FTX-6058, a novel HbF-inducing agent for the treatment of Sickle Cell Disease and β-Thalassemia

Presented by Christopher Moxham on behalf of:

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Fulcrum Therapeutics, Cambridge MA 02139
Disclosure

All authors are current or former employees and equity holders of Fulcrum Therapeutics.
Fulcrum Overview

Clinical stage biopharmaceutical company using systematic approach to identify small molecules able to rebalance gene expression

- ~7,000 genetically defined diseases today
- We are building on decades of research highlighting gene expression role in disease
- High-throughput product engine designed to rapidly identify and validate drug targets that can modulate gene expression and treat disease at its root cause
- Focus on small molecules as therapeutic modality

Our vision is to treat genetically defined diseases by addressing their root cause
Fetal Hemoglobin Mitigates Mortality and Morbidity Risks Associated with Sickle Cell Disease (SCD)

SCD Patient

- RBC sickling
- VOCs
- Hemolysis
- Stroke
- Pulmonary Hypertension
- Nephropathy
- Osteonecrosis
- Acute Chest Syndrome
- Ulcer / Pain

SCD Patient with High Fetal Hemoglobin (HbF)

- Increased F-cells*
- Reduced VOCs
- Reduced hemolysis

Pancellular HbF Expression and Induction

HbF Level

30%
20%
10%

Asymptomatic presentation
Reduced recurring events (VOCs, ACS, Hospitalization)
Reduced mortality

*F-cells - fetal hemoglobin expressing cells

Preclinical Executive Summary: FTX-6058 for Sickle Cell Disease

• Highly potent (~1 nM) and selective small molecule with clean off-target profile
• Superior pre-clinical activity relative to SOC and competitor compounds
• Potent upregulation of HBG mRNA and pancellular induction of HbF protein in primary human erythroid cells
• Clinically desirable globin profile (e.g., % HbF) in differentiated CD34+ cells from multiple healthy and SCD donors

• PK/Target Engagement relationship established
• Elevation of human fetal hemoglobin mRNA (HBG1), protein (HbF), and F-cells in Townes mouse model of SCD
• 28-day GLP toxicology studies completed, and GMP material scale-up for Phase 1 is complete
• PK and human dose projections support once-daily, oral dosage of FTX-6058
FTX-6058: A Product of Fulcrum Research Laboratories

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

Gene Regulation Drug Targets

Identified Embryonic Ectoderm Development (EED) as a critical regulator of HbF

BCL11A, NuRD, HDACs, LSD1, DNMT1, IKZF1, IKZF3, SPOP

Computational Data Mining
Computationally mined candidate targets

Structure-Based Drug Design

• EED $K_D = 0.163 \text{ nM}$
• PRC2 $IC_{50} < 5 \text{ nM}$
• Highly Selective
• Clean Off-target Profile

FTX-6058
FTX-6058 Displays Robust Increases in HbF and F-cells
Superior in vitro Activity Relative to Other Mechanisms

<table>
<thead>
<tr>
<th>Agent</th>
<th>HbF Elisa</th>
<th>HbF HPLC</th>
<th>%F-cells</th>
<th>HbF/cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>N/A</td>
<td>N/A</td>
<td>59%</td>
<td></td>
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<tr>
<td>FTX-6058</td>
<td></td>
<td>2 – 3 Fold</td>
<td>88%</td>
<td></td>
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<tr>
<td>DNMT inhibitor (5-azacytidine)</td>
<td></td>
<td>1.5 – 2 Fold</td>
<td>77%</td>
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<tr>
<td>G9a inhibitor (EPZ-35544)</td>
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<td>1.5 – 2 Fold</td>
<td>83%</td>
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<tr>
<td>PDE9 inhibitor (PF-04447943 / IMR-687)</td>
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<td>None</td>
<td>72%</td>
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</table>
FTX-6058 Robustly Induces Fetal Hemoglobin in CD34⁺ Cells from Healthy and SCD Donors

- Observe an absolute 8 – 18% increase in HbF upon treatment with FTX-6058, which has the potential to address mortality risk and recurring events in SCD patients
- Small increases in HbF (1 – 5%) have the potential to provide clinical benefits to all SCD patients

Meaningful Target Engagement is Anticipated in Clinic

- Provides Fulcrum a facile way to measure target engagement in peripheral blood

**Target Engagement**

(Bone Marrow)

<table>
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<tr>
<th>Dose Level</th>
<th>TE Marker MFI / Control MFI (as % of Vehicle)</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>0%</td>
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<tr>
<td>1mg/kg</td>
<td>81%</td>
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<tr>
<td>3mg/kg</td>
<td>97%</td>
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<tr>
<td>10mg/kg</td>
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**Target Engagement**

(Blood Monocytes)

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<th>Treatment</th>
<th>TE Marker MFI / Control MFI (as % of Vehicle)</th>
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<tr>
<td>Vehicle</td>
<td></td>
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<tr>
<td>FTX-6058 10mpk/QD</td>
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<td>FTX-6058 5mpk/BID</td>
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WT CD1 mice; 5 days of QD PO treatment
Superior Induction of Human Fetal Hemoglobin mRNA and Protein Versus HU in Townes SCD Mice

Hydroxyurea was administered once daily at 100 mg/kg for 28 days; FTX-6058 was administered twice per day at 5 mg/kg for 28 days

**p<0.01; ***p<0.001
FTX-6058 Selectively Upregulates Fetal Globin, with No Observed Effect on Beta Globin Expression

**In vivo pharmacology**
(Townes SCD mouse model)

Townes mouse model (28 days treatment):
- Hydroxyurea was administered once daily at 100 mg/kg;
- FTX-6058 was administered twice per day at 5 mg/kg

**In vitro pharmacology**
(Human CD34+ cells)

Human primary CD34+ cells (Donor 224):
- CD34+ cells expanded and differentiated for 14 days
- In a two-phase culture system; treated for final 7 days

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### HBG1

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<th>SCD Mice</th>
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<tbody>
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### HBG1/2

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FTX-6058 Has Potential to be Transformative Therapy for SCD

Open IND - Phase 1 in healthy volunteers initiated 4Q2020

- Target identified from Fulcrum Product Engine
- Delivered a potent and selective EED Inhibitor
- Oral, once-daily dosing supported by PK and human dose projections
- Anticipated plasma exposures required to elevate HbF in clinic are predicted to be achievable
- Demonstrates impressive preclinical pharmacological profile to act as disease-modifying therapeutic (See abstracts #789 and #2612)
Thank you!

Additional questions:
Please contact us at info@fulcrumtx.com

fulcrumtx.com