First in Human Phase 1 Single Dose Escalation Studies of the E-Selectin Antagonist GMI-1271 Show a Favorable Safety, Pharmacokinetic, and Biomarker Profile

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Background

GMI-1271 is a potent, small molecule E-selectin antagonist. E-selectin inhibition has been shown to increase tumor sensitivity to chemotherapy by targeting the interactions between tumor cells and the bone marrow niche while suppressing hematopoietic stem cell mobilization. GMI-1271 is currently being investigated in the treatment of acute myeloid leukemia, multiple myeloma, and solid tumors.

In addition, E-selectin inhibition with GMI-1271 diminishes inflammation generated during an acute venous thromboembolism (VTE) thereby decreasing and delaying inflammatory cell recruitment into the post-thrombus vein wall. This phenomenon has been shown to decrease thrombus weight and has the potential to reduce complications of VTE. Cancer associated thrombosis is also a significant issue associated with decreased survival and both malignancy and chemotherapy are known pro-thrombotic risk factors. E-selectin inhibition, with GMI-1271, may have the potential to both treat malignancy and decrease the VTE risk associated with cancer and chemotherapy.

Here we report first-in-human evaluation of GMI-1271 with data gathered across two studies.

Study 1: GlycoMimetics, Inc. (GMI) healthy volunteer study.

Study 2: NHLBI Vascular Interventions/Innovations and Therapeutic Advances (VITA) Study performed at the University of Michigan.

Objectives

STUDY 1
Primary objective
- To assess the safety and tolerability of single intravenous (IV) doses of GMI-1271 when administered to healthy volunteers

Secondary objectives
- To assess the pharmacokinetics (PK) of single IV doses of GMI-1271 when administered to healthy adult subjects
- To assess the pharmacodynamics (PD) of single IV doses of GMI-1271 when administered to healthy adult subjects, including:
  - Drug specific biomarkers (e.g., soluble selectins and integrins, markers of the coagulation cascade, and other markers of cell activation and adhesion)
  - Evaluation of hematopoietic stem cells (HSC).

STUDY 2
Primary Objective
- To evaluate the safety and PK profile of GMI-1271 in a Phase 1 single ascending dose (SAD) study in healthy volunteers.

Secondary Objectives
- To evaluate the incidence of bleeding and other adverse events (AE)
- To evaluate the effects of GMI-1271 on the following biomarkers *(bolded markers presented in current analysis, remaining will be presented upon completion of the study)*:
  - Coagulation - **soluble P-selectin (sPsel), soluble E-selectin (sEsel)**, D-dimer, CRP, sTF, IL-10, von Willebrand factor activity, Prothrombin fragment 1.2, thrombin antithrombin complexes
  - Cell adhesion - **sICAM-1, CD34+ cell count**
  - Leukocyte and platelet activation - MAC1, LFA1, CD44, sCD40L, MPO, circulating free DNA, platelet monocyte aggregates (PMA).

Methods

Two Phase I single dose escalation, double-blind, placebo-controlled trials in healthy subjects are presented.

Patient Eligibility Criteria:
- Age 18-75
- Medically healthy (defined by absence of clinically significant screening assessment)
- No history of bleeding disorder (study 2 criterion only)
- BMI 18-35 k/m2
- No evidence of lower extremity VTE at baseline by ultrasound (study 2 criterion only)
- Voluntary consent to participate in the study
- No use of any prescription, investigational, or OTC medication within 14 days prior to study.
- Negative toxicology screening including alcohol and drug screen
- Negative HIV, Hepatitis B and C screening studies
- Liver function tests <1.4 times ULN and creatinine clearance >30ml/min

Methods

	STUDY 1	STUDY 2
Treatment Groups	GMI-1271 vs. Placebo	GMI-1271 vs. Placebo vs. Enoxaparin
Dose Levels	2, 5, 10 mg/kg	2, 5, 20, 40 mg/kg
Control	Placebo	Placebo; Enoxaparin (positive control)
Status	Complete, unblinded	Ongoing, remains blinded

The two studies are reported in aggregate. Partial biomarker data is reported for Study 2 (2mg/kg cohort only) and assessment of remaining cohorts will be reported separately once available.

Both studies included assessment and reporting of the following:
- Safety (Study 1 & 2 all dose levels): adverse events (AEs), clinical labs, bleeding time, PT/aPTT, vitals, and exam
- PK (Study 1 & 2 all dose levels): drug levels in plasma and urine
- Biomarkers (Study 1): sESel, sPSel, sICAM-1, CD34+
- Biomarkers (Study 2; cohort 2mg/kg only): sESel, sPSel, sICAM-1, CD34+

Analysis includes comparisons to baseline by ANOVA and paired t-test models. Both absolute comparison to baseline and change from baseline were assessed.

PK analyses was performed for total clearance (CL), volume of distribution (Vz), elimination half-life ($t_{½}$), fraction excreted (Fe), and renal clearance (CLr).

BIOMARKERS	ASSAY & LABORATORY
STUDY 1	
sESel	R&D Systems Quantikine ELISA; QPS, LLC., Newark, DE
sPsel	R&D Systems Quantikine ELISA; QPS, LLC., Newark, DE
sICAM-1	R&D Systems Quantikine ELISA; QPS, LLC., Newark, DE
CD34+	CD34 antigen; LabCorp Clinical Trials, Cranford, NJ
STUDY 2	
sESel	Affymetrix eBioscience ELISA; University of Michigan, Ann Arbor, MI
sPsel	R&D Systems Quantikine ELISA; University of Michigan, Ann Arbor, MI
sICAM-1	R&D Systems Quantikine ELISA; University of Michigan, Ann Arbor, MI
CD34+	CD34 antigen; LabCorp Clinical Trials, Cranford, NJ

Results

Cohort	Dose mg/kg	n	Age Median (Range)	Gender		Race			BMI Median (Range)
				Female n (%)	Male n (%)	Black or AA n	Native Hawaiian/ Pacific Islander n	White n	
Study 1									
GMI-1271	**2**	**6**	36 (21-52)	1 (17%)	5 (83%)	0	0	6	27.4 (24.4-29.5)
GMI-1271	**5**	**6**	28 (27-42)	2 (33%)	4 (67%)	0	1	5	27.2 (20.6-31.2)
GMI-1271	**10**	**6**	35.5 (29-45)	1 (17%)	5 (83%)	1	0	5	29.7 (23.5-31)
Placebo	**n/a**	**10**	31 (21-38)	3 (30%)	7 (70%)	0	0	10	26.1 (21.3-30.9)
Study 2									
GMI-1271/ Placebo	**2**	**5**	38.6 (20-47)	3 (60%)	2 (40%)	1	0	4	26.4 (21.2-31.1)
GMI-1271/ Placebo	**5**	**5**	39.2 (31-52)	3 (60%)	2 (40%)	1	0	4	29.3 (23-34.1)
GMI-1271/ Placebo	**20**	**5**	21 (1-25)	2 (40%)	3 (60%)	1	0	4	24.8 (19.7-34.4)
GMI-1271/ Placebo	**40**	**5**	33 (21-55)	0	5 (100%)	0	0	5	24.5 (19-32.7)
Enoxaparin	**1**	**4**	40.5 (23-57)	1 (25%)	3 (75%)	0	0	4	25.4 (22-29.8)

Results

Biomarkers

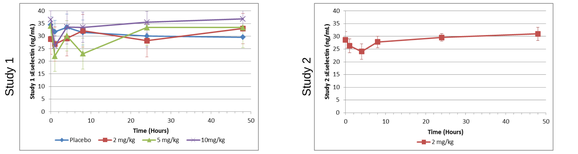
Biomarkers Summary
- Across both studies, absolute CD34+ and %CD34+ cell counts were normal indicating CD34+ cells are not mobilized into the periphery at any of the dose levels tested.
- Plasma concentrations of sEsel were reduced in subjects receiving GMI-1271, with significant reduction vs. baseline at multiple dose levels and timepoints; levels returned to baseline within 24-48 hours.
- While reductions were not as large or significant for sPsel or ICAM-1, individual timepoints at some of the dose levels tested did near or achieve significant reduction.

Mean absolute changes are shown; change from baseline was also assessed for all markers shown and did not substantially alter conclusions drawn.

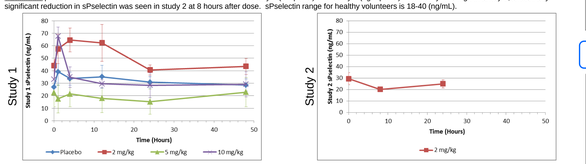
sEselectin plasma concentrations after IV administration of GMI 1271 – Study 1 (left panel) and Study 2 (right panel). Absolute mean values [ng/mL (SD)] are shown in table. Reductions were seen in both studies, reaching significance in study 1 at 5 and 10 mg/kg. sEselectin range for healthy volunteers is 13.0-51.3 (ng/mL

Time (hrs) →		0	0.167	0.333	0.417	0.667	1	1.5	2	3	4	5	6	8	10	12	24	48
Study 1	Placebo	34.5 (3.2)	30.4 (4.5)	29.1 (5.2)	27.5 (5.0)	29.2 (4.4)*	31.7 (2.5)	29.3 (4.1)	28.6 (5.2)	30.2 (5.4)*	33.5 (3.0)	30.1 (4.5)	28.7 (3.9)	31.4 (3.6)*	28.8 (4.2)	29.6 (4.2)	30.0 (4.2)	29.5 (4.5)
	2 mg/kg	28.8 (6.0)	26.0 (6.8)	26.1 (7.0)	25.4 (6.5)	26.9 (6.5)	26.8 (6.0)	27.3 (6.7)	29.2 (7.4)	30.4 (8.1)	29.1 (7.3)	29.2 (7.3)	29.4 (7.4)	32.1 (8.7)	30.5 (8.7)	25.6 (5.5)	28.2 (5.8)	33.0 (7.5)
	5 mg/kg	34.0 (6.4)	13.5 (6.0)§	13.4 (6.0)§	13.8 (6.2)§	15.6 (7.1)§	22.1 (8.1)§	19.7 (6.9)†	21.7 (7.9)‡	21.6 (7.7)†	30.1 (8.3)†	22.2 (7.8)	18.6 (8.5)†	23.0 (7.9)‡	21.3 (7.2)†	31.0 (8.4)†	33.4 (9.7)	33.4 (6.5)
	10mg/kg	36.5 (3.5)	24.5 (4.1)§	13.9 (6.8)§	16.6 (6.0)§	23.9 (4.3)§	26.0 (4.4)§	27.4 (4.6)§	28.2 (4.9)§	30.3 (5.1)§	33.6 (5.4)†	32.0 (4.9)	33.3 (5.3)*	33.5 (5.3)	33.2 (5.1)	33.3 (2.8)	35.5 (3.9)	36.8 (3.5)
Study 2	Placebo	27.5 (5.5)					27.5 (6.2)				25.6 (6.5)			29.5 (7.4)			29.9 (4.6)	29.2 (6.6)
	2 mg/kg	28.7 (3.2)					26.3 (2.7)				24.0 (3.1)			27.8 (2.2)			29.6 (1.5)	31.0 (2.6)

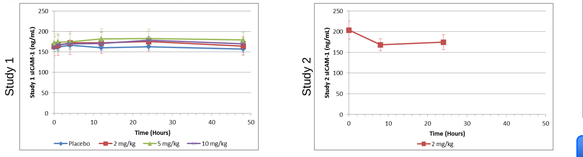
p-value for comparison at each time point to baseline: *p ≤ 0.05; †p ≤ 0.01; ‡p ≤ 0.001; §p ≤ 0.0001



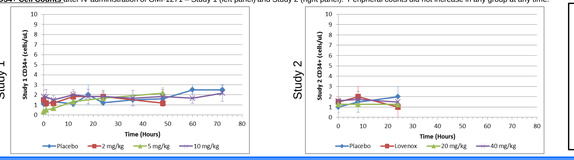
sPselectin plasma concentrations after IV administration of GMI 1271 – Study 1 (left panel) and Study 2 (right panel). Variability was high in Study 1; statistically significant reduction in sPselectin was seen in study 2 at 8 hours after dose. sPselectin range for healthy volunteers is 18-40 (ng/mL).



sICAM-1 plasma concentrations after IV administration of GMI 1271 – Study 1 (left panel) and Study 2 (right panel). Reduction was seen in study 2 but did not reach statistical significance. sICAM-1 range for healthy volunteers is 102-381 (ng/mL).



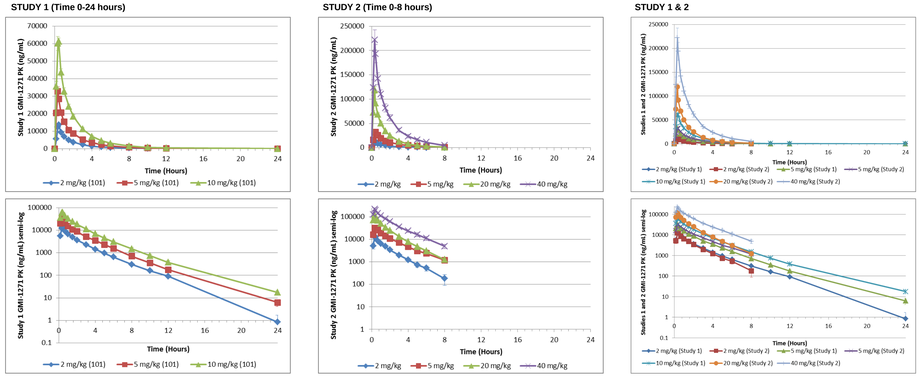
CD34+ Cell Counts after IV administration of GMI-1271 – Study 1 (left panel) and Study 2 (right panel). Peripheral counts did not increase in any group at any time.



Pharmacokinetics

Pharmacokinetics Summary
- Plasma concentrations and C_{max} are consistent for GMI-1271 between Study 1 and Study 2
- Plasma levels, C_{max}, and AUC increased in a consistent dose-related manner in Study 1 and Study 2
- CL, Vz, and $t_{½}$ were not dose dependent; $t_{½}$ ranged between 1.6 and 2.3 hours
- Majority (~ 66%) of the dose was excreted unchanged in the urine independent of dose level. CLr averaged 86 mL/min, which is less than estimated CrCl and suggests that tubular reabsorption is one component of CLr

PK Analysis: GMI-1271 plasma concentrations after IV administration of GMI-1271 - linear (top panel) and semi-logarithmic (bottom panel) axes.



Safety

Safety Summary
- All subjects completed respective studies
- No clinically significant findings were seen in laboratory analysis, vital signs, ECG testing, and physical exams
- No changes seen with GMI-1271 in bleeding time or coagulation studies including PT/aPTT
- No reported SAEs
- Conclusion - GMI-1271 was well tolerated and demonstrated a benign safety profile in these studies

AEs occurring in ≥ 2 subjects	GMI-1271 2 mg/kg (N=11) n (%)	GMI-1271 5 mg/kg (N=11) n (%)	GMI-1271 10 mg/kg (N=6) n (%)	GMI-1271 20 mg/kg (N=5) n (%)	GMI-1271 40 mg/kg (N=5) n (%)	Study 1 Placebo (N=10) n (%)	Enoxaparin (N=4) n (%)	Overall (N=52) n (%)
Active	10	10	6	4	4	10	4	48
Placebo (blinded, included)	1	1	0	1	1	0	0	4
Any AE	8 (73)	8 (73)	4 (67)	5 (100)	5 (100)	5 (50)	4 (100)	39 (75)
Fatigue	1 (9)	0	0	0	0	1 (10)	0	2 (4)
Headache	1 (9)	2 (18)	0	2 (40)	1 (20)	0	0	6 (12)
Infusion site AE	3 (27)	6 (55)	1 (17)	1 (20)	1 (20)	4 (40)	1 (25)	17 (33)
Oropharyngeal pain	0	1 (9)	1 (17)	0	0	0	0	2 (4)
Presyncope	1 (9)	1 (9)	0	1 (20)	0	0	0	3 (6)
Rash	0	3 (27)	0	0	4 (80)	0	2 (50)	9 (17)
Upper respiratory tract infection	0	1 (9)	0	0	1 (20)	0	0	2 (4)

All above AEs reported as mild
All above AEs reported as unrelated to GMI-1271/placebo
All rashes were localized and most were related to adhesive bandage use

The following occurred in <2 subjects:
- Moderate AE: infusion site pain occurring in 1 subject in dosing cohorts 2, 5, 10, and placebo
- Possibly related AEs : dizziness, dysgeusia, blood in urine (enoxaparin cohort), headache
- Definitely related AE: injection site bruise for 1 subject in the enoxaparin cohort

Summary and Conclusions

- **GMI-1271 is well tolerated with a favorable safety profile and no evidence of changes in bleeding time**
- **GMI-1271 shows a consistent PK profile from 2mg/kg to 40mg/kg**
- **Biomarkers show reductions in both sEsel and sPsel showing on-target effects of GMI-1271**
- **Decreased sICAM-1 levels with GMI-1271 are of interest for possible decreased leukocyte adhesion**
- **Stable CD34+ levels indicate no mobilization of HSCs**

The potential anti-thrombotic effects of GMI-1271 may provide a clinical advantage in both the treatment of isolated VTE as well as cancer related VTE as this compound has a benign safety profile with minimal bleeding risk. Studies of GMI-1271 are ongoing to evaluate activity in both hematologic malignancies and thrombosis.

Conflict of Interest Disclosures: M Hemmer, H Flanner, C Nietubicz, J Magnani, and H Thackray are employees of and have equity ownership in GlycoMimetics, Inc. W Kramer performed PK analysis under contract with GlycoMimetics, Inc. D Myers and T Wakefield received research funding from GlycoMimetics, Inc.
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