2024 Summer Series of R&D Webinars
Part 1 – Muscle Programs

May 23, 2024

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Neuromuscular Programs Webinar – May 23, 2024

Welcome and Introductions

Vince Anzalone, CFA
Vice President

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Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, entering into new collaborations and achieving existing projected milestones, rapid technological changes in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Who We Are

Arrowhead is an **RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** product candidates

Broad Pipeline

- **14 clinical stage programs** (10 wholly-owned; 4 partnered)
- Mix of **early, mid, and late-stage** candidates targeting **rare and high prevalence diseases**
- Growing pipeline with **2–3 new clinical programs planned per year**

Proprietary Platform

- **Targeted RNAi Molecule (TRiM™)** platform achieves **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**

Financial Resources

- **Non-dilutive capital** from Amgen, Takeda, GSK, and Royalty Pharma as milestones are achieved and royalties are earned
- Potential for **additional** product, platform, and structured finance **deals**

20 in '25: We Expect to Have 20 Individual Drugs in Clinical Trials or At Market in 2025

Arrowhead Pipeline

Therapeutic Area		Pre-clinical	Phase 1	Phase 2	Phase 3	Product Rights
Cardiometabolic	**Plozasiran (ARO-APOC3)** Hypertriglyceridemia					
	Zodasiran (ARO-ANG3) Dyslipidemia					
	Olpasiran CVD					AMGEN
	GSK4532990 NASH					gsk
	ARO-PNPLA3 NASH					
Pulmonary	**ARO-RAGE** Inflammatory					
	ARO-MUC5AC Muco-Obstructive					
	ARO-MMP7 IPF					
Liver	**Fazirsiran** Alpha-1 Liver Disease					Takeda
	JNJ-3989 HBV					gsk
Muscular	**ARO-DUX4** FSHD					
	ARO-DM1 DM1					
Other	**ARO-C3** Complement Mediated Disease					
	ARO-CFB Complement Mediated Disease					

Tissue Targets: Liver Lung Muscle

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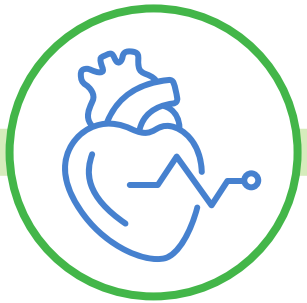
Muscle

ARO-DM1 and ARO-DUX4

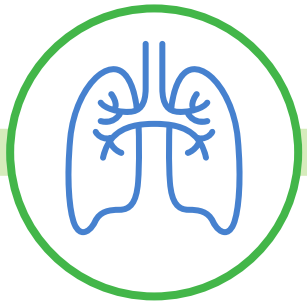
May 23, 2024



Cardiometabolic

Plozasiran and Zodasiran

June 25, 2024



Pulmonary

ARO-RAGE, ARO-MUC5AC, ARO-MMP7

July 16, 2024

Obesity/ Metabolic

ARO-INHBE and New Adipose Target

August 15, 2024

Central Nervous System

Platform and Pipeline Updates

Sept. 25, 2024

2024 Summer Series Goals

- Provide focused time to cover underappreciated parts of our pipeline
- Detail advances in the TRiM™ platform
- Hear directly from the Arrowhead team that worked on the programs
- Get external physician perspective on each disease area

Neuromuscular Programs Agenda

Time	Topic	Presenter
11:00-11.05	Introductions and Agenda	Vince Anzalone CFA
11:05-11:10	TRiM™ Muscle Delivery Platform	James Hamilton M.D., MBA
11:10-11:20	DM1 – Disease overview and unmet need	Lawrence Korngut M.D.
11:20-11:30	DM1– Preclinical data	Jonathan Van Dyke Ph.D.
11:30-11:40	DM1 – Clinical trial design and status	James Hamilton M.D., MBA
11:40-11:50	FSHD – Disease overview and unmet need	Lawrence Korngut M.D.
11:50-12:00	FSHD – Preclinical data	Jonathan Van Dyke Ph.D.
12:00-12:10	FSHD – Clinical trial design and status	James Hamilton M.D., MBA
12:10-12:30	Q&A	Panel

Neuromuscular Opinion Leader

Lawrence Korngut, MD MSc FRCPC

Dr. Lawrence Korngut is a neuromuscular neurologist at the Calgary Neuromuscular Program where he served as Director from 2017 through 2021. He is an Associate Professor at the University of Calgary Cumming School of Medicine in the Department of Clinical Neurosciences. He is a full member of the Hotchkiss Brain Institute. His research program focuses on collecting real world health data to improve health outcomes of patients with neuromuscular disease. He has published 62 peer-review articles and is a regular speaker at international conferences.

Dr. Korngut is a member of the Scientific Advisory Committee at SOLVE-FSHD and the Steering Committee of the 2024 FSHD IRC Meeting in Denver, Colorado. He is a member of the Global Task Force for Project Mercury that aims to build a global cohort of 10,000 clinical-trial-ready, well-characterized patients; expand and optimize the world-wide clinical trial infrastructure; and remove the barriers that delay patient access to therapies once approved.

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TRiM™ Platform for Muscle Delivery

James Hamilton, MD, MBA,
Chief of Discovery & Translational Medicine

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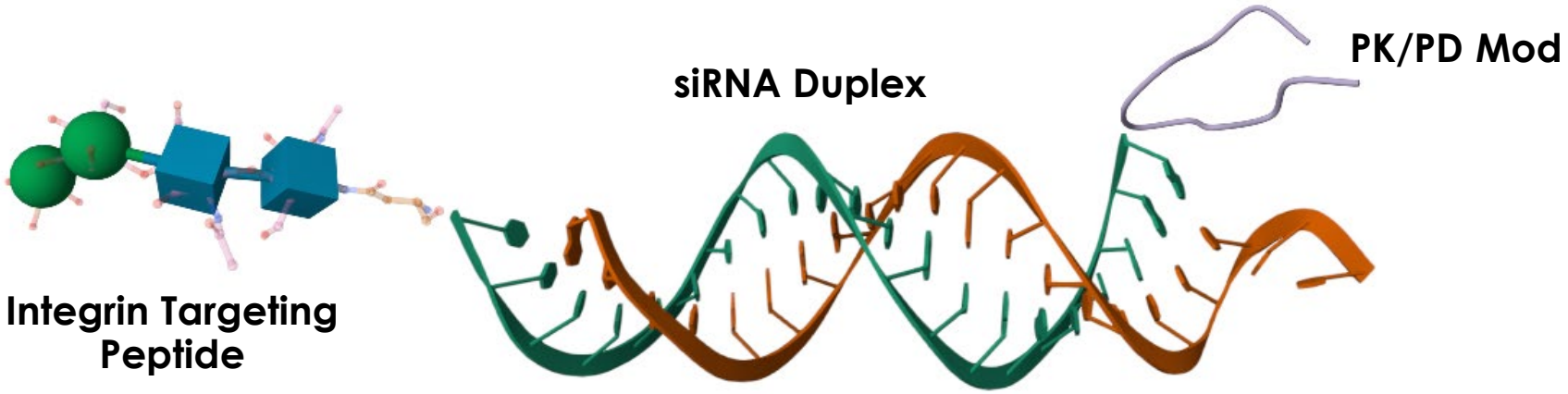
TRiM Platform for siRNA Delivery to Skeletal Muscle

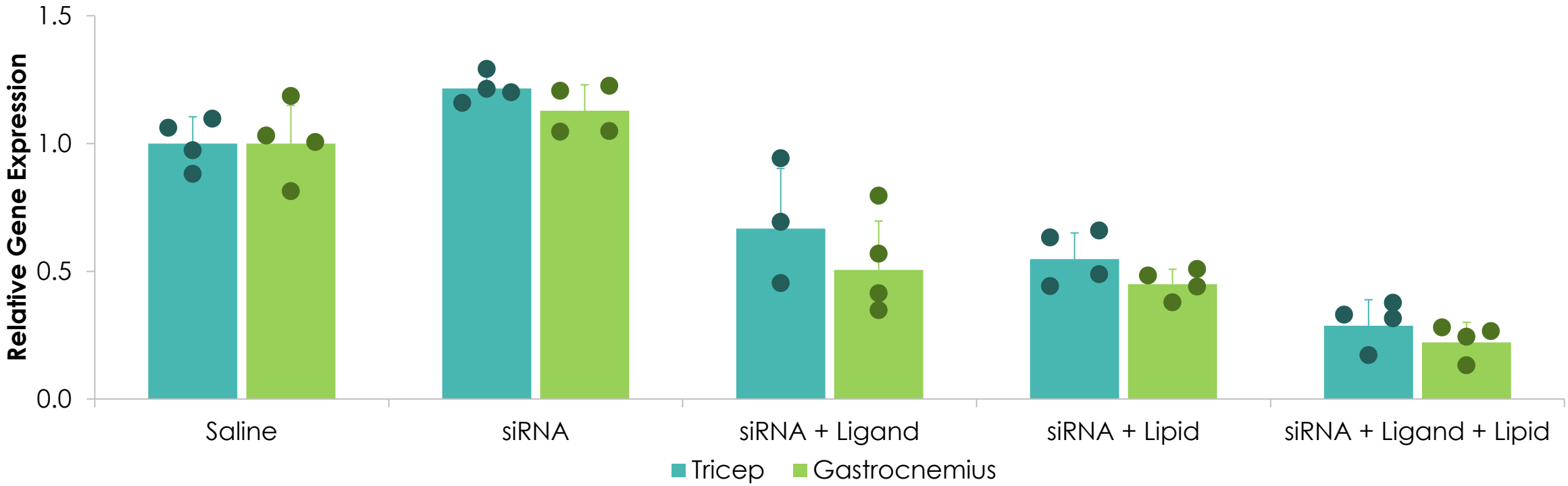


ARO-DUX4 and **ARO-DM1** leverage a unique skeletal muscle targeting platform optimized for delivery, stability, and target knockdown

ARO-DUX4/DM1 Components	Select Characteristics/Impact
Targeting Ligand	Peptide ligand targeting avb6 integrin receptor; ligand is stable in plasma, improves delivery to targeted tissue and cell
Linkers	Improve RISC loading efficiency
PK/PD modulator	Improve delivery and cellular uptake
RNAi Trigger	Sequence specific and optimized to yield deep on-target knockdown with long duration

Platform Component Evaluation Using Tool Trigger in Mouse

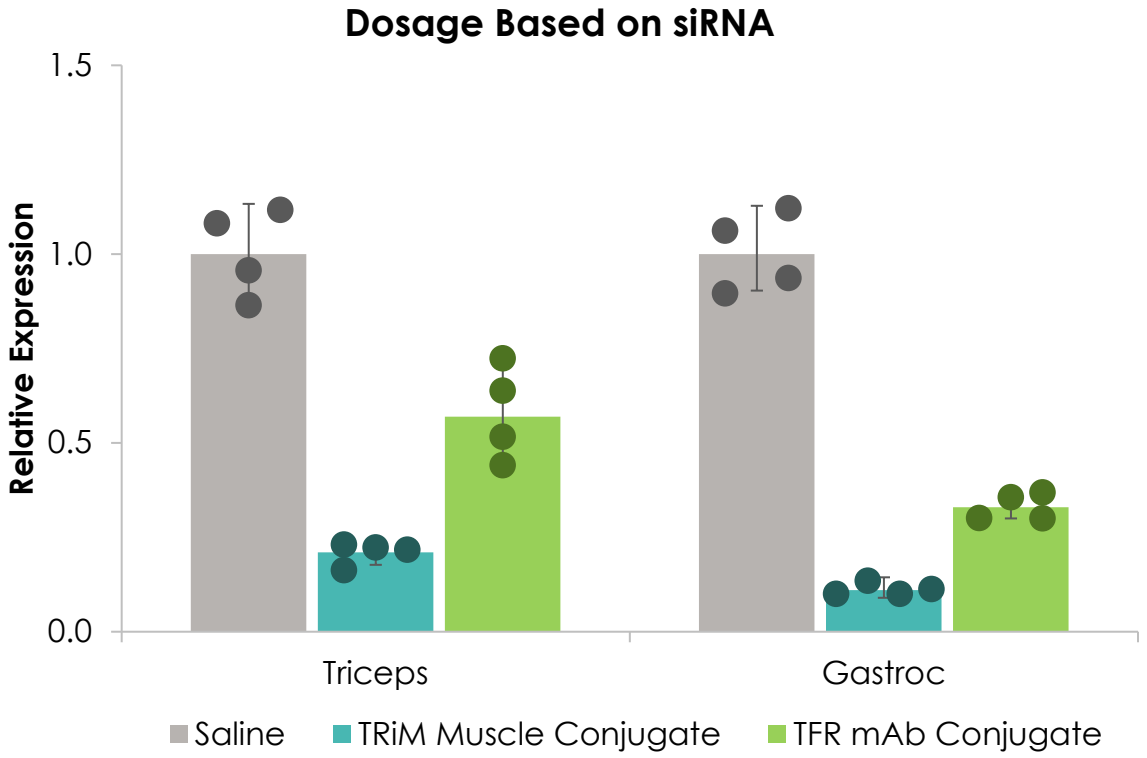
Mouse MSTN — D1 2mpk IV, D22 sac



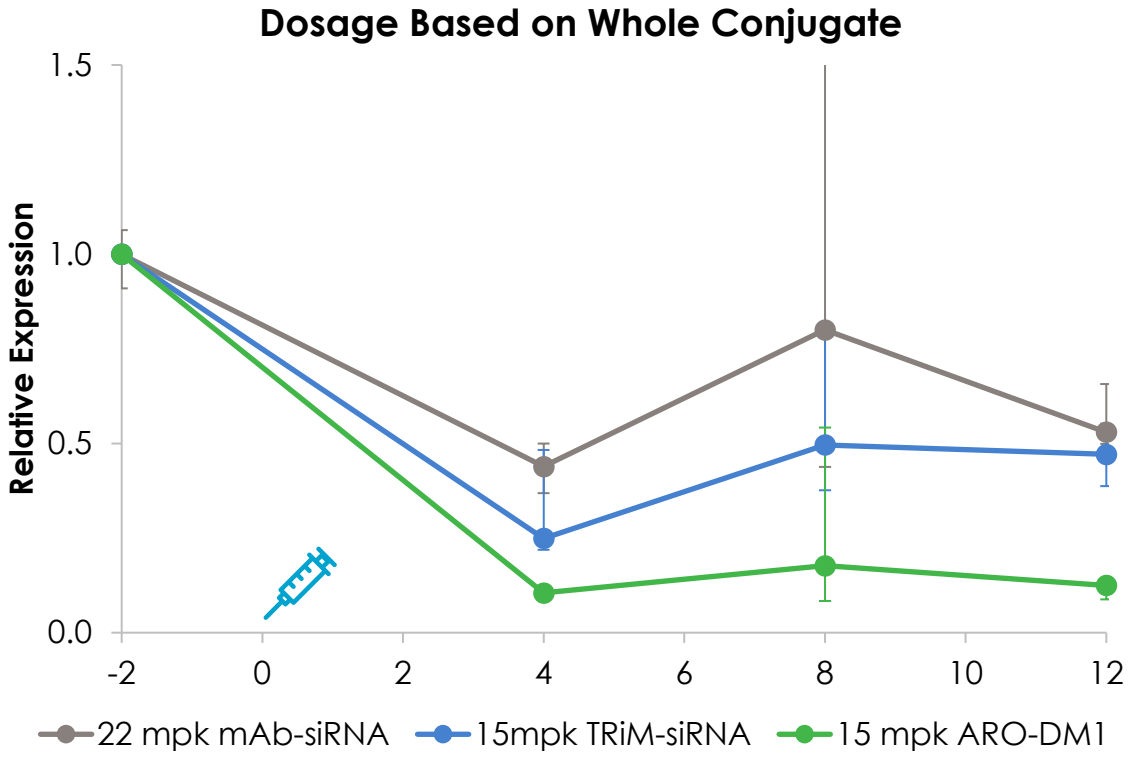
The Full Conjugate Containing Integrin Ligand Peptide and PK/PD Modifier Are Both Required to Maximize Target Gene Silencing

TRiM™ Conjugate Outperforms TfR mAb Conjugate in Mouse and NHP

MSTN KD in Mouse — 3 mpk, IV



DMPK KD in Cyno Triceps — IV



15 mg/kg IV Dose of ARO-DM1 Conjugate Achieved Up to 92% Knockdown and Maintained ≥80% Knockdown Over 12 Weeks in NHP

Integrin Targeting vs. Transferrin Receptor Antibody Conjugation Approaches

- **Potential for improved skeletal muscle gene target silencing**
  - ARO-DUX4 utilizes a dual targeting approach with a combination of integrin receptor ligand and lipid PK/PD modifier may yield improved safety and efficacy over transferrin receptor targeted approaches

- **Less drug is always better:** transferrin receptor targeted AOC requires a higher total dose compared with integrin peptide targeted approach
  - Normalizing for siRNA dose: 12 mg/kg ARO-DUX4 siRNA content ~ 100 mg/kg DUX4-AOC siRNA content (antibody + siRNA)
  - Potential efficacy, safety, COGS implications

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Myotonic Dystrophy (DM1) – Disease Background and Unmet Need

Lawrence Korngut, MD MSc FRCPC, Associate Professor (Neurology)
Director, Innovation and Commercialization,
Hotchkiss Brain Institute, Calgary

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Myotonic Dystrophy Type 1

Dr. Lawrence Korngut MD
Neuromuscular Neurologist
Associate Professor of Neurology
University of Calgary

Myotonic Dystrophy Type 1 (DM1)

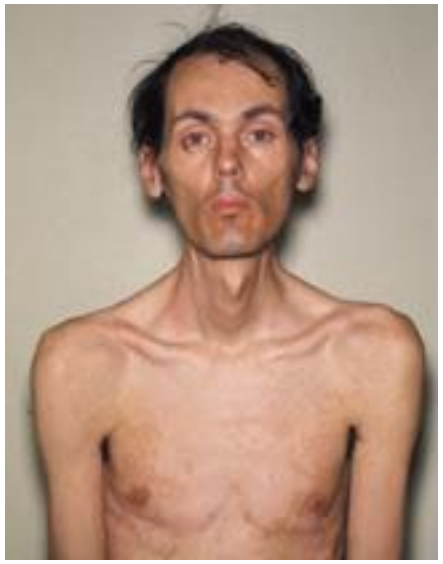
- A multisystem disorder that affects skeletal and smooth muscle
- Also the eye, heart, endocrine system, and central nervous system.
- The clinical findings (mild to severe) categorized
  - Mild
  - Classic
  - Congenital

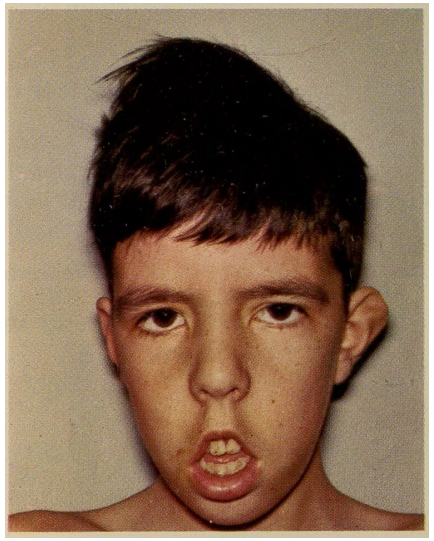
Manifestations and Life Expectancy

Phenotype	Clinical Signs	CTG Repeat Size	Age of Onset	Average Age of Death
Intermediate (unaffected)	None	35-49	NA	NA
Mild	Cataracts Mild myotonia	50-~150	20-70 yrs	60 yrs to normal life span
Classic	Weakness Myotonia Cataracts Balding Cardiac arrhythmia	~100-~1,000	10-30 yrs	48-55 yrs
Congenital	Infantile hypotonia Respiratory deficits Intellectual disability Classic signs in adults	>1,000	Birth to 10 yrs	45 yrs [4]

Adapted from genereviews.org

Source: Wikipedia

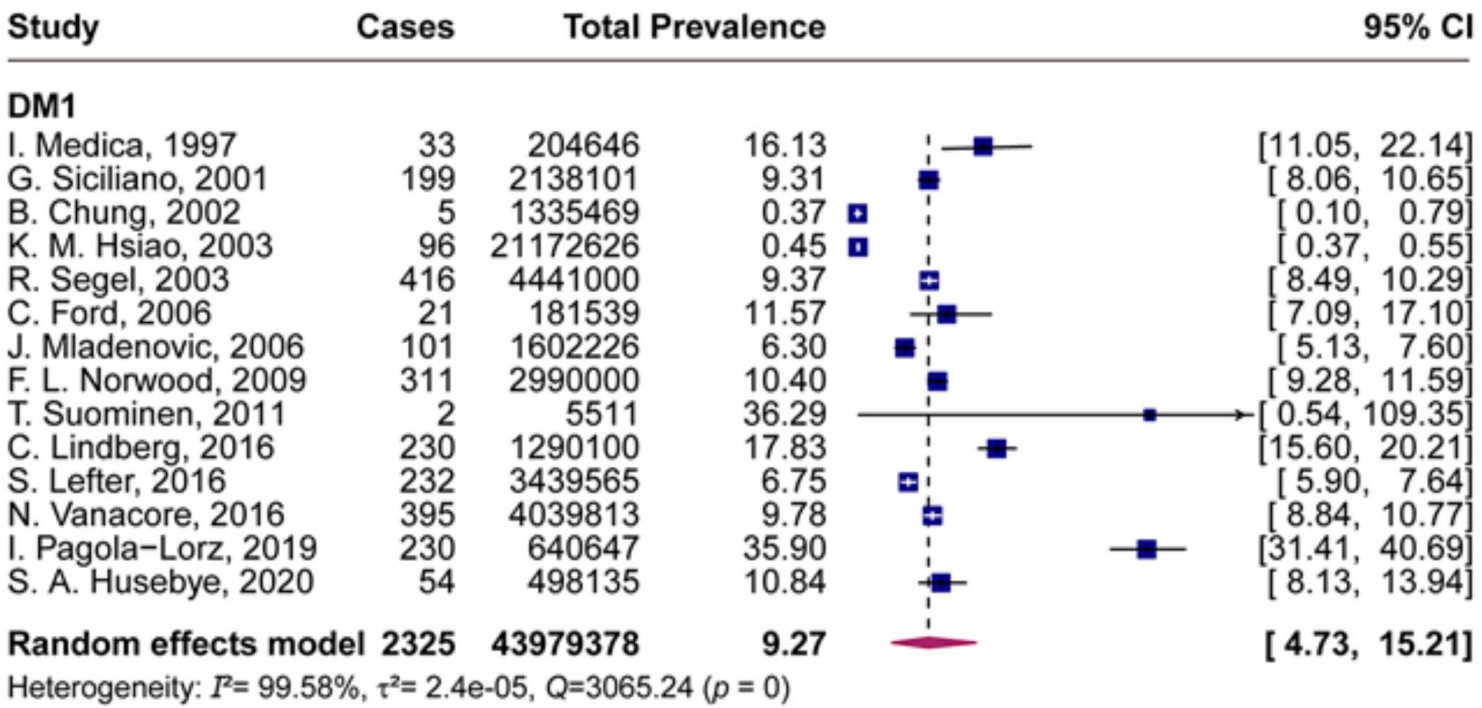




Prevalence

The proportion of a population who have a specific characteristic

Liau et al., Neuroepidemiology 2022



Study	Cases	Total	Prevalence	95% CI
DM1				
I. Medica, 1997	33	204646	16.13	[11.05, 22.14]
G. Siciliano, 2001	199	2138101	9.31	[8.06, 10.65]
B. Chung, 2002	5	1335469	0.37	[0.10, 0.79]
K. M. Hsiao, 2003	96	21172626	0.45	[0.37, 0.55]
R. Segel, 2003	416	4441000	9.37	[8.49, 10.29]
C. Ford, 2006	21	181539	11.57	[7.09, 17.10]
J. Mladenovic, 2006	101	1602226	6.30	[5.13, 7.60]
F. L. Norwood, 2009	311	2990000	10.40	[9.28, 11.59]
T. Suominen, 2011	2	5511	36.29	[0.54, 109.35]
C. Lindberg, 2016	230	1290100	17.83	[15.60, 20.21]
S. Lefter, 2016	232	3439565	6.75	[5.90, 7.64]
N. Vanacore, 2016	395	4039813	9.78	[8.84, 10.77]
I. Pagola−Lorz, 2019	230	640647	35.90	[31.41, 40.69]
S. A. Husebye, 2020	54	498135	10.84	[8.13, 13.94]
Random effects model	**2325**	**43979378**	**9.27**	**[4.73, 15.21]**

Heterogeneity: I^2= 99.58%, τ^2= 2.4e-05, Q=3065.24 (p = 0)

Based on this about 1 in 10,800 people had DM1 but 1 in 20,000 is generally accepted

Life Expectancy and Cardiac Manifestations

- Reduced life expectancy
  - Mean age at death of 53 years
  - Mortality rate approximately 7.3 times that of an age-matched general population (Matthieu at al. Neurology. 1999)
  - Cause of death: Respiratory failure in 40%, cardiac in 30%
    - Lau et al. Int J Cardiology 2015

- Cardiac manifestations
  - Cardiac fibrosis and fatty infiltration -> His–Purkinje +/- sino-atrial and atrio-ventricular (AV) nodes

Cardiac abnormalities (continued)

- A meta-analysis of 1828 patients (Petri et al. Int J Cardiology 2012)
  - 1st degree AV block in 28.2%
  - QTc > 440 ms in 22.0%
  - Atrial fibrillation/flutter in 5.0%
  - Non-sustained ventricular tachycardia in 4.1%
  - Bradycardia a frequent cause of sudden cardiac death but risk persists even with pacemakers and may result from ventricular tachycardia or ventricular fibrillation
- Prevalence of cardiac involvement was 66% after a median follow-up of 10.5 years (Petri et al. Int J Cardiology 2024)

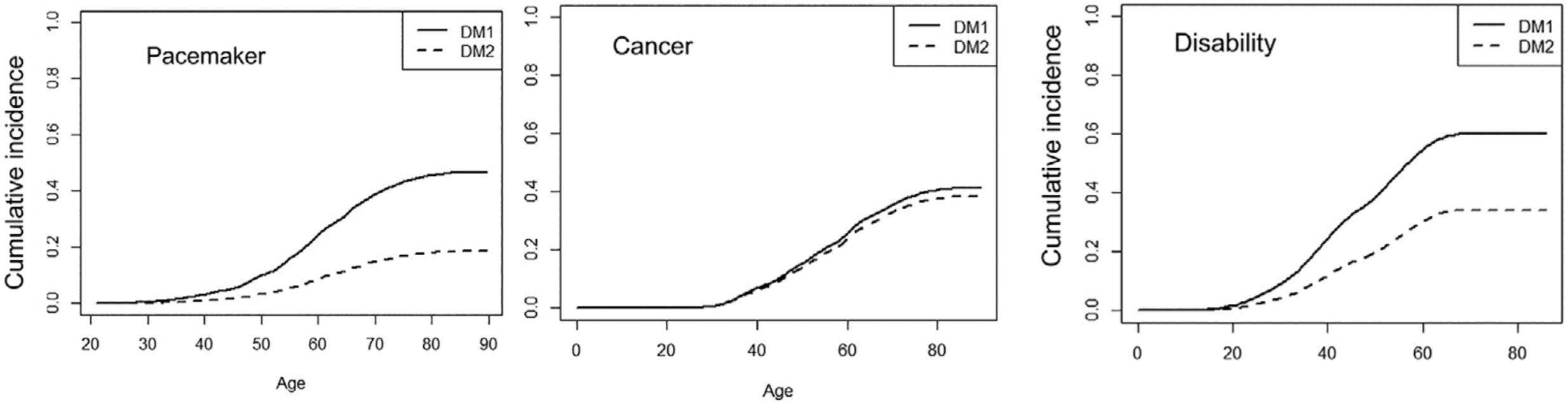
Other Systemic Manifestations

- Respiratory
  - Frequent and may require mechanical ventilation
- Gastrointestinal
  - Dysphagia, constipation, intestinal pseudo-obstruction, or diarrhea
  - Gallstones from increased gallbladder tone
- Central nervous system
  - Widespread domains of involvement (i.e. memory, processing speed, executive function)
  - Intellectual deficits in some individuals (50-65% of congenital DM1)
- Eyes
  - “Christmas tree” cataracts

Severity of Disability

- Registry study of 929 DM1 patients with 7 years mean follow up
- Disability: off work due to DM1

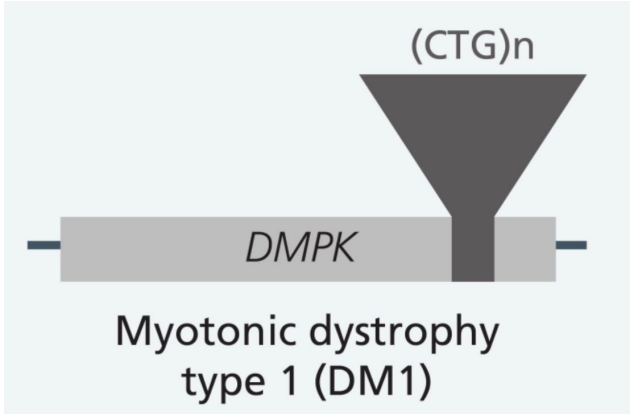
Hamel et al., Muscle and Nerve 2022



DM1 Diagnosis

Caused by expansion of a CTG trinucleotide repeat in the noncoding region of DMPK.

- CTG repeat length :
  - <35 repeats normal
  - 35-50 intermediate (asymptomatic but offspring at risk)
  - > 50 repeats symptomatic
- Inherited in an autosomal dominant manner
- Offspring of an affected individual have a 50% chance of inheriting the expanded allele.



Source: UK NHS

Treatment of DM1 Manifestations

- Current Treatment Options
  - **No disease modifying therapy available**
  - Use of ankle-foot orthoses, wheelchairs, or other assistive devices
  - Pain management
  - Treatment of systemic manifestations
    - Cataracts, hypothyroidism, gallstones, hypogonadism in males, cancer (pilomatrixoma and basal cell carcinomas among others)
    - Cardiac pacemakers or implantable cardioverter-defibrillators may prevent life-threatening arrhythmias
- Screening for Complications
  - Cardiologist monitoring for symptoms or EKG evidence of arrhythmia
  - Annual fasting glucose/glycated hemoglobin
  - Ophthalmologist review every 2 years for cataracts
  - Sleep study for sleep disturbances (variable frequency)

Opportunity and unmet need

- Important cause of progressive disability and premature death in children and adults
- Systemic manifestations
- No disease modifying treatment available
- One mutation type with variable repeat length
- Small number of phase 1 and 2 trials ongoing/completed evaluating sensitivity of outcome measures
- Trial readiness and market access planning underway by stakeholder community (i.e. Global network of disease registries)

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DM1 Program – Preclinical Data

Jonathan Van Dyke, PhD,
Sr Scientist, Discovery Pharmacology, Biology

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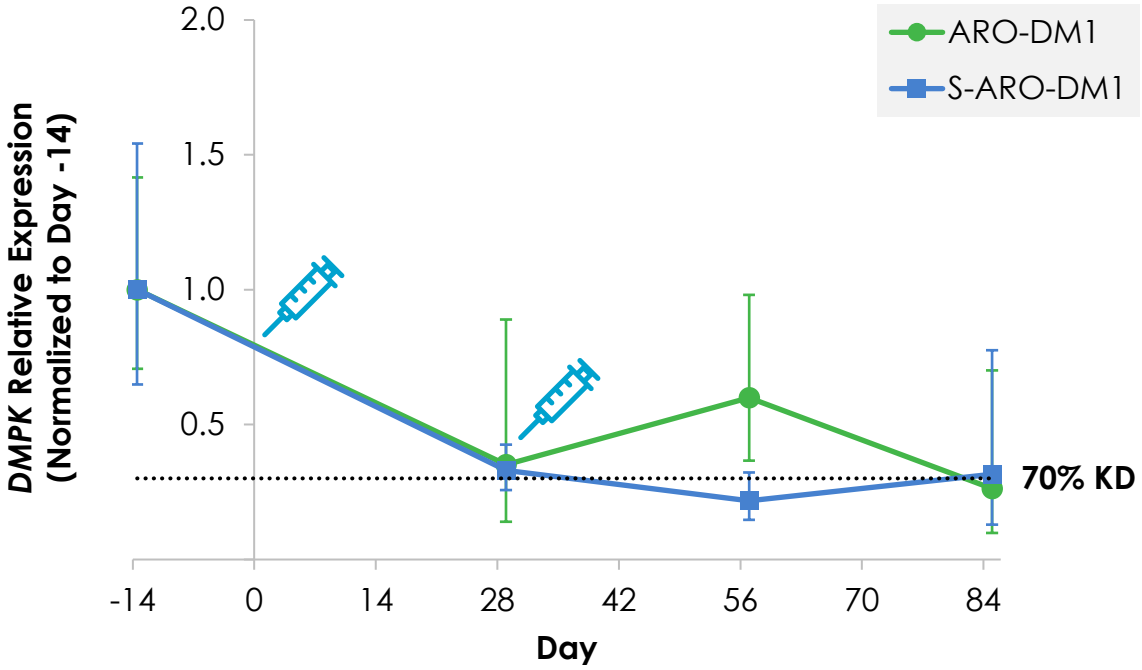
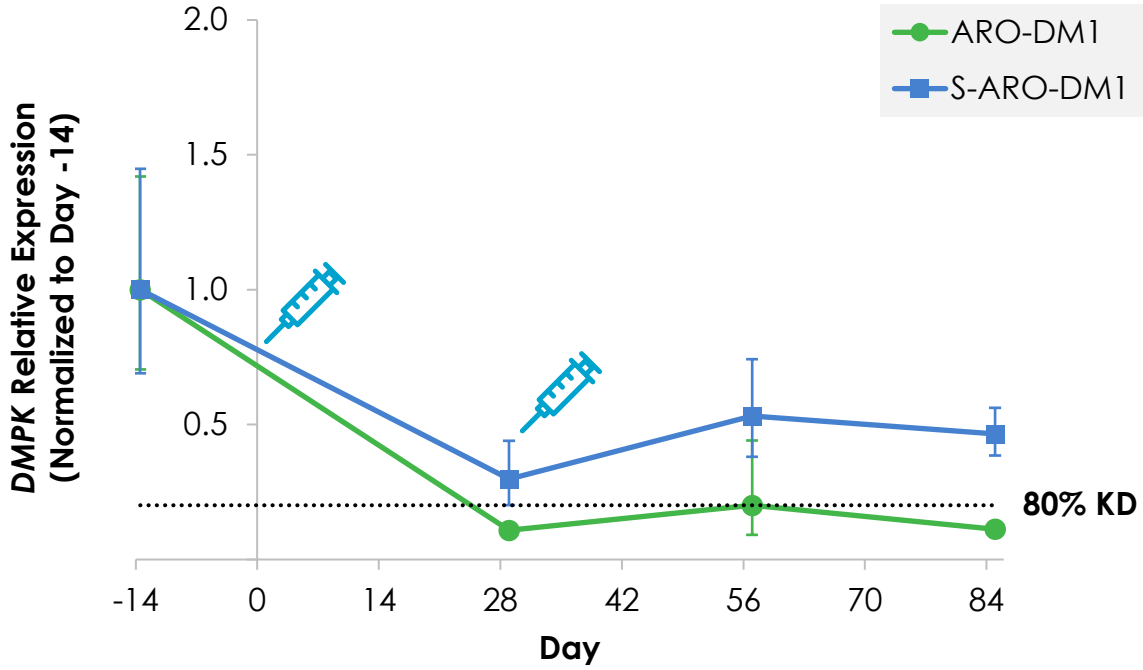
ARO-DM1 is a Potent siRNA Therapeutic Targeting Skeletal Muscle *DMPK* Transcripts

Quadriceps — 13.2 mpk, IV



ARO-DM1 is our therapeutic trigger with human/NHP cross-reactivity

Triceps brachii — 13.2 mpk, IV

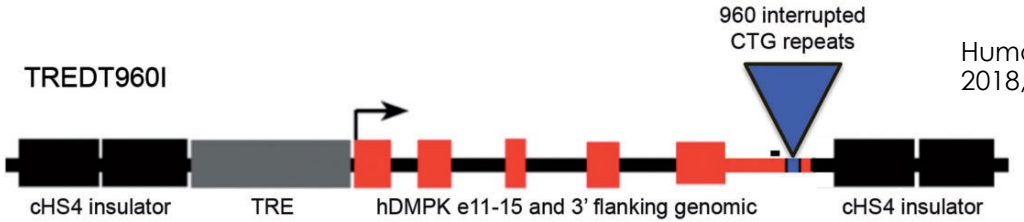


S-ARO-DM1 is a PoC trigger with human/mouse/NHP cross-reactivity

- Loading dose used for initial dosing on Day 1 followed by a second dose on Day 29
- Follows the initial Intended dose regimen in human patients. Clinical dosing is quarterly thereafter to maintain KD

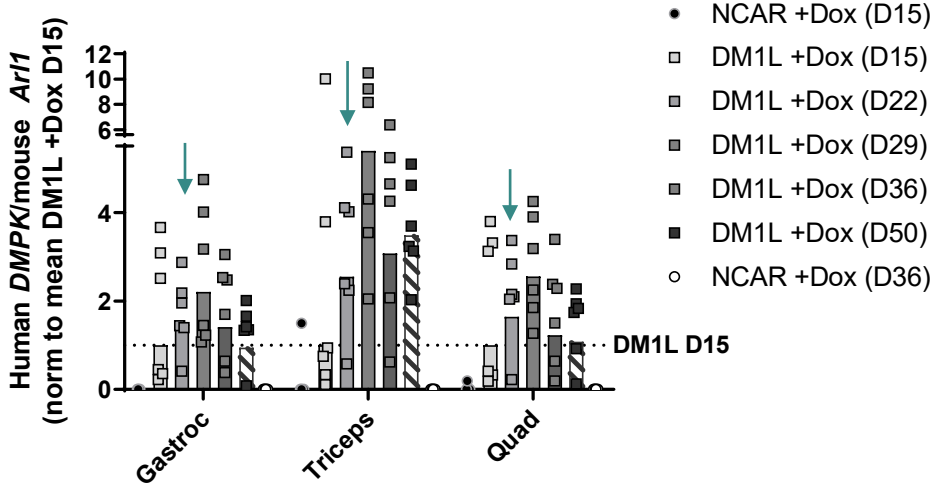
Transgenic DM1-like Mouse: A Model of Mis-splicing

- TREDT960I/HSA-rtTA
  - DM1-like mice (DM1L)
  - Noncarrier control (NCAR)
- h*DMPK* ex10-14 + 960 CTG repeats behind doxycycline switch (TRE)
- Crossed w/ HSA-rtTA mice (inducible expression in skeletal muscle only)
- With doxycycline-laced chow:
  - *DMPK-CUG* foci
  - Missplicing
  - Reversible upon removal of dox

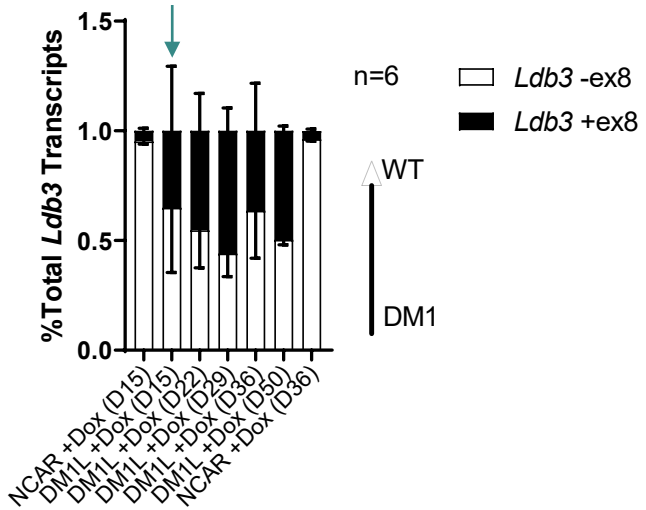


Human Molecular Genetics, 2018, Vol. 27, No. 16, 2789–2804

Human DMPK-CUG Expression

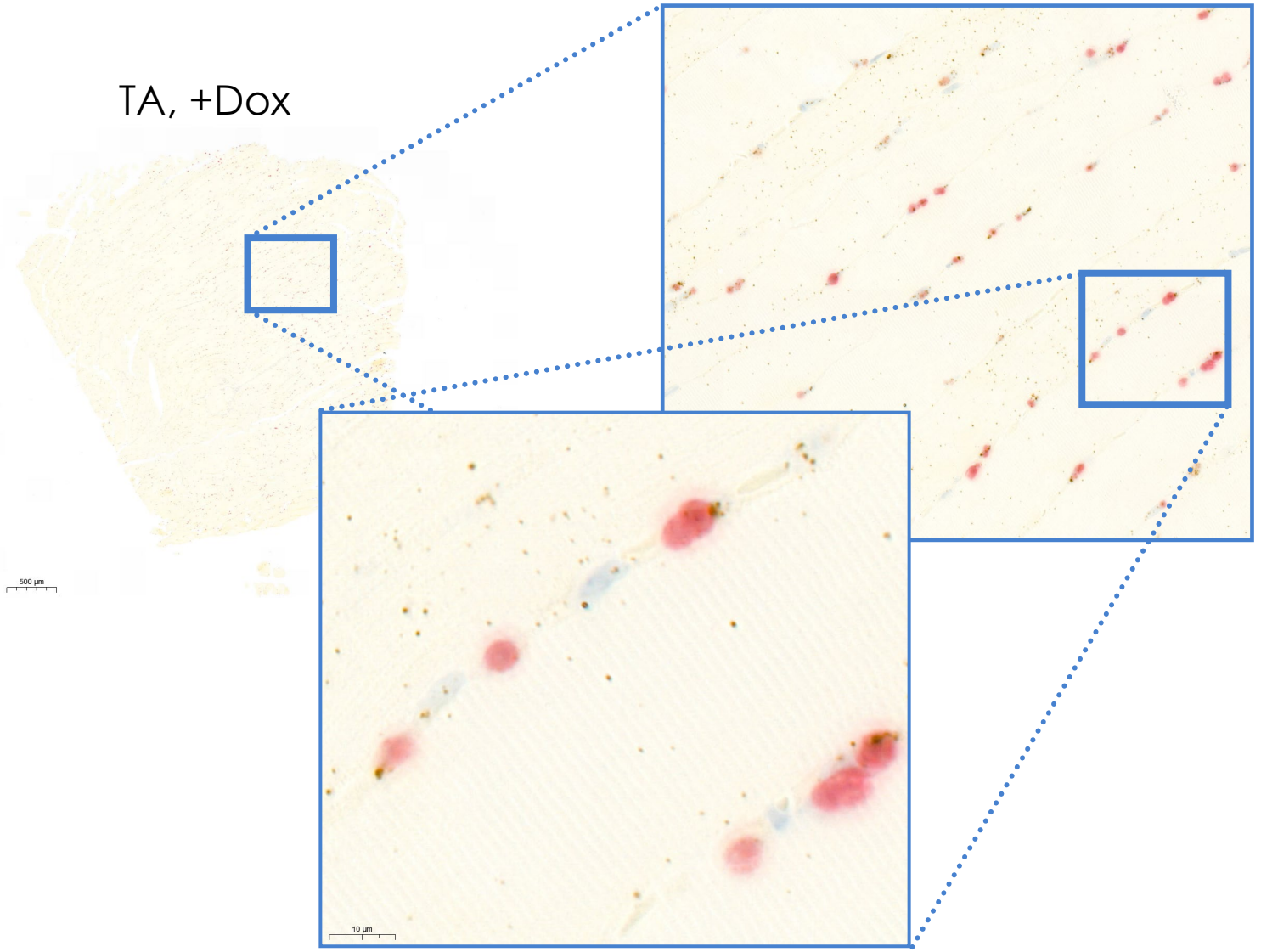


Gastroc Ldb3 Ex 8 Inclusion (% Splicing)



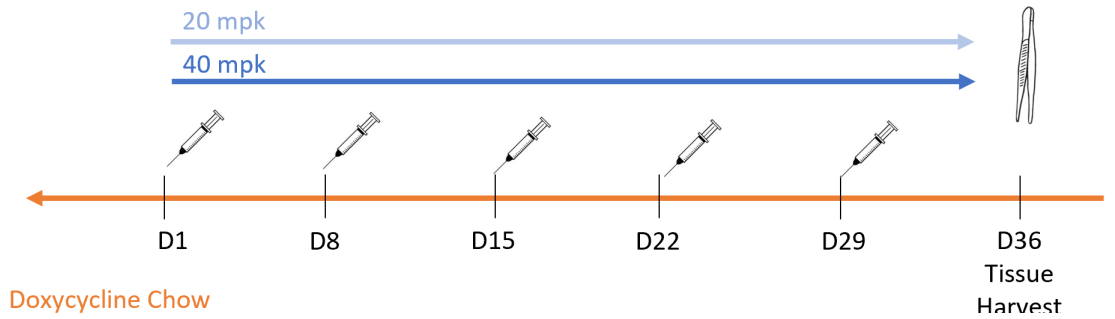
Human DMPK Transgene Accumulates in Myonuclei in DM1-like Mice

- RNAscope Co-stain using
  Mouse *Dmpk* Probe
  and
  Human *DMPK*
  (no X with Mm) Probe
- Human DMPK signal limited to nucleus
- Suggests that human *DMPK-CUG* unable to exit nucleus
- Human *DMPK* expression as measure of nuclear KD

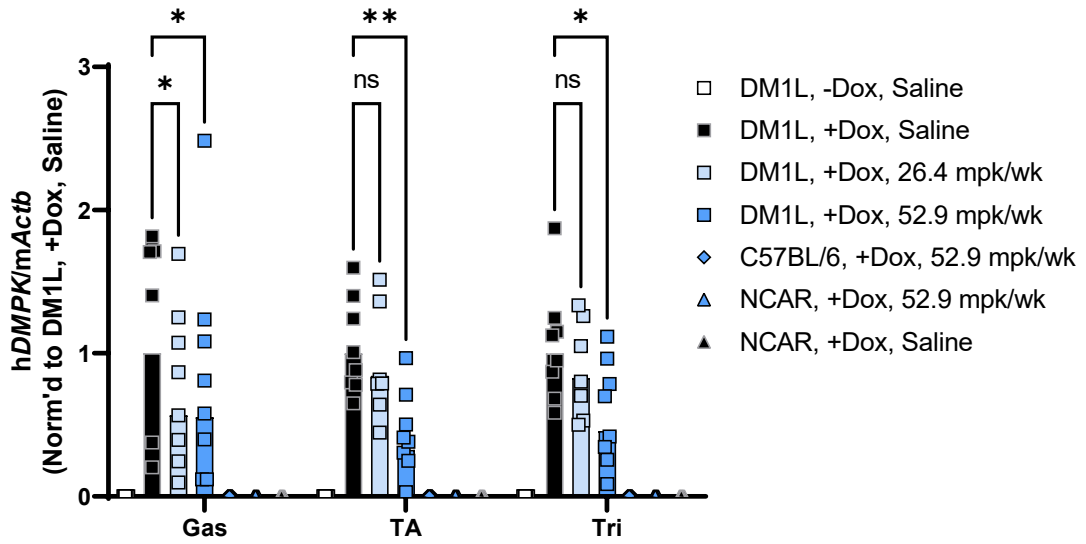


Multi-dose Intervention Successfully Reduced Human *DMPK-CUG*

- Transgenic *DMPK-CUG* was significantly knocked down by S-ARO-DM1 in TREDT960I/HEMI rtTA mice when administered weekly
- Intervention strategy: Animals had been exposed to doxycycline since birth
- Administered 26.4 or 52.9 mpk weekly
- By Day 36
  - ~40% nuclear *DMPK KD* was observed in gastrocnemius at 26.4 mpk/wk
  - >50% nuclear *DMPK KD* at 52.9 mpk/wk in TA and Tri



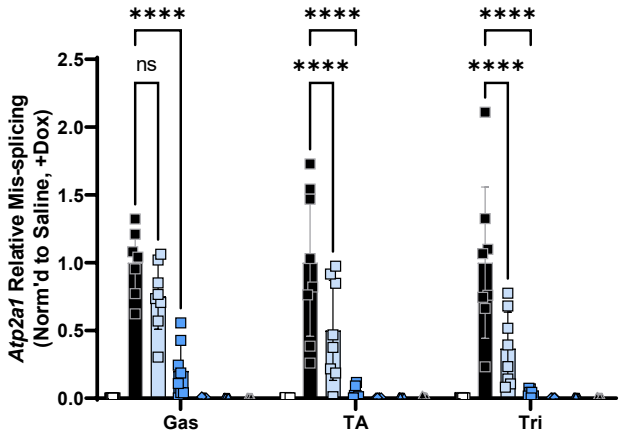
h*DMPK* Transcript Following IV RNAi Intervention



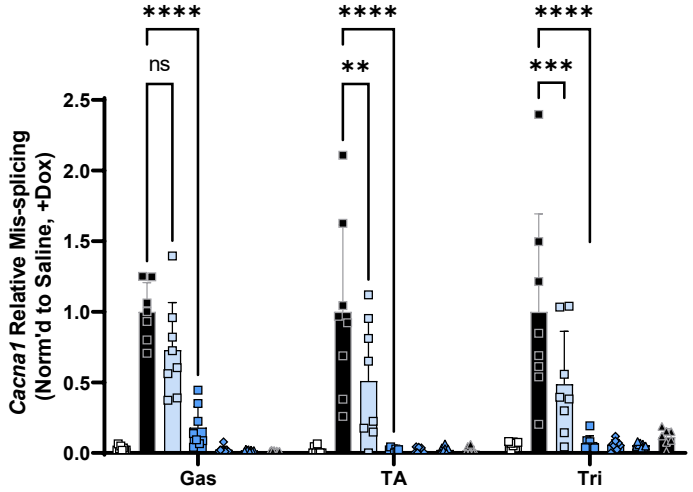
S-ARO-DM1 Repairs Mis-splicing in DM1-like Mice

- PCR-based competitive mis-splicing assay
- Mis-splicing repair tended to correlate well with nuclear *DMPK KD*
- For all muscles tested
  - 26.4 mpk repaired mis-splicing by >20%
  - 52.9 mpk repaired mis-splicing by >75%
- Mis-splicing repair greatly improves at higher dose levels of S-ARO-DM1

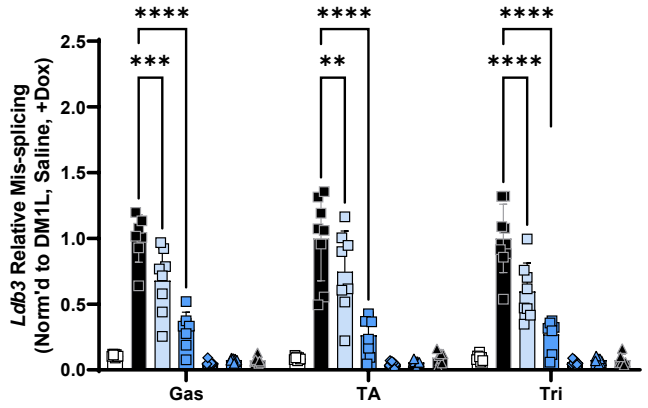
***Atp2a1* Relative Mis-splicing**



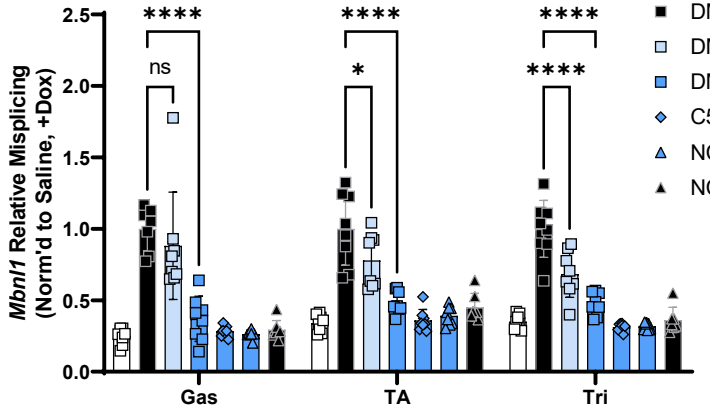
***Cacna1s* Relative Mis-splicing**

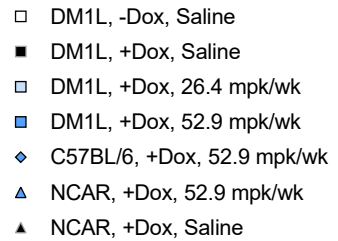


***Ldb3* Relative Mis-splicing**



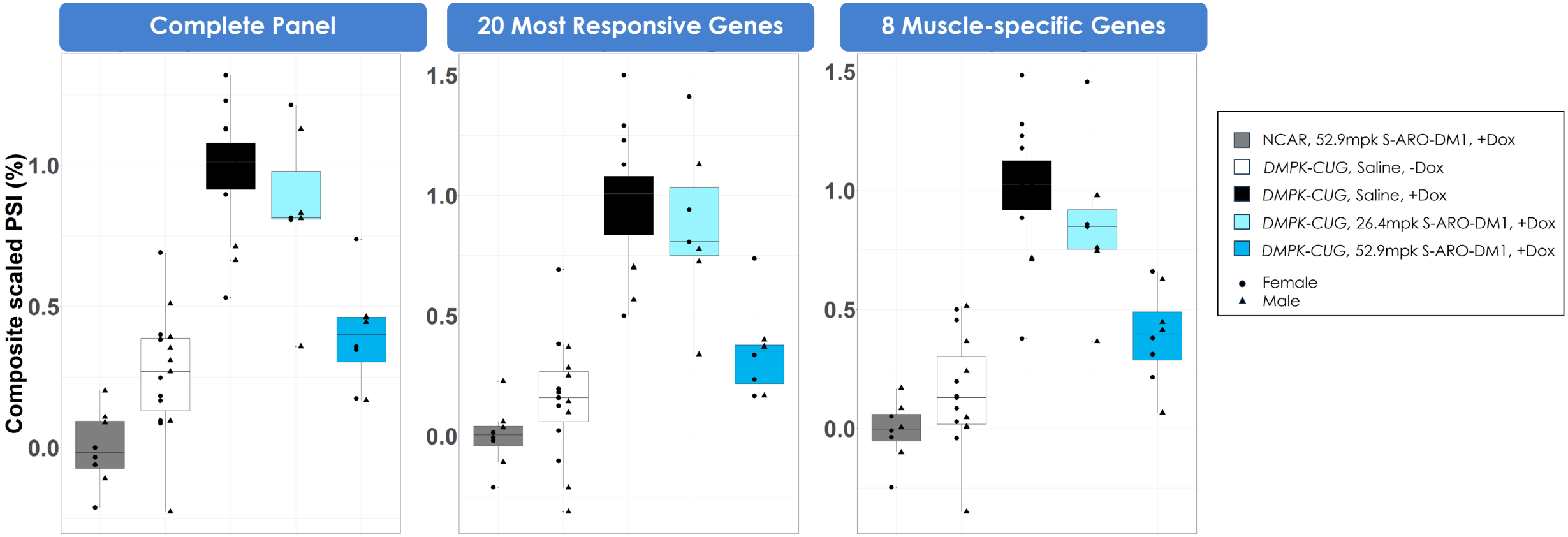
***Mbnl1* Relative Mis-splicing**





Mis-splicing Repair Assessed by RNAseq Composite Score

Composite Score is the Mean Scaled and Normalized PSI of Panel Genes



52.9 mpk S-ARO-DM1 Achieved ~60% Mis-splicing Repair

DM1 Preclinical PoC Summary

- TREDT960I/HSA-rtTA mice as a DM1-like (DM1L) model that exhibits missplicing
  - Truncated human DMPK+960 CUG repeats transcript behind doxycycline switch
  - DMPK+960 CUG repeats transcript primarily localized to myonuclei
  - Resulting RNAopathy yields mis-splicing pattern similar to that observed in DM1 patients
- A human/mouse cross-reactive trigger in the DM1L mouse model can prevent and reverse mis-splicing caused by mutant DMPK transcript accumulation in the myonuclei and appears to be dose-responsive
  - Observed via competitive missplicing assay and RNAseq misspliced gene panel
- This PoC work has demonstrated that a TRiM conjugate can be used to prevent and correct missplicing caused by mutant DMPK transcript accumulation in the myonuclei
- ≤17% missplicing repair has been shown to be clinically relevant in reducing myotonia and improving function in patients

Neuromuscular Programs Webinar – May 23, 2024

DM1 Program – Clinical Plan Design and Status

James Hamilton, MD, MBA,
Chief of Discovery & Translational Medicine

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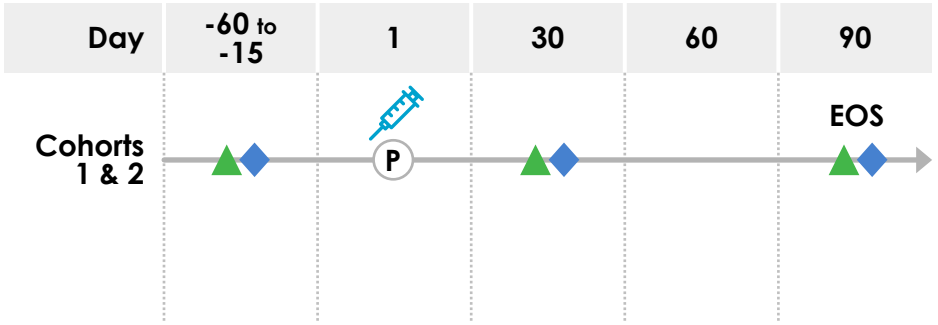
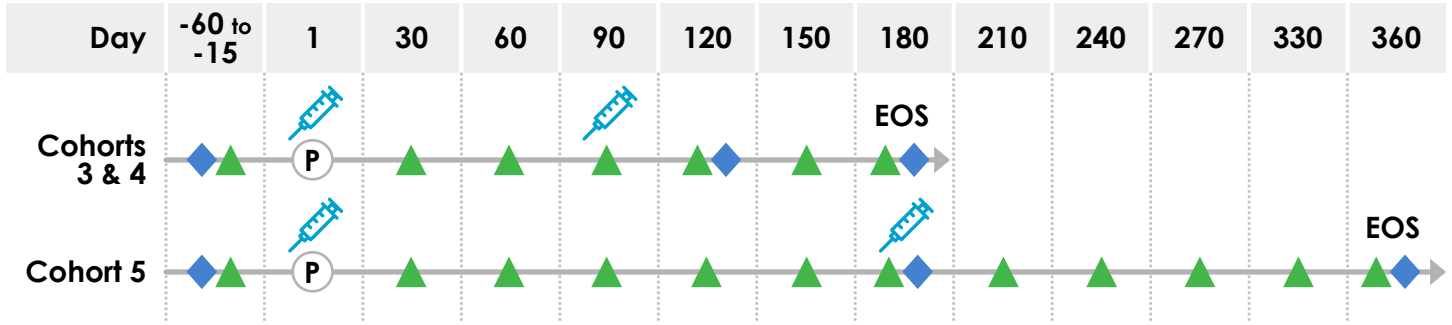
ARODM1-1001 Phase 1 Study Design: Cohort 1 is Actively Enrolling DM1 Patients

Part 1: SAD in Subjects with DM1



Part 2: MAD in Subjects with DM1



Cohorts

Cohort 1 (1.5 mg/kg): 2:1 ARO-DM1, placebo
Biopsy at baseline (-15) and Days 30 and 90

Day 15 Safety Evaluation

Cohort 2 (3 mg/kg): 2:1 ARO-DM1, placebo
Biopsy at baseline (-15) and Days 30 and 90

Day 15 Safety Evaluation

Cohort 3 (6 mg/kg Q3 mo): 3:1 Biopsy at baseline (-15,), Days 120 and 180

Day 15 Safety Evaluation

Cohort 4 (12 mg/kg Q3 mo): 3:1 Biopsy at baseline (-15), Days 120 and 180

Day 15 Safety Evaluation

Cohort 5 (12 mg/kg Q6 mo): 3:1 Biopsy at baseline (-15) and Days 180 and 360

Clinical assessment and muscle biopsy occur before administration of Dose 2 on Day 180

▲ PROs, COAs (P) PROs Only ◆ Muscle Biopsy Dosing

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DM1 Clinical Trial Endpoints and Sites

Primary Endpoint

Safety and tolerability of ARO-DM1 in patients with DM1

Secondary Endpoints

PK profile of single and multiple doses and major metabolites

Key Exploratory Endpoints

- ***DMPK* mRNA**
- **Spliceopathy repair**
- Myotonia
  - **Video hand opening time (vHOT)**
- **Functional Tests:**
  - 10-meter walk/run
  - Timed Up and Go (TUG)
  - Climb and descend 4 steps
- **Muscle Strength:**
  - Hand-held Dynamometry
- **Patient Reported Outcomes:**
  - Patient global impression of change (PGIC)
  - DM1-Activ-c
  - Checklist Individual Strength Fatigue Score (CIS)
  - Myotonic Dystrophy – Health Index
  - Short Form Survey – 36

Sites


New Zealand


Australia


South Korea


Canada


Taiwan


Thailand


European Union

Neuromuscular Programs Webinar – May 23, 2024

FSHD Program – Disease Background and Unmet Need

Lawrence Korngut, MD MSc FRCPC, Associate Professor (Neurology)
Director, Innovation and Commercialization,
Hotchkiss Brain Institute, Calgary

arrowhead pharmaceuticals

Facioscapulohumeral Muscular Dystrophy Type 1

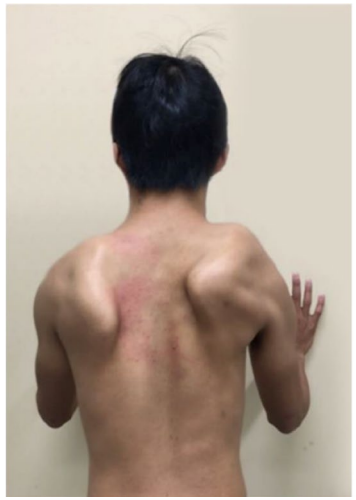
Dr. Lawrence Korngut MD
Neuromuscular Neurologist
Associate Professor of Neurology
University of Calgary

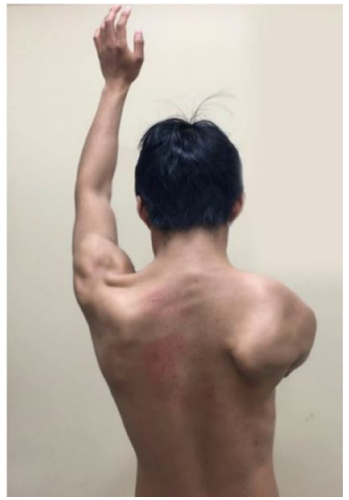
Facioscapulohumeral Muscular Dystrophy (FSHD Type 1)

Facio -> face

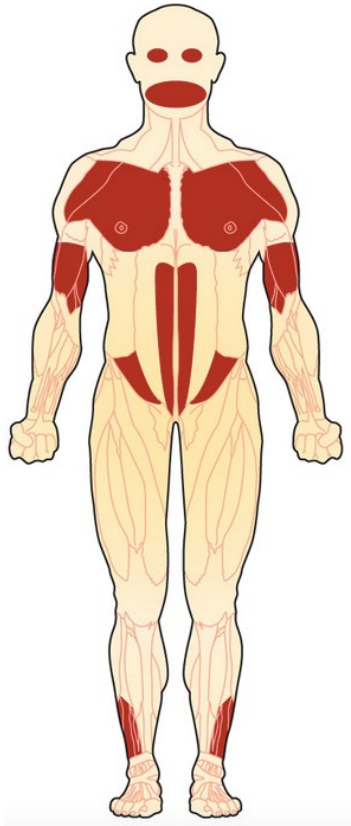
Scapulo -> shoulder

Humeral -> upper arm





Source: Wikipedia



Tawil et al Neurology 2015;85:357–364

Mah, Korngut et al. Can J Neurol Sci. 2016; 43: 163-177

Prevalence

The proportion of a population who have a specific characteristic

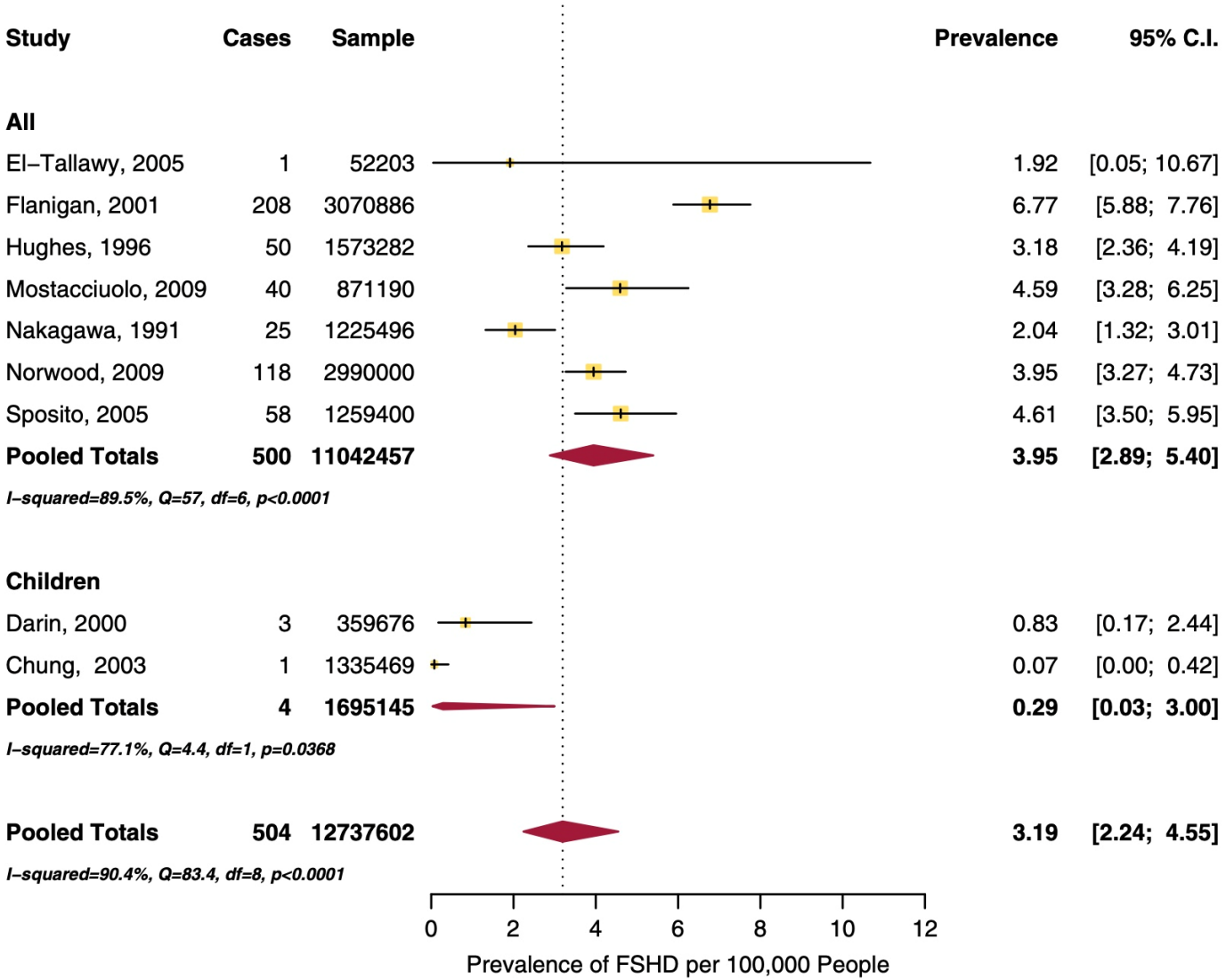
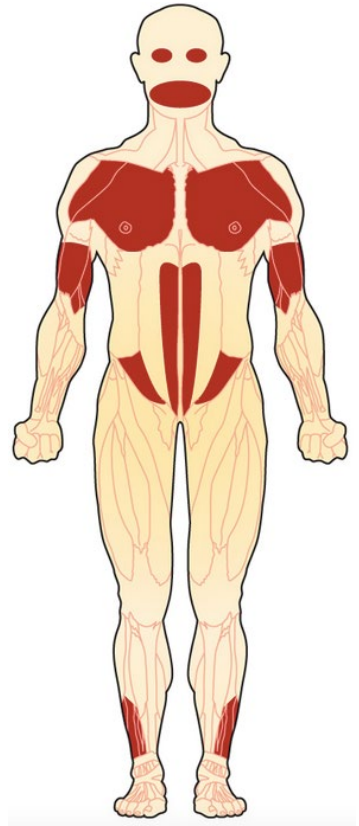


Figure 3: *Forest plots of individual studies and pooled prevalence estimates of facioscapulohumeral muscular dystrophy (FSHD).*

Presentation

- Onset and course
  - Teen years onset but is variable
  - Stepwise progressive course
  - Asymmetric proximal arm and mostly distal leg weakness
  - Facial weakness
  - Pain (89-97%) of patients > 90% in shoulder region (Morris et al, 2018)
  - Scapular winging is the most common initial finding



Tawil et al Neurology 2015;85:357–364

Severity of Weakness

Age of Weakness Onset (years)	Median Age of Required Wheelchair Use (years)
< 10	25 (95% CI: 23, 27)
11-20	35 (95% CI: 19, 51)
>20	52 (95% CI: 49, 55)

Qiu et al., Brain 2022

Systemic Symptoms

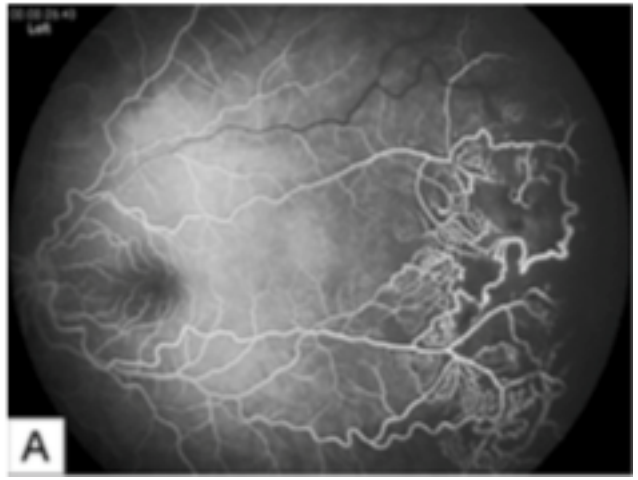
- Hearing
  - Loss in ~15% overall, can be progressive
  - Annual audiology screening especially in childhood onset FSHD and symptomatic adults

- Cardiac
  - Increased risk of arrythmia without cardiomyopathy
  - Abnormal ECG 23%, Echo 20% but most clinically benign

- Respiratory dysfunction
  - Relatively uncommon.
  - Restrictive lung disease pattern in 38% [Moreira et al 2017]
  - Respiratory support with noninvasive ventilation is uncommon (1%-3%) [Santos et al 2015].

Systemic Symptoms

- Ocular
  - Eye closure weakness
    - Irritation of sclera from exposure (exposure keratopathy)
    - Reduced blink protection
  - Coat's disease
    - 0.8% of people with FSHD
  - Retinal vascular changes
    - 25% of people with FSHD
  - Exudative retinopathy
  - Annual ophthalmology screening
    - Laser treatment, surgery, oculoplastics



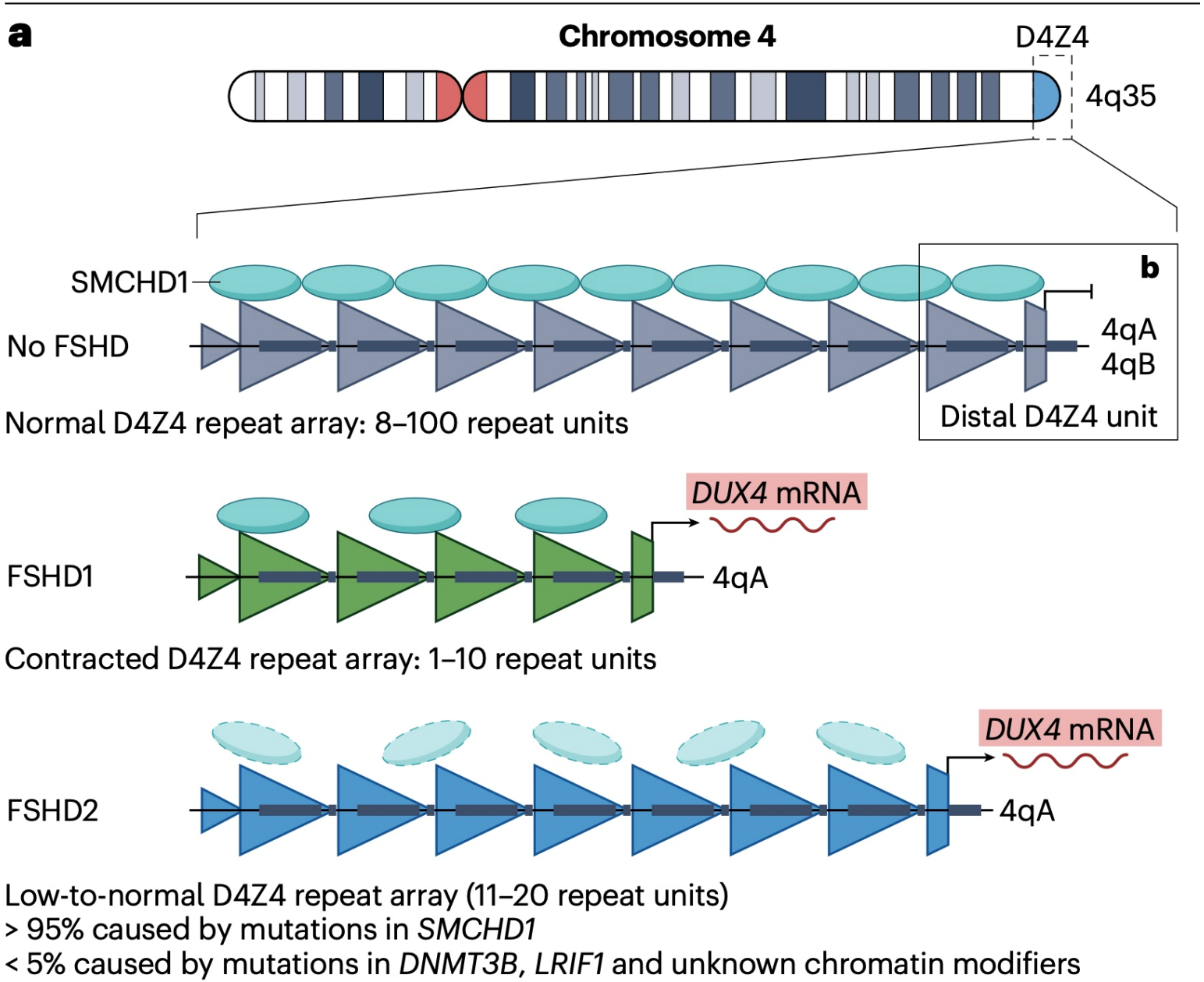
Lee et al. J AAPOS 2014;18:303-305.

Diagnosis

- FSHD1 is inherited in an autosomal dominant manner.
- ~70%-90% inherited deletion
- ~10%-30% *de novo* deletion

FSHD1 (~95% of FSHD)

- heterozygous pathogenic contraction of the D4Z4 repeat array
- In the subtelomeric region of chromosome 4q35
- On the permissive chromosome 4 haplotype



Tihaya et al., Nature Reviews Neurology | Volume 19 | February 2023 | 91–108

Treatment of Manifestations

- Current Treatment Options
  - **No disease modifying therapy available**
  - Physiatry, physiotherapy and occupational therapy
    - Ankle foot orthosis
    - surgical fixation of the scapula
    - Eye lubricants, taping the eyes shut during sleep to treat exposure keratitis
  - Screening
    - Audiology annually in children or symptomatic adults
    - Cardiology if suggestion of arrythmia
    - Ophthalmology annually for retinal vascular changes, Coat's disease, Exudative retinopathy
    - Pulmonary consultation for FVC < 60%

Opportunity and unmet need

- Important cause of progressive disability in children and adults
- 870,000 people worldwide
  - Curr Opin Neurol. 2023 Oct; 36(5): 455–463
- Systemic manifestations
- One mutation type with variable repeat contraction length
- No disease modifying treatment available
- Multiple phase 2 and 3 trials ongoing/completed evaluating sensitivity of outcome measures
- Trial readiness and market access planning underway by stakeholder community (i.e. FSHD Society, Project Mercury)

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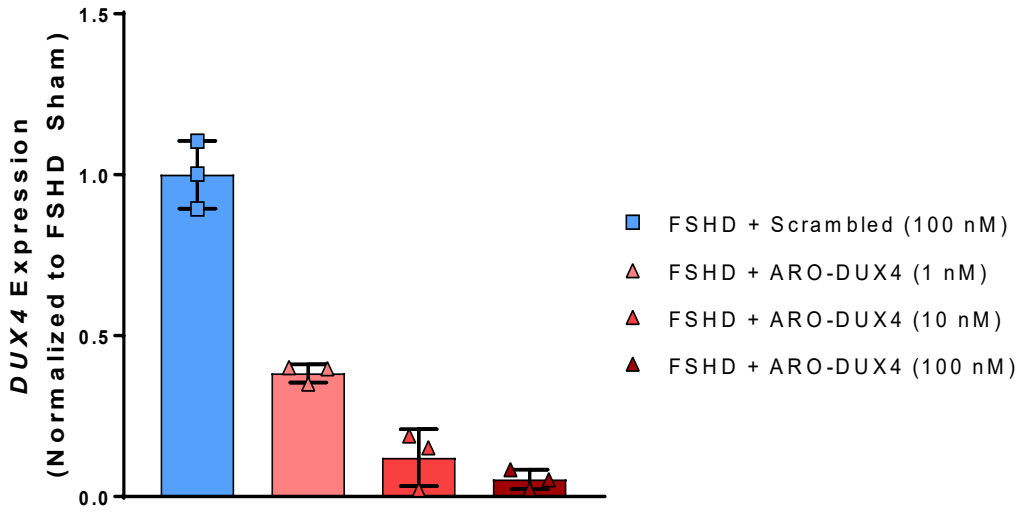
FSHD Program – Preclinical Data

Jonathan Van Dyke, PhD,
Sr Scientist, Discovery Pharmacology, Biology

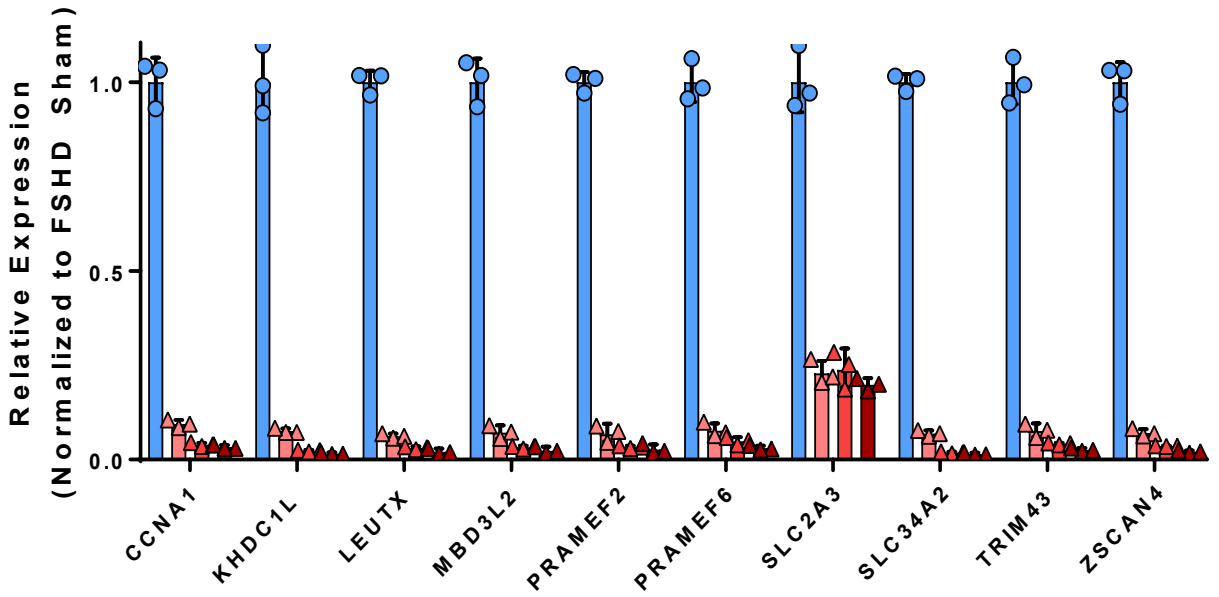
arrowhead pharmaceuticals

ARO-DUX4 Knocks down *DUX4* and targets of DUX4 in FSHD patient-derived myotubes

DUX4



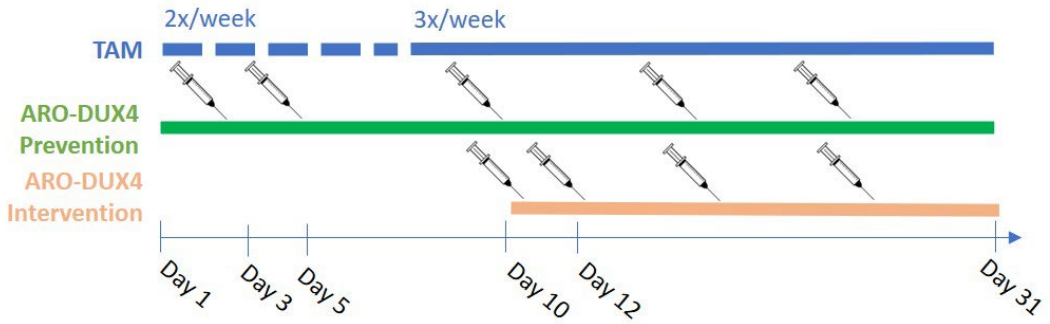
DUX4 Target Genes



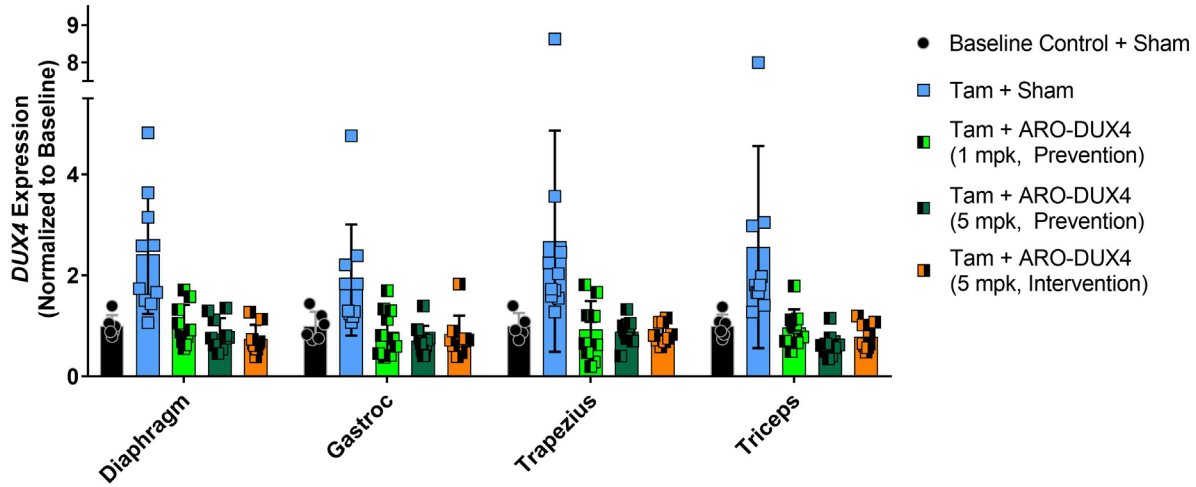
- FSHD1 patient-derived myotubes (short 4q35 EcoRI fragment--21 kb; ~6-7 repeats—on a 4qA background)
- ARO-DUX4 achieved dose-dependent knockdown of *DUX4* and deep reduction of DUX4 target gene expression in differentiated FSHD patient-derived myotubes

ARO-DUX4 Knocks Down Human *DUX4*, Preventing and Reversing Increased Expression of DUX4 Target Genes in FSHD-like Mice

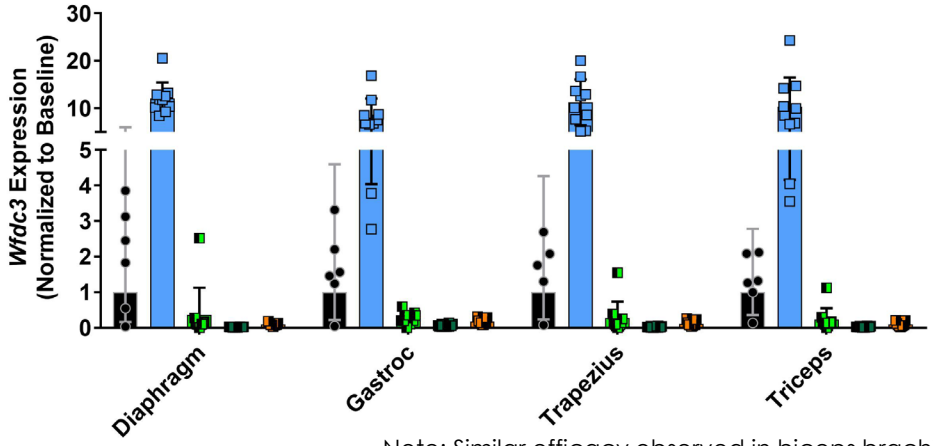
- HSA-MCM/FLExDUX4 Mice
  - Tamoxifen-controlled, skeletal muscle-specific expression of human *DUX4* transcript
  - Increased expression of DUX4 target genes
  - Develop FSHD-like muscle phenotype and functional loss
  - Known "leaky" *DUX4* expression in uninduced animals
- ARO-DUX4 prevented and reversed tamoxifen-induced increase in *DUX4* and DUX4 target gene expression



DUX4



Known Target in Mouse

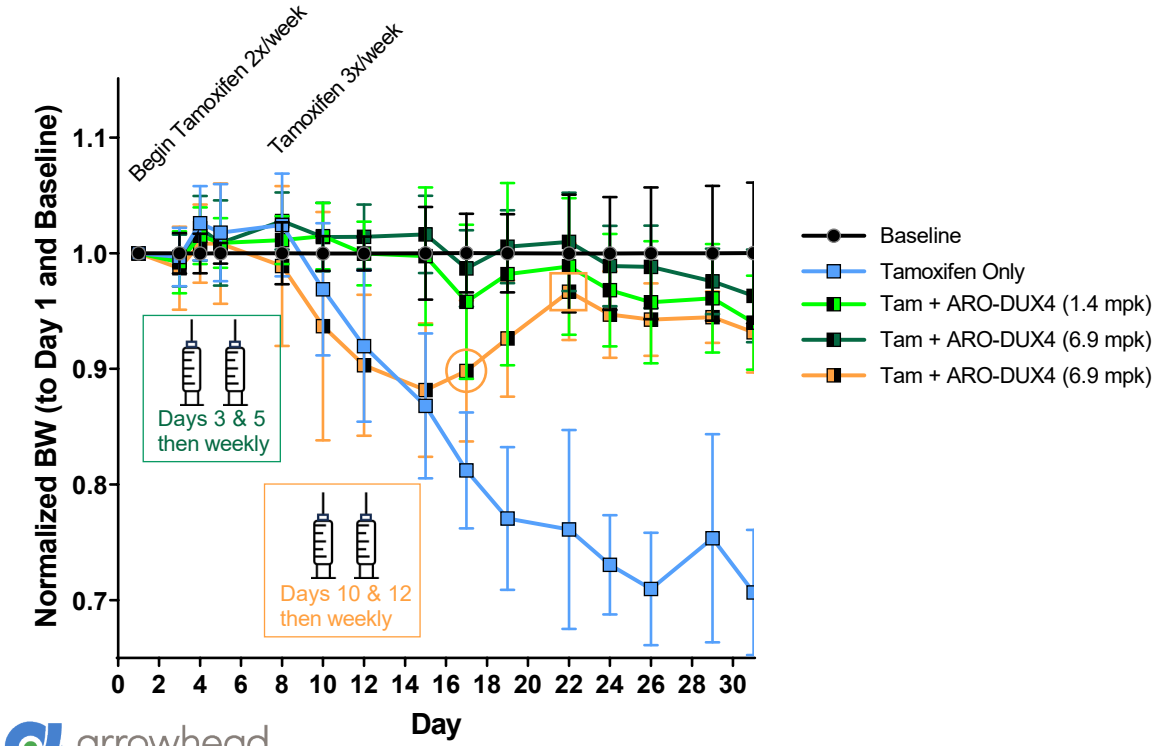


Note: Similar efficacy observed in biceps brachii, extensor digitorum longus (EDL), masseter, soleus, and tibialis anterior (TA)

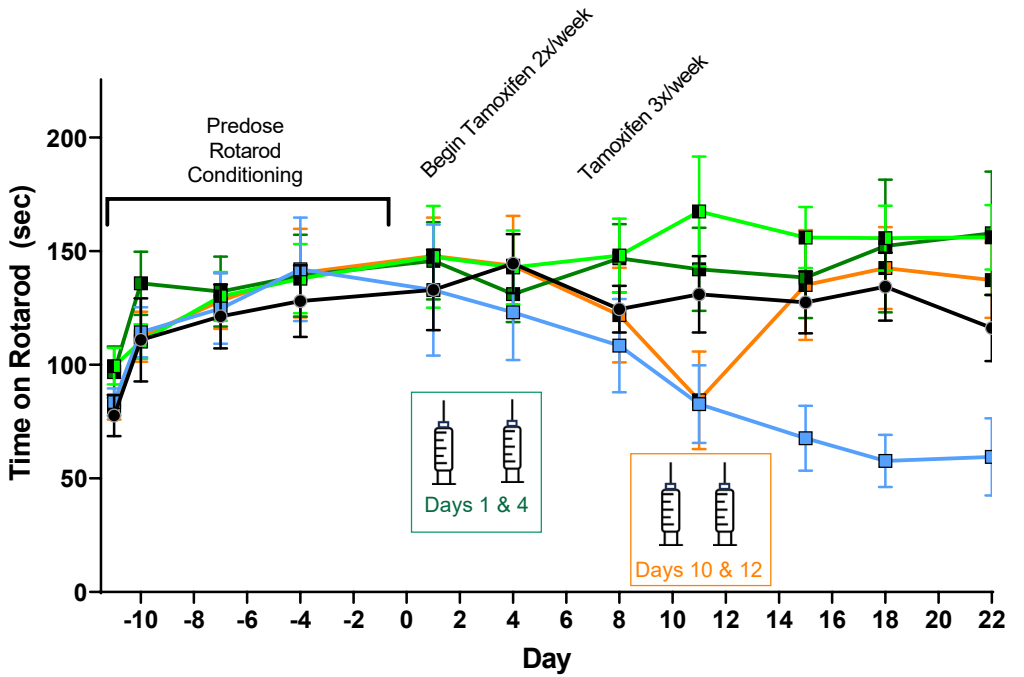
ARO-DUX4 Prevented and Reversed FSHD-like Phenotype: Bodyweight and Rotarod Performance

- In HSA-MCM/FLExDUX4 mice, induced DUX4 expression resulted in significant BW loss apparent by Day 10
- ARO-DUX4 treatment:
  - Prevented DUX4-induced BW and Rotarod performance loss
  - Reversed DUX4-induced BW loss by Day 17 allowing a return to baseline BW by Day 22; Rotarod performance loss was reversed by Day 15

Bodyweight



Rotarod Performance



FSHD Preclinical PoC Summary

- TRiM platform delivers siRNA to myofibers with deep target knockdown lasting at least 3 months in NHP
- ARO-DUX4 silences misexpressed *DUX4* and corrects the altered expression of DUX4 target genes in FSHD patient-derived myotubes
- In HSA-MCM/FLExDUX4 mice, a transgenic FSHD-like mouse model, ARO-DUX4 knocks down *DUX4* and its target genes
- ARO-DUX4 prevents and reverses the DUX4-induced
  - BW loss
  - Impaired rotarod performance

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FSHD Program – Clinical Trial Design and Status

James Hamilton, MD, MBA,
Chief of Discovery & Translational Medicine

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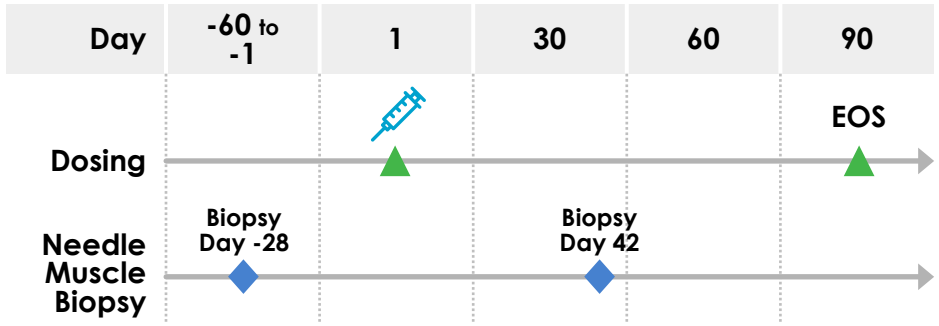
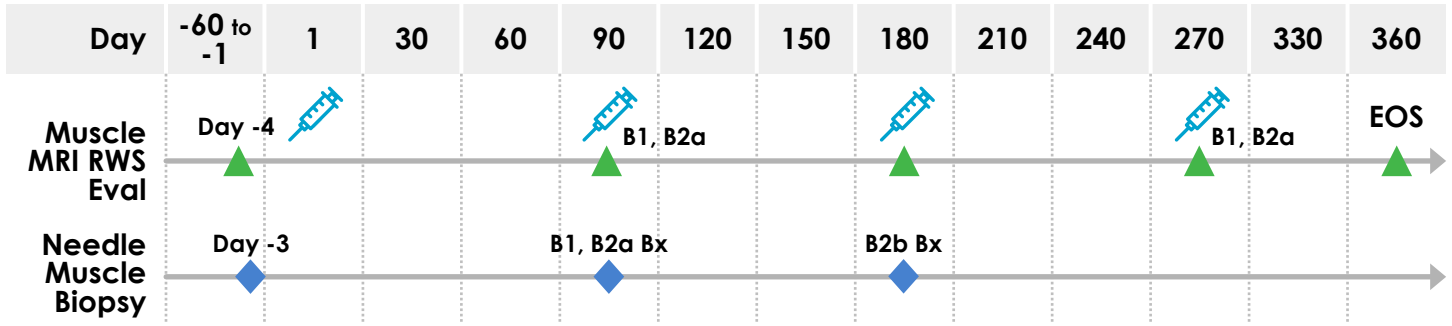
ARODUX4-1001 Clinical Trial: Cohort 1 is Actively Enrolling Patients

Part 1: SAD in Subjects with FSHD1



Part 2: MAD in Subjects with FSHD1



Cohorts

- **Cohort 1 (1.5 mg/kg):** 3:1 (n=4)
  - Day 15 Safety Evaluation
- **Cohort 2 (3 mg/kg):** 3:1 (n=4)
  - Day 15 Safety Evaluation
- **Cohort 3 (6 mg/kg):** 3:1 (n=4)
  - Day 15 Safety Evaluation → **Cohort B1 (6 mg/kg Q3 mo):** 9:3 post baseline biopsy Day 90 (up to n=12)
- **Cohort 4 (12 mg/kg):** 3:1 (n=4)
  - Day 15 Safety Evaluation → **Cohort B2a (12 mg/kg Q3 mo):** 9:3 post baseline biopsy Day 90 (up to n=12)
  - **Cohort B2b (12 mg/kg Q6 mo):** 9:3 post baseline biopsy Day 180 (up to n=12)

FSHD Clinical Trial Endpoints and Sites

Primary Endpoint

Safety and tolerability of ARO-DUX4 in patients with FSHD

Secondary Endpoints

PK profile of single and multiple doses and major metabolites

Key Exploratory Endpoints

- **Muscle concentration of ARO-DUX4**
- **Muscle *DUX4* mRNA expression and expression of related genes**
- **Changes in muscle fat fraction and infiltration based on MRI**
- **Functional Testing**
  - Reachable Work Space (RWS)
  - 6-minute walk test
- **Muscle strength**
  - Hand-held Dynamometry

Sites


New Zealand


Australia

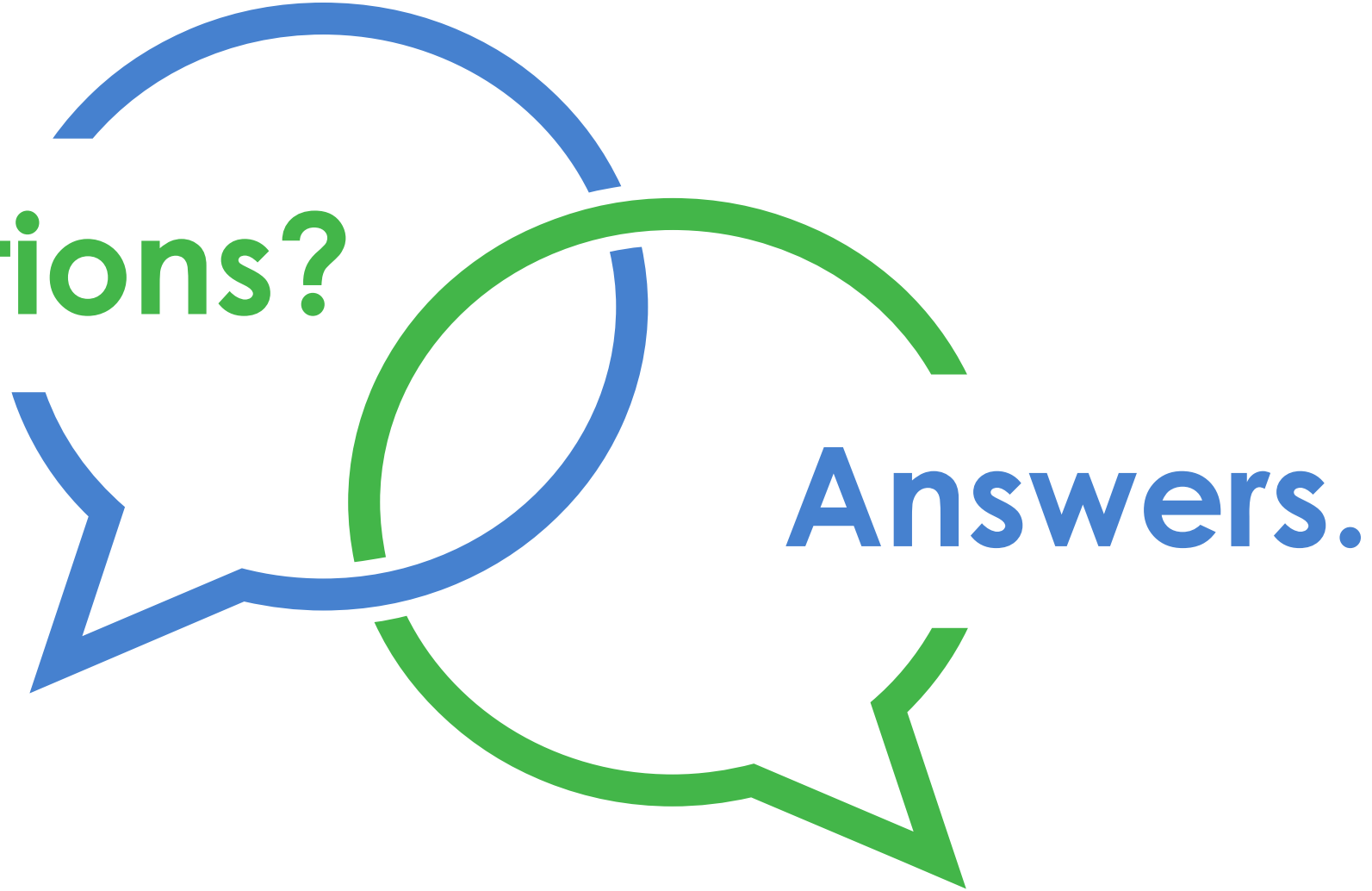

South Korea


Canada


Thailand


European Union

Questions?



Answers.