GMI-1070: A Novel Potential Study Treatment During Sickle Cell Crisis

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Current Available Treatment for Vaso-Occlusive Crisis (VOC)

- VOC results in life-threatening complications and reduced life expectancy
- 60% of patients with Hb SS have at least 1 VOC/yr
- Only supportive care is available
  - Hydration, pain control, transfusion
  - ~80,000+ US hospitalizations
  - Average length of stay ~6 days
  - Expensive care and associated with complications
- No mechanism-based therapies available
The Role of Selectins in Inflammation

- Selectins are a family of cell adhesions molecules (CAMs).
- During inflammation, stimuli such as histamine and thrombin cause endothelial cells to mobilize P-selectin to the cell surface.
- Cytokines such as TNF-alpha stimulate the expression of E-selectin and more P-selectin.
- As the WBCs roll along the blood vessel wall, the WBC selectin binds to the blood vessel and allows the WBC to get out to the site of infection.
Role of the Selectins as Adhesion Molecules in the Inflammatory Response
Sickle Cell Disease

- Abnormal red blood cells and a vascular disease
- Inflammation is a key mediator
- Adhesion molecules such as E-selectin, vascular cell adhesion molecule-1, intracellular adhesion molecule-1 levels are higher in patients with SCD during crisis than baseline SCD than people without SCD.
- Sickle cell mice lacking E- and P-selectin are protected from developing vaso-occlusion

[Turhan, Proc Natl Acad Sci, 2002]
Red Cell and White Cell Adhesion Underlies Sickle Cell VOC

GMI-1070

- Experimental new anti-selectin drug
- Not approved by the FDA
- Undergoing clinical trials in SCD
- Given intravenously (IV)
Microvascular Blood Flow in Sickle Cell Mice

Courtesy of Dr. Paul Frenette, Mount Sinai
GMI-1070 Improves Blood Flow in Sickle Cell Mice During VOC

*As seen by intravital microscopy; Dr. Paul Frenette, Mt. Sinai*
Effects of GMI-1070 in Sickle Cell Mice in Crisis as Determined By Intravital Microscopy

**Blood Flow**

![Blood flow rate (nL/s)]

- **PBS**
- **GMI-1070**

**Adherent WBCs**

- **Adherent WBCs/100 μL**

- **PBS**
- **GMI-1070**

**RBC/WBC Interactions**

- **Interactions/WBC, min**

- **PBS**
- **GMI-1070**

*Significance levels: ***P<0.001, **P<0.05, *P<0.05*.*
GMI-1070 Extends Survival in Sickle Cell Mice with VOC

Median survival
PBS=5 hrs
GMI-1070>9 hrs

Logrank Test: Chi square=7.342; **P=0.0067
GMI-1070 Demonstrates Activity and Benefit Against VOC in Sickle Cell Mouse Model

- Treatment Results in **Significant** Improvements
  - Increased Survival
  - Improved Blood Flow
  - Reduced Leukocyte/Endothelial Interactions
  - Reduced Leukocyte/Sickle RBC Interactions
Phase 1a and 1b Clinical Safety Studies (Single and Multiple Ascending Doses)

- Single doses of up to 40 mg/kg IV
- Multiple doses of up to 20 mg/kg every 8 hrs for 4 days
- Studies complete - 72 healthy volunteers enrolled
- Unremarkable clinical safety profile
  - No Serious Adverse Events
  - All adverse events were mild or moderate (grade 1-2)
  - Equally represented between drug and placebo groups
  - Two subjects in high dose groups had rash; one stopped drug
Phase 2 Safety and Efficacy Study in VOC (GMI-1070-201) - Objectives

- Multi-Center Randomized, Double-Blind, Placebo Controlled Study

- Primary Objective:
  - Evaluate the effect of multiple IV doses of GMI-1070 on time to resolution of VOC in patients hospitalized for sickle cell VOC
  - Patient will receive morphine or hydromorphone (Dilaudid) for pain control besides receiving GMI-1070 or placebo
Phase 2 Study in VOC - Overview

- ~20 centers – US and Canada
- 76 patients, ages 12 – 60
- Two arms randomized at a 1:1 ratio
  - GMI-1070 loading dose, then every 12 hrs IV, max 15 doses
  - Placebo – with same dosing regimen & volume
  - Requires separate IV for the study drug
- Enroll at hospitalization for VOC
- Administer study drug IV in addition to standard analgesia
- Treat until fully transitioned to oral pain meds
  - ~2-5 days anticipated in most cases
- Follow up for study endpoints to 28 days after last dose
Phase 2 Study - Inclusion Criteria

- 12-60 years old
- Confirmed diagnosis of HbSS or HbS-β⁰thal
- Diagnosis of VOC, hospitalized or being admitted
- Able to dose within 18 hours of first medical evaluation for VOC (not including triage)
- Written informed consent/assent
Study Visits

- Visit 1, hospital stay for VOC – max 7 days of dosing
- Visit 2 – 36 hours (± 12) after last dose
  - Inpatient or outpatient, depending on timing
- Visit 3 – clinic follow up 7 days after last dose
- Visit 4 – clinic follow up 28 days after last dose
Possible Side Effects from GMI-1070

- Headache
- Dizziness
- Mild irritation at the IV site
- Rash
- Increased white blood cell count
Study Update (August 23, 2011)

- 34 of 76 subjects were enrolled to date.
- No significant toxicity
- Data is typical for study population
- Data is blinded; no data of effect of the drug when compared to placebo.
Questions