Comparison of Predicted GMI-1070 Human Intravenous Pharmacokinetics from in silico PBPK and Allometric Scaling Models

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Introduction

GMI-1070, a novel, glycomimetic inhibitor of E-, P- and L- selectins, is being developed for the treatment of vaso-occlusive crisis in patients with sickle cell disease. This new molecular entity has been rationally designed to maximize properties such as half-life, metabolism, and safety profile in addition to the high in vitro affinity and selectivity exhibited toward selectins. The predicted pharmacokinetics in human via intravenous administration was important for the selection of the molecular structure and provides validation of animal models or in silico models for future lead candidate selection.

Objectives

Predict human pharmacokinetics of GMI-1070 in human from animal data using allometric scaling.

Predict human pharmacokinetics of GMI-1070 in humans from in vitro ADME data using an in silico PBPK model.

Compare allometric scaling and PBPK modeling predictions.

Materials and Methods

Animal Studies
Mice and rats were administered a 20mg/kg injection of GMI-1070. The pharmacokinetics in mice was determined from a composite of one sample of three mice per timepoint. The pharmacokinetics in rats was determined from a composite of 3 rats per timepoint. Each rat was sampled three times over the course of 24 hours. Four Cynologous monkeys were administered a 150mg/kg injection of GMI-1070. The pharmacokinetics was determined from PK samples taken over 24 hours.

Human Studies
Five cohorts of healthy volunteers were randomized to receive a single 20 minute intravenous infusion of GMI-1070 at doses of 2, 5, 10, 20 and 40 mg/kg. Each cohort consisted of 8 subjects, 2 of which were randomly assigned to receive placebo. Plasma and urine samples were collected for bioanalysis.

Bioanalysis
A HPLC/UV method was utilized to determine GMI-1070 concentrations in mice and rats. A validated LC/MS/MS method was utilized to determine GMI-1070 concentrations in monkeys and humans. Both methods provide comparable results as evidenced from later rodent studies analyzed a validated LC/MS/MS method.

Pharmacokinetic Analysis
PK parameters for GMI-1070 were calculated using non-compartmental analysis. Only plasma concentrations that were equal to or greater than the LOQ for the respective assay were used in the PK analysis. PK parameters included Cmax, Tmax, AUC(0-t), AUC(inf), $t_{1/2}$, Kel, CL, and Vz .

Materials and Methods (continued)

Allometric Scaling
The PK parameters Vz and CL from mouse, rat, and monkey were scaled via allometry to arrive at a prediction of human Vz and CL. A power equation of the form $y=x^a$ was fitted to a log-log plot of the PK parameter of interest vs. weight, and the square of the correlation coefficient determined. Human parameters were predicted from the fitted equations.

PBPK Modeling
Gastro Plus™ was utilized to develop a PBPK model for GMI-1070 pharmacokinetics in humans. Physicochemical properties such as pKa, logD, and molecular weight and ADME properties such as hepatocyte stability across species, interaction with CYPs, and cross species protein binding were used as inputs for the PBPK model. The PBPK model was then utilized to predict human pharmacokinetic parameters, Vz, CL, and half-life.

Results

Allometric Scaling

A plot of the allometric scaling of GMI-1070 is provided in Figure 1 below. Inspection of the allometric scaling data revealed the following:

- Good correlation for both Clearance and Volume of Distribution with weight, $r^2 > 0.97$
- Fitted exponent for both Clearance and Volume of Distribution in the expected range

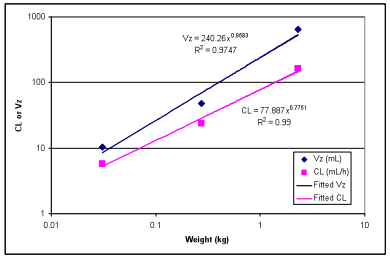

Figure 1. Relationship Between the Clearance and Volume of Distribution in the mouse, rat and monkey and weight after IV administration of GMI-1070

PBPK Modeling

A human PBPK model for GMI-1070 was set up within Gastro Plus™ utilizing the following physicochemical and ADME properties:

- Molecular weight: 1535
- LogD: -1 @ pH 7.4 and pKa values of four ionizable groups
- Negligible hepatocyte metabolism and CYP interaction
- 75% protein binding
- Negligible degradation in plasma

Predictions of human Vz and Cl were obtained with the model as well as predicted human plasma profiles of GMI-1070.

Single Ascending Dose Study in Humans

Human pharmacokinetic parameters for comparison of the two predictive techniques was obtained from a Phase 1 study, 1070-101. Analysis of the plasma and urine concentration data from the single ascending dose study revealed the following:

- Linear PK over the dose range 2 – 40 mg/kg *Figs. 2, 3*
- Elimination half-life of approximately 7 hours
- A minimum of 90% of GMI-1070 is recovered in the urine

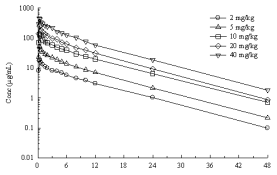

Figure 2. Mean Plasma Concentrations of GMI-1070 After Intravenous Administration of Single 2 to 40 mg/kg

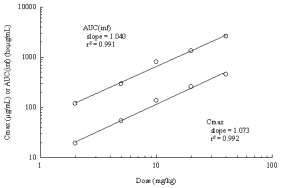

Figure 3. Relationship Between the Mean Cmax and AUC(Inf) and Dose of GMI-1070 After Intravenous Administration of Single 2 to 40 mg/kg Doses

Comparison of Human PK Predictions

The observed human pharmacokinetic parameters were compared to the predicted values from allometric scaling and PBPK modeling, and a % prediction error was calculated (Table 1).

Table 1. Predicted versus Observed Human PK Parameters

	Allometry		Gastro Plus PBPK		Human
Parameter	Pred.	PE (%)	Pred.	PE (%)	Observed
Vz (L)	14.6	32.7	15.6	41.8	11
Cl (L/h)	2.1	90.9	1.9	72.7	1.1
t1/2 (h)	4.6	34.3	5.7	18.6	7

Analysis of the data in Table 1 reveals the following:

- Half-life predictions are within 50% prediction error
- Prediction error highest for clearance at > 70%
- Clearance and Vz overestimated by both techniques
- Half-life underestimated by both techniques
- Both methods give approximately the same predicted values of Vz, CL and $t_{1/2}$ and are not that different from observed values

PBPK Plasma Profile Prediction

The PBPK model predicted vs observed human PK profile for 2, 5, and 20 mg/kg doses was plotted, *Fig. 4*. The predicted profile was surprisingly close considering the PBPK model was based only physicochemical and in vitro ADME data.

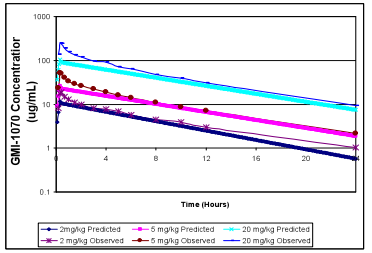

Figure 4. PBPK Model Predicted and Observed Human PK Profile for GMI-1070

Conclusions

Allometric scaling and PBPK modeling were both found to predict the plasma half-life of GMI-1070 within a 50% prediction error of the observed half-life of ~ 7 to 8 hours after a single and multiple doses. For both models, the predicted Clearance was the least accurate parameter, with a prediction error of greater than 70%. Clearance and volume of distribution were overestimate for GMI-1070 in both models.

The PBPK model offers a potentially less expensive route to human PK predictions for discovery and early development compounds, since the model is based on physicochemical and in vitro ADME data which have low material and analytical method requirements. Both techniques provide suitable mechanisms to predict human PK.

GMI-1070, a rationally designed pan selectin inhibitor, is well suited to human PK predictions via the classical allometric scaling model and the contemporary PBPK model. Additional compounds from the GlycoMimetics, Inc. pipeline will be examined in the future to establish whether one technique is preferable for this novel class of compounds.

For further information

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

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