

***In vivo* characterization of FTX-6058, a novel small molecule fetal hemoglobin inducer for sickle cell disease**

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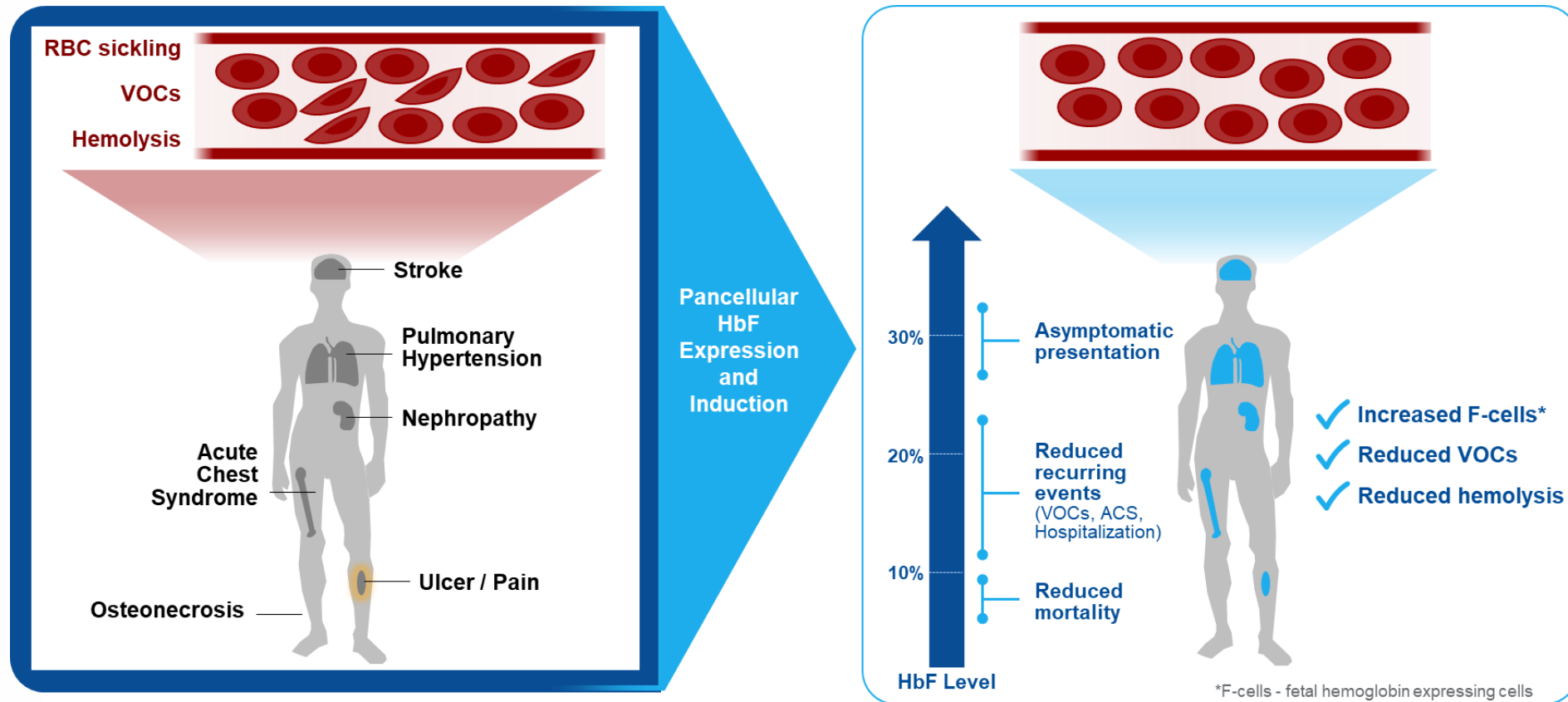
** equal contribution*

Disclosure

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

Therapeutic approach: upregulate fetal hemoglobin to clinically meaningful levels

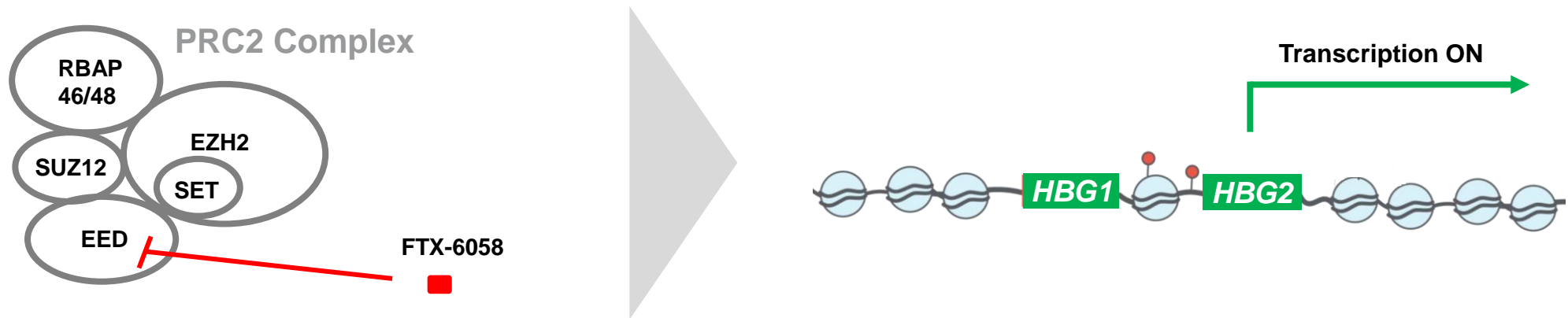
HbF Mitigates Mortality and Morbidity Risks Associated with SCD



- HbF levels are positively correlated with reduced mortality and comorbidity
- Human genetics: Individuals with HPFH (hereditary persistence of fetal hemoglobin, with ~30% HbF level) are devoid of SCD and hemolytic anemia

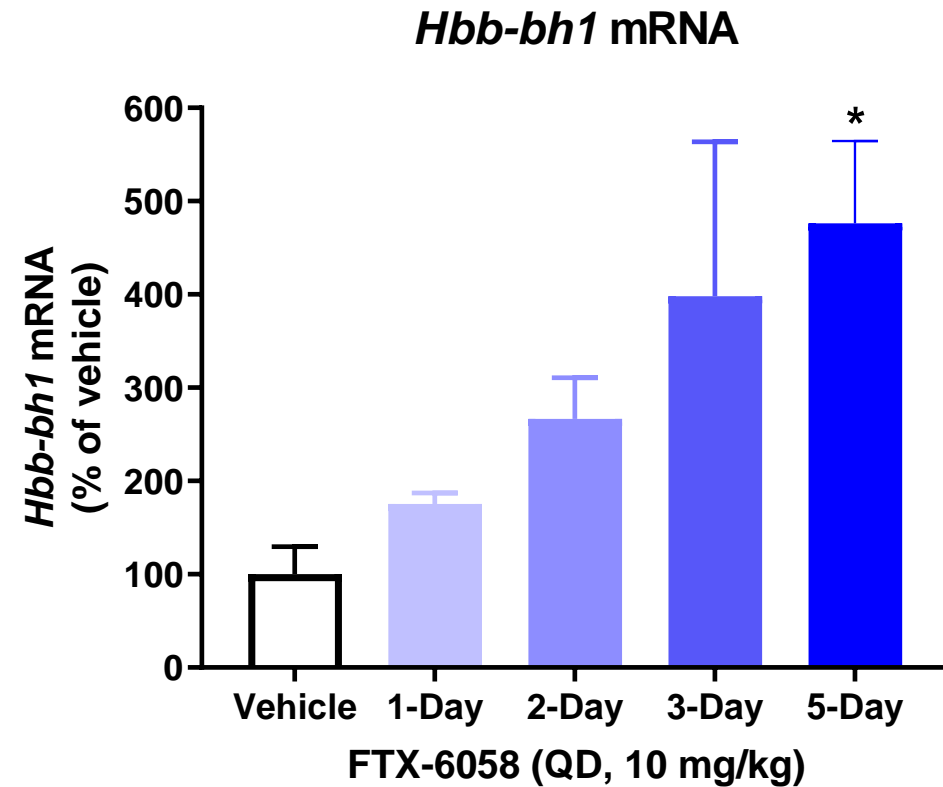
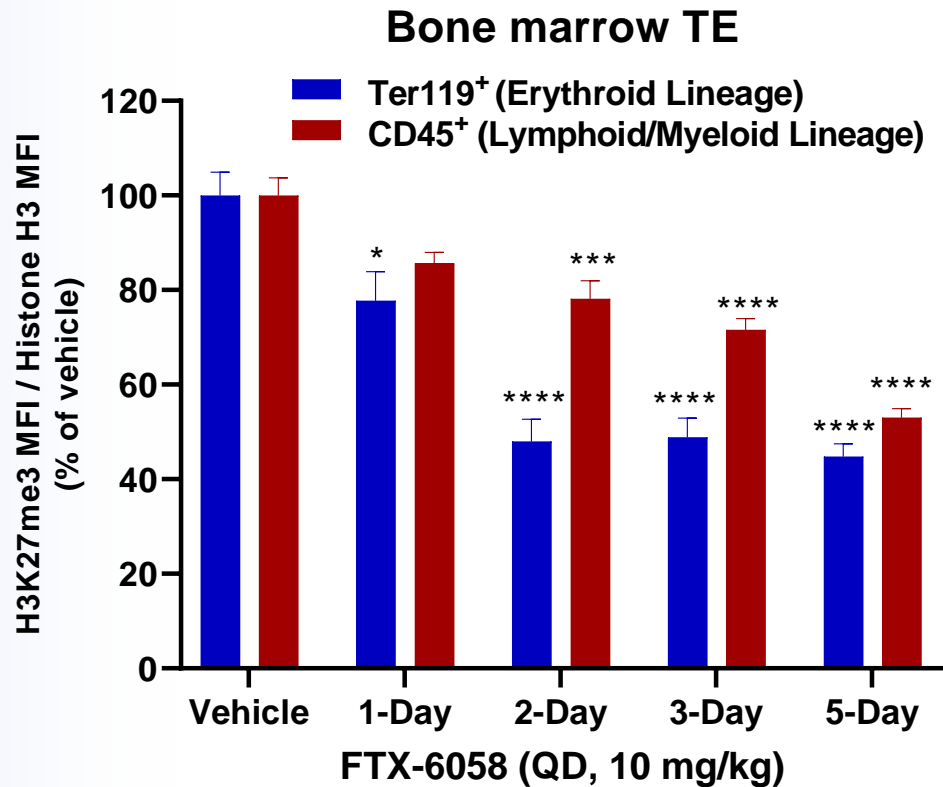
FTX-6058 mechanism of action: inhibition of PRC2 via binding EED

Fetal hemoglobin induction with FTX-6058



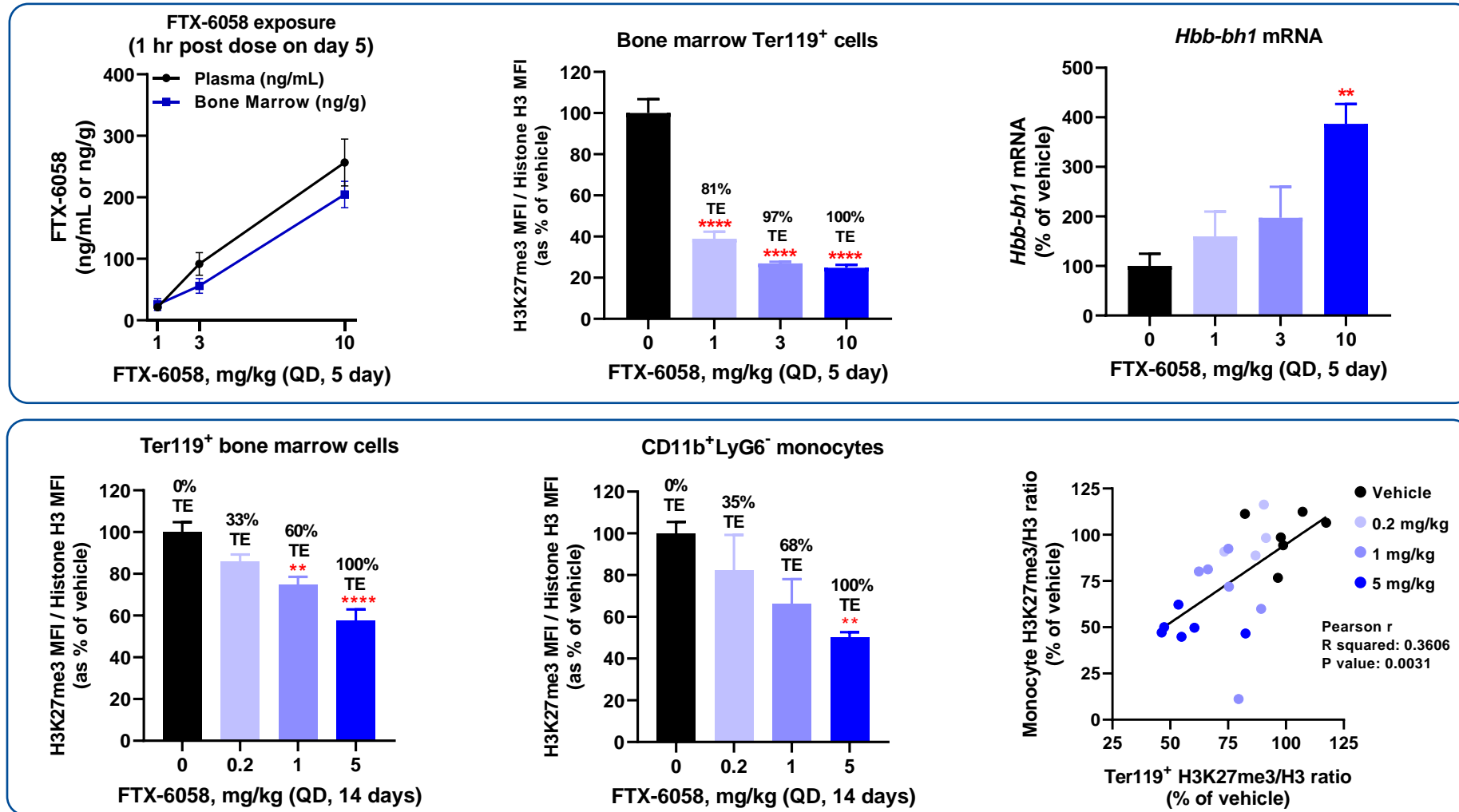
- Polycomb Repressive Complex 2 (PRC2) catalyzes tri-methylation of histone H3 at lysine 27 (H3K27me3), leading to nucleosome compaction and gene transcriptional silencing.
- FTX-6058 selectively binds Embryonic Ectoderm Development (EED), one of 4 core subunits of PRC2, resulting in inhibition of PRC2 activity, thus elevating gene expression (e.g., HBG1/2)
- We believe HbF induction occurring through PRC2 inhibition is likely due to a mechanism that is independent of BCL11A or reduction of H3K27 trimethylation levels at HBG1/2 (i.e., other transcriptional networks)
- FTX-6058 demonstrated on-target activity accompanied by an increase in *HBG* mRNA, as well as pan-cellular induction of fetal hemoglobin (HbF) in primary human CD34+ cells.
- More information can be found in [abstracts #2612](#) and [#1548](#).

Repeated FTX-6058 dosing is required for profound target engagement and transcriptional effect



- FTX-6058 was administered at 10 mg/kg (once daily, by oral) for the indicated consecutive days in WT CD-1 mice
- Target engagement (TE) was assessed in bone marrow cells via FACS; Hemoglobin mRNA was assessed in whole blood via qPCR

Dose-dependent target engagement in bone marrow and surrogate peripheral cells

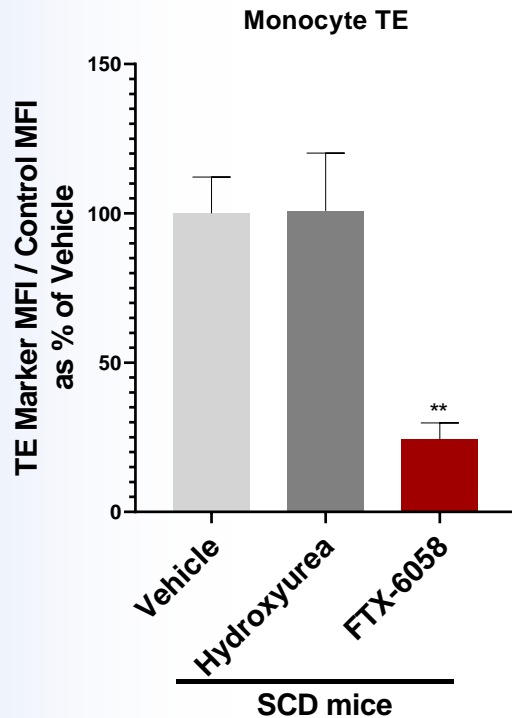


FTX-6058 was administered by oral once daily for the 5 or 14 consecutive days in WT CD-1 mice

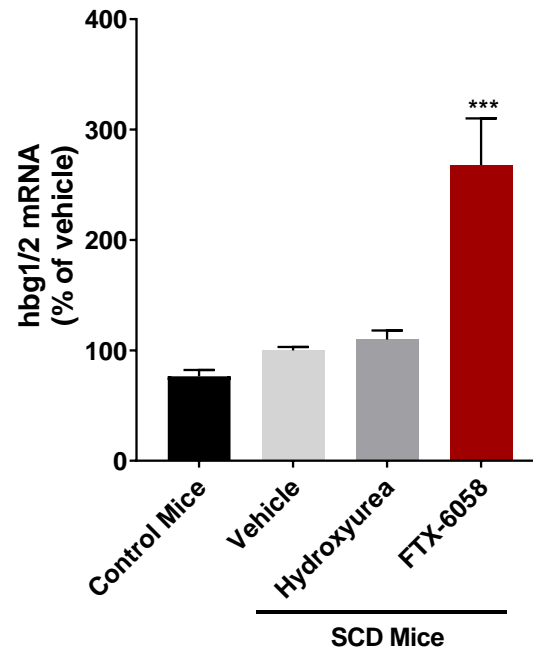
FULCRUM THERAPEUTICS ■ **Peripheral blood provides TE measure that can be translatable to the clinic**

Superior induction of human fetal hemoglobin mRNA and protein vs. hydroxyurea in Townes SCD mice

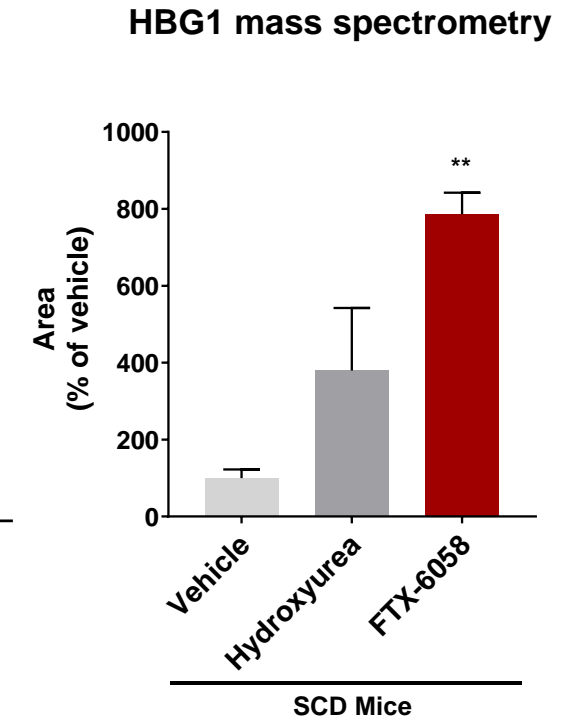
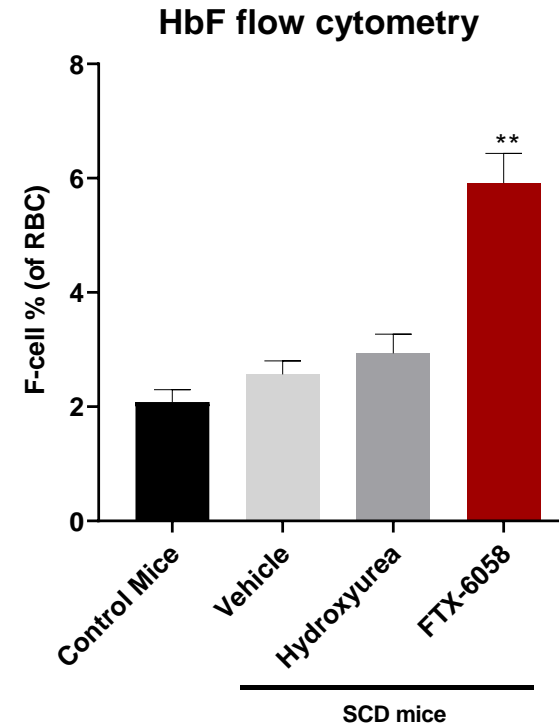
Target Engagement



HBG1 mRNA levels



Fetal hemoglobin protein levels

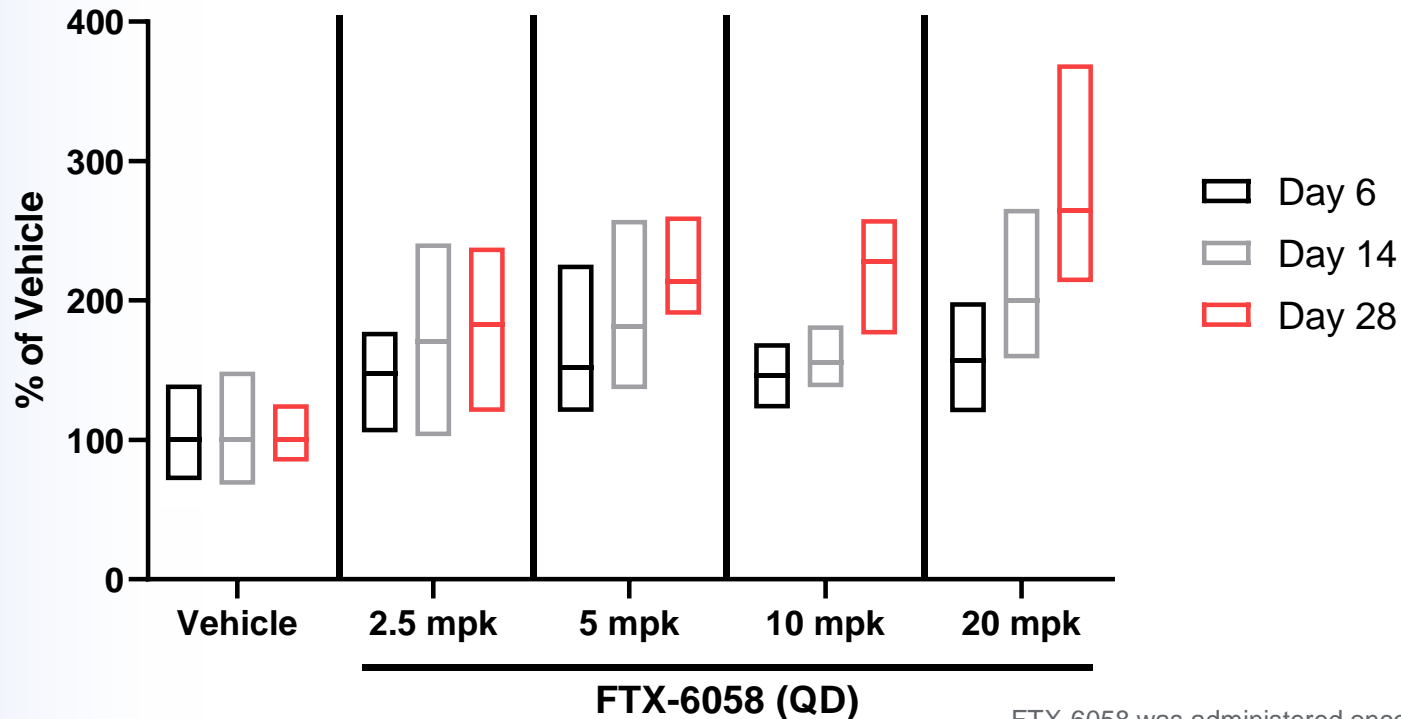


- Hydroxyurea was administered once daily by oral at 100 mg/kg for 28 days
- FTX-6058 was administered twice per day by oral at 5 mg/kg for 28 days

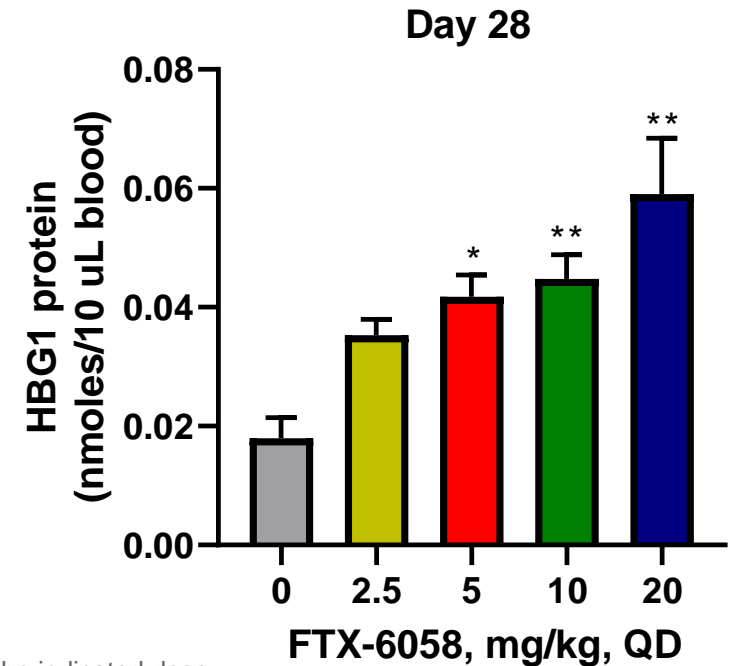
p<0.01; *p<0.001

Time- and dose-dependent increase in HbF in Townes SCD mice upon FTX-6058 treatment

% F-cells (HbF flow cytometry)

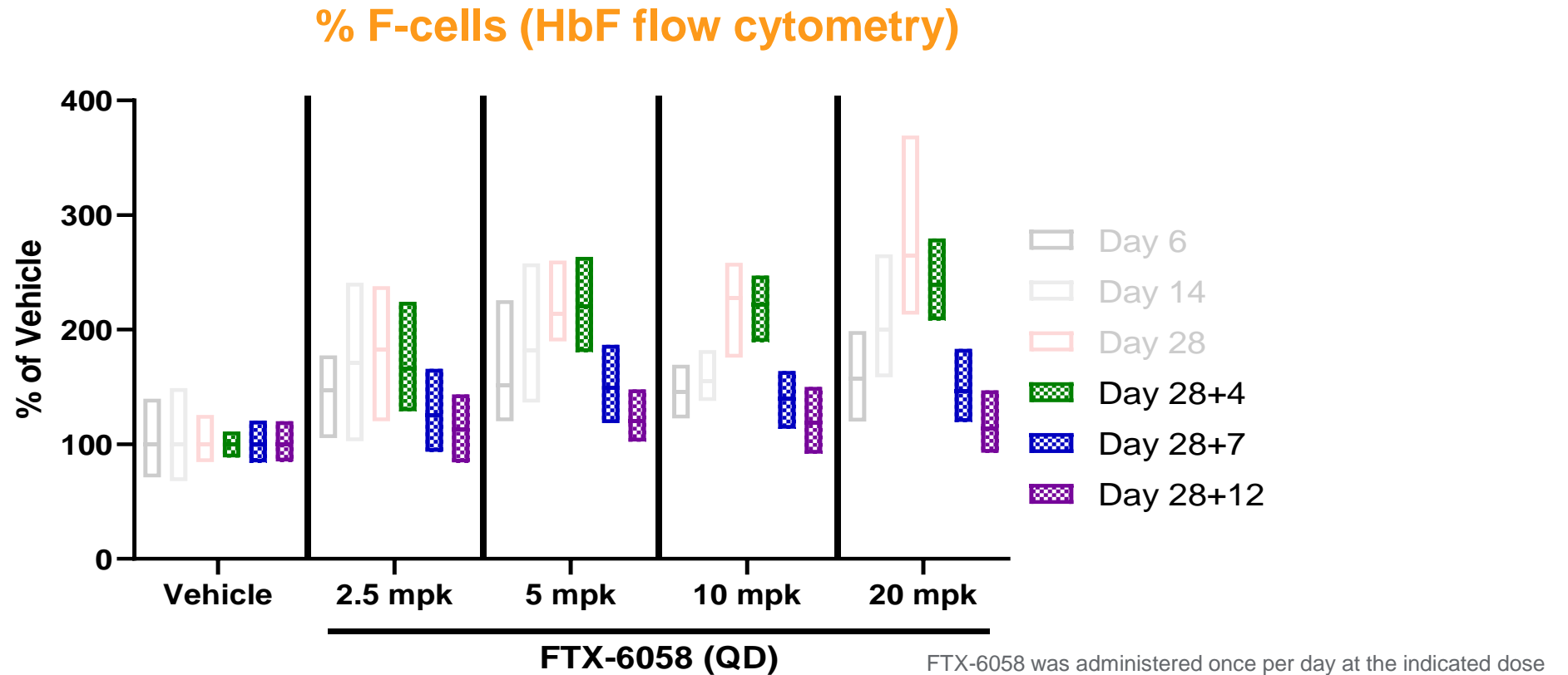


HbG1 protein (Mass Spec)



- Dose-dependent increases in HbF detected with QD dosing as low as 2.5 mg/kg
- Time-dependent increases in HbF induction observed as early as 14 days of dosing in the Townes SCD mice

Durable HbF induction: increase observed 4 days post last dose in Townes SCD mice



- **Consistent with MOA, HbF induction with FTX-6058 demonstrates robust persistence, with no loss of effect up to 4 days after dosing cessation.**

FTX-6058 has potential to be a transformative therapy for SCD

- FTX-6058 is a potent, selective and orally active small molecule EED inhibitor.
- Proof of concept studies provided *in vitro* evidence for FTX-6058 in inhibiting PRC2 activity, which leads to elevation of HbF in human primary CD34+ cells.
- FTX-6058 demonstrated potent TE and HbF induction *in vivo* in animal models at plasma concentrations reasonably expected to be achieved in the clinic.
- FTX-6058 pharmacological activity in target cells can be readily monitored in the clinic since TE in bone marrow correlates with TE in peripheral monocytes in animals.
- FTX-6058 demonstrated an impressive preclinical pharmacological profile with the potential to be a disease-modifying therapeutic for sickle cell patients.

Thank you!



Additional questions:

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