New Hope For Patients with Rare Myopathies Characterized by an Immune Component

John Mendlein, PhD, CEO of aTyr Pharma
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Guest: John Vissing, MD, Professor of Neurology at University of Copenhagen, Denmark
Principal Investigator for aTyr Pharma's 004 Trial

December 13, 2016

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Our Agenda: 8:30am – 9:30am (EST)

Resolaris: Derived from the Resokine Pathway

- John Mendlein, PhD
  Chief Executive Officer at aTyr Pharma

Potential Therapeutic Approaches to Rare Myopathies with an Immune Component

- John Vissing, MD
  Professor of Neurology at the University of Copenhagen, Denmark

Resolaris Clinical Data Review from 3 Trials

- Sanjay Shukla, MD, MS
  Chief Medical Officer at aTyr Pharma

Resolaris Discussion and 2017 Outlook

- John Mendlein, PhD

Question and Answer Session

RESOLARIS: DERIVED FROM THE RESOKINE PATHWAY

JOHN MENDLEIN, PHD, CEO

DECEMBER 13, 2016

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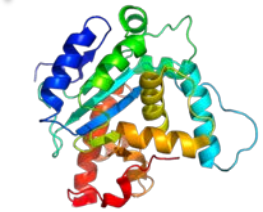
Rare Myopathies with an Immune Component

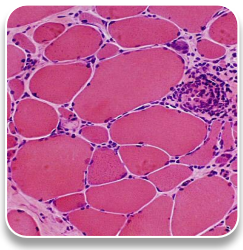
Chronic damage, homeostasis disrupted

Disruption of Homeostasis
(untapped therapeutic intervention point)

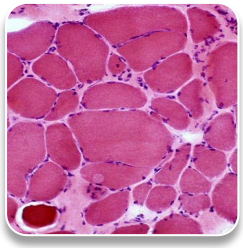


Genetic Mutation	Aberrant Protein Expression & Profile
Facioscapulohumeral Muscular Dystrophy (FSHD)	Aberrant expression of multiple proteins in muscle
Limb Girdle Muscular Dystrophy 2B (LGMD2B)	Aberrant dysferlin proteins
Duchenne Muscular Dystrophy (DMD)	Aberrant dystrophin proteins

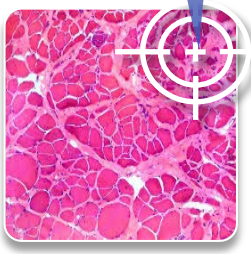
Localized T Cell Invasion & Proliferation



FSHD



LGMD2B



DMD

Potential to link genotype to specific T cell phenotype

Frisullo et al., J. Clin. Immunol., 2011
Gallardo et al. Neurology, 2001
Flanigan et al. Human Gene Therapy, 2013

Anti-Dystrophin T Cell Responses in Duchenne Muscular Dystrophy: Prevalence and Glucocorticoid Treatment Effect

REFERENCE

Anti-Dystrophin T Cell Responses in Duchenne Muscular Dystrophy: Prevalence and a Glucocorticoid Treatment Effect

Kevin M. Flanigan,[1*] Katie Campbell,[2] Laurence Viollet,[1] Wei Wang,[3] Ana Maria Gomez,[1] Christopher M. Walker,[2] and Jerry R. Mendell[1*]

Abstract

Duchenne muscular dystrophy (DMD) typically occurs as a result of truncating mutations in the *DMD* gene that result in a lack of expression of the dystrophin protein in muscle fibers. Various therapies under development are directed toward restoring dystrophin expression at the subsarcolemmal membrane, including gene transfer. In a trial of intramuscular adeno-associated virus (AAV)-mediated delivery of a therapeutic minidystrophin construct, we identified in two of six subjects the presence of a population of T cells that had been primed to recognize dystrophin epitopes before transgene delivery. As the presence of preexisting T cell immunity may have a significant effect on the success of therapeutic approaches for restoring dystrophin, we sought to determine the prevalence of such immunity within a DMD cohort from our Muscular Dystrophy Association clinic. Dystrophin-specific T cell immunity was evaluated in subjects with DMD who were either receiving the glucocorticoid steroid prednisone ($n=24$) or deflazacort ($n=29$), or who were not receiving steroids ($n=17$), as well as from normal age-matched control subjects ($n=21$). We demonstrate that increasing age correlates with an increased risk for the presence of anti-dystrophin T cell immunity, and that treatment with either corticosteroid decreases risk compared with no treatment, suggesting that steroid therapy in part may derive some of its benefit through modulation of T cell responses. The frequency of dystrophin-specific T cells detected by enzyme-linked immunospot assay was lower in subjects treated with deflazacort versus prednisone, despite similar overall corticosteroid exposure, suggesting that the effects of the two corticosteroids may not be identical in patients with DMD. T cells targeted epitopes upstream and downstream of the dystrophin gene mutation and involved the $CD4^+$ helper and/or $CD8^+$ cytotoxic subsets. Our data confirm the presence of preexisting circulating T cell immunity to dystrophin in a sizable proportion of patients with DMD, and emphasize the need to consider this in the design and interpretation of clinical gene therapy trials.

Flanigan et al, Human Gene Therapy, 2013

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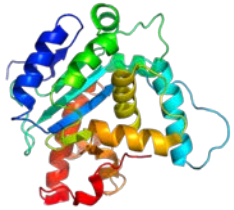
Connecting Genotype to Immune Cell Phenotype in Duchenne Muscular Dystrophy Patients

Disruption of Homeostasis
(untapped therapeutic intervention point)



Genetic Mutation	Etiology of Aberrant Protein	Localized T Cell invasion & proliferation
DMD Patients: • Splice exon 12 • Del ex 45 • Del ex 46 – 50 • Del ex 49 – 54 • Nonsense ex 59 • Nonsense ex 69	**Locations of Immune Response:** • Exons 1 – 9 • Exons 17 – 26 • Exons 42 – 50 • Exons 50 – 59 • Exons 59 – 69 • Exons 70 - 79	**T Cell Phenotype:** CD4 and/or CD8

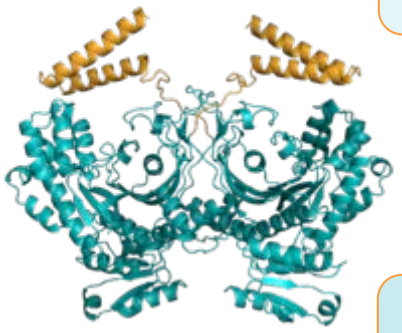
Frisullo et al., J. Clin. Immunol., 2011 *Gallardo et al. Neurology, 2001*
Flanigan et al. Human Gene Therapy, 2013

Resokine Pathway Paradigm

Directed at activated, local T cells in RMIC patient muscle

1ST PHYSIOCRINE BASED PRODUCT CANDIDATE

An extracellular homeostatic pathway that sets T cell responses as an agonist



Arising from histidine aminoacyl tRNA synthetase (HARS) gene

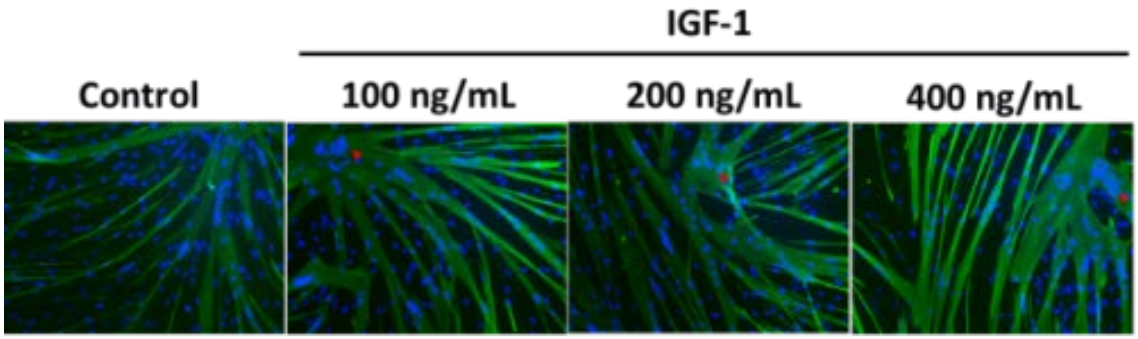
Changes activated T cell responses at levels <100pM

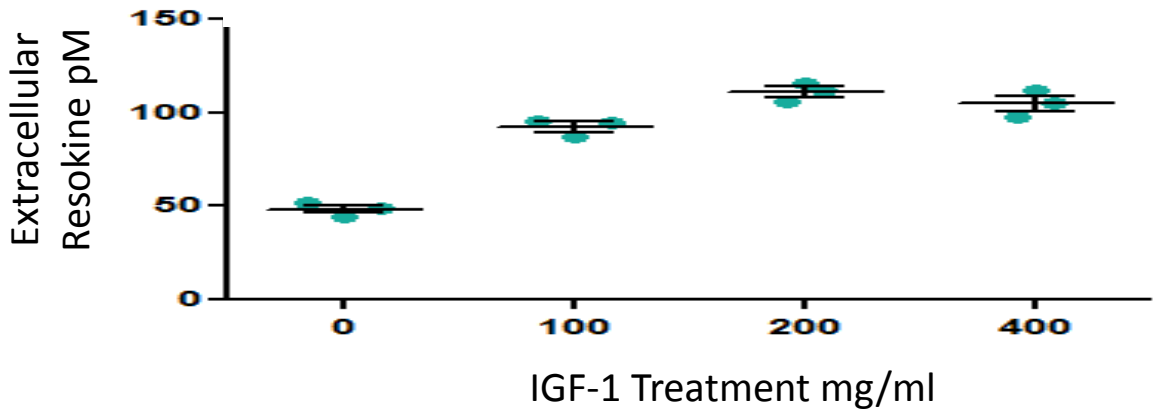
Pathway insufficiency leads to inappropriate immune responses

Resolaris, an agonist, is intended to promote homeostasis in muscle

IGF-1 Increases Resokine Release From Myoblasts Differentiating to Myotubes

Linking the Resokine pathway to muscle biology





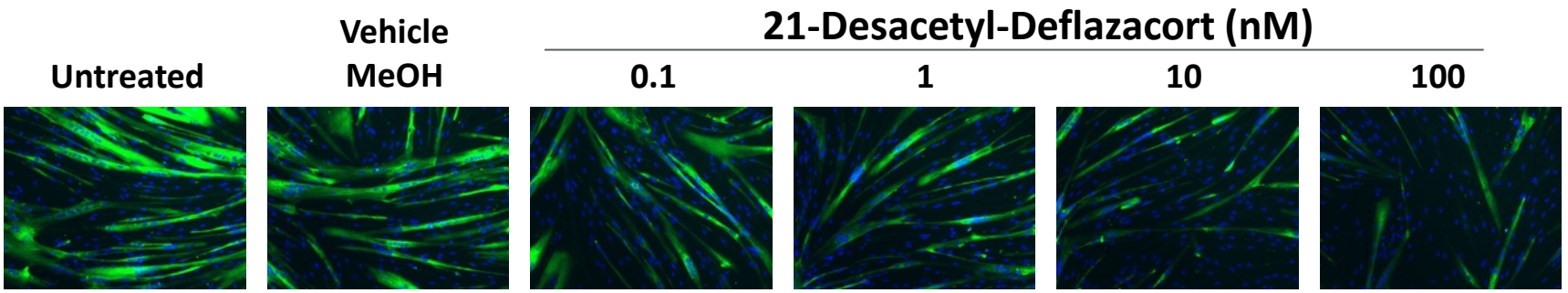
Antibodies sufficient to block 100pM Resokine
block >50% of differentiation & growth (slower)

Human myoblasts were isolated from a healthy volunteer properly consented and not in a clinical trial

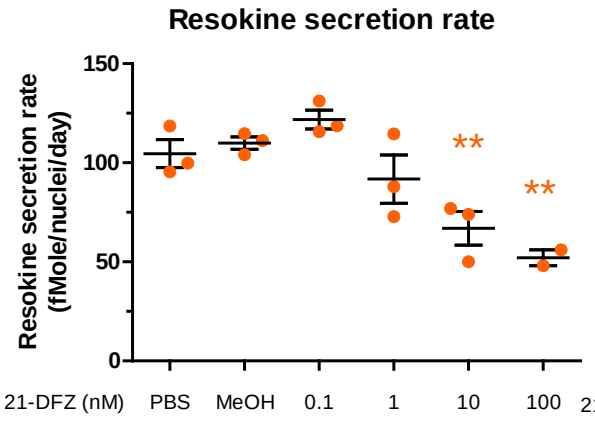
Deflazacort Inhibits Muscle Growth and Resokine Release

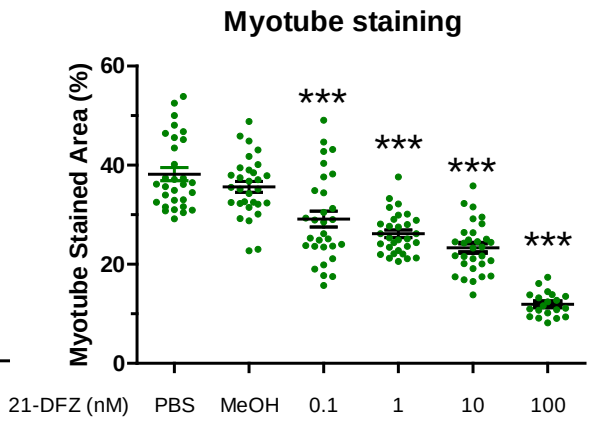
Steroid use to treat RMIC patients

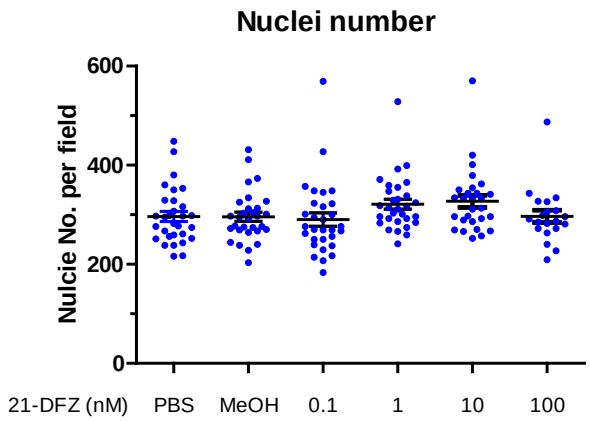
DEFLAZACORT NEGATIVE IMPACT HUMAN CELLS



Myotube (myosin)/Nuclei (Hoechst), Images at 100× magnification; **Differentiation Day 0-5**







**p<0.05, **p<0.01, ***p<0.001*

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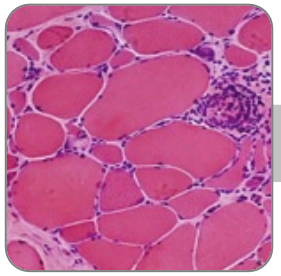
Muscle Franchise Strategy: Looking Into The Future

Resolaris: Potential to Promote Muscle Homeostasis

Aberrant protein expression from aberrant genetics
Phenotype dysfunction:
Muscle degeneration/regeneration
Immune dysregulation
Fibrosis



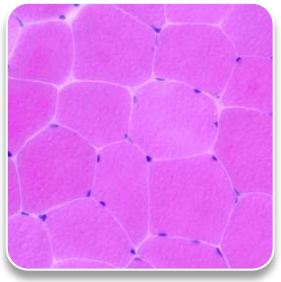
Diseased muscle

Genetic Modifiers

Growth Augmenters

Primed T cells Targeting muscle

Increased mass, Larger T cell target



Healthy muscle

Resolaris:
- Naturally designed homeostatic protein
- Single agent, multiple diseases
- Potentially helpful with other MOAs

John Vissing, MD

Professional:

- Professor of Neurology at the University of Copenhagen, Denmark
- Director of the Neuromuscular Clinic & Research Unit at National Hospital, Rigshospitalet

Disease Focus:

Facioscapulohumeral muscular dystrophy, Kennedy disease, Becker muscular dystrophy, different forms of limb girdle muscular dystrophy, myotonic dystrophy, mitochondrial myopathies and glycogenoses

Research:

Authored more than 250 scientific articles in international journals in the area of muscle disease

Education:

- MD degree from the Medical School at the University of Copenhagen
- Research fellowship training at University of Copenhagen and UT, Southwestern Medical Center, Dallas, US

Potential Therapeutic Approaches to Rare Myopathies With an Immune Component

John Vissing, MD, Professor of Neurology at University of Copenhagen, Denmark
Principal Investigator for aTyr Pharma's 004 Trial

December 13, 2016

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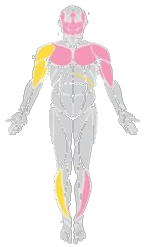
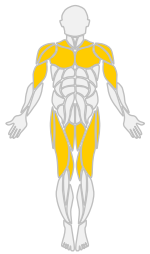
Facioscapulohumeral Muscular Dystrophy (FSHD) and Limb-Girdle Muscular Dystrophy 2B (LGMD2B)

	FSHD	LGMD2B
Genetics	Toxic gain of function (DUX4 region)	Loss of function mutations (Dysferlin gene)
Immune Pathology	Immune infiltration by activated T cells[1] (primarily $CD8^+$)	Immune infiltrates consisting of $CD4^+$, $CD8^+$ and macrophages[2]
Clinical	Debilitating, progressive skeletal muscle weakness Pain, fatigue, difficulty moving limbs, may have respiratory distress	
Standard of Care	No therapeutic treatments, only supportive care provided	
Disease Progression	Heterogeneous by muscle	Homogeneous by muscle group





[1]*Frisullo et al. J Clin Immunol (2011) 31:155–166*
[2]*Gallardo et al. Neurology 2001;57:2136–2138; Yin et al. Int J Clin Exp Pathol 2015;8(3):3069-3075*

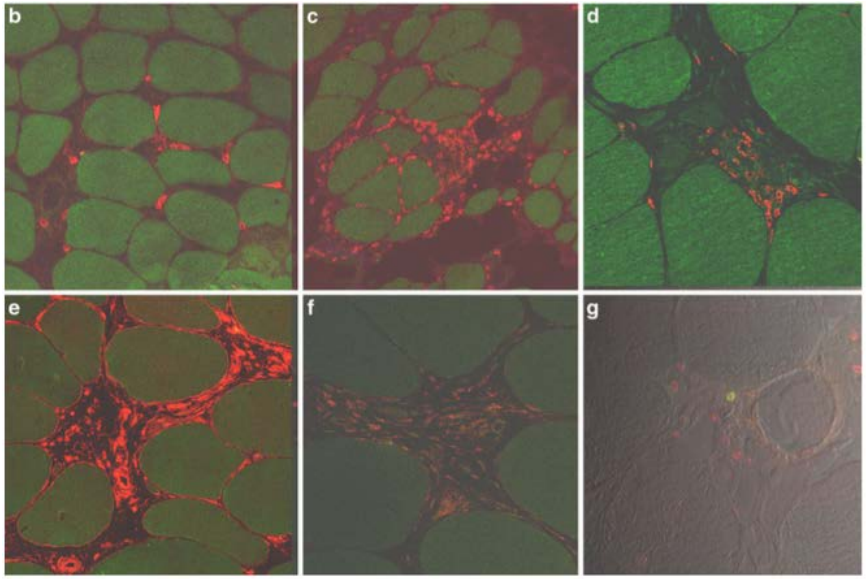
LGMD2B Disease Progression Case History

	First symptoms	Misdiagnosed w/ polymyositis	LGMD2B Diagnosis	Part time wheelchair-bound	Full time wheelchair-bound	Full dependency due to severe physical disability
Age	<15	16 – 18		19 – 27		28 - 34
	• Walks normally, active childhood	• Abnormal gait • Knees locked • Difficulty climbing stairs and running	• Difficulty rising from a chair, raising hands above head • Uses a cane and leg braces	• Slight improvement when steroids stopped • Unable to rise from a chair	• Requires assistance in daily living	• Unable to turn over in a bed or raise hands above head • Uses service dog for daily activities

https://www.youtube.com/watch?v=JLqHis1yPUI
http://mwtn2013blisswelch.blogspot.com/

T Cell Involvement in the Pathophysiology of RMICs
(For example: FSHD, LGMD2B, DMD)

FSHD



Endomysial infiltrates, in which CD8+ cells predominated (Fig. 2b–d), and perivascular infiltrates, mainly constituted by CD4+ cells (Fig. 2f) in all samples

LGMD2B

***Table 2** Endomysial mononuclear cell infiltrates in clusters*

Cells	Polymyositis	Dysferlinopathies
Mean cells per cluster	141 ± 74	88.6 ± 48
$CD8^+$	46.5 ± 10.3	11.1 ± 6.6
$CD4^+$	27.3 ± 11.5	40.6 ± 22.8
Macrophages	27.7 ± 7.6	36.7 ± 23.7
$CD20^+$	≤0.1	0

LGMD2B & DMD

Table 2. Comparison of inflammatory cells in muscle biopsy samples of dysferlinopathy, DMD/BMD, and polymyositis patients

	$CD4^+$ cells (mean ± SD)	$CD8^+$ cells (mean ± SD)	B cells (mean ± SD)	Macrophages (mean ± SD)
Dysferlinopathy	5.7 ± 4.4[a]	1.3 ± 1.1[c]	2.3 ± 2.2	7.8 ± 4.3[d]
Polymyositits	12.3 ± 6.4	3.3 ± 1.8	2.6 ± 1.9	10.8 ± 6.5
DMD/BMD	4.9 ± 5.7[b]	2.0 ± 1.6	2.5 ± 3.4	3.7 ± 3.1[e]

[a]Dysferlinopathy versus polymyositis; $P = 0.009$; [b]DMD/BMD versus polymyositis; $P = 0.009$; [c]dysferlinopathy versus polymyositis; $P = 0.005$; [d]dysferlinopathy versus DMD/BMD; $P = 0.047$; [e]DMD/BMD versus polymyositis; $P = 0.006$. No other statistically significant differences were found among the different subgroups.

Gallardo et al. Inflammation in dysferlin myopathy: Immunohistochemical characterization of 13 patients. Neurol. 2001;57:2136–2138
Yin et al. CD4+ cells, macrophages, MHC-I and C5b-9 involve the pathogenesis of dysferlinopathy.Int J Clin Exp Pathol 2015;8(3):3069-3075
Frisullo et al. CD8+ T Cells in Facioscapulohumeral Muscular Dystrophy Patients with Inflammatory Features at Muscle MRI. J Clin Immunol (2011) 31:155–166

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Treatment of Dysferlinopathy with Deflazacort: A Double-Blind, Placebo-Controlled Clinical Trial

REFERENCE

Treatment of dysferlinopathy with deflazacort: a double-blind, placebo-controlled clinical trial

Maggie C Walter[1*†], Peter Reilich[1†], Simone Thiele[1], Joachim Schessl[1], Herbert Schreiber[2], Karlheinz Reiners[3], Wolfram Kress[4], Clemens Müller-Reible[4], Matthias Vorgerd[5], Peter Urban[6], Bertold Schrank[7], Marcus Deschauer[8], Beate Schlotter-Weigel[1], Ralf Kohnen[9] and Hanns Lochmüller[10]

Abstract

Background: Dysferlinopathies are autosomal recessive disorders caused by mutations in the dysferlin (*DYSF*) gene encoding the dysferlin protein. DYSF mutations lead to a wide range of muscular phenotypes, with the most prominent being Miyoshi myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B).

Methods: We assessed the one-year-natural course of dysferlinopathy, and the safety and efficacy of deflazacort treatment in a double-blind, placebo-controlled cross-over trial. After one year of natural course without intervention, 25 patients with genetically defined dysferlinopathy were randomized to receive deflazacort and placebo for six months each (1 mg/kg/day in month one, 1 mg/kg every 2nd day during months two to six) in one of two treatment sequences.

Results: During one year of natural course, muscle strength declined about 2% as measured by CIDD (Clinical Investigation of Duchenne Dystrophy) score, and 76 Newton as measured by hand-held dynamometry. Deflazacort did not improve muscle strength. In contrast, there is a trend of worsening muscle strength under deflazacort treatment, which recovers after discontinuation of the study drug. During deflazacort treatment, patients showed a broad spectrum of steroid side effects.

Conclusion: Deflazacort is not an effective therapy for dysferlinopathies, and off-label use is not warranted. This is an important finding, since steroid treatment should not be administered in patients with dysferlinopathy, who may be often misdiagnosed as polymyositis.

Trial registration: This clinical trial was registered at www.ClincalTrials.gov, identifier: NCT00527228, and was always freely accessible to the public.

Keywords: Limb girdle muscular dystrophy (LGMD), Dysferlinopathy, Therapy, Deflazacort, Muscle strength, Steroids

Walter et al, Orphanet Journal of Rare Diseases, 2013

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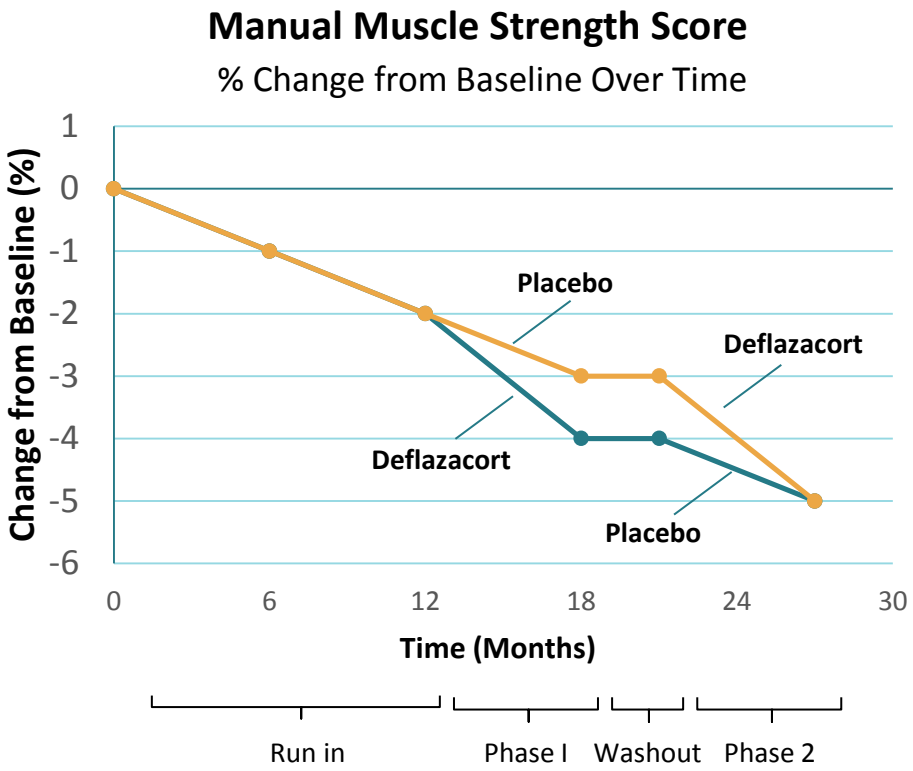
LGMD Patients Manual Muscle Strength* Decline at Double the Rate on Deflazacort vs Placebo



Treatment with Deflazacort was for 6 months in each arm Single site, placebo controlled, cross over design (n=25)

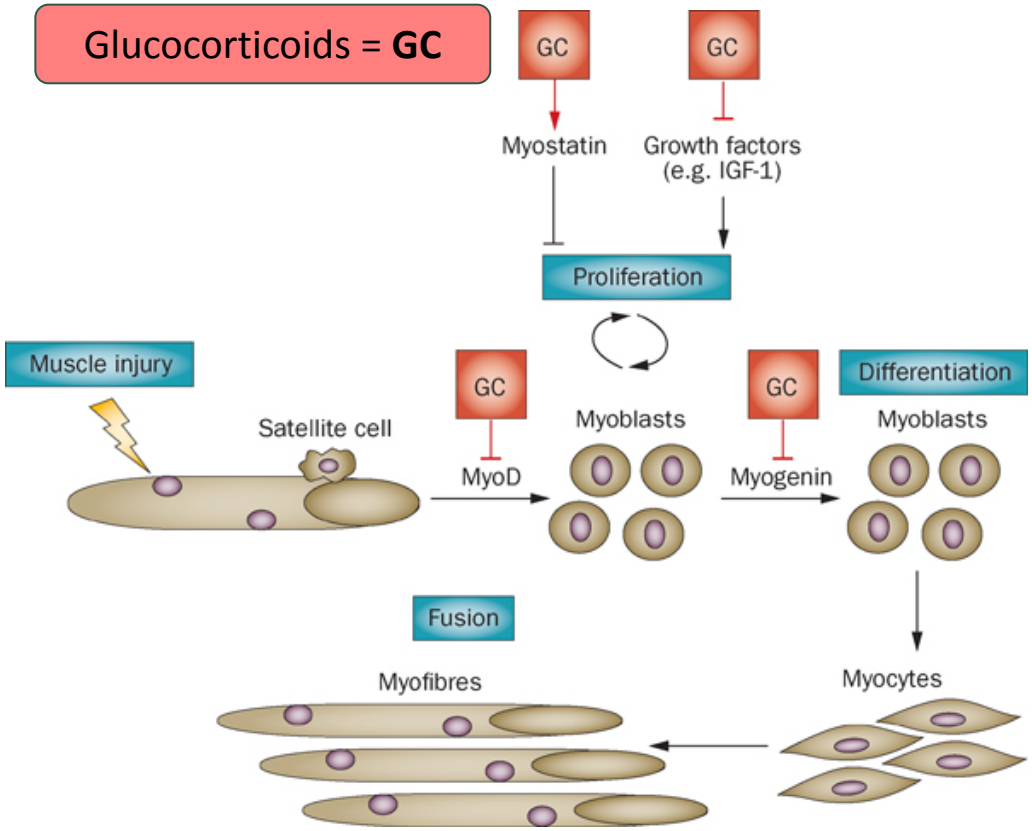
**Manual muscle strength assessed bilaterally by the modified Medical Research Council Scales (MRC) CIDD (Clinical Investigation of Duchenne Dystrophy) score, graded from 0 (worst) to 10 (best)*

Walter et al, Orphanet Journal of Rare Diseases, 2013

Limitations of Steroids as Potential Treatment in RMICs

The effects of glucocorticoids on postnatal skeletal muscle regeneration[1]

Glucocorticoids = **GC**



Muscle cell homeostasis disrupted by steroids

[1]Hanaoka, B. Y. *et al.* (2012) Implications of glucocorticoid therapy in idiopathic inflammatory myopathies *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2012.85

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Different Approaches to Treating Rare Myopathies

1. **Genetic based modifiers: gene therapy & editing; oligo approaches**
   - Delivery of the agent
   - Immune response to new protein
   - Requires new molecules for many approaches

2. **Muscle modifiers: various pathways to promote muscle growth**
   - Such as myostatin blockade agents & other pathways
   - Potentially increases immune response from more diseased tissue
   - Potentially accelerate regeneration/degeneration cycles

3. **Treat immuno-pathophysiology of rare genetically distinct myopathies**
   A. Steroids act as immuno-suppressants
      - Limited by side-effects
      - May have negative effects on muscle
      - Used in DMD, often with drug holidays

   B. Resolaris as natural homeostasis factor & immuno-modulator
      - Safety and tolerability looks promising
      - Potential activity in multiple myopathies with an immune component
      - Recent Phase 1b/2 is promising
      - Would like to see as next step:
        - Larger trial with placebo-control
        - Endpoints to augment MMT: QMT, Timed Function Tests, etc.

RESOLARIS CLINICAL PROGRAM – DATA UPDATE

SANJAY SHUKLA, MD, MS, CMO

DECEMBER 13, 2016

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Resolaris Clinical Program Summary

Trial	Indication(s)	Patients	Highest Dose	Design	Data Timing
002	Adult FSHD	3 dose cohorts (n=20 Total)	3mg/kg weekly	Placebo controlled, Double blinded; Interpatient Dose Escalation	Announced 1Q 2016
003	Early onset FSHD	Stage 1 (n=8)	3mg/kg weekly	Open-label, Intrapatient Dose Escalation	Interim-Results Announced Today
004	Adult LGMD2B, Adult FSHD	LGMD2B (n=10) FSHD (n=8)	3mg/kg biweekly	Open-label, Intrapatient Dose Escalation	Top-line Results Announced Today
005	Adult FSHD	Rollover from 002	3mg/kg weekly	Long-term Safety Extension	Updated Today
006	LGMD2B, FSHD, Early onset FSHD	Rollover from 003 & 004	3mg/kg weekly	Long-term Safety Extension	TBD

Adult LGMD2B and FSHD (004) Trial

Objective & Rationale

Objective:

- Evaluate the safety/tolerability of total weekly exposure of 6.0mg/kg in LGMD2B and FSHD
- Assess drug activity more proximal to dosing

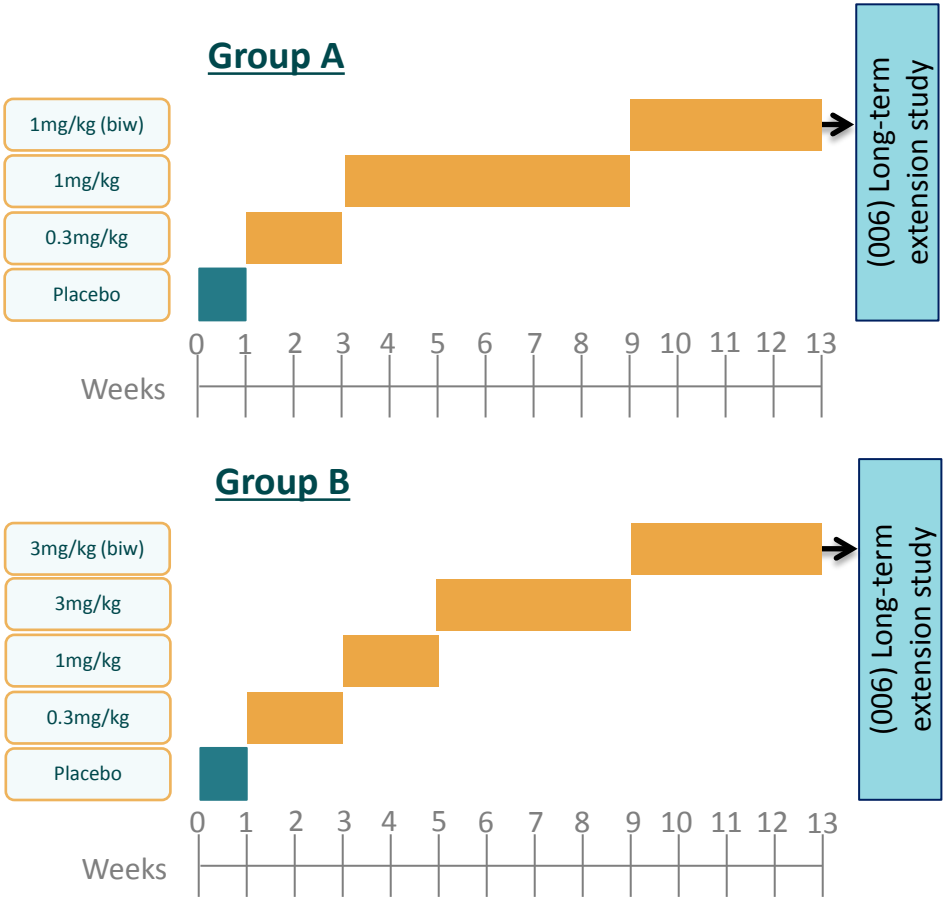
Rationale:

- To evaluate different dosing regimens

Study Design

- Open-label, intra-patient dose escalation
- Multiple sites in US & Europe
- N = 18 patients; enrollment complete
- **Group A:** 4 FSHD patients
- **Group B:** 4 FSHD patients / 10 LGMD2B patients
- 18-75 years of age
- Targeted MRI positive or circulatory markers*
  *(*in LGMD2B patients only)*

Dose Escalation



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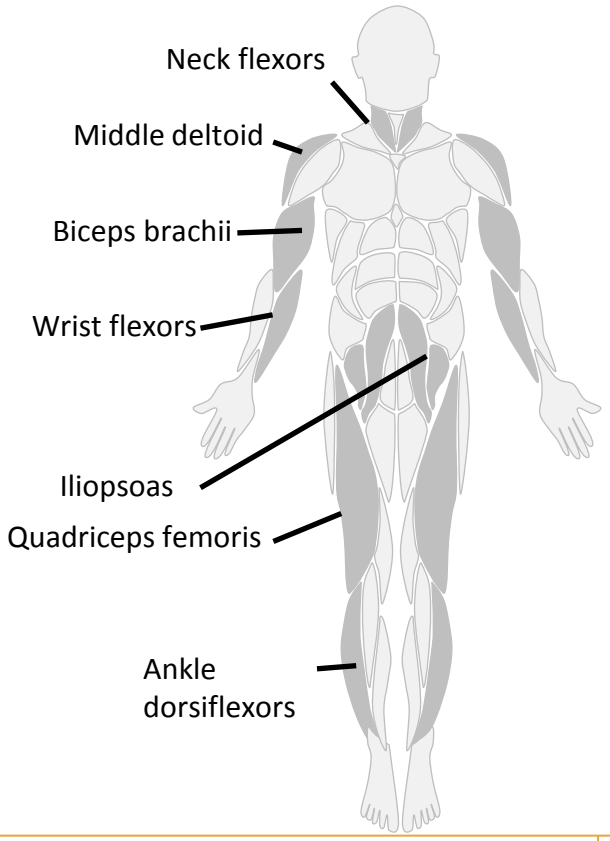
Demographics and Baseline Characteristics

Characteristic	Group A FSHD	Group B FSHD	Group B LBMD2B
Enrolled	4	4	10
Age (Mean years)	45.0	34.0	37.2
Median (Range)	45.0 (39, 51)	33.5 (33, 36)	33.5 (22, 62)
Male (number, %)	3, 75%	4, 100%	3, 30%
White (number, %)	4, 100%	4, 100%	9, 90%
BMI (kg/m^2), mean (SD)	23.38 (1.1)	24.83 (2.0)	27.67 (4.4)

Global Manual Muscle Testing

Muscle function/strength was formally assessed by investigators using Manual Muscle Testing (MMT)

- 14 muscles evaluated at different time points in studies
- Muscles scored individually
- Composite score calculated
- Progression: lower scores
  - Negative change from baseline
- Improvement: higher scores
  - Positive change from baseline



On Back (not pictured):
Neck Extensors;
Trapezius;
Gluteus medialis;
Hamstrings;
Ankle plantar flexors;
Gluteus maximus

Light grey = untested muscles Dark grey = tested muscles

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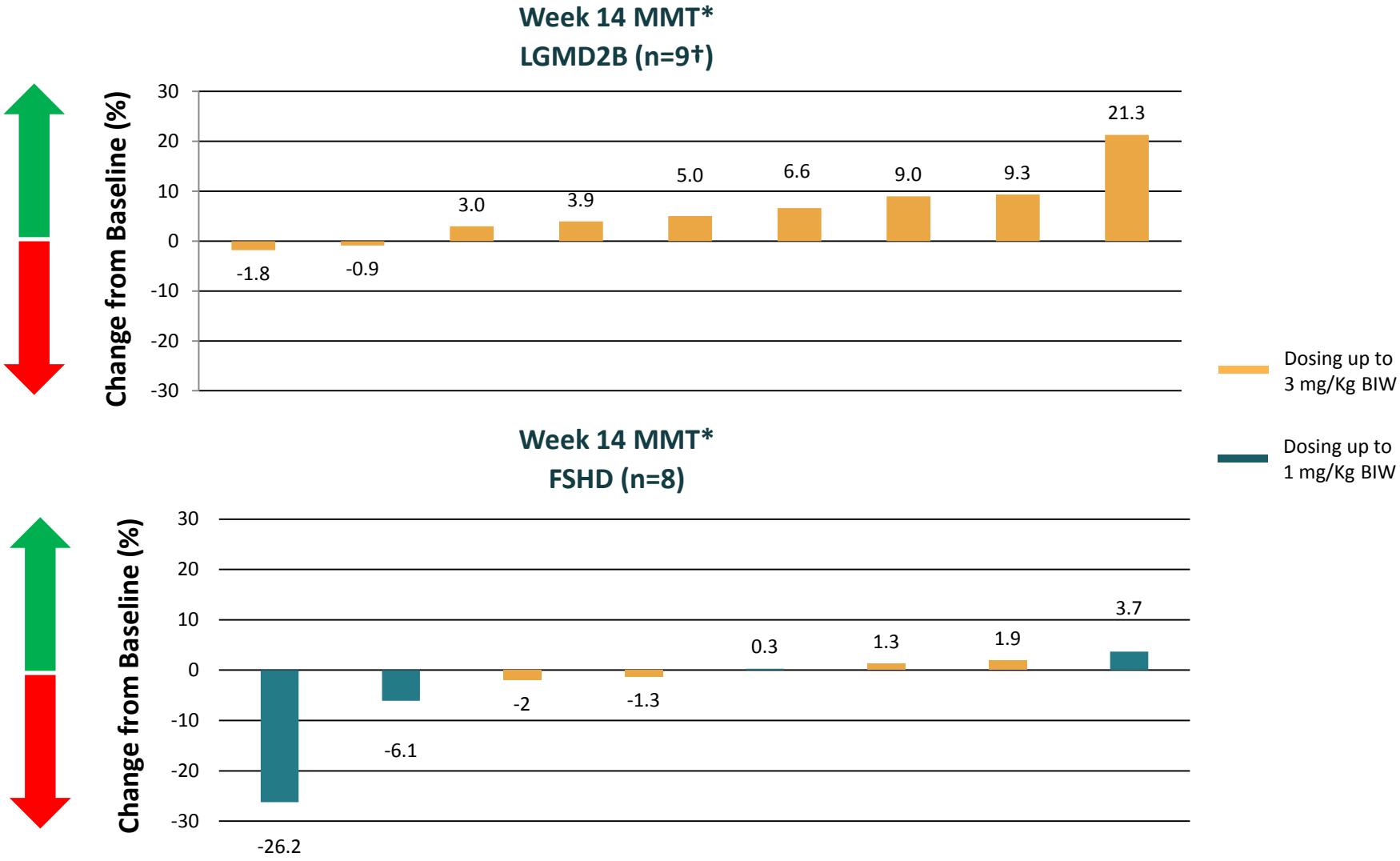
MMT Scores FSHD and LGMD2B (004 Trial)
Individual Patient Changes from Baseline (%)



1-week follow-up is earlier than week 14 for 2 early discontinuations

†One patient did not complete the MMT assessments due to being wheel chair bound

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Global Patient Reported Outcomes: INQoL

Individualized neuromuscular quality of life assessment

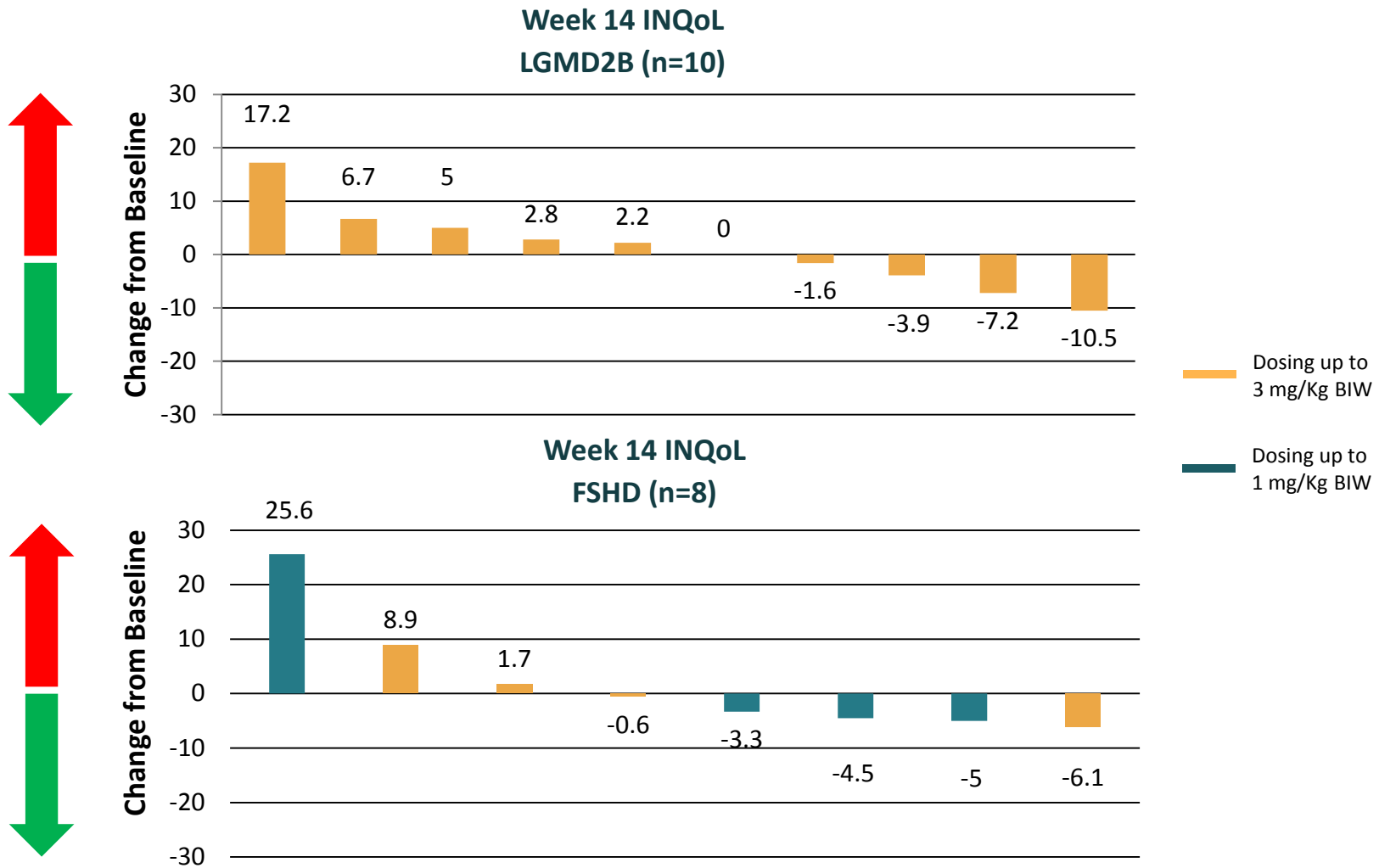
Validated Neuromuscular Assessment Tool*	• Global systematic assessment used in clinical studies and trials (to test for increased disease burden)
Self-Administered Questionnaire	• Questionnaire focuses on 4 dimensions: Symptoms, **Life Domains**, Treatment Effects, and Quality of Life • **Life Domains** comprised of 5 subsections: Activities, Independence, Social, Emotions, and Body Image
Improvement = <u>Decreased Scores</u> (Decreased Disease Burden)	• Overall INQoL score calculated from translating individual life domain scores into a 100 point scale

FDA: *"Generally, findings measured by a well-defined and reliable PRO instrument in appropriately designed investigations can be used to support a claim in medical product labeling if the claim is consistent with the instrument's documented measurement capability."***

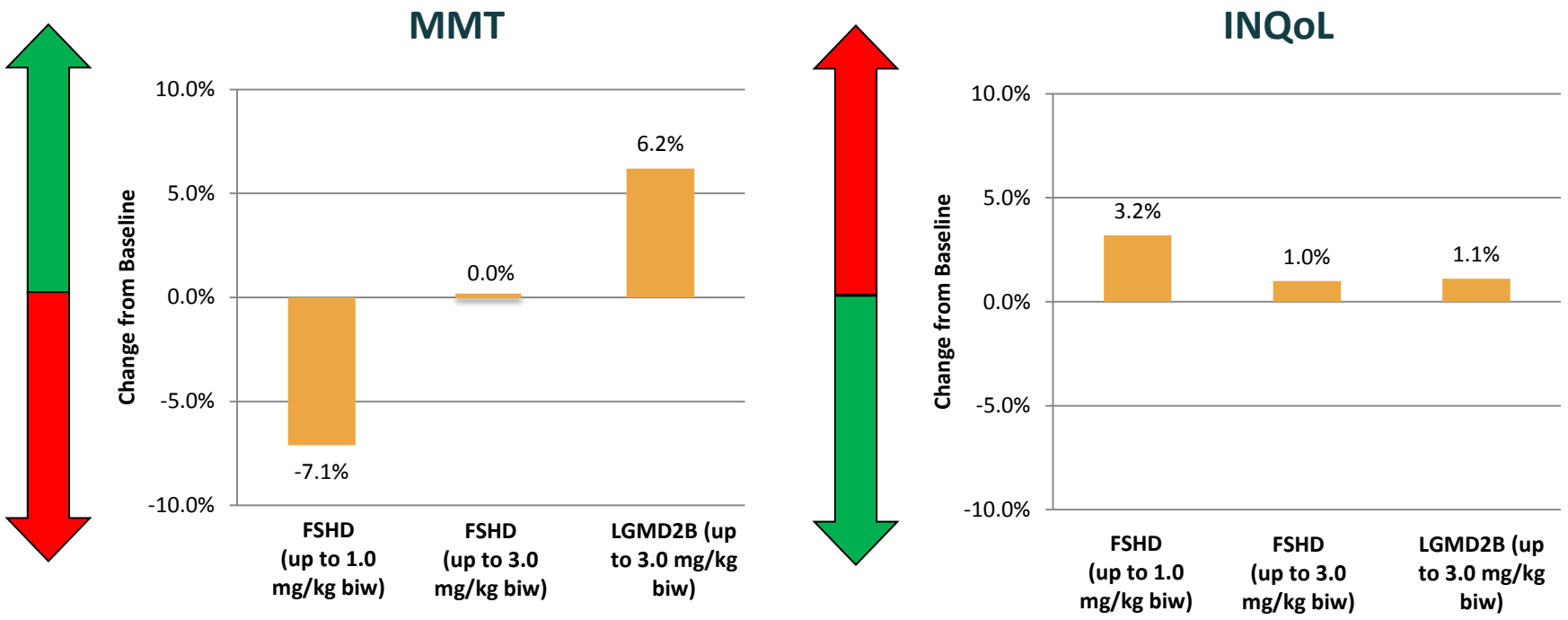
** Vincent KA et al: Construction and Validation of a Quality of Life Questionnaire for Neuromuscular Disease (INQoL). Neurology 2007, 68:1051-1057.*

*** FDA Guidance for industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; 2009.*

Overall INQoL Score (004 Trial)
Individual Change from Baseline



Summary 004 Trial Clinical Activity Assessments



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Biomarker Evaluation 004 Trial

- 004 Trial included various exploratory biomarkers
- Exploratory biomarkers did not generally establish sufficiently high or consistent levels or robust signals across a sufficient number of patients to determine test article effects
  - Including targeted muscle T2 and STIR MRI; and various plasma proteins
- Targeted muscle T2/STIR MRI will not be prioritized as a biomarker in the near-term
- Peripheral cell based biomarkers will be assessed at a later date

Early Onset FSHD (003) Trial

Objective & Rationale

Objective:

- Evaluate the safety/tolerability in a potentially different indication Early Onset FSHD
- Assess drug activity in new patient population and with additional endpoints

Rationale:

- Investigate an often more severe form of disease, involves additional organ systems

Status:

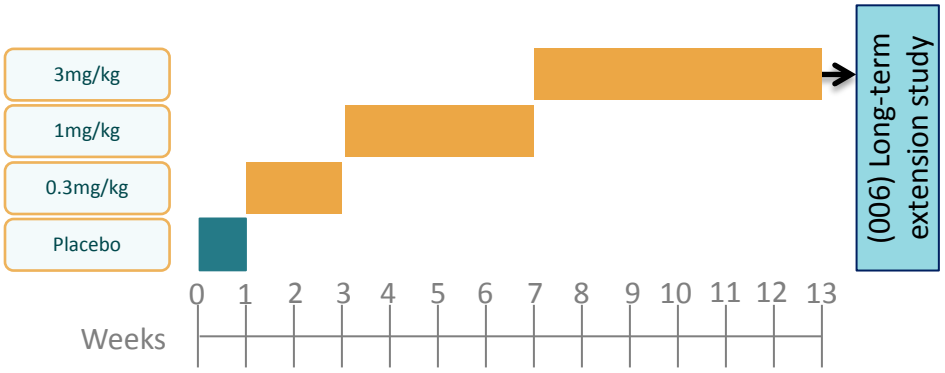
- Reported interim data analysis from the 4 patients today who completed treatment from Stage 1

Study Design

- Open-label, intra-patient dose escalation
- Multiple sites in US & Europe
- N = 16 patients
- **Stage 1:** 8 patients 16-25 years of age
- **Stage 2:** 8 patients 12-15 years of age

- Genetically confirmed diagnosis of FSHD and onset of symptoms prior to age 10

Dose Escalation



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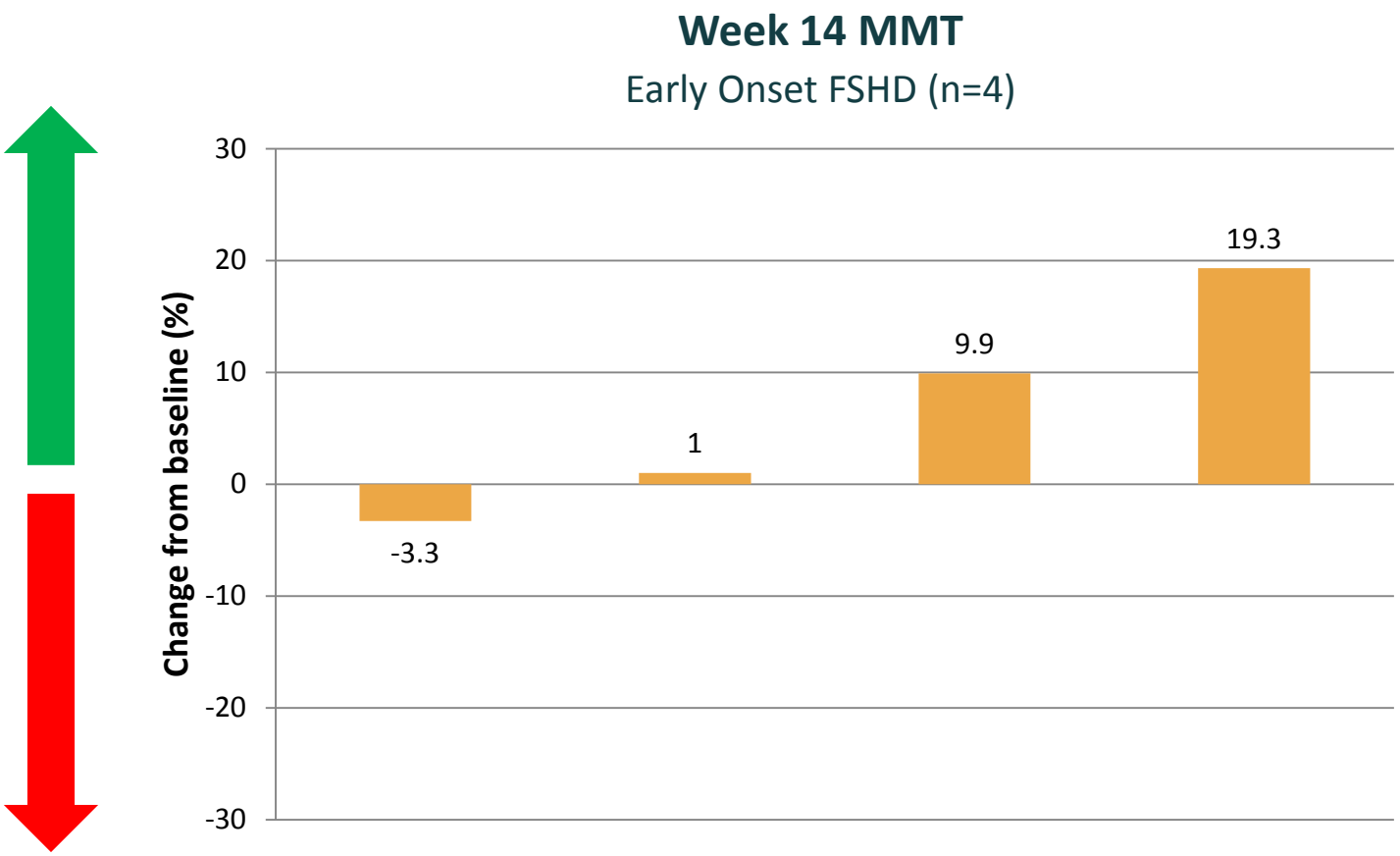
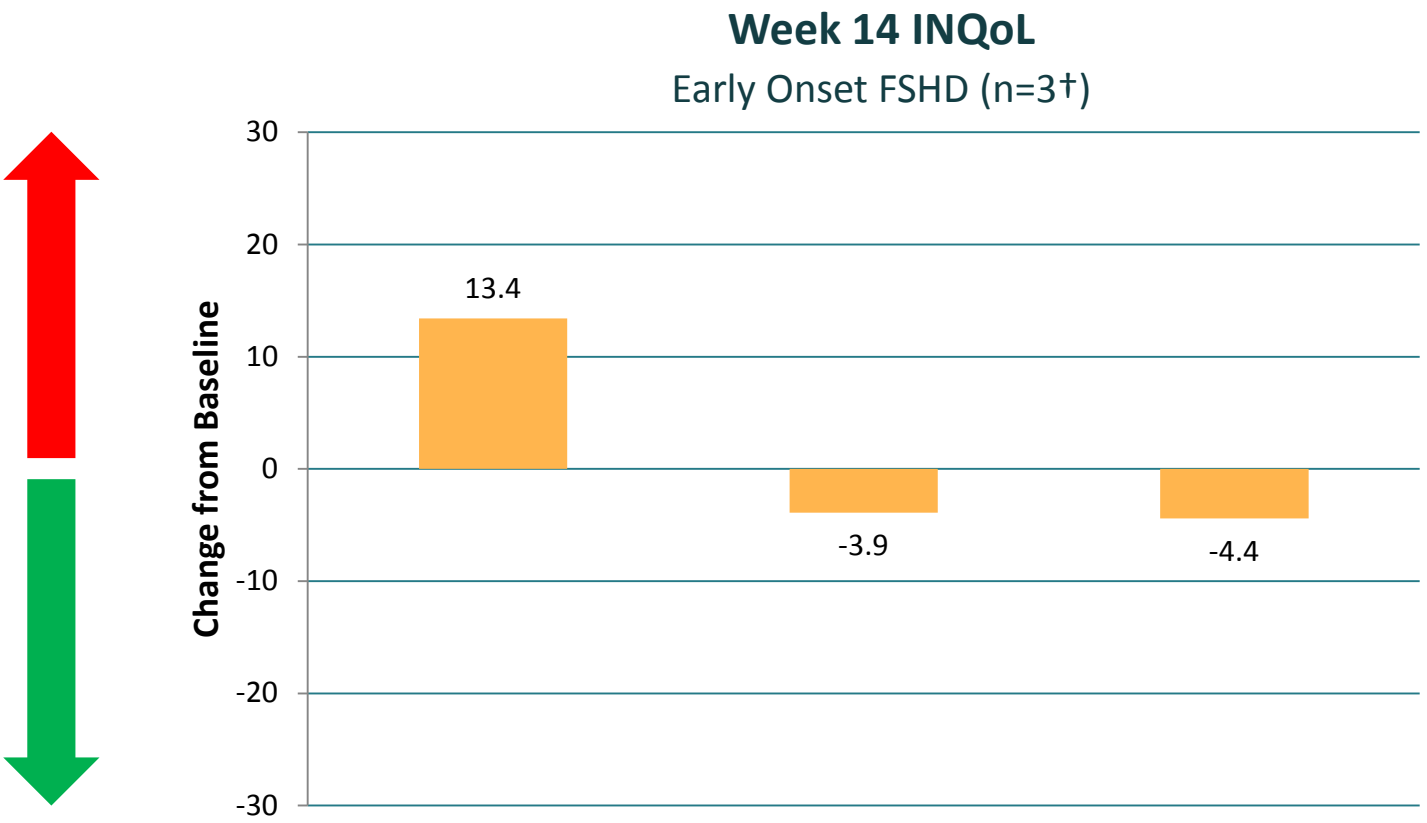
Overall MMT Score (003 Trial)
Individual Change from Baseline (%), Per Protocol Pop.

Early Onset FSHD



Overall INQoL Score (003 Trial)
Individual Change from Baseline, Per Protocol Pop.

Early Onset FSHD



† *One patient did not complete INQoL at baseline*

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Adult FSHD Long-Term Safety Extension (005) Trial

Study Design

- Patients receive weekly doses of 3.0 mg/kg
- Patients from Cohort 3 (3.0 mg/kg for 3 months) and Cohort 2 (1.0 mg/kg for 1 month) were eligible to roll-over to our long-term safety extension clinical trial
- Patients from Cohort 2 had greater than 12 months in between dosing (from end of 002 to initiation of 005)
- Patients from Cohort 3 were able to roll over directly into the 005 trial
- Open-label safety trial
- Initially 9 patients enrolled
- 3 sites in 3 countries

Study Objectives

Evaluate Safety and Tolerability:

- Build safety dossier for Resolaris

Evaluate Potential Activity Assessments:

1. Manual Muscle Test (MMT)
2. Individualized Neuromuscular Quality of Life (INQoL)
3. Biomarker Assessments

Clinical Findings

- 3 of the 9 patients enrolled from the adult FSHD (002) Trial are still receiving treatment
- Of the 4 patients who received at least 6 months of therapy, there were no significant trends in worsening or improvement in either MMT or INQoL scores

Safety & Tolerability Overview: 003, 004 & 005

As of December 1, 2016, 44 patients have received Resolaris, across all trials (including 002, 003, 004, and 005), for a total drug exposure of 149 patient months

Resolaris demonstrated a favorable safety profile and was generally well-tolerated across all doses tested in:

- ✓ Adult FSHD, Early onset FSHD (age range 16 to 20), and Adult LGMD2B
- ✓ Long-term exposure in adult FSHD patients (4 patients on drug ≥6 months)

No Serious Adverse Events (SAE) or deaths were reported

- ✓ All Adverse Events (AE) were in general mild or moderate in intensity
- ✓ No notable differences in AEs between adult FSHD, adult LGMD2B and early onset FSHD patients
- ✓ There were no dose limiting changes in lab parameters, vital signs or pulmonary tests

Protocol Discontinuations & Related Changes Going Forward

Protocol related discontinuations:

- Discontinued with a single IRR*(4 FSHD/1 LGMD): all IRRs mild to moderate, transient
- If Jo-1 Ab unit levels reach cut-off (5 FSHD): without associated clinical symptoms
- One LGMD patient discontinued from the 004 Trial for non-drug related reasons

- After changing the infusion protocol to a 90-minute infusion, 3 of 31 patients 9.1% experienced IRRs (previously the rate was 16.7% with an infusion rate of 30 minutes)

- Discontinuation rate in the 003/004/005 Trials under all protocols is 11 out of 35 patients (31%)

- Low level anti-drug antibody (ADA) assay signals 19/35 (54%; 13 FSHD and 6 LGMD) without associated clinical symptoms

Potential Safety & Tolerability Related Protocol Changes Going Forward:

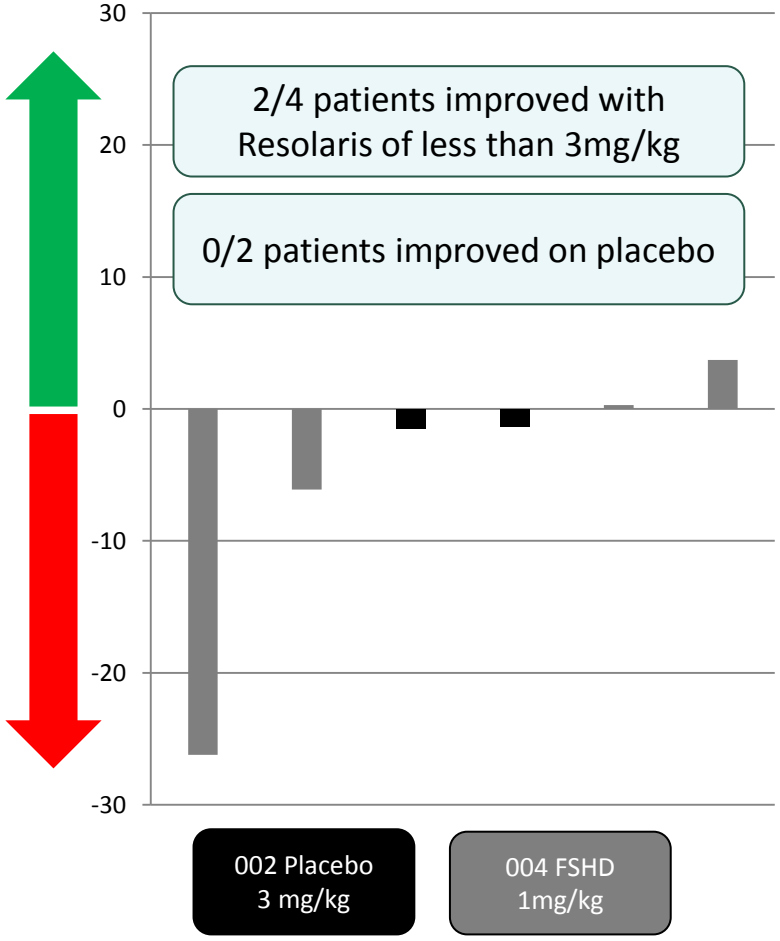
- Potential for pre-medicating patients
- Potential to continue dosing depending on the nature of the IRR
- Raising threshold for Jo-1 Levels above 1.5 U/mL (current cut off)

**Infusion Related Reaction*

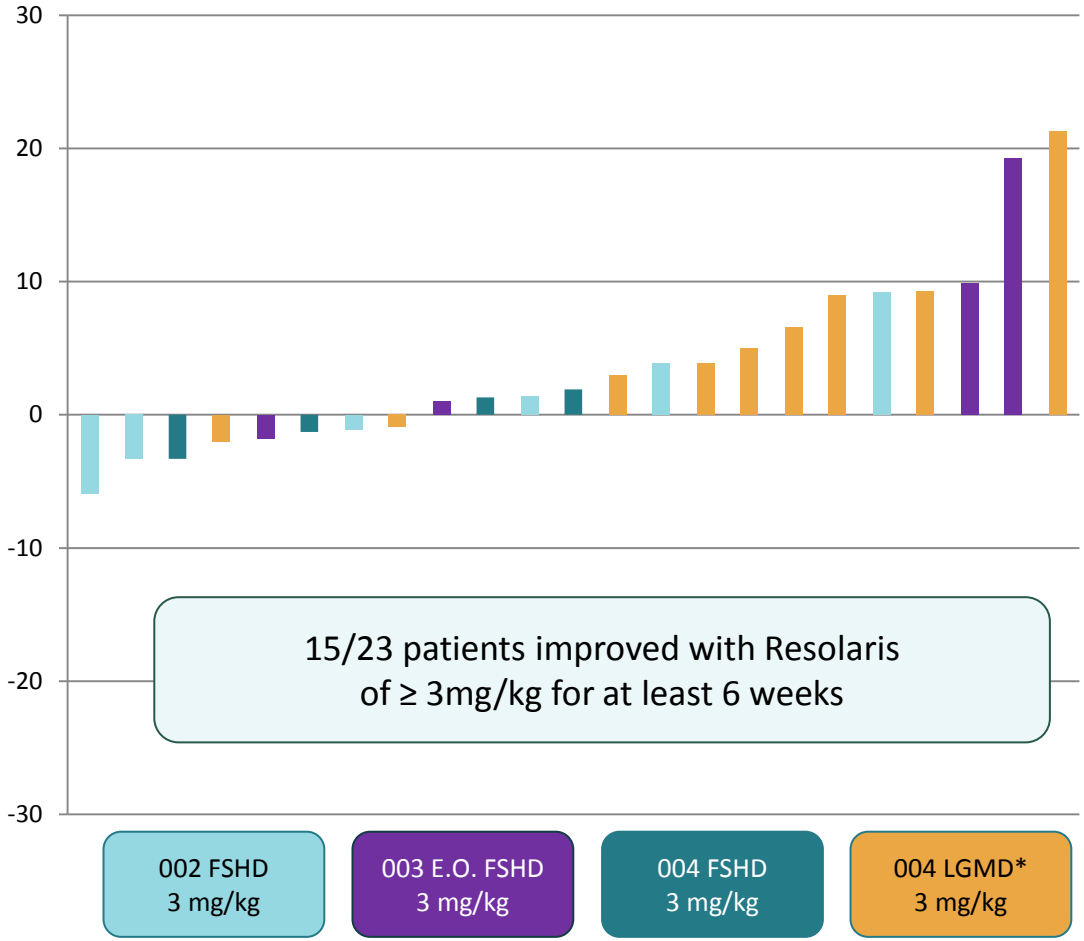
Overall MMT: FSHD, LGMD2B & Placebo

Change from baseline at week 14

Individual Patient MMT Change Week 14
FSHD & LGMD Patients Taking Placebo or Less Than 3mg/kg (002, 004 Trials)



Individual Patient MMT Change Week 14
FSHD & LGMD Patients Taking ≥ 3mg/kg for at least 6 weeks (002, 003, 004 Trials)



**One patient in 004 Trial did not have an MMT measurement due to being wheelchair bound*

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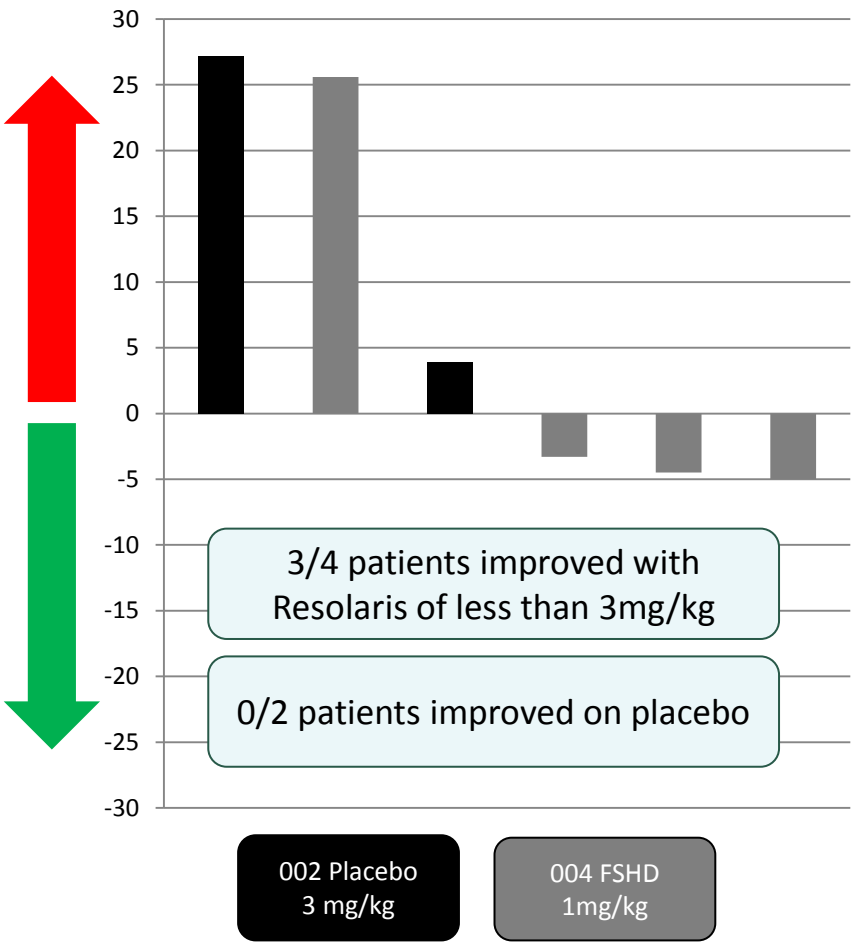
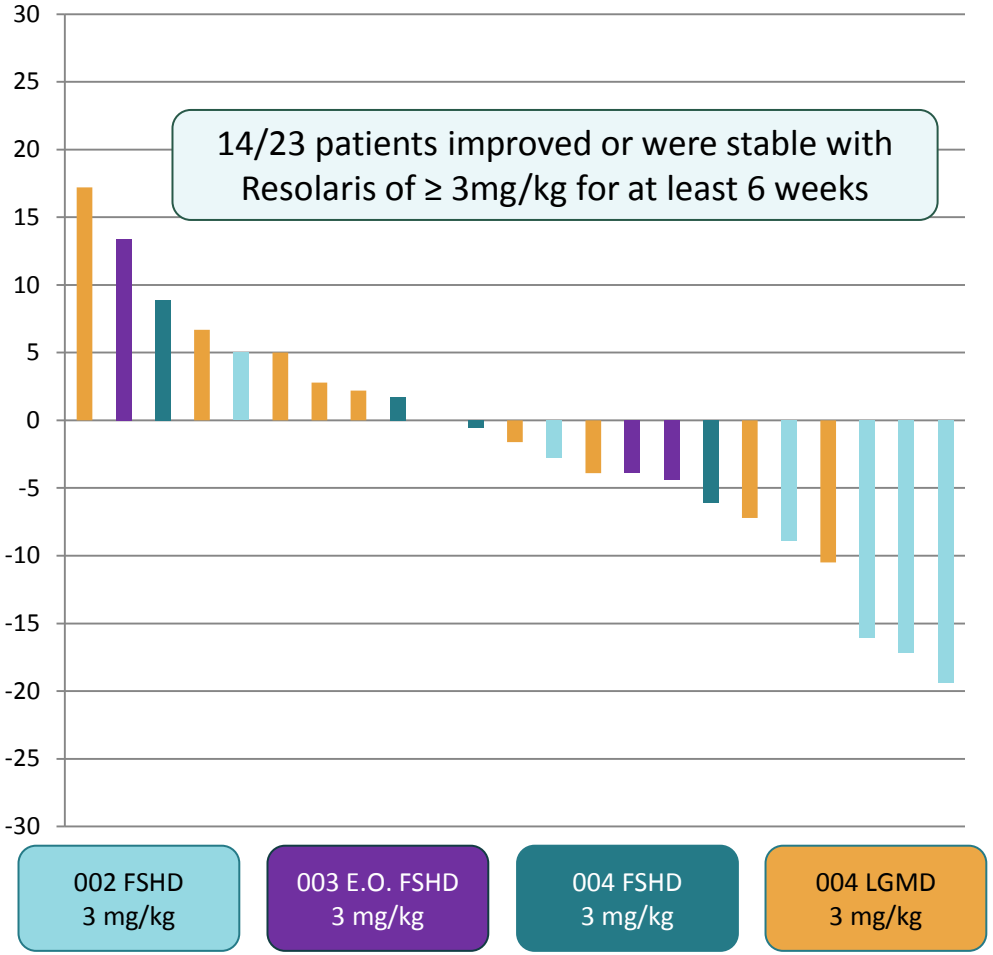
Overall INQoL: FSHD, LGMD2B & Placebo

Change from baseline at week 14

Individual Patient INQoL Change Week 14
FSHD & LGMD Patients Taking Placebo or Less Than 3mg/kg (002, 004 Trials)



Individual Patient INQoL Change Week 14
FSHD & LGMD Patients Taking ≥ 3mg/kg for at least 6 weeks (002, 003, 004 Trials)



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Resolaris Discussion and Next Steps

John Mendlein, PhD, Chief Executive Officer at aTyr Pharma

December 13, 2016

aTyr Pharma

2017 Rationale and Plan

Emphasis on Single RMIC Indication in 2017, dependent on:

- Leverage safety and activity data reviewed today
- Natural history & disease progression; favor homogeneous phenotype
- Ability to examine MOA with mechanistic assay in patients
  - Peripheral cell and or biopsy samples
  - Ideally, ability to connect genotype to immune cell

Advancement of iMod.Fc into Humans:

- Program for rare lung diseases with an immune component (i.e. interstitial lung diseases)

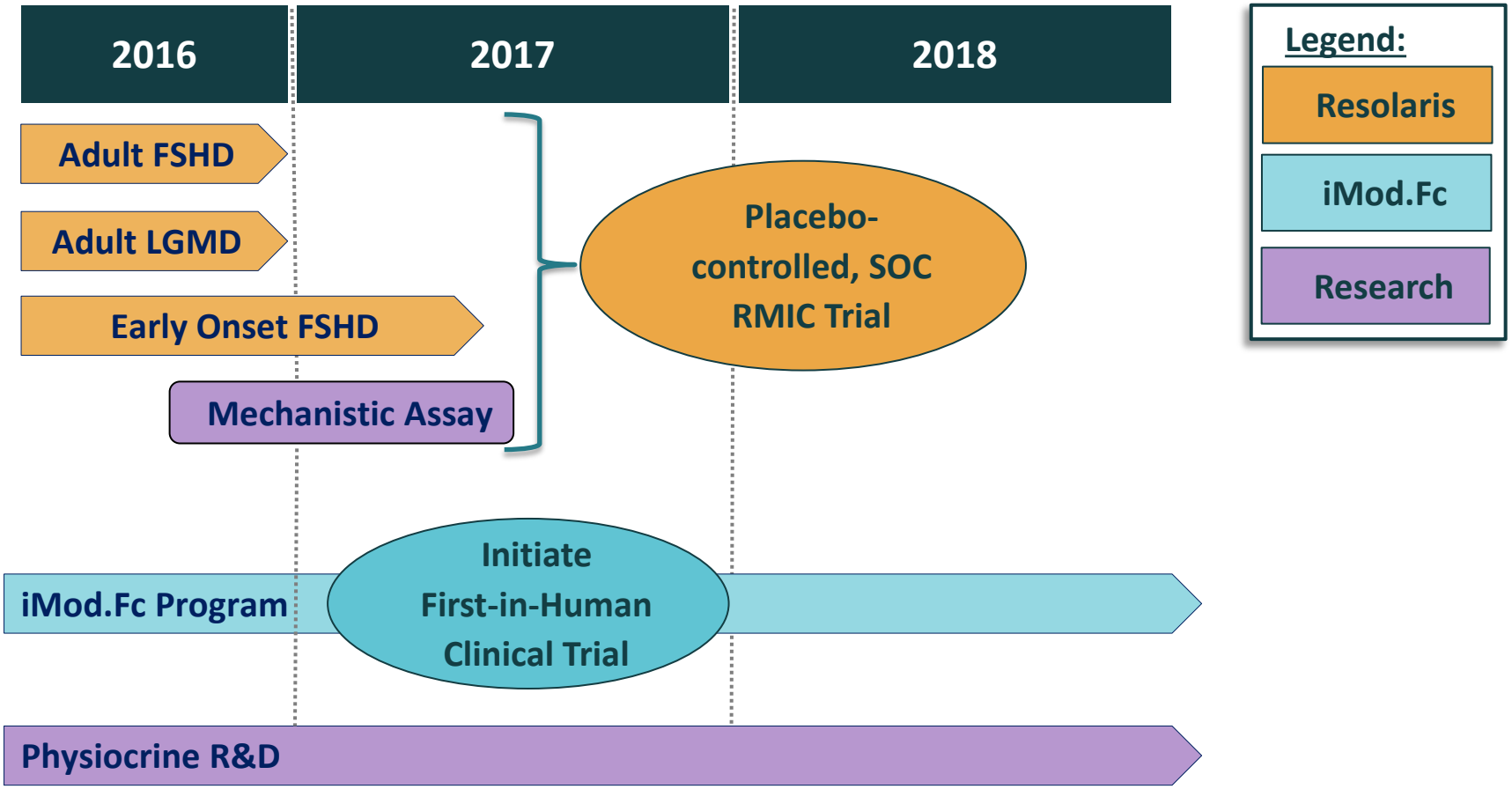
Advancement of Preclinical Pipeline:

- Potential for novel applications of Physiocrines

Cost of Capital Considerations for Pipeline Advancement:

- $80.9M in cash, cash equivalents, and investments as of 9/30/16; runway into 3Q 2018
- Partnering one or more of our programs to enhance the advancement of the pipeline

Next Steps: Potential Clinical Development Strategy*



**Clinical advancement will be linked with the development of a mechanistic assay and prudent cost of capital considerations*

QUESTIONS?

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APPENDIX: REFERENCE PAPERS

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Anti-Dystrophin T Cell Responses in Duchenne Muscular Dystrophy: Prevalence and Glucocorticoid Treatment Effect

REFERENCE

Anti-Dystrophin T Cell Responses in Duchenne Muscular Dystrophy: Prevalence and a Glucocorticoid Treatment Effect

Kevin M. Flanigan,[1*] Katie Campbell,[2] Laurence Viollet,[1] Wei Wang,[3] Ana Maria Gomez,[1] Christopher M. Walker,[2] and Jerry R. Mendell[1*]

Abstract

Duchenne muscular dystrophy (DMD) typically occurs as a result of truncating mutations in the *DMD* gene that result in a lack of expression of the dystrophin protein in muscle fibers. Various therapies under development are directed toward restoring dystrophin expression at the subsarcolemmal membrane, including gene transfer. In a trial of intramuscular adeno-associated virus (AAV)-mediated delivery of a therapeutic minidystrophin construct, we identified in two of six subjects the presence of a population of T cells that had been primed to recognize dystrophin epitopes before transgene delivery. As the presence of preexisting T cell immunity may have a significant effect on the success of therapeutic approaches for restoring dystrophin, we sought to determine the prevalence of such immunity within a DMD cohort from our Muscular Dystrophy Association clinic. Dystrophin-specific T cell immunity was evaluated in subjects with DMD who were either receiving the glucocorticoid steroid prednisone ($n=24$) or deflazacort ($n=29$), or who were not receiving steroids ($n=17$), as well as from normal age-matched control subjects ($n=21$). We demonstrate that increasing age correlates with an increased risk for the presence of anti-dystrophin T cell immunity, and that treatment with either corticosteroid decreases risk compared with no treatment, suggesting that steroid therapy in part may derive some of its benefit through modulation of T cell responses. The frequency of dystrophin-specific T cells detected by enzyme-linked immunospot assay was lower in subjects treated with deflazacort versus prednisone, despite similar overall corticosteroid exposure, suggesting that the effects of the two corticosteroids may not be identical in patients with DMD. T cells targeted epitopes upstream and downstream of the dystrophin gene mutation and involved the $CD4^+$ helper and/or $CD8^+$ cytotoxic subsets. Our data confirm the presence of preexisting circulating T cell immunity to dystrophin in a sizable proportion of patients with DMD, and emphasize the need to consider this in the design and interpretation of clinical gene therapy trials.

Flanigan et al, Human Gene Therapy, 2013

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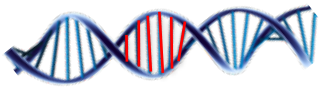
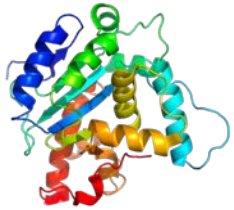
Connecting Genotype to Immune Cell Phenotype in Duchenne Muscular Dystrophy Patients

Disruption of Homeostasis
(untapped therapeutic intervention point)

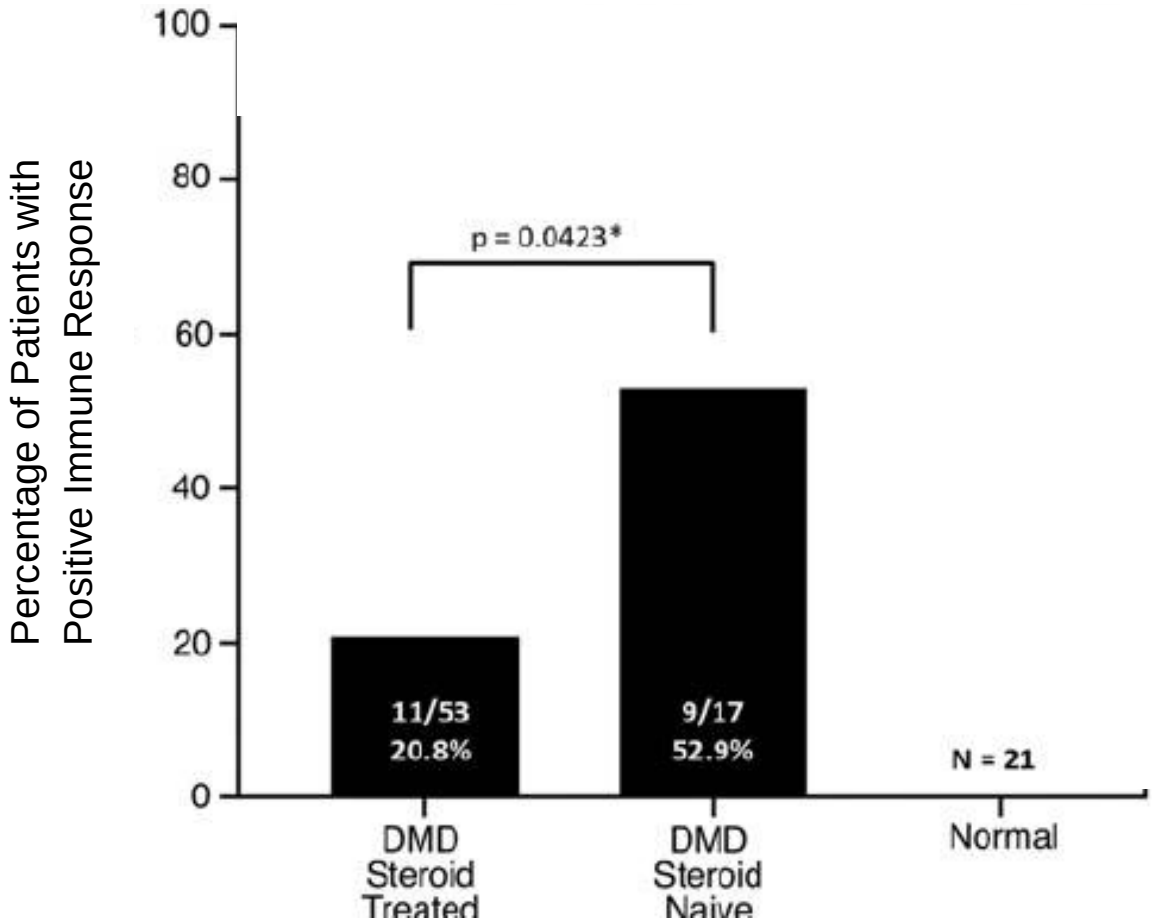




Genetic Mutation	Etiology of Aberrant Protein	Localized T Cell invasion & proliferation
DMD Patients: • Splice exon 12 • Del ex 45 • Del ex 46 – 50 • Del ex 49 – 54 • Nonsense ex 59 • Nonsense ex 69	**Locations of Immune Response:** • Exons 1 – 9 • Exons 17 – 26 • Exons 42 – 50 • Exons 50 – 59 • Exons 59 – 69 • Exons 70 - 79	**T Cell Phenotype:** CD4 and/or CD8

Frisullo et al., J. Clin. Immunol., 2011 *Gallardo et al. Neurology, 2001*
Flanigan et al. Human Gene Therapy, 2013

Steroids Suppress Dystrophin Specific Peripheral T Cell Response in Duchenne Muscular Dystrophy



Flanigan et al, Human Gene Therapy, 2013

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Treatment of Dysferlinopathy with Deflazacort: A Double-Blind, Placebo-Controlled Clinical Trial

REFERENCE

Treatment of dysferlinopathy with deflazacort: a double-blind, placebo-controlled clinical trial

Maggie C Walter[1*†], Peter Reilich[1†], Simone Thiele[1], Joachim Schessl[1], Herbert Schreiber[2], Karlheinz Reiners[3], Wolfram Kress[4], Clemens Müller-Reible[4], Matthias Vorgerd[5], Peter Urban[6], Bertold Schrank[7], Marcus Deschauer[8], Beate Schlotter-Weigel[1], Ralf Kohnen[9] and Hanns Lochmüller[10]

Abstract

Background: Dysferlinopathies are autosomal recessive disorders caused by mutations in the dysferlin (*DYSF*) gene encoding the dysferlin protein. DYSF mutations lead to a wide range of muscular phenotypes, with the most prominent being Miyoshi myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B).

Methods: We assessed the one-year-natural course of dysferlinopathy, and the safety and efficacy of deflazacort treatment in a double-blind, placebo-controlled cross-over trial. After one year of natural course without intervention, 25 patients with genetically defined dysferlinopathy were randomized to receive deflazacort and placebo for six months each (1 mg/kg/day in month one, 1 mg/kg every 2nd day during months two to six) in one of two treatment sequences.

Results: During one year of natural course, muscle strength declined about 2% as measured by CIDD (Clinical Investigation of Duchenne Dystrophy) score, and 76 Newton as measured by hand-held dynamometry. Deflazacort did not improve muscle strength. In contrast, there is a trend of worsening muscle strength under deflazacort treatment, which recovers after discontinuation of the study drug. During deflazacort treatment, patients showed a broad spectrum of steroid side effects.

Conclusion: Deflazacort is not an effective therapy for dysferlinopathies, and off-label use is not warranted. This is an important finding, since steroid treatment should not be administered in patients with dysferlinopathy, who may be often misdiagnosed as polymyositis.

Trial registration: This clinical trial was registered at www.ClincalTrials.gov, identifier: NCT00527228, and was always freely accessible to the public.

Keywords: Limb girdle muscular dystrophy (LGMD), Dysferlinopathy, Therapy, Deflazacort, Muscle strength, Steroids

Walter et al, Orphanet Journal of Rare Diseases, 2013

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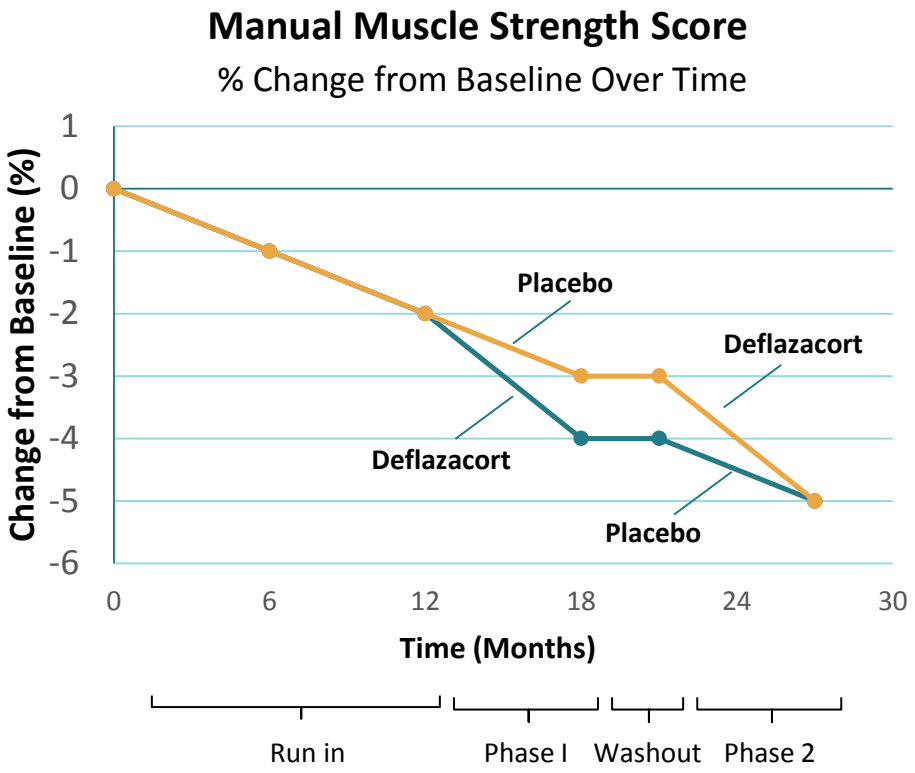
Manual Muscle Testing by CIDD

Clinical Investigation of Duchenne Dystrophy (CIDD)

- Primary outcome measures were manual muscle strength assessed bilaterally by the modified Medical Research Council Scales (MRC) CIDD (Clinical Investigation of Duchenne Dystrophy) score, graded from 0 (worst) to 10 (best)
  - http://www.researchrom.com/masterlist/view/4
- Testing was performed by two experienced neurologists after sufficient training with clinical trial procedures
- Inter-rater and intra-rater variability was assessed prior to the clinical trial, and reassessed 12-monthly during the trial period on the enrolled dysferlinopathy patients

Walter et al, Orphanet Journal of Rare Diseases, 2013

LGMD Patients Manual Muscle Strength* Decline at Double the Rate on Deflazacort vs Placebo



Treatment with Deflazacort was for 6 months in each arm Single site, placebo controlled, cross over design (n=25)

**Manual muscle strength assessed bilaterally by the modified Medical Research Council Scales (MRC) CIDD (Clinical Investigation of Duchenne Dystrophy) score, graded from 0 (worst) to 10 (best)*

Walter et al, Orphanet Journal of Rare Diseases, 2013