An Analysis of the Pediatric Sub-group from the Phase 2 Study of GMI-1070

TL McCavit[1], L Krishnamurti[2], L Hsu[3], CT Quinn[4], I Odame[5], O Alvarez[6], C Driscoll[7], K Smith Whitley[8], S Rhee[9], T Wun[10], M Telen[11], H Thackray[12]

[1]UT Southwestern Medical Center, Dallas, TX; [2]University of Pittsburgh Medical Center, Pittsburgh, PA; [3]University of Illinois Chicago Medical Center, Chicago, IL; [4]Cincinnati Children's Hospital, Cincinnati, OH; [5]The Hospital for Sick Children, Toronto, ON, Canada; [6]University of Miami Medical Center, Miami, FL; [7]Albert Einstein College of Medicine, New York, NY; [8]Children's Hospital of Philadelphia, Philadelphia, PA; [9]Rho, Inc., Chapel Hill, NC; [10]University of California, Davis Medical Center and VANCHCS, Sacramento, CA; [11]Duke University Medical Center, Durham, NC; [12]GlycoMimetics, Inc., Gaithersburg, MD

Background

- Painful vaso-occlusive crisis (VOC) is clinical hallmark of sickle cell disease
  - Recent advances have focused on VOC prevention
  - VOC treatment essentially unchanged for > 30 years
    - Current treatments focus - ameliorating sequelae of vaso-occlusion
    - No treatments interrupt the sickle-specific mechanisms underlying VOC
- 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, 116:1779-1786, 2010)
- Phase 1 studies in healthy volunteers and sickle cell patients have been reported, with evaluations for safety and PK . (Xie et al, ASH Annual Meeting 2009, Styles et al, ASH Annual Meeting 2010)

Objectives

Primary objective:

- To evaluate the efficacy of GMI-1070 in the pediatric patients of a phase 2 clinical trial

Secondary objectives:

- To evaluate the safety of GMI-1070 in pediatric patients
- To compare baseline characteristics and efficacy of GMI-1070 between pediatric and adult subjects

Methods

A randomized, double blind, placebo-controlled phase 2 clinical trial of GMI-1070 was conducted at 22 academic medical centers. Seven sites enrolled pediatric patients. Eligibility were changed through the study to facilitate enrollment (see Table 1).

Inclusion Criteria:

- Hb SS or Sβ^{0}thal
- Diagnosis of VOC at time of enrollment
- Hospitalized or in process of admission at enrollment
- Informed consent obtained

Exclusion Criteria:

- Infection – diagnosed or strongly suspected
  - Fever > 39°C
  - Fever > 38.5°C with positive cultures or radiographs, or determination by treating physician that serious infection was highly likely
- Acute chest syndrome
- SCD pain atypical of VOC (e.g., cholecystitis, splenic / hepatic pain)
- Hb < 5g/dL; Plt < 100,000/mm^3
- Creatinine >1.2 mg/dL if age 16-60; > 1.0 if 12-15; ALT >2x ULN
- Major surgery in the past 30 days
- Cerebrovascular accident, transient ischemic attack, or seizure in past 90 days
- Systemic steroid therapy in 48 hrs prior to enrollment
- For those on long-acting opioids, no dose change in past 14 days

Methods

Table 1 - Trial Characteristics – Changes During The Trial

Characteristic	Study Beginning	Study End
INCLUSION CRITERIA		
Age, years	16 – 45	12 – 60
Time from initial medical evaluation to first study drug administration	18 hours	24 hours
EXCLUSION CRITERIA		
Timing of most recent PRBC transfusion	< 60 days	< 14 days
Frequent, recent hospitalizations for VOC	> 6 in 12 months	> 5 in 6 months
Timing of recent hospitalization or parenteral treatment for VOC	within 14 days	within 48 hours
DOSING		
Loading and maintenance doses, mg/kg	20, 10	40, 20

Study Methods:

- GMI-1070 or placebo administered via IV infusions every 12 hrs
- Dosing – 20mg/kg loading dose followed by up to 14 maintenance doses of 10mg/kg
  - After enrollment of 11 subjects (1 pediatric) interim PK analysis, dosing increased to 40mg/kg loading dose and 20mg/kg maintenance doses
- Other clinical care at discretion of treating physicians
- Pain intensity measured every 4 hours on visual-analog scale (VAS)
- Primary outcome: Time to readiness for discharge defined as whichever occurred first:
  1) Sustained decrease in pain score by 1.5cm from baseline with concurrent cessation in parenteral opioids; **or**
  2) Agreement about readiness for discharge by patient and physician; **or**
  3) Hospital discharge
- Secondary outcomes: time to discharge, time to transition from IV to oral analgesics, parenteral opioid usage in morphine equivalent units per kilogram (MEU/kg), and safety profile
- Follow-up visits 36 hours, 7 days, and 28 days post last dose
- Median time-to-event compared between arms using Kaplan-Meier (KM) method
- Analysis of covariance compared mean hourly opioid use, by hospital day
- Fisher's exact test and Wilcoxon rank-sum test used to compare pediatric and adult hospitalization features (Table 3)

Results

Demographics

- 20 pediatric subjects (76 total)
- Genotype: 20 with HbSS
- Gender: 12 males, 8 females
- Race: 18 African-American; 1 Native Hawaiian/Islander; 1 More than 1 Race
- Median age: 14 years (range 12-17)
- Concurrent hydroxyurea: 11 (55%)
- Which criterion of the primary outcome was fulfilled by pediatric subjects:
  #1 Sustained VAS decrease & cessation of opioids: 9/20 (45%)
  #2 Agreement about readiness for discharge: 8/20 (40%)
  #3 Hospital discharge: 4/20 (20%)
  **One subject met both #2 and #3 simultaneously and was counted in each
- Mean (SD) time to first dose of study drug: peds 15.2h (4.5) vs adults 15.0h (4.8)

Results

Figure 1 – Primary Outcome for Pediatric Subjects

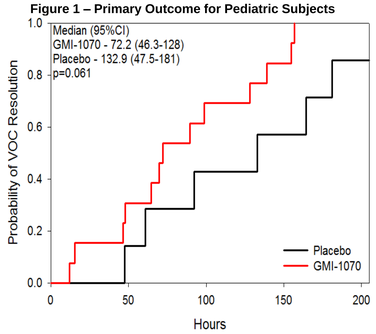

Figure 2 – Time to Transition to Oral Pain Meds

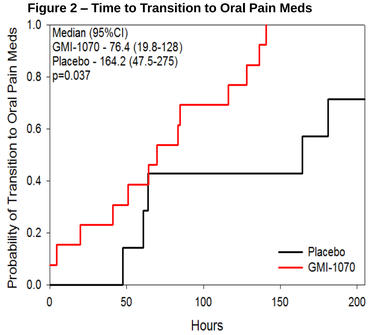

Figure 3 – Time to Discharge

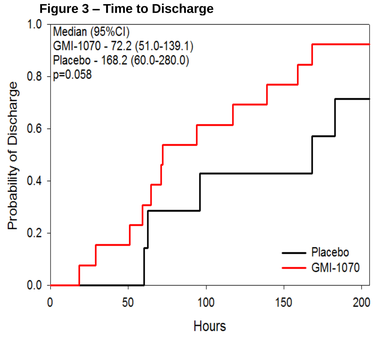

Figure 4 – Mean Hourly Opioid Use

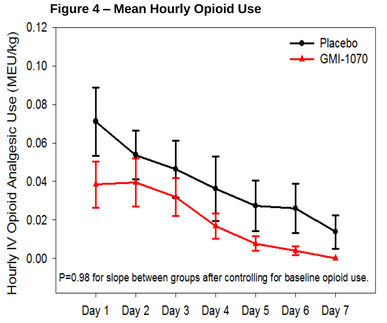

Table 2 – Comparison of Outcomes Between Pediatric and Adult Subjects*

Outcome Variables	Pediatric (N=20)			Adult (N=56)		
	Placebo	GMI 1070	% Reduction	Placebo	GMI 1070	% Reduction
Time to VOC resolution, median (95% CI), hrs	132.9 (47.5-181)	72.2 (46.3-128.0)	45.7	130 (52.2-165.3)	61.3 (38.9-139.7)	52.8
Time to transition to oral opioids, median (95% CI), hrs	164.2 (47.5-275)	76.4 (19.8-128.0)	53.5	140.8 (52.2-188.1)	67 (39.7-136.9)	52.4
Time to discharge, median (95% CI), hrs	168.2 (60.0-280)	72.2 (51.0-139.1)	57.1	149.9 (67.0-189.0)	77.5 (47.9-140.4)	48.2
Time to 1st sustained decrease in VAS score, median (95% CI), hrs	146.2 (4.1, --)	101.3 (55.1-156.9)	30.7	125.3 (16.7-192.6)	43.8 (20.5-92.0)	65.0
Time to readiness for discharge, median (95% CI), hrs	132.9 (60, --)	73.2 (46.3-139.1)	44.9	137.4 (67.0-196.4)	72.4 (44.3-141.7)	47.3

* Statistical testing which compared the % reduction between pediatric and adult subjects revealed no significant differences

Table 3 – Comparison of Baseline, Pain, and Safety Features Between Pediatric and Adult Subjects

Characteristic	Pediatric (N=20)	Adults (N=56)	*P*
Hydroxyurea use (at enrollment), %	55	61	0.78
Patient controlled analgesia (PCA) use, %	80	86	0.65
Opioid agent used in PCA, % **Morphine** **Hydromorphone**	 80 20	 20 80	 <0.001
Cumulative IV opioid, MEU/kg, mean (SD)*	5.7 (7.0)	41.6 (86.3)	0.10
Antibiotics within 24 hours of 1st study drug, %	35	14	0.06
Antibiotics within 7 days of 1st study drug, %	55	25	0.09
Pain score at presentation, mean (SD)	7.9 (1.9)	8.8 (1.4)	0.10
Pain score at resolution, mean (SD)	5.2 (2.9)	4.2 (2.6)	0.15
30 day VOC readmission, %	20	21	0.90
SAE occurrence, %	35	29	0.59

* To calculate MEU/kg, 1.4 mg hydromorphone = 10mg morphine

Safety

- SAE occurrence – N=7 (35%)
  - VOC - 4; VOC & ACS – 1; cholelithiasis – 1; gastroenteritis - 1
- No severe or unusual infections
- ACS – 4 episodes in pediatric subjects
  - All ACS episodes occurred in GMI-1070 arm (4/13; 30%) vs none in placebo arm (0/7, 0%); 3 of 4 within 24 hours of 1st dose of study drug;
  - 1 of 4 received pRBC transfusion; 0 of 4 required intensive care; 0 of 4 died
  - For adults, ACS occurred in 2/30 (6.7%) in GMI-1070 arm vs 3/26 (11.5%) in placebo arm
- Readmission rate – 25% of subjects (N=5, 4 VOC recurrence, 1 – gastroenteritis)

Summary and Conclusions

- GMI-1070 – promising agent for reducing duration of VOC in sickle cell disease
- Effect size
  - approximate 2 day reduction in VOC duration – similar in pediatric and adult subjects
  - effect size comparable among various criteria of primary outcome
- Compared to adult subjects, pediatric subjects more often received morphine as parenteral opioid (vs. hydromorphone). Children also received less cumulative opioids, and more antibiotics during VOC
- ACS cases in the GMI-1070 arm
  - noteworthy but because of early onset, not definitively associated with study drug
  - consistent with expected incidence and small sample size
  - ACS is more common, more often related to respiratory infections, and associated with decreased morbidty / mortality in children compared to adults
- The strong efficacy signal in adolescents, along with minimal safety concerns, warrants inclusion of younger children in a subsequent phase 3 clinical trial of GMI-1070.

Conflict of Interest Disclosures: TL McCavit, L Krishnamurti, L Hsu, CT Quinn, I Odame, O Alvarez, C Driscoll, K Smith-Whitley, T Wun and M Telen performed the clinical trial under contract with GlycoMimetics, Inc., the Sponsor of the trial. Seungshin Rhee is an employee of Rho, Inc. and Helen Thackray is an employee of GlycoMimetics, Inc.

For further information please contact **hthackray@glycomimetics.com**

More information on this and related GlycoMimetics projects can be obtained at glycomimetics.com

GlycoMimetics, Inc.