GMI-1070, a Pan-Selectin Inhibitor: Safety and PK in a Phase 1/2 Study in Adults with Sickle Cell Disease

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Abstract

Introduction: GMI-1070 is a pan-selectin inhibitor that targets E-, P-, and L-selectins and has shown activity in multiple animal models of disease. Sickle cell disease (SCD) is characterized by periodic vaso-occlusive (VOC) episodes in which cell adhesion and aggregation play a crucial role. GMI-1070 has previously been shown to restore blood flow and improve survival in a mouse model of VOC, and safety and PK have been evaluated in normal, healthy volunteers in phase 1. Here we report safety and PK results from the first study of GMI-1070 in individuals with SCD.

Methods: An open-label phase 1/2 study was performed, enrolling adults with SCD at steady state. GMI-1070 was administered in two IV doses given on the same day: 20 mg/kg in the first dose, followed 10 hours later by 10 mg/kg. Patients were evaluated for safety on days 0, 1, 2, 7 and 28, including adverse events (AEs), routine clinical labs, and clinical exam. Plasma and urine concentrations of GMI-1070 were measured on days 0, 1, and 2, and PK parameters calculated and compared with those from healthy volunteers.

Results: Fifteen adults were enrolled at three centers; 13 with HbSS, 2 with HbSβ^{0}thal. All were African-American, 9 were male, mean age was 32 years (range 19-50), mean weight was 65 kg; 4 were on hydroxyurea. In the past year, 6 had experienced VOC requiring medical care; 2 had ACS; 2 required transfusions; and 1 had an episode of priapism. Five were hospitalized in the past year; 12 were hospitalized in the past 5 years. All subjects received both doses of study drug; all but one were followed for 28 days. The PK in adults with SCD was in good agreement with that in the controls. The elimination half-life of GMI-1070 averaged 7.70 ± 2.38 hours. Renal clearance averaged 18.0 ± 7.94 mL/min and accounted for essentially all elimination. Physical exam parameters after dosing were unchanged, and all infusions were well tolerated. Four subjects reported headache within 24 hours of dosing, all of which were mild or moderate and resolved within 24 hours. Two subjects experienced VOC not requiring hospitalization, at 2 and 4 weeks after dosing. One subject had worsening anemia requiring transfusion 5 days after dosing. Other adverse events typical of SCD were reported without apparent association with study drug; none were serious adverse events. Routine labs demonstrated no changes from baseline (Hb, reticulocytes, platelets, electrolytes, glucose, ALT, LDH, BUN, Cr, bilirubin, urinalysis) with the exception of white blood cell counts (WBC) and absolute neutrophil counts (ANC). At 24 hours, mean WBC change from baseline was 1.9K/mm^3, or 20% (p=0.076, using parametric test with mixed model); mean ANC change was 2.7, or 67% (p=0.019); all returned to baseline by 7 days. One individual had marked leukocytosis 24 hours after dosing (from 10.4 to 28K/mm^3), returning to baseline by day 7; no other effects were observed in this subject. Mean C-reactive protein (CRP) increased at 24 and 48 hours, returning to baseline by day 7. Two subjects had marked increases in CRP: one exhibited leukocytosis with dosing and the other had a high baseline WBC count. There was otherwise no apparent correlation between PK, WBC/ANC, hydroxyurea use, or adverse events.

Conclusion: GMI-1070, a pan-selectin inhibitor, when administered to adults with SCD at steady state, has a similar safety and PK profile to that in healthy volunteers. However, SCD patients had moderate WBC and ANC increases at 24-48 hours after dosing, which return to baseline without other observed symptomatic adverse events. This study supports further evaluation of GMI-1070 for the treatment of vaso-occlusive crisis.

Background

- GMI-1070 is a pan-selectin antagonist which inhibits selectin binding *in vitro* and selectin-mediated effects *in vivo*.
- Selectin binding is a key early step in the inflammatory process leading to leukocyte adhesion and recruitment to inflamed tissue; and is known to be involved in many disease processes that involve inflammation.
- Sickle cell disease is one such area where selectin-mediated cell adhesion and cell aggregate formation are thought to be a primary component of vaso-occlusion.
- GMI-1070 has been shown to prevent and interrupt vaso-occlusion in a sickle mouse model. (Chang et al, Blood, 9 September 2010, Vol. 116, No. 10, pp. 1779-1786)
- Phase 1 studies in healthy volunteers have been reported, with evaluations for safety and PK in humans. (Xie et al, ASH Annual Meeting 2009)

Objectives

Primary objective:

- To evaluate the safety of multiple intravenous (IV) doses of GMI-1070 in adults with sickle cell disease

Secondary objectives:

- To evaluate the pharmacokinetics (PK) of multiple IV doses of GMI-1070
- To evaluate biomarkers of adhesion, inflammation, and downstream selectin effect (reported elsewhere)

Methods

An open-label phase 1/2 study of GMI-1070 was conducted at 3 academic medical centers. Adults with sickle cell disease who were at their medical baseline (not experiencing a painful episode) were eligible for the study.

Inclusion Criteria:

- Age 18-50 years
- Hb SS or Sβ^{0}thal
- At medical baseline
- Informed consent obtained

Exclusion Criteria:

- Serum creatinine >1.5 mg/dL
- ALT (SGPT) >2x ULN
- Hb ≤ 6 g/dL
- Vaso-occlusive crisis within last 14 days (an episode requiring a visit to a medical facility resulting in medical treatment for pain)
- Recent major medical events or transfusions
- Currently taking systemic steroids

Study Methods:

- Setting was a day hospital or outpatient clinical research setting
- GMI-1070 was administered as two brief IV infusions in one day
- All subjects received a loading dose of 20 mg/kg in the morning, followed by a second dose of 10 mg/kg, 10 hours later.
- Subjects went home at the end of the first day, after receiving both doses of GMI-1070, and returned for further evaluation at 24 and 48 hours after initial dose, and at 7 days. Telephone follow up was done at 28 days.
- Clinical data included adverse events (AEs), vital signs, physical exam and concurrent medications.
- Laboratory data included CBC with differential, platelets & reticulocytes, hsCRP, chemistries including renal and liver function, and urinalyses.
- Plasma and urine concentrations of GMI-1070 were measured with use of limited samples. Seven plasma samples and a single 6-hour urine collection were taken from each subject.
- PK parameters were estimated by fitting the data to a two-compartment model with first-order elimination, and comparing to the PK data from healthy volunteers. Actual drug doses and infusion, blood sampling, and urine collection times were used.

Baseline Data

Demographics

- 15 adults enrolled
- Genotype: 13 with HbSS, 2 with HbSβ^{0}thal
- Gender:9 males, 6 females
- Race: All African American
- Mean age 32 years (range 19-50)
- Mean weight 65 kg (range 48-91)
- Concurrent hydroxyurea: 4

Disposition

- Study completion: 14
- Lost to follow up: 1 (completed first day only)

Medical events	In lifetime (N=15)	In past year (N=15)
Hospitalized for sickle cell disease-related reason	15	5 (12 in past 5 yrs)
VOC requiring medical care	15	6
Acute chest syndrome	12	2
Transfusions	14	2
Priapism	5	1
Aplastic crisis	2	0
Skin ulcers	2	1
Splenic sequestration	2	0
Hepatic sequestration	1	0
Stroke	2	0

Results

Safety

Summary of Clinical Findings:

- No changes in vital signs or physical exam findings
- All IV infusions were well tolerated
- No change in lab findings, with the exception of WBC, ANC, and hsCRP
- Adverse Events:
  - 16 adverse events were reported in 9 subjects
  - No Serious Adverse Events were reported
  - No adverse events required discontinuation of study drug

Number (%) Experiencing an AE	Number of AEs	Severity Grade of AEs				
		Grade 1	Grade 2	Grade 3	Grade 4	Serious Adverse Event*
9 (60)	16	5	3	0	1	0

*A Serious Adverse Event is defined as an event that results in death, hospitalization, disability, is life-threatening or an important medical event

Adverse Events by Subject:

Adverse Event	N (%)
Headache	4 (27)
VOC	2 (13)
Anemia (worsening)	1 (7)
Leukocytosis	1 (7)
Arthralgia (hip pain)	1(7)
Pruritus	1 (7)

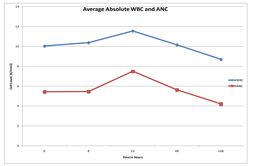
Adverse Events Summary:

- The most common AE was headache, which occurred in 4 subjects within 24 hours of dosing, were mild or moderate (grades 1-2), and resolved within 24 hours.
- Vaso-occlusive pain episodes occurred in 2 subjects at 2 and 4 weeks after dosing. These episodes resolved without requiring hospitalization.
- Leukocytosis, to 28.0 K/mm^3 at 48 hours after drug (baseline 10.4 K/mm^3), occurred in one individual, considered probably related to the drug. This was driven by neutrophil count of 23.0 K/mm^3. hsCRP was also elevated; no other effects were observed in this subject.
- Other adverse events (emesis, hypokalemia, infusion site pain, cough) were also reported as single events.
- No other association was seen between AEs and WBC, ANC, concurrent medication use, or plasma levels of drug.

Laboratory Findings Summary:

- Peripheral WBC counts rose consistently at 24-48 hours after start of first dose
- Mean change in WBC was <25% from baseline
- WBC range at peak was 4.5-28.0 K/mm^3
- The increase was driven by neutrophils in all cases; other cell type counts were not changed.
- ANC range at peak was 1.7-23.0 K/mm^3
- All WBC and ANC values returned to baseline by 7 days
- Mean hsCRP increased at 24 and 48 hours, with return to baseline at 7 days
- Two subjects had marked increases in hsCRP: one associated with leukocytosis after dosing, and one with a high baseline WBC count. Both individuals had no other associated events.

Mean WBC and ANC Over Time:



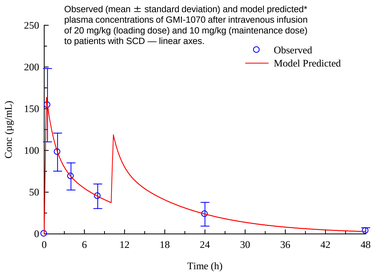
Parameter	Mean Change from Baseline (K/mm^3)	Mean Change from Baseline (Percent)	p-value*
WBC	1.9	20	0.076
ANC	2.7	67	0.019

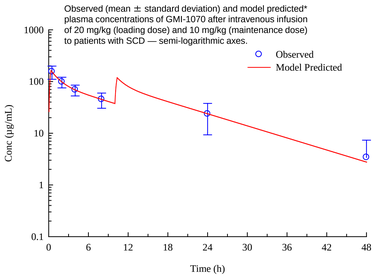
*Using parametric test with mixed model, and change at 24 hours

Other Laboratory Findings (Mean, Range):

Timepoint	Hb (g/dL)	Plt (10^6/L)	Retic (%)	BUN (mg/dL)	Cr (mg/dL)	hsCRP (mg/L) Mean
Baseline	7.6 (5.4-9.2)	325 (180-491)	10 (4.1-19.3)	9.7 (5-19)	0.7 (0.4-1.4)	4.3 (0.8-17)
8 hours	7.2 (5.3-9.4)	312 (168-496)	11.2 (5.2-20.7)	NA	NA	NA
24 hours	8.0 (5.5-10.5)	306 (175-425)	9 (3.9-19.5)	8.6 (6-15)	0.7 (0.5-1.1)	6.0 (1.1-37)
48 hours	8.0 (5.9-10.6)	309 (202-449)	9.5 (4.5-15.9)	8.6 (5-13)	0.7 (0.5-1.1)	9.0 (0.6-50.4)
7 days	7.8 (5.9-10.1)	343 (217-430)	9.31 (4.1-19.1)	9.4 (5-19)	0.7 (0.5-1.4)	4.2 (0.3-19.3)

Pharmacokinetics





PK Parameter	Results†
Primary‡	
CL (mL/h/kg)	19.6 ±6.42
V1 (mL/kg)	120 ±30.7
CLD2 (mL/h/kg)	31.6 ±17.2
V2 (mL/kg)	64.2 ±19.6
Secondary‡	
Vss (mL/kg)	184 ±40.1
Cmax (µg/mL)	167 ±48.4
AUC(inf) (h×µg/mL)	1,129 ±367
α (h^{-1})	0.8610 ±0.3985
β (h^{-1})	0.0969 ±0.0249
T½ (h)	7.70 ±2.38
Tertiary§	
CLr (mL/min)	18.0 ±7.94

†Arithmetic mean ± standard deviation (N).

‡Primary parameters were those used to fit the model and secondary parameters were estimated from the primary parameters.

§ Tertiary parameters were estimated from the primary parameters plus the urinary excretion of GMI-1070.

Pharmacokinetics Summary:

- Greater than 90% of the drug was excreted intact in the urine.
- Observed plasma GMI-1070 concentrations and those predicted by the model showed excellent agreement.
- Even with limited sampling, the model was well fit to and consistent with each subject's data.
- Estimates for clearances, volumes of distribution, $t_{1/2}$, and CLr were consistent with those of healthy volunteers
- The closeness of the fit to healthy volunteer data indicates similar behavior of GMI-1070 in adults with sickle cell disease. This is consistent with linear and dose-proportional PK behavior.

Summary and Conclusions

GMI-1070, a pan-selectin inhibitor, was administered in two IV doses at 20 and 10 mg/kg to 15 adults with sickle cell disease. Clinical results show no changes in most clinical parameters, and an adverse event profile not atypical for the population. Laboratory data show a moderate reversible effect on white blood cell count, driven by neutrophil count. This is consistent with the expected mechanism, where inhibition of cell adhesion to the vascular wall may keep more cells circulating in the blood. PK data show that plasma levels, half life, and urinary clearance are consistent with model predictions and similar to healthy volunteer results. In summary, GMI-1070, in this limited study of adults with sickle cell disease, appears to have a safety and PK profile largely consistent with that of healthy volunteers. This study supports proceeding with an interventional clinical trial to evaluate the effect of GMI-1070 on acute vaso-occlusive episodes in individuals with sickle cell disease.

Conflict of Interest Disclosures: Lori Styles, Ted Wun, Laura DeCastro, and Marilyn Telen performed the clinical trial under contract with GlycoMimetics, Inc., the Sponsor of the trial. William Kramer is a consultant to GlycoMimetics, Inc. Henry Flanner, John Magnani and Helen Thackray are employees of GlycoMimetics, Inc.

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