Fulcrum Therapeutics

Fulcrum Q2 2020 Conference Call

August 11, 2020

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Agenda

- **Overview of the ReDUX4 interim analysis and recent progress made at Fulcrum**
  - ReDUX4 interim analysis
  - Losmapimod for COVID-19
  - Hemoglobinopathies Program
  - Research Programs
- **Overview of company financials**
- **Q&A Session**

FSHD Program Overview – Interim Results from ReDUX4

- **Today we announced interim results from 29 FSHD subjects in our Phase 2b ReDUX4 trial**
- **The interim analysis provided data from the primary endpoint, which is an assessment of DUX4-driven gene expression**
  - Other endpoints were not evaluated
- **Large reduction observed with losmapimod treatment in muscle biopsies with highest pre-treatment level of DUX4-driven gene expression**
  - Observed a 38-fold reduction in losmapimod treated arm and 5.4-fold reduction in placebo arm in muscle biopsies with highest baseline DUX4 driven gene expression
  - Separation from placebo in the total population was not observed

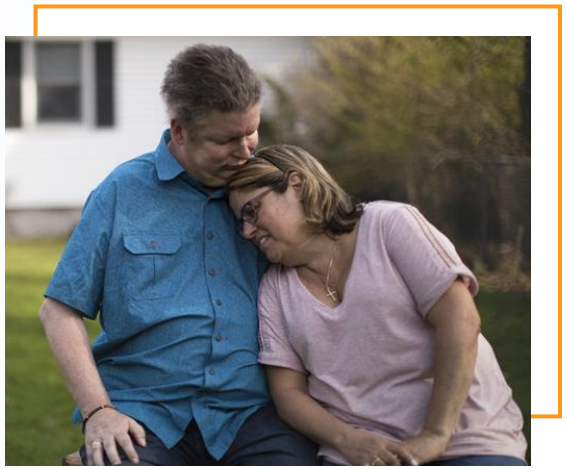
Key Company Highlights

- **Losmapimod for COVID-19**
  - IND in effect, initiated Phase 3 trial in Q2 2020
  - Trial site activation underway in the United States, Mexico and South America
  - Topline results anticipated in 1Q 2021 and futility analysis anticipated in 4Q 2020
- **Hemoglobinopathies Program**
  - On-track to submit IND for FTX-6058 in Q3 2020
  - Anticipate initiating Phase 1 trial of FTX-6058 in Q4 2020
- **Other Research Programs**
  - Significant expansion of FulcrumSeek screening underway
  - MyoKardia collaboration to identify therapeutics that control the expression of genes know to be underlying drivers of genetic cardiomyopathies; Eligible for over $400M in milestones and research reimbursement
- **Private Placement**
  - Completed $68.5 million private placement, extending cash runway in Q1 2022

Fulcrum Therapeutics

ReDUX4 Interim Analysis

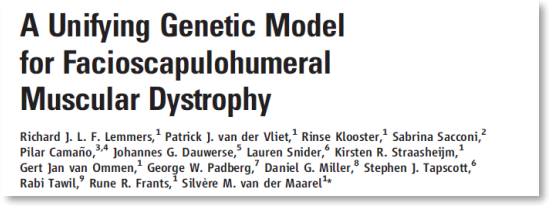
Losmapimod for Facioscapulohumeral Muscular Dystrophy (FSHD)



"They told me that I was probably going to die from muscular dystrophy at 30 years old—that I would probably roll over and suffocate myself in my sleep."

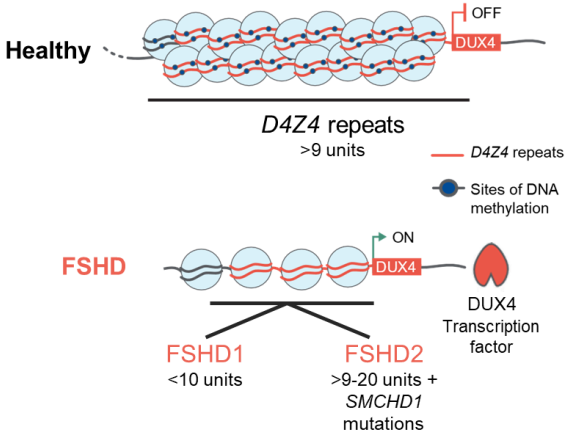
"You know how many years it took to get out of that? That's a scary feeling."

DUX4 is the Root Cause of FSHD

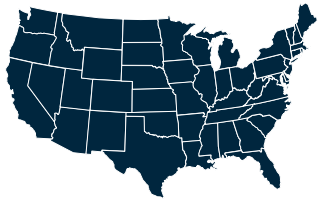


A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy

Richard J. L. F. Lemmers,[1] Patrick J. van der Vliet,[1] Rinse Klooster,[1] Sabrina Sacconi,[2] Pilar Camaño,[3,4] Johannes G. Dauwerse,[5] Lauren Snider,[6] Kirsten R. Straasheijm,[1] Gert Jan van Ommen,[1] George W. Padberg,[7] Daniel G. Miller,[8] Stephen J. Tapscott,[6] Rabi Tawil,[9] Rune R. Frants,[1] Silvère M. van der Maarel[1*]



Estimated US FSHD Population*
16,000-38,000



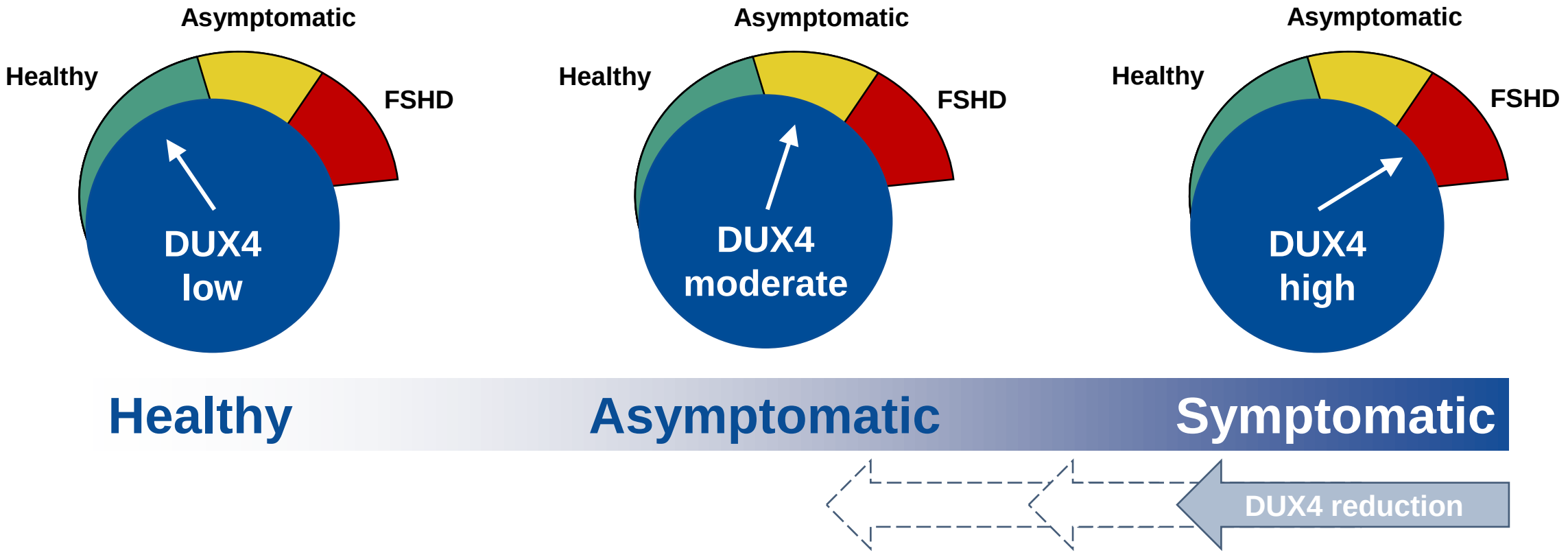
Estimated Global FSHD Population*
300,000-780,000

Discovered losmapimod, a selective p38 MAP kinase inhibitor, reduced DUX4-driven gene expression

*Deenen, JCW, et al. Neurology. 2014; Preston, MK et al. GeneReviews – FSHD. 2020

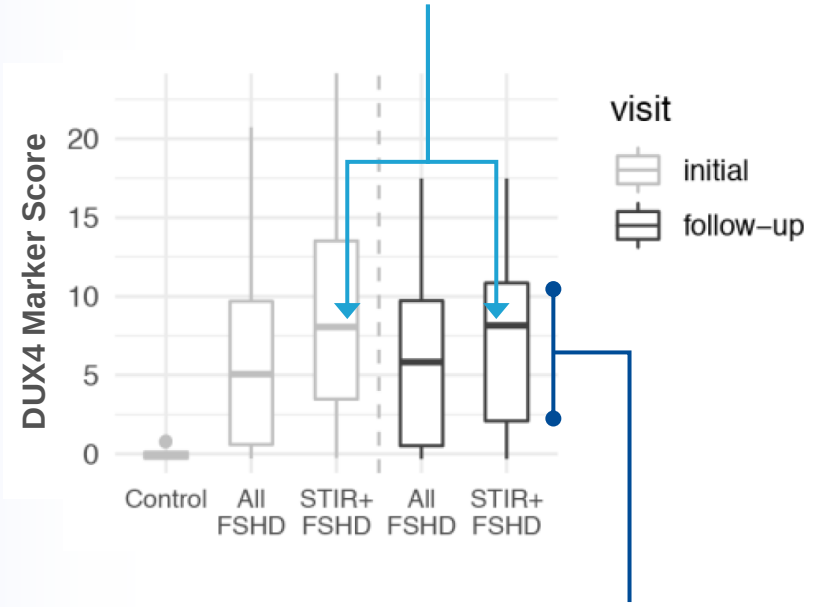
Reduction In DUX4 May Provide Functional Benefit in FSHD Patients

Relationship between DUX4 expression and FSHD disease presentation



Wide Range in Baseline DUX4-driven Gene Expression in Affected FSHD Muscles

Stable DUX4 signature between initial and one-year follow-up biopsies in untreated STIR+ muscles



Wide range in baseline DUX4-driven gene expression between untreated STIR+ muscle biopsies

- **DUX4-driven gene expression is elevated in STIR+ muscle from FSHD subjects compared to healthy muscle**
- **DUX4 expression can vary across and within patient muscles**
  - Previously demonstrated baseline DUX4-driven gene expression is stable at site of biopsy in preparatory studies

Wong, C. Hum Mol Genet. 2020; Note: DUX4 marker score of RNA-seq biopsy samples was based on four FSHD/DUX-4 positive biomarkers (LEUTX, KHDC1L, PRAMEF2, TRIM43)

Phase 2b ReDUX4 Trial (n=80)

Randomized, double-blind, placebo-controlled, multi-site international
15 mg twice per day for 24 or 48 weeks

- **Primary endpoint:**
  - Change from baseline in DUX4 driven gene expression in skeletal muscle needle biopsy at 16 or 36 weeks, as measured by qRT-PCR in a panel of DUX4-regulated gene transcripts
- **Secondary endpoints:**
  - Safety and tolerability
  - PK in blood
  - Losmapimod concentration in skeletal muscle biopsies
  - Target engagement in blood and in skeletal muscle biopsies
  - MRI Lean Muscle Volume & MRI Fat Fraction
- **Exploratory endpoints:**
  - Reachable Workspace (RWS)
  - FSHD-Timed up and Go (TUG)
  - Muscle Function Measure (MFM)
  - Muscle Strength (Dynamometry)
  - PROs

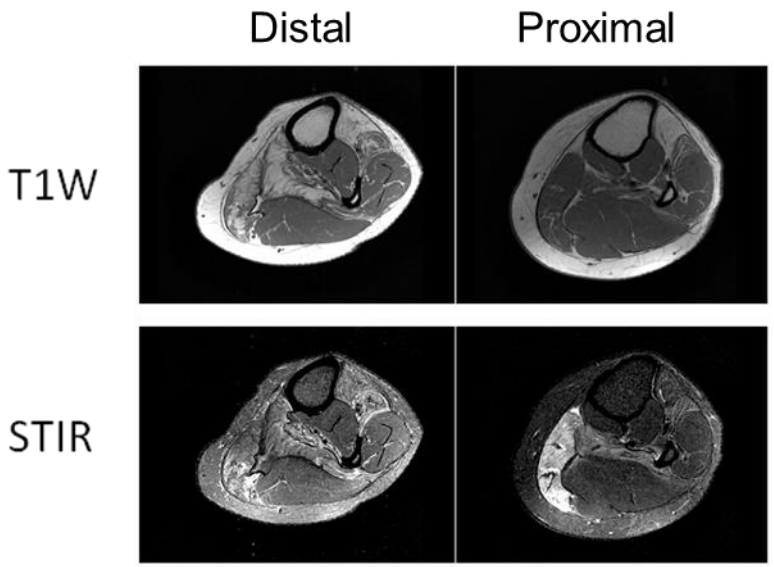
- Interim analysis on first 29 randomized subjects in Q3 2020
- Topline data on all subjects expected Q1 2021

MRI-guided Biopsy Can Identify DUX4 Expressing Muscle, But Not Level of Expression

- MRI guided biopsy is utilized to identify those muscles most likely to express DUX4-driven gene expression

- **MRI can accurately identify affected muscle, but cannot determine level of DUX4-driven gene expression**, which varies by muscle and by tissue sample, but is stable over time across the population

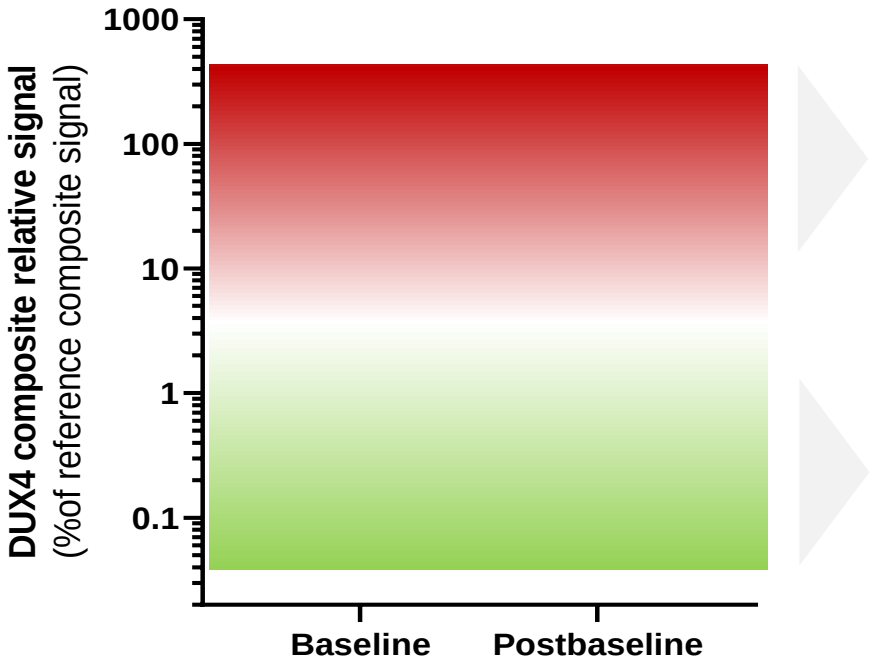
MRI Images of Affected Muscle in FSHD Patient



Marked differences in the degree of fatty replacement and edematous signal are shown progressing distal to proximal as evidenced by T1W and STIR images

Friedman, SD; Shaw, DW. Longitudinal Progression of Edema and Fatty Replacement of Lower Extremity Muscles in FSHD. 2011.

Greater Than 1000-fold Difference Between Higher and Lower Expressing Pre-treatment Muscle Biopsies



Higher DUX4-driven gene expression

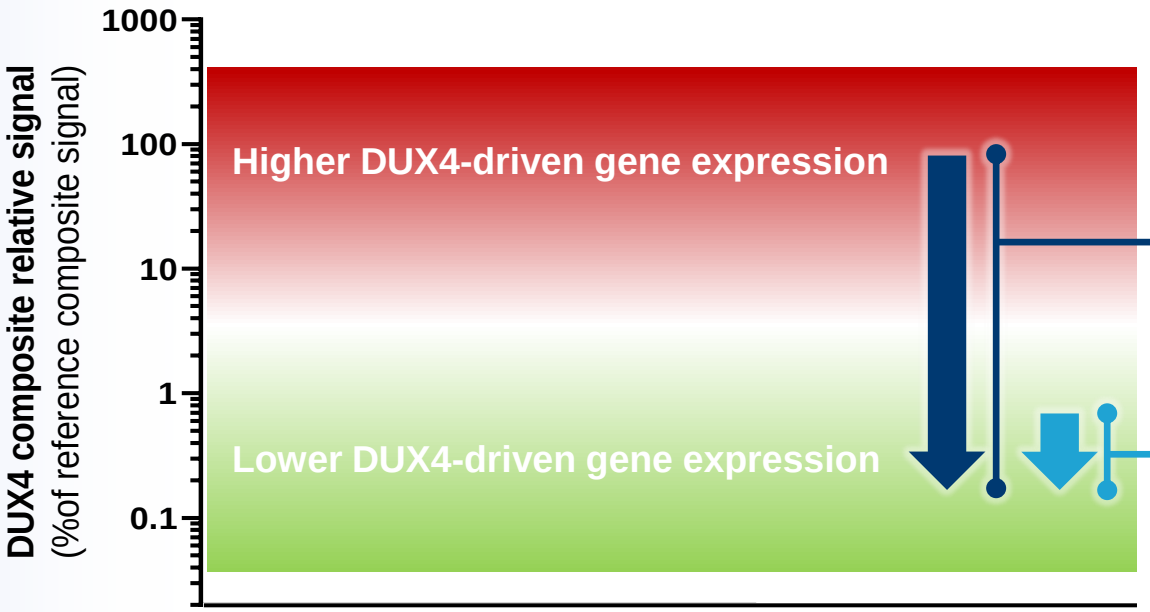
All preclinical data conducted in patient-derived cell lines had higher baseline DUX4-driven gene expression

Lower DUX4-driven gene expression

IA measured 6 DUX4 transcripts, with 24 additional muscle health transcripts to be evaluated

Note: Data from from both Fulcrum and academic FSHD clinical studies

Observing a Reduction in DUX4-driven Gene Expression May Require Higher Range of Baseline Expression



Higher baseline has greater dynamic range to observe a reduction

Lower baseline has small dynamic range to observe a reduction

- **Phase 2 OLS trial helped inform pre-specified sensitivity analysis of ReDUX4 IA**
- **Pre-specified sensitivity analysis was included in the IA to evaluate treatment effects on DUX4-driven gene expression in muscle biopsies with the highest baseline level of DUX4-driven gene expression**

Phase 2b ReDUX4 Trial Interim Analysis

- **Interim analysis of DUX4-driven gene expression on first 29 randomized subjects**
  - Change from baseline in DUX4-driven gene expression signature in 29 subjects who had 16-week biopsy
- **Study remains blinded**
  - Individual patient data not available
- **All subjects eligible to rollover to OLE**
- **Not powered for statistical significance**
- **A pre-specified sensitivity analysis was included to evaluate treatment effects on muscle biopsies with the highest baseline DUX4-driven gene expression**

Topline data of DUX4-driven gene expression and MRI expected Q1 2021 and full data (including functional data) expected Q2 2021

Phase 2b ReDUX4 Trial Interim Analysis Subject Demographics

	Losmapimod 15 mg BID (N=15)	Placebo BID (N=14)	Total (N=29)
Age (Years)			
N	15	14	29
Mean (SD)	45.6 (15.88)	46.9 (13.98)	46.2 (14.74)
Median	53.0	52.5	53.0
Min, Max	20, 65	21, 62	20, 65
Sex n (%)			
Male	11 (73.3)	8 (57.1)	19 (65.5)
Female	4 (26.7)	6 (42.9)	10 (34.5)
Race n (%)			
White	12 (80.0)	13 (92.9)	25 (86.2)
African American	0	0	0
Asian	2 (13.3)	0	2 (6.9)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (6.7)	0	0
Not Applicable	0	0	0
Missing	0	1 (7.1)	1 (3.4)

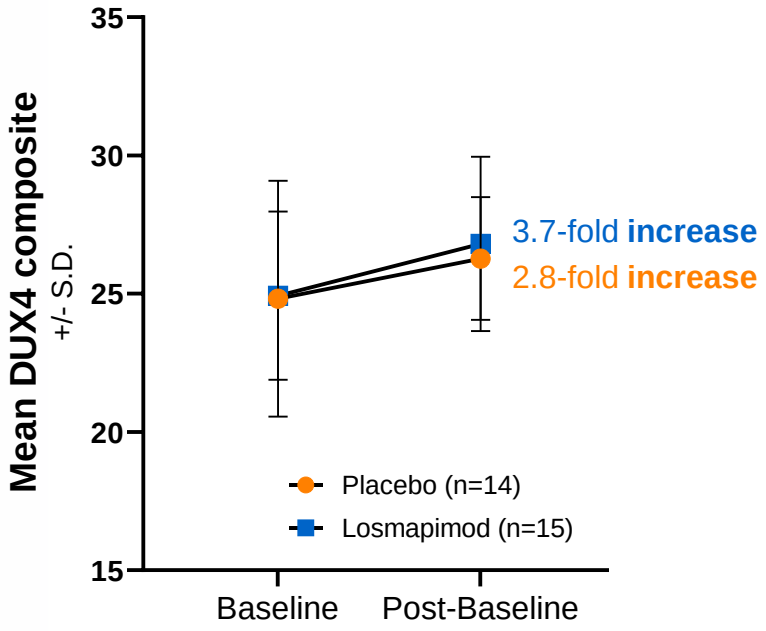
- **In losmapimod treated subjects, mean/median drug concentration was >100 nM in muscle**
- **No drug-related SAEs to date**

Results of Interim Analysis of Primary Endpoint (Linear Scale)

Large reduction observed with losmapimod treatment in highest expressing muscle biopsies

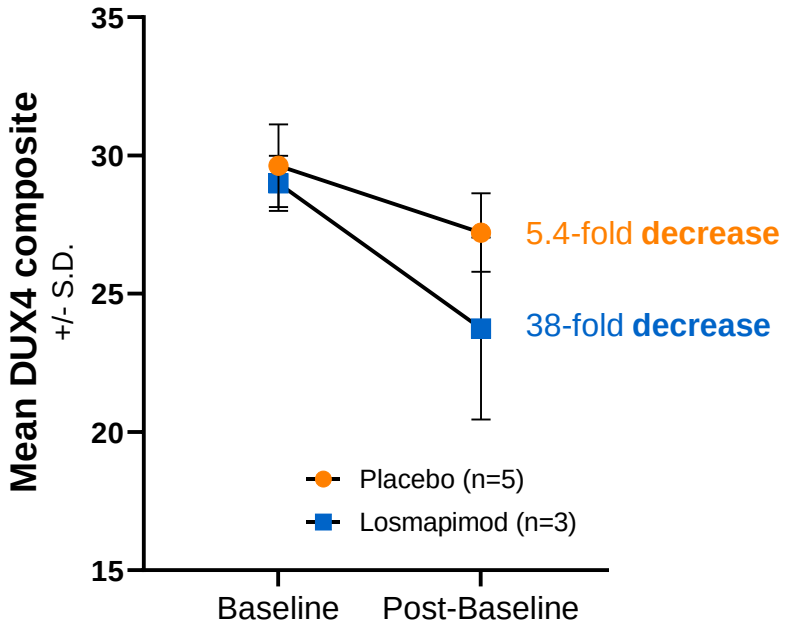
Observed a 38-fold reduction in losmapimod arm and 5.4-fold reduction in placebo treated arm

IA Results
(All muscle biopsies)



Data from IA is displayed as inverted ΔCT values (relative to housekeeping gene)

IA Results
(Highest Expressing Muscle Biopsies)



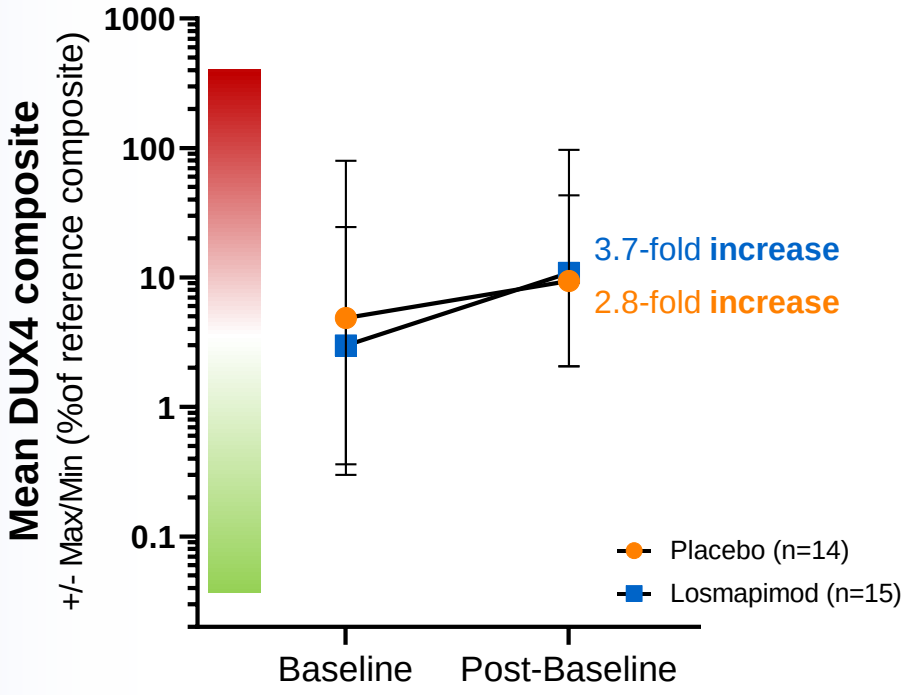
Highest expressing muscle biopsies represent the top quartile of biopsies assessed for baseline DUX4-driven gene expression

Results of Interim Analysis of Primary Endpoint (Log_{10} Scale)

Large reduction observed with losmapimod treatment in highest expressing muscle biopsies

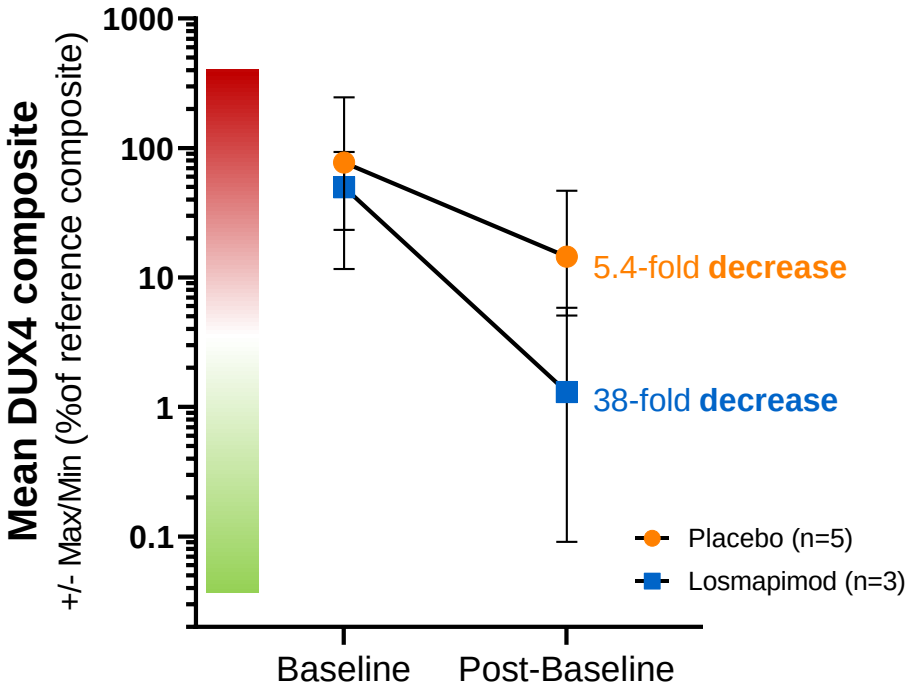
Observed a 38-fold reduction in losmapimod arm and 5.4-fold reduction in placebo treated arm

IA Results
(All muscle biopsies)



Data from IA is displayed as inverted ΔCT values (relative to housekeeping gene)

IA Results
(Highest Expressing Muscle Biopsies)



Highest expressing muscle biopsies represent the top quartile of biopsies assessed for baseline DUX4-driven gene expression

ReDUX4 Interim Analysis Key Highlights

- **Due to COVID-19, amended ReDUX4 that extended trial from 24 to 48 weeks**
  - Introduced 16-week IA on initial 29 randomized subjects
- **Encouraging IA data suggests losmapimod may be reducing DUX4 driven gene expression, the root cause of FSHD**
  - Observed a 38-fold reduction in losmapimod arm and 5.4-fold reduction in placebo treated arm in highest expressing muscle biopsies
  - Separation from placebo in the total population was not observed
  - Muscle biopsies with higher DUX4-driven gene expression at baseline may be needed to observe a reduction
  - We believe that all FSHD patients have muscles with high baseline DUX4-driven gene expression, and that losmapimod has the potential to offer a benefit to all FSHD patients
- **Interim analysis data is consistent with limited initial data from Open Label Study (OLS)**
  - Highest expressing biopsies demonstrated reduction of DUX4-driven gene expression

Next Steps

- **Anticipate topline data from ReDUX4 in Q1 2021 and full data in Q2 2021**
  - Topline data expected to include analyses of DUX4 gene signature and MRI
- **Obtain and analyze additional data, validate key insights, and gain increased understanding of muscle health from ongoing studies**
  - IA measured 6 DUX4 transcripts, with 24 additional muscle health transcripts to be evaluated
- **Further leverage Open Label study**
  - Obtain and analyze additional biopsy data from OLS as well as additional clinical readouts from OLS, pending regulatory approvals
  - Evaluate the long-term effects of losmapimod in additional FSHD subjects receiving losmapimod for 48 weeks, as in ReDUX4

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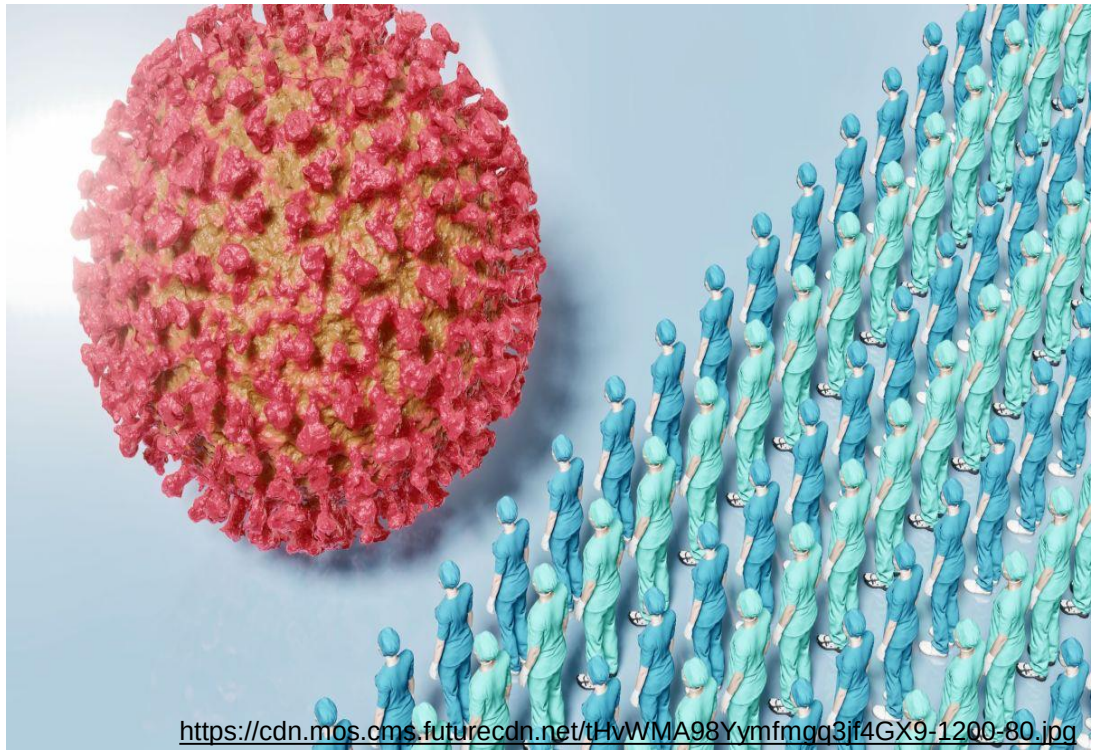
COVID Program

Losmapimod for COVID-19

Potential to transform COVID-19 into a milder and treatable disease

- **Solid scientific rationale**
  - p38 MAPK pathway plays a key role in severe viral infections, including COVID-19
  - Losmapimod could impact multiple components of the disease and prevent COVID-19 morbidity and mortality
  - Previous losmapimod clinical data demonstrate potential activity against pathogenic processes in COVID-19
- **Extensively studied (>3600 subjects), generally safe and well-tolerated in previous clinical studies**
- **Oral administration, rapid drug absorption**
- **IND in effect, Initiate Phase 3 Q3 2020**


https://cdn.mos.cms.futurecdn.net/tHvWMA98Ymfmgq3jf4GX9-1200-80.jpg

Phase 3 LOSVID Trial (n=~400)

Randomized, double-blind, placebo-controlled multi-center trial in hospitalized COVID-19 subjects when administered concurrently with standard of care

- ~400 subjects randomized 1:1 to 15mg PO BID losmapimod or placebo for 14 days on top of standard of care
- Received IRB approval
- ~21 sites across 5 countries in the U.S., Mexico, and South America
- Interim analysis for futility and sample size re-estimation by independent DMC **(anticipated Q4 2020)**

- **Primary endpoint:**
  - Proportion of progressors to critical illness, defined as death or respiratory failure (severe hypoxia) by day 28
- **Secondary endpoints:**
  - Clinical Status on Days 7 and 14 as measured on the 9-point WHO ordinal scale
  - Total number of study days free of oxygen supplementation
  - Length of hospitalization and ICU stay
  - Percentage of subjects discharged from the hospital by days 14 and 28
  - All-cause mortality
  - Frequency and severity of AEs
  - Viral Clearance

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Hemoglobinopathies Program

Hemoglobinopathies: The Fulcrum Product Engine at Work

Hemoglobinopathies Strategy:

Induce expression of fetal hemoglobin (HbF) to compensate for the mutated adult hemoglobin in SCD and β-thalassemia

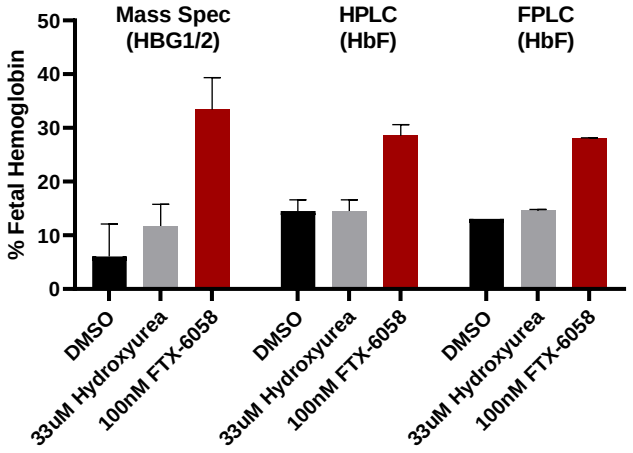
FTX-6058 Molecular Innovation

- Potent, efficacious & selective molecule with clean off-target profile
- Optimized drug-like properties for oral, QD dosing
- Superior preclinical activity relative to SOC and competitor compounds
- Nonprovisional composition of matter patent application filed
- 28-day GLP toxicology studies completed and GMP material scale-up for Phase 1 is complete
- **IND filing expected - Q3 2020 and initiation of Phase 1 - Q4 2020**

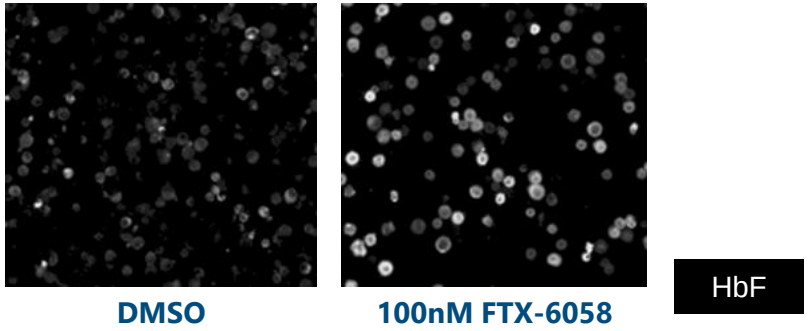
FTX-6058 Therapeutic Innovation

- Increased HBG gene and HbF protein expression in an SCD mouse model (Townes mouse)
- Clinically desirable globin profile (e.g., % HbF) in differentiated CD34+ cells from multiple healthy and SCD donors
- Pancellular HbF protein induction
- Demonstrated comparable *in vitro* profile to gene editing, but with advantages of small molecule therapy

FTX-6058 increased HbF in CD34+ cells using multiple quantification methods



FTX-6058 induced pan-cellular increase in HbF expression in CD34+ donor cells



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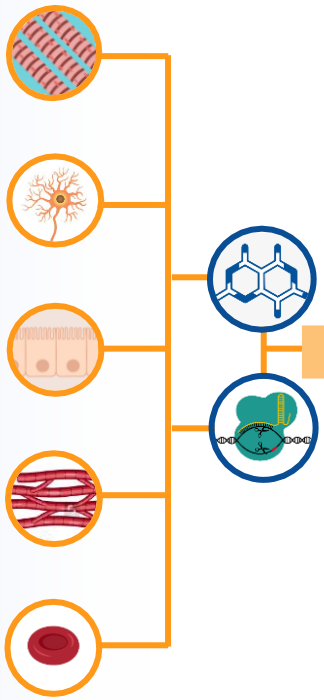
Research Program Updates

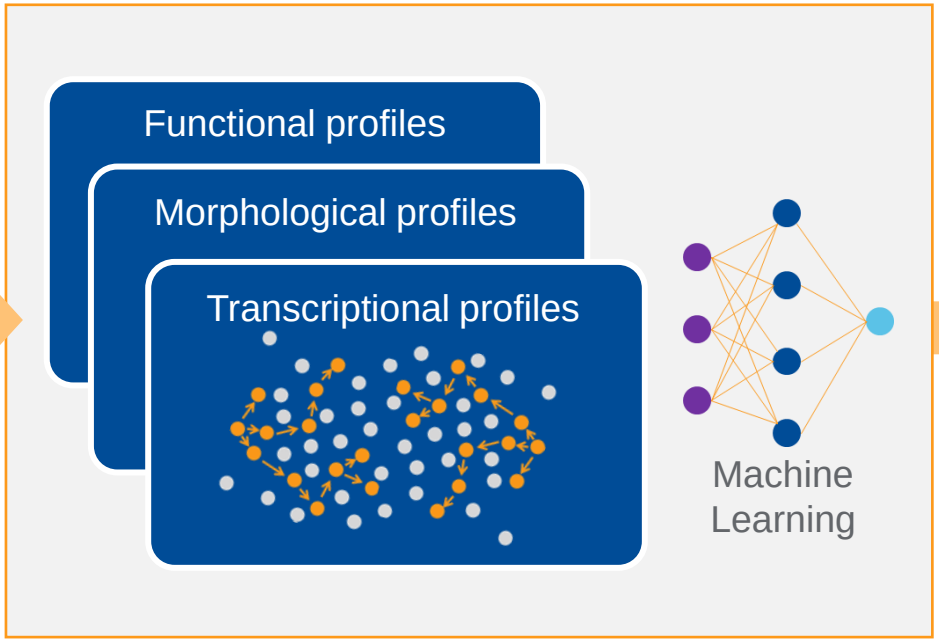
FulcrumSeek Screening

Intelligent drug discovery in disease relevant models through high dimensional data and machine learning

Discovery Engine



Computational Engine



Proprietary datasets in relevant cellular models that recapitulate tissue and disease biology

Accelerated Drug Discovery Programs

- Targets with desired profile of **specificity, selectivity and tolerability**
- Identification of tissue-relevant **translatable biomarkers**
- Characterization of lead candidates to understand **potential issues (toxicity or off-target activity)**

Data-rich target hypotheses and clinical candidates

Cardiomyopathy Research and Discovery Collaboration

Fulcrum eligible to receive >$400M in milestone payments + upfront and R&D reimbursement

Fulcrum Therapeutics / MYOKARDIA

Financial Terms	▪ Fulcrum receives $12.5M at the close of the transaction & MyoKardia to reimburse all relevant research expenses ▪ Fulcrum eligible to receive: – Research, development and commercial milestone payments and additional research reimbursement of up to $298.5 million for a first product – Up to $150M in milestone payments if MyoKardia chooses to develop and commercialize any additional targets – Tiered royalty payments on net sales ranging from mid-single to low double-digits
Transaction Overview	▪ Research collaboration & license agreement to identify therapeutic targets that modulate genes associated with genetically defined cardiomyopathies – Fulcrum to utilize its proprietary product engine to identify therapeutic targets that control the expression of genes at the root cause of genetically defined cardiomyopathies – MyoKardia responsible for all development & commercialization activities for any potential therapeutics identified

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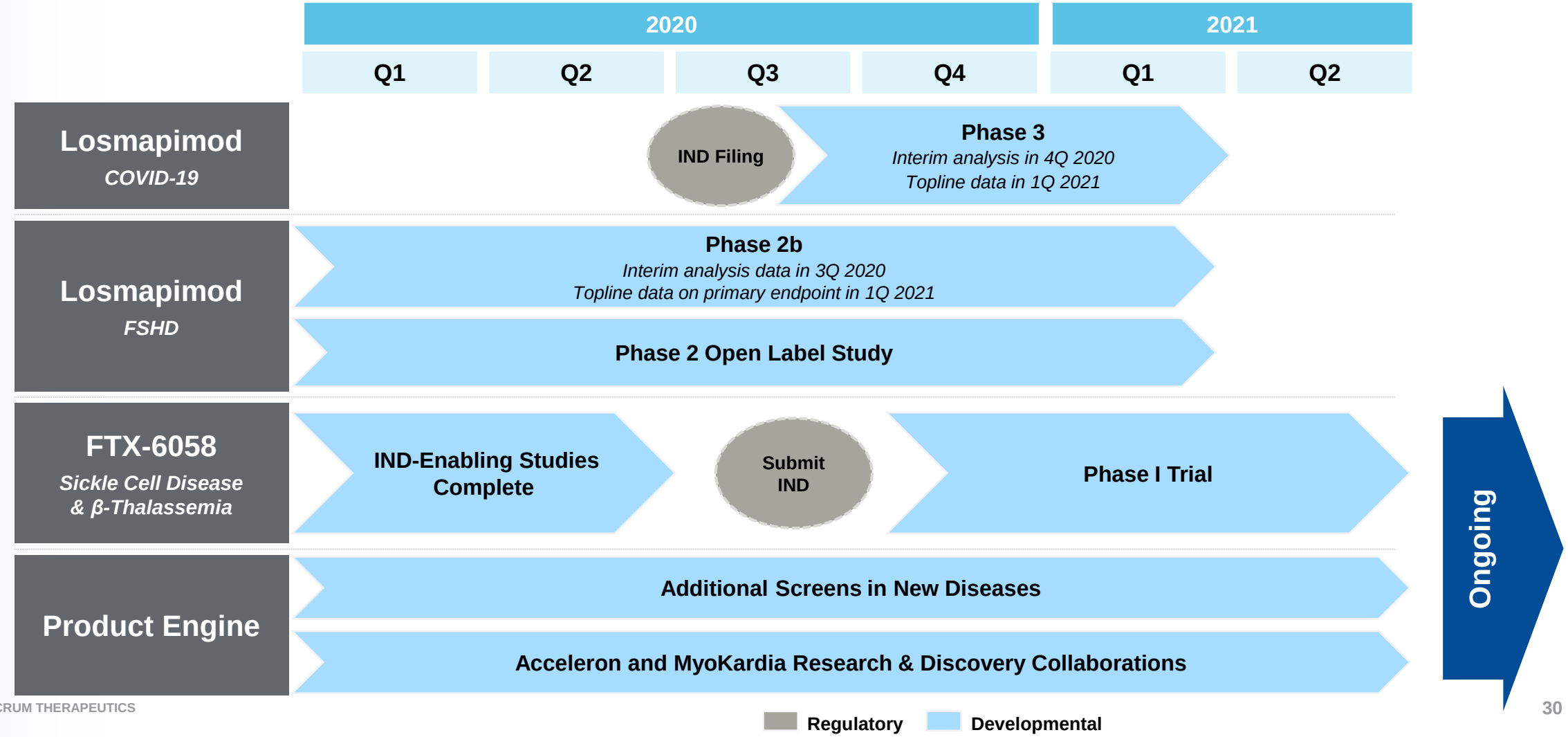
Financial Results

Second Quarter 2020 Financial Results

- **Ended the second quarter of 2020 with $131.7M in cash, cash equivalents, and marketable securities**
  - This does not include the $12.5M we received from MyoKardia since the close of the quarter
- **Based on our current operating plans and projections as well as the $12.5M we received from MyoKardia, we expect our cash position will be sufficient to fund operating expenses and capital expenditures into Q1 2022**
- **Research and development expenses were $12.8 million for the second quarter of 2020, as compared to $10.9 million for the second quarter of 2019**
  - Increase of $1.9M was primarily due to increased personnel-related costs to support growth of Fulcrum's R&D organization, as well as increased costs related to advancing losmapimod for the treatment of FSHD and
- **General and administrative expenses were $5.1 million for the second quarter of 2020, as compared to $2.6 million for the second quarter of 2019**
  - The increase of $2.5 million was primarily due to increased costs associated with operating as a public company, as well as increased personnel-related costs to support the growth of our organization
- **Net loss was $15.7 million for the second quarter of 2020, as compared to a net loss of $13.2 million for the second quarter of 2019**

Anticipated Milestones

Cash runway into Q1 2022



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Q&A