Fulcrum Therapeutics

J.P. Morgan Presentation

January 2023

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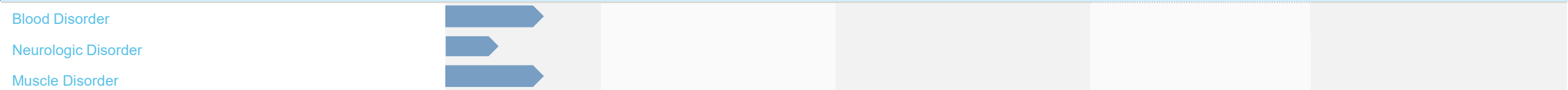
Unlocking the Power of Small Molecules to Change the Course of Genetically Defined Diseases

Two Wholly Owned Clinical Programs

Wholly Owned Discovery Programs



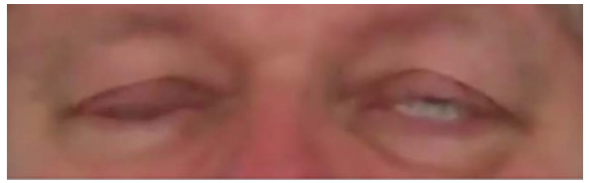
Losmapimod

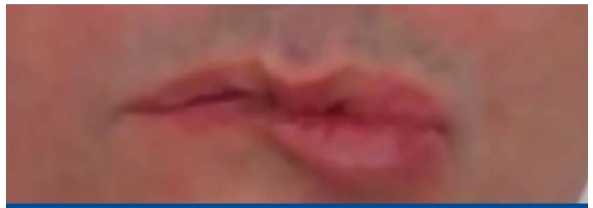
for Facioscapulohumeral Muscular Dystrophy (FSHD)

Fast Track Designation

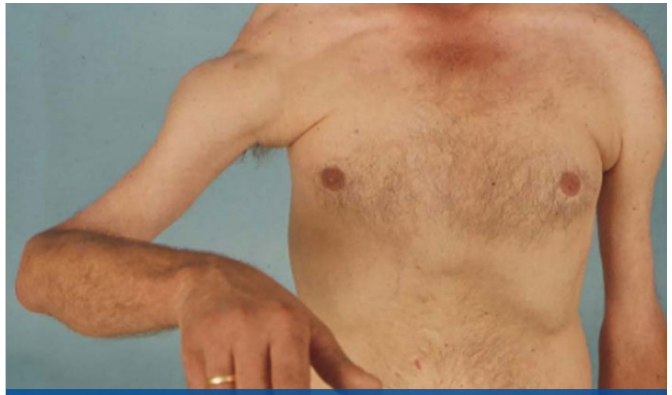
Orphan Drug Designation

FSHD: Debilitating Disease with No Approved Therapies

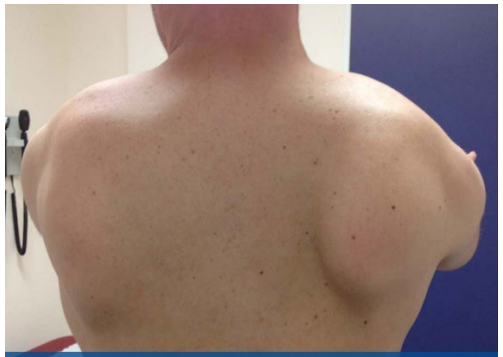




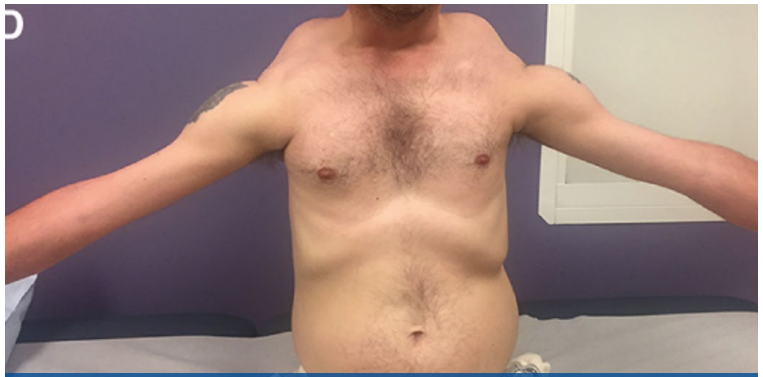
Facial weakness



Wasting of muscles in chest, shoulders, and upper arms; Protuberant abdomen



Scapular winging



Impaired ability to raise arms caused by scapular elevation

Wheelchair dependence

Implementing Innovative Clinical Outcome Measures and Metrics

Reachable Workspace (RWS):

Measure of disease progression

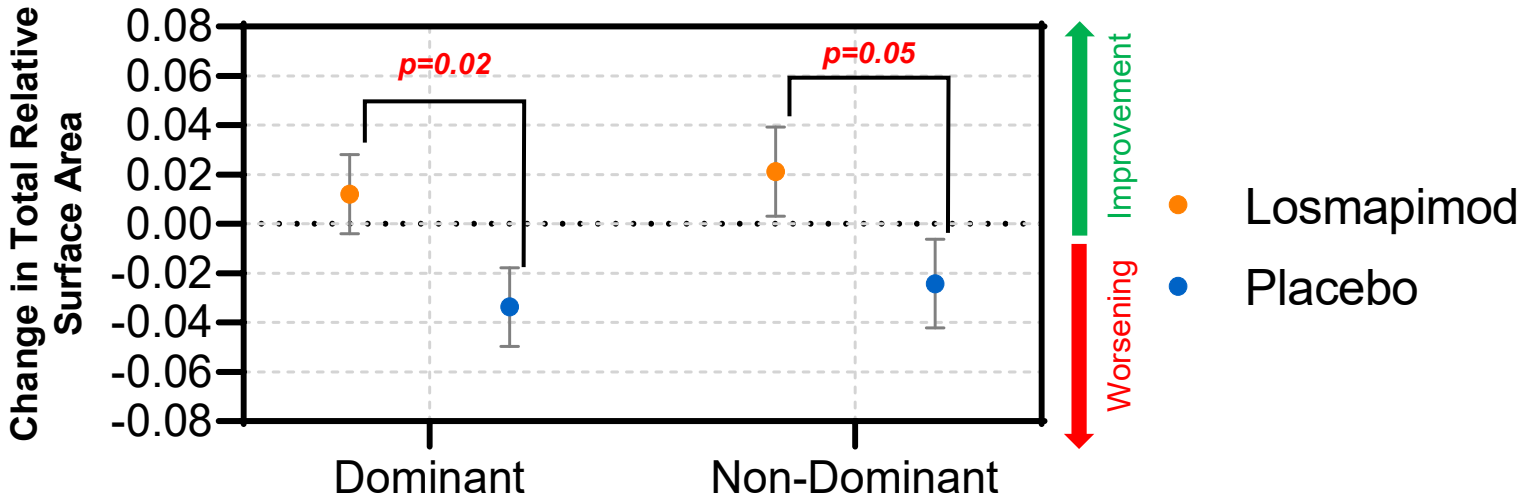
Muscle Fat Infiltration (MFI):

Measure of muscle health

Quantifying disease progression is a key focus

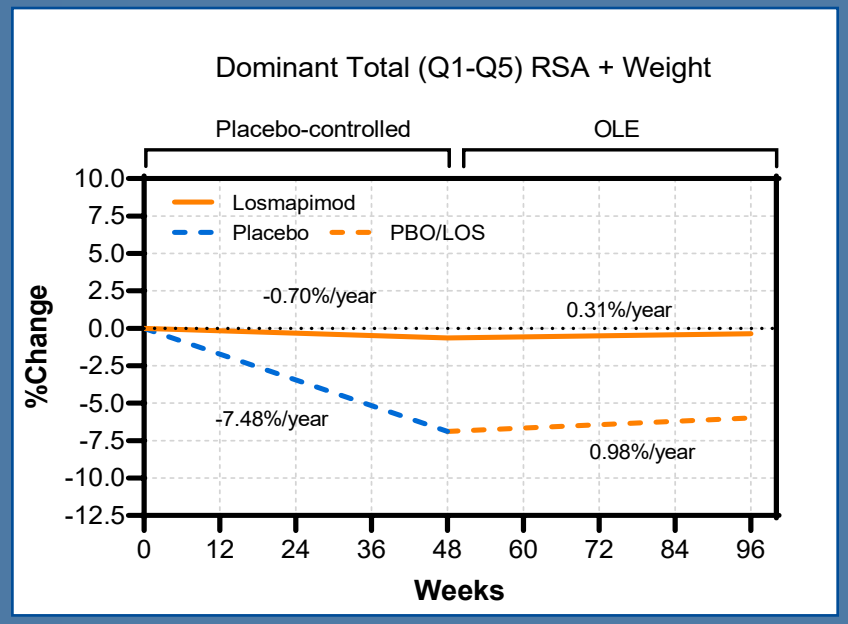
Losmapimod Demonstrated Significant Improvement in RWS Relative to Placebo at 48 Weeks

Reachable Workspace using 500 g Weight at 48 weeks

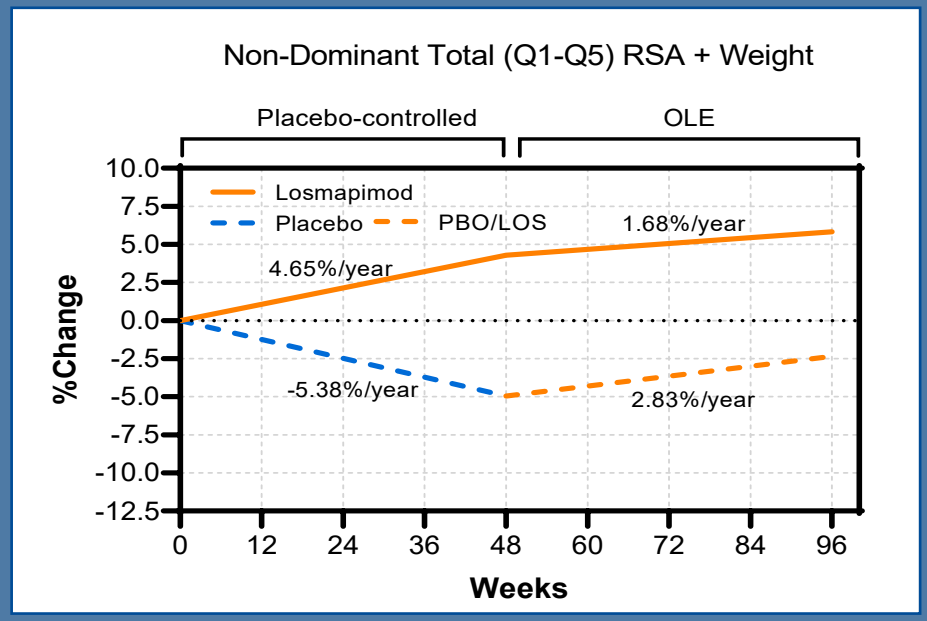


96-week OLE Results Demonstrate Durability of Effect in Treatment Arm and Stabilization in Cross-over Arm

Dominant Total (Q1-Q5) RSA+ Weight



Non-Dominant Total (Q1-Q5) RSA+ Weight



Phase 3 trial enrollment ongoing, plan to complete enrollment in 2H 2023

NCT04264442: Efficacy and Safety of Losmapimod in Treating Subjects With Facioscapulohumeral Muscular Dystrophy (FSHD) With Open-Label Extension (OLE)

FTX-6058

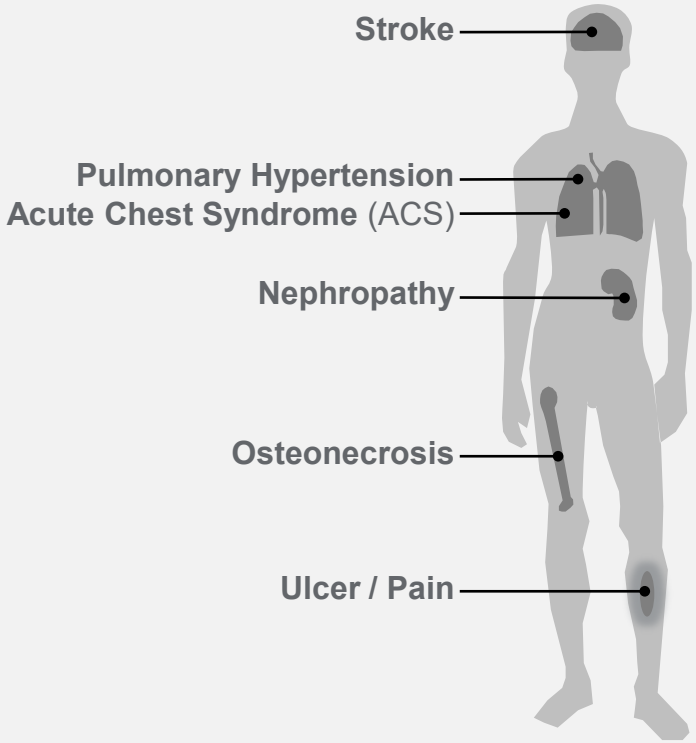
for Sickle Cell Disease

Fast Track Designation

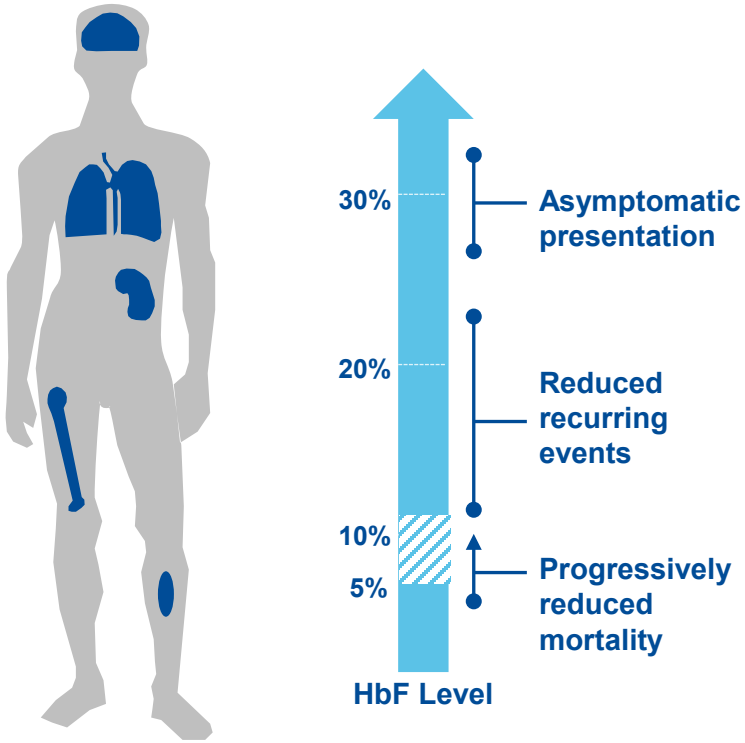
Orphan Pediatric Designation

Higher HbF Levels Result in Reduced Symptomology in People Living with Sickle Cell Disease

Even incremental increases in HbF can lead to meaningful improvement in disease severity



Typical SCD Subject



SCD Subject with High HbF Levels

HbF: fetal hemoglobin; VOCs: Vaso-occlusive crisis; HPFH: Hereditary Persistence of Fetal Hemoglobin; *Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.*

FTX-6058: Potential Best-in-Class Therapeutic Profile

HbF Induction

Hydroxyurea
Gene Editing
FTX-6058

Physiologic
Disease
Modification

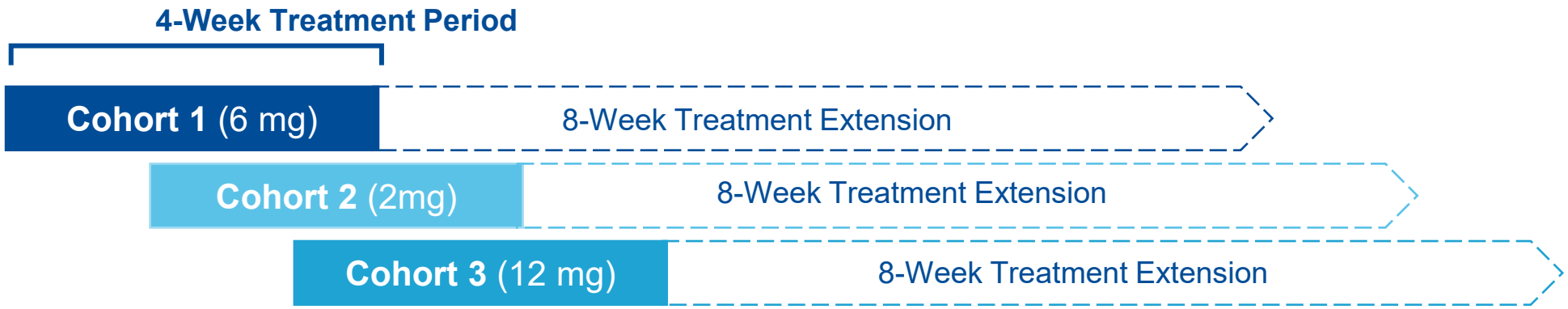
FTX-6058

- Raises HbF level
- Potential to ameliorate disease pathology
- Convenient oral dosing
- Potential to differentiate on safety and tolerability

Ongoing Phase 1b Clinical Trial in SCD Subjects

Study Design

Subjects with SCD, Age 18 – 65, on or off hydroxyurea
(if on HU, must have been on stable dose for 3 months, if not on HU, must have been off for 60 days)



Study Endpoints

Primary

- Safety and tolerability
- Pharmacokinetic measurements

Secondary

- Change from baseline in HbF
- Change from baseline in reticulocytes

Exploratory

- Biomarkers of hemolysis
- Target engagement
- Incidence of VOCs
- QOL measures

SCD Phase 1b Demographics

- 2 subjects at 2 mg
- 10 subjects at 6mg
- 8.4% mean baseline HbF
- 3 subjects at 6mg on Hydroxyurea

Overall FTX-6058 Was Generally Well Tolerated

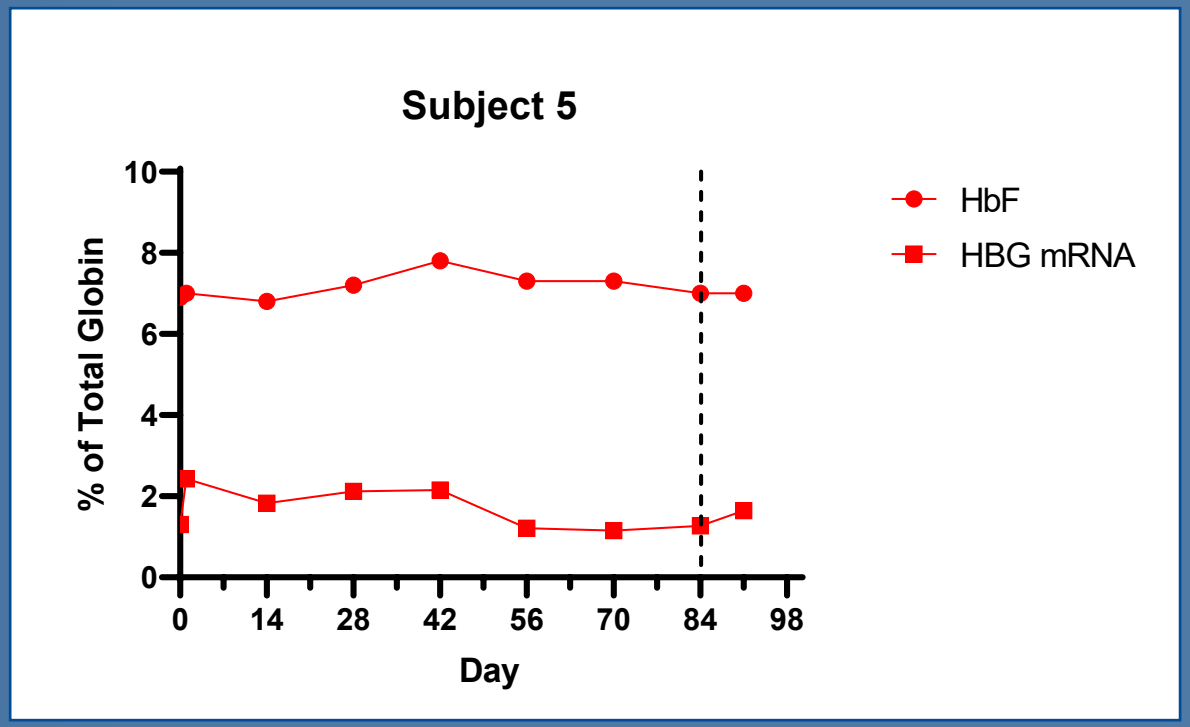
- 14 Treatment-emergent Adverse Events (TEAEs)
  - 2/14 TEAEs reported as possibly related to study drug (headache, lip numbness)
  - Mild severity and non-serious
- 2/14 TEAEs characterized as VOCs unrelated to study drug
  - One VOC reported as an SAE with acute chest syndrome (in non-adherent subject)
- No lab-related adverse events
- No discontinuations due to TEAEs

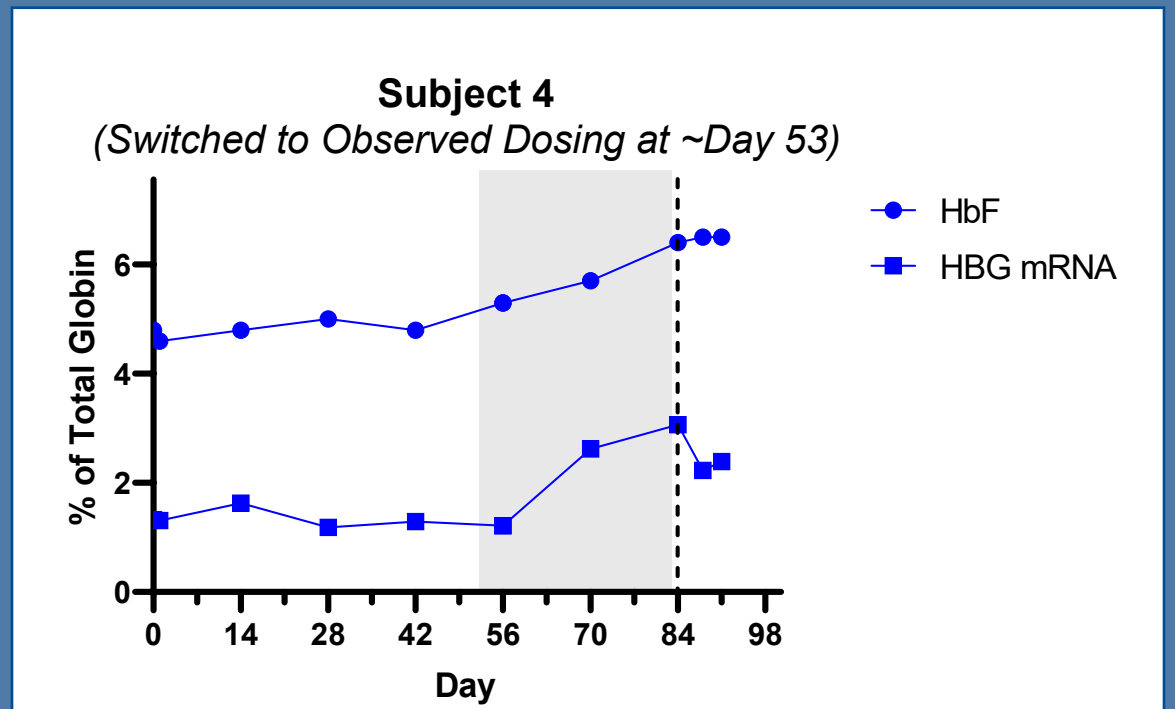
Instituted Observed Dosing and On-Treatment Analysis Following Initial Non-Adherence

Subject	Dose	Confirmed treatment duration (days)	On-treatment analysis eligible[+]
1	6 mg	56	✔
2	6 mg	42	✔
3	6 mg	42	✔
4*	6 mg	0	
5	6 mg	0	
6	6 mg	0	
7**	6 mg	84	✔
8	6 mg	84	✔
9**	6 mg	28	✔
10**	6 mg	28	✔
11	2 mg	56 (ongoing)	✔
12	2 mg	56 (ongoing)	✔

* Subject #4 initiated observed dosing on day 53
** Subjects concurrently receiving hydroxyurea
[+] On-treatment analysis eligible requires Detectable Drug Levels (PK) and drug accountability/subject interview
Confirmed treatment duration days are consecutive days of dosing starting on first day of dosing
Shading indicates subjects enrolled after observed dosing initiated

Non-Adherent Subject Switched to Observed Dosing Demonstrated HbF Induction

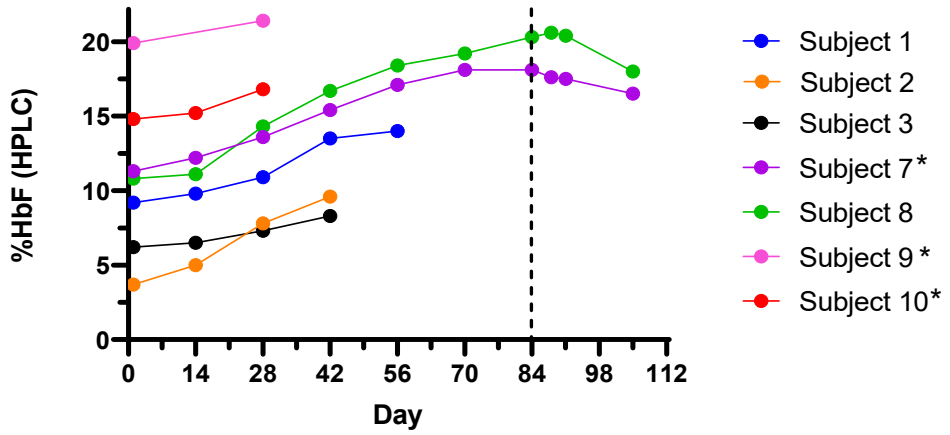


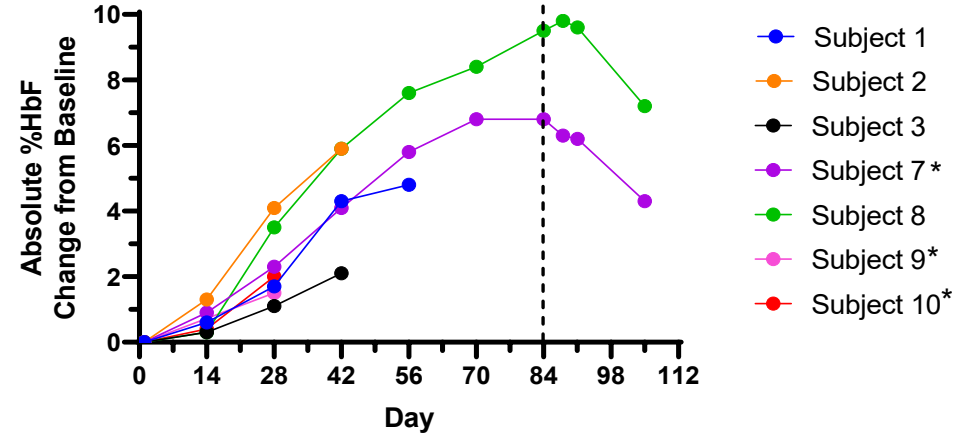


Subjects were not included in the on-treatment analysis
----- Represents last dose

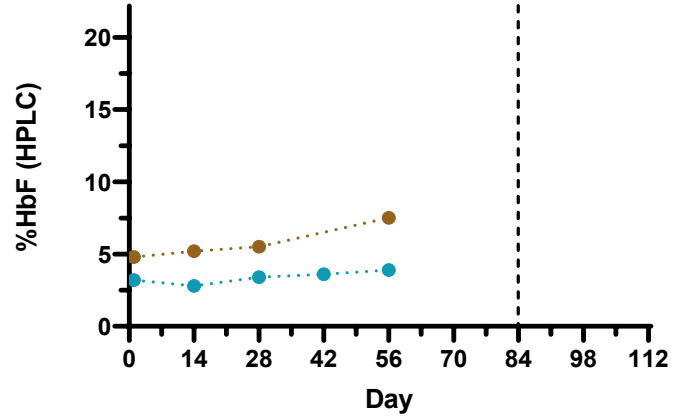
FTX-6058 Appears to Have a Dose Dependent, Clinically Relevant and Consistent Increase in HbF

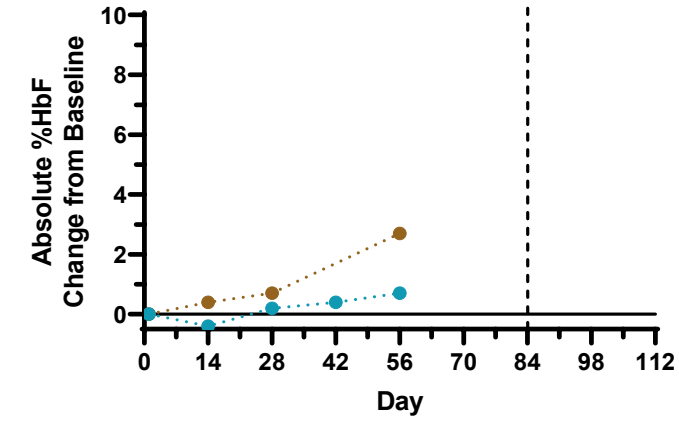
6 mg





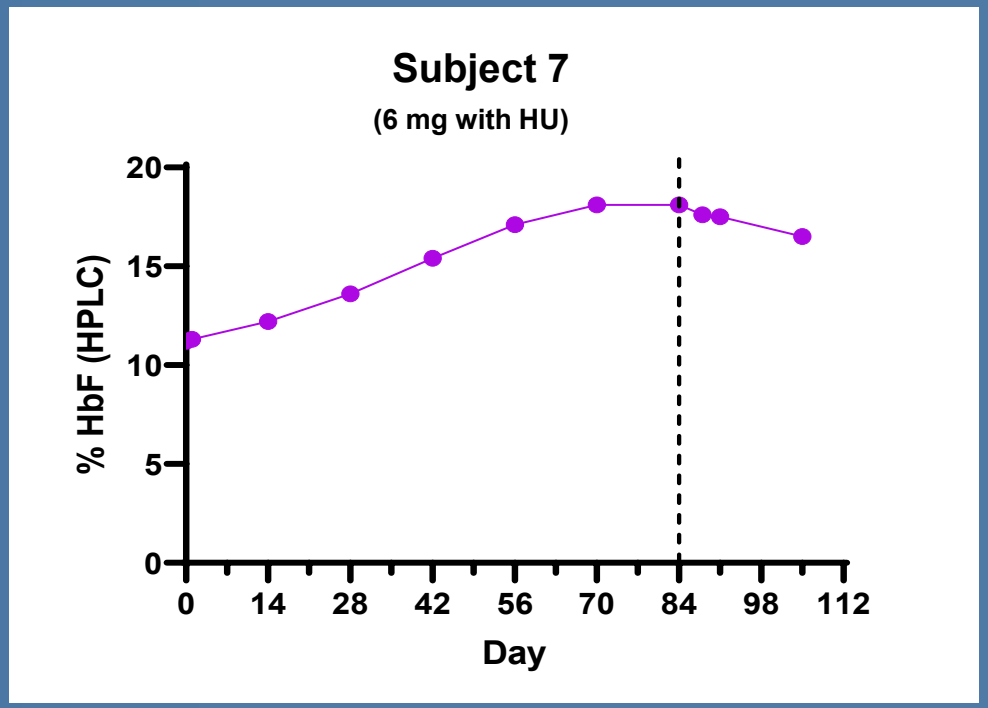
2 mg (ongoing)

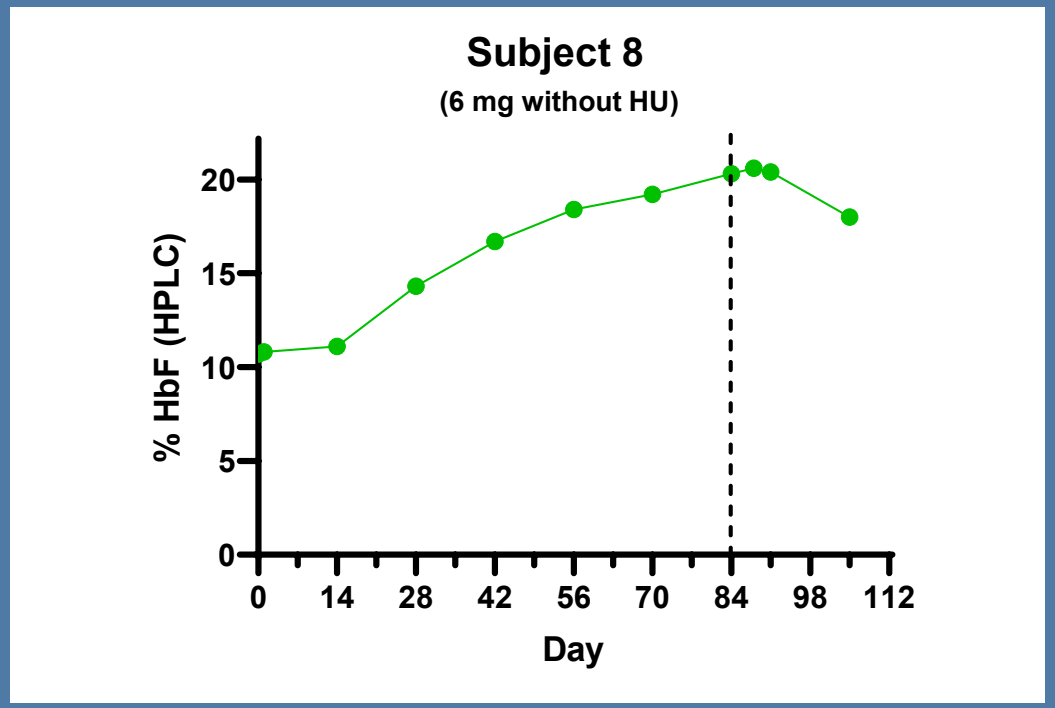




----- Represents last dose
* Subjects also on hydroxyurea

Adherent Subjects, On and Off Hydroxyurea, Reach Robust HbF Increases





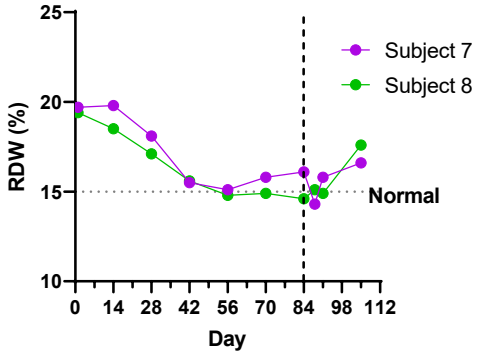
HbF increase was robust (6.8%-9.5%) at day 84
No apparent response differences in HU vs non-HU treated subjects
Potential for further HbF induction beyond 3 months
Observed dosing was used to ensure adherence

----- Represents last dose

FTX-6058 (6 mg) Improved Biomarkers of Hemolysis

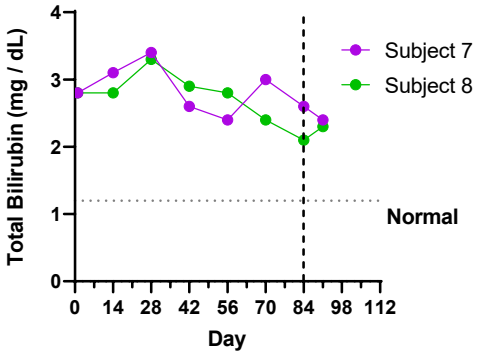
Hemolysis Impact

Red Cell Distribution Width



Reductions in RDW indicate RBCs are becoming more uniform in shape

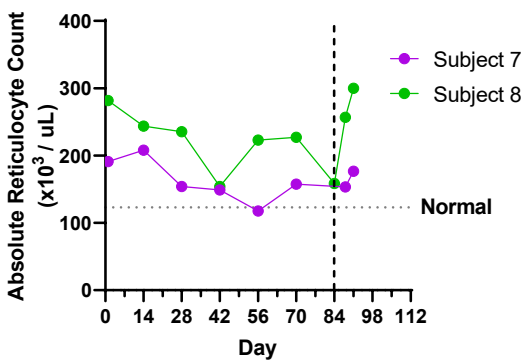
Total Bilirubin



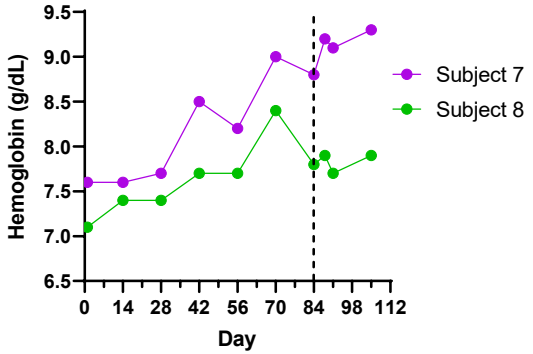
Bilirubin decreases indicate less hemolysis

Amelioration of Anemia

Absolute Reticulocyte Count



Total Hemoglobin



Reductions in reticulocytes and increases in total hemoglobin indicate less anemia and healthier bone marrow function

----- Represents last dose
RDW: red cell distribution width

Next Steps:
Complete Phase 1b to Enable Registration Dose Selection

Amend Protocol and Increase Number of Sites:
Streamline PK Collection and Reduce Patient Burden

Accelerate Enrollment

Optimize Treatment Effect:
Continue Dose Escalation to 12 mg

Completion of Phase 1b

Refine PK / PD Model:
Select Optimal Therapeutic Dose

Final Dose for Pivotal Trial

Diversified, Differentiated Pipeline of Clinical Assets

Losmapimod:
Complete enrollment in REACH Phase 3 in 2H 2023

Positions losmapimod to be first-to-market for patients living with FSHD

FTX-6058:
Complete Phase 1b and select registrational dose in 4Q 2023

FTX-6058 has best-in-class potential

Cash runway through late 2024

Well positioned to deliver on goals