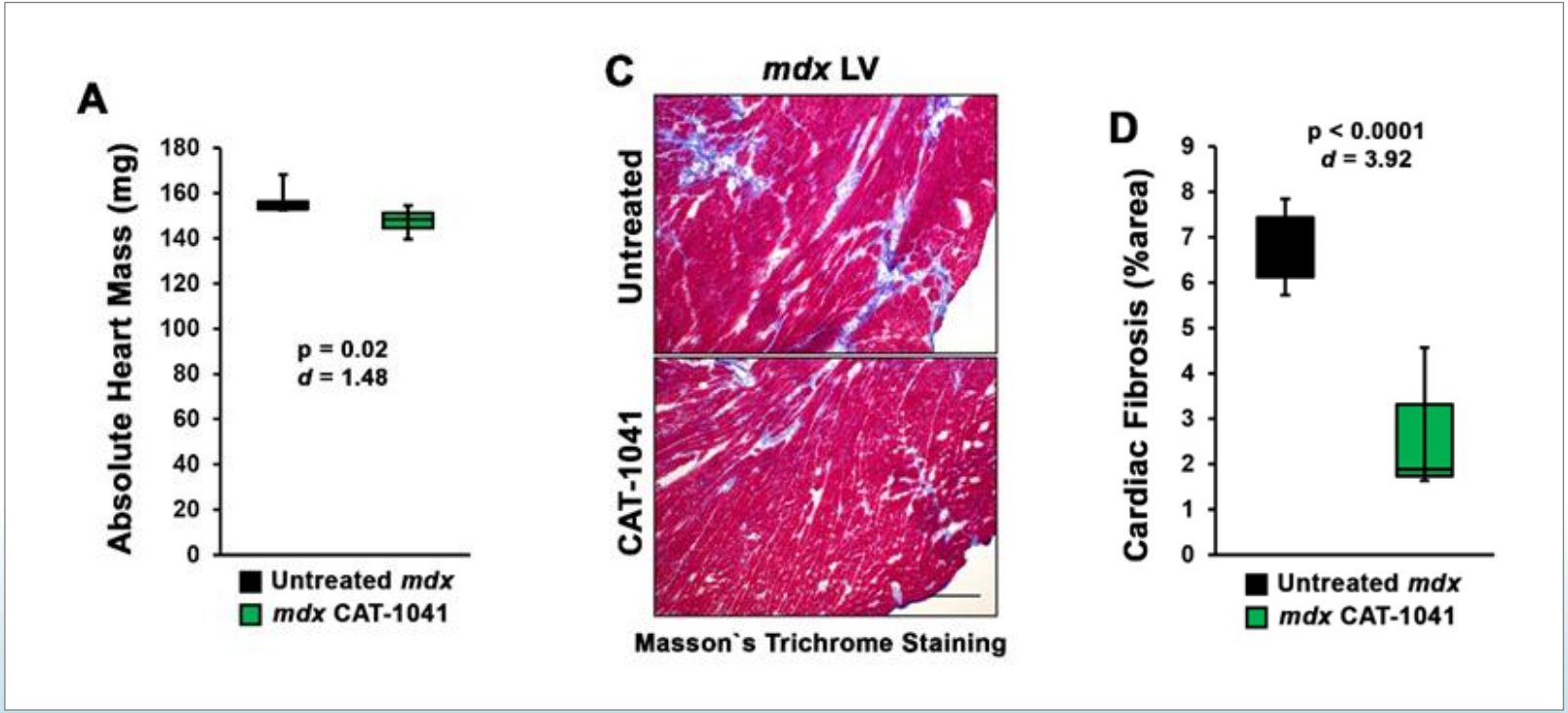
CAT-1041 Improves Exacerbated *mdx* Phenotype: Fibrosis in Limb and Diaphragm





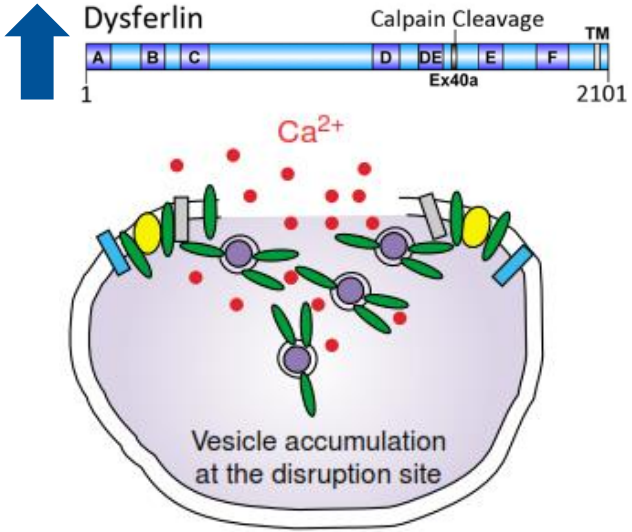
Hammers et al., JCI Insights, in press

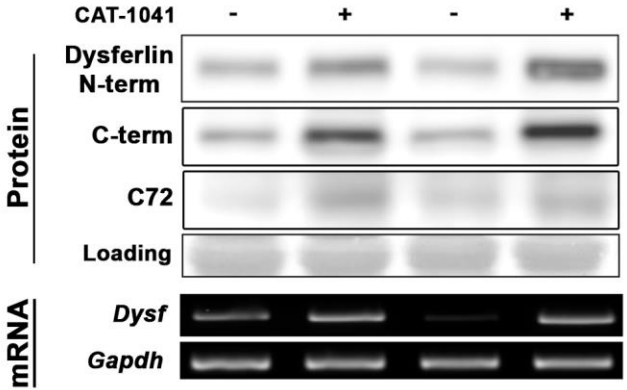
CAT-1041 Improves Exacerbated *mdx* Phenotype: Cardiac Effects

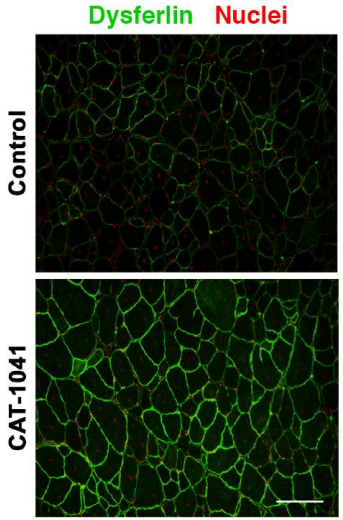


Hammers et al., JCI Insights, in press

Membrane Repair Protein, Dysferlin, Is Increased by CAT-1041





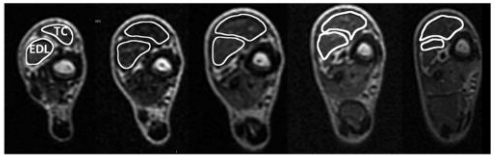


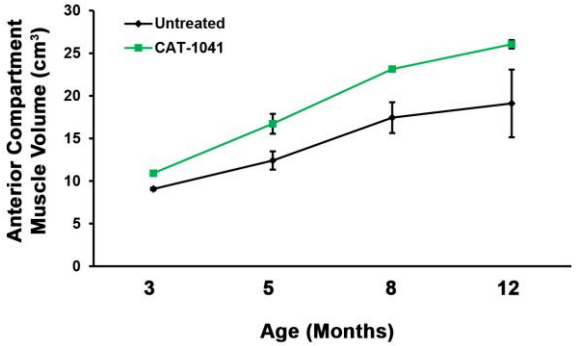
Dysferlin is a disease modifier

Hammers et al., JCI Insights, in press

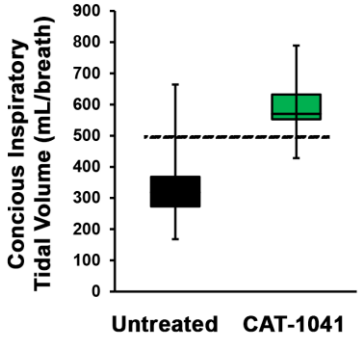
CAT-1041 Improves GRMD Phenotype: Hind Limb Muscle Mass and Diaphragm Function

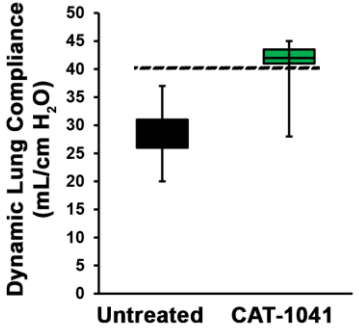
Improved hind limb muscle mass





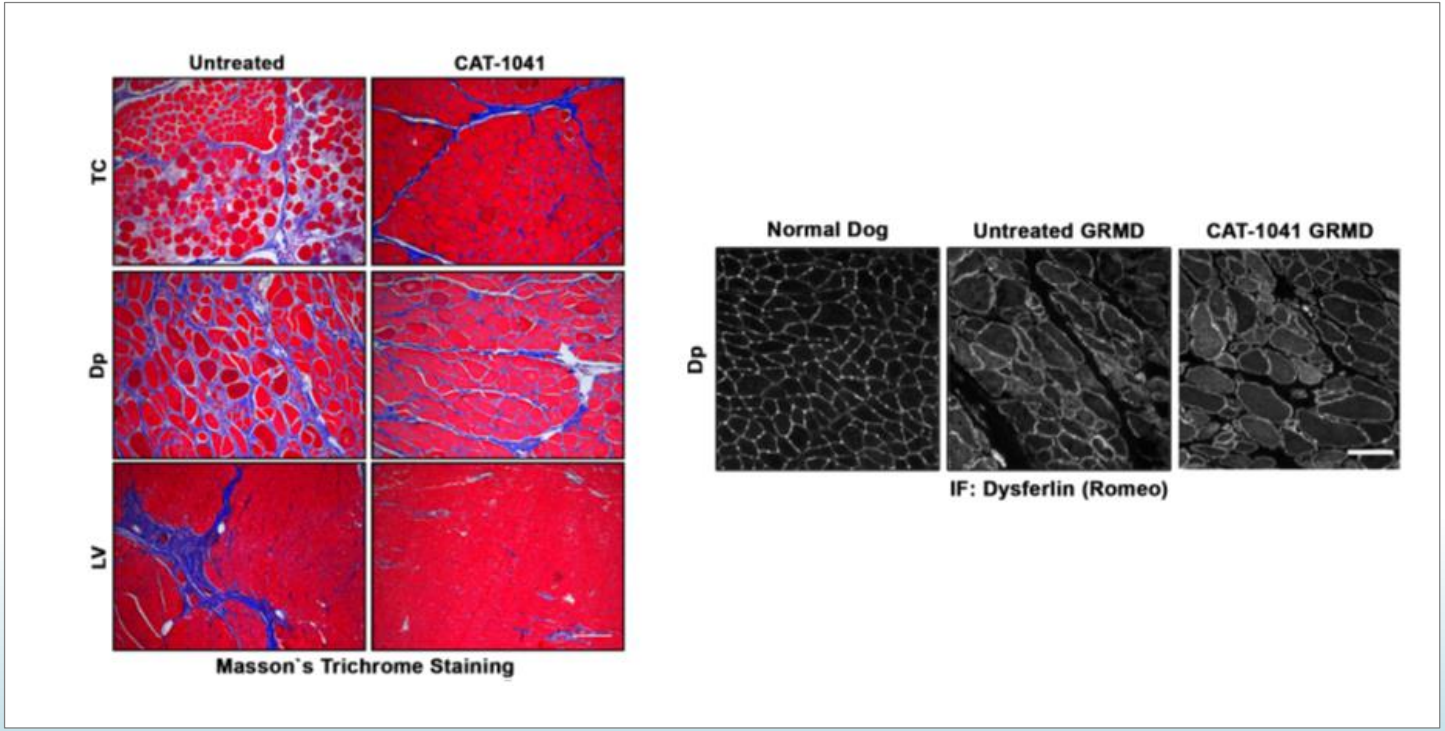
Improved diaphragm function





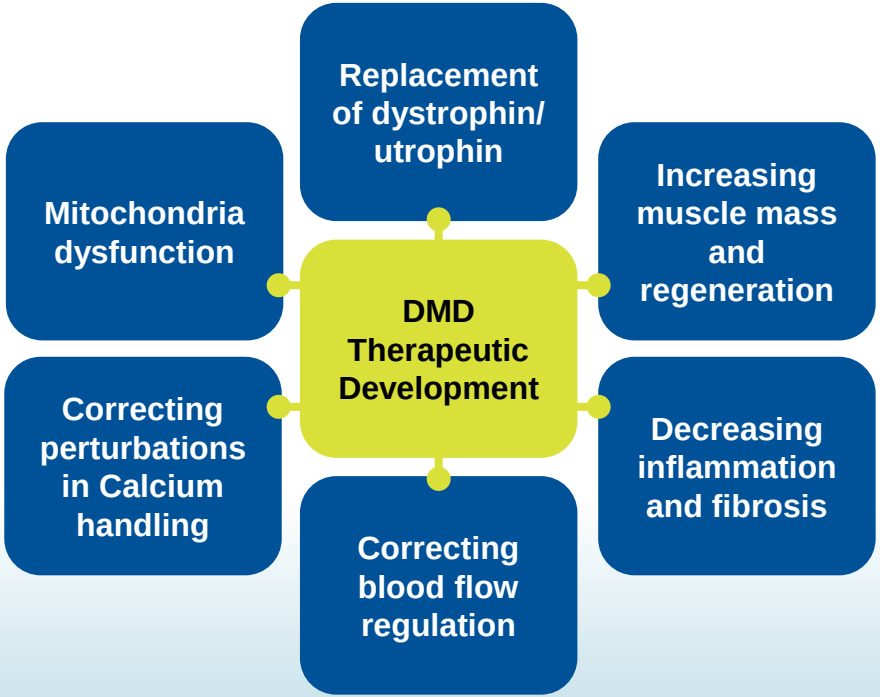
Hammers et al., JCI Insights, in press

CAT-1041 Improves GRMD Phenotype: Decreased Fibrosis, Increased Dysferlin



Hammers et al., JCI Insights, in press

Potential for Combination Treatments in DMD



- Six categories for therapeutic targets for DMD
- One addresses primary genetic defect; rest address downstream aspects of the pathogenesis
- Targeting any single pathway may be an approvable monotherapy
- Future treatment paradigm may involve targeting multiple pathways to have greater patient impact

Summary of Preclinical Studies

- **Activated NF-κB plays a central role in DMD pathophysiology driving muscle inflammation, fibrosis and degeneration, and inhibiting muscle regeneration**
- **Edasalonexent (CAT-1004) and CAT-1041 are novel inhibitors of NF-κB with similar activity; CAT-1041 was used in preclinical studies as a close-in analog of edasalonexent**
- **Edasalonexent, or its analog CAT-1041, has shown:**
  - Reduction in NF-κB, inflammation and fibrosis and increase in dysferlin
  - Improvement in *mdx* mouse and golden retriever dog phenotype
  - Benefits in muscle mass and function
  - Effects in limb, diaphragm and heart
- **Potential for edasalonexent as a disease-modifying therapy for DMD as monotherapy or in combination with other approaches**

10 Minute Break

Duchenne Muscular Dystrophy: Clinical Landscape and Natural History

Craig McDonald, MD Professor of PM&R and Pediatrics
Study Chair CINRG Duchenne Natural History Study
University of California

UCDAVIS CHILDREN'S HOSPITAL

Neuromuscular Research Center
Discovering Creates Hope

Disclosures

- **Consulting work on Duchenne muscular dystrophy clinical trials for**
  - Catabasis Pharmaceuticals
  - PTC Therapeutics
  - Sarepta
  - Prosensa
  - Pfizer
  - Eli Lilly
  - Halo Therapeutics
  - Bristol Myers Squib
  - Novartis
  - Italfarmaco
  - Mitobridge
  - Cardero Therapeutics
  - Gilead
  - Marathon

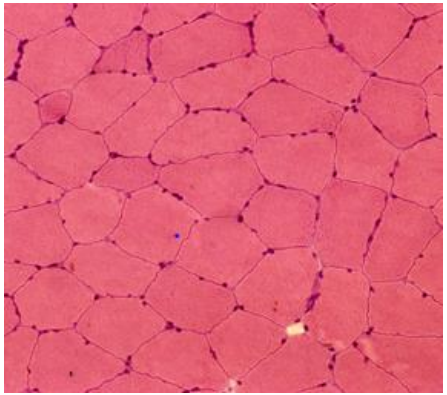
Outline

- **DMD Natural History**
- **Current Care**
- **Clinical End Points**
  - 6-Minute Walk Test (6MWT)
  - Timed Function Tests (TFTs)
  - Muscle Strength
  - North Star Ambulatory Assessment (NSAA)
  - Pediatric Outcomes Data Collection Instrument (PODCI)
- **Summary**

Duchenne Muscular Dystrophy Is a Devastating Progressive Disease with Significant Unmet Need

- **Rare recessive X-linked disorder caused by mutation in the *DMD* gene**
- **Leads to dystrophin deficiency in muscle tissue and subsequently chronic activation of NF-κB**
- **Progressive disease that leads to devastating deteriorating muscle strength and early death**
- **Only limited treatments are available**
  - Physical therapy
  - Orthopedic surgery for contractures and scoliosis
  - Assisted ventilation
  - Heart failure management (e.g., afterload reduction)
  - Off-label use of corticosteroids
  - Eteplirsen in the US for exon-51 mutations and ataluren in the EU for nonsense mutations

Disease Progression Is Characterized by Muscle Damage and Replacement of Muscle Fibers with Fat Infiltration and Sclerosis, Resulting in Loss of Function



Normal muscle tissue

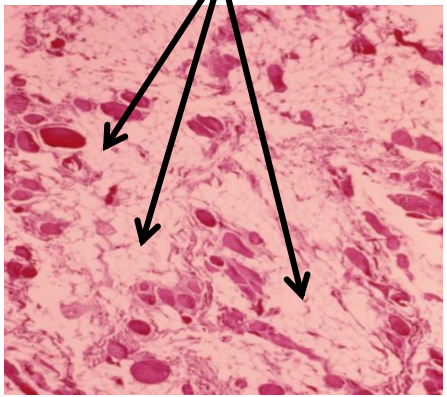
Lack of dystrophin causes shearing of the sarcolemma and activation of NF-κB, increasing cellular damage and muscle fiber loss

Progressive loss of muscle fibers and replacement of functional muscle units by fat infiltration and sclerosis

Loss of function; walking capacity preserved in spite of significant loss of muscle strength due to

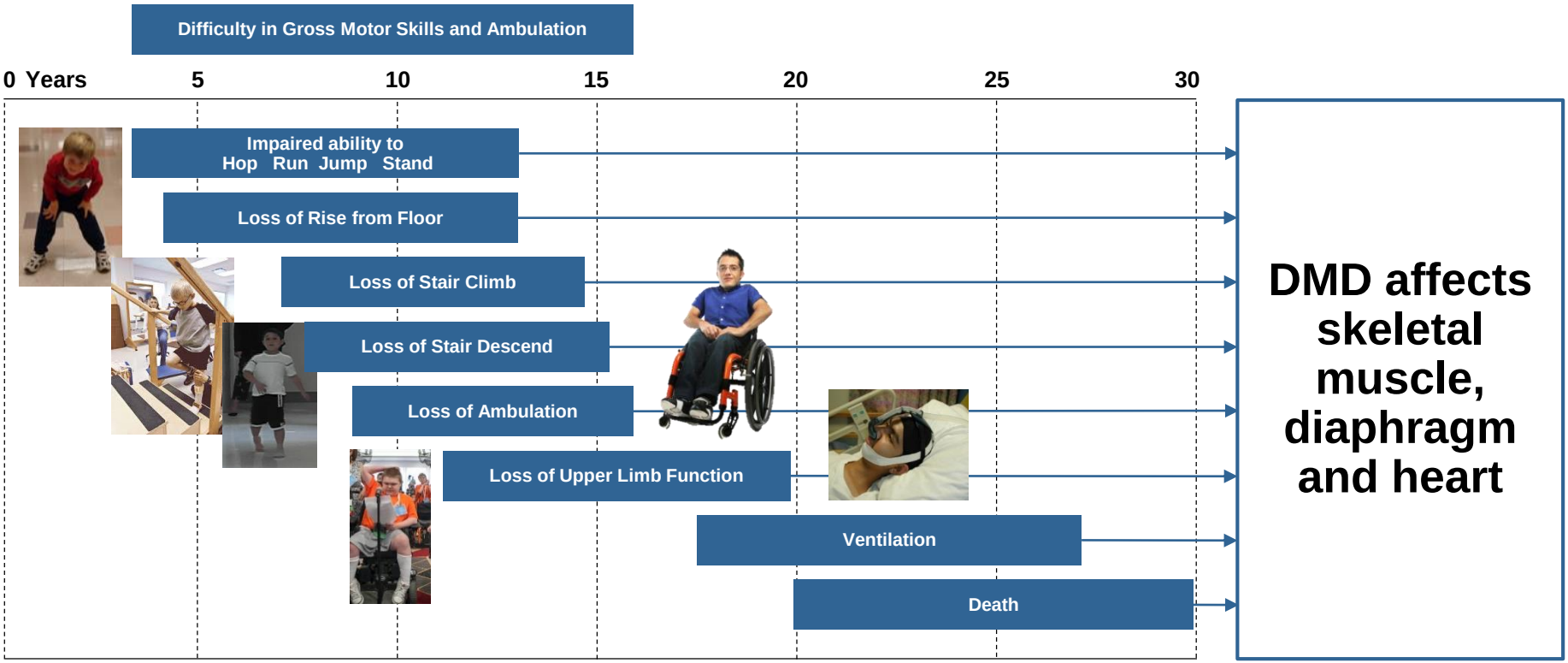
- Reserve capacity in muscle function
- Biomechanical compensations

Fat infiltration, sclerotic changes and loss of muscle fibers



Muscle tissue from 19 year old DMD patient post-mortem

Progressive Loss of Function Is Seen in Skeletal Muscle, Diaphragm and Heart and Results in Premature Death

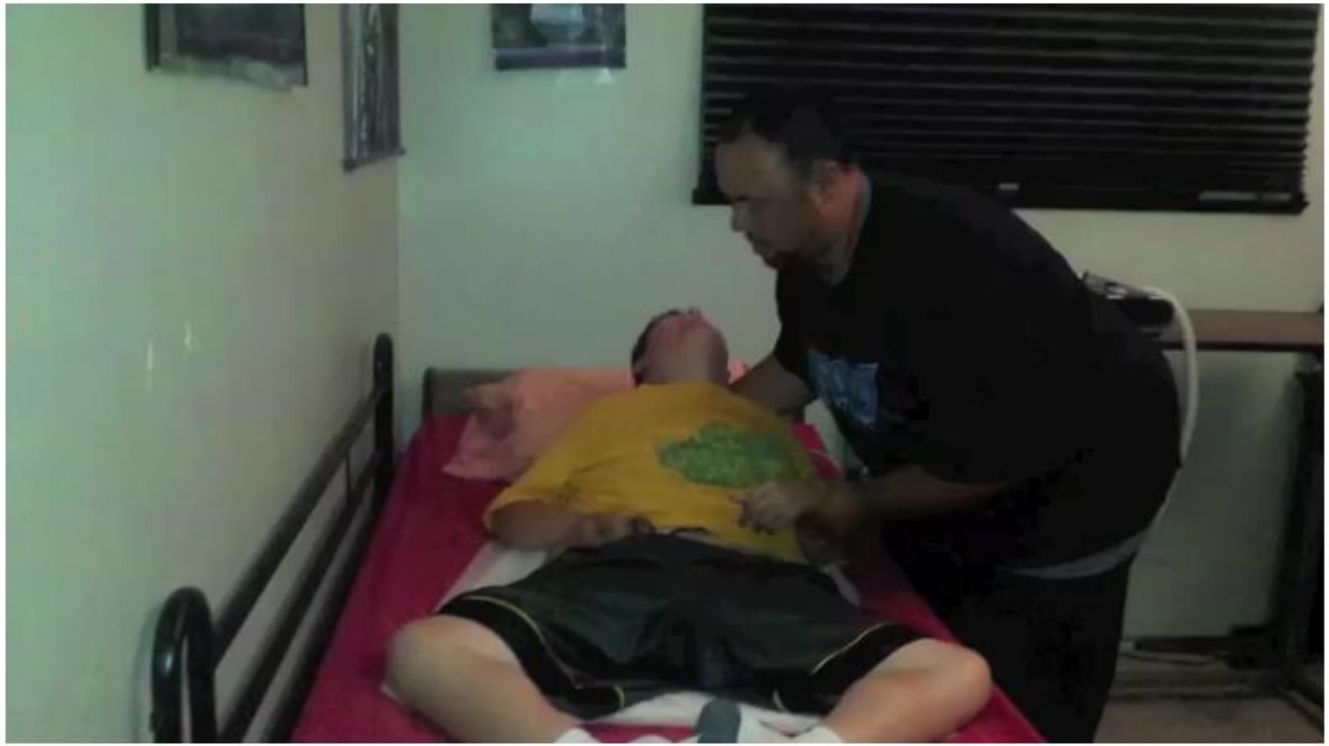


Case Study: Burden of Disease

DMD Patient

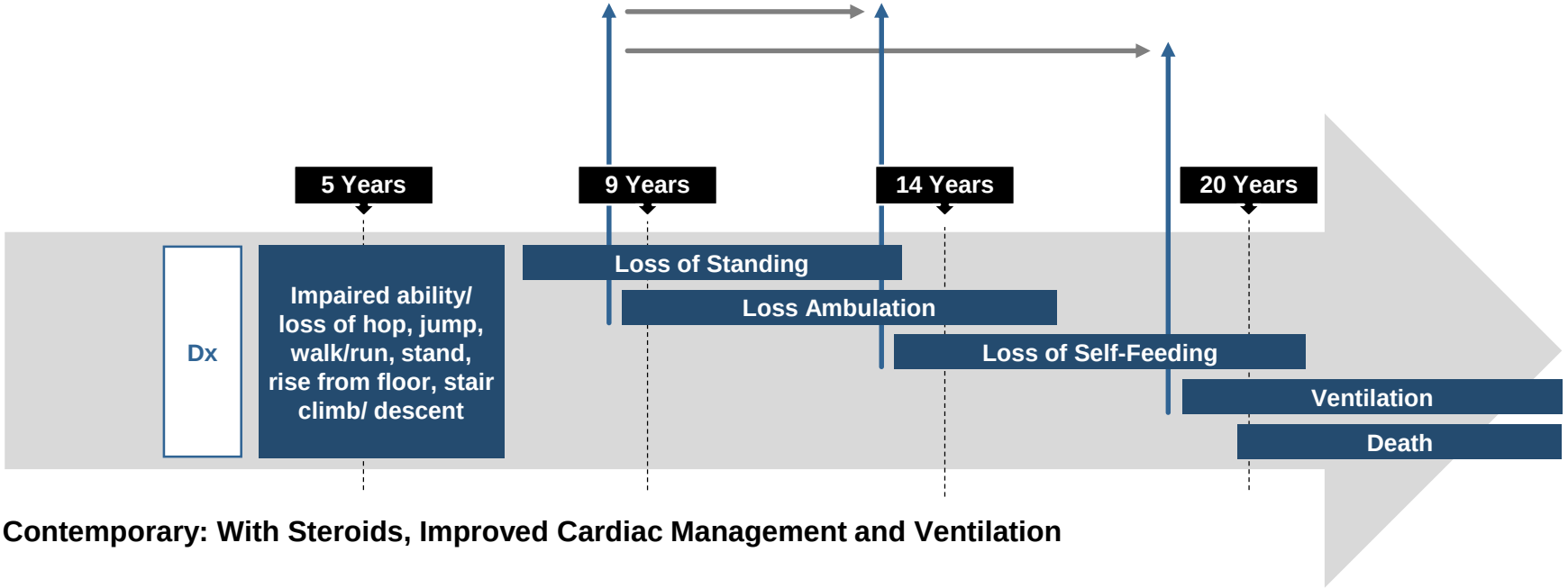
- **Age 9.5**
- **10-meter Walk/Run = 6.5 seconds**
- **6MWD = 330 Meters**

Case Study: Burden of Disease



- Same boy age 17
- Assessment 2015

Schematic of Natural History: DMD Follows a Characteristic Natural Course, with Contemporary Treatment Delaying Loss of Function



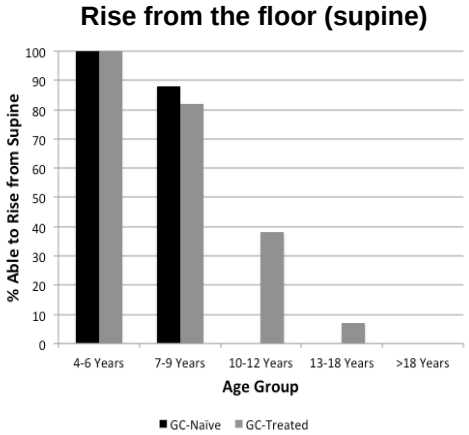
Contemporary: With Steroids, Improved Cardiac Management and Ventilation

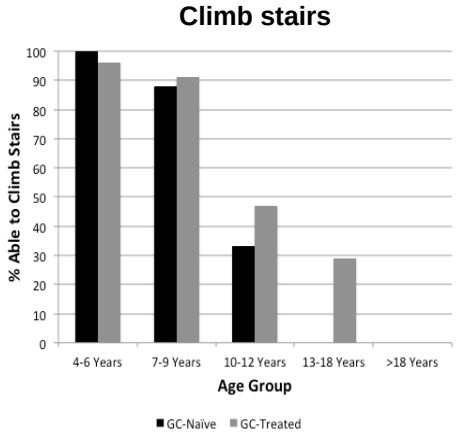
Adapted from Bushby, Connor. Clin Investig (Lond). 2011; McDonald, et al. Muscle Nerve. 2013

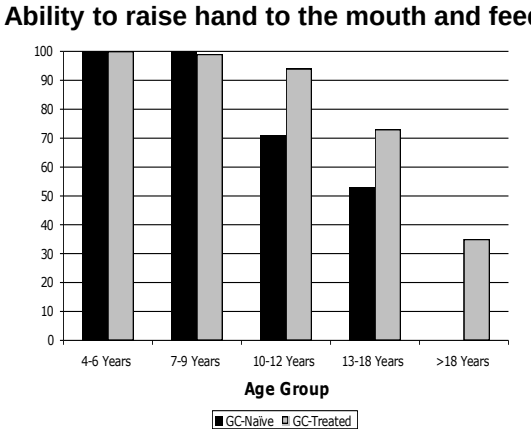
Contemporary Treatments that have Affected the Natural History of Disease Progression and Survival in DMD

1. **Glucocorticoids**
2. **Management of spine deformity**
   - Glucocorticoids
   - Timely spine surgery for curves >30 to 40 degrees
3. **Pulmonary management**
   - Airway clearance strategies/mechanical cough assistance
   - Noninvasive ventilation
4. **Cardiac management**
   - Early afterload reduction (e.g., ACE inhibitors)
   - Recognition and management of heart failure

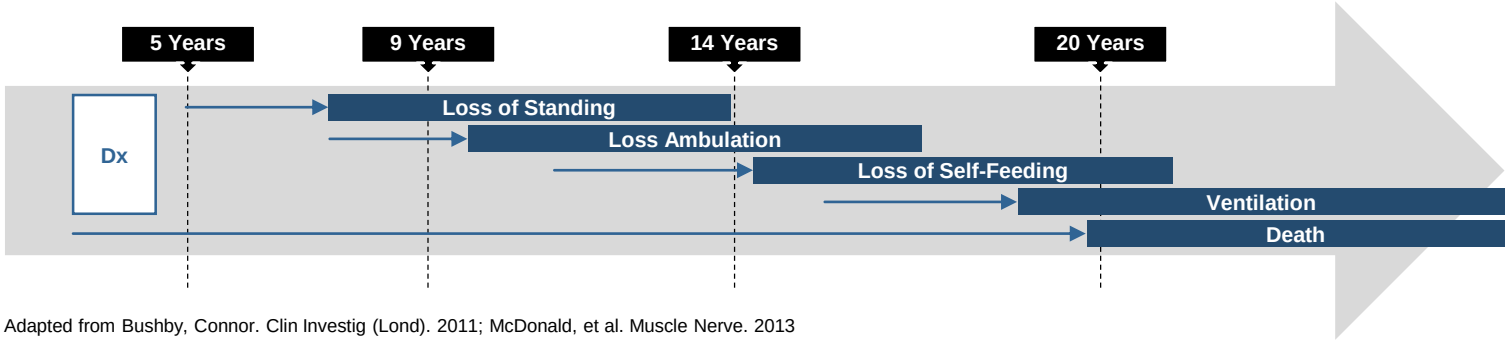
Effect of Glucocorticosteroids on Function







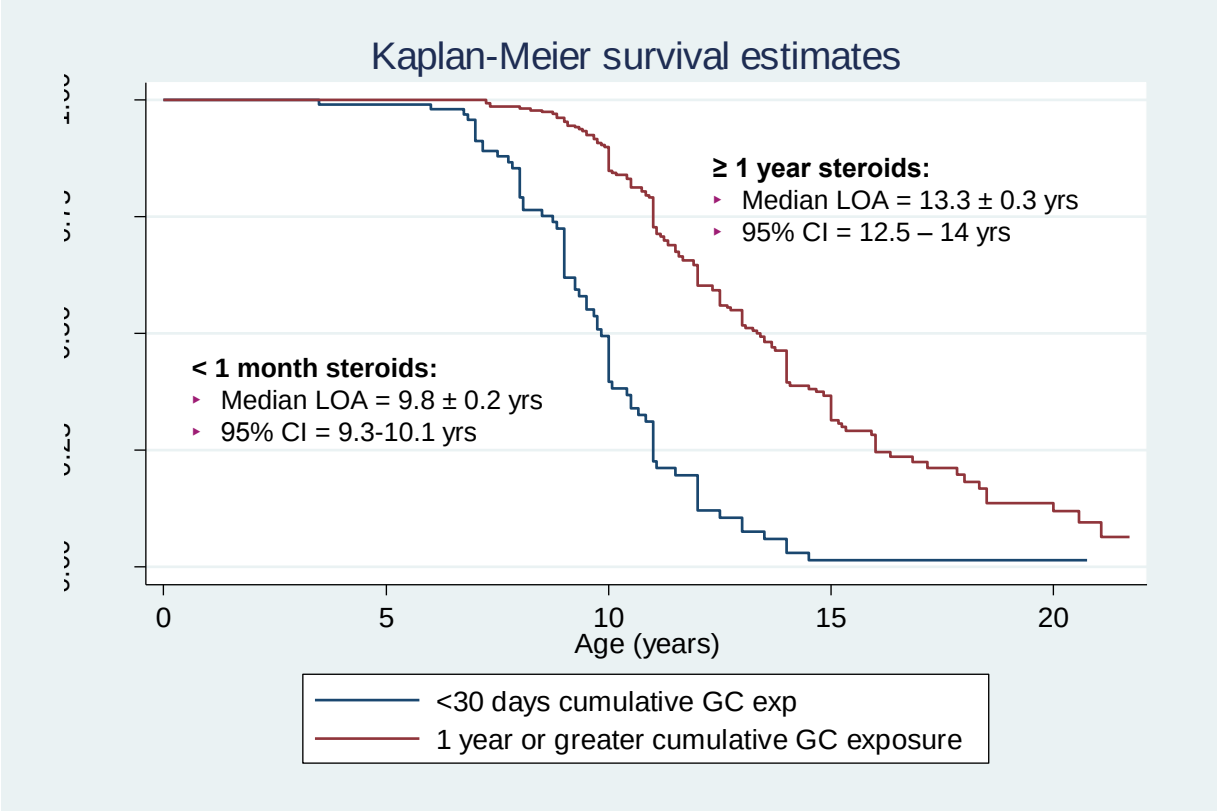
Henricson et al. Muscle & Nerve 2013



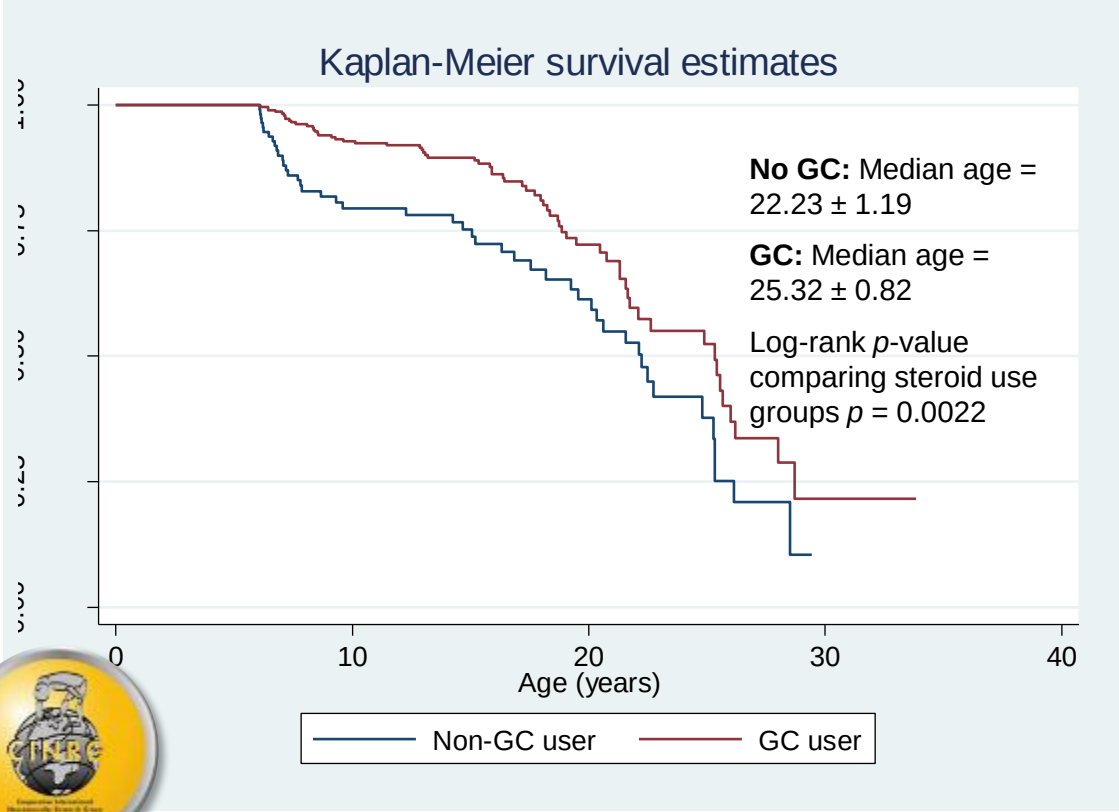
Steroids affect disease progression in DMD over the entire course of the disease, prolonging clinically meaningful functions (time to loss of milestones)

Adapted from Bushby, Connor. Clin Investig (Lond). 2011; McDonald, et al. Muscle Nerve. 2013

Effect of Glucocorticosteroids on Loss of Ambulation (CINRG Data: Loss of Ambulation, All Mutation Subtypes and Steroid Use, N = 309)



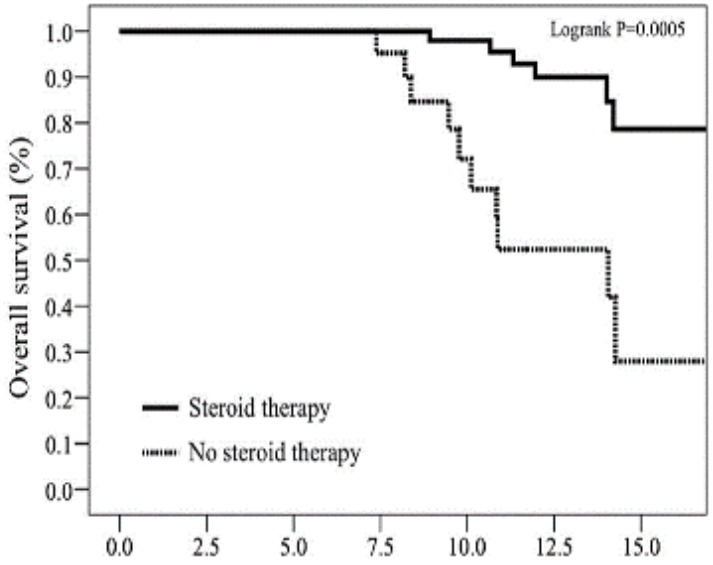
Effect of Glucocorticosteroids on Preserving Lung Function (FVC 1 Liter)



- **K-M curve comparing the time to reaching a FVC of ≤ 1 Liter between those with and without GC**
- **% FVC Related to Survival in DMD**
  - Median survival of 3.1 years and 5-year survival of only 8% when the FVC fell below 1 L (Phillips et al., 2001)
  - Having an FVC less than 1 L remains the best negative predictor of survival in patients with DMD (Finder et al., 2004)
- **Similar results for FVC % Predicted 30%**

Changing Natural History in DMD Over the Last 4 Decades

1980s – Present
Glucocorticoids/Steroids

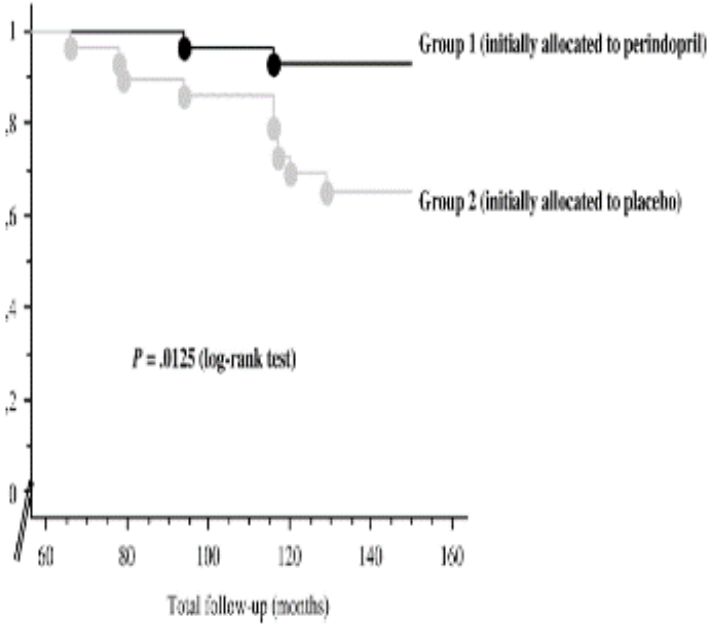


Number at risk

Steroid therapy	63	61	59	53	41	28	3
No steroid therapy	23	23	23	20	11	5	2

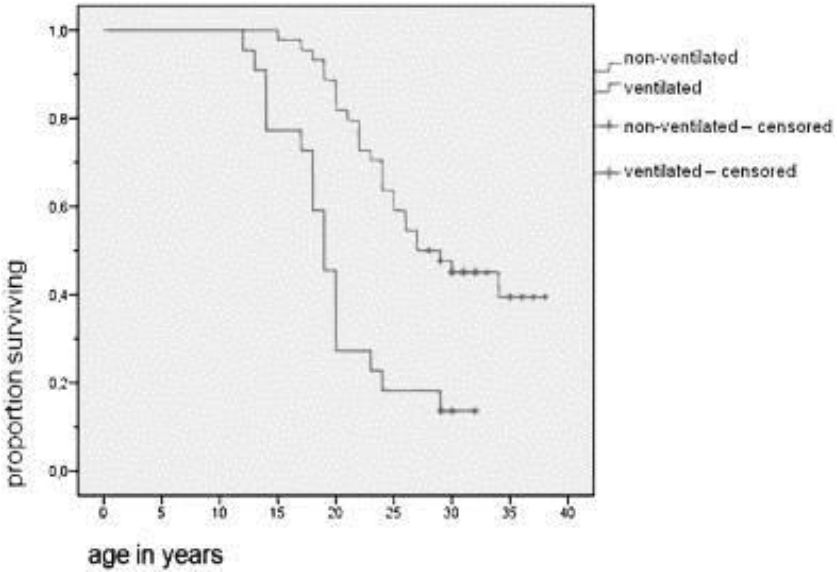
Schram, et al. *J Am Coll Cardiol*. 2013;61(9):948-954.

2000 – Present
Afterload Reduction with ACE Inhibitors



Duboc D, et al. *Am Heart J*. 2007;154(3):596-602.

DMD Survival Affected Primarily by Ventilation



Rall and Grimm: Acta Myol. 2012 Oct;31(2):117-20.

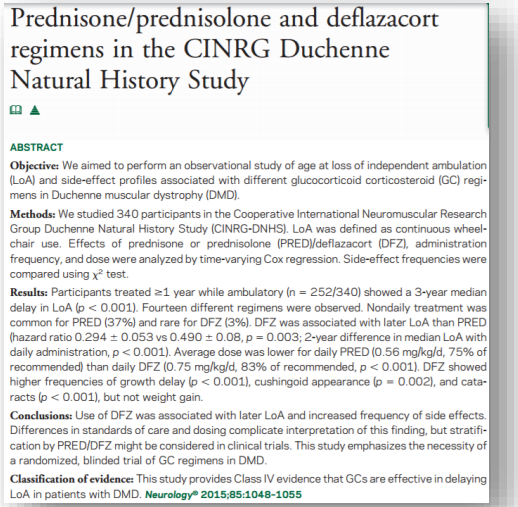
- **Ventilation was recognized as a main intervention affecting survival**
- Ventilated median survival = 27.0 yr
- Without ventilation = 19.0 yr

Passamano, et al. *Acta Myol*. 2012;31(2):121-125.

- **Ventilation was recognized as a main intervention affecting survival**
- Ventilated mean survival = 27.9 yr (range, 23 - 38.6 yr)
- Without ventilation = 17.7 yr (range, 11.6-27.5 yr)

Glucocorticosteroids Have a Significant Adverse Event Profile

- **Weight gain**
- **Cushingoid syndrome**
- **Growth delay**
- **Behavioral changes**
- **Low bone mass density and / or fracture**
- **Cataracts**
- **Skin abnormalities**



Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study

ABSTRACT

Objective: We aimed to perform an observational study of age at loss of independent ambulation (LoA) and side-effect profiles associated with different glucocorticoid corticosteroid (GC) regimens in Duchenne muscular dystrophy (DMD).

Methods: We studied 340 participants in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG-DNHS). LoA was defined as continuous wheelchair use. Effects of prednisone or prednisolone (PRED)/deflazacort (DFZ), administration frequency, and dose were analyzed by time-varying Cox regression. Side-effect frequencies were compared using χ^2 test.

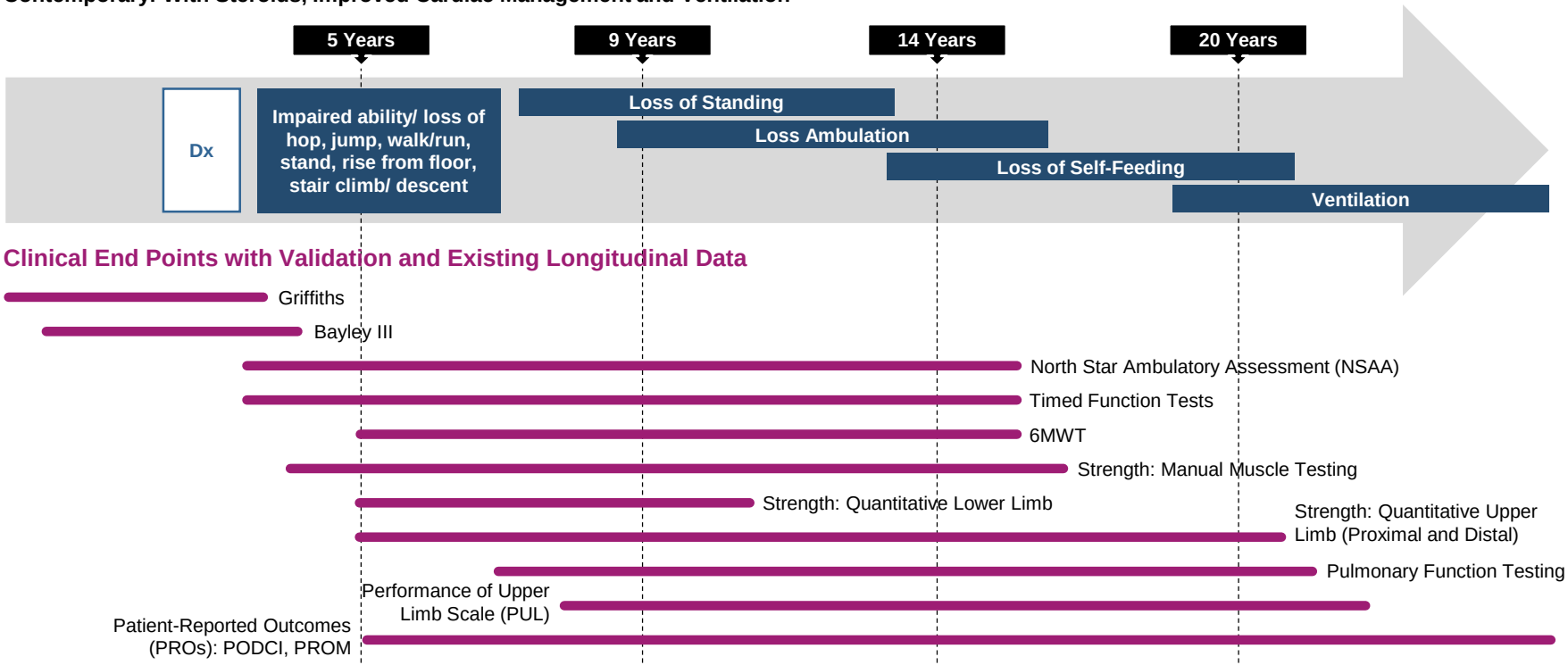
Results: Participants treated ≥1 year while ambulatory (n = 252/340) showed a 3-year median delay in LoA ($p < 0.001$). Fourteen different regimens were observed. Nondaily treatment was common for PRED (37%) and rare for DFZ (3%). DFZ was associated with later LoA than PRED (hazard ratio 0.294 ± 0.053 vs 0.490 ± 0.08, $p = 0.003$; 2-year difference in median LoA with daily administration, $p < 0.001$). Average dose was lower for daily PRED (0.56 mg/kg/d, 75% of recommended) than daily DFZ (0.75 mg/kg/d, 83% of recommended, $p < 0.001$). DFZ showed higher frequencies of growth delay ($p < 0.001$), cushingoid appearance ($p = 0.002$), and cataracts ($p < 0.001$), but not weight gain.

Conclusions: Use of DFZ was associated with later LoA and increased frequency of side effects. Differences in standards of care and dosing complicate interpretation of this finding, but stratification by PRED/DFZ might be considered in clinical trials. This study emphasizes the necessity of a randomized, blinded trial of GC regimens in DMD.

Classification of evidence: This study provides Class IV evidence that GCs are effective in delaying LoA in patients with DMD. *Neurology*® 2015;85:1048–1055

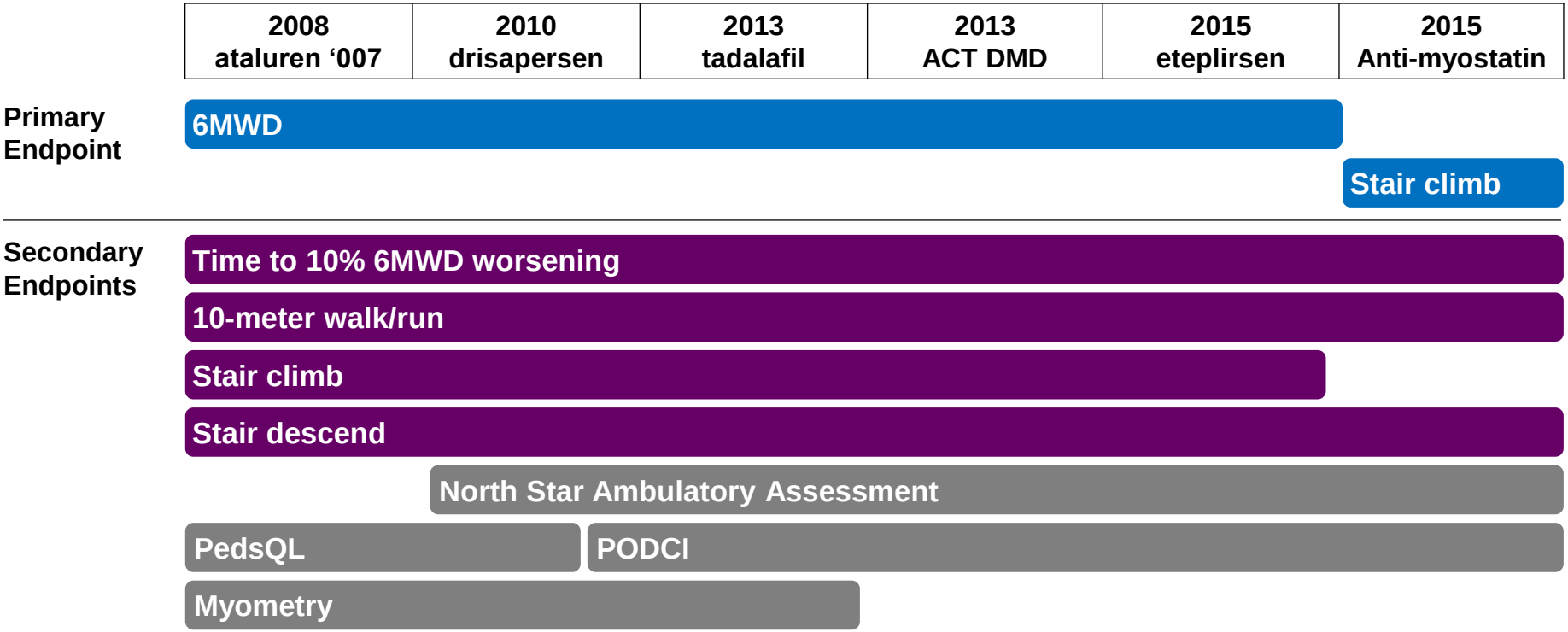
Variety of Clinical End Points Needed to Measure Disease Progression Depending on Age and Stage of Disease

Contemporary: With Steroids, Improved Cardiac Management and Ventilation



Adapted from Bushby, Connor. Clin Investig (Lond). 2011; McDonald, et al. Muscle Nerve. 2013

6MWT, TFTs, Muscle Strength, NSAA and PODCI Have all Been Included in DMD Trials to Measure Disease Progression



Note: ataluren study conducted by PTC Therapeutics; drisapersen study conducted by GSK / Prosensa (Biomarin); tadalafil study conducted by Lilly; eteplirsen study conducted by Sarepta; anti-myostatin mAb study conducted by Pfizer.

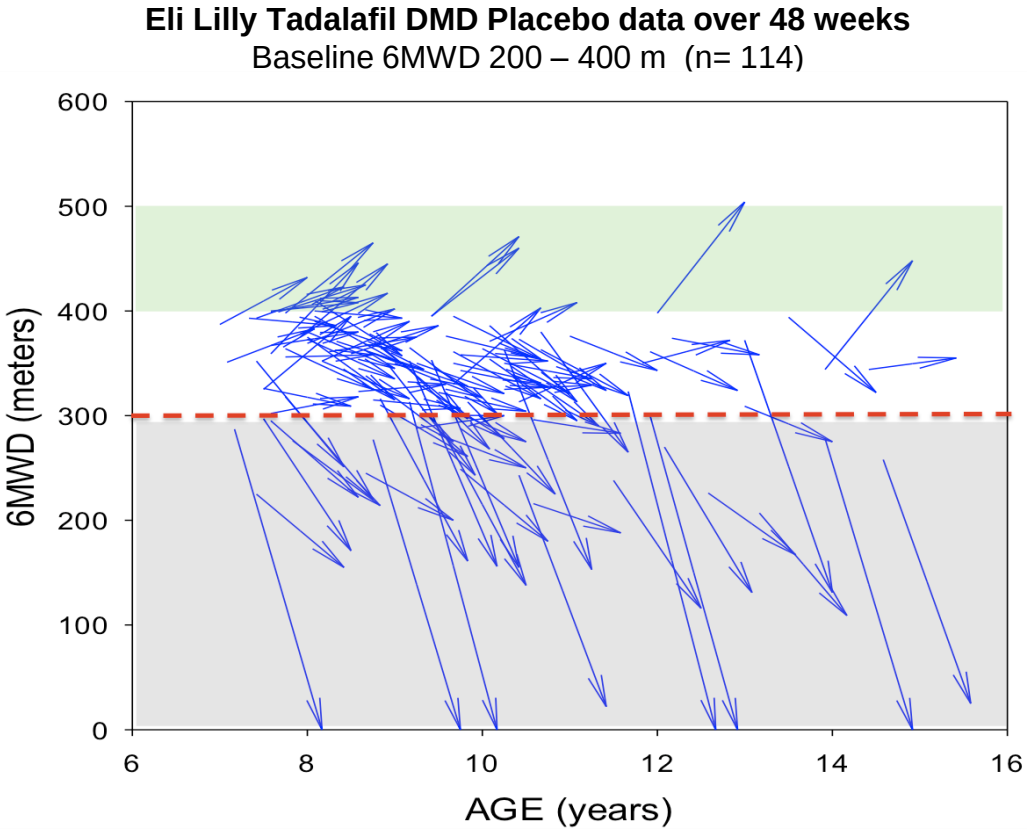
Measuring Disease Progression

6-minute Walk Test and Timed Function Tests

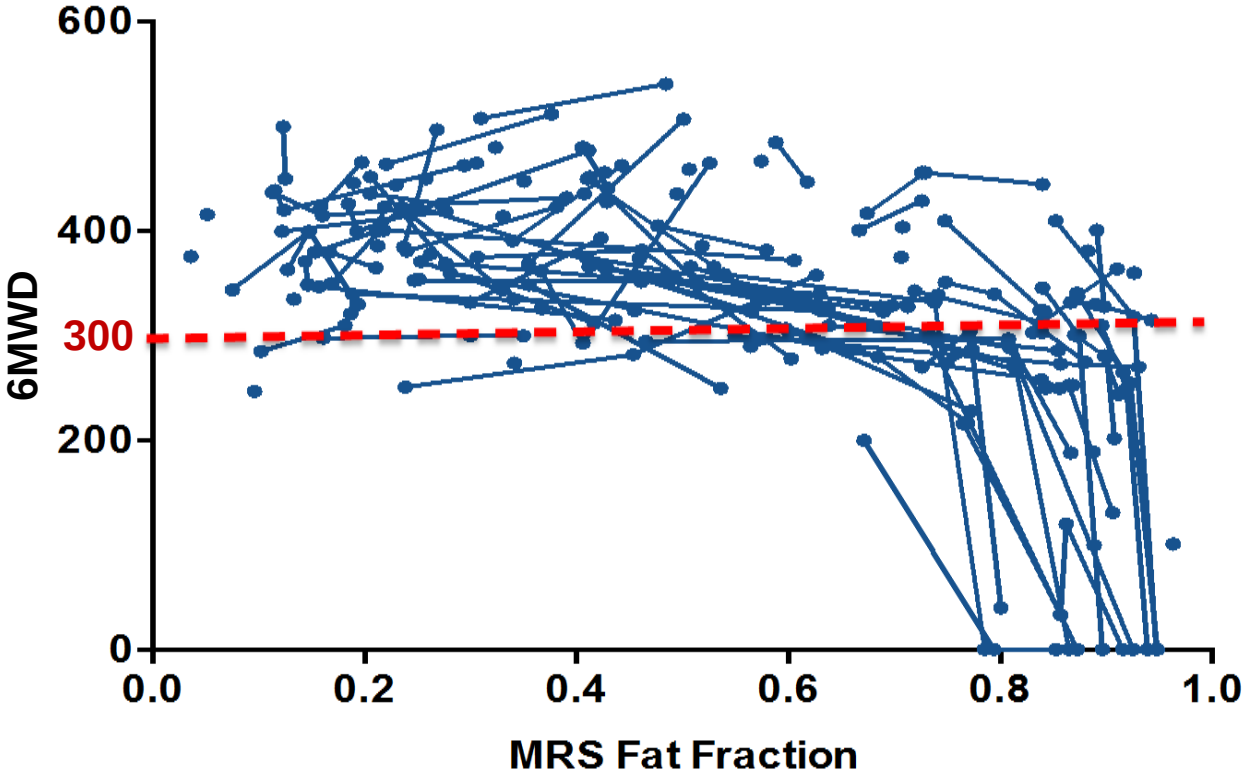
6MWT: Integrated Global Measure of Strength, Endurance and Cardiorespiratory Function

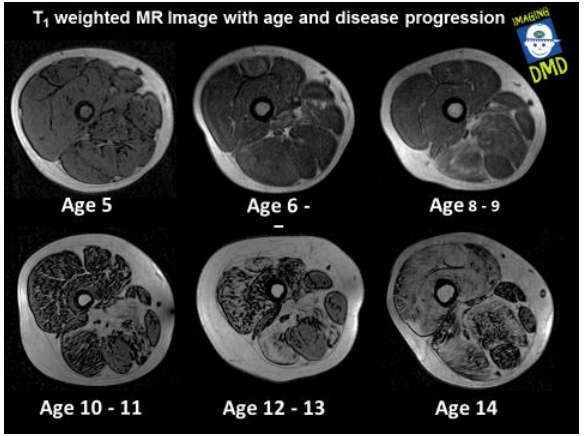
- Validated as a measure of disease progression (stride length, strength, energy cost, gross motor skills, community mobility)
- Prognostic for future loss of ambulation
- Anchored to QoL in DMD
- Walk for six minutes on flat ground
  - 25-meter course marked by a cone at each end
- Modified for DMD population
  - 2 examiners
    - One records time and distance
    - One walks behind patient for safety
  - Standardized encouragement to maintain attention and limit bias

Recent Natural History Data Demonstrate Challenges of the 6MWT as an Endpoint in DMD for 12-month trials



MR Imaging Is a Useful Biomarker in DMD (Loss of Ambulation Linked with VL Fat Fraction; Baseline 6MWD <300m at Higher Risk of Losing Ambulation)

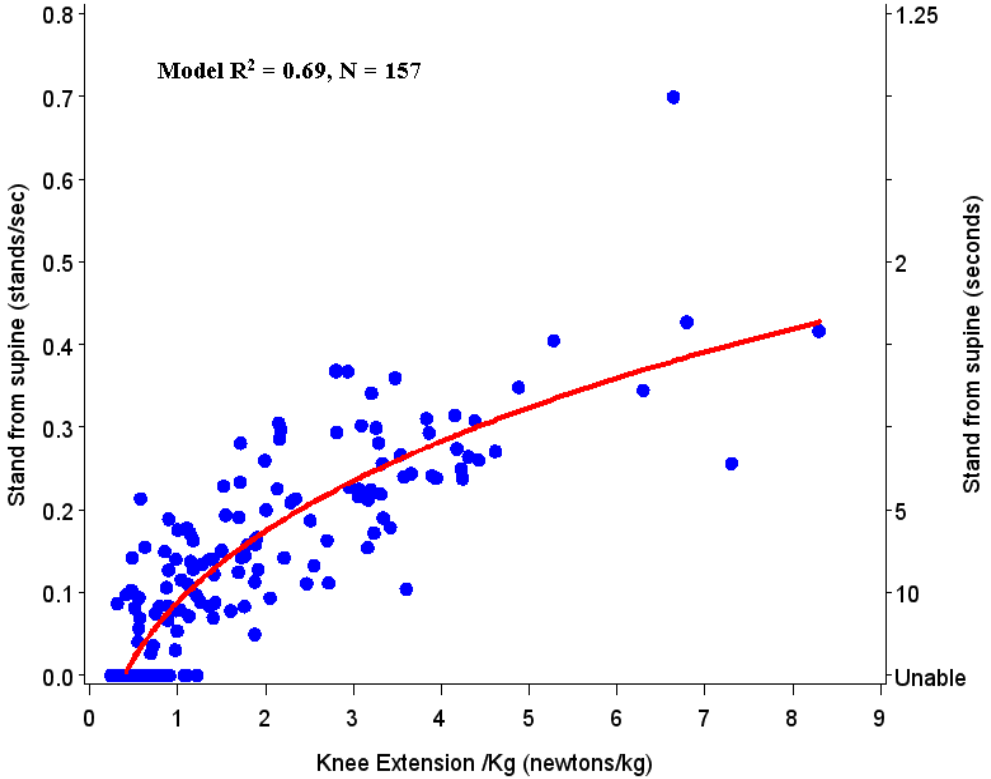




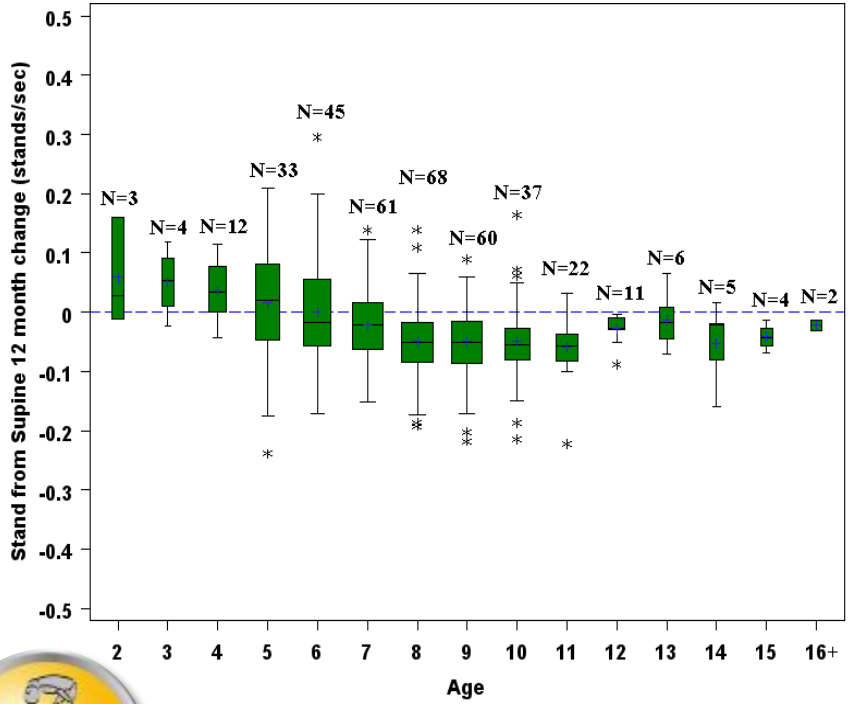
Imaging data illustrate infiltration of muscle by fat and fibrous tissue

Data courtesy of H. Lee Sweeney, PhD, Myology Institute, University of Florida

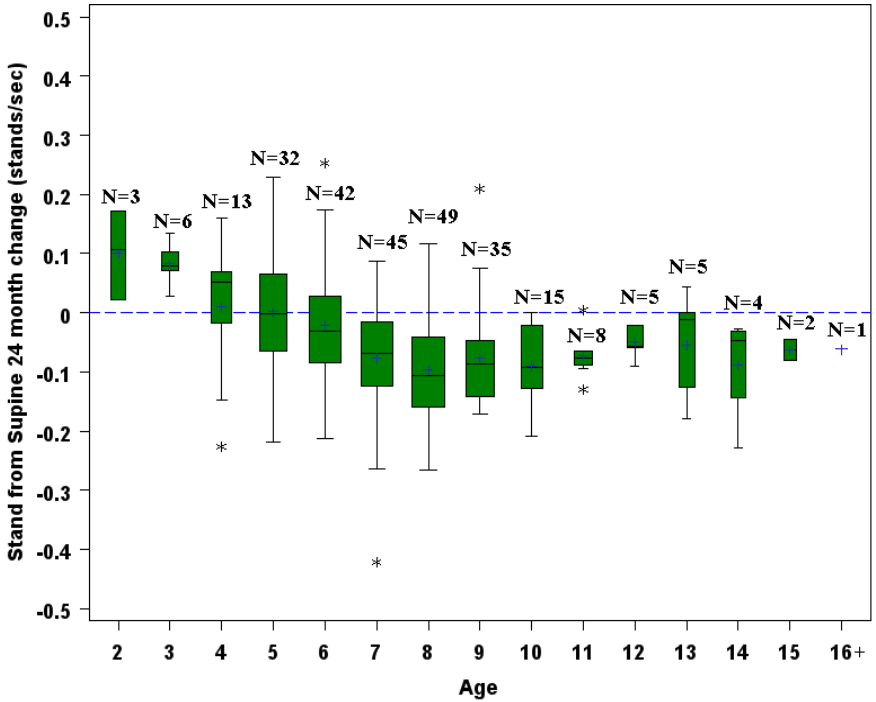
Timed Function Tests in DMD
Stand from Supine (Rise from Floor) and Quantitative Strength



Timed Function Tests in DMD
Stand from Supine / Rise from Floor Velocity (12 and 24 Month Changes)

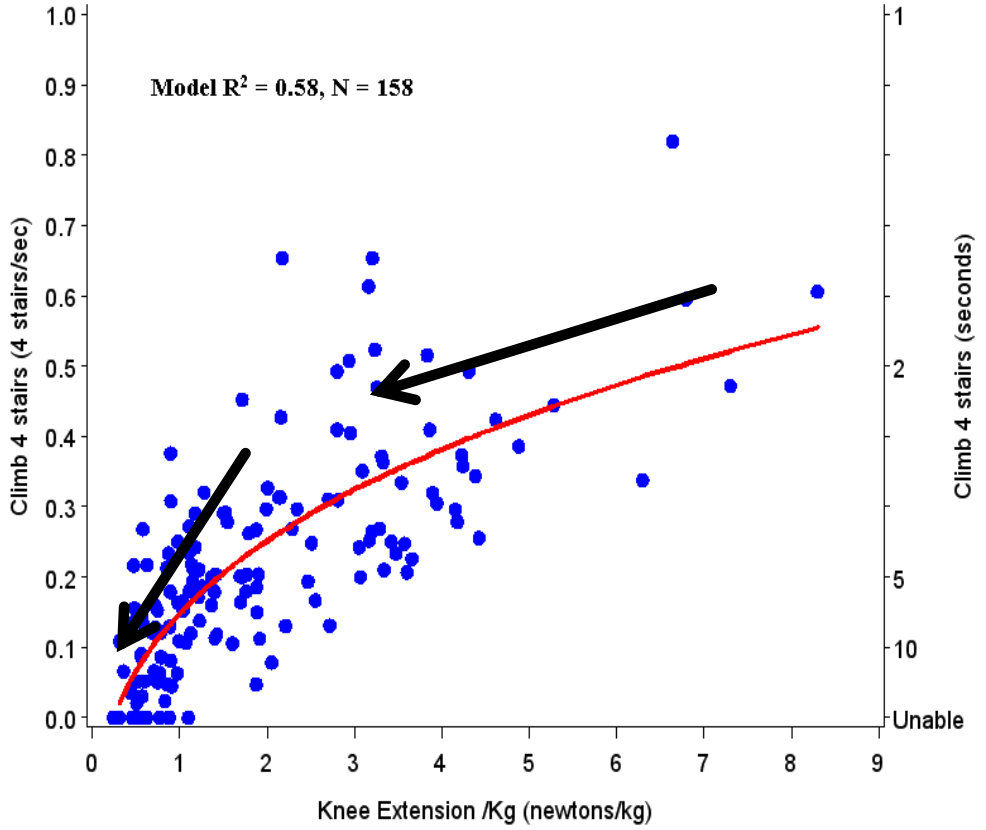


CINRG:
(1-year longitudinal data)

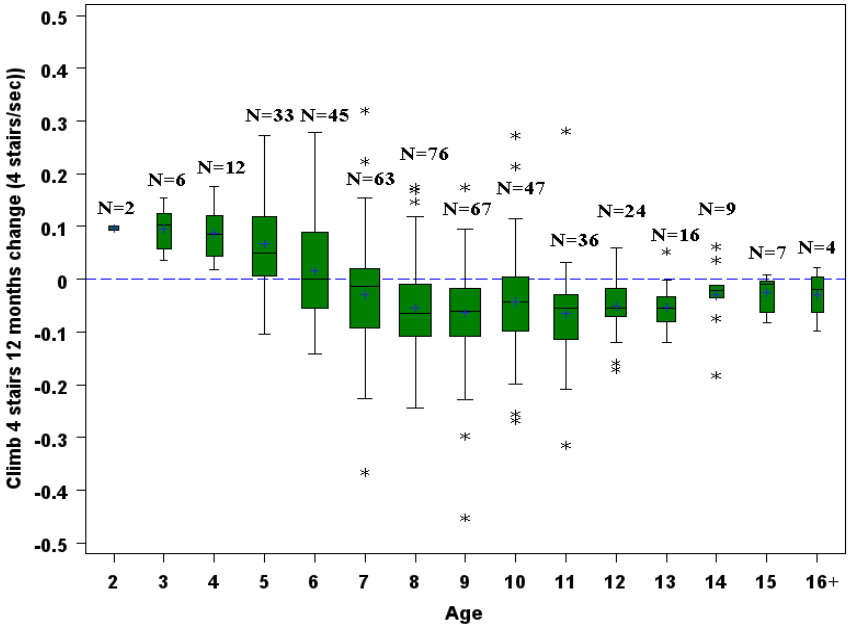


CINRG:
(2-year longitudinal data)

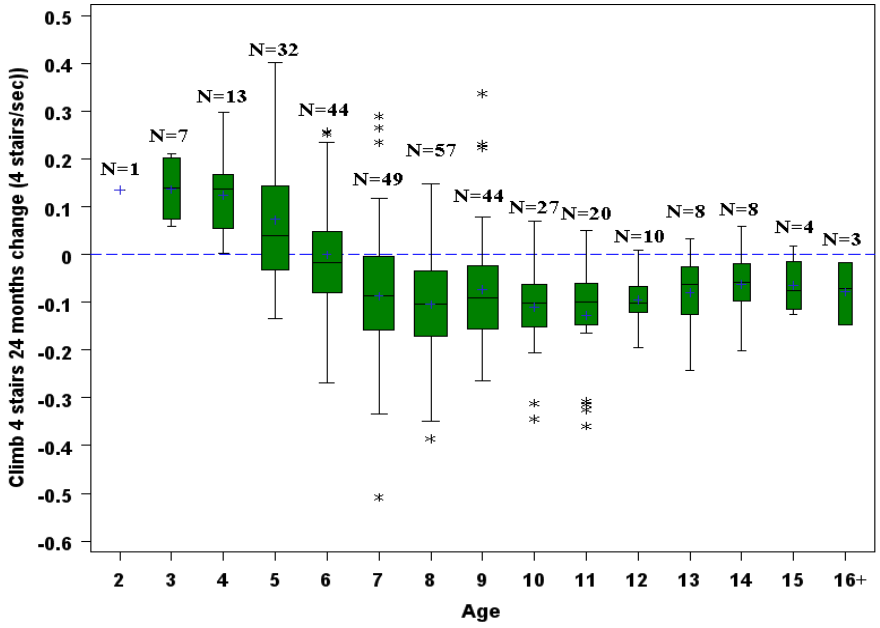
Timed Function Tests in DMD
4-Stair Climb and Quantitative Strength



Timed Function Tests in DMD
4-Stair Climb Velocity (12 and 24 Month Changes)

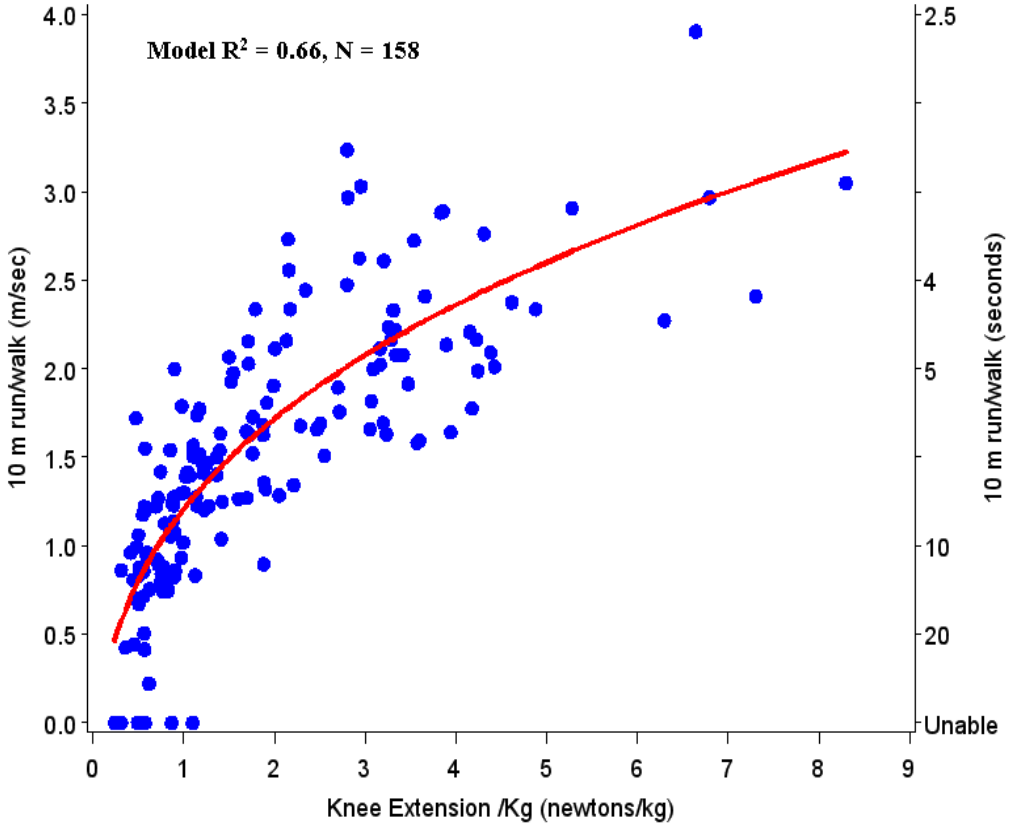


CINRG:
(1-year longitudinal data)

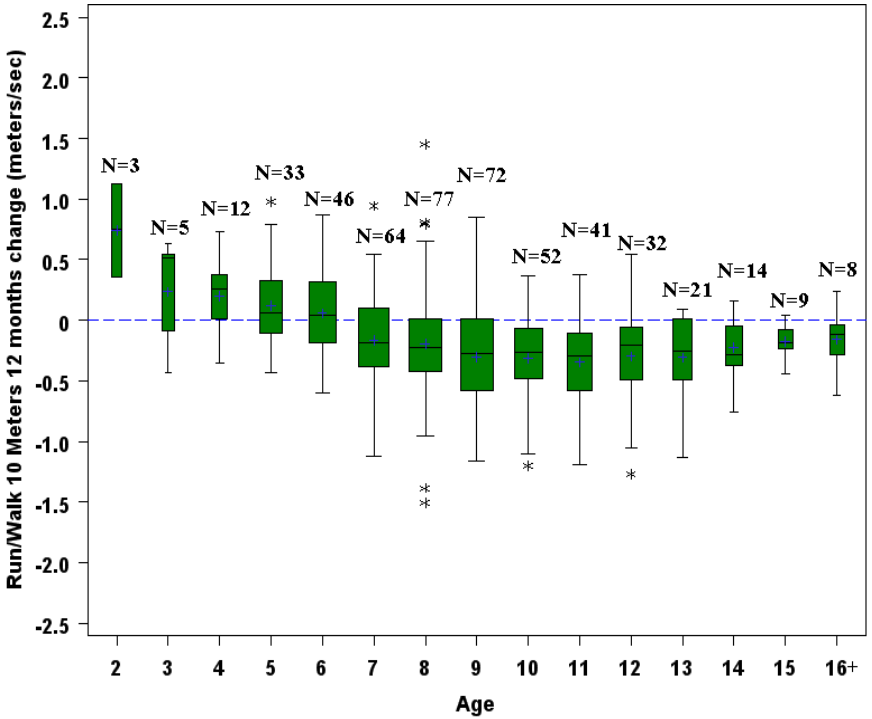


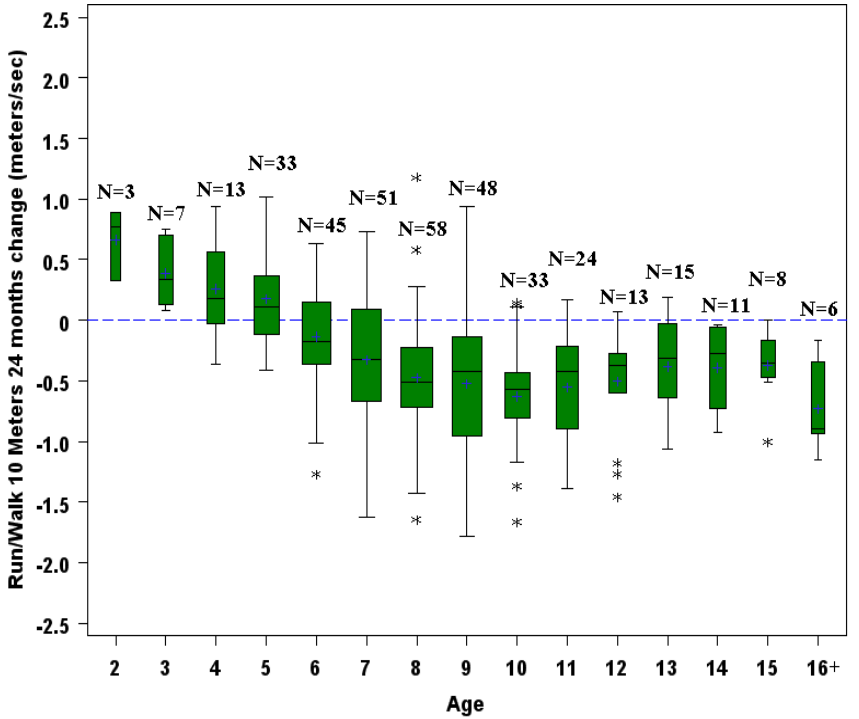
CINRG:
(2-year longitudinal data)

Timed Function Tests in DMD
10-Meter Walk/Run and Quantitative Strength



Timed Function Tests in DMD
10-Meter Walk/Run Velocity (12 and 24 Month Changes)





Prognostic Versus Predictive Endpoints

Prognostic

- A ***prognostic factor*** **is a clinical or biologic characteristic that is objectively measurable and that provides information on the likely outcome of the disease in an untreated individual.**

Predictive

- A ***predictive factor*** **is a clinical or biologic characteristic that provides information on the likely benefit from treatment with regard to specific clinical endpoints.**

Prognostic Versus Predictive Endpoints

Prognostic

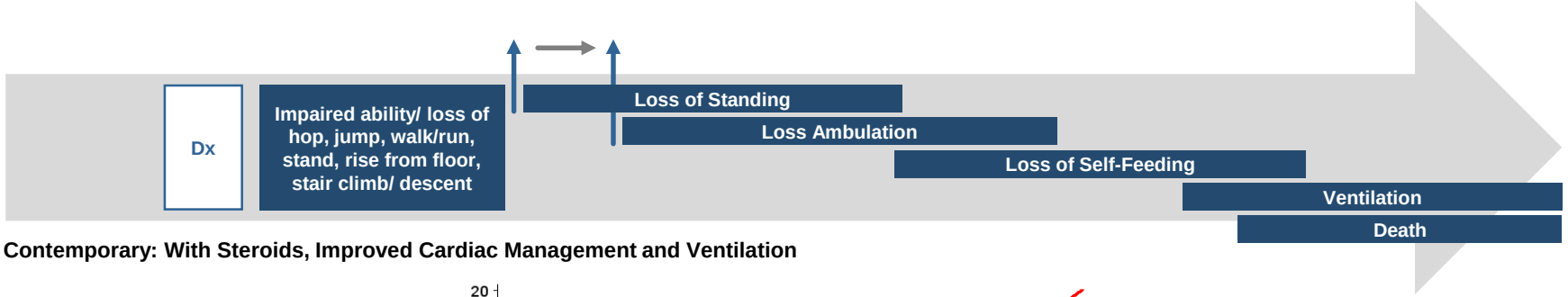
- **Time to stand from supine is broadly prognostic of future disease course in DMD**
  - > 5 sec prognostic for *functional decline* as measured by multiple endpoints
  - Loss of stand from supine prognostic for future loss of ambulation
- **A change from stand from supine from 3 seconds to 4 seconds or 5 to 6 seconds is not prognostic for future disease course**
- **Stand from supine less reliably assessed (not a optimal clinical endpoint for assessing treatment effect)**
- **Decline in 6MWD below 300 meters prognostic for LOA**

Predictive

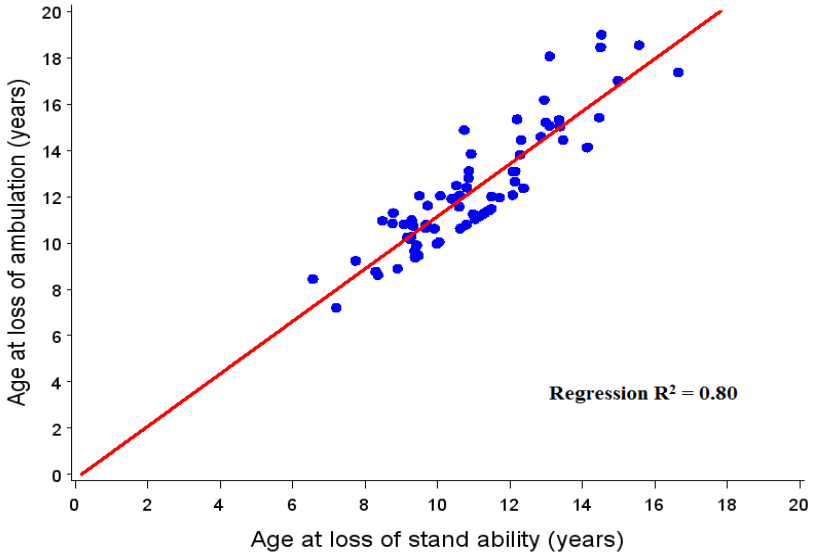
- **Change by 20-30 meters in 6MWD is predictive of a treatment effect that is meaningful to a DMD patient**
- **Change in other TFTs such as 4-stair climb or 10-meter run/walk of 1-1.5 sec predicts a treatment effect that is meaningful to the patient**

Timed Function Tests Predict Loss of Clinically Meaningful Milestones

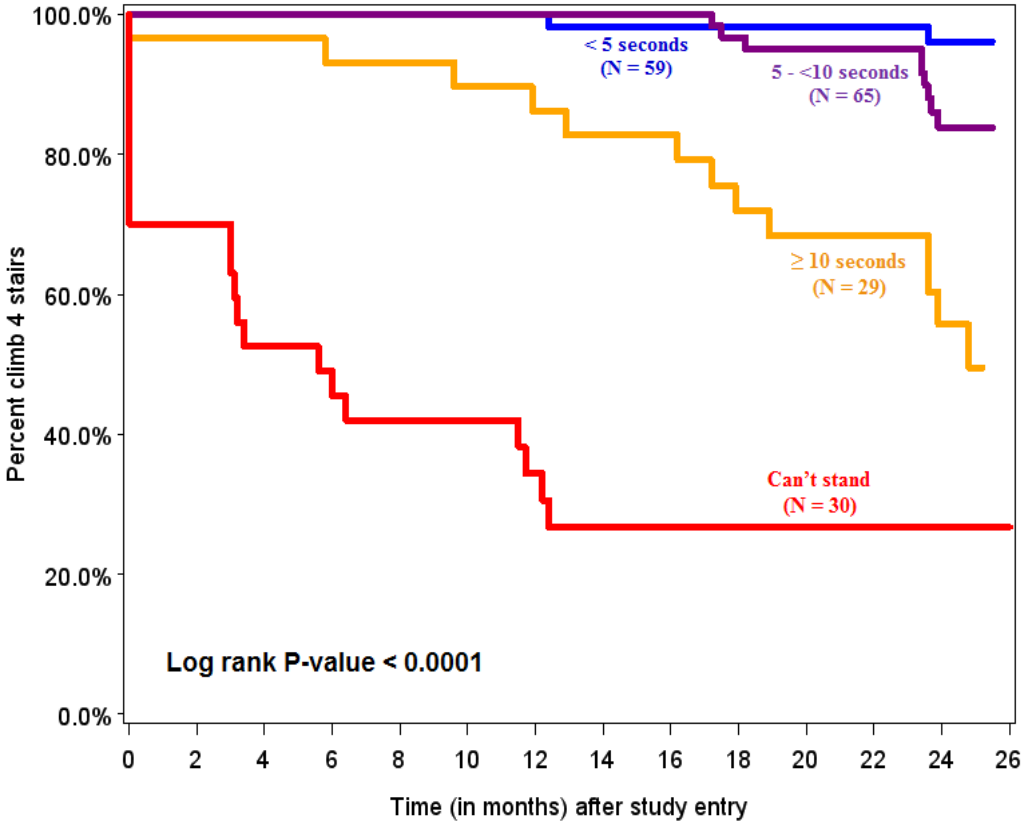
Prognostic: Timed Function Tests Predict Loss of Clinically Meaningful Milestones



Contemporary: With Steroids, Improved Cardiac Management and Ventilation

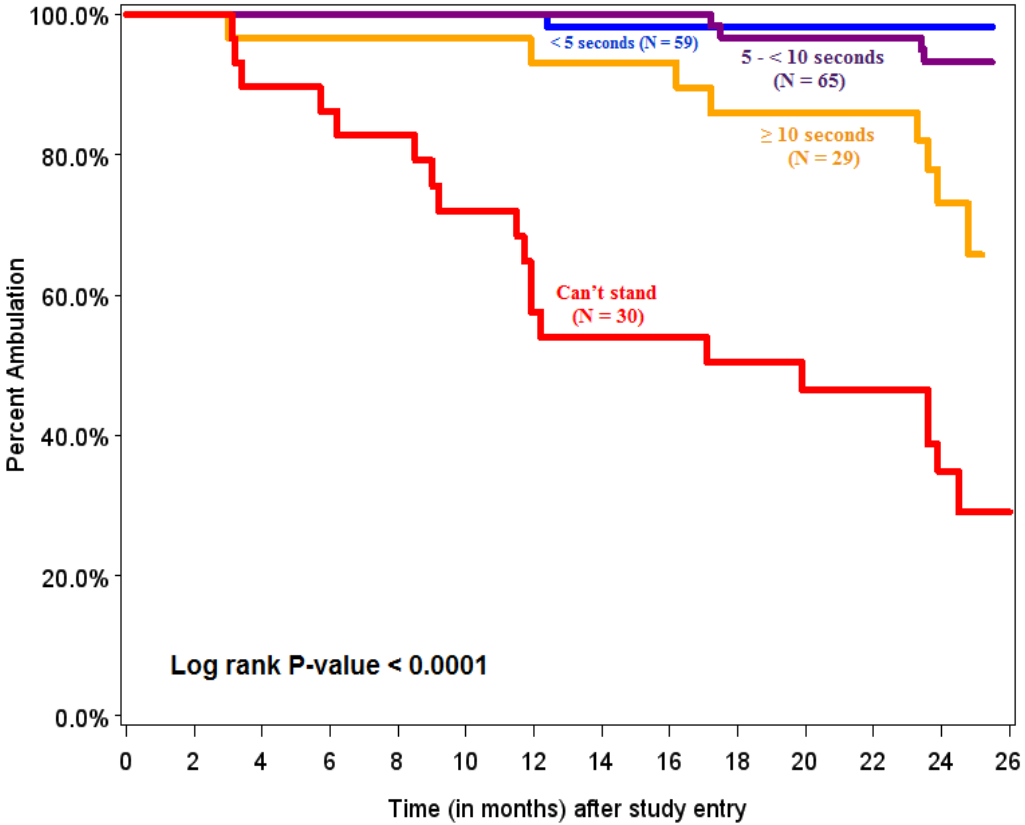


Prognostic: Prediction of Loss of Stair-climbing Using Baseline Time to Stand



McDonald et al. Neuromuscular Disorders, 2013

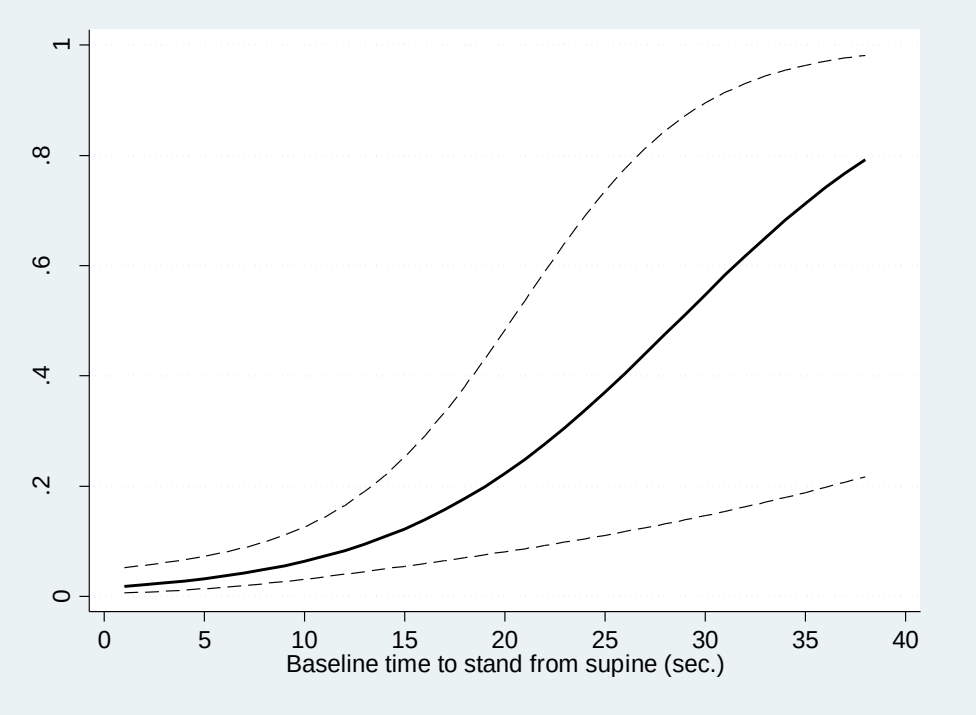
Prognostic: Prediction of Loss of Ambulation
Using Baseline Time to Stand (≥ 10 Seconds or Lost Ability to Stand from Supine)



McDonald et al. Neuromuscular Disorders, 2013

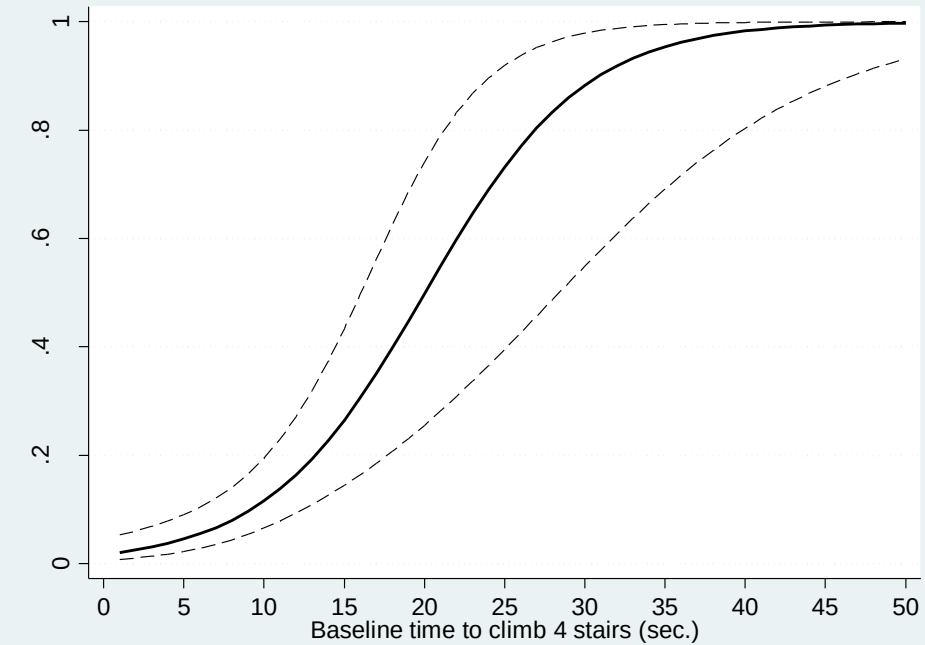
CINRG Data: Logistical Regression Showing Probability of Losing Ambulation Over 2 Years Based on Baseline Rise from Floor

(With adjustment for baseline age and cumulative steroid use at baseline)
(n=185)



CINRG Data: Logistical Regression Showing Probability of Losing Ambulation at 24 Months Given Baseline Time to Climb 4 Stairs Assessment

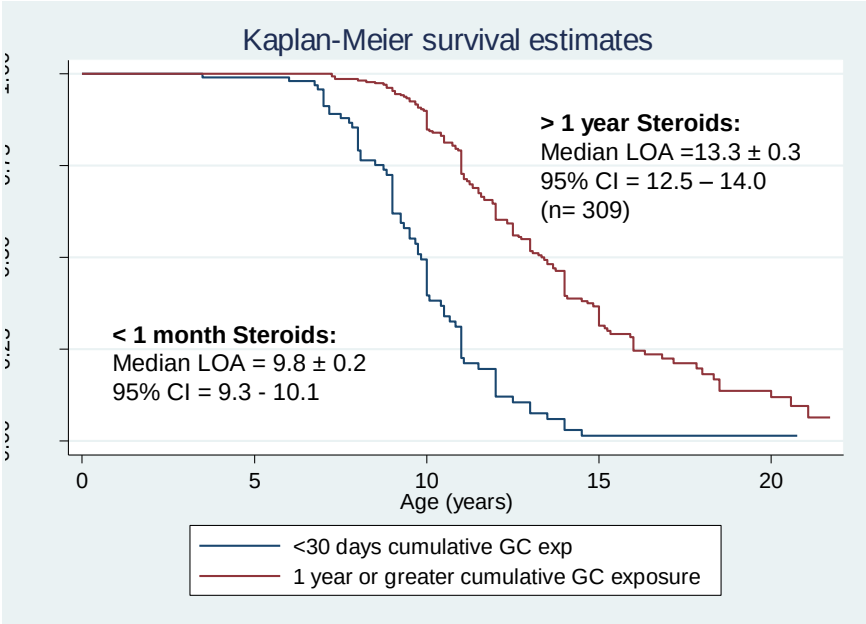
(With adjustment for baseline age and cumulative steroid use at baseline)
(n=200)



Improvement in 10-meter Walk/Run and 4-Stair Climb Are Associated with Prolongation of Ambulation

Endpoint	Prednisone (N=31)	Placebo (N=27)	Δ
Time to run/walk 10 meters	9.55	11.26	-1.71
Time to climb 4 stairs	7.15	8.78	-1.63

- **In a placebo-controlled 12 mo RCT (Hu et al. 2015), prednisone produced a:**
  - 1.7 second Δ for 10-meter walk/run
  - 1.6 second Δ for 4-stair climb

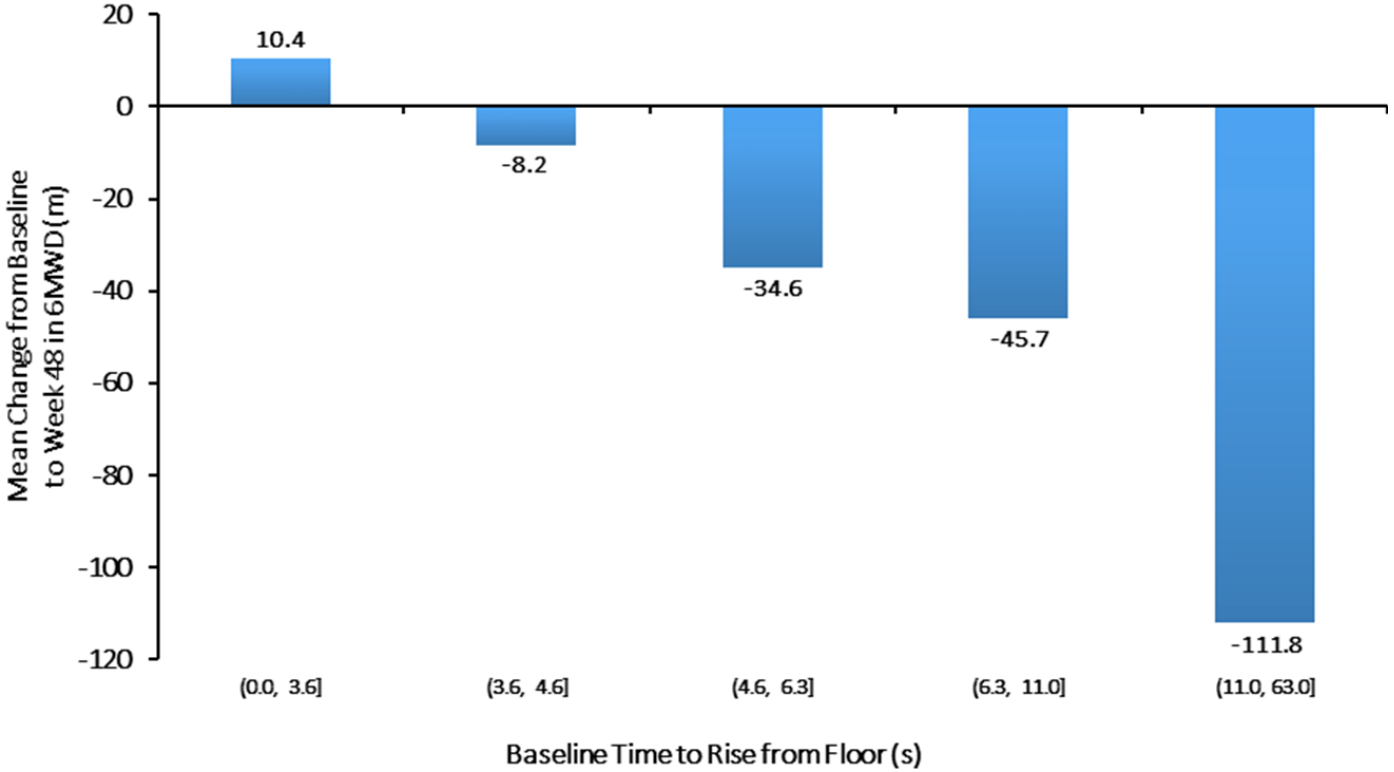


- **A 1.6 to 1.7 second change over 12-months in TFTs translates to a 3-year prolongation of ambulation in DMD (all mutations)***

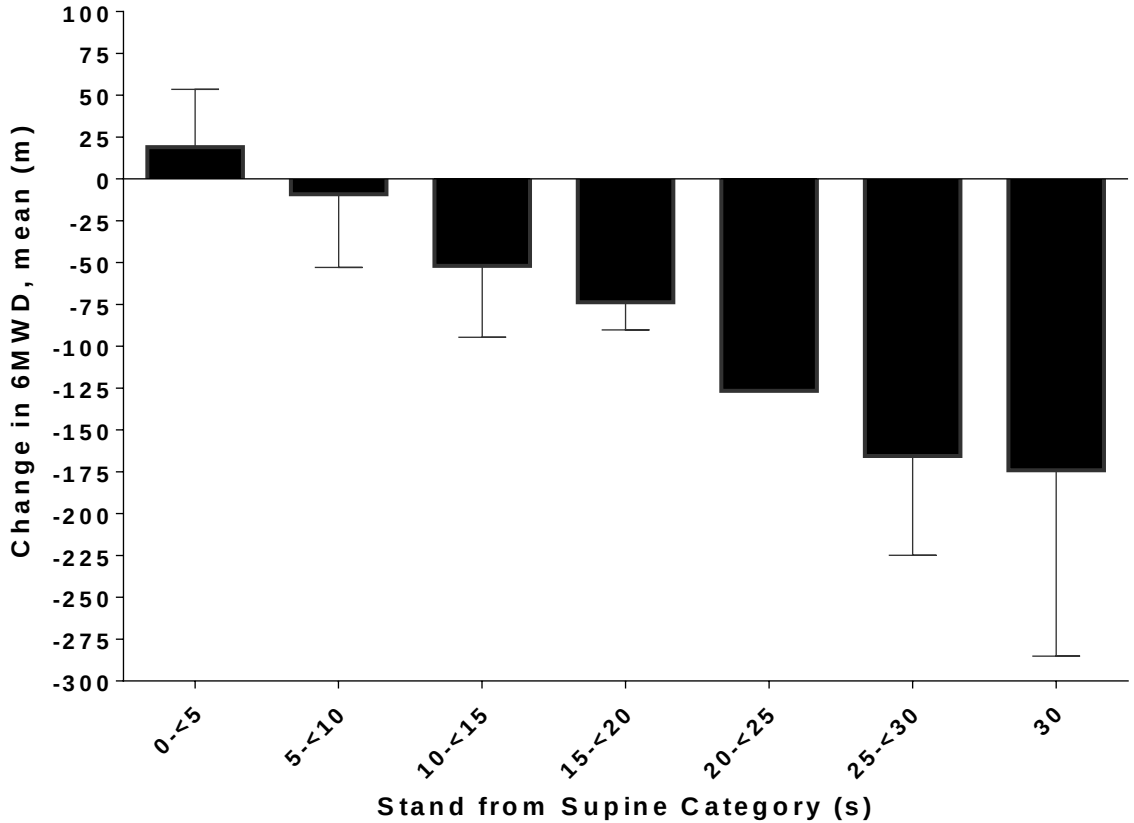
* CINRG Duchenne Natural History Study, 2016
Bello et al. Neurology 2016, in press

Exon 51 Amenable Placebo Patients Rise from Floor Is Associated with Change in 6MWD Over 48 Weeks

(Placebo Data (n=86) from Biomarin studies 044, 117, 876)

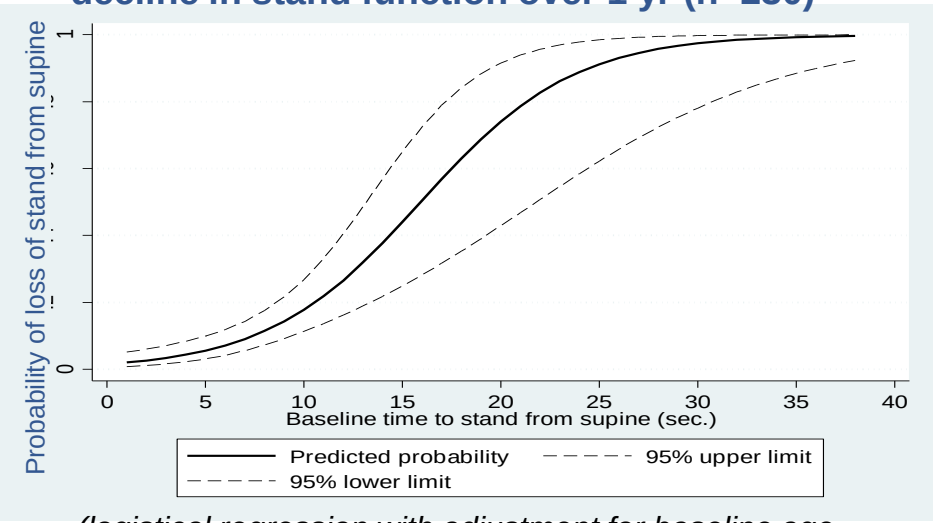


Rise from Floor Is Associated with Change from Baseline in 6MWD at Week 48 (PTC 020 Placebo)



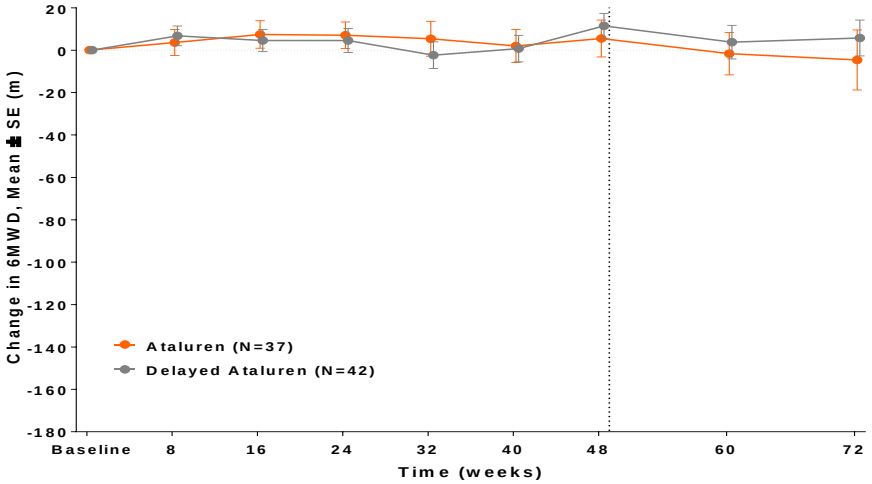
< 5 Second Time to Stand from Supine Is a Newly Defined Prognostic Indicator for Lack of Functional Decline in DMD

CINRG: ≥ 5 second stand from supine predicts decline in stand function over 1 yr (n=230)



(logistical regression with adjustment for baseline age and cumulative steroid use at baseline)

PTC Study 020/e: Stand from supine < 5s



> 5 second stand from supine is prognostic for decline in 6MWD and NSAA

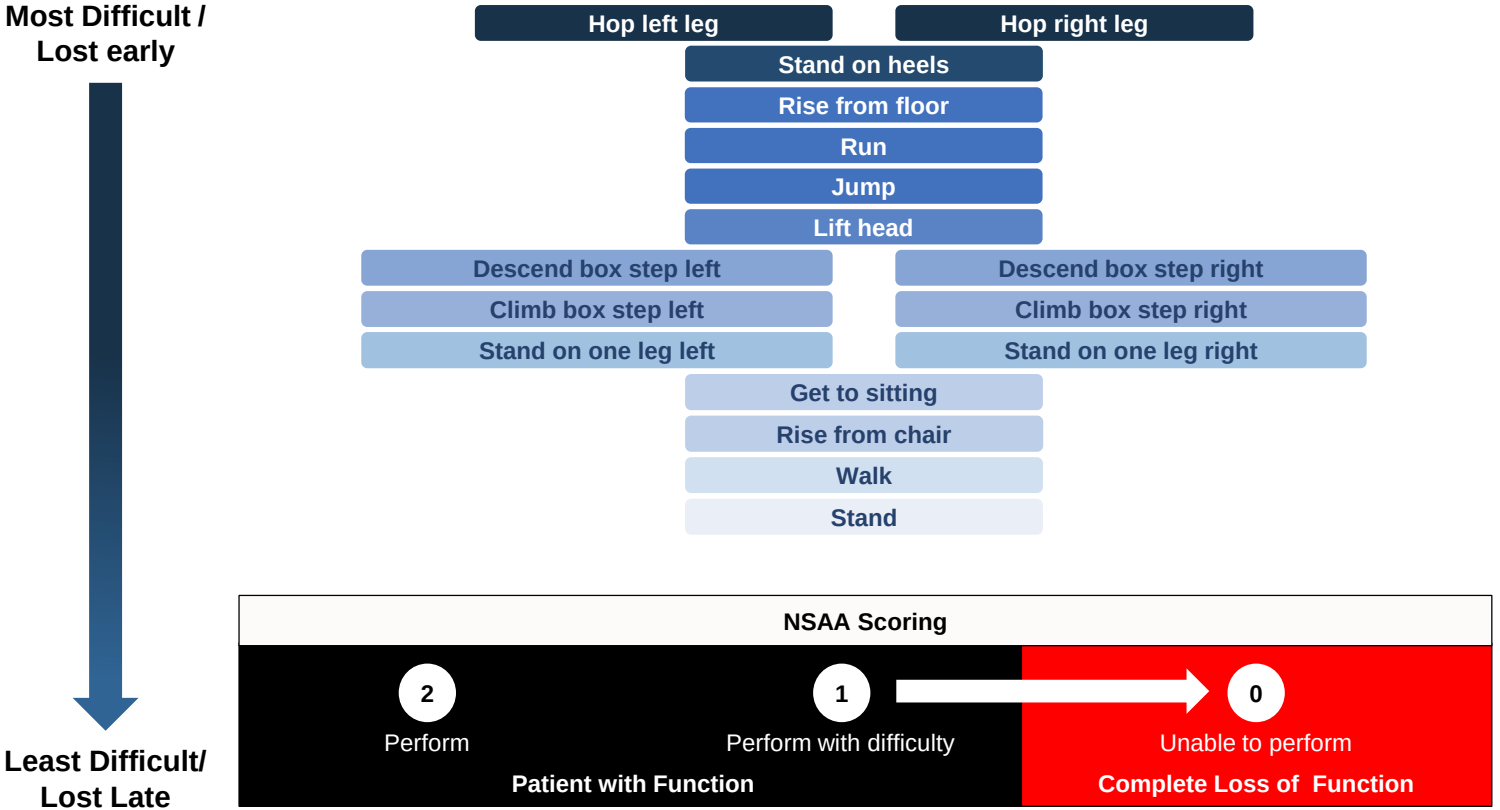
[1] Mercuri E, et al. Neuromuscul Disord. 2016 Sep;26(9):576-83.
[2] Goemans N, et al. PLoS One. 2016 Oct 13;11(10):e0164684.

Summary of 6MWT and Timed Function Tests

- **Timed function tests are predictive of changes in 6-minute walk test in DMD**
- **A Stand from supine $\geq$ 5 seconds is predictive of functional deterioration**
- **(The 6-minute walk test is not age appropriate for 4 – 7 year olds with DMD)**
- **1 to 1.5 second change in TFTs is meaningful**

North Star Ambulatory Assessment (NSAA)

NSAA Is a Composite Endpoint Evaluating Physical Function Across 17 Tests with Increasing Difficulty



North Star Ambulatory Assessment in DMD: Significant Muscle Impairment in Patients with Reasonably Preserved Function

- **Example: Age 9.75 prior to treatment**
  - Rise from floor = 7 seconds
  - 6MWD = 414 meters

Implications of Using Ordinal Endpoints

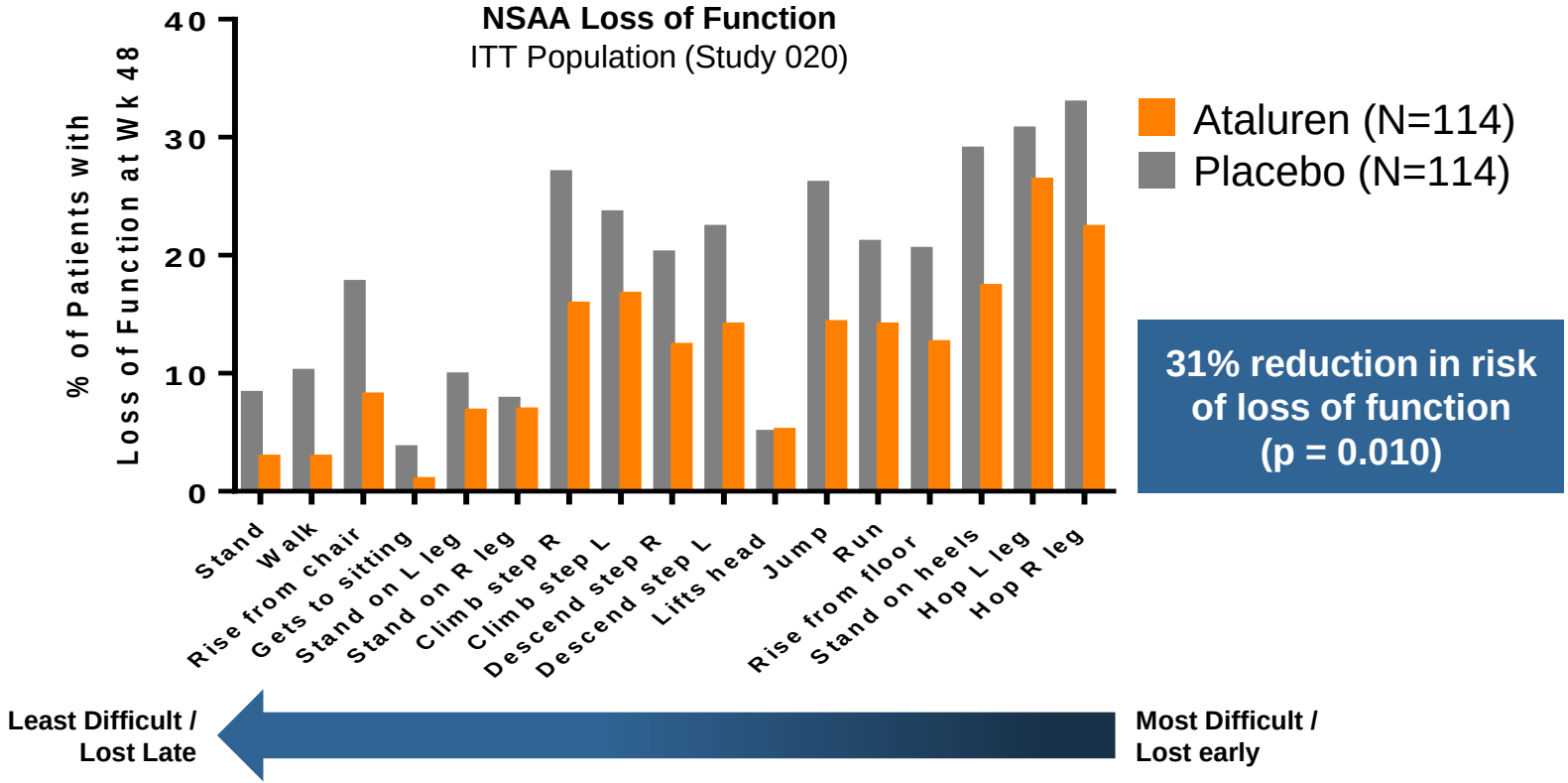
- **NSAA is an objective and independent assessment**
- **Certainty of measure – clear cut between a score of zero and non-zero**
- **Total score does not differentiate between 2 to 1 or 1 to 0; treats as a reduction of 1**

Changes from Baseline in NSAA Can Be Informative in Gauging Loss of Function

- **NSAA scoring system was developed to assess clinically significant changes [Scott 2012]**
  - 2 = Performs the activity normally
  - 1 = Performs the activity by employing a modified method to compensate for his muscle weakness
  - 0 = Unable to perform the activity
- **Loss of function (i.e., a shift from 1 to 0 or from 2 to 0) is a devastating milestone**
  - Gain of function is rare and not expected
- **Analyzing the proportion of patients with loss of function over 48 weeks is more meaningful than summing the 17 items to achieve a total score**

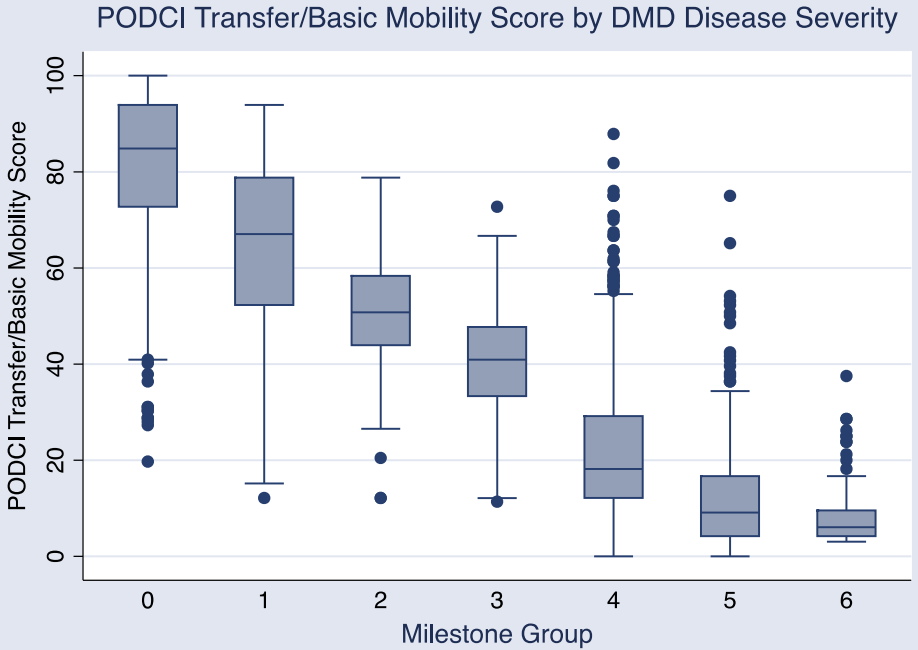
Toe Walking

Example NSAA Analysis: Ataluren Reduced the Risk by 31% Allowing More Patients to Preserve Functions in Study 020 (ITT)



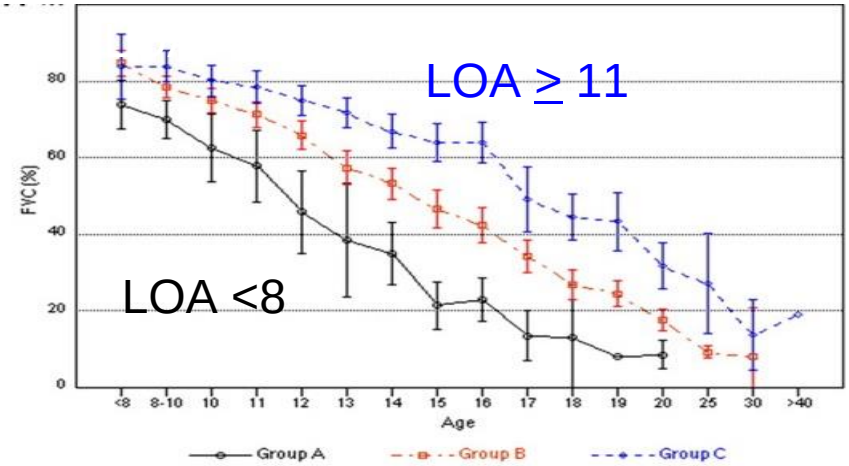
Pediatric Outcomes Data Collection Instrument (PODCI)

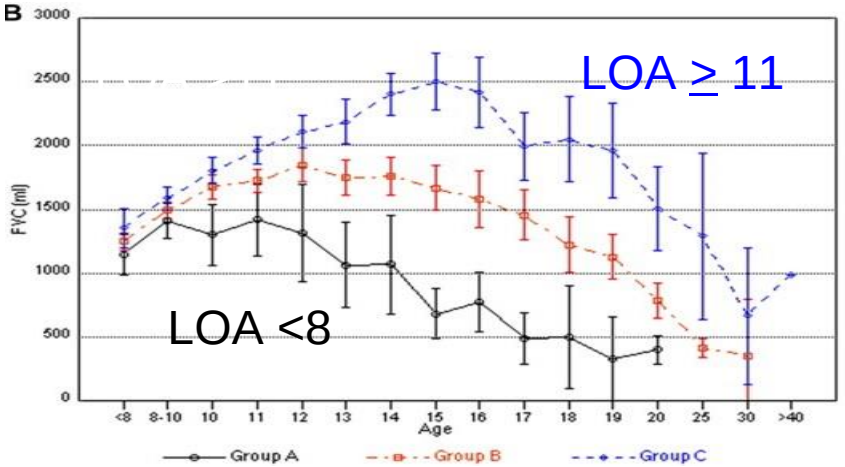
PODCI HrQOL Transfers / Basic Mobility PRO Demonstrates Clinical Meaningfulness of the Key Milestones in DMD



Pulmonary Assessment in DMD

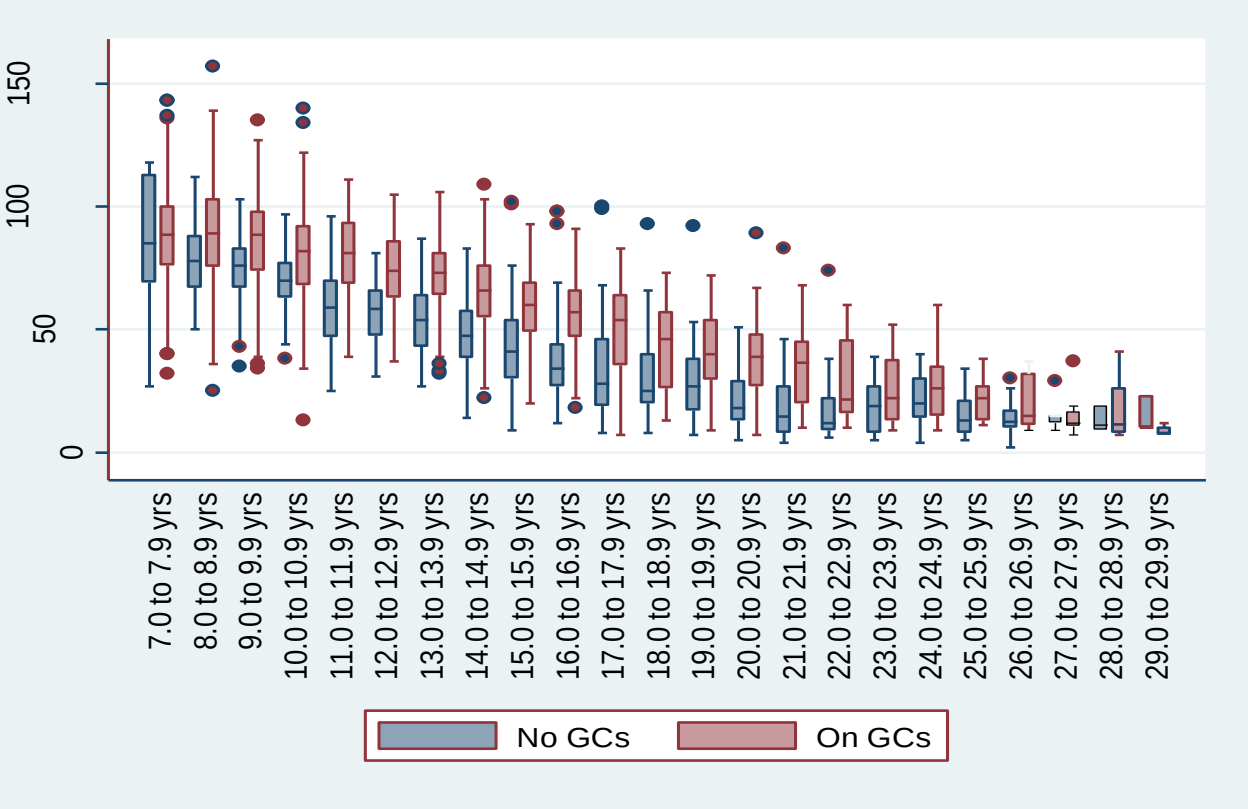
Later Age at Loss of Ambulation Predicts Higher Peak FVC and Slower Rate of Decline in Absolute FVC and % Predicted FVC



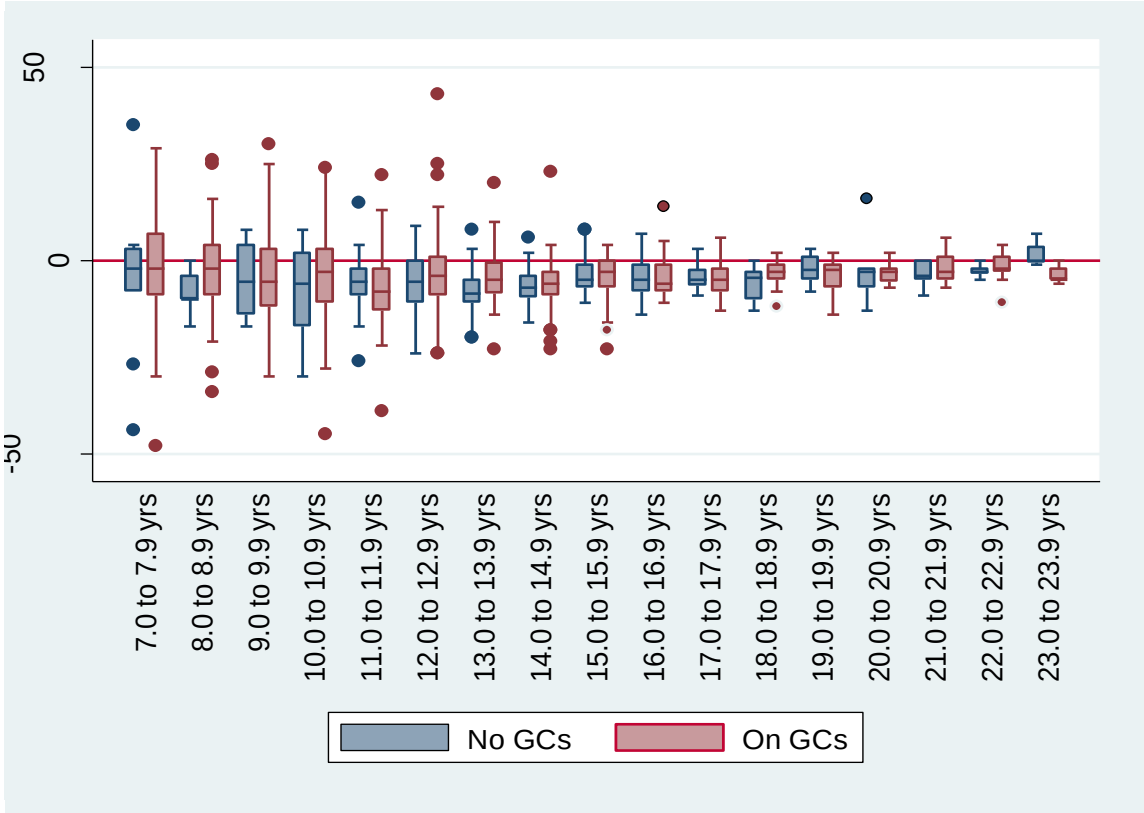


Humbertclaude et al. European J. of Paediatric Neurology 2012

Pulmonary Function Declines with Age
% Predicted FVC by Age

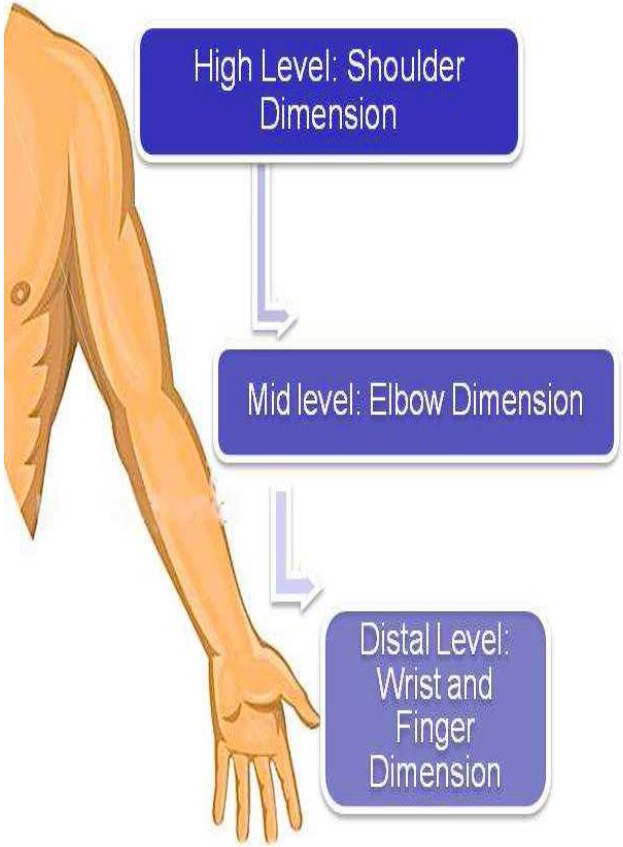


12-month Change in % Predicted FVC by Age



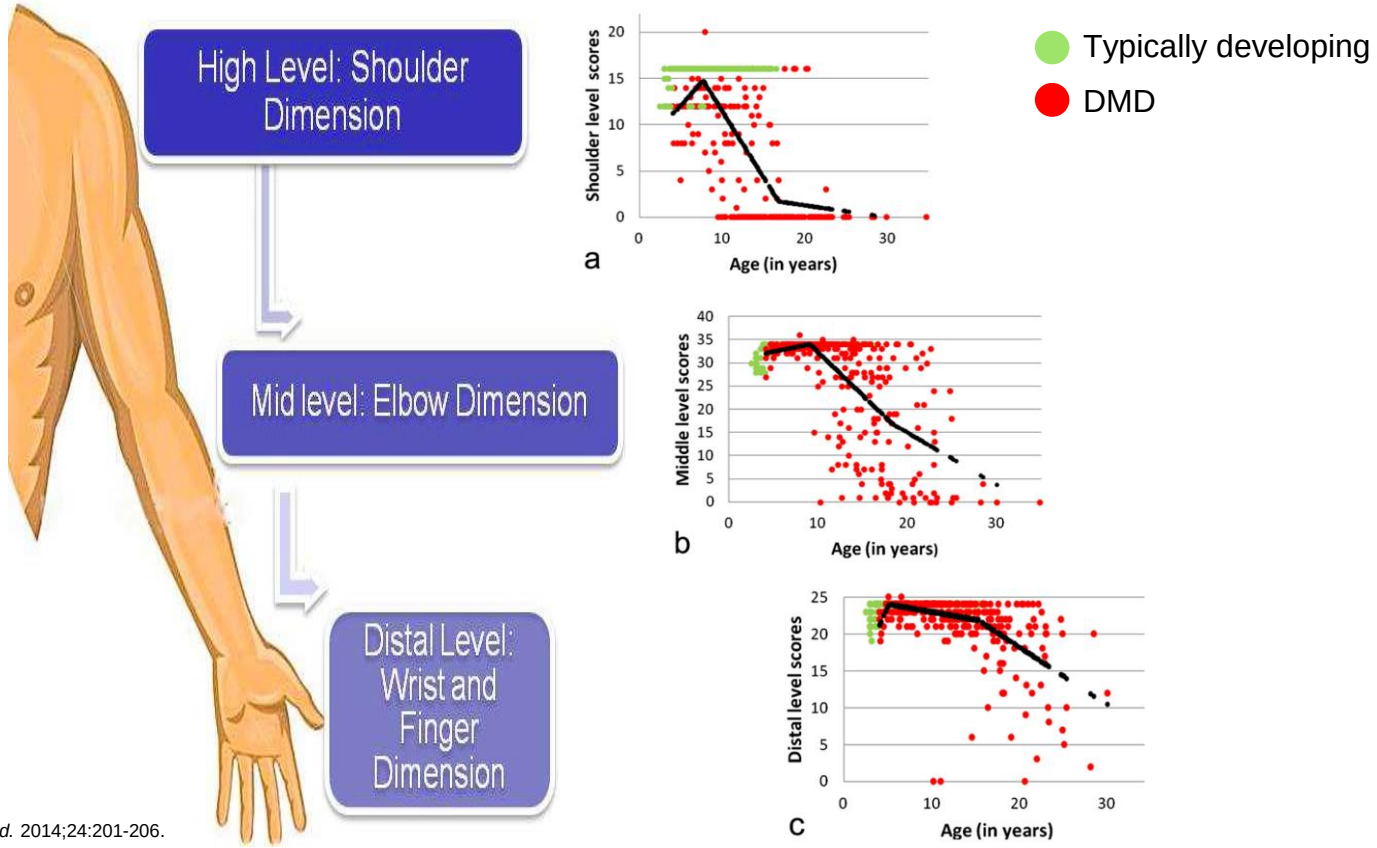
Performance of Upper Limb (PUL)

PUL Assessment Items for Non-Ambulant DMD



- **1 entry item to define the starting functional level**
- **4 items: HIGH LEVEL – SHOULDER DIMENSION**
- **9 items: MID LEVEL – ELBOW DIMENSION**
  4 timed items
- **8 items: DISTAL LEVEL – WRIST and HAND DIMENSION**

Distribution of PUL Scores by Age (Longitudinal Total Score Changes by 3 Points Over 2 Years)



Pane M, et al. *Neuromuscul Disord.* 2014;24:201-206.

Key Takeaways

- **DMD is a devastating progressive disease with significant unmet need**
  - Loss of function in skeletal muscle, diaphragm and heart and results in premature death
  - Contemporary treatments have improved course of disease: glucocorticosteroids, management of spinal deformity, pulmonary and cardiac management
  - Glucocorticosteroids have significant side effects
- **Variety of clinical end points needed to measure disease progression depending on age and stage of disease**
- **Timed function tests used for DMD patients 4 to 7 years of age**
  - Supine to stand, 4-stair climb, 10-meter walk/run
- **6MWT is sub-optimal for 4 - 7 year old boys with DMD**
- **Loss of functions in NSAA meaningful (face validity)**
- **PODCI is a PRO tool that can demonstrate clinical meaningfulness of key milestones in DMD**
- **Pulmonary function tests can be applied through a large portion of the non-ambulant population**
- **PUL is a validated endpoint for the non-ambulant population (shoulder and middle dimensions lost earlier)**
- **MR Imaging is a useful biomarker in DMD**

Acknowledgments

UC Davis Neuromuscular Medicine & Rehabilitation Research Center and CINRG Network

NATIONAL INSTITUTE ON DISABILITY AND REHABILITATION RESEARCH
NIDRR
SCHOOL OF MEDICINE · UC DAVIS ·
MDA MUSCULAR DYSTROPHY ASSOCIATION
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CDMRP
Department of Defense
National Institute of Neurological Disorders and Stroke
National Institutes of Health

Muscle MRI as a Biomarker for Assessing Disease Progression and Therapeutic Intervention in DMD

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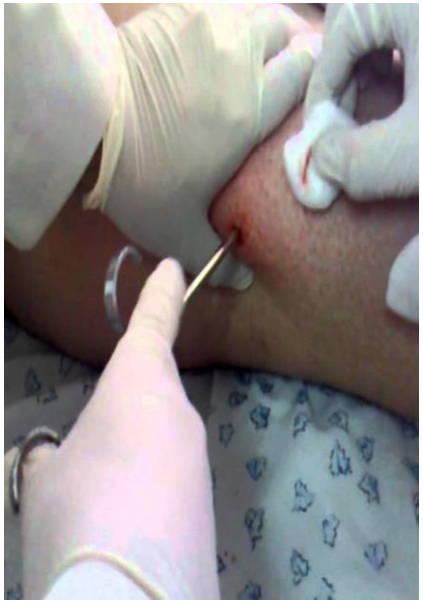
SCHOOL OF MEDICINE

Outline

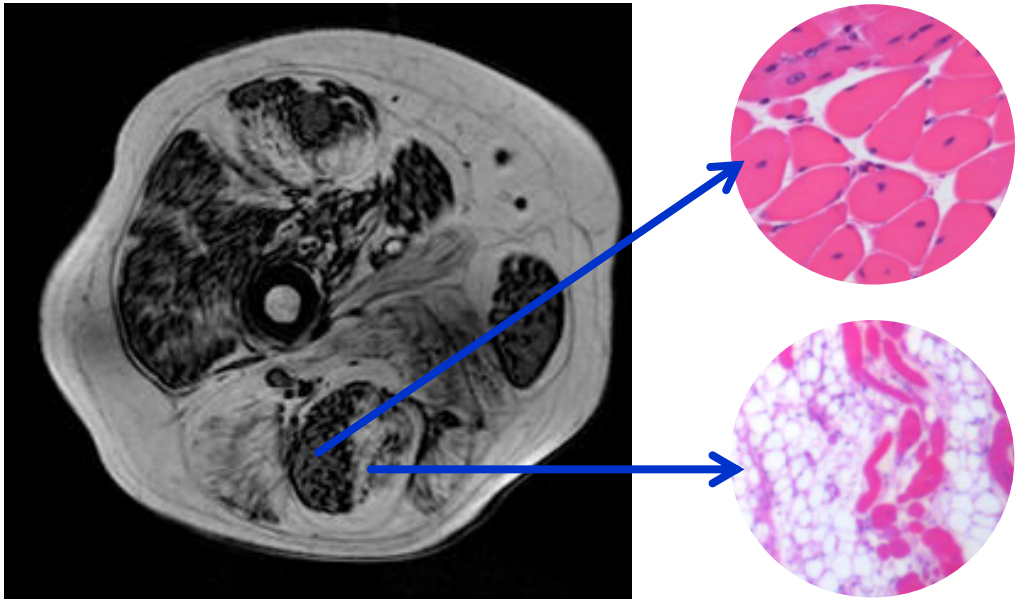
- **Limitations of muscle biopsy**
- **Overview of ImagingDMD Group and MRI techniques and measures**
- **Key studies showing utility of MRI as a biomarker in DMD**
  - Study 1: Natural history
  - Study 2: Effects of initiation of corticosteroids
  - Study 3: Cross-sectional view of effects of corticosteroids
  - Summary of findings from studies
- **Application of findings to the MoveDMD trial**

Need for a Biomarker that Addresses the Limitations of Muscle Biopsy

Biopsy is Invasive



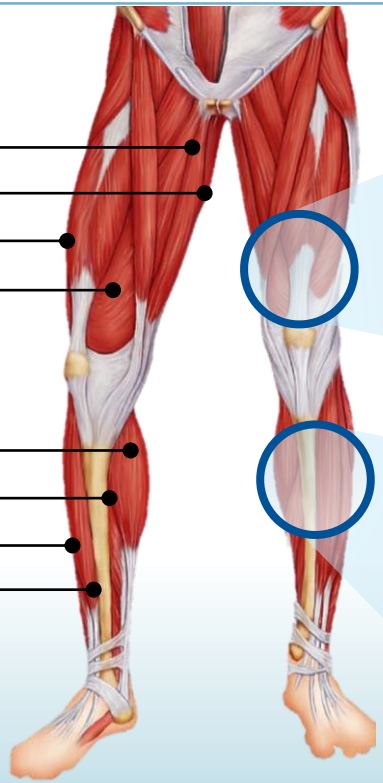
Biopsy is Subject to Sampling Bias



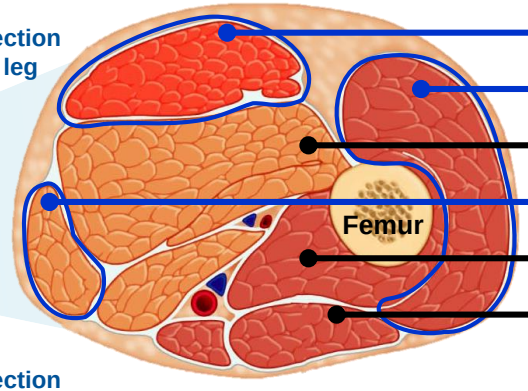
ImagingDMD Group

- **Consortium of academic groups started in 2005 to develop skeletal muscle MRI as a non-invasive, objective, quantitative, reliable biomarker for assessing disease progression and therapeutic intervention in DMD**
- **Sites involved**
  - Children's Hospital Of Pennsylvania (CHOP) - Philadelphia, PA
  - Oregon Health Sciences University (OHSU)/Shriner's – Portland, OR
  - University of Florida (UF) - Gainesville, FL
- **Achievements to-date**
  - Database of boys affected with DMD followed for years
  - Developed standardized protocols of MRI techniques
  - Generated data demonstrating validity of measures
  - More than 15 published manuscripts
  - Running multiple clinical trials using MRI as an end point
  - In discussions with regulatory agencies to explore use as a surrogate biomarker

Overview of Leg Muscle Anatomy

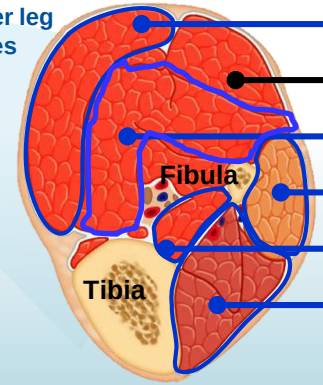


Cross-section of upper leg muscles



Biceps Femoris (BFLH)
Vastus Lateralis (VL)
Adductor Magnus
Gracilis (Gra)
Vastus Intermedius
Rectus Femoris

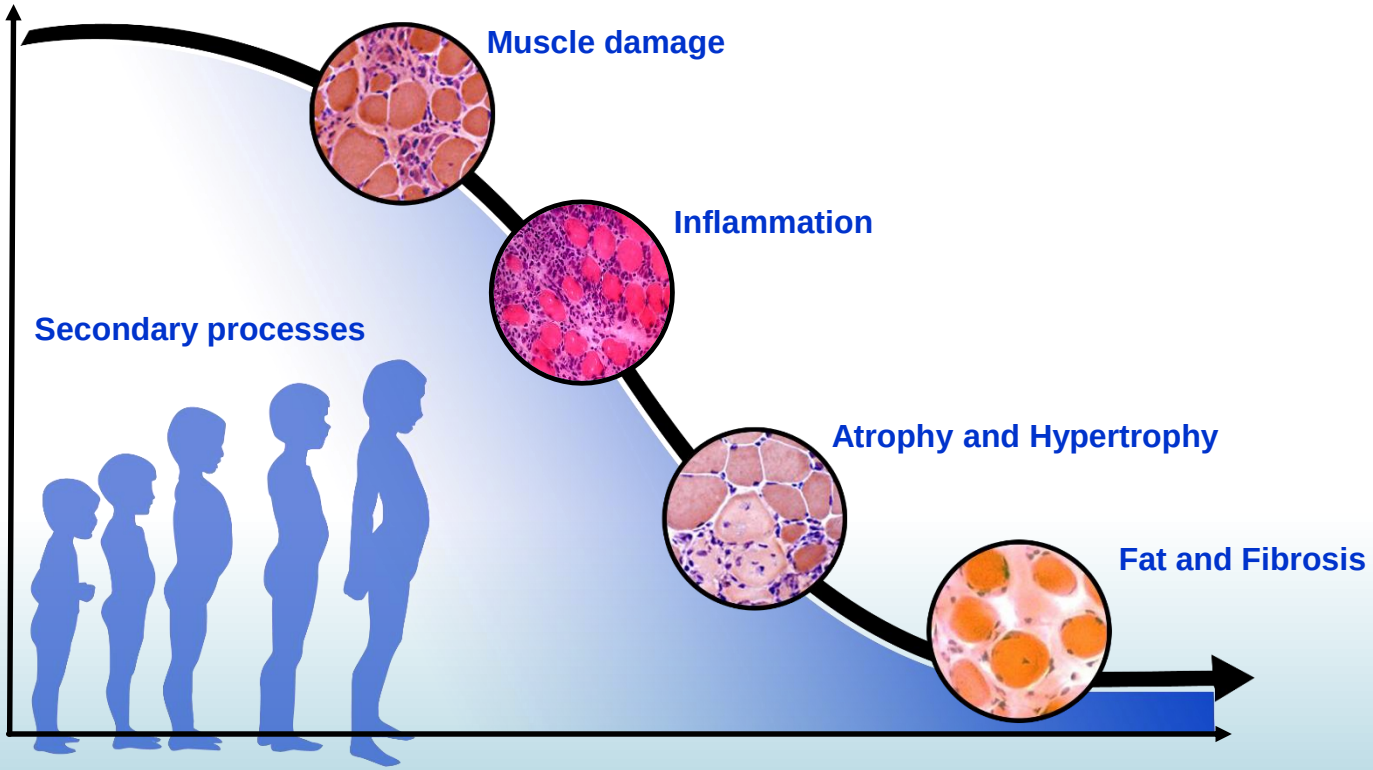
Cross-section of lower leg muscles



Gastrocnemius Medial (MG)
Gastrocnemius Lateral
Soleus (Sol)
Peroneals (Per)
Tibialis Posterior (TP)
Tibialis Anterior (TA)

MRI studies have focused on muscles shown in blue

Different MR Measurements Can Target Various Points of Disease Progression



Overview of MR Techniques and Measures

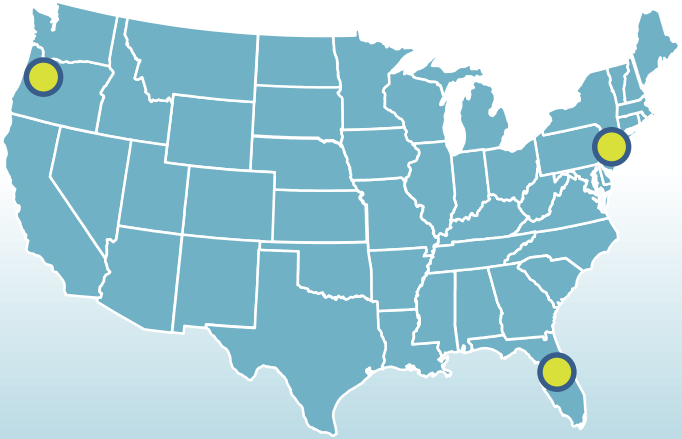
Technique	Measure	What it measures
MRI	Qualitative T1 imaging	• Visual changes in muscle structure and morphology
	T1-weighted quantitative imaging (maximal cross-sectional area, contractile and non-contractile area and specific force production)	• Changes in muscle fat and fibrosis
	T2-provides excellent coverage and spatial resolution allowing distinction from fat fraction	• Changes in muscle inflammation
	$^{1}H_2O$ T2-can detect early muscle pathology	
MRS	T2-highly quantitative but loses some spatial resolution and distinction from fat fraction	
	Fat Fraction (FF)	• Changes in muscle fat
Dixon	Fat Fraction (FF)	

ImagingDMD Group

- **>150 boys followed for 5+ years**
  - Boys with DMD and controls
  - On steroids and steroid-naïve
- **Multiple analyses / studies including 3 seminal studies using leg muscles to develop MRI/MRS as a biomarker for therapeutic development looking at various MRI, TFTs, muscle strength measures**
  - Study 1: Natural history
  - Study 2: Effects of initiation of corticosteroids
  - Study 3: Cross-sectional view of effects of corticosteroids

Study 1: Natural History

	Controls	DMD
Number	51	138
Mean Age (years)	8.8 ± 2.4	8.0 ± 3.3
Steroid positive (number)	NA	104
BMI	17.3 ± 3.4	19.1 ±4.1

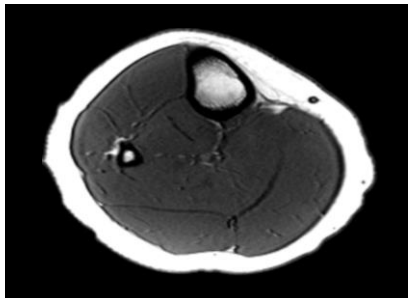
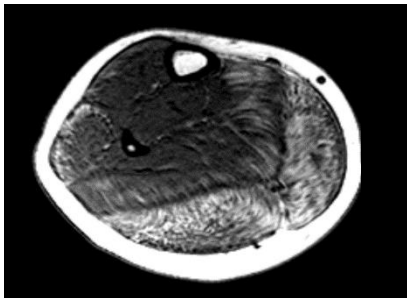
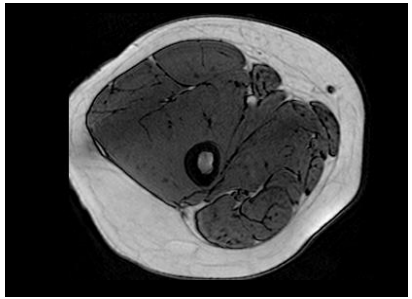
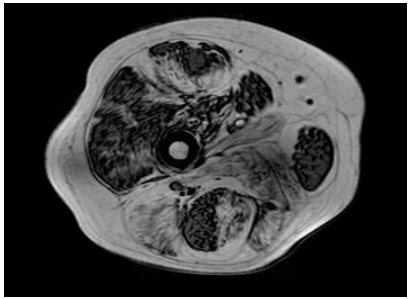


- **CHOP** — Philadelphia, PA
- **OHSU/Shriner's** — Portland, OR
- **UF** — Gainesville, FL

- **Krista Vandenborne (UF), PI**
- **Lee Sweeney (UF, UPenn/CHOP), Co-PI**

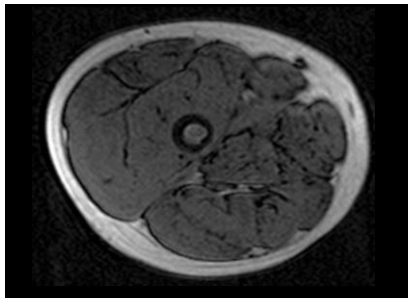
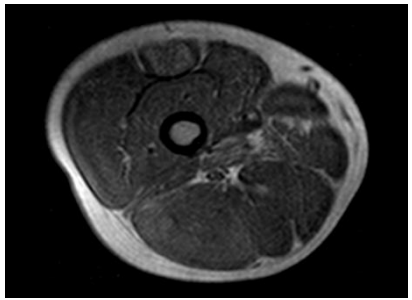
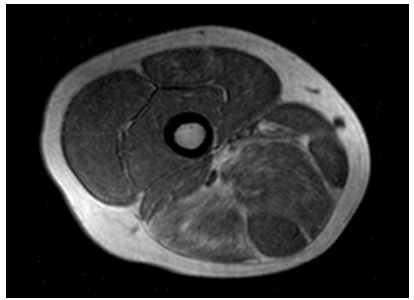
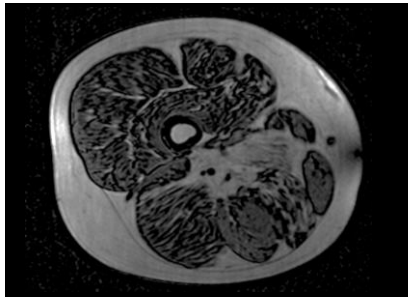
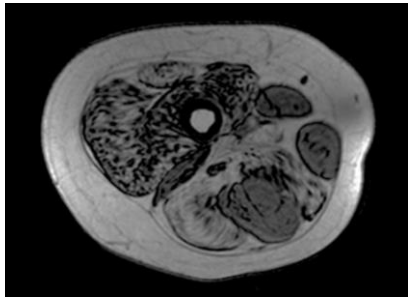
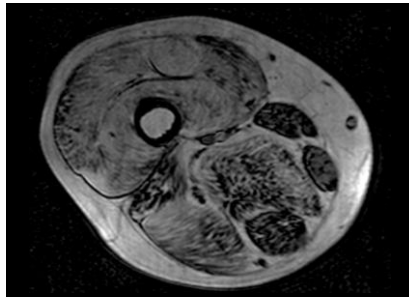
T1-Weighted MR Image Can Show Qualitative Changes in Entire Muscles and in Multiple Muscles

Age
10 – 12

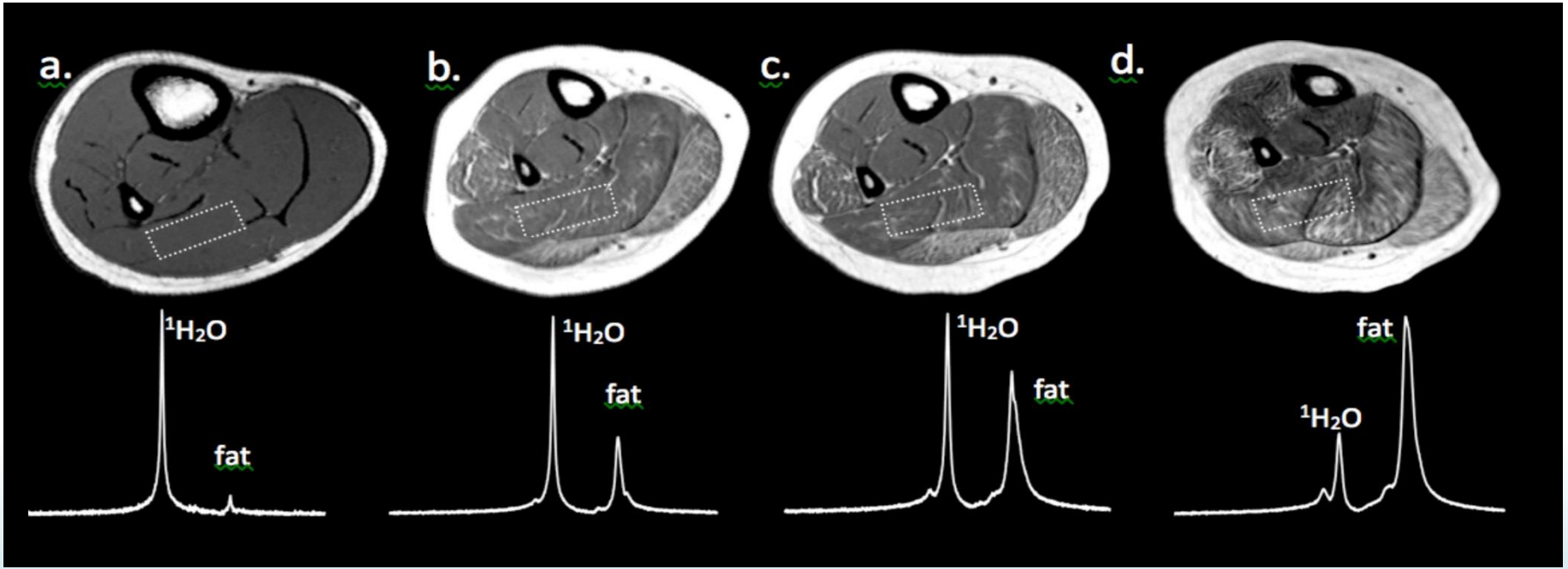
	Control	Duchenne
Lower leg muscles		
Thigh muscles		

Lower leg muscles such as soleus show the most inflammation (not visible using T1-weighted image); replacement of thigh muscles, such as vastus lateralis, with fat is easier to visualize

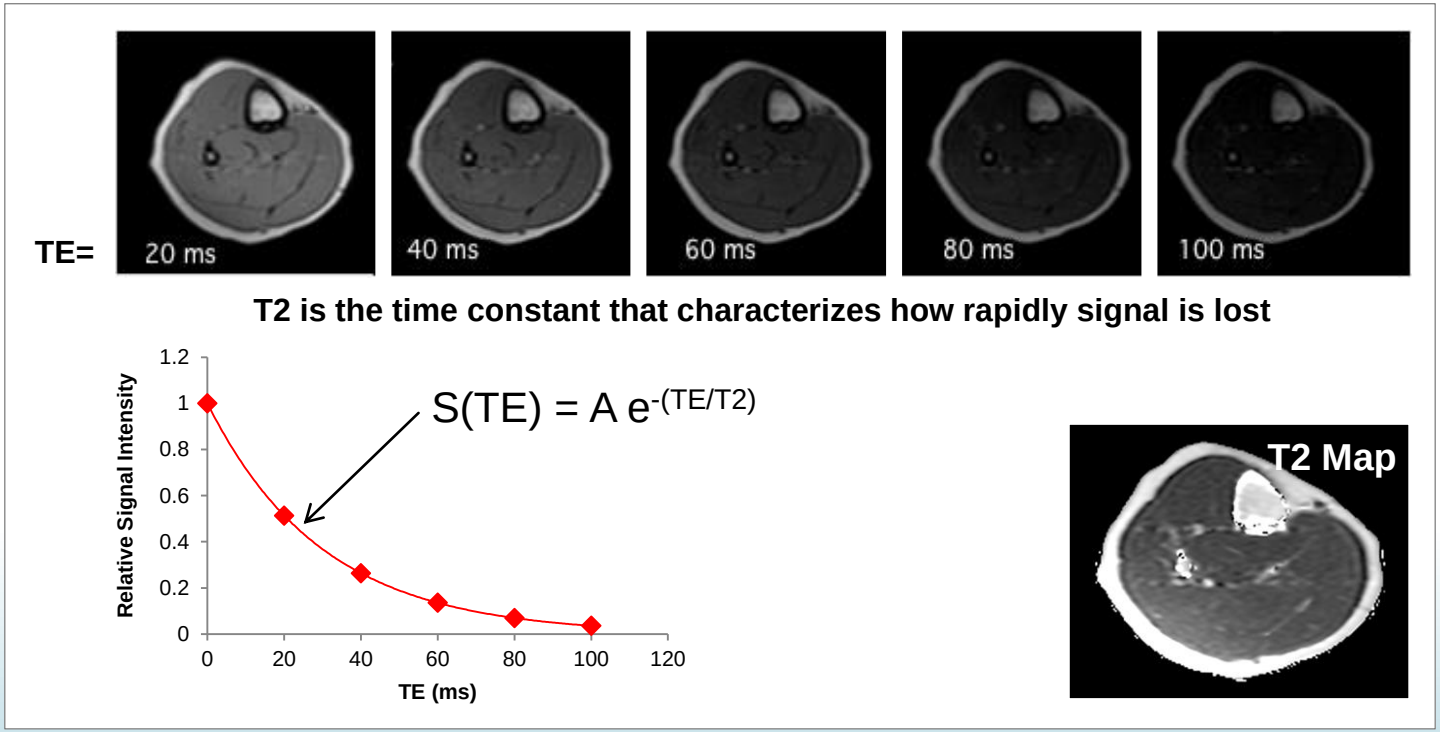
T1-Weighted Changes Are Seen with Increasing Age and with Disease Progression; Limited Quantification Possible by Measuring Cross-sectional Area

		
Age 5	Age 6 - 7	Age 8 - 9
		
Age 10 - 11	Age 12 - 13	Age 14

Quantitative MRI/MRS Can Detect DMD Disease Progression and Measure it Accurately and Quantitatively



Quantitative T2 MRI Provides Excellent Coverage and Spatial Resolution



Quantitative T2 MRI Is Highly Objective and Reproducible

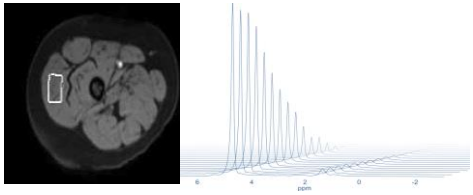
Coefficient of Variability (CV) in MRI T2 Signal

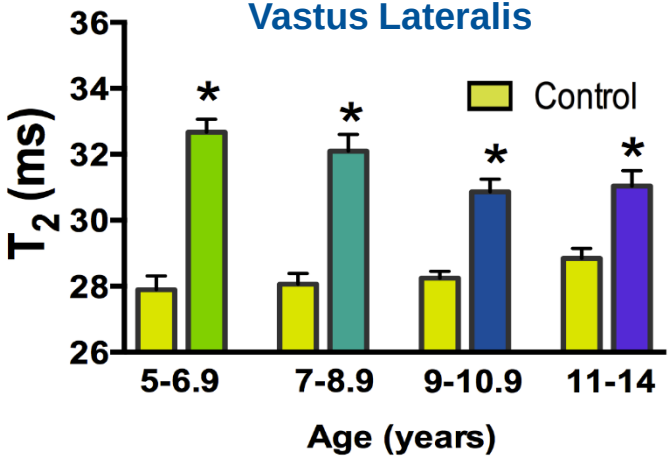
MRI T2 Measure	CV
Day-to-day variability in phantom	0% - 0.7%
Day-to-day variability in soleus of normal boys	1.3%
Day-to-day variability in soleus of boys with DMD	1.9%
Inter-rater variability	1.2%
Inter-site variability in leg muscles of normal adults	1.9 – 4.7%

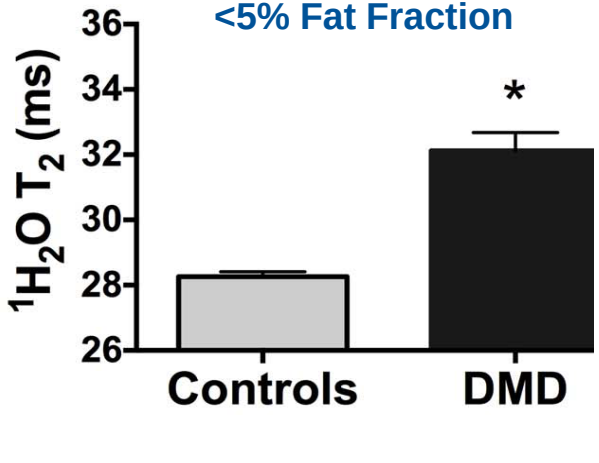
Excellent reproducibility: Covariance intra-site: ~2%; inter-site: ~5%

Forbes *et al,* Radiology (2013)

$^{1}H_2O$ T2 Detects Early Muscle Pathology

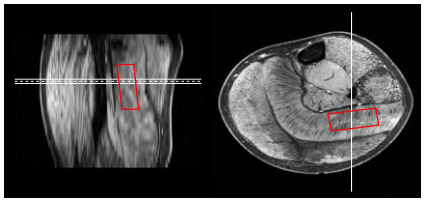


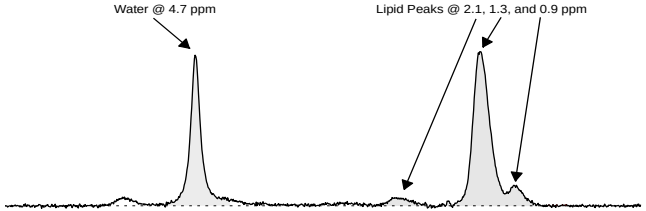


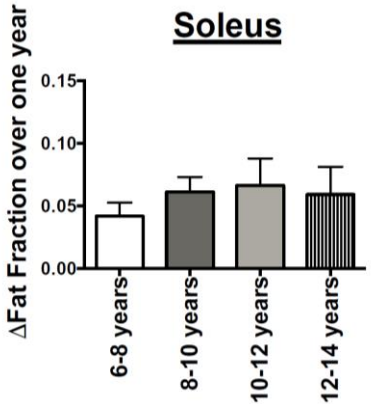


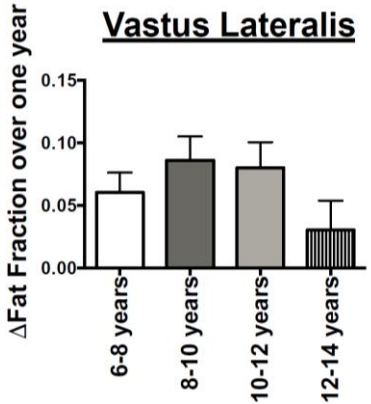
Forbes *et al,* PLoS 2014

MR Spectroscopy Fat Fraction
MRS Δ(Fat Fraction) and Age



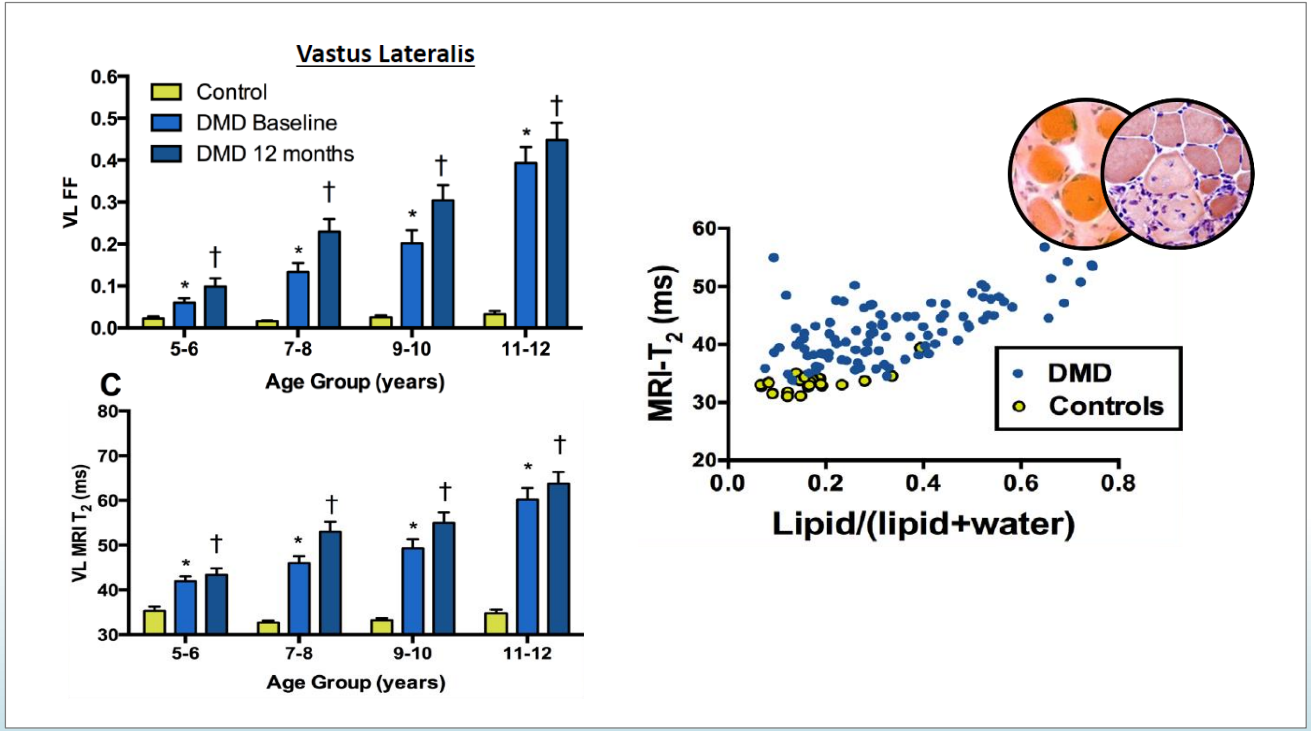






ImagingDMD data on file

MRI T2 and Fat Fraction Increase with Age in DMD



ImagingDMD data on file

MRI T2 and FF are Correlated with Timed Function Tests

- Correlations between the change in the MRI variables and the change in functional test times
- Treat each time point as a separate observation (n=421)

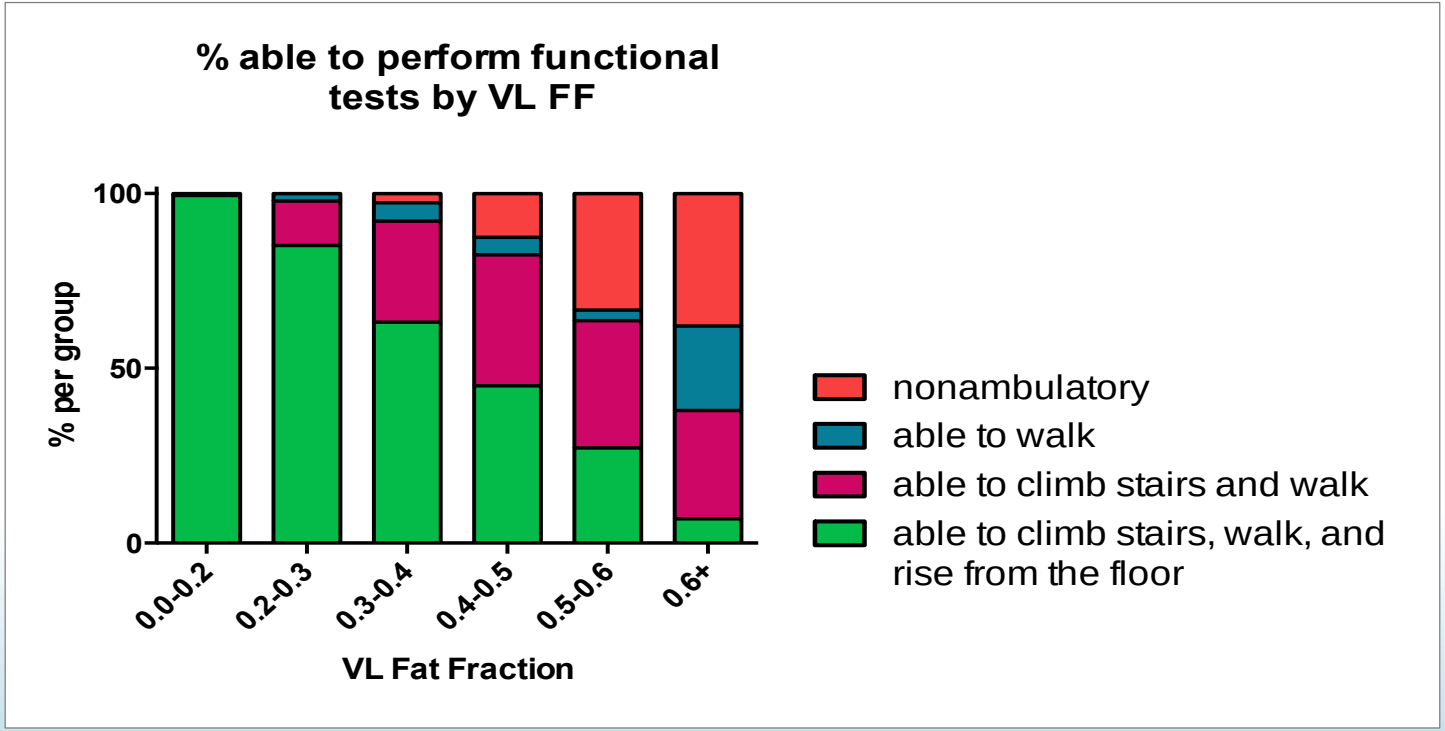
	VL FF	SOL FF
Supine to stand	0.77	0.64
10-meter walk/run	0.75	0.65
4 Stairs	0.73	0.66
6MWT	-0.63	-0.57

	BFLH T2	VL T2	GRA T2	PER T2	MG T2	SOL T2	TA T2	TP T2
Supine to stand	0.75	0.76	0.26 P=.044	0.72	0.57	0.65	0.61	0.54
10-meter walk/run	0.66	0.76	0.38	0.72	0.64	0.65	0.64	0.6
4-stair climb	0.68	0.73	0.35	0.73	0.65	0.68	0.65	0.6
6MWT	-0.55	-0.64	-0.21 P>.05	-0.57	-0.54	-0.55	-0.57	-0.53

p<0.0001 unless otherwise specified

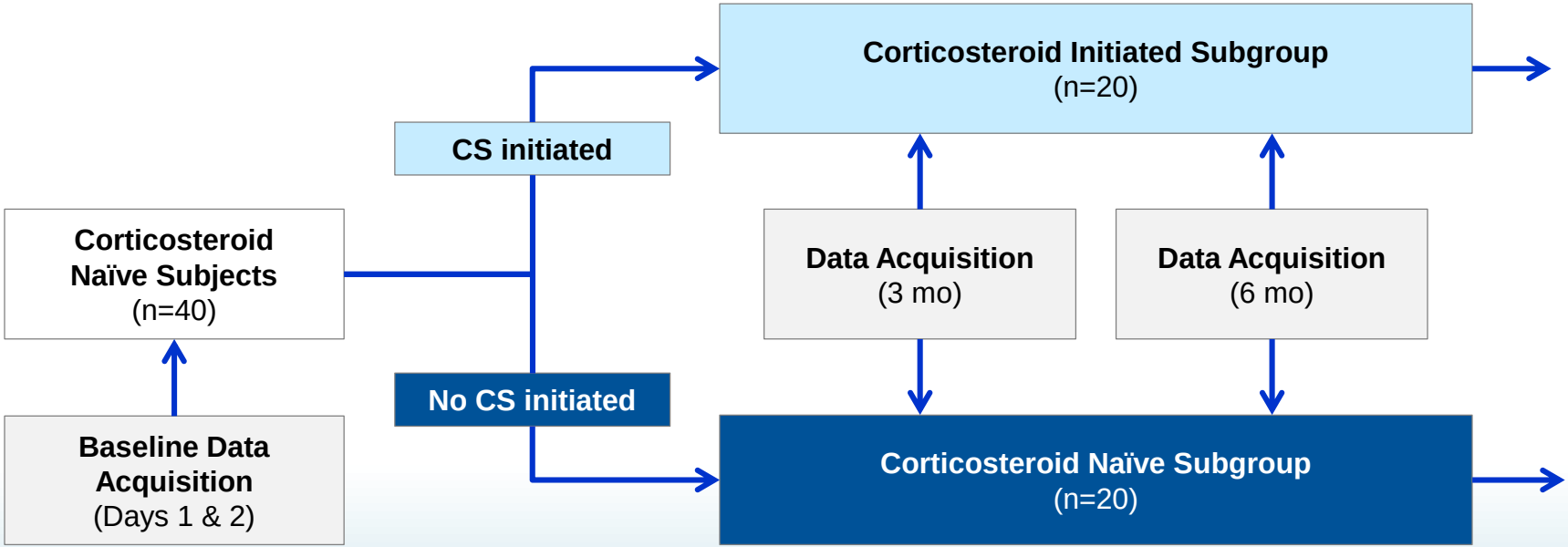
ImagingDMD data on file

Increase in FF Is Associated with Loss of Functional Ability



ImagingDMD data on file

Study 2: Effects of Initiation of Corticosteroids Study



Boys ages 5-8 years; CDC care consideration: Start corticosteroids when boys experience functional decline or “plateau” phase. Corticosteroid treatment arm: Prednisone (0.75mg/kg/day) or an equivalent dose of an alternative corticosteroid. Exclusion: tapering to below 0.30mg/kg/day.

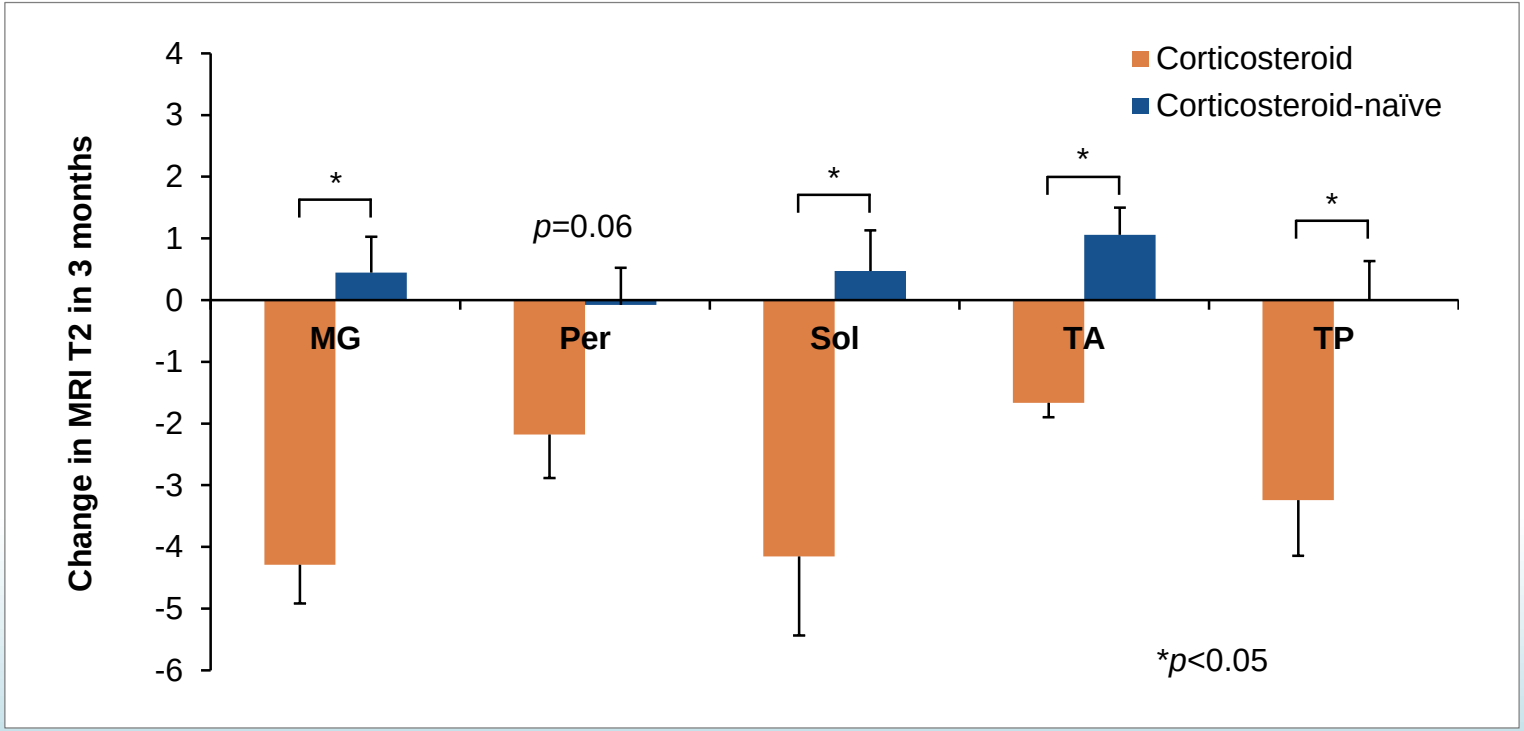
Baseline Demographics

	CS (n=6)	CS naive (n=11)	*p* Value
Age (yrs)	6.7±1.3	6.2±1.0	0.36
6 minute Walk Test (m)	388±49	340±73	0.20
10-meter Walk/Run (sec)	6.21±0.20	6.65±1.30	0.47
4-stair Climb (sec)	4.17±0.53	4.91±1.25	0.23
Floor to Stand (sec)	6.17±0.90	8.52±6.82	0.46

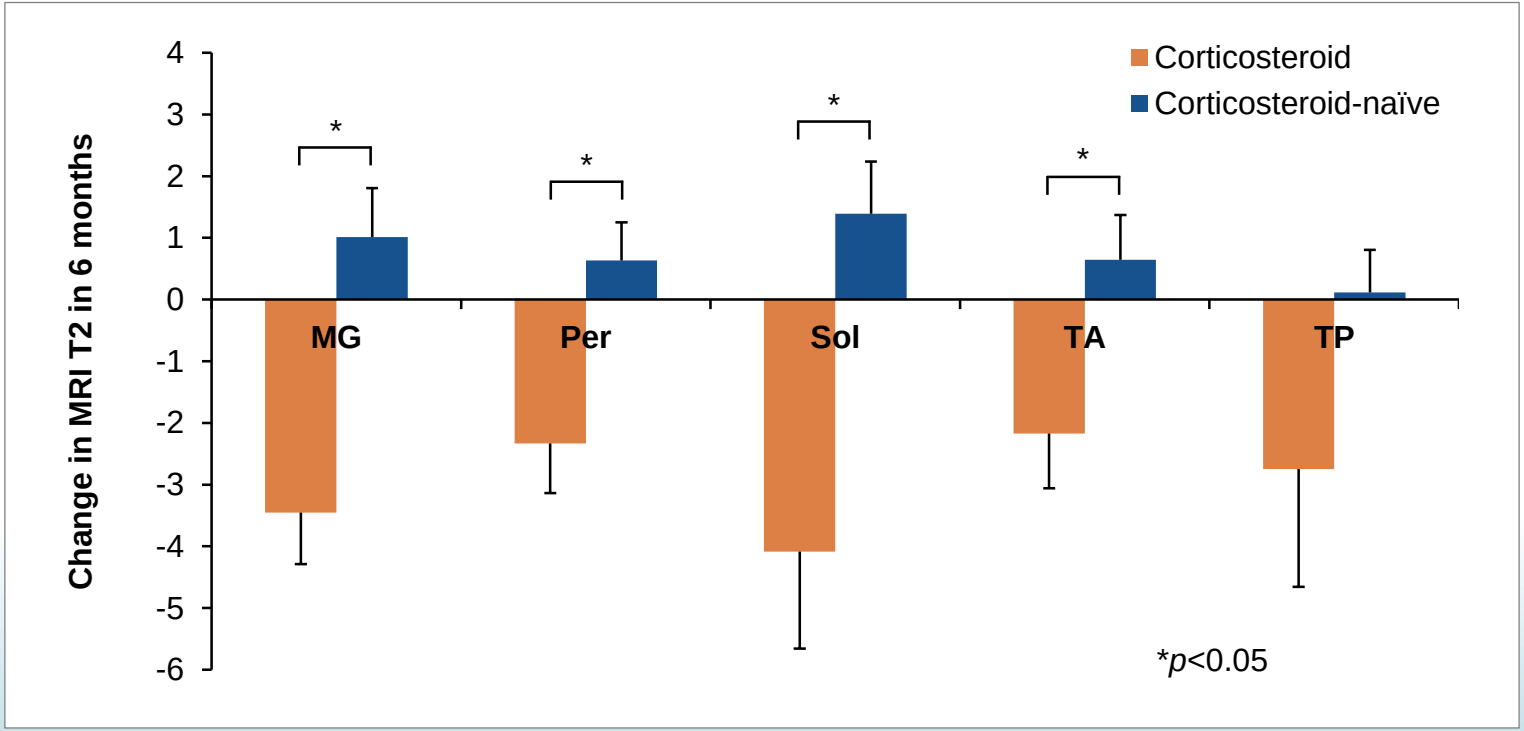
Mean±SD

Corticosteroid dose: Age at initiation: 6.7±1.3 years; 5 deflazacort: dose 0.82-0.9 mg/kg/day; 1 prednisone: 0.75 mg/kg/day

Significant Changes in MRI T2 Seen in 3 Months in Most Lower Leg Muscles

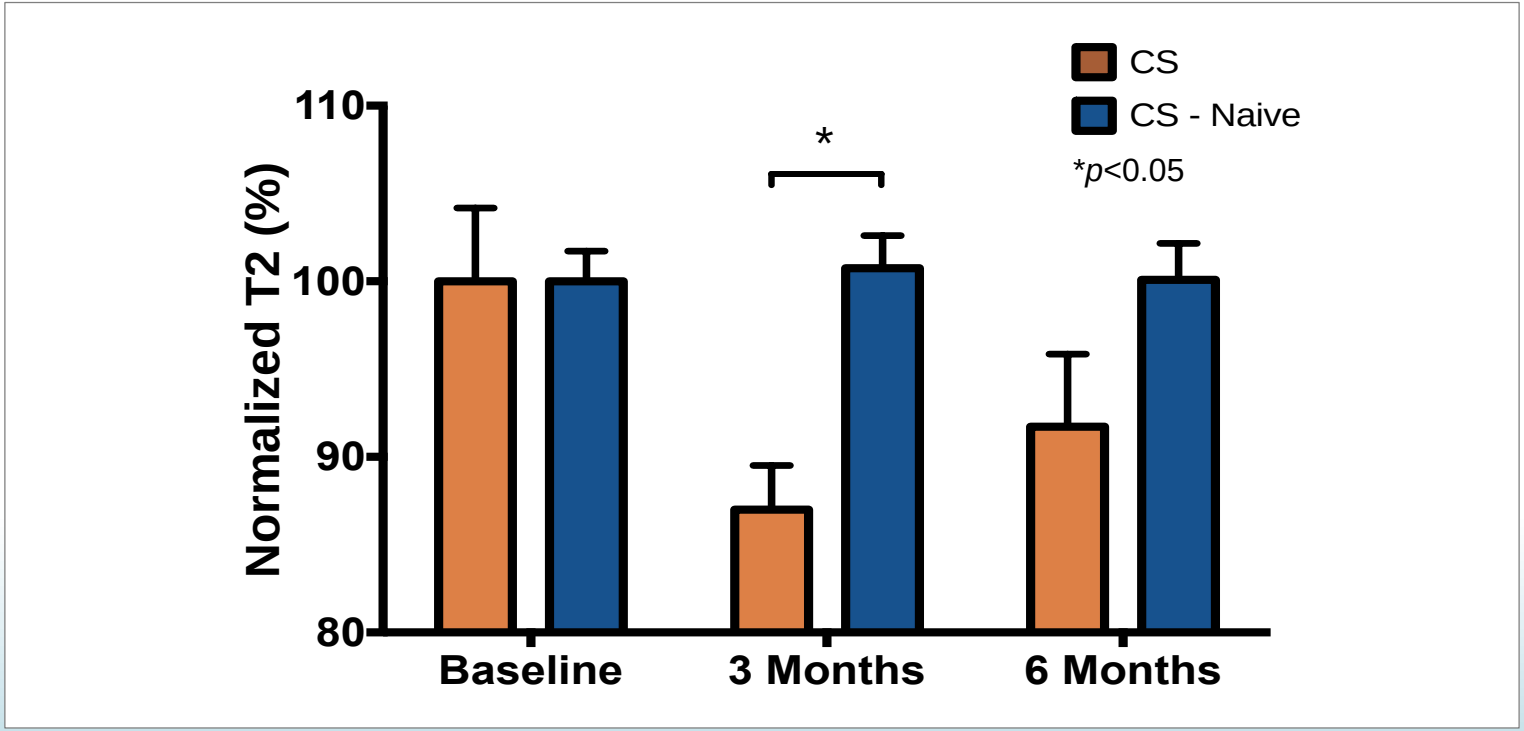


Significant Changes in MRI T2 Seen in 6 Months in Most Lower Leg Muscles



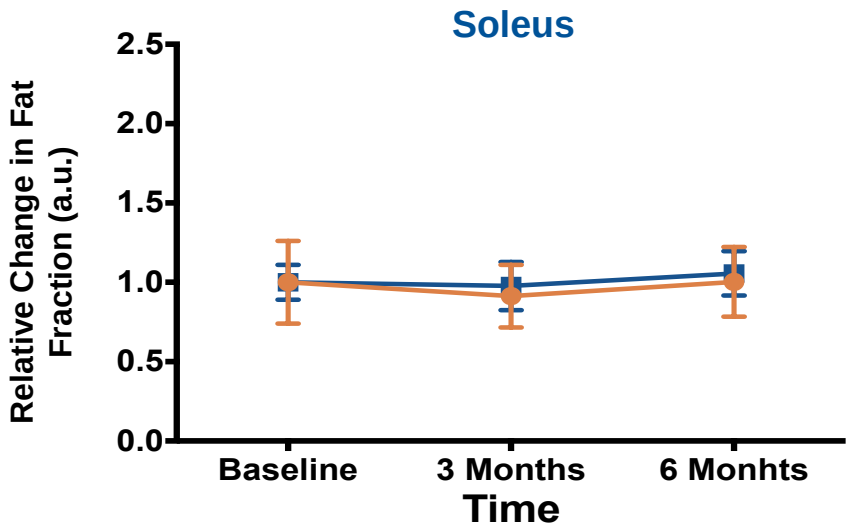
Arpan et al Neurology 2014 83:1-7

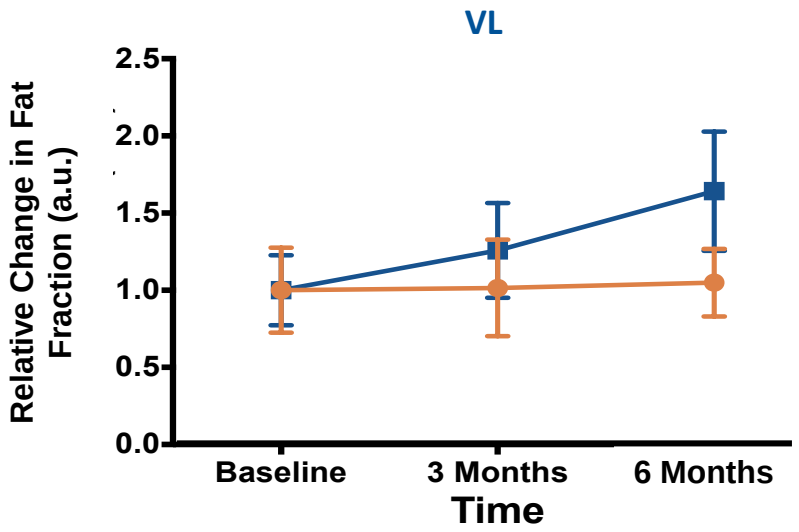
Significant Changes Seen in $^{1}H_2O$ T2 in 3 Months in Soleus



ImagingDMD data on file

Relative Changes in Fat Fraction in Soleus and Vastus Lateralis Less Discernible in 3 Months



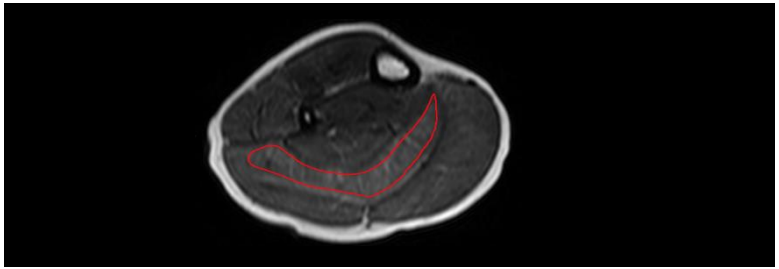


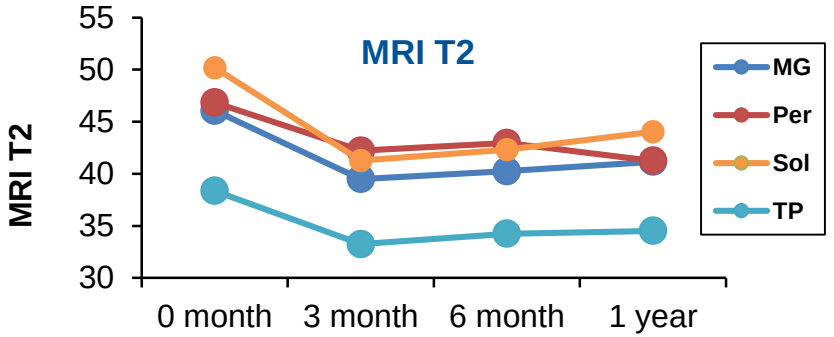
Mean ± SEM

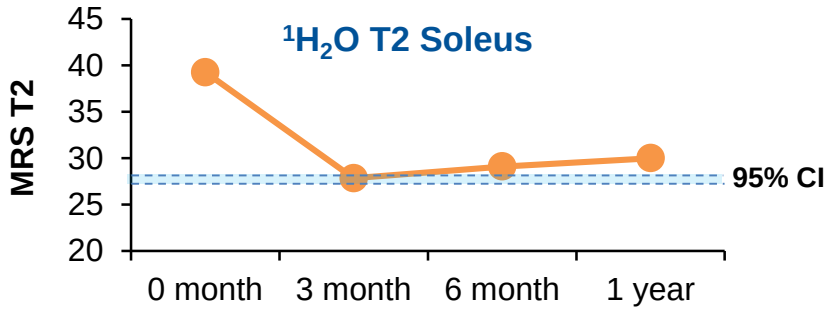
CS CS-Naive

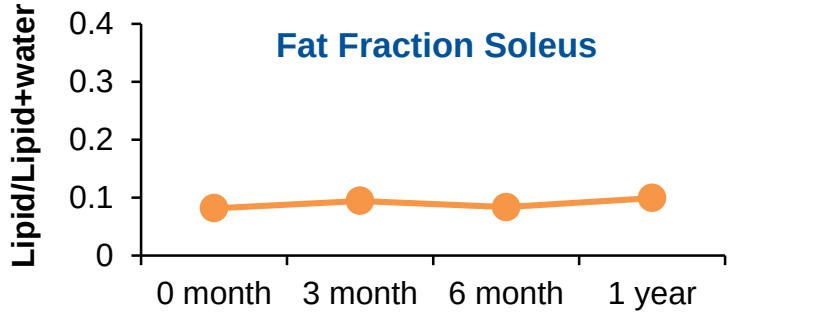
ImagingDMD data on file

1 Year Corticosteroid Treatment in 8 YO Subject: Significant Changes Seen in MRI T2 and ^1H_2O T2 within 3 Months but not in FF of Soleus



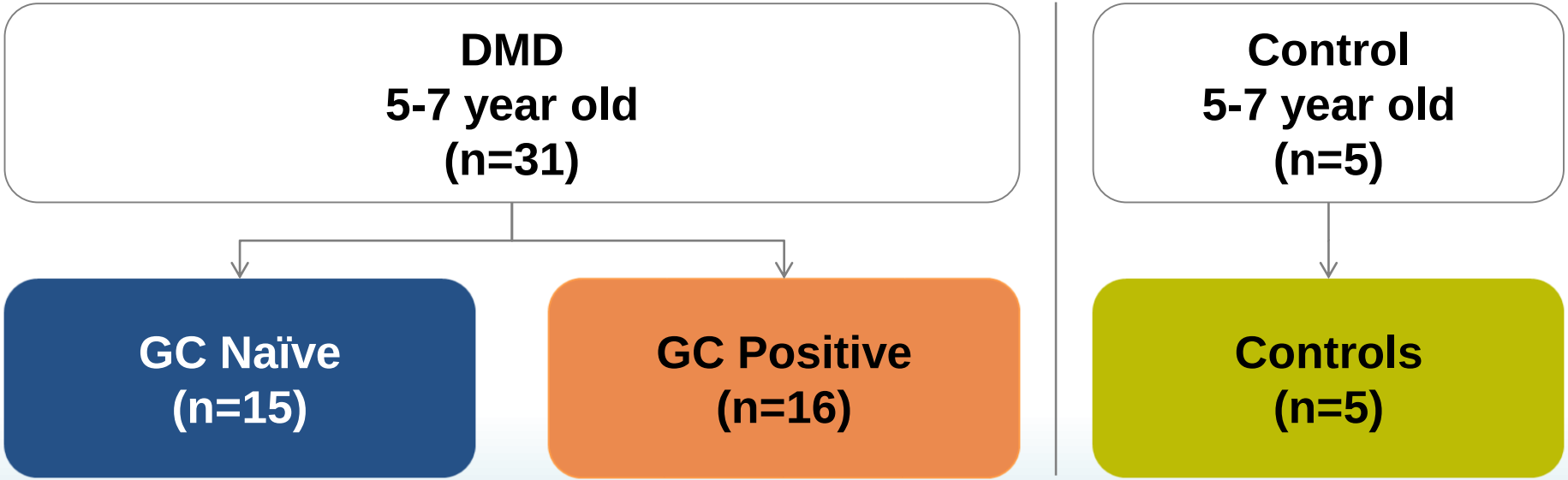






ImagingDMD data on file

Study 3: Cross-sectional Comparison Based on Corticosteroid Use



Look at multiple measures of MRI/MRS, function and strength

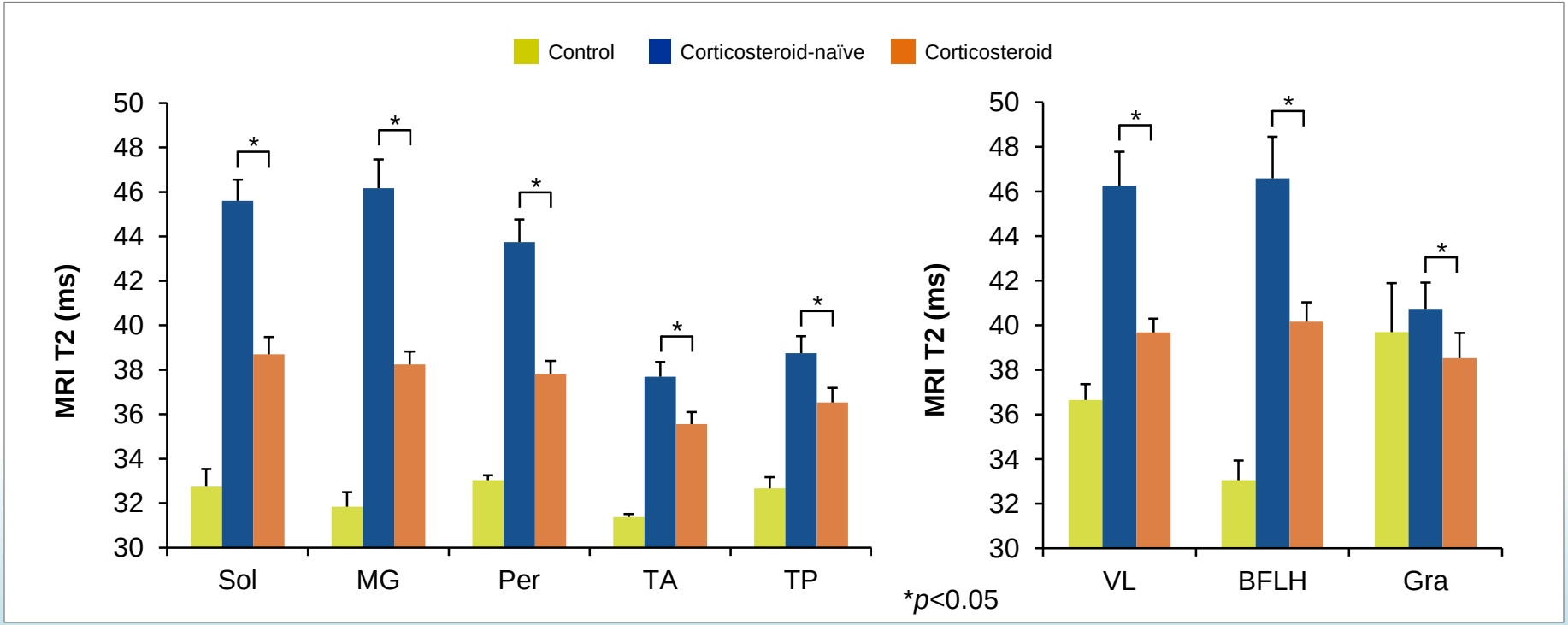
Demographics

	Controls (n=5)	Corticosteroid-naïve (n=15)	Corticosteroid (n=16)
Age (years)	6.2±0.3	6.1±0.1	6.2±0.1
Weight (kg)	22.2±2.7	20.7±1.1	20.4±0.7
Height (cm)	120.6±4.1	111.7±1.3	109.4±1.2
BMI (kg/m^2)	15.1±0.9	16.6±0.7	17.0±0.4

No significant differences

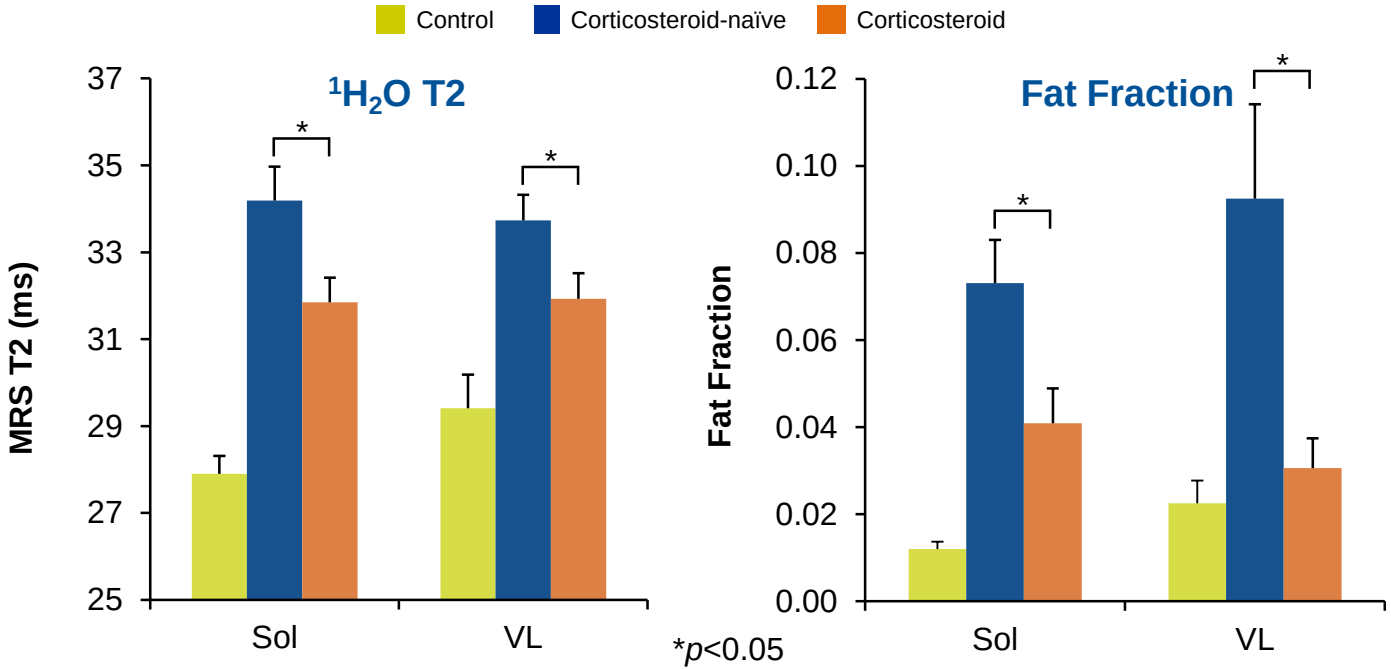
Corticosteroid dose: Age at initiation: 4.3± 1.3years; 12 Deflazacort: 0.73±0.27mg/kg/day *[CDC:0.9];* 4 Prednisone: 0.63±0.05 mg/kg/day *[CDC:0.75];* Length: 7 mo – 4 yrs, except 1 subject (4 mo)

Significant Differences in MRI T2 for Boys Stable on Steroids vs. Boys Not on Steroids



Stable on steroids: Boys were on steroids for 7 months – 4 years in this study

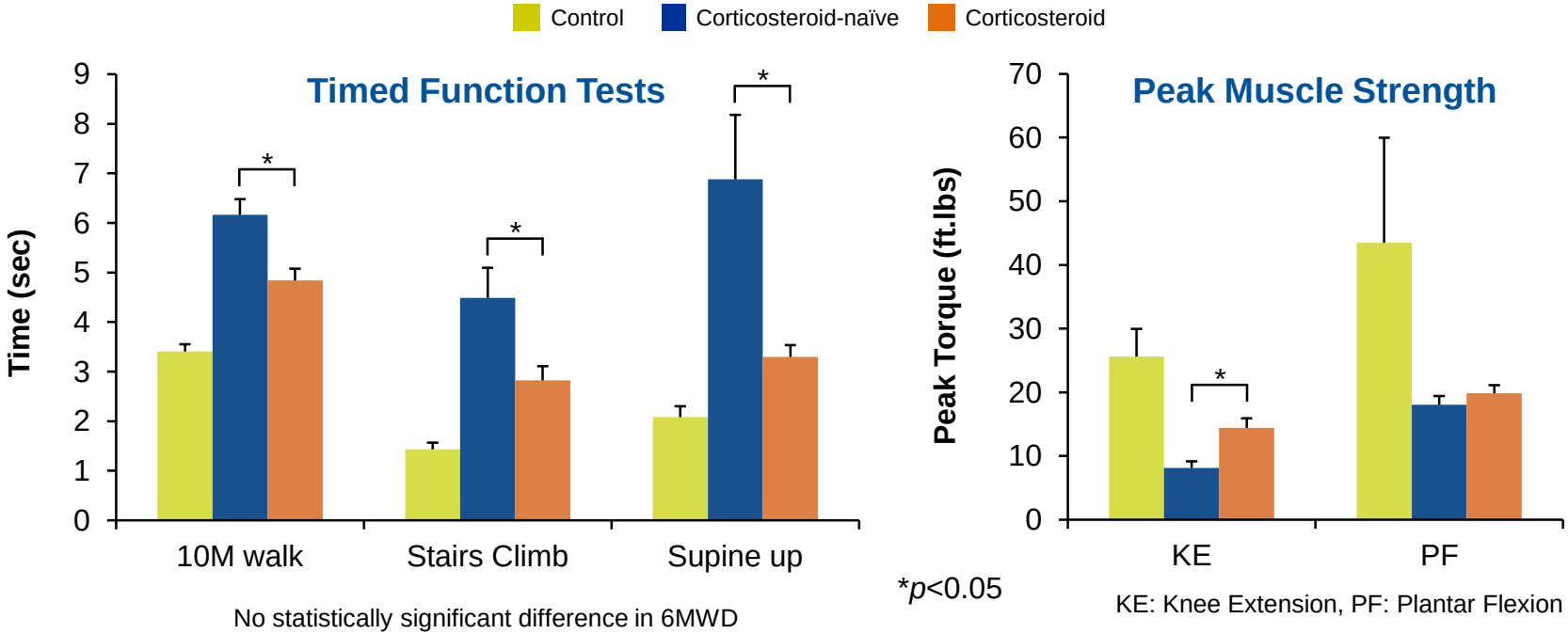
Significant Differences in ^1H_2O T2 and FF for Boys Stable on Steroids vs. Boys Not on Steroids



Stable on steroids: Boys were on steroids for 7 months – 4 years in this study

ImagingDMD data on file

Significant Differences in Functional Tests for Boys Stable on Steroids vs. Boys Not on Steroids



Stable on steroids: Boys were on steroids for 7 months – 4 years in this study

ImagingDMD data on file

Overview of MR Techniques and Measures

Technique	Measure	What it measures	Considerations
MRI	Qualitative T1 imaging	• Visual changes in muscle structure and morphology	• Simple to see • Non-quantitative
	T1-weighted quantitative imaging (maximal cross-sectional area, contractile and non-contractile area and specific force production)	• Changes in muscle fat and fibrosis	• Somewhat quantitative • Higher signal-to-noise and less correlated to clinical measures
	T2-provides excellent coverage and spatial resolution allowing distinction from fat fraction	• Changes in muscle inflammation	• Quantitative • Significant natural history data • Lower signal-to-noise • Well correlated to clinical function
	$^{1}H_2O$ T2-can detect early muscle pathology		
MRS	T2-highly quantitative but loses some spatial resolution and distinction from fat fraction		
	Fat Fraction (FF)	• Changes in muscle fat	• Strongly correlated to clinical function and loss of milestones
Dixon	Fat Fraction (FF)		• Sophisticated analyses • Exploratory

Summary

- **MRI/MRS measures well suited to be used as a biomarker in therapeutic development in DMD**
  - Allows the quantitative assessment of the amount and health of defined skeletal muscles
  - Sensitive to disease progression and correlate with specific functional measures
  - Non-invasive, unbiased, quantitative and excellent reproducibility
- **Different techniques and muscles offer unique strengths to capture aspects of disease pathology**
  - MRI T2 and ^{1}H-MRS can measure disease progression (inflammation) over 3 months
  - Fat fraction can measure disease progression (fat, fibrosis) over > 3 months
  - Lower leg muscles such as soleus show the most inflammation
- **Effect of corticosteroids**
  - Initiation of corticosteroids was associated with a significant decline in T2 in 3 months, which was easily detected by both MRI and MRS
  - For boys on corticosteroids for 7 months – 4 years, cross-sectional comparison showed significantly lower T2 values and fat fraction and significantly better performance on the timed function tests (10-meter walk/run, 4-stair climb and time to stand)

MoveDMD Trial: Study Powered for MRI T2 Changes Based on Analyses from the ImagingDMD Database

✓ = Planned Assessments ▭ Primary end point: change from baseline in MRI T2 composite of lower leg muscles

Muscles	Part A Baseline	Part B Baseline	Part B 12 Weeks	Part C (Multiple Timepoints)
MRI T2				
Soleus	✓	✓	✓	✓
Medial Gastrocnemius	✓	✓	✓	✓
Peroneals	✓	✓	✓	✓
Tibialis Anterior	✓	✓	✓	✓
Tibialis Posterior	✓	✓	✓	✓
Vastus Lateralis	✓	✓	✓	✓
Biceps Femoris Long Head	✓	✓	✓	✓
Gracilis	✓	✓	✓	✓
MR Spectroscopy T2				
Soleus	✓	✓	✓	✓
Vastus Lateralis	✓	✓	✓	✓
MR Spectroscopy Fat Fraction and Dixon Fat Fraction				
Soleus	✓	✓	✓	✓
Vastus Lateralis	✓	✓	✓	✓

Baseline Characteristics for Timed Function Tests in MoveDMD Trial Are Similar to those in ImagingDMD Study

	CS naïve group of ImagingDMD: Effects of Initiation of Corticosteroids Study (n=11)	MoveDMD Part A Baseline (n=15)	MoveDMD Part B Baseline (n=15)
10-meter Walk/Run (sec)	6.7 ± 1.3	6.2 ± 1.3	6.8 ± 1.7
4-stair Climb (sec)	4.9 ± 1.3	4.7 ± 2.3	6.0 ± 3.5
Floor to Stand (sec)	8.5 ± 6.8	6.1 ± 2.7	8.5 ± 5.9

MoveDMD trial not powered for statistically significant changes in TFTs

Comparison of MoveDMD Trial with ImagingDMD Study

	ImagingDMD Study: Effects of Initiation of Corticosteroids	MoveDMD Trial Part B
Comparison	Corticosteroids vs. Corticosteroid-naive	Edasalonexent vs. Corticosteroid-naive
No. of Patients	N = 16	N = 31
Study Sites	ImagingDMD group	ImagingDMD and associated sites
Primary End Point	MRI: Change in T2 of lower leg muscles	MRI: Change in T2 of lower leg muscles
Duration	12 weeks	12 weeks
MRI T2 Results	**Positive** $p \leq 0.01$	**Results expected first half Q1 2017**

MRI and Preclinical Study Acknowledgments

IMAGING DMD
ON TOP OF THE FIGHT FOR A CURE

NIAMS

National Heart Lung and Blood Institute

NATIONAL INSTITUTES OF HEALTH

David Hammers
Elisabeth Barton
Meg Sleeper
Sean Forbes

Glenn Walter
Krista Vandenborne
Rebecca Willcocks

Edasalonexent Clinical Overview and MoveDMD® Trial

Joanne Donovan, MD, PhD
Chief Medical Officer & SVP, Clinical Development

Our Vision for the Clinical Profile of Edasalonexent in DMD

- **Potential disease-modifying non-steroid oral therapy for Duchenne**
  - Intended for all patients, regardless of mutation type
  - Inhibits muscle degeneration and enhances muscle regeneration
  - Benefits in skeletal muscle, diaphragm and heart
- **Potential foundational therapy**
  - Initiate upon diagnosis
  - Potentially effective as monotherapy and in combination with dystrophin / utrophin upregulation approaches

Edasalonexent Clinical Trial Dataset

Study	Design	Population	Duration	N	Maximum Daily Dose	Status
CAT-1004-101	First-in-human single ascending-dose, randomized, double-blind, placebo-controlled	Adults	Single-dose	52	6,000 mg	Complete
CAT-1004-102	Multiple ascending-dose, randomized, double-blind, placebo-controlled	Adults	14 days	44	4,000 mg	Complete
CAT-1004-103	Single-dose biomarker study comparing edasalonexent to equimolar ratio of component bioactives	Adults	Single-dose	9	2,000 mg	Complete
CAT-1004-201 (MoveDMD trial)	**Part A:** Multiple ascending-dose, open-label	Boys with DMD	7 days	17	100 mg/kg	Complete
	Part B: Randomized, double-blind, placebo-controlled	Boys with DMD	12 weeks	31	100 mg/kg	Ongoing
	Part C: Open-label extension	Boys with DMD	36 weeks	31	100 mg/kg	Ongoing

Edasalonexent: Multiple Clinical and Regulatory Milestones Achieved

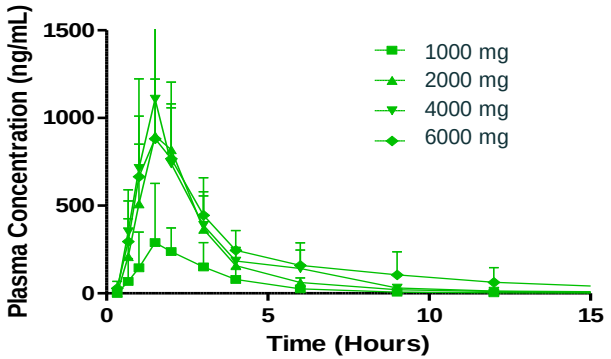
	Clinical	
	Adults	Boys with DMD
Safety and tolerability	✓	✓
Adequate exposure	✓	✓
NF-κB target engagement	✓	✓

- Received fast track, rare pediatric disease and orphan drug designations from the FDA and orphan medicinal product designation from the European Commission
- MoveDMD Phase 2 (Part B) trial with open-label extension underway; top-line results for Phase 2 portion expected first half Q1 2017

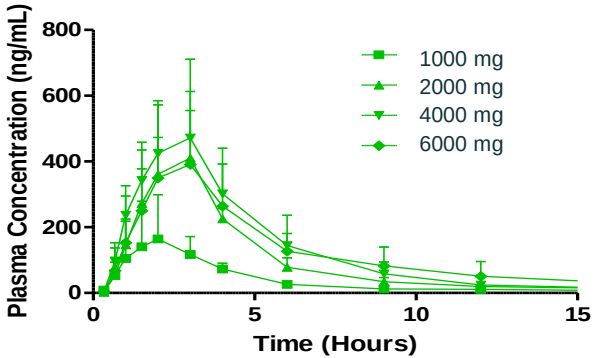
Phase 1 SAD Study in Adults: No Safety Signals, Well Tolerated and Good Exposure

- No safety signals and generally well tolerated
- Edasalonexent absorbed with C_{max} ~2 hours and sustained production of the metabolite salicyluric acid
- Metabolism to salicylurate consistent with known intracellular metabolic pathways of salicylic acid
- Neither salicylic acid, nor dose-dependent increases in DHA, were observed in plasma

Edasalonexent: Fed



Salicylurate: Fed



Donovan et al., J Clin Pharm, in press

Phase 1 MAD Study in Adults: No Safety Signals, Well Tolerated, Good Exposure and Target Engagement

- **Exposure:**
  - 79 adults who received up to 2000 mg BID (~67 mg/kg total) for 14 days
- **Assessments:**
  - Laboratory: no safety signals, including liver, renal, hematology
  - PE, EKG, vitals: no safety signals
- **Adverse events in multiple ascending dose study (14 days):**

Adverse Events in > 1 Patient	Placebo n=12	300 mg n=6	1000 mg n=8	2000 mg n=9	4000 mg n=9	Total n=44
Diarrhea	0	0	0	0	2	2
Gastroenteritis	1	0	1	0	0	2
Upper respiratory infection	0	0	0	0	2	2

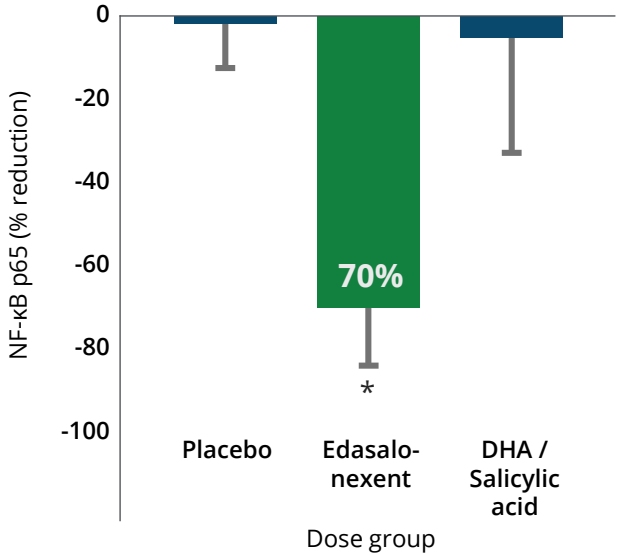
- **No discontinuations**

Donovan et al., J Clin Pharm, in press

Phase 1 Biomarker Study in Adults: Edasalonexent Significantly Inhibits Activation of NF-κB

- **Design:**
  - Three-way crossover design in 9 adult subjects
  - NF-κB activity: p-65 DNA binding activity in PMBC nuclear extracts and NF-κB-target gene set
- **Results:**
  - Significant reductions in NF-κB biomarker activity with single 2,000 mg dose of edasalonexent compared to placebo or the co-administration of the bioactives, salicylic acid and the omega-3 fatty acid, DHA
  - In MAD, significantly reduced expression of NF-κB target gene set after 14 days of dosing

Phase 1 Clinical Data
Inhibition of Activated NF-κB



*p<0.005

Donovan et al., J Clin Pharm, in press

Key Takeaways of Edasalonexent Phase 1 Clinical Studies in Adults

- **Established safety and tolerability of single and multiple doses**
  - No safety issues
  - Generally well-tolerated
- **Established clinical exposure and provide proof of concept for SMART linker technology**
  - No significant levels of salicylic acid
  - Evidence for cellular metabolism to salicylic acid metabolites
  - Demonstrated synergistic activity on NF-κB as compared to the simple combination of salicylic acid and DHA
- **Proof of concept for pharmacological effects**
  - Reduction in NF-κB p65 DNA binding activity
  - Reduction of expression of NF-κB target genes – proinflammatory cytokines and proteasome pathway components

Learnings from DMD Landscape Applied to the Edasalonexent Clinical Program in DMD

	DMD Disease Knowledge		Clinical Measures		Regulatory Path	
Key Learnings	Greater insights into disease progression in age groups	Deeper understanding of natural history	Variability in end points and susceptibility to motivation	Ability to quantify biomarkers and correlate to function	Size of studies needed and ability to rely on natural history data	Interpretation of regulatory guidance in NDA reviews
Catabasis Strategy	Study 4-7 year old population, which is more homogenous	Access to several natural history databases	10-meter walk/run, 4-stair climb and time to stand as age-appropriate timed function tests	MRI T2 as an objective, quantitative end point correlated to timed function tests	Randomized double-blind placebo-controlled trials core to development strategy	Insights taken into account plus leveraging interactions with the agency

Overview of 3-Part MoveDMD Trial in Boys with DMD

Study Population: All DMD mutations, ages 4 – 7, steroid naïve or off steroids for ≥6 months

Part A 7-day, open-label dose-ranging trial of edasalonexent N ~ 6 per arm	**Part B** 12-week, randomized, double-blind placebo-controlled trial N ~ 10 per arm	**Part C** 36-week, open-label treatment period N ~ 10 per arm
33 mg/kg/day	Edasalonexent 67 mg/kg/day	Edasalonexent 67 mg/kg/day
67 mg/kg/day	Edasalonexent 100 mg/kg/day	Edasalonexent 100 mg/kg/day
100 mg/kg/day	Placebo	Edasalonexent 100 mg/kg/day or 67 mg/kg/day

- Assess the safety and PK of edasalonexent in ~18 boys with Duchenne aged 4-7
- Identify doses of edasalonexent that have plasma exposures known to have effects on NF-κB

- Assess the safety of edasalonexent over 12 weeks in ~30 boys with Duchenne aged 4 – 7
- Measure the efficacy of edasalonexent versus placebo on MRI, timed function tests (10-meter walk/run, 4-step climb, time to stand), muscle strength, NSAA, PODCI

- Assess same safety and efficacy parameters as in Part B of the trial over a longer term in an open-label extension

MoveDMD Study Population

Strategy	▸ Initial approach is to assess safety, pharmacokinetics and MRI as a biomarker of inflammation in young boys (4 – 7 years age) not on steroids
Rationale	▸ Provides clean proof of drug effect without confounding factor of overlapping NF-κB mechanism of steroids
Key Trial Inclusion / Exclusion Criteria	▸ Diagnosis of DMD based on clinical phenotype and presence of mutation in dystrophin gene ▸ Ambulatory ▸ Age ≥4 years and <8 years ▸ Not on corticosteroids within prior 6 months to treatment initiation or planning to initiate steroid therapy within the next 6 months

MoveDMD Part A Objectives

Objectives

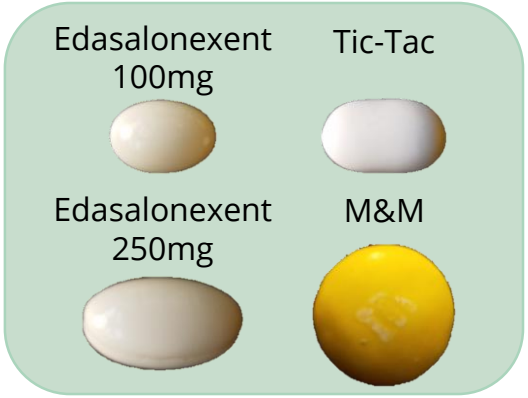
- **Assess safety in 3 cohorts of boys age 4 -7 with Duchenne**
  - Cohort 1 – 33 mg/kg per day given BID
  - Cohort 2 – 67 mg/kg per day given BID
  - Cohort 3 – 100 mg/kg per day given TID
- **Assess pharmacokinetics in pediatric patients under various dietary conditions**
  - On Day 1 and Day 7 single doses (17, 33 and 67 mg/kg) administered with high or low-fat diet in random sequence
- **Compare pharmacokinetics in pediatric and adult population**
- **Assess whether pediatric exposures are similar to those at which NF-κB inhibition was observed in adults**

Dose Selection Rationale

- **Doses shown to have:**
  - No safety signals and to be well tolerated in adult clinical studies
  - Exposures that produced NF-κB inhibition in adults and disease-modifying effects and acceptable toxicity profile in animal studies

MoveDMD Part A Results: Safety and Tolerability

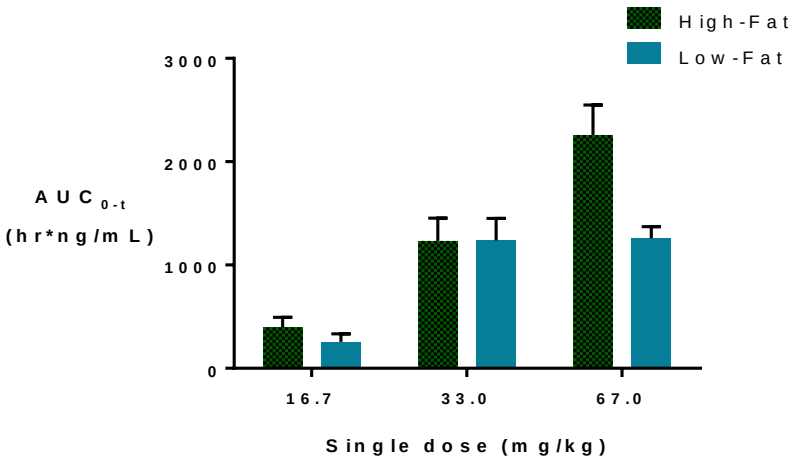
- **Generally well tolerated**
  - No serious adverse events, no discontinuations
  - All patients able to take edasalonexent capsules
  - Adverse events (AE) predominantly mild, most common AE was diarrhea
- **Assessments:**
  - Laboratory: no trends or safety issues in liver, renal, hematology
  - Physical exam, EKG, vitals: no safety issues
- **Adverse events (7 days):**



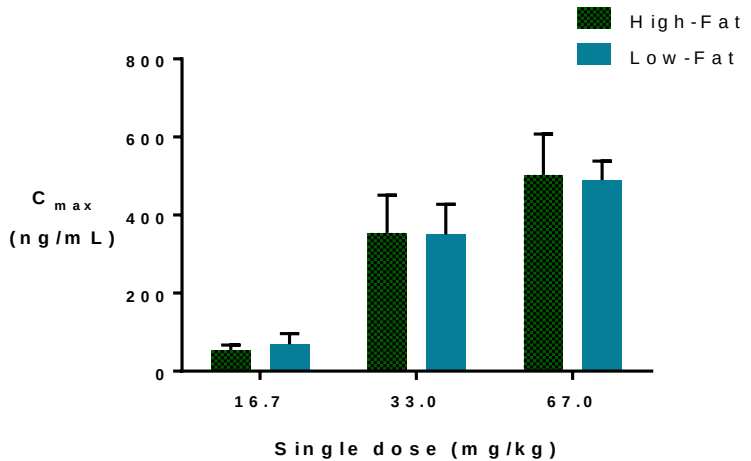
	33 mg/kg n=5	67 mg/kg n=6	100 mg/kg n=6	Total n=17
Diarrhea	0	0	4	4
Soft feces	1	1	1	3
Abdominal pain upper	1	0	1	2

MoveDMD Part A Results: Dose-Dependent Increases in Exposure, with Modest Effect of Meal Composition

Dose dependent AUC



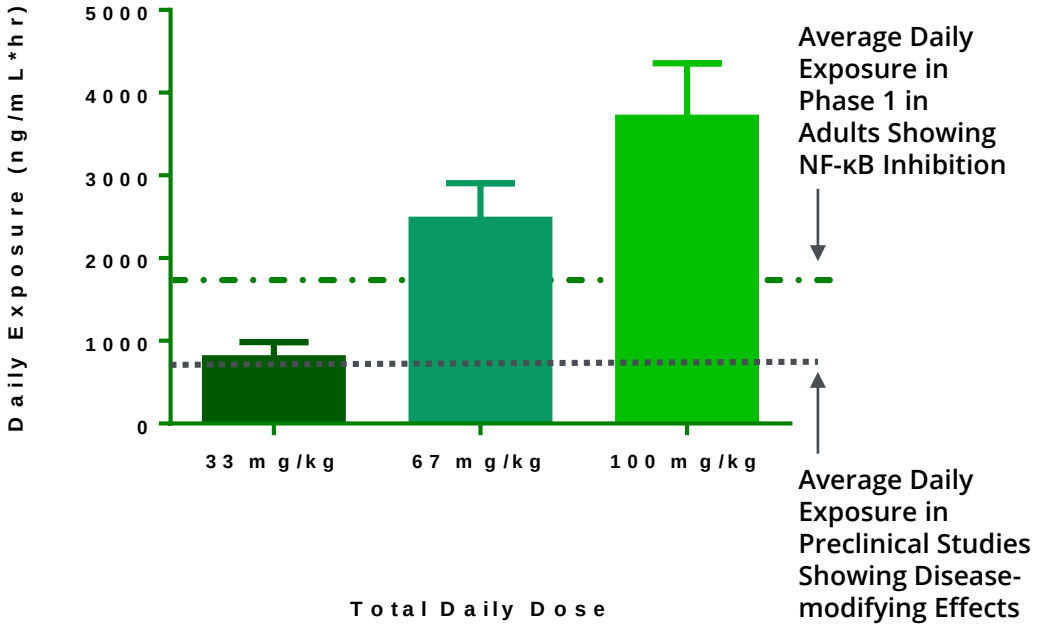
Dose dependent C_{max}



- With single doses of 33 mg/kg there were minimal differences in AUC or C_{max} when edasalonexent was administered either with a high-fat or a low-fat meal
- A total daily dose of 67 or 100 mg/kg can be administered with food as 33 mg/kg either 2 or 3 times daily

MoveDMD Part A Results: Comparison of Pediatric and Adult Exposures

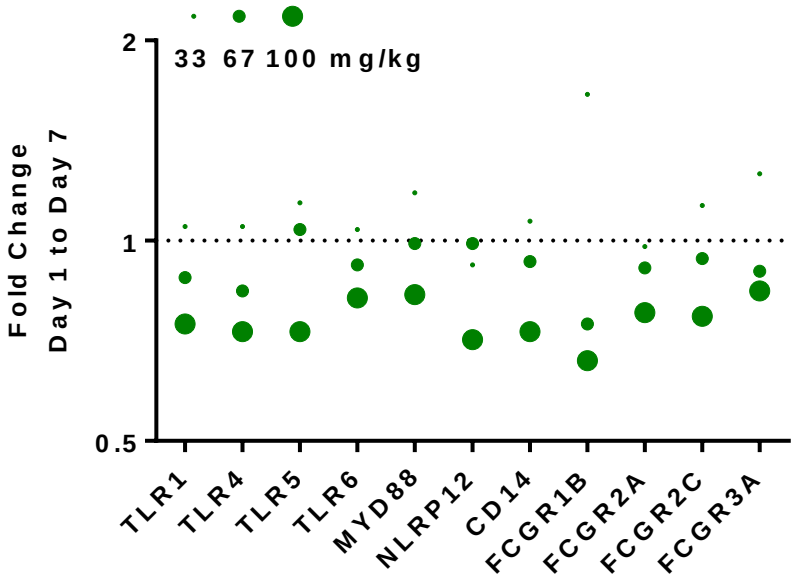
- In Phase 1 in adults, changes in expression of NF-κB driven genes were observed at a dose of approximately 33 mg/kg BID
- In the MoveDMD study, when doses of 33 mg/kg were given BID or TID (total daily doses of 67 or 100 mg/kg), systemic exposures were reached at which NF-κB inhibition was observed in adults



MoveDMD Part A Results: Reduction in NF-κB Gene-signature in Blood from Boys with DMD After 1 Wk of Treatment

- One week of edasalonexent treatment in boys with DMD results in a significant reduction in NF-κB target genes in peripheral blood
- Reduction in NF-κB target genes is dose-related and is observed at both 100 mg/kg and 67 mg/kg cohorts

All Cohorts
NF-κB regulated TLR and Fc Receptor Genes



Key Takeaways from Part A of the MoveDMD Trial

	▸ No safety signals and generally well tolerated at all 3 doses tested in boys with DMD
	▸ Plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed, and which are higher than exposure levels in animal models at which disease modifying effects were seen
	▸ Target engagement demonstrated in boys with DMD with significant reduction in NF-κB activity with the 67 mg/kg/day and 100 mg/kg/day doses

▸ **Supports initiation of Part B of the trial with 67 mg/kg/day and 100 mg/kg/day edasalonexent administered with meals**

Part B Objectives

Objectives

- Assess safety and tolerability in boys age 4 – 7 with DMD
- Assess effects on muscle inflammation as measured by MRI
- Assess physical function, parent/proxy-reported physical functioning/quality of life as well as PK and blood biomarker effects

Randomization

- Randomized 1:1:1 to receive edasalonexent 67 mg/kg/day, 100 mg/kg/day, or placebo
- Randomization stratified by baseline age and time to complete 10-meter walk/run

Part B Efficacy Measures

✓ = Planned Assessments

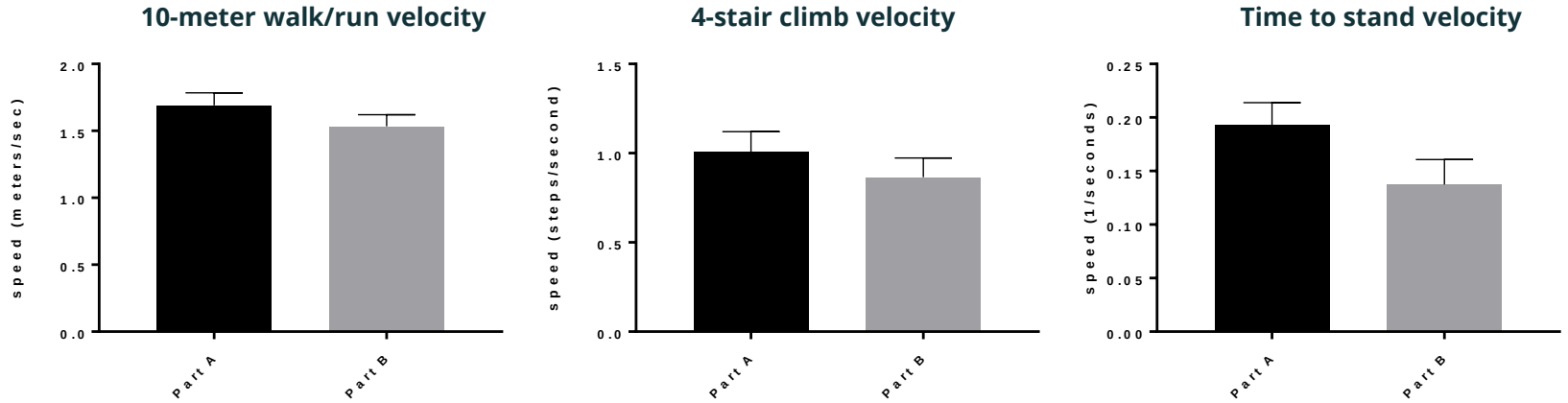
	Muscles	Part A Baseline	Part B Baseline	Part B 12 Weeks	Part C (Multiple Timepoints)
MRI/MRS	T2	✓	✓	✓	✓
	Fat Fraction	✓	✓	✓	✓
Timed function tests	10-meter walk/run	✓	✓	✓	✓
	4-stair climb	✓	✓	✓	✓
	Time to stand	✓	✓	✓	✓
Muscle strength	Knee extension	✓	✓	✓	✓
	Plantar flexion	✓	✓	✓	✓
Parent/proxy	NSAA	✓	✓	✓	✓
	PODCI	✓	✓	✓	✓

MoveDMD Trial: Baseline TFTs Similar to Those in ImagingDMD Dataset

	CS naïve group of ImagingDMD: Effects of Initiation of Corticosteroids Study (n=11)	MoveDMD Part A Baseline (n=15)	MoveDMD Part B Baseline (n=15)
10-meter Walk/Run (sec)	6.7 ± 1.3	6.2 ± 1.3	6.8 ± 1.7
4-stair Climb (sec)	4.9 ± 1.3	4.7 ± 2.3	6.0 ± 3.5
Floor to Stand (sec)	8.5 ± 6.8	6.1 ± 2.7	8.5 ± 5.9

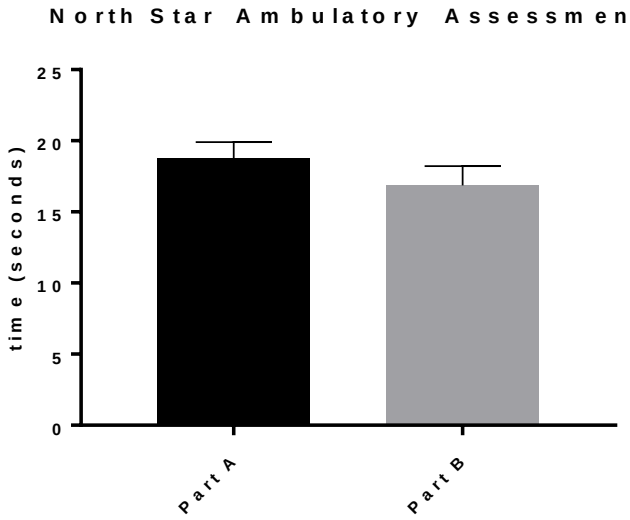
MoveDMD trial not powered for statistically significant changes in TFTs

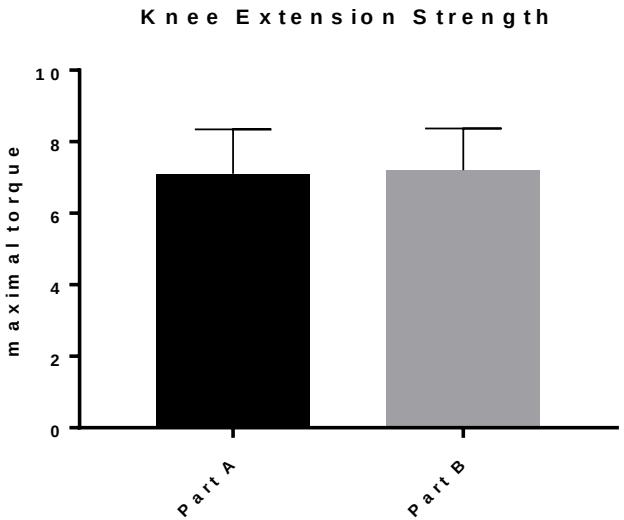
MoveDMD Trial: Observations During Off-treatment Period from Baseline of Part A to Baseline of Part B



- Data for 15 boys who continued from Part A and with Part B baseline TFT assessment complete
- Time from Part A to Part B was between 4 and 12 months
- Declines in TFTs during off-treatment period

MoveDMD Trial: Observations During Off-treatment Period from Baseline of Part A to Baseline of Part B





- Data for 15 boys who continued from Part A and with Part B baseline TFT assessment complete
- Time from Part A to Part B was between 4 and 12 months

Key Takeaways from ImagingDMD MRI/MRS Studies

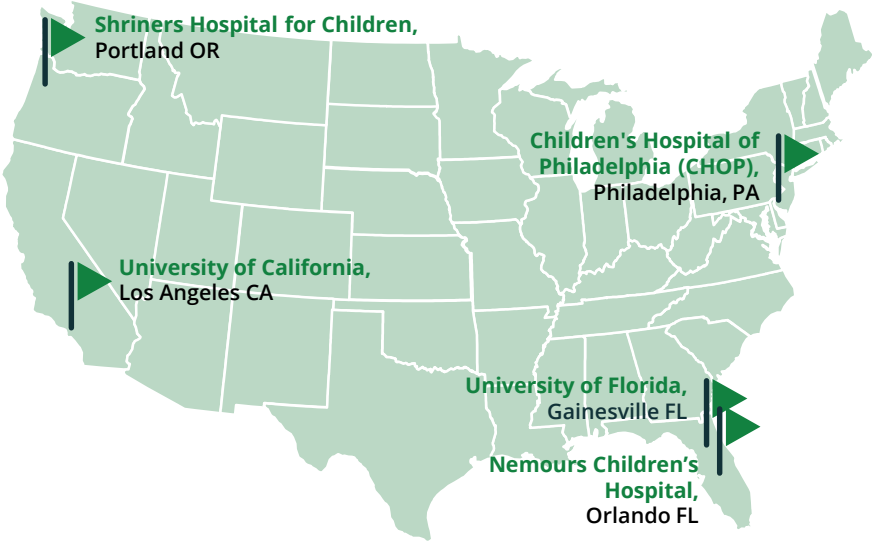
- **MRI/MRS measures well suited to be used as a biomarker in therapy development in DMD**
  - Allows the quantitative assessment of the amount and health of defined skeletal muscles
  - Sensitive to disease progression and correlate with specific functional measures
  - Non-invasive, unbiased, quantitative and excellent reproducibility
- **Different techniques and muscles offer unique strengths to capture aspects of disease pathology**
  - MRI T2 and ^{1}H-MRS can measure disease progression (inflammation) over 3 months
  - Fat fraction can measure disease progression (fat, fibrosis) over >3 months
  - Lower leg muscles such as soleus show the most inflammation
- **Effect of corticosteroids**
  - Initiation of corticosteroids was associated with a significant decline in T2 in 3 months, which was easily detected by both MRI and MRS
  - For boys on corticosteroids for 7 months – 4 years, cross-sectional comparison showed significantly lower T2 values and fat fraction and significantly better performance on the timed function tests (10-meter walk/run, 4-stair climb and time to stand).

MoveDMD Part B Trial Mirrors ImagingDMD Study

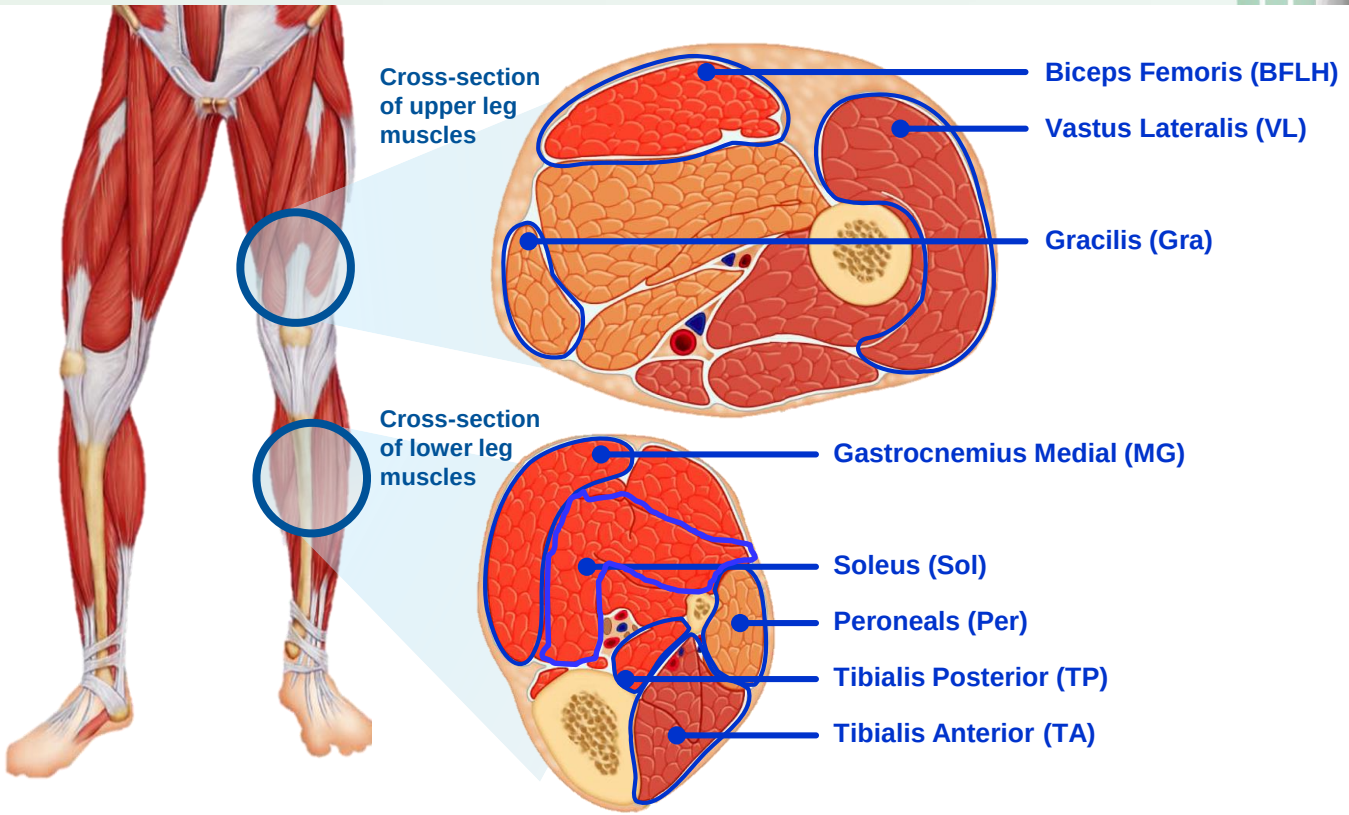
	ImagingDMD Study: Effects of Initiation of Corticosteroids	MoveDMD Trial Part B
Comparison	Corticosteroids vs. Corticosteroid-naive	Edasalonexent vs. Corticosteroid-naive
No. of Patients	N = 16	N = 31
Study Sites	ImagingDMD group	ImagingDMD and associated sites
Primary End Point	MRI: Change in T2 of lower leg muscles	MRI: Change in T2 of lower leg muscles
Duration	12 weeks	12 weeks
MRI T2 Results	Positive $p \leq 0.01$	Results expected first half Q1 2017

Site Selection and MRI/MRS Techniques Are Standardized to Drive Low Variability

- **Careful site selection and training**
  - The 5 MoveDMD trial sites are ImagingDMD or associated sites
  - Site training and qualification
- **Standardized MRI techniques across sites**
  - Implementation of an MRI charter
  - MRI machine calibration via validated phantom
  - Quality control check of all images and re-scanning when needed
  - Consistent operator training
  - Reproducible anatomic coverage
- **Central, objective, unbiased reading of MRI**
  - MRIs to be read centrally at U. Florida
  - Two experienced independent reviewers, blinded to patient information
  - Adjudicated by third reader if needed



Leg Muscles Being Evaluated via MRI Are Same as Those Studied by ImagingDMD

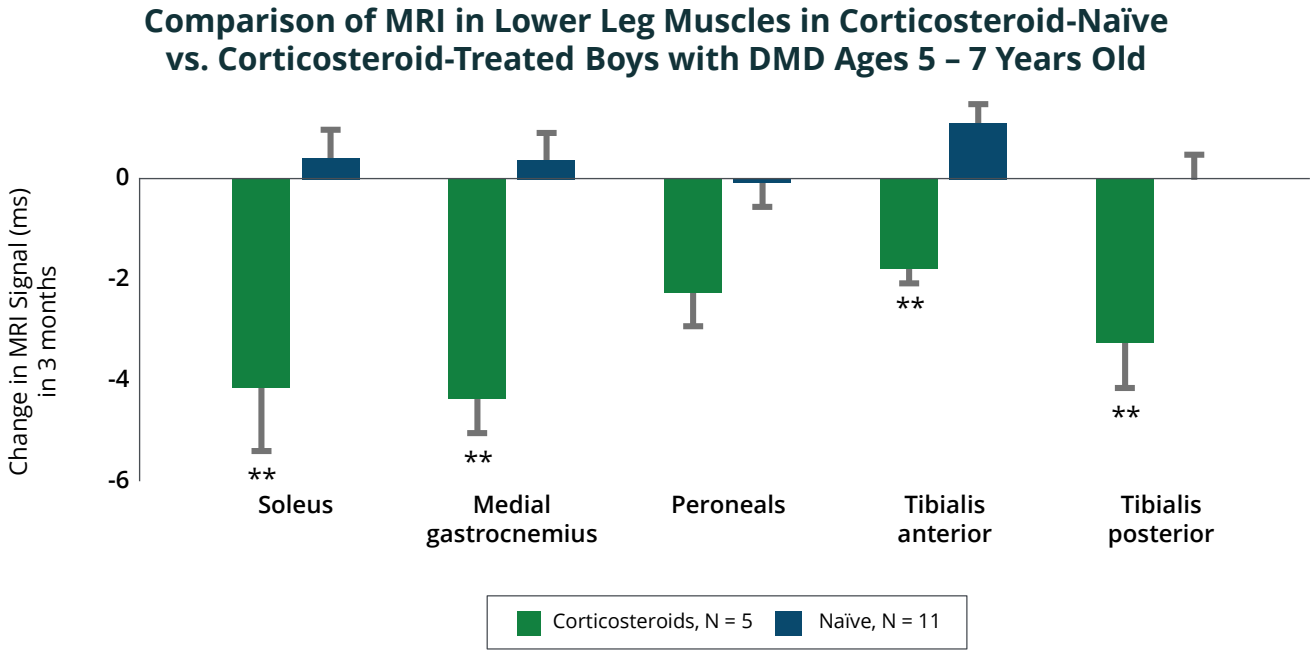


MRI End-points in MoveDMD Trial Are Same as Those Most Studied by ImagingDMD

✓ = Planned Assessments Primary end point: change from baseline in MRI T2 composite of lower leg muscles

Muscles	Part A Baseline	Part B Baseline	Part B 12 Weeks	Part C (Multiple Timepoints)
MRI T2				
Soleus	✓	✓	✓	✓
Medial Gastrocnemius	✓	✓	✓	✓
Peroneals	✓	✓	✓	✓
Tibialis Anterior	✓	✓	✓	✓
Tibialis Posterior	✓	✓	✓	✓
Vastus Lateralis	✓	✓	✓	✓
Biceps Femoris Long Head	✓	✓	✓	✓
Gracilis	✓	✓	✓	✓
MR Spectroscopy T2				
Soleus	✓	✓	✓	✓
Vastus Lateralis	✓	✓	✓	✓
MR Spectroscopy Fat Fraction and Dixon Fat Fraction				
Soleus	✓	✓	✓	✓
Vastus Lateralis	✓	✓	✓	✓

Primary End Point Is Composite of the 5 Lower Leg Muscles Imaged



- **Rationale:**
  - Composite of 5 muscles results in substantial improvement in signal-to-noise vs. any single muscle
  - Pooling of data from the 2 active arms improves study power

Arpan et al Neurology 2014 83:1-7

MoveDMD Trial: Powering for Efficacy Measures

- **Primary end point**
  - Change from baseline in average T2 of the 5 lower leg muscles being measured in pooled active dosing arms compared with that of placebo
  - Study is powered at >95% for change in composite T2 using various scenarios of anticipated effect size of edasalonexent relative to corticosteroids
- **Timed Function Tests, muscle strength, North Star Ambulatory Assessment and PODCI**
  - Study not powered for statistical significance between active and placebo arms at week 12
  - Assess for trends over longer periods

- **Trial anticipated to be data-rich and informative**
  - Assess totality of evidence in interpreting results and designing anticipated Phase 3 trial

Top-line Data from Part B of MoveDMD Trial Expected First Half Q1 2017

Study Population: All DMD mutations, ages 4 – 7, steroid naïve or off steroids for ≥6 months

Part B
12-week, randomized, double blind placebo-controlled trial
N ~ 10 per arm

- Edasalonexent 67 mg/kg/day
- Edasalonexent 100 mg/kg/day
- Placebo

Timing

- **First half Q1 2017; after JPM conference**

Data expected to be shown

- **Primary end point**
  - MRI T2 measures for composite of 5 lower leg muscles for pooled 67 and 100 mg/kg/day of edasalonexent versus placebo
  - Safety and tolerability
- **Secondary end point**
  - Timed function tests (not powered for statistical significance)

MoveDMD Trial: Observations to Date

- **31 patients enrolled in Part B**
  - 16 of 17 patients from Part A continued to Part B (one lost to follow-up)
  - Majority of patients have completed 12-week dosing
  - All patients to date crossed over into open-label extension
- **Independent DSMB has met twice during study per a predefined schedule**
  - Reviewed un-blinded safety data
  - No change in study design or conduct

Summary of 3-Part MoveDMD Trial in Boys with DMD

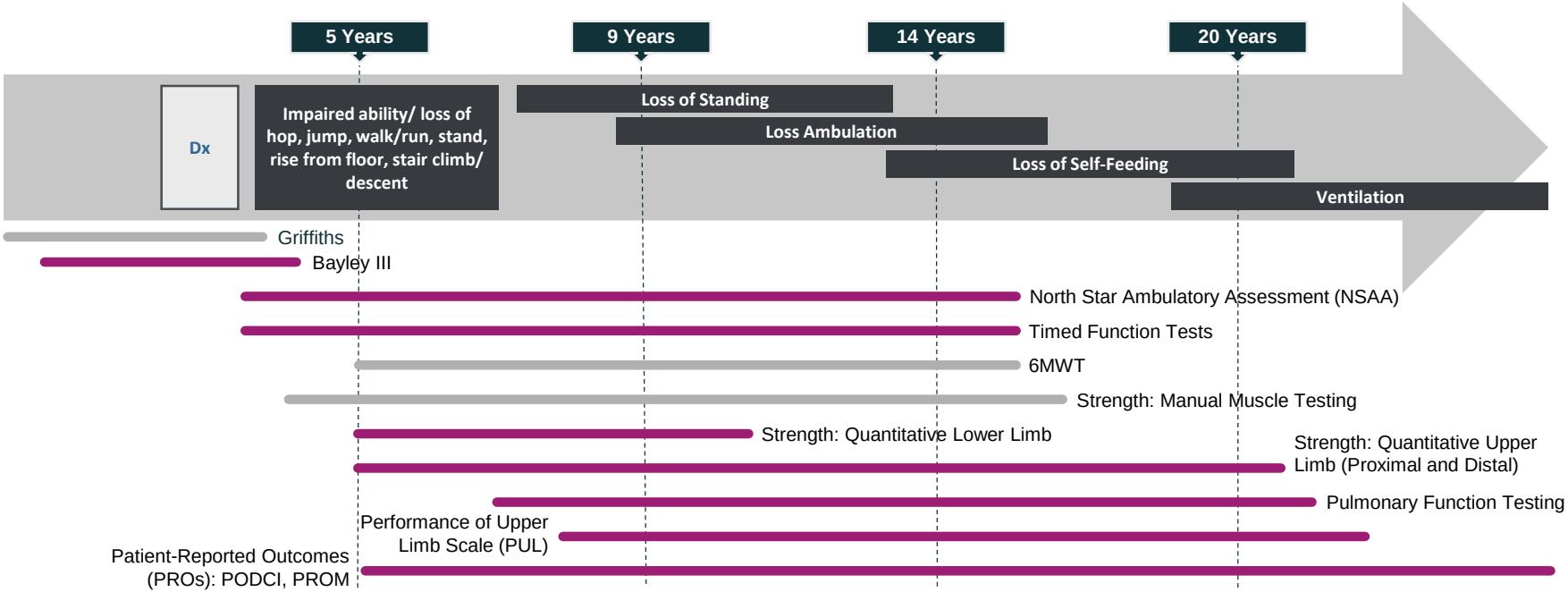
Study Population: All DMD mutations, ages 4 – 7, steroid naïve or off steroids for ≥6 months

Part A 7-day, open-label dose-ranging trial of edasalonexent N ~ 6 per arm	**Part B** 12-week, randomized, double-blind placebo-controlled trial N ~ 10 per arm	**Part C** 36-week, open-label treatment period N ~ 10 per arm
33 mg/kg/day	Edasalonexent 67 mg/kg/day	Edasalonexent 67 mg/kg/day
67 mg/kg/day	Edasalonexent 100 mg/kg/day	Edasalonexent 100 mg/kg/day
100 mg/kg/day	Placebo	Edasalonexent 100 mg/kg/day or 67 mg/kg/day
Reported positive safety, tolerability, pharmacokinetics and biomarker results	Expect top-line results first half Q1 2017	Periodic results during 2017 from open-label extension

Overall Edasalonexent Development Strategy in Duchenne – Current Thinking

- **Initial development focus on early ambulatory patients: boys aged 4-7 not yet on steroids**
  - Expect to initiate Phase 3 in boys aged 4-7 in H2 2017
- **Next: non-ambulatory patients not on steroids**
  - Expect to initiate trial in non-ambulatory patients in H2 2017
- **Once efficacy established, additional trials in late ambulatory patients and boys younger than 4**

Overall Edasalonexent Development Strategy in Duchenne



catabasis

Adapted from Bushby, Connor. Clin Investig (Lond). 2011; McDonald, et al. Muscle Nerve. 2013

included edasalonexent development plan

not included edasalonexent development plan

Edasalonexent: a Potential Disease-modifying Therapy for All DMD Patients

- **Edasalonexent has shown safety, tolerability, adequate exposure and NF-κB target engagement consistently in clinical studies completed to date in adults and in boys with DMD**
- **Part B of the MoveDMD trial and OLE are expected to provide a robust set of data to assess drug effect and design the anticipated Phase 3 trial**
  - Design mirrors that of the positive ImagingDMD study
  - Primary endpoint: change from baseline in MRI T2 composite of lower leg muscles
- **Top-line results from Part B of the trial are expected in the first half Q1 2017**
  - Powered >95% for primary end point: change from baseline in MRI T2 at week 12
  - Assess for trends over longer periods in other efficacy measures: TFTs, muscle strength and parent/proxy-reported physical functioning / quality of life measures

Catabasis Investor Day

Q&A

Closing Remarks

Jill Milne, PhD
Co-Founder & Chief Executive Officer

Since Founding the Company, We Have Been Executing Relentlessly on Our Strategic Plan

Set the foundation
Develop technology
Capitalize company
Attract leadership

Build the pipeline
Engineer conjugates
Move to clinic
Pursue partnerships

Benefit patients
Commercialize
Expand capabilities
Access new assets

2008
An Idea

Today
A public clinical-stage company

Our goal
A premier rare disease company

We Are Building a Robust Pipeline of Product Candidates in Rare Diseases

Product Candidate (Pathway)	Potential Indications	Discovery	Preclin	Phase 1	Phase 2	Phase 3
Edasalonexent CAT-1004 (NF-κB)	Duchenne muscular dystrophy					
Edasalonexent CAT-1004 (NF-κB)	Additional rare disease					
CAT-4001 (Nrf2/NF-κB)	Friedreich's ataxia Amyotrophic lateral sclerosis					
CAT-5571 (Autophagy)	Cystic fibrosis					

Upcoming Events

- Report top-line results from MoveDMD Phase 2 trial first half Q1 2017
- Report periodic results from open-label extension of MoveDMD trial in 2017
- Initiate Phase 3 trial for edasalonexent in DMD in H2 2017
- Initiate trial in non-ambulatory patients with DMD for edasalonexent in H2 2017
- Ongoing preclinical research for CAT-4001 in ALS and FA in 2017
- Initiate Phase 2 trial for additional rare disease indication for edasalonexent in Q4 2017 or Q1 2018
- Initiate Phase 1 trial for CAT-5571 in CF in Q4 2017 or Q1 2018

Our Value Proposition

- **Building a premier rare disease company**
  - Experienced management team
  - Nimble and efficient organization with strong execution
  - Developing capabilities to take product candidates from idea to commercialization
- **Targeting rare diseases with a unique pathway approach**
  - Selecting central pathways implicated in multiple rare diseases
  - Simultaneously target multiple points in a disease pathway with SMART Linker Drug Discovery platform
- **Robust product pipeline of clinical and preclinical candidates**
  - Edasalonexent: potential disease-modifying therapy for all DMD patients
  - Edasalonexent: Potential for additional rare disease indication
  - CAT-4001: Potential treatment of rare neurodegenerative diseases such as FA and ALS
  - CAT-5571: Potential treatment of CF and other rare diseases