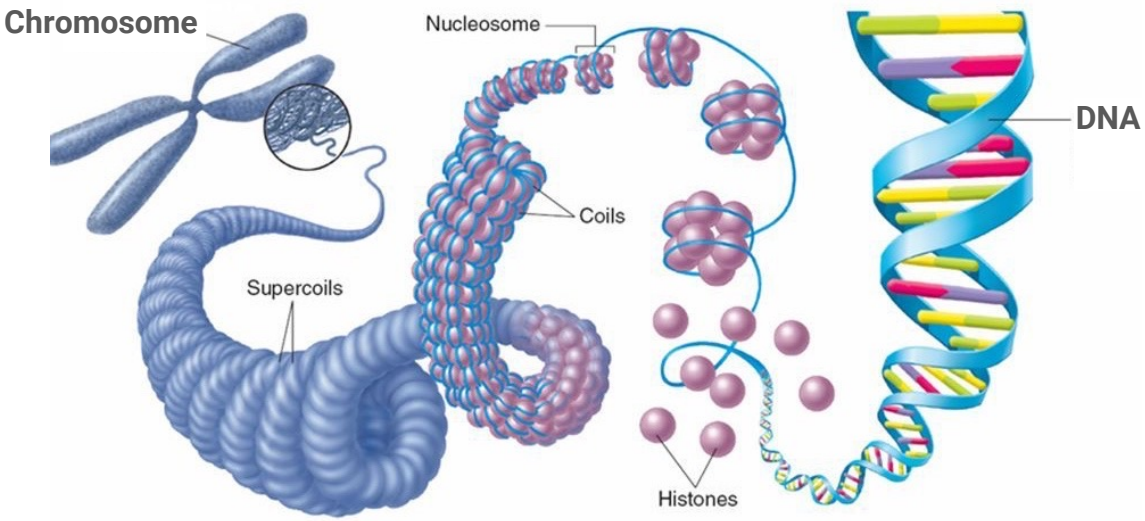
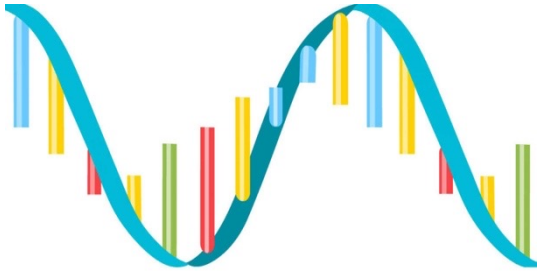
Clinical Trials and Therapeutic Development Updates

Patient Connect, June 2024

Lucienne Ronco, Ph.D.
Chief Scientific Officer

Molecular Biology 101





Chromosome → **DNA** → **RNA** → **Protein**

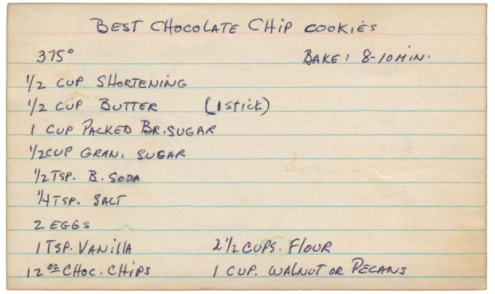
Epigenetic-controlled access → Transcription → Translation

"Gene Expression"

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Molecular Biology Healthy DUX4 Locus

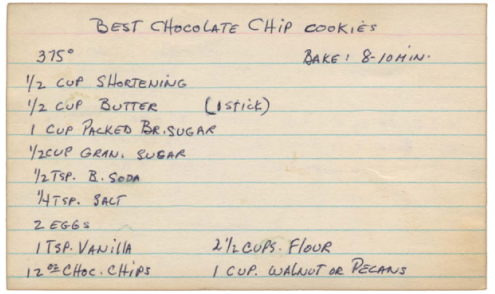
Healthy Chromosome

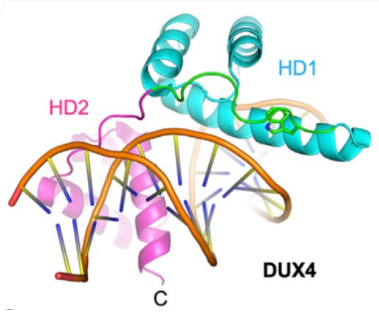


Chromosome → Epigenetic-controlled access → **DNA** → ~~Transcription~~ → **RNA** → ~~Translation~~ → **DUX4 Protein**

Molecular Biology FSHD Locus

FSHD Chromosome





Chromosome → **DNA** → **RNA** → **DUX4 Protein**

Epigenetic-controlled access → Transcription → Translation

Ways to treat FSHD

Correct the DNA sequence (D4Z4 shortening or mutation)

Block or remove DUX4 RNA

Block or remove DUX4 protein

Chromosome → **DNA** → **RNA** → **Protein**

Epigenetic-controlled access

Transcription

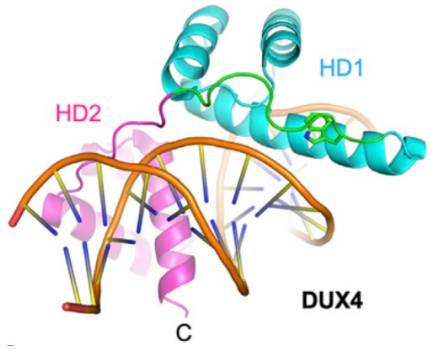
Translation

Re-repress access to DUX4 DNA

Interfere with DUX4 transcription

Interfere with DUX4 translation

Ways to treat FSHD



DUX4 Protein

Muscle Cell Death

Help muscles grow or regenerate

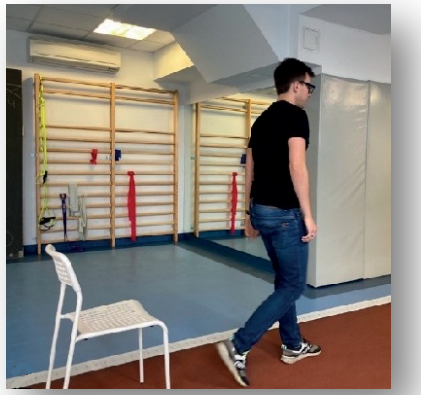
Reduce or eliminate Dux4

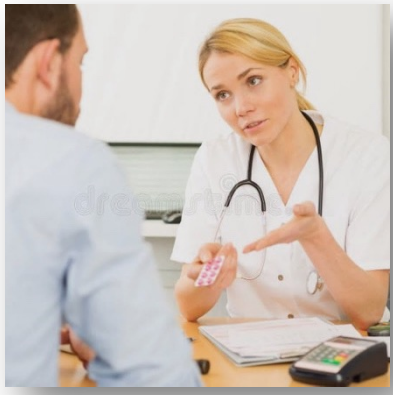
Stop muscle cell death

Reduce fibrosis

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Overview of Therapeutic Development





Pre-Clinical Research

- Disease mechanism
- Drug discovery
- Animal models to understand disease progress

Clinical Research

- Natural history
- Physical assessments
- Biomarkers
- Trial design

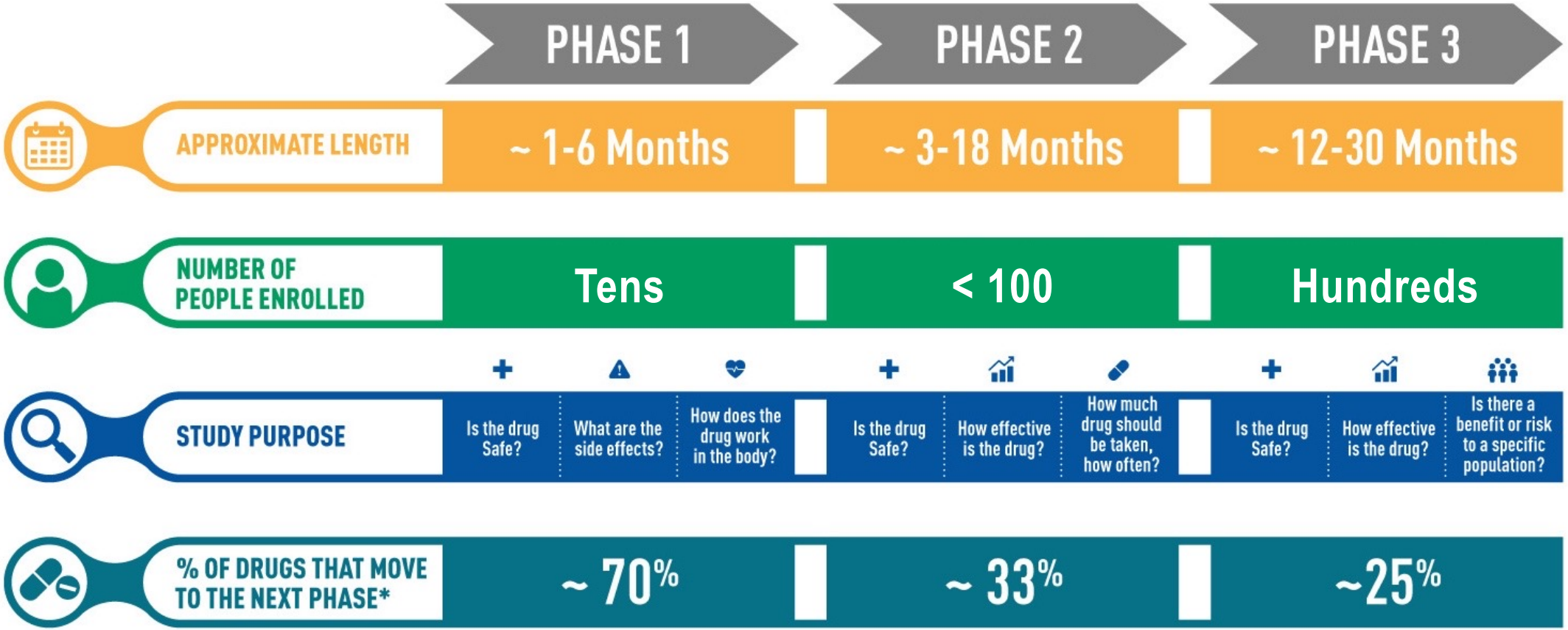
Clinical Trials

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

Launch

- Regulatory approval
- Payor reimbursement
- Longer term safety studies

Phases of Clinical Trials



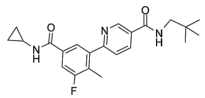
Adapted from ifopa.org/clinical_trial_phases

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Fulcrum REACH

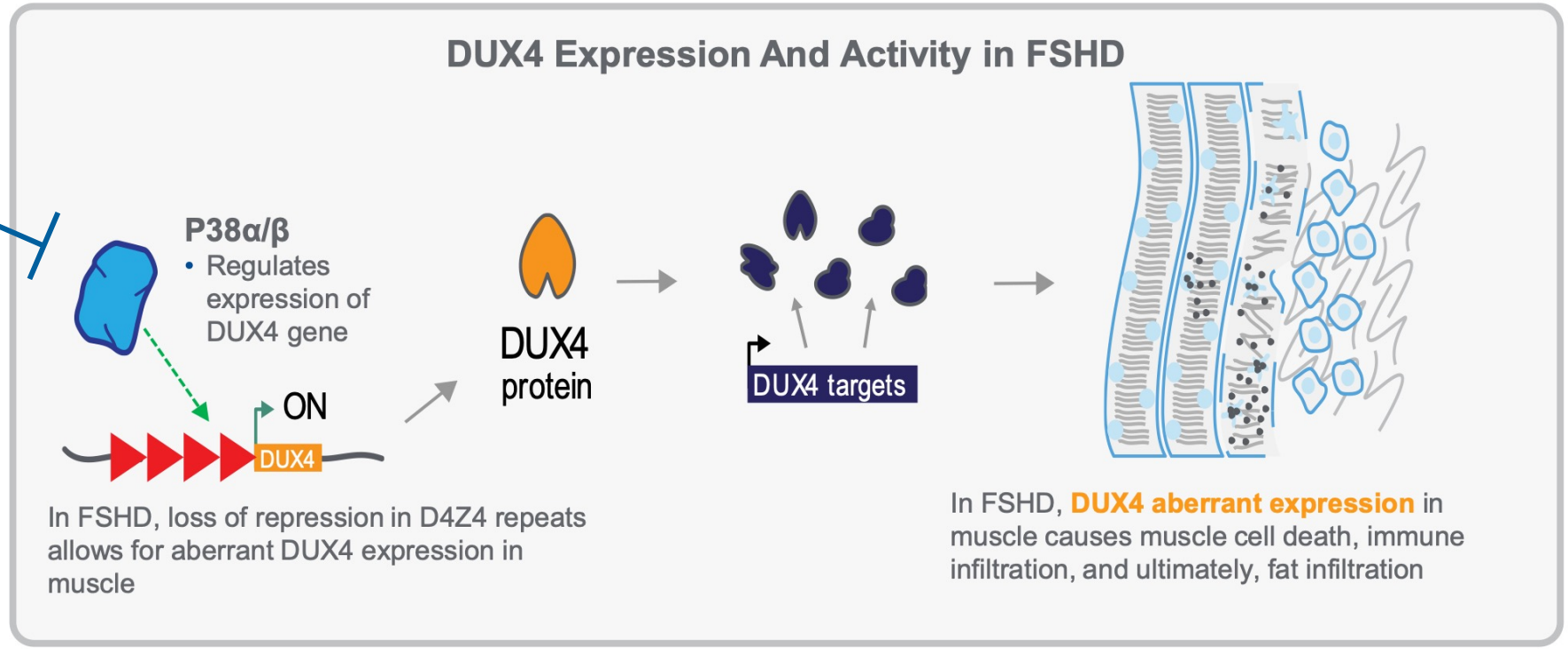
Fulcrum REACH: The Medicine

Fulcrum Therapeutics



Losmapimod

Interfere with DUX4 transcription



Administration:

Other Notes:

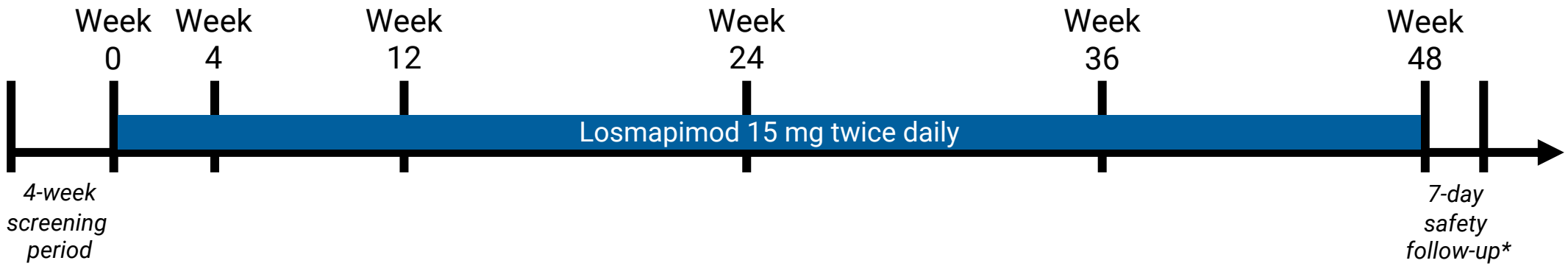
- Repurposed drug
- No safety concerns in 3,600 previous study participants

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

Fulcrum REACH: Clinical Trial Readout end of 2024

Fulcrum Therapeutics

REACH sponsored by Fulcrum Therapeutics

QUICK FACTS

Drug	Losmapimod
How Is It Given?	Pill, taken twice a day
Phase	3
Participants	260
Placebo	Yes, 1:1
Genetic Testing	Required, provided by study
Rx Duration	48 weeks in the double-blind stage
Study Visits	6 + screening and follow-up
Notable Activities	MRI
Open-Label Extension	Yes

STATUS

Enrollment	Completed
Data Expected	Q4 2024
Locations	US, Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK
Learn More	*clinicaltrials.gov/study/NCT05397470* *fshdsociety.org/fulcrum-reach-trial*

WHO CAN PARTICIPATE?

- 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

Fulcrum Therapeutics

Roche MANOEUVRE

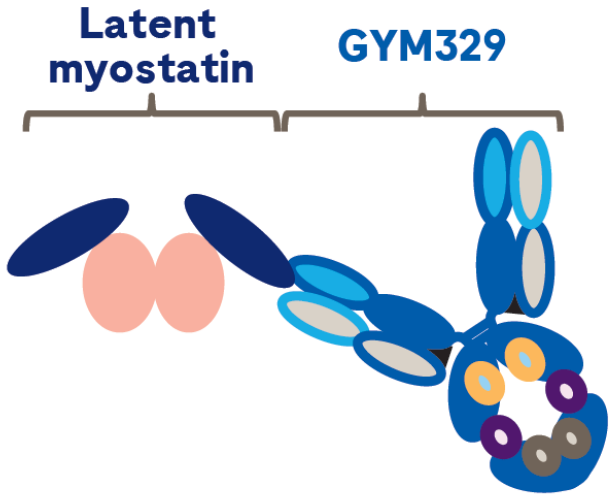
Roche MANOEUVRE: The Medicine

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:

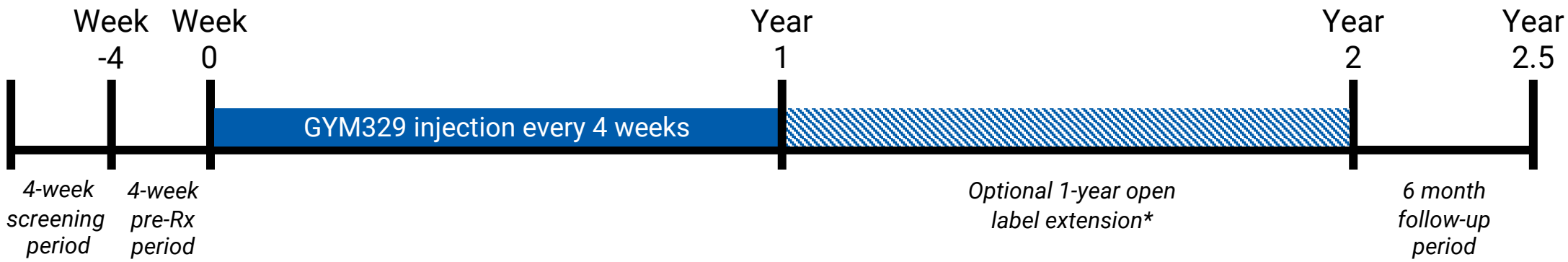
Other Notes:

- AKA RO7204239
- Next generation of anti-myostatin agents
- May require lower and less frequent dosing (every 4 weeks)

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:	
Phase	2
Participants	48
Placebo	Yes, 1:1
Rx Duration	52 weeks
Study Visits	At least every 4 weeks
Notable Activities	Wearable device, MRI
Open Label Extension	Yes*, for 52 weeks
Genetic Testing	Required; not paid for by study

Who Can Take Part?
Age 18-65
FSHD1 or FSHD2
Ricci score 2.5-4 (must be able to walk unassisted)
Must be able to do MRI

FSHD SOCIETY
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Roche MANOEUVRE: Enrollment is Complete

MANOEUVRE sponsored by Hoffmann-La Roche

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

STATUS	
Enrollment	Complete. Study is active.
Data Expected	Q3 2026
Locations	US, Denmark, Italy, UK
Learn More	*forpatients.roche.com* *clinicaltrials.gov/study/NCT05548556* *fshdsociety.org/roche-manoeuvre-trial/*

FSHD SOCIETY
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Roche REINFORCE: Getting Involved in France

REINFORCE by Centre Hospitalier Universitaire de Nice, principal investigator Sabrina Sacconi, funded by Hoffmann-La Roche

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

STATUS

Enrollment	Beginning early 2024
Data Expected	After 2027
Locations	Ottawa, Canada; Nice, France
Learn More	*clinicaltrials.gov/study/NCT06222827*

WHO CAN PARTICIPATE?

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

Centre Hospitalier Universitaire de Nice

Satralizumabis an antibody that binds to and blocks the IL-6 receptor.

Dr. Sacconi has found high levels of IL-6 in FSHD patient blood and will test if IL-6 drives FSHD.

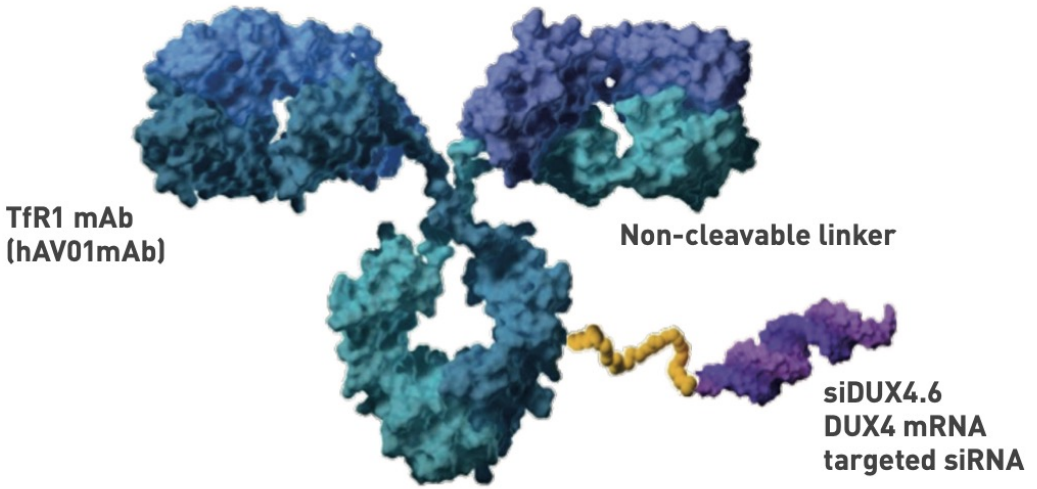
Avidity FORTITUDE

Avidity FORTITUDE: The Medicine

AVIDITY BIOSCIENCES

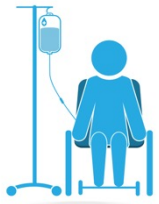
- **Figure 2** illustrates the structure of AOC 1020 and its three components:
  1. **Antibody:** Human transferrin receptor 1 (TfR1) targeting, effector function-null, humanized IgG1 antibody (hAVO1mAb) to affect delivery to skeletal muscle[7,8]
  2. **Non-cleavable linker:** MCC maleimide linker, enhanced 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:

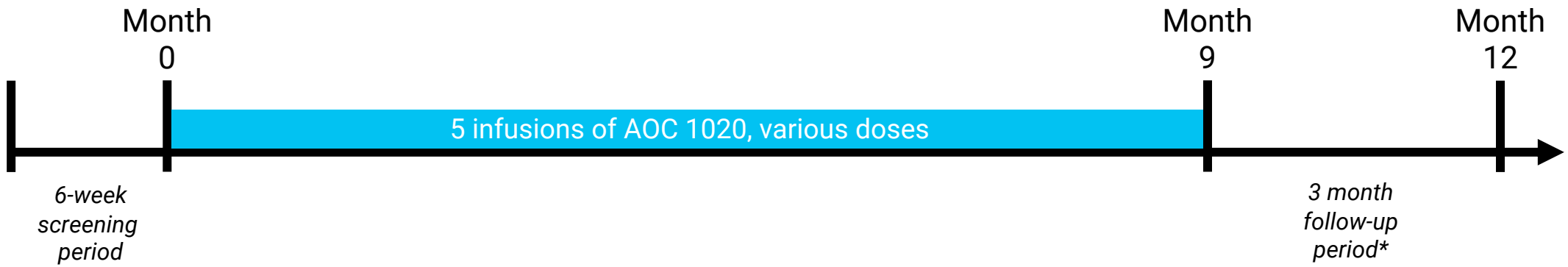


Other Notes: Related drug in Myotonic Dystrophy (AOC 1001) was first ever AOC in clinic, performing favorably in Phase 1/2

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

FSHD SOCIETY LIGHTING THE WAY TO A CURE

Avidity FORTITUDE: Study Design



Quick Facts:	
Phase	1/2a
Participants	72
Placebo	Yes, 2:1
Rx Duration	5 doses over 9 months
Study Visits	~20, some may be virtual
Notable Activities	MRI, leg muscle biopsy
Open Label Extension	Yes*
Genetic Testing	Required, provided by study

Who Can Take Part?
Age 18-65
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

FORTITUDE sponsored by Avidity Biosciences

An expanded cohort is enrolling

QUICK FACTS

Drug	AOC1020
How Is It Given?	Intravenous infusion
Phase	1/2a
Participants	72
Placebo	Yes, 2:1
Genetic Testing	Required, provided by study
Rx Duration	5 doses over 9 months
Study Visits	~20, some may be virtual
Notable Activities	MRI, leg muscle biopsy
Open-Label Extension	Yes

STATUS

Enrollment	Currently enrolling
Data Expected	Preliminary data Q2 2024
Locations	US, Canada, UK
Learn More	*fortitude-study.com* *clinicaltrials.gov/study/NCT05747924* *fshdsociety.org/avidity-fortitude-trial/*

WHO CAN PARTICIPATE?

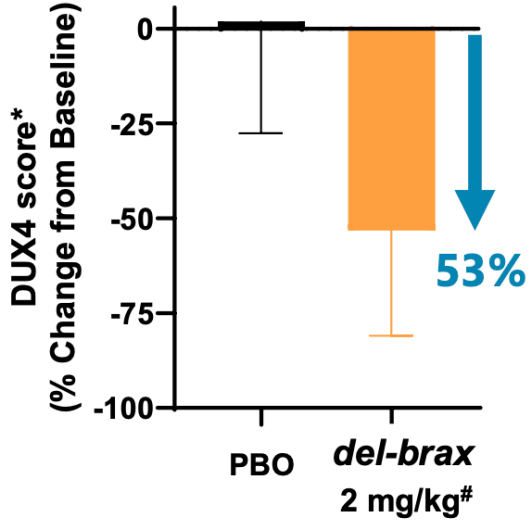
- Age 18-65
- FSHD1 or FSHD2
- FSHD clinical score of 2-14
- Able to walk 10 meters without assistance
- Reachable Workspace score
- Must have leg muscle suitable for biopsy and be able to do MRI

US & Canada Locations:

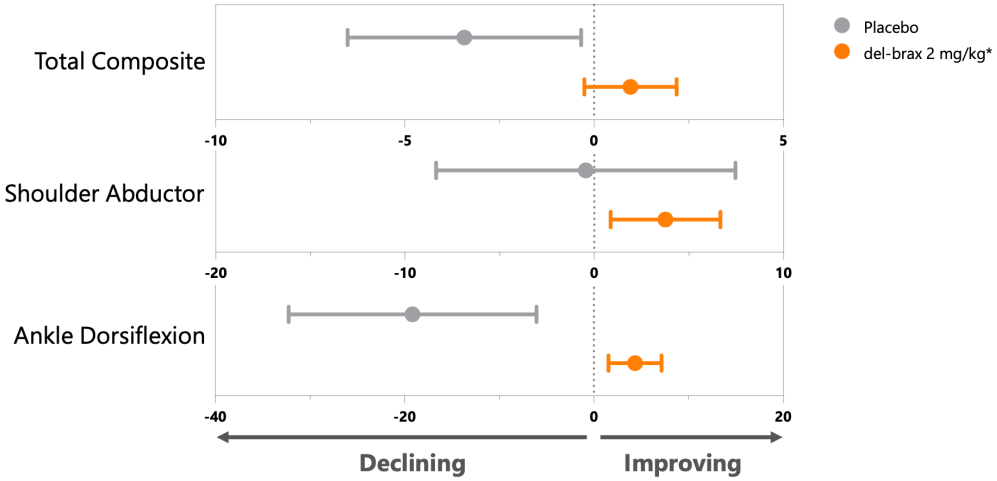
UC Los Angeles
UC San Diego
Stanford
University of Colorado
University of Florida
Rare Disease Research (Atlanta)
Kansas University Medical Center
University of Rochester
Duke University
Ohio University
University of Pennsylvania
UT Southwest
Virginia Commonwealth
University of Washington
University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

AOC1020 - Abbreviated Name is Del-brax. Data reported Wed. Jun 12

Avidity Panel[1]

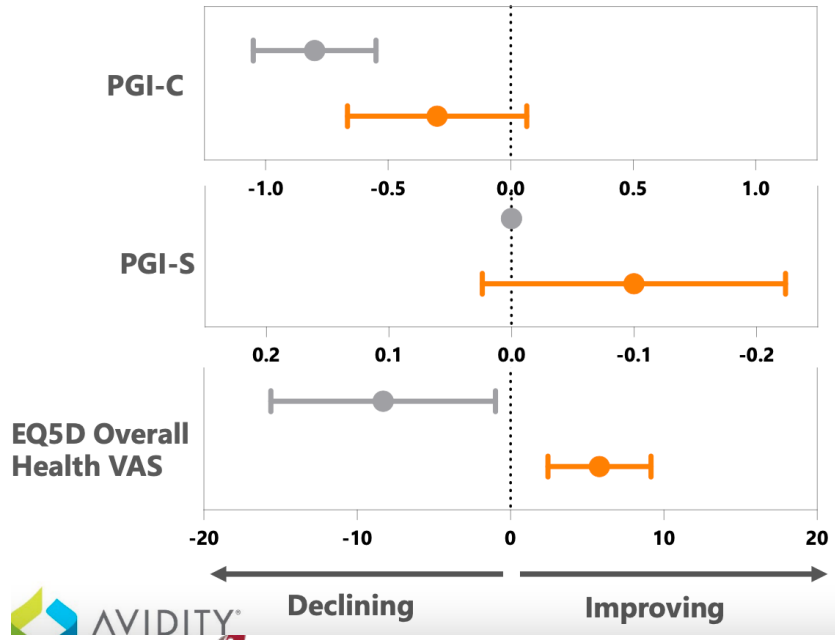


Del-brax Improved Muscle Strength in Both Upper and



Patient Reported Outcome Measures

Change from Baseline at Month 4 (SEM)



AVIDITY

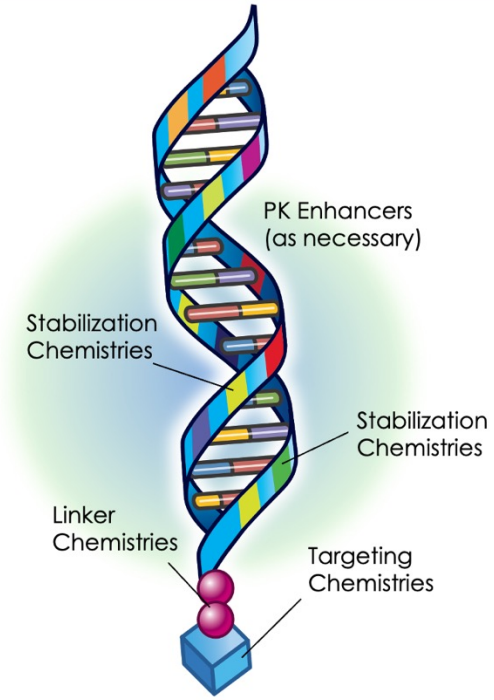
FSHD SOCIETY
LIGHTING THE WAY TO A CURE

COMING SOON:
Arrowhead ARO-DUX4

Arrowhead ARO-DUX4: The Medicine

arrowhead pharmaceuticals

Arrowhead TRiM™ Platform for Muscle Diseases



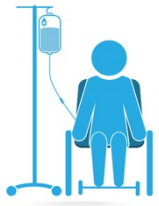
Components:

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

Remove DUX4 RNA

TRIM Platform
Targeted
RNAi Molecule

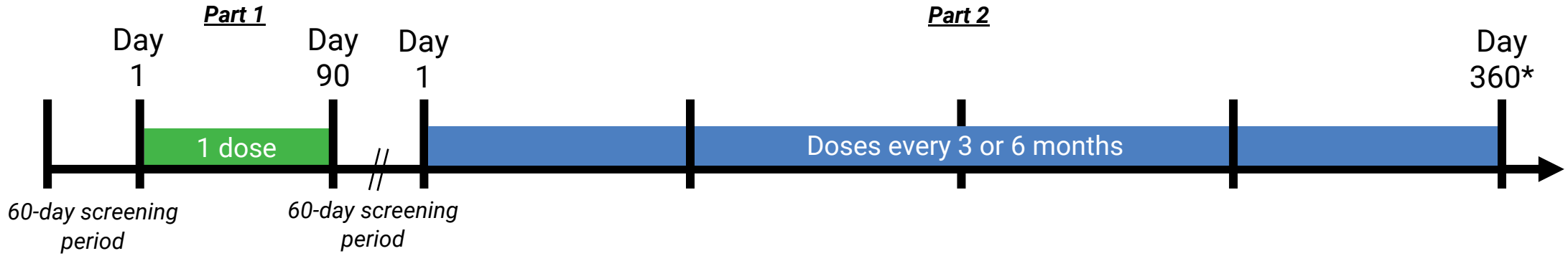
Administration:



Other Notes: Similar approach to Avidity

FSHD SOCIETY
LIGHTING THE WAY TO A CURE

Arrowhead ARO-DUX4: Study Design



Quick Facts:	
Phase	1/2
Participants	52
Placebo	Yes, 3:1
Rx Duration	Part 1: 1 dose Part 2: 2 or 4 doses over 1 year
Study Visits	~20
Notable Activities	MRI, leg muscle biopsy
Open Label Extension	Yes*
Genetic Testing	Required, provided by study

Who Can Take Part?
Age 18-70
FSHD1
Clinical Severity Scale 3-8
Must have leg muscle suitable for biopsy (and be able to do MRI)

Arrowhead ARO-DUX4: LEARN MORE

ARO-DUX4 trial sponsored by Arrowhead Pharmaceuticals

QUICK FACTS

Drug	ARO-DUX4
How Is It Given?	Intravenous injection
Phase	1/2a
Participants	52
Placebo	Yes, 3:1
Genetic Testing	Required, provided by study
Rx Duration	Part 1: duration 3 months Part 2: 2 or 4 doses over 1 year
Study Visits	~20
Notable Activities	MRI, leg muscle biopsy
Open-Label Extension	Yes

STATUS

Enrollment	Beginning early 2024
Data Expected	TBD
Locations	New Zealand, Canada (TBC)
Learn More	*fshdsociety.org/arrowhead-trial* *clinicaltrials.gov/study/NCT06131983*

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 pharmaceuticals

FSHD SOCIETY
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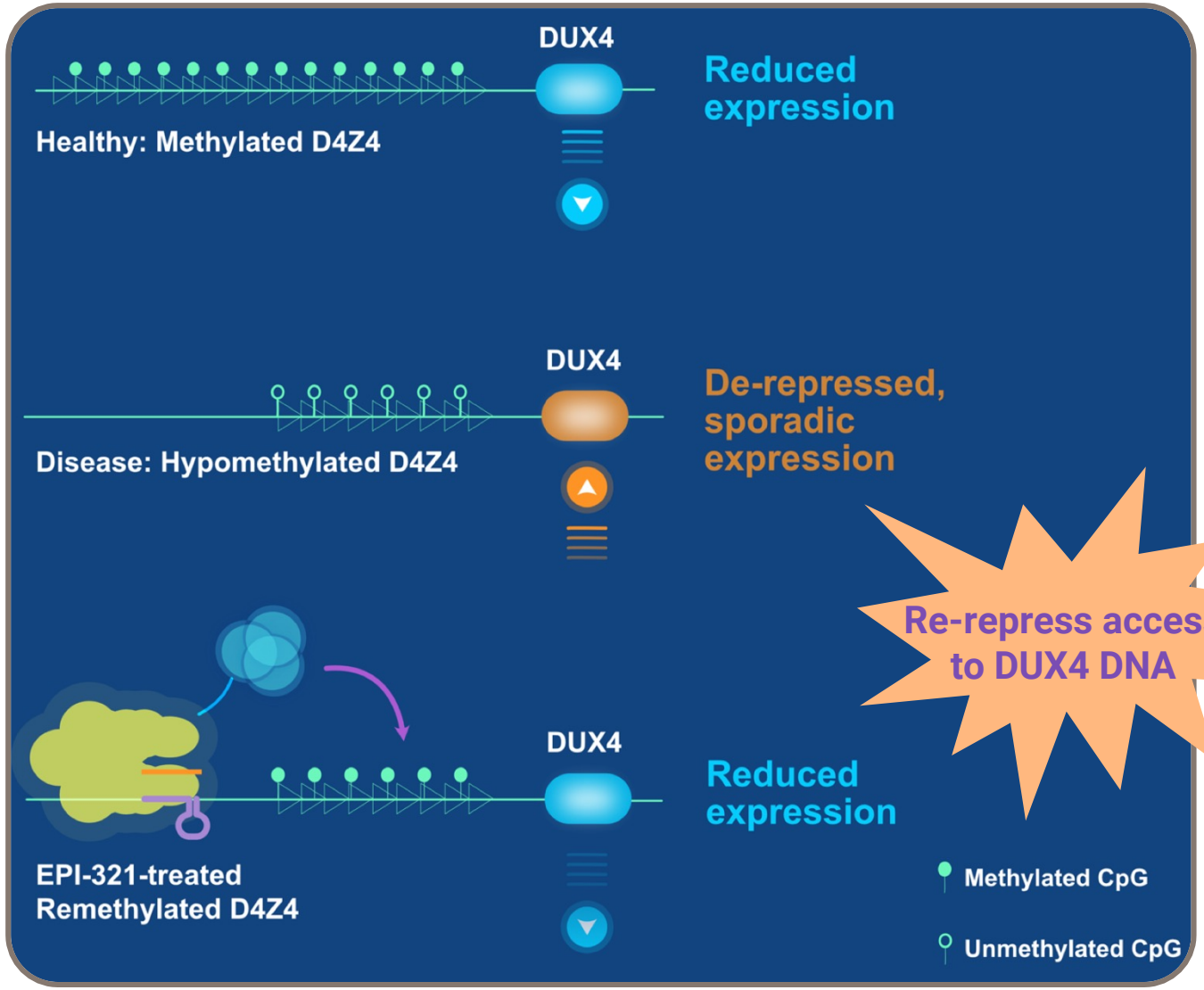
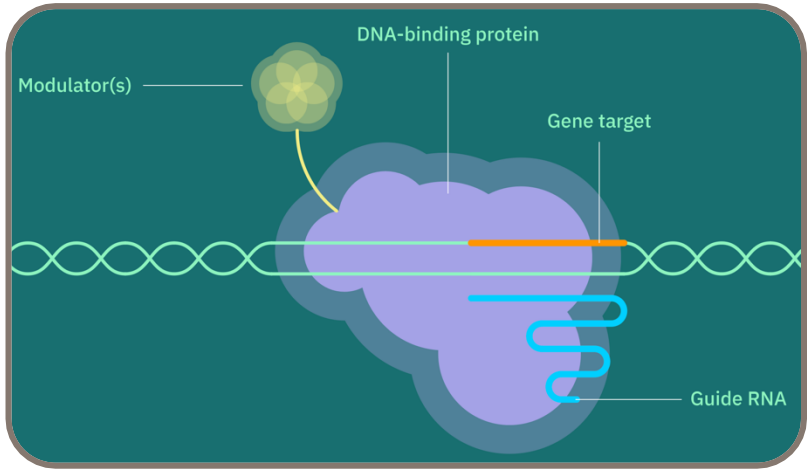
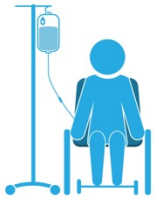
COMING SOON:
Epic Bio EPI-321

Epic Bio EPI-321: The Medicine





Administration:

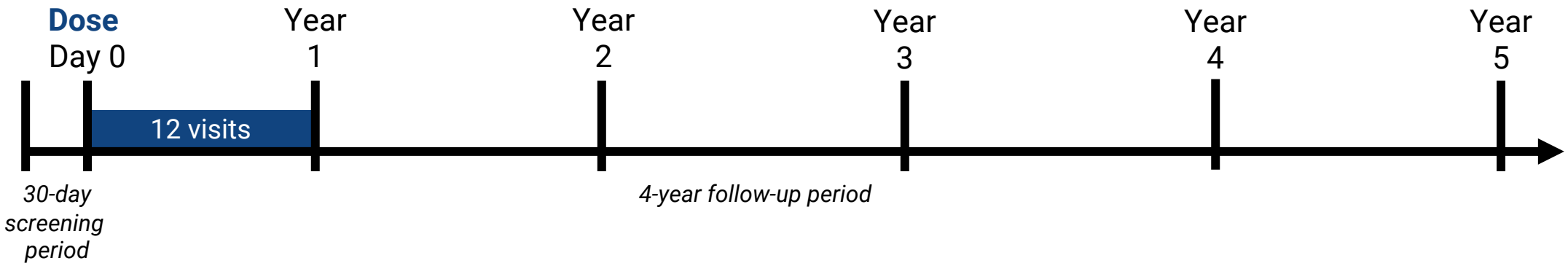


Other Notes:

- 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/

Epic Bio 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

Epic Bio EPI-321: Getting Involved

Get Involved:	
Enrollment	TBD in 2024
Data Expected	TBD
Locations	US, Canada, UK, Germany, Netherlands
Learn More	FSHD Society YouTube → FSHD University → Epic Bio

Stay tuned for more info!

Many more therapies coming down the pipeline!

Dyne THERAPEUTICS

VITA Therapeutics

myogênica

KATE THERAPEUTICS

ALTAY THERAPUTICS

miRecule RNA Therapeutics

ECM Therapeutics

MYOCEA

RENOGENYX

healx

satellos

ARMATUSBIO

9 Academic research labs working on drug discovery

Additional companies in ‘stealth’ mode

MOVE and MOVE+ Natural History Studies

FSHD CTRN
FSHD CLINICAL TRIAL RESEARCH NETWORK

Why are NATURAL HISTORY STUDIES 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
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MOVE and MOVE+ Natural History Studies

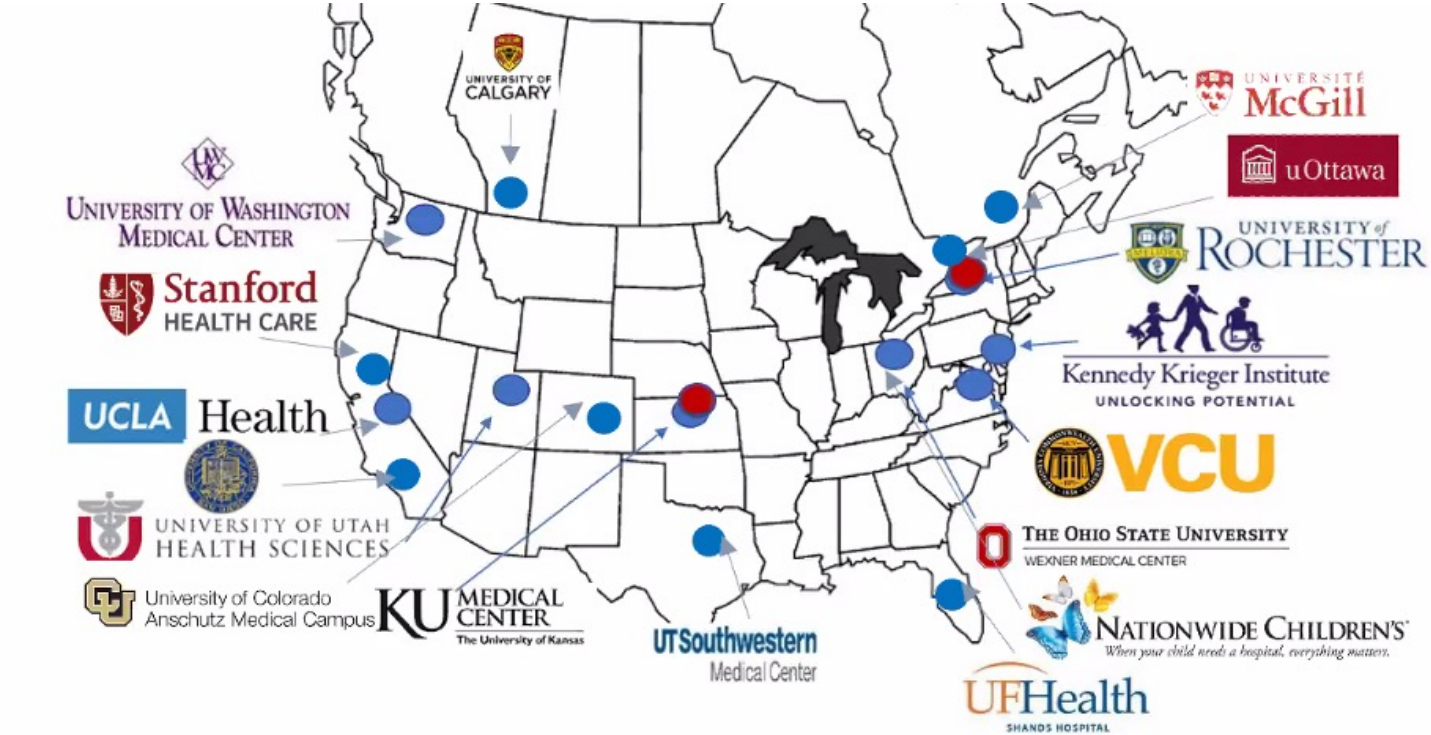
FSHD CTRN
FSHD CLINICAL TRIAL RESEARCH NETWORK

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



FSHD SOCIETY
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Summary and how you can be involved

Research you can take part in RIGHT NOW:

- Avidity 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

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Thank you!

Questions?

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