SINGLE ASCENDING DOSE PHARMACOKINETICS OF THE E-SELECTIN/CXCR4 DUAL ANTAGONIST GMI-1359 AFTER INTRAVENOUS INFUSIONS OF 0.1, 0.2, 0.5, 1, 2, AND 3.5 MG/KG TO HEALTHY VOLUNTEERS.

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Introduction

GMI-1359 is a dual antagonist of both E-selectin and C-X-C chemokine receptor Type 4 (CXCR4). The proposed mechanism of action is the interference of E-selectin and CXCR4 binding with E-selectin ligands or CXCL12 (SDF-1α, the natural ligand of CXCR4), respectively, in the tumor microenvironment and periphery. One important outcome of this dual antagonism is the potential for mobilization of tumor cells from the bone marrow (BM)/tumor microenvironment to the systemic circulation, thereby making tumor cells more susceptible to the cytotoxic effects of standard-of-care chemotherapeutic agents.

Objectives

Determine the safety and pharmacokinetics (PK) of GMI-1359 in healthy adult volunteers after administration of a single dose.

Materials and methods

Subjects and Drug Administration

Seven cohorts of healthy volunteers were randomized to receive a single 60 minute intravenous infusion of GMI-1359 at doses of 0.1, 0.2, 0.5, 1.0, 2.0 and 3.5 mg/kg (2 cohorts). In each cohort subjects were randomly assigned to receive active or placebo. Plasma and urine samples were collected for bioanalysis.

Bioanalysis

Plasma and urine samples were analyzed for GMI-1359 using validated LC/MS/MS assays.

Pharmacokinetic Analysis

PK parameters for GMI-1359 were calculated using non-compartmental analysis. Only plasma and urine concentrations that were equal to or greater than the LOQ for the respective assay (0.02 µg/mL in plasma and 0.5 µg/mL in urine) were used in the PK analysis. PK parameters included Cmax, Tmax, AUC(0-t), AUC(inf), t1/2, Kel, CL, Vz , Ue, Fe, and CLr.

Data and Results

The maximum tolerated dose of GMI-1359 was not identified. Analysis of the plasma and urine concentration data from the single ascending dose study revealed the following:

- A dose related increase in concentration (*Figure 1*)
- Linear PK over the dose range 0.1 to 3.5 mg/kg *(Figures 2 and 3)*
- Plasma and renal clearances, volume of distribution, and t½ (~3 hr) were independent of dose.*(Table 1)*
- Urinary recovery was somewhat dependent on dose, ranging from 31 to 70% of dose (*Figure 4)*

Figure 1: Geometric mean plasma concentrations of GMI-1359 after IV administration of 0.1, 0.2, 0.5, 1, 2 and 3.5 mg/kg single doses over one hour to healthy volunteers.

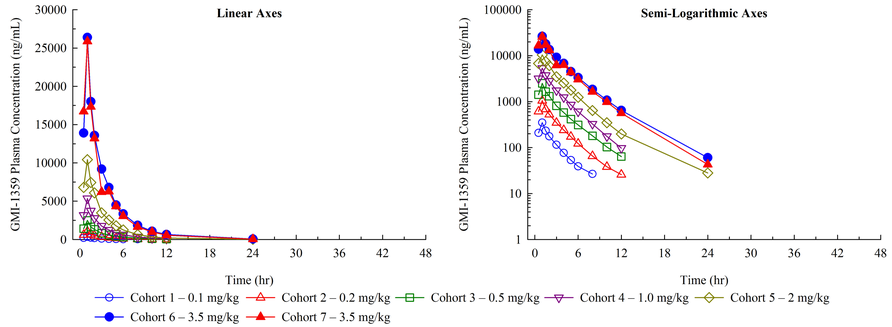


Table 1: Summary of pharmacokinetic parameters for GMI-1359 after IV administration over 1 hour to healthy volunteers (non-compartmental analysis)

Parameter*	Cohort 1 0.1 mg/kg	Cohort 2 0.2 mg/kg	Cohort 3 0.5 mg/kg	Cohort 4 1 mg/kg	Cohort 5 2 mg/kg	Cohort 6 3.5 mg/kg	Cohort 7 3.5 mg/kg	Cohorts 6&7 3.5 mg/kg
Cmax (ng/mL)	349 [14.4] (6)	1,056 [13.0] (6)	2,500 [13.0] (6)	5,346 [17.3] (6)	10,426 [11.3] (6)	26,387 [12.7] (6)	25,881 [19.3] (5)	26,155 [15.2] (11)
Tmax (hr)	1.02 (6) [1.02 – 1.02]	1.03 (6) [1.02 – 1.04]	1.03 (6) [1.02 – 1.06]	1.03 (6) [1.02 – 1.07]	1.03 (6) [1.02 – 1.03]	1.03 (6) [1.03 – 1.03]	1.03 (5) [1.01 – 1.03]	1.03 (11) [1.01 – 1.03]
AUC(0-t) (hr×ng/mL)	817 [13.1] (6)	2,740 [13.3] (6)	6,712 [13.3] (6)	14,120 [12.7] (6)	29,860 [10.4] (6)	76,087 [17.4] (6)	72,293 [7.38] (5)	74,338 [13.4] (11)
AUC(inf) (hr×ng/mL)	915 [11.9] (6)	2,827 [13.3] (6)	6,957 [14.3] (6)	14,431 [12.9] (6)	30,207 [10.1] (6)	76,392 [17.4] (6)	72,500 [7.34] (5)	74,597 [13.4] (11)
λz (1/hr)	0.3369 [20.1] (6)	0.3197 [15.2] (6)	0.2744 [12.5] (6)	0.3182 [5.63] (6)	0.2490 [33.3] (6)	0.2112 [7.80] (6)	0.2267 [7.96] (5)	0.2181 [8.34] (11)
t½ (hr)	2.06 [20.1] (6)	2.17 [15.2] (6)	2.53 [12.5] (6)	2.18 [5.63] (6)	2.78 [33.3] (6)	3.28 [7.80] (6)	3.06 [7.96] (5)	3.18 [8.34] (11)
CL								
(L/hr)	8.24 [10.5] (6)	5.12 [11.8] (6)	5.88 [18.0] (6)	5.34 [8.93] (6)	4.34 [17.1] (6)	3.64 [9.92] (6)	3.49 [18.7] (5)	3.57 [13.9] (11)
(L/hr/kg)	0.109 [11.9] (6)	0.071 [13.3] (6)	0.072 [14.3] (6)	0.069 [12.9] (6)	0.066 [10.1] (6)	0.046 [17.4] (6)	0.048 [7.34] (5)	0.047 [13.4] (11)
Vz								
(L)	24.5 [21.4] (6)	16.0 [13.1] (6)	21.4 [14.6] (6)	16.8 [5.27] (6)	17.4 [32.3] (6)	17.2 [17.2] (6)	15.4 [11.8] (5)	16.4 [15.4] (11)
(L/kg)	0.324 [18.7] (6)	0.221 [9.57] (6)	0.262 [10.6] (6)	0.218 [12.0] (6)	0.266 [26.1] (6)	0.217 [21.9] (6)	0.213 [13.4] (5)	0.215 [17.6] (11)
Urinary Excretion								
Amount (µg)	2,363 [54.1] (6)	7,193 [36.4] (6)	24,274 [49.2] (6)	46,488 [51.6] (6)	62,421 [46.7] (6)	193,583 [30.9] (6)	126,204 [23.2] (5)	159,374 [35.1] (11)
Percent of Dose	31.3 [59.1] (6)	49.7 [26.4] (6)	59.4 [38.3] (6)	60.3 [39.6] (6)	47.7 [49.6] (6)	69.6 [31.6] (6)	49.9 [39.4] (5)	59.8 [38.1] (11)
CLr (mL/min)	43.1 [59.2] (6)	42.4 [25.1] (6)	58.2 [41.4] (6)	53.7 [49.2] (6)	34.4 [38.0] (6)	42.2 [41.3] (6)	29.0 [25.7] (5)	35.6 [39.1] (11)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [range] is reported.

Figure 2: Relationship between GMI-1359 Cmax and total dose

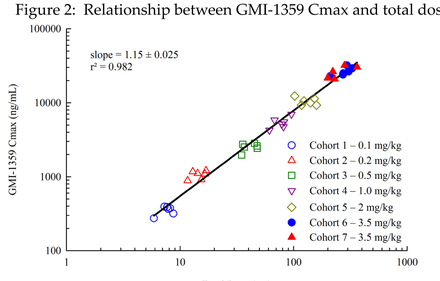


Figure 3: Relationship between GMI-1359 AUC and total dose

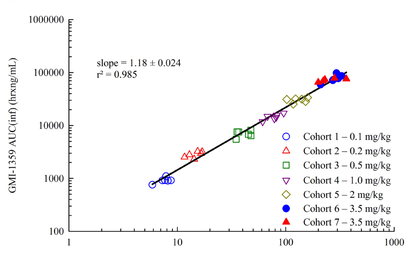
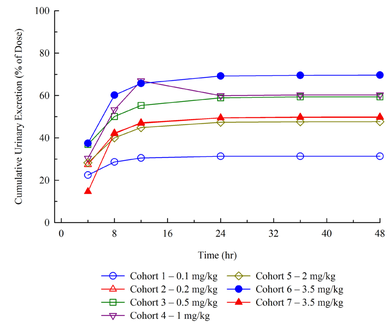


Figure 4: Geometric mean cumulative urinary excretion of GMI-1359 after IV administration of 0.1, 0.2, 0.5, 1, 2 and 3.5 mg/kg single doses over one hour to healthy volunteers.



Conclusions

The PK in humans are consistent with preclinical evaluations confirming successful rational design of this new molecular entity to maximize drug-like properties such as half-life. There was a dose proportional increase in exposure with low between-subject variability. GMI-1359 demonstrates PK parameters that are well suited to administration in an acute care setting and support continuing development of this important new molecular entity.

For further information

Please contact *hthackray@glycomimetics.com*. More information on this and related GlycoMimetics, Inc. projects can be obtained at *www.glycomimetics.com*

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