DRUG DEVELOPMENT OVERVIEW AND TRIAL READINESS FOR FSHD

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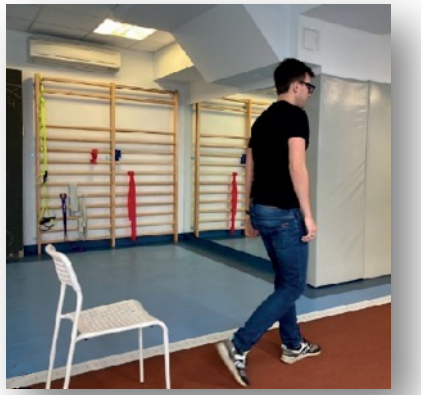
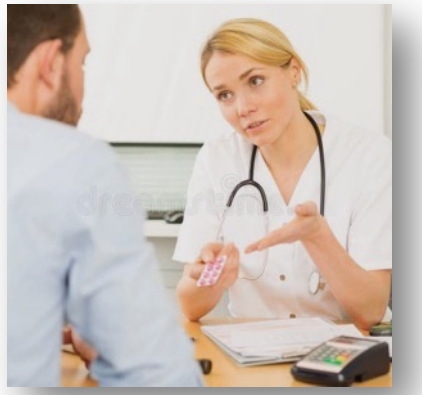
Overview of Therapeutic Development





Pre-Clinical Research

- Disease mechanism
- Drug discovery
- Animal models

Clinical Research

- Natural history
- Physical assessments
- Biomarkers
- Trial design

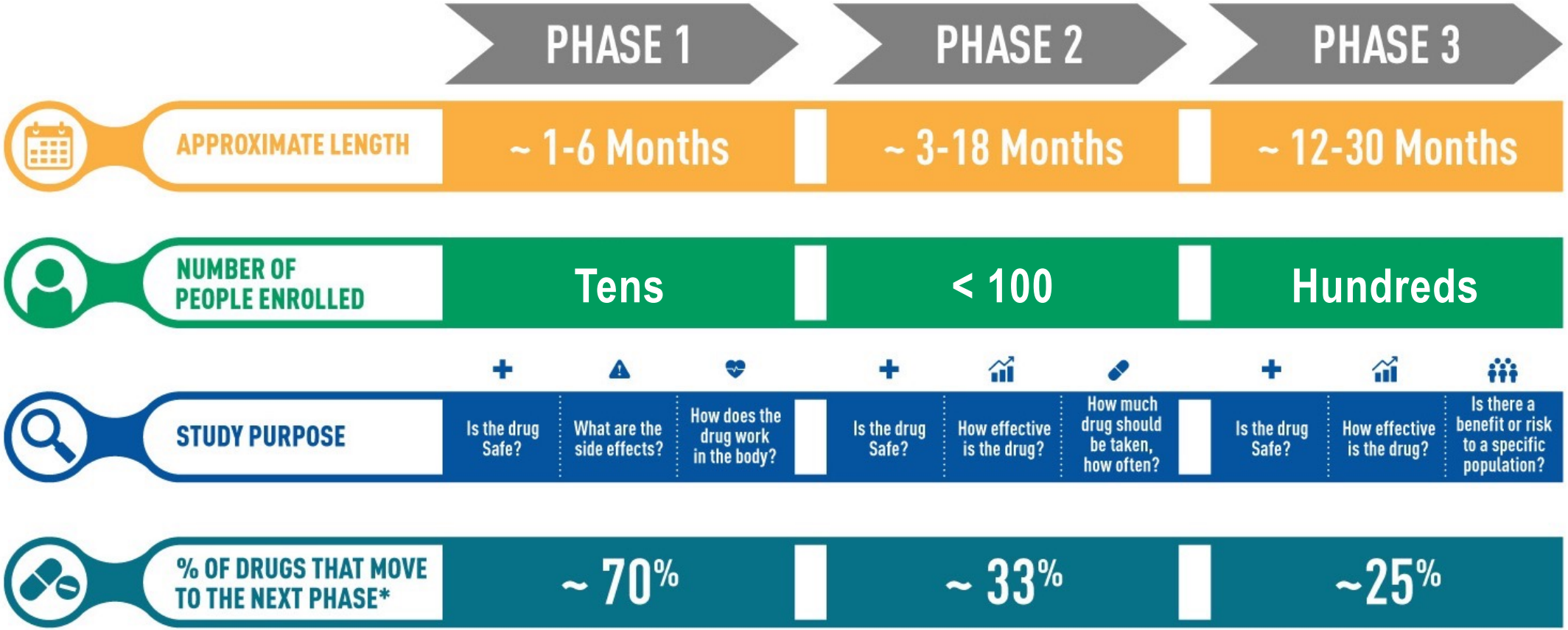
Clinical Trials

- 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

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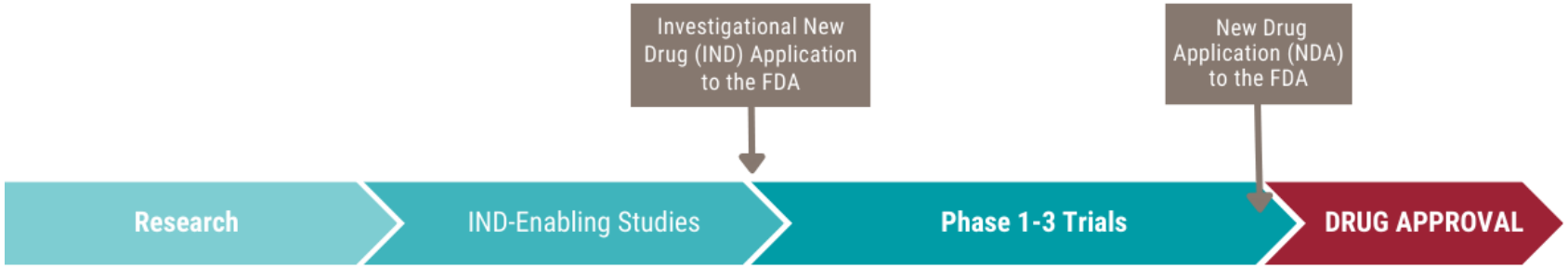


Small molecule therapies to block *DUX4*

- Fulcrum Therapeutics (repurposed drug*)
- Anonymous biotechs/pharma**
- Myocea (repurposed drug*)
- Altay
- ~~Facio~~
- Healx

Indicates the program was halted

Biologics to block *DUX4*

- Avidity Biosciences
- Dyne Therapeutics
- ~~Anonymous biotechs/pharma**~~
- Arrowhead Pharmaceuticals
- Armatus Bio
- Epic Bio
- miRecule / Sanofi
- RENOGENYX
- Kate Therapeutics
- Anonymous biotech

Arrowhead Pharmaceuticals

Armatus Bio

Epic Bio

miRecule / Sanofi

RENOGENYX

Kate Therapeutics

Anonymous biotech

Other therapeutic mechanisms

Acceleron

Hoffman-La Roche (muscle-growth drug)

Vita Therapeutics (iPSC)

Myogenica (iPSC)

ECM (tissue engineering)

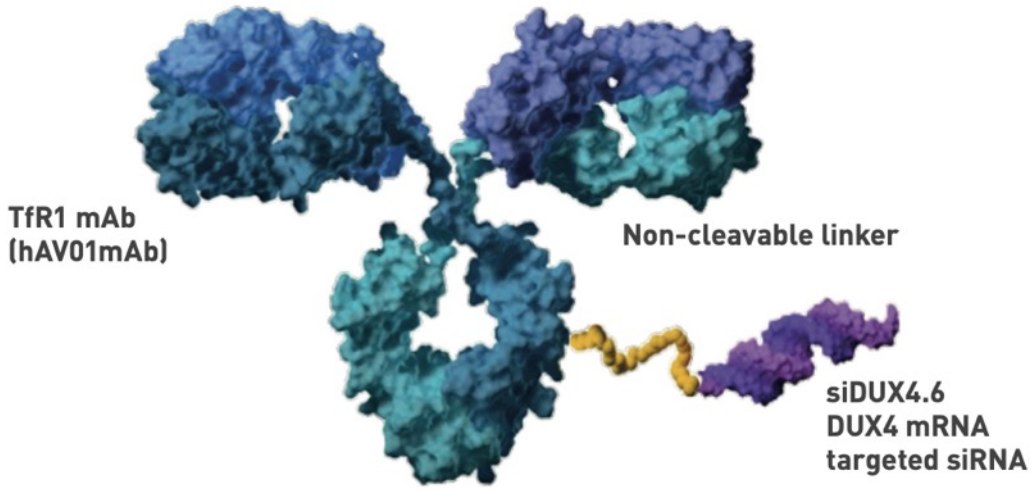
Academic labs engaged in early-stage FSHD drug discovery

- Chen Lab, Children's National Hospital
- Dumonceaux Lab, University College London
- Emerson Lab, UMass Medica
- Harper Lab, Nationwide Children's Hospital
- Gabellini Lab, San Raffaele Scientific Institute
- Lek Lab, Yale University
- Popplewell Lab, Royal Holloway University
- Saad Lab, Nationwide Children's Hospital
- Zammit Lab, King's College

Avidity FORTITUDE Clinical Trial

- **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

FORTITUDE sponsored by Avidity Biosciences

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

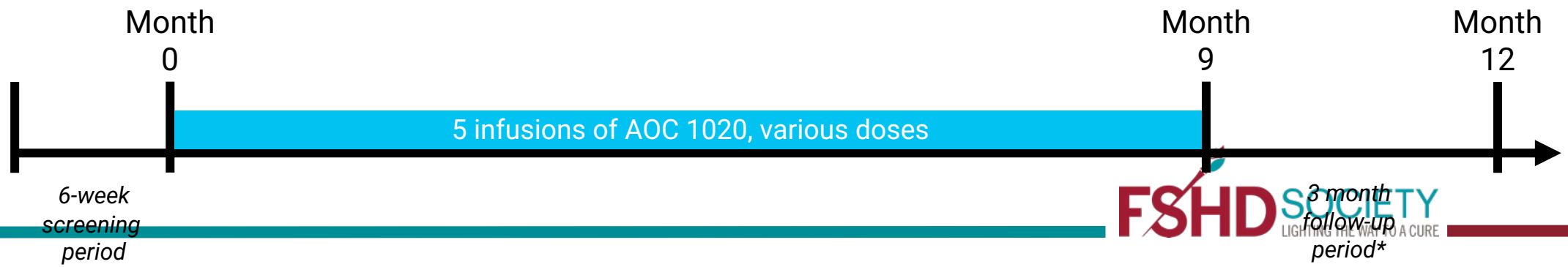
STATUS

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

AVIDITY BIOSCIENCES



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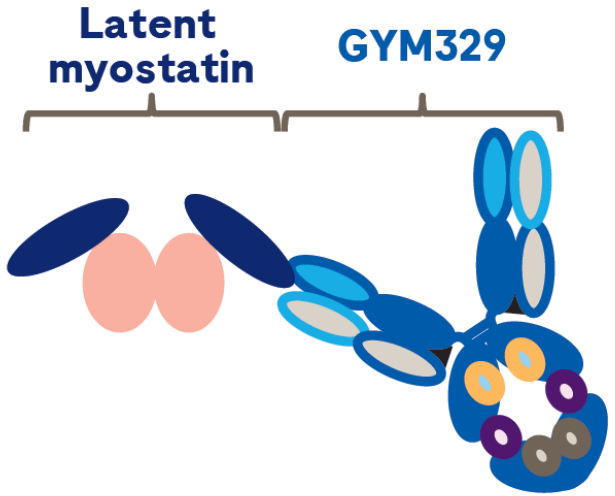
Roche MANOEUVRE Clinical Trial

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

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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

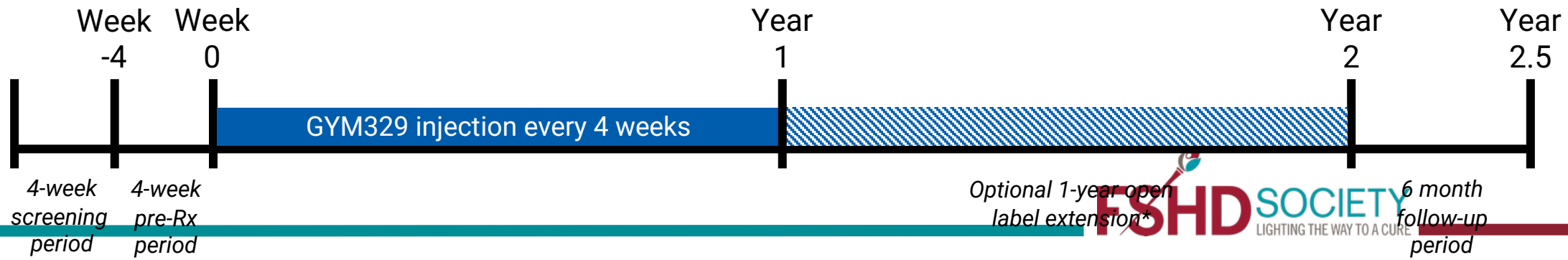
WHO CAN PARTICIPATE?

- Age 18-65
- FSHD1 or FSHD2
- Ricci score 2-4 (must be able to walk unassisted)
- Must be able to do MRI

STATUS

Enrollment	Currently enrolling
Data Expected	TBD
Locations	US, Denmark, Italy, UK
Learn More	*forpatients.roche.com* *clinicaltrials.gov/study/NCT05548556* *fshdsociety.org/roche-manoeuvre-trial/*

Roche



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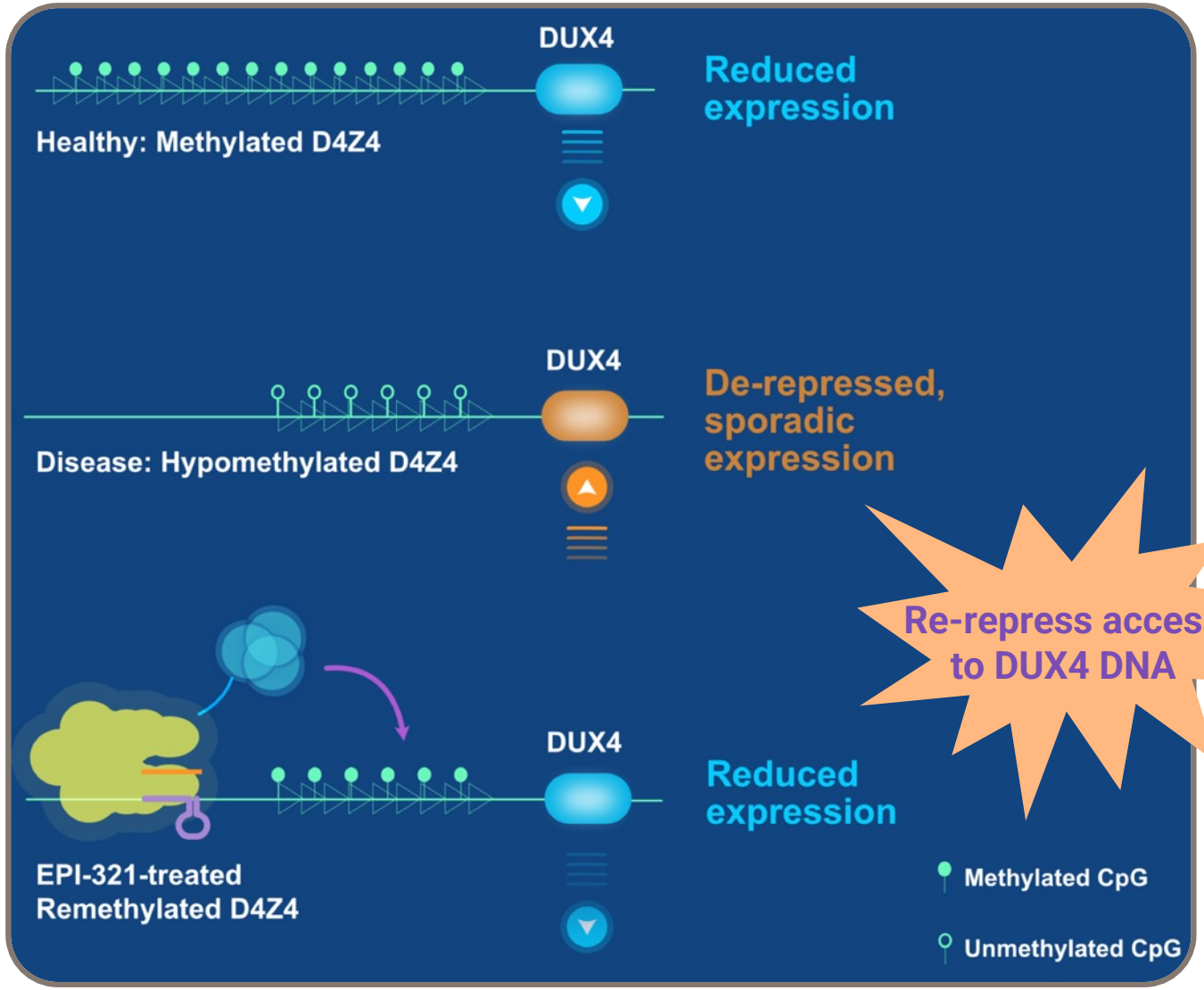
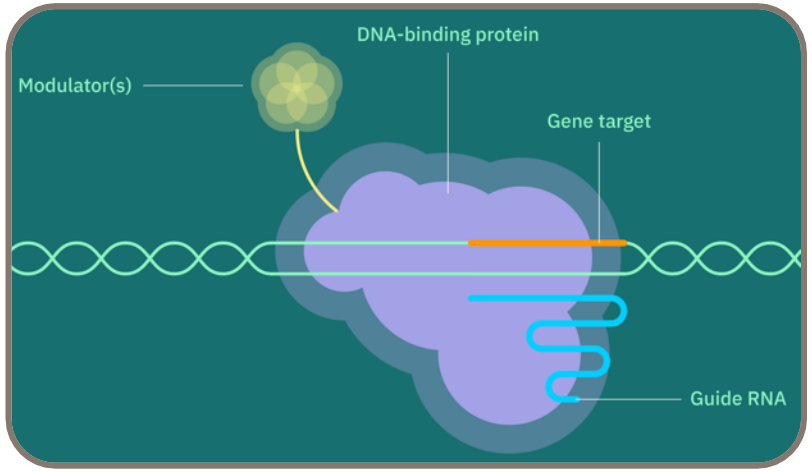
COMING SOON: Epic Bio





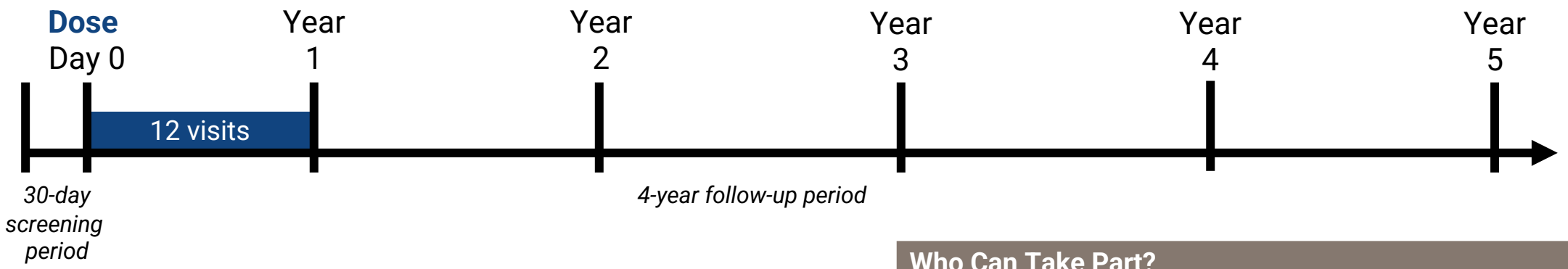
Administration:

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/

COMING SOON: Epic Bio



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

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

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

Many more therapies coming down the pipeline!

Dyne THERAPEUTICS

VITA Therapeutics

myogênica

KATE THERAPEUTICS

ALTAY THERAPUTICS

miRecule RNA Therapeutics

ECM Therapeutics

MYOCEA

RENOGENYX

healx

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 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

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MOVE and MOVE+ Natural History Studies

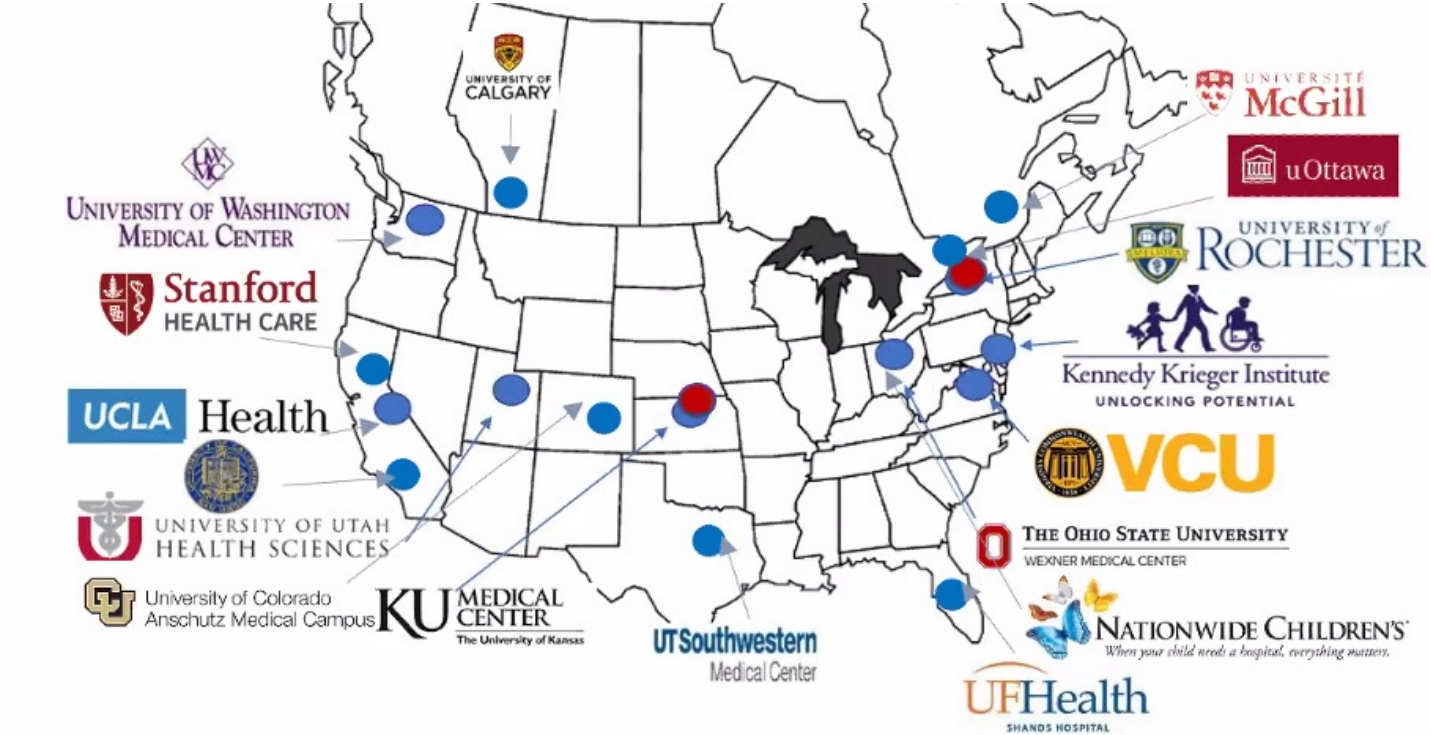
FSHD CTRN
FSHD CLINICAL TRIAL RESEARCH NETWORK

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 Carissa Wong
Clinical Study Coordinator, Calgary
carissa.wong@ucalgary.ca



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Summary and how you can be involved

Research you can take part in RIGHT NOW or SOON:

- National registry
- MOVE and MOVE+ natural history studies
- Carissa Wong: carissa.wong@ucalgary.ca

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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