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.

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

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

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

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Cmax (µg/mL)</th>
<th>Tmax (hr)</th>
<th>AUC(0-t) (µg*h/mL)</th>
<th>AUC(inf) (µg*h/mL)</th>
<th>t1/2 (hr)</th>
<th>Kel (L/h)</th>
<th>CL (L/h)</th>
<th>Vz (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.024 ± 0.005</td>
<td>6 ± 3</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>4 ± 2</td>
<td>0.001 ± 0.000</td>
<td>1.0 ± 0.5</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>0.2</td>
<td>0.081 ± 0.013</td>
<td>6 ± 3</td>
<td>1.0 ± 0.5</td>
<td>1.0 ± 0.5</td>
<td>4 ± 2</td>
<td>0.002 ± 0.001</td>
<td>2.0 ± 1.0</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td>0.5</td>
<td>0.21 ± 0.04</td>
<td>6 ± 3</td>
<td>2.5 ± 0.7</td>
<td>2.5 ± 0.7</td>
<td>4 ± 2</td>
<td>0.003 ± 0.001</td>
<td>5.0 ± 2.5</td>
<td>2.5 ± 1.2</td>
</tr>
<tr>
<td>1.0</td>
<td>0.43 ± 0.07</td>
<td>6 ± 3</td>
<td>5.0 ± 1.0</td>
<td>5.0 ± 1.0</td>
<td>4 ± 2</td>
<td>0.006 ± 0.001</td>
<td>10.0 ± 5.0</td>
<td>5.0 ± 2.5</td>
</tr>
<tr>
<td>2.0</td>
<td>0.86 ± 0.14</td>
<td>6 ± 3</td>
<td>10.0 ± 2.0</td>
<td>10.0 ± 2.0</td>
<td>4 ± 2</td>
<td>0.012 ± 0.001</td>
<td>20.0 ± 10.0</td>
<td>10.0 ± 5.0</td>
</tr>
<tr>
<td>3.5</td>
<td>1.29 ± 0.23</td>
<td>6 ± 3</td>
<td>15.0 ± 3.0</td>
<td>15.0 ± 3.0</td>
<td>4 ± 2</td>
<td>0.018 ± 0.001</td>
<td>30.0 ± 15.0</td>
<td>15.0 ± 7.5</td>
</tr>
</tbody>
</table>

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.