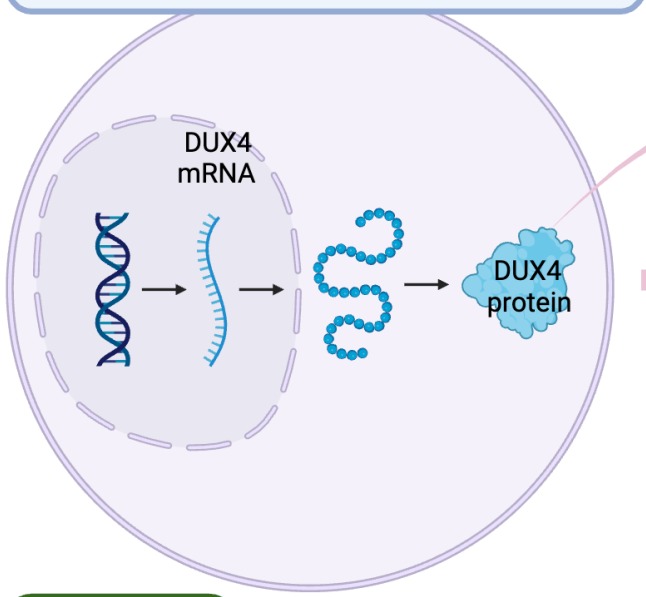
FSHD Clinical Trials and Therapeutic Development Updates

FSHD disease mechanism and drug development

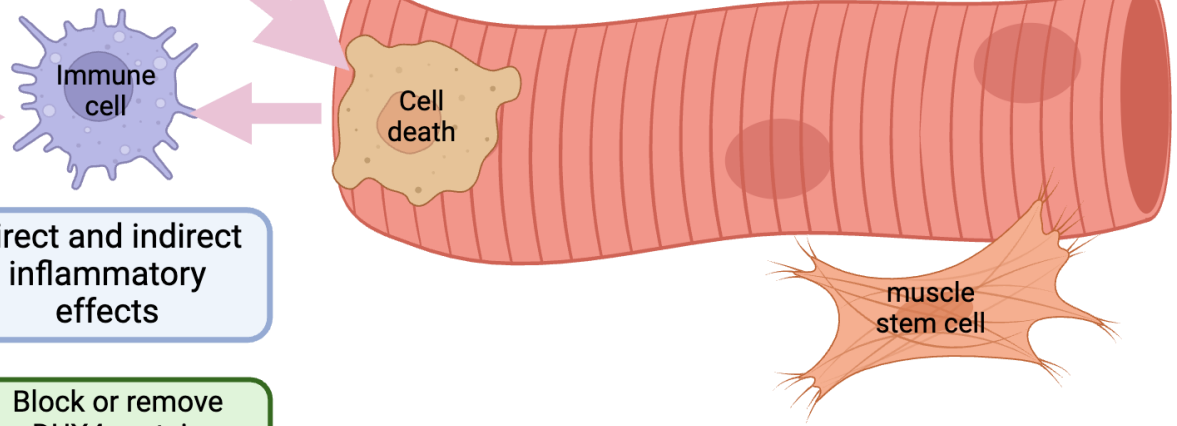
FSHD disease mechanism

Reduced number of D4Z4 repeats + Permissive polyA haplotype + Hypomethylation of D4Z4



DUX4 protein Toxic to muscle

Muscle toxicity



Direct and indirect inflammatory effects

Therapeutic strategies

Epigenetic repression of *DUX4*

Knock down DUX4 mRNA

Block or remove DUX4 protein

Suppress inflammation

Anti-myostatin to boost muscle growth

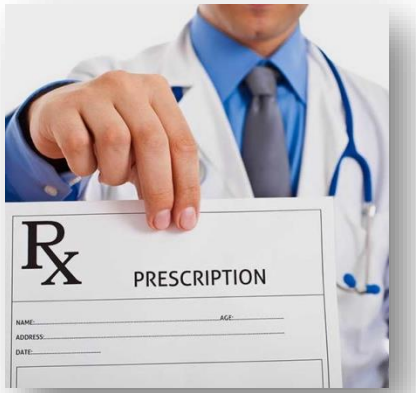
Stimulate muscle growth or transplant healthy stem cells

Dev status

Preclinical	HISTONE THERAPEUTICS, RENOGENYX	YDyne, miRecule		VITA Therapeutics, satellos, myogênica
Phase 1	epicrispr biotechnologies	arrowhead pharmaceuticals		
Phase 2	AVIDITY BIOSCIENCES	Roche	Roche	
Phase 3				

FSHD SOCIETY LIGHTING THE WAY TO A CURE

Overview of Therapeutic Development



Pre-Clinical Research

- Disease mechanism
- Drug discovery
- Animal models

Clinical Research

- Natural history
- Physical assessments
- Biomarkers
- Trial design

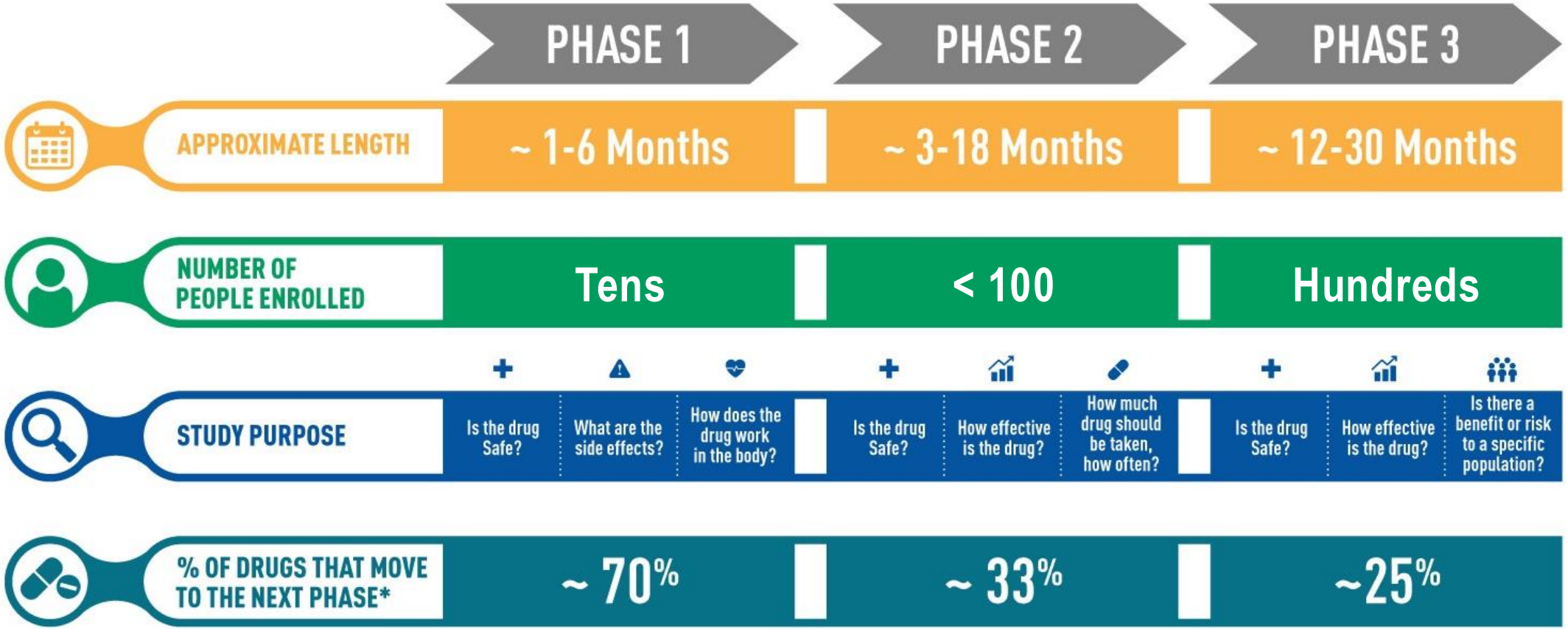
Clinical Trials

- Optimal dosing
- Safety and side effects
- Efficacy against disease

Launch

- Regulatory approval
- Payor reimbursement
- Longer term safety studies

Phases of Clinical Trials



Adapted from ifopa.org/clinical_trial_phases

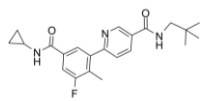
FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Fulcrum REACH

Discontinued

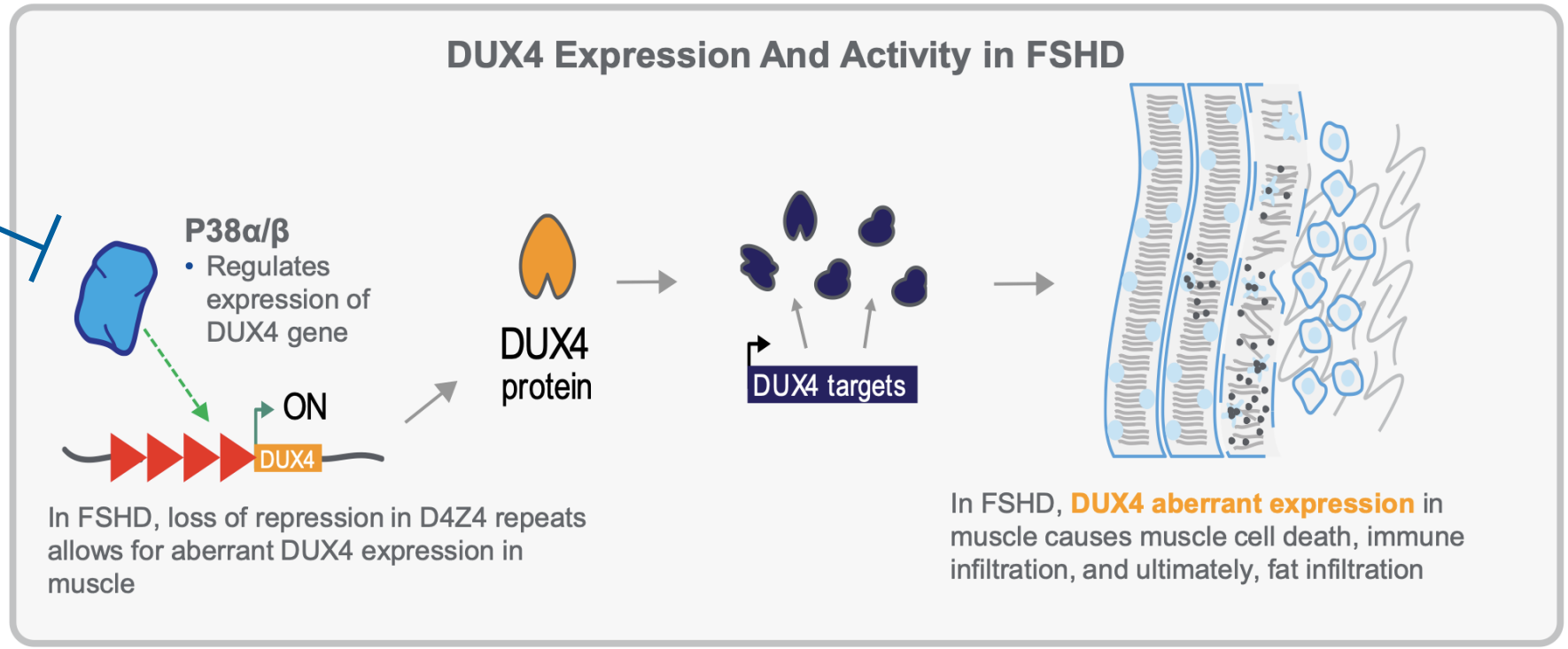
Fulcrum REACH: The Medicine

Fulcrum Therapeutics



Losmapimod

Interfere with DUX4 transcription



Administration:

Other Notes:

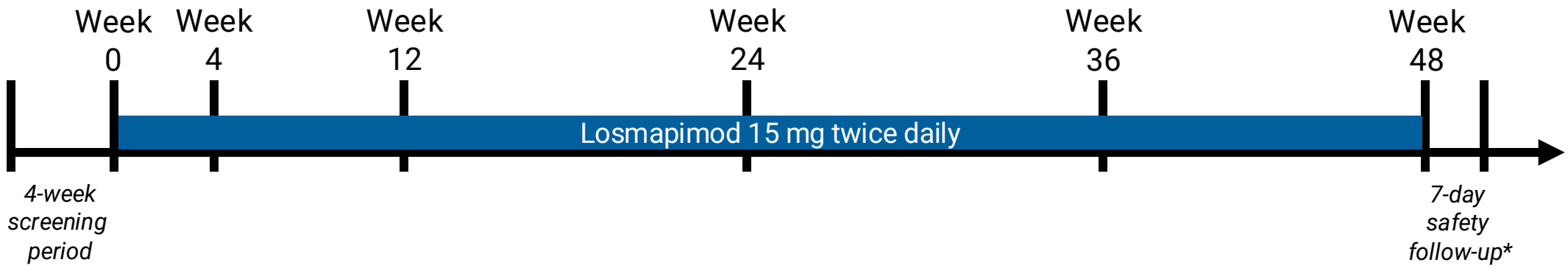
- Repurposed drug
- No safety concerns in 3,600 previous study participants

https://www.fulcrumtx.com/wp-content/uploads/Annualized-Data-Presentation-MDA-Final_220408.pdf

FSHD SOCIETY LIGHTING THE WAY TO A CURE

Fulcrum REACH: Study Design

Fulcrum Therapeutics



Quick Facts:	
Phase	3
Participants	260
Placebo	Yes, 1:1
Rx Duration	48 weeks
Study Visits	6 + screening and follow-up
Notable Activities	MRI
Open Label Extension	Yes*
Genetic Testing	Required; provided by study

Who Can Take Part?
Age 18-65
FSHD1 or FSHD2
Ricci score 2-4 (cannot be dependent on wheelchair or walker for activities)
Reachable Workspace total RSA 0.2-0.7
Must be able to do MRI

FSHD SOCIETY LIGHTING THE WAY TO A CURE

Roche MANOEUVRE

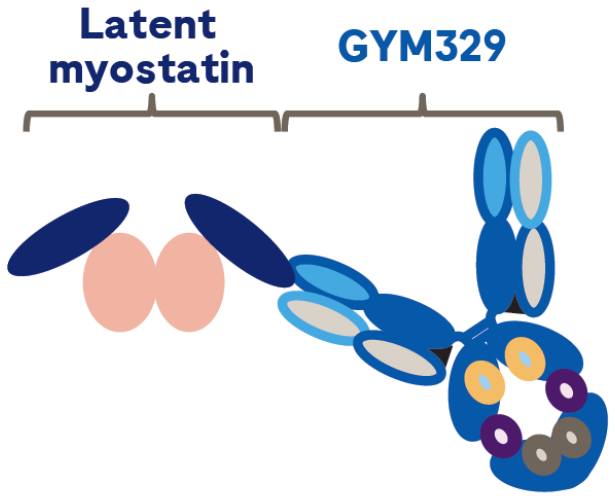
Roche MANOEUVRE: The Medicine

Helps muscles grow

What is GYM329 and how does it work?

GYM329 is an investigational, anti-latent myostatin antibody that specifically binds to inactive latent myostatin[4]

- Myostatin is a negative regulator of muscle growth and acts to prevent muscular hypertrophy.[5]
- GYM329 specifically binds to inactive latent myostatin and blocks its conversion to active myostatin, an intervention that is hypothesized to lead to increased muscle growth.[4]
- Preclinical animal studies have demonstrated increases in muscle mass and strength following treatment with GYM329.[4]



Administration:

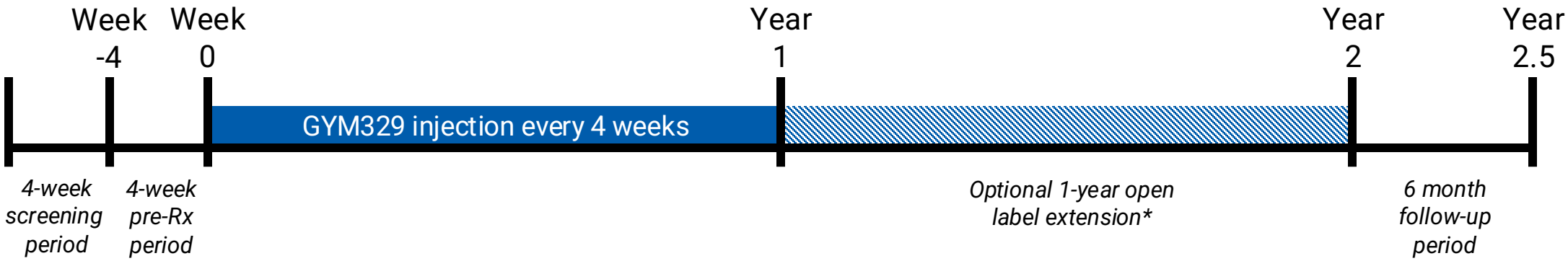
Other Notes:

- AKA RO7204239
- Next generation of anti-myostatin agents
- May require lower and less frequent dosing

https://medically.gene.com/content/dam/pdmahub/restricted/neurology/mda-2023/MDA-2023-poster-statland-MANOEUVRE-study-design-a-study-of-GYM329-RO7204239.pdf

FSHD SOCIETY LIGHTING THE WAY TO A CURE

Roche MANOEUVRE: Study Design



QUICK FACTS	
Drug	GYM329 (aka RO7204239)
How Is It Given?	Injection under skin
Phase	2
Participants	48
Placebo	Yes, 1:1
Genetic Testing	Required, talk to your local site
Rx Duration	Every 4 weeks for 52 weeks
Study Visits	At least every 4 weeks
Notable Activities	Wearable device, MRI
Open-Label Extension	Yes, for 52 weeks

WHO CAN PARTICIPATE?

- Age 18-65
- FSHD1 or FSHD2
- Ricci score: ≥ 2.5 and ≤ 4 (must be able to walk unassisted)
- Must be able to do MRI

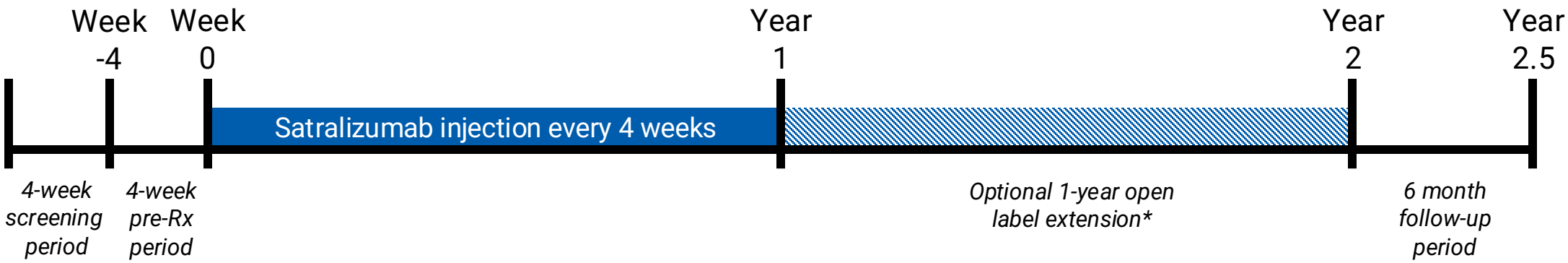
FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Roche MANOEUVRE: Recruitment complete

STATUS	
Enrollment	Complete. Study is active.
Data Expected	Q3 2026
Locations	US, Denmark, Italy, UK
Learn More	*forpatients.roche.com* *clinicaltrials.gov/study/NCT05548556fshdsociety.org/roche-manoeuvre-trial/*

US Locations:
UC Irvine
University of Colorado
Kansas University Medical Center
Kennedy Krieger
Virginia Commonwealth

REINFORCE: Study Design



QUICK FACTS

Drug	**Satralizumab**
How Is It Given?	**Injection under skin**
Phase	**2**
Participants	**40**
Placebo	**Yes**
Genetic Testing	**Required**
Rx Duration	**Double-blind phase, at weeks 0, 2, 4, and every 4 weeks thereafter for 48 weeks; open-label phase, same dosing for 48 weeks + follow-ups; total 116 weeks**
Study Visits	**~16**
Notable Activities	**MRI**
Open-Label Extension	**Yes**

WHO CAN PARTICIPATE?

- **Age 18-65**
- **FSHD1**
- **Ricci score 2-4, able to walk without support**
- **Must be able to do MRI**

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

REINFORCE: Getting Involved

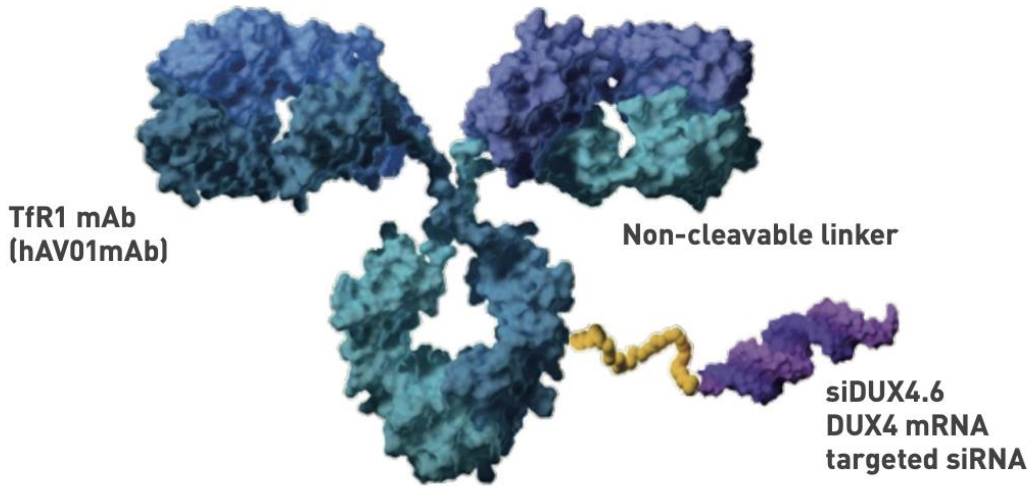
STATUS	
Enrollment	**Fully enrolled**
Data Expected	Mid-2026
Locations	Ottawa, Canada; Nice, France
Learn More	*clinicaltrials.gov/study/NCT06222827*

Avidity FORTITUDE

Avidity FORTITUDE: The Medicine

- **Figure 2** illustrates the structure of AOC 1020 and its three components:
  1. **Antibody:** Human transferrin receptor 1 (TfR1) targeting, effector function-null, humanized IgG1 antibody (hAVO1mAb) to affect delivery to skeletal muscle[7,8]
  2. **Non-cleavable linker:** MCC maleimide linker, enhanced for safety and durability[7,8]
  3. **Oligonucleotide:** Stabilized siRNA targeting DUX4 mRNA (siDUX4.6); engineered and stabilized to withstand lysosomal enzymes, selected for potency and specificity, and modified to diminish off-target effects[7,8]

Figure 2. AOC 1020: An antibody oligonucleotide conjugate targeting DUX4 mRNA for degradation



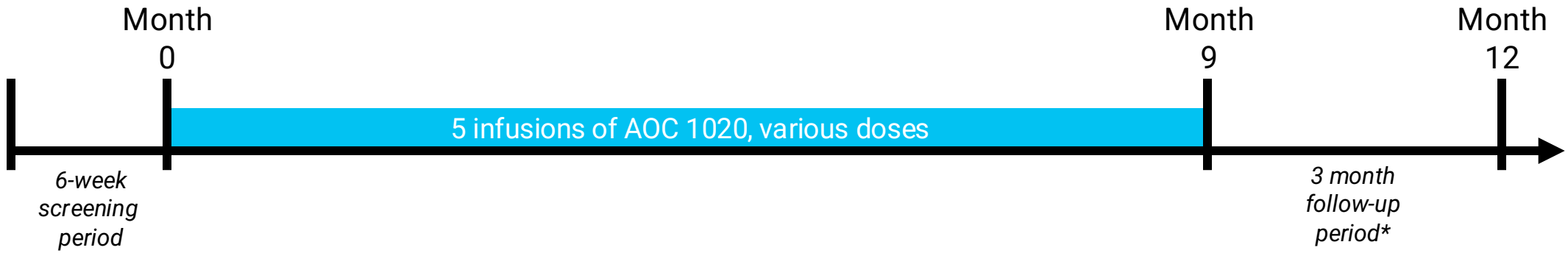
Remove DUX4 RNA

Administration:

Other Notes: Related drug in Myotonic Dystrophy (AOC 1001) was first ever AOC in clinic, performing favorably in Phase 1/2

https://www.aviditybiosciences.com/wp-content/uploads/2023/03/Fortitude-Poster_MDA-2023_FINAL.pdf

Avidity FORTITUDE: Study Design



QUICK FACTS

Drug	Del-brax (AOC 1020)
How Is It Given?	Intravenous infusion
Phase	1/2
Participants	72
Placebo	Yes, 2:1
Genetic Testing	Required, provided by study
Rx Duration	8 doses
Study Visits	~20, some may be virtual
Notable Activities	MRI, leg muscle biopsy
Open-Label Extension	Yes

WHO CAN PARTICIPATE?

- Age 16-70
- FSHD1 or FSHD2
- FSHD clinical score of 2-14
- Able to walk 10 meters without assistance
- Reachable Workspace score
- Must have leg muscle suitable for biopsy and be able to do MRI

Avidity FORTITUDE: Getting Involved

STATUS	
Enrollment	Phase 2/2D fully enrolled
Data Expected	Second half of 2026
Locations	US, Canada, UK
Learn More	*fortitude-study.com* *clinicaltrials.gov/study/NCT05747924* *fshdsociety.org/avidity-fortitude-trial/*

US & Canada Locations:

UC Los Angeles
UC San Diego
Stanford
University of Colorado
University of Florida
Rare Disease Research (Atlanta)
Kansas University Medical Center
University of Rochester
Duke University
Ohio University
University of Pennsylvania
UT Southwest
Virginia Commonwealth
University of Washington
University of Ottawa

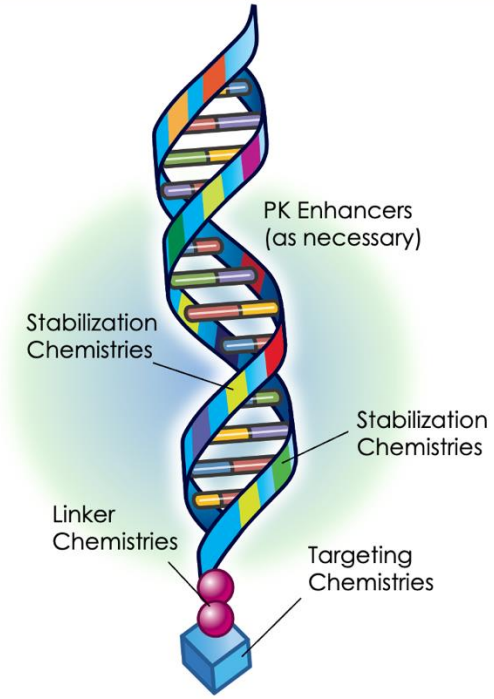
Arrowhead ARO-DUX4

Arrowhead ARO-DUX4: The Medicine

arrowhead pharmaceuticals

Remove DUX4 RNA

Arrowhead TRiM™ Platform for Muscle Diseases



Components:

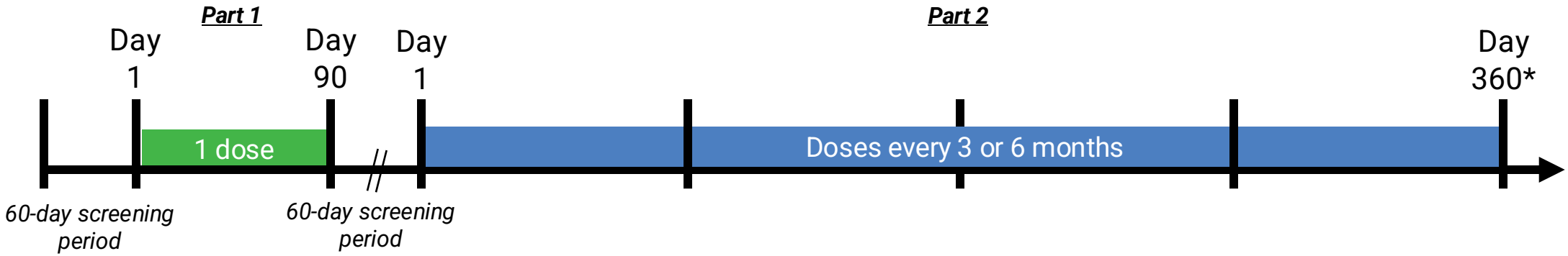
- Unique sequence selection targeting the DUX4 gene
- Stabilization chemistries
- Linker chemistries
- Targeting ligands for muscle cells

Administration:

Other Notes: Similar approach to Avidity

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Arrowhead ARO-DUX4: Study Design



QUICK FACTS	
Drug	ARO-DUX4
How Is It Given?	Intravenous infusion
Phase	1/2a
Participants	60
Placebo	Yes, 3:1
Genetic Testing	Required, provided if needed
Rx Duration	Part 1: duration 3 months Part 2: 4 doses over 1 year
Study Visits	~20
Notable Activities	MRI, leg muscle biopsy
Open-Label Extension	Yes, if warranted by study results

WHO CAN PARTICIPATE?

- Age 18-70
- FSHD1
- Clinical Severity Scale 3-8
- Must have leg muscle suitable for biopsy and be able to do MRI

Arrowhead ARO-DUX: Getting Involved

arrowhead pharmaceuticals

STATUS	
Enrollment	Currently enrolling
Data Expected	TBD
Locations	New Zealand, Australia, Thailand
Learn More	*fshdsociety.org/arrowhead-trial* *clinicaltrials.gov/study/NCT06131983*

FSHD SOCIETY
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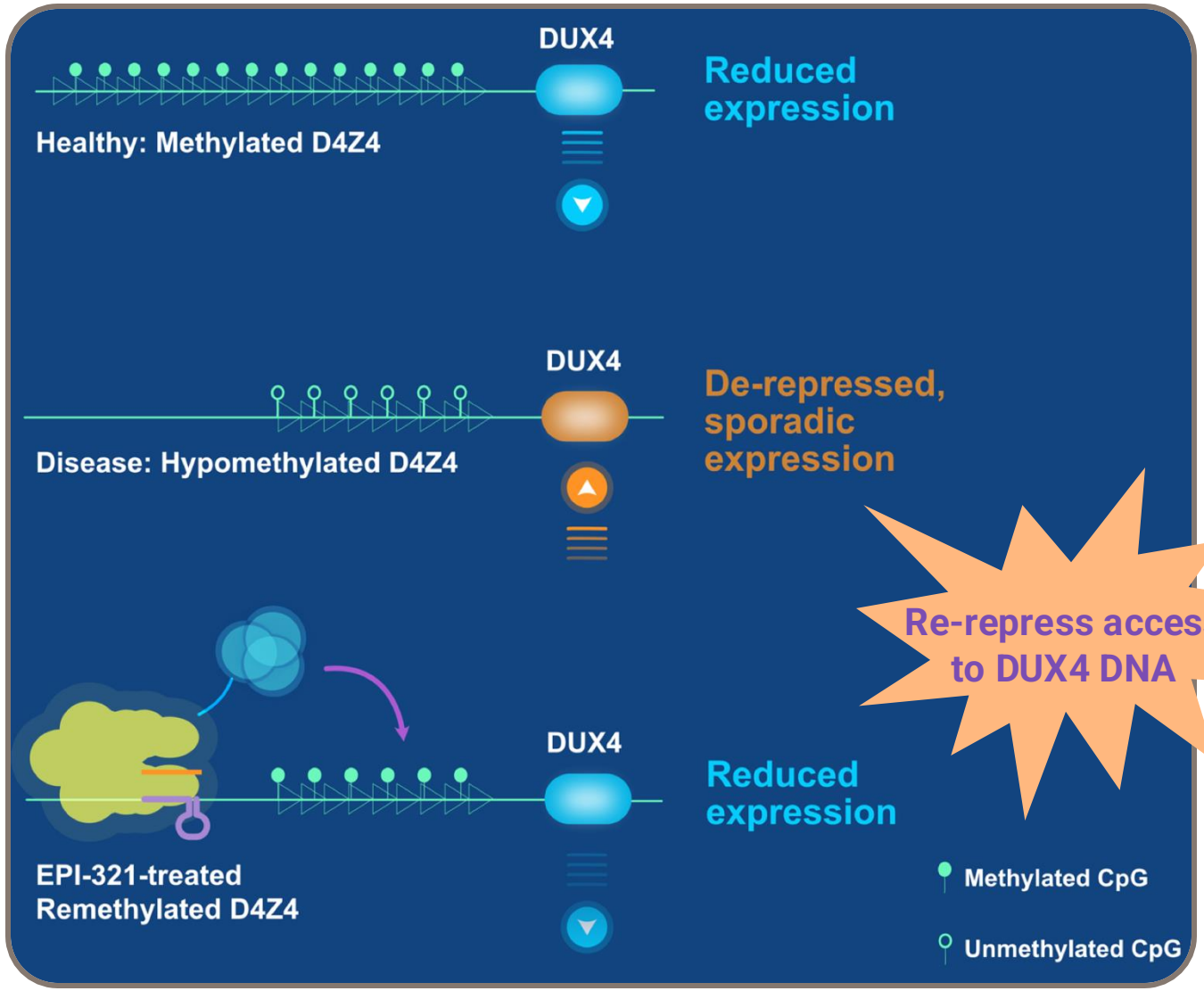
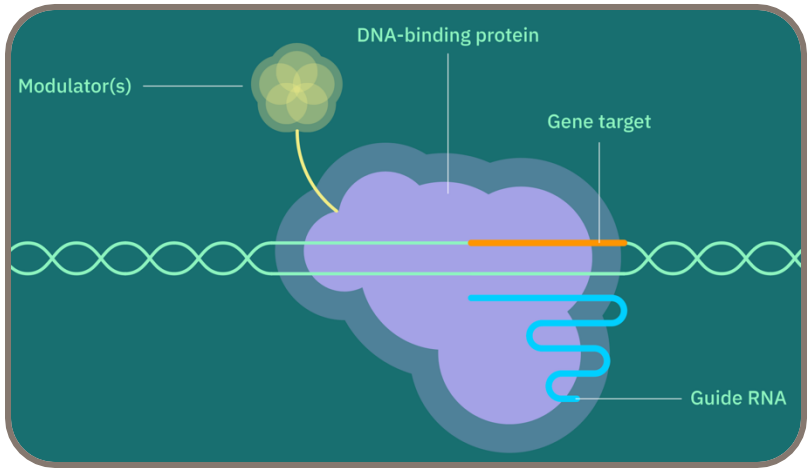
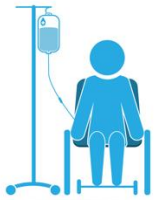
Epicrispr EPI-321

Epicrispr EPI-321: The Medicine





Administration:

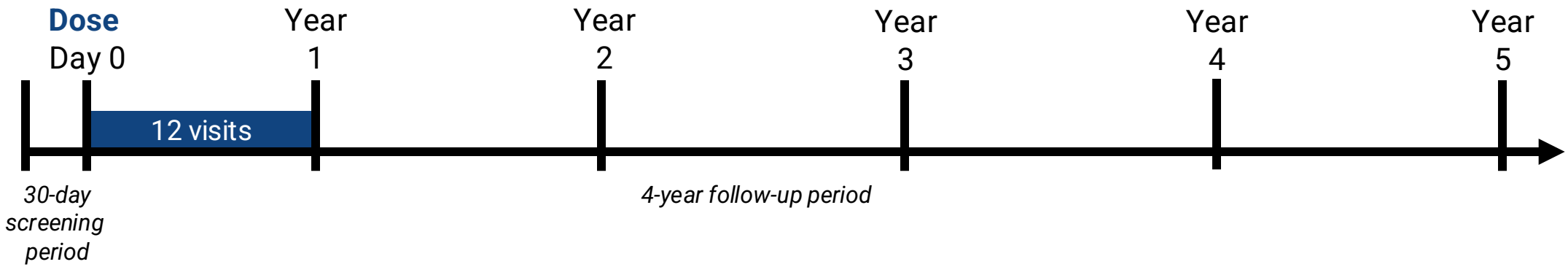


Other Notes:

- Expected to be long lasting, potentially even one-time
- Platform utilizes CRISPR-based technology

https://epic-bio.com/wp-content/uploads/2023/10/WMS2023-Final-Poster.pdf and https://epic-bio.com/science/

Epicrispr EPI-321: Study Design



Quick Facts:	
Phase	1/2
Participants	~6-9
Placebo	No, all patients receive drug
Rx Duration	1 dose
Study Visits	~12 over 1 year
Notable Activities	MRI, muscle biopsy
Open Label Extension	N/A
Genetic Testing	Required; providing unknown

Who Can Take Part?
Age 18-75
FSHD1
Ricci score 2-4
Must be able to walk 10 meters
Must be able to do MRI

Epicrispr EPI-321: Getting Involved

Get Involved:	
Enrollment	Started in Q2 of 2025
Data Expected	TBD
Locations	New Zealand
Learn More	FSHD Society YouTube → FSHD University → Epic Bio

Many more therapies coming down the pipeline!

Dyne THERAPEUTICS

VITA Therapeutics

myogênica

KATE THERAPEUTICS

ALTAY THERAPEUTICS

miRecule RNA Therapeutics

ECM Therapeutics

MYOCEA

RENOGENYX

healx

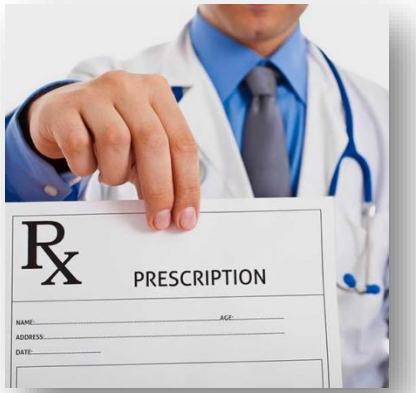
satellos

ARMATUSBIO

9 Academic research labs working on drug discovery

Additional companies in ‘stealth’ mode

Overview of Therapeutic Development



Pre-Clinical Research

- Disease mechanism
- Drug discovery
- Animal models

Clinical Research

- Natural history
- Physical assessments
- Biomarkers
- Trial design

Clinical Trials

- Optimal dosing
- Safety and side effects
- Efficacy against disease

Launch

- Regulatory approval
- Payor reimbursement
- Longer term safety studies

MOVE and MOVE+ Natural History Studies

FSHD CTRN
FSHD CLINICAL TRIAL RESEARCH NETWORK

Why are they important ?

Information from these studies will be used to:

- Understand what assessments and measurements of disease are meaningful in FSHD → “Outcome measures”
- Design better clinical trials and increase their chance of success
- Help clinicians provide better care for people with FSHD

What will happen?

- You will attend at least 3 study visits over 3 years
- You will perform strength and movement tests and fill out questionnaires
- MOVE+ will also include blood and saliva samples, MRI, muscle biopsy

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

MOVE and MOVE+ Natural History Studies

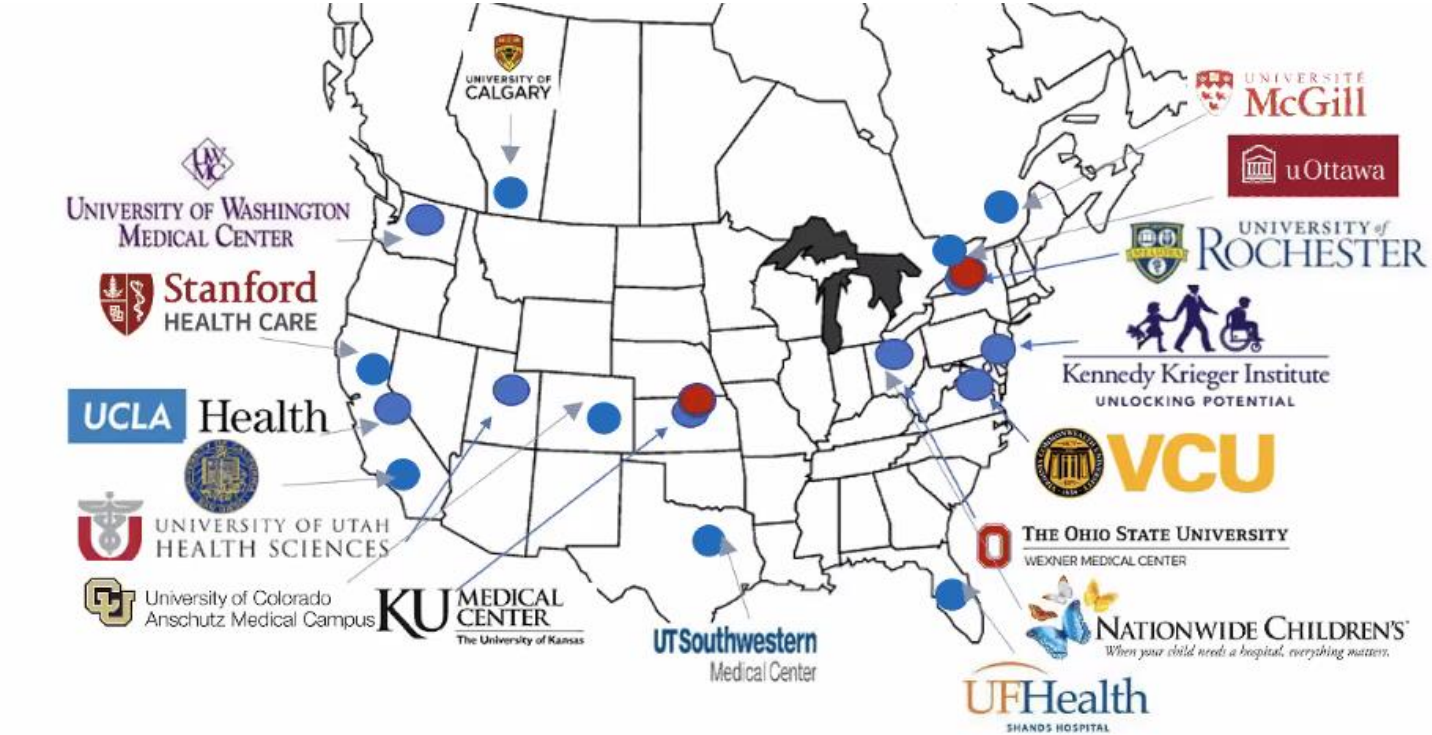
FSHD CTRN
FSHD CLINICAL TRIAL RESEARCH NETWORK

Who can join MOVE and MOVE+?

- Anyone with a confirmed diagnosis of FSHD
- For MOVE+, must also:
  - ✓ Be between age 18-75
  - ✓ Have lower leg weakness
  - ✓ Be able to walk 30 meters without assistance from another person

Learn more at
https://clinicaltrials.gov/study/NCT04635891

Contact Michaela Walker
Project Manager
mwalker20@kumc.edu



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LIGHTING THE WAY TO A CURE

Summary and how you can be involved

Research you may be able to take part in:

- Avidity FORTITUDE clinical trial
- Roche MANOEUVRE clinical trial
- MOVE and MOVE+ natural history studies

Additional ways to be involved and prepared:

- Make sure you (and your community members) are on the FSHD Society email list for updates!
- Participate in research surveys
- Be known to your local neuromuscular clinic
- Get the best care available and stay as healthy as possible
- Get genetic testing

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Thank you!

Questions?

FSHD SOCIETY
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