



FTX-6058

for Sickle Cell Disease

Program Update

Disclaimer and Notice

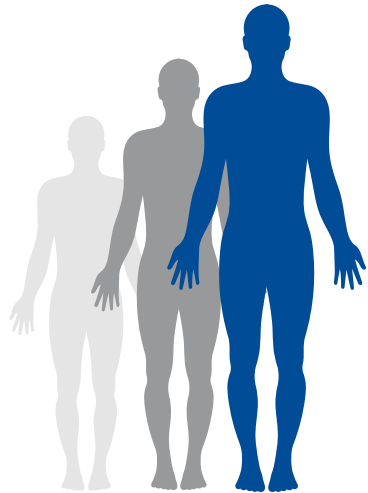
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Phase 1b Clinical Trial in SCD Subjects

Study Population

Males and females with SCD, between age 18 – 65

Approximately 10 subjects per cohort



Study Design



Study Endpoints

Primary

Safety and tolerability
Pharmacokinetic measurements

Secondary

Change in %HbF protein
Change in reticulocytes
Red cell distribution width

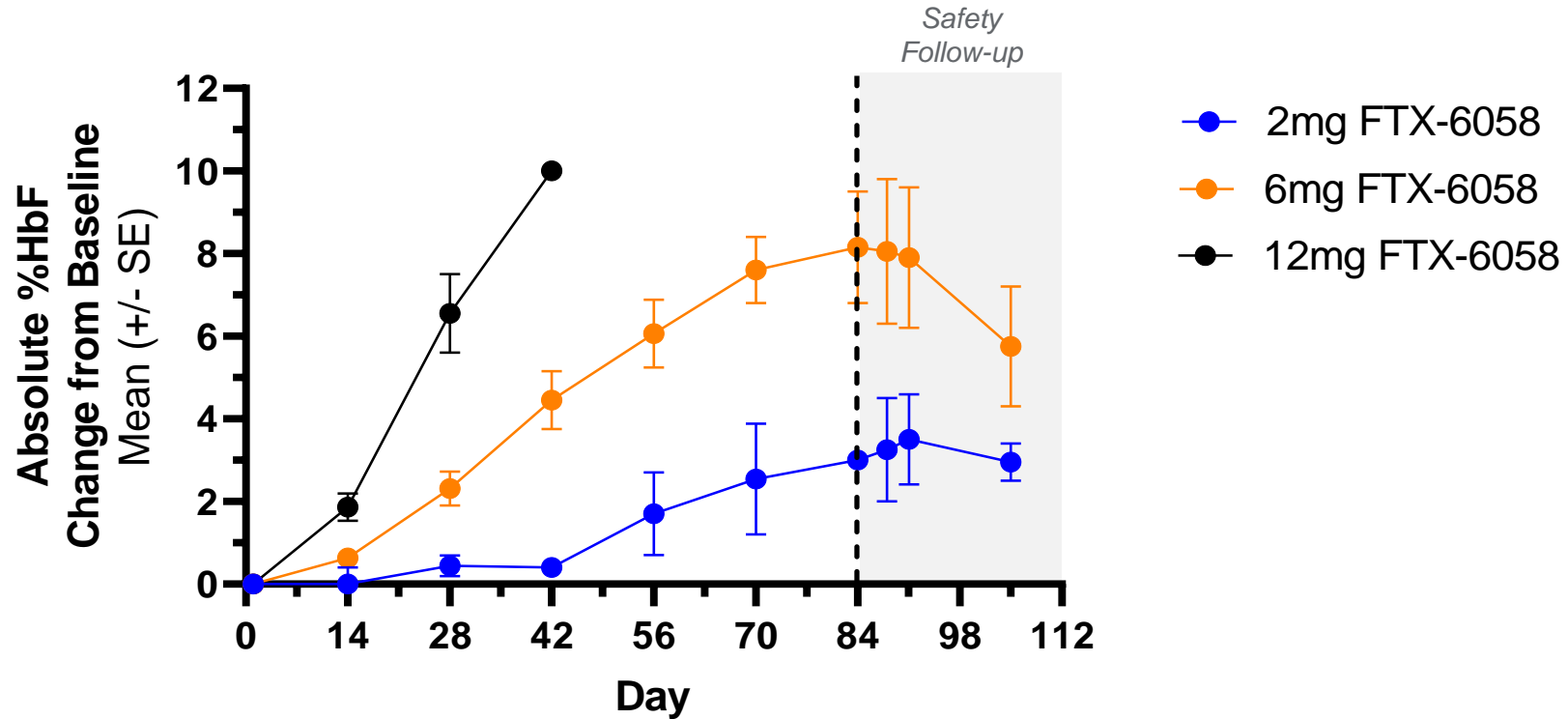
Exploratory

Target engagement
Incidence of VOCs
Biomarkers of hemolysis
QOL measures
% F cells

*Plans to resume enrollment at the 12mg dose followed by the 20mg dose

Initial FTX-6058 Data Demonstrates Dose-dependent Increases in HbF

Absolute %HbF Change from Baseline



U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

Note: Summary data includes both subjects on and off hydroxyurea; Subject 15 ceased dosing on Day 22 and therefore, was only included in the analysis up to Day 14

Overview of Key Inclusion and Exclusion Criteria



Key Inclusion Criteria

Patient Severity

Previous experience with **hydroxyurea**

AND

Previous experience with a stable dose of **voxelotor or crizanlizumab or L-glutamine**

OR

Lack of access to these advanced therapies



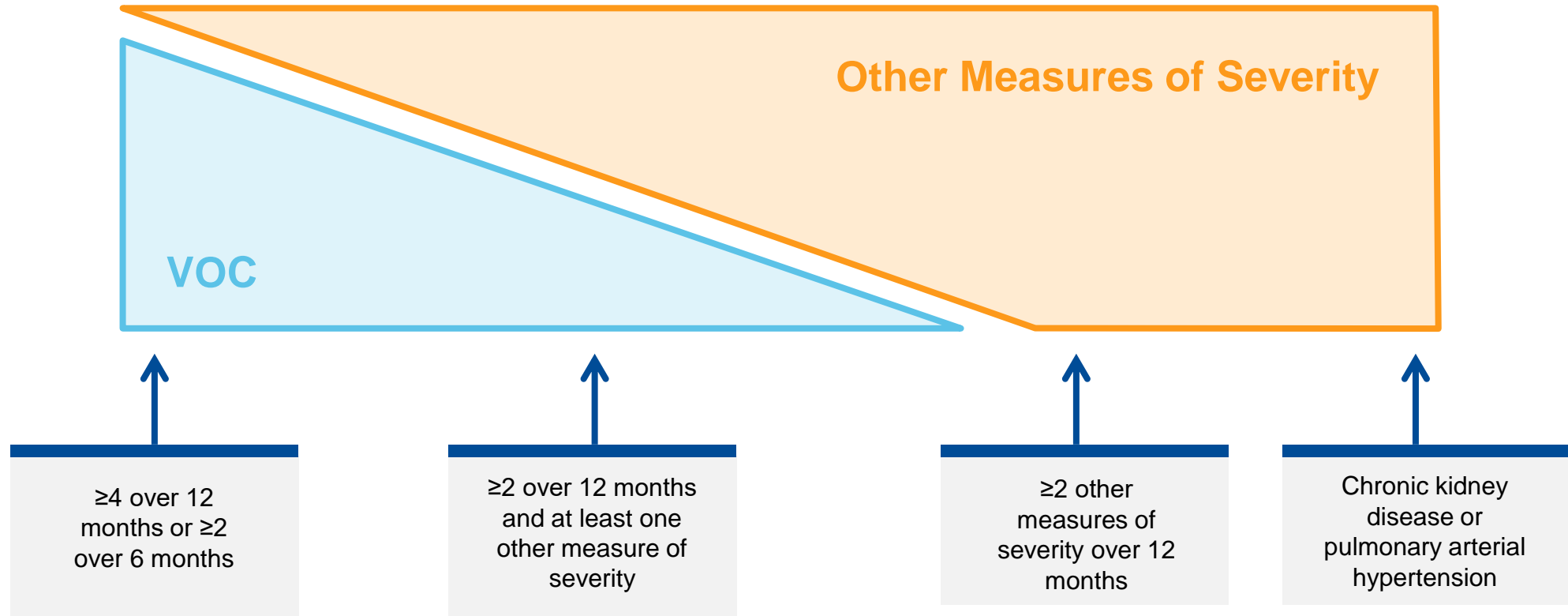
Key Exclusion Criteria

Exclude subjects currently on /having received the following therapies within 60 days prior to initiating FTX-6058:

hydroxyurea and voxelotor or crizanlizumab or L-glutamine

We estimate that there are approximately 7,500 to 10,000 patients in the U.S. that meet the inclusion and exclusion criteria of the amended protocol

Overview of Key Inclusion Criteria: Patient Severity



Overview of Key Inclusion Criteria: Previous Use of Hydroxyurea AND One Other Approved Therapy

Hydroxyurea

- Continued VOC or episodes of acute chest syndrome for at least 6 months at the maximum tolerated dose
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Patient refusal

And

Voxelotor or crizanlizumab or L-glutamine

- Continued pain crises and other VOCs while on stable dose for at least 6 months
- Failure to increase Hb by 1 g/dL (for vox.) or continued VOC episodes (for criz. or L-glutamine)
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Patient refusal

Or

Lack of access to advanced therapies

- Lack of availability
- Lack of insurance coverage



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Supplemental Detail

Modifications to Key Inclusion Criteria: Patient Severity

- ≥ 4 episodes of SCD pain crisis over 12 months or ≥ 2 over 6 months prior to screening
- ≥ 2 episodes of SCD pain crisis plus at least one of the following over previous 12 months:
 - Acute chest syndrome (ACS)
 - Hepatic or splenic sequestration
 - Priapism
- ≥ 2 of the following events over the previous 12 months:
 - ACS
 - Hepatic or splenic sequestration
 - Priapism
- Tricuspid regurgitant jet velocity (TRV) ≥ 3.0 m/s **OR** TRV ≥ 2.5 m/s + N-terminal pro b-type natriuretic peptide (NT-proBNP) plasma level ≥ 160 pg/mL **OR** documented ongoing pulmonary hypertension diagnosed from previous echocardiogram or right-sided heart catheterization with mean pulmonary artery pressure > 25 mm Hg
- SCD-related chronic kidney disease (CKD) defined by at least one of the following criteria measured on 2 separate and consecutive occasions:
 - Estimated glomerular filtration rate (eGFR) ≥ 30 and < 60 mL/min/1.73 m²
 - Proteinuria as defined by albumin to creatinine ratio > 300 mg/g or protein to creatinine ratio > 30 mg/mmol
- Meet medical criteria to receive (e.g., post-cerebrovascular accident) but are contraindicated for chronic transfusions (e.g., alloimmunization, transfusion reactions)

Modifications to Key Inclusion Criteria: Previous Use of Hydroxyurea and One Other Approved Therapy

Previous experience with hydroxyurea (HU) for at least 6 months at the maximum tolerated dose but have shown to be unresponsive and/or intolerant or ineligible based on at least one of the following criteria:

- Compared with baseline, same or higher number of pain crises and/or other VOCs while on HU for at least 6 months at the maximum tolerated dose
- Episode(s) of ACS while on HU for at least 6 months at the maximum tolerated dose
- Inability to tolerate HU as defined by at least one of the following:
 - Severe allergic reaction
 - Hematologic toxicity defined by clinically significant decrease in red blood cells, white blood cells, or platelets
 - Inability to tolerate gastrointestinal side effects such as nausea, vomiting, diarrhea, or abdominal pain
 - Inability to tolerate side effects including fatigue, dizziness, headache, fever, leg ulcers, and/or skin changes
- Unmanageable drug-drug interactions
- Patient refusal

Previous experience with a stable dose of voxelotor, crizanlizumab, or L-glutamine for at least 6 months but have shown to be unresponsive and/or intolerant or ineligible based on one of the following criteria:

- For voxelotor, failure to increase hemoglobin (Hb) by at least 1 g/dL after being on a stable dose of voxelotor for at least 6 months
- For crizanlizumab or L-glutamine compared with baseline, same or higher number of pain crises and/or other VOCs while on a stable dose of therapy for at least 6 months
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Lack of access to therapy
- Patient refusal

Summary of Exclusion Criteria

- Major surgery, serious illness, infection, fever, significant bleeding, cerebrovascular accident, or seizure within 14 days prior to starting study drug; elective surgery planned for the time period of the trial
- Sickle cell complication requiring care from a medical provider in the 14 days prior to starting study drug
- Use of anticoagulants or medications that induce or inhibit cytochrome P450 (CYP) 3A4, inhibit P-glycoprotein, breast cancer resistance protein, or multidrug and toxin extrusion protein 2-K, or are substrates of CYP2B6 within 14 days prior to first dose of study drug or anticipated need for any of these medications during the study.
- Participation in any other study with an investigational agent within the past 60 days of enrollment
- History of bone marrow transplant or human stem cell transplant or gene therapies
- Vaccination in the previous 7 days prior to initiating study drug
- Alanine aminotransferase $\geq 3\times$ the upper limit of normal (ULN), albumin < 2.0 mg/dL, direct (conjugated) bilirubin ≥ 1.5 mg/dL, or prothrombin time > 1.5 ULN
- Subjects with a history of severe renal disease defined as eGFR < 30 mL/min/1.73 m². Subjects on dialysis of any kind are excluded
- Subjects with abnormal laboratory results or medical history indicative of any significant medical disease that, in the opinion of the Investigator, would preclude the subject's participation in the study or potentially obscure the interpretation of the scheduled assessments. Screening laboratory assessments may be performed twice at the discretion of the Investigator
- History of human immunodeficiency virus (HIV), or history of hepatitis B, or active hepatitis C. Subjects treated for and cured of hepatitis C are allowed if no longer on therapy prior to initiating study drug

Summary of Exclusion Criteria (Continued)

- Subjects receiving regularly scheduled transfusions or any subject who has been transfused within 60 days prior to initiating study drug
- Clinically diagnosed substance use disorder for alcohol or other illicit drugs of abuse
- A positive urine drug screen for illicit drugs of abuse (other than opioids and marijuana/tetrahydrocannabinol [THC]/cannabidiol [CBD]) is exclusionary
- Pregnant or lactating female; or a female of childbearing age unable or unwilling to comply with birth control or abstinence during the study, Subject is investigative site personnel or member of their immediate family (spouse, parent, child, or sibling whether biological or legally adopted)
- Heart rate corrected QT interval-Fridericia's method (QTcF) >450 msec (male) or >470 msec (female)
- Subject with active malignancy or history of cancer (except for squamous cell skin cancer, basal cell skin cancer, or stage 0 cervical carcinoma in situ, with no recurrence for the last 5 years) or with an immediate family member with known or suspected familial cancer syndrome. Known presence of a chromosomal abnormality or genetic mutation that may put the subject at an increased risk of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)
- Subject currently on HU, voxelotor, crizanlizumab, and/ or Lglutamine or have received HU, voxelotor, crizanlizumab, and/ or L-glutamine within 60 days prior to initiating study drug