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113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

HbF Inducing Eed Inhibitor Ftx-6058 Selectively and Reversibly Impacts Bone Marrow in Wild-Type Mice

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Sickle cell disease (SCD) is a genetic disorder characterized by red blood cell sickling, hemolysis, vaso-occlusive crises (VOCs), and other complications resulting from a mutation in the HBB gene. Increasing fetal hemoglobin (HbF) levels has shown promise in mitigating disease-related pathophysiology. In individuals with SCD who exhibit hereditary persistence of fetal hemoglobin (HPFH) and have HbF levels ranging from 20% to 30%, a remarkable reduction in symptoms is observed, highlighting the protective effect of increased HbF in SCD.

Preclinical and clinical findings indicate that compounds inhibiting the embryonic ectoderm development (EED) component of polycomb repressive complex 2 (PRC2) leads to elevations in HbF to therapeutic levels. These results suggest the potential for a substantial benefit for individuals living with SCD. To further understand the effects of PRC2 inhibition, this study aims to characterize the onset and reversibility of EED inhibition by FTX-6058.

Results from in vivo studies in wild-type mice demonstrated upregulation of the mouse fetal hemoglobin ortholog mRNA (Hbb-bh1) as well as target engagement in bone marrow though quantification of H3K27 trimethylation during seven days of active dosing of FTX-6058. Target engagement and differential gene expression profiles in the bone marrow subsequently returned to baseline shortly after the dosing period. These findings demonstrate that inhibition of EED through FTX-6058 leads to a minimal, transient impact on the bone marrow in mice, and any transcriptional changes are rapidly reversible following cessation of dosing. A small molecule EED inhibitor has the potential to provide a new treatment for sickle cell disease without irreversibly altering the bone marrow.

Disclosures Fitz: *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Allen:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Edwards:** *Fulcrum Therapeutics:* Current Employment. **Raghunathan:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Steward:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Matson:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Sartain:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Bruno:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Jacobs:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Stuart:** *Fulcrum Therapeutics:* Current Employment, Current equity holder in publicly-traded company.

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