



PHARMACOKINETIC MODELING OF ACH-2684, A HEPATOSELECTIVE PHASE I PAN-GENOTYPIC HCV NS3 PROTEASE INHIBITOR: PREDICTIONS AND CORRELATION WITH HUMAN PHARMACOKINETICS

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ABSTRACT P361
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BACKGROUND

The use of pharmacokinetic modeling and simulation programs, such as GastroPlus (Simulations Plus, CA) has become an integral part of drug discovery and development. These programs can be employed to predict dosage regimens, assess formulation strategies, and discern underlying processes for the observed data. Typically, models are initiated at the preclinical stage with ongoing optimization as the program progresses through clinical development.

ACH-2684, a pan-genotypic HCV NS3 protease inhibitor, is in Phase 1 for treatment of Hepatitis C (HCV). The compound demonstrates picomolar in vitro potency against HCV NS3 proteases and clinical trials demonstrating proof of concept in HCV GT-1- and GT-3-infected individuals are ongoing. The aim of this work was to characterize the hepatoselectivity of ACH-2684 and to utilize these observations and other preclinical data to retrospectively model human pharmacokinetic data obtained in healthy volunteers (clinical trial ACH684-001).

METHODS

Preclinical Studies

- Intravenous pharmacokinetic profiling was conducted in rats, dogs, and monkeys. The concentration of ACH-2684 in plasma and tissue homogenates (where applicable) was analyzed by LC-MS/MS.
- ACH-2684 hepatic uptake was studied using isolated human and rat cryopreserved hepatocytes. ACH-2684 was incubated with hepatocytes for 25 sec up to 2 min at 4°C and 37°C. At discrete time points, intact hepatocytes were separated from media by oil centrifugation and the cellular concentration of ACH-2684 was measured by LC-MS/MS. Intrinsic clearance was calculated from the rate of active (37°C - 4°C) uptake over time.

Clinical Trial ACH684-001

- Consenting healthy volunteers were enrolled for participation in Segment 1, single ascending dose, to assess ACH-2684 safety and pharmacokinetics. ACH-2684 was administered in the fasted state as a 50 or 100 mg/mL solution in Cremophor® RH40:Lutrol® F127:ethanol:water (5:10:5:80) with flavoring. The dose was followed by a 100- mL water intake. A robust plasma sample design was employed and ACH-2684 concentrations were measured in plasma using a validated LC-MS/MS assay. Pharmacokinetics were determined using noncompartmental modeling.

Pharmacokinetic Modeling

- The Advanced Compartmental Absorption and Transit (ACAT) model in GastroPlus™ (Simulations Plus, Lancaster, CA) was used to simulate human pharmacokinetics after an oral dose of ACH-2684. The 2-compartment ACAT model was developed in the dog using intravenous pharmacokinetic parameters to describe distribution and elimination characteristics. ACAT parameters were estimated through experimental or in silico predictions (Table 1) as well as program default parameters. The dog absorption model was fit to the plasma profile observed following oral administration of a capsule formulation of Cremophor® RH40:Lutrol® F127:ethanol:water (5:10:5:80) to the fasted dog. Optimized dog ACAT model parameters were then used to develop the human pharmacokinetic model using clinical data from the 10 mg ACH-2684 dose group. Emerging clinical data were used to refine the model. Development of the final model included scaling from nonclinical pharmacokinetics, improved ACH-2684 solubility in the clinical formulation, and a first-pass hepatic extraction supported by the observation of active uptake of ACH-2684 into human hepatocytes observed in vitro. Virtual trials randomizing clearance and volume of distribution parameters of the optimized model were conducted using 25 simulations per trial.

DISCLOSURES
KS, EO, JR, CM, LR, MH, AP, and MD are employees of Achillion Pharmaceuticals

RESULTS

1 NONCLINICAL STUDIES

Figure 1. Plasma and Liver Concentrations in the Rat and the Dog After a 1 mg/kg Intravenous Dose

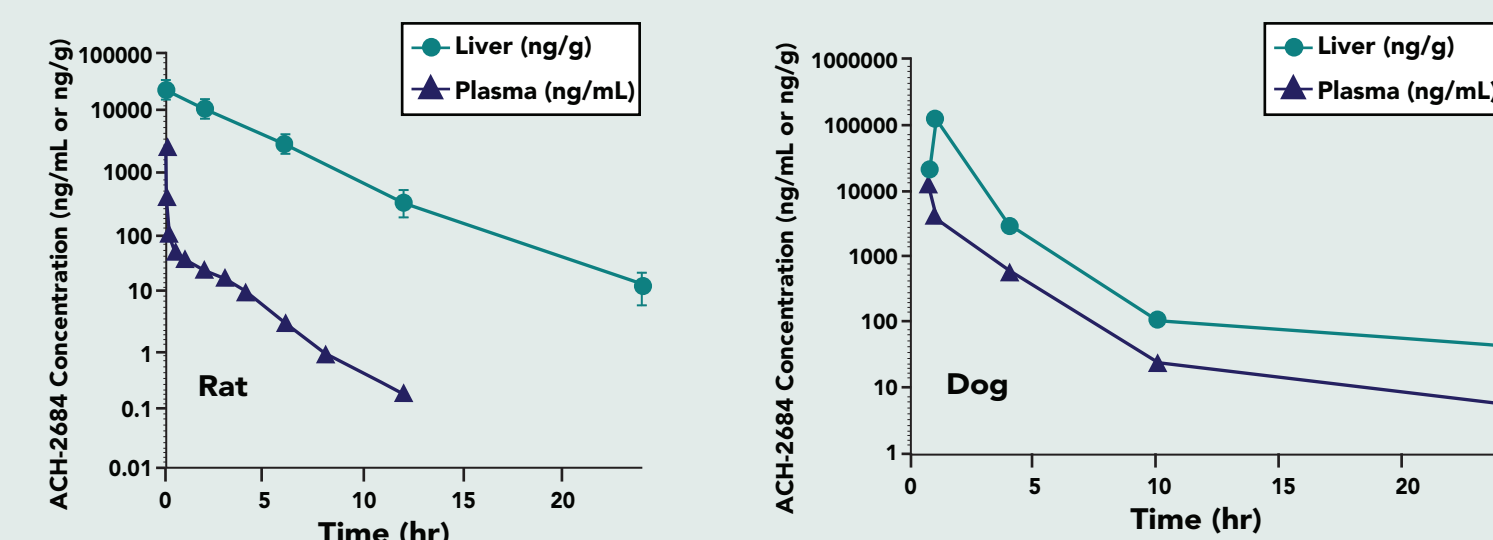
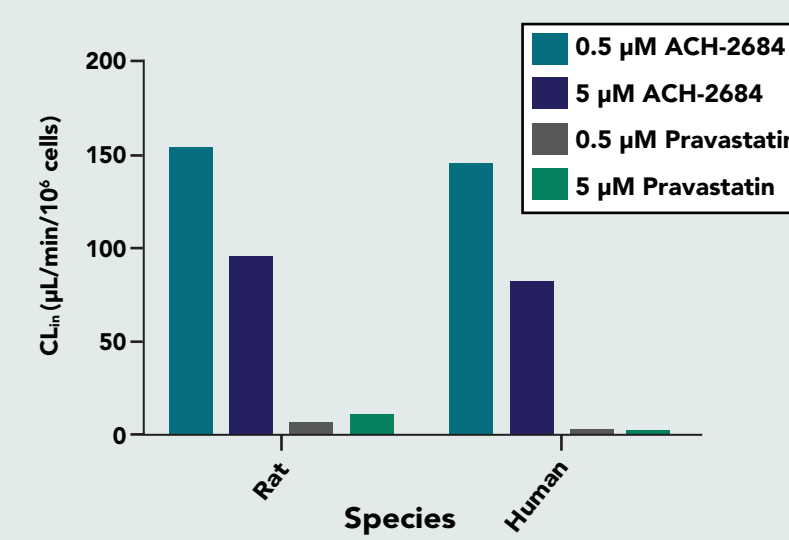


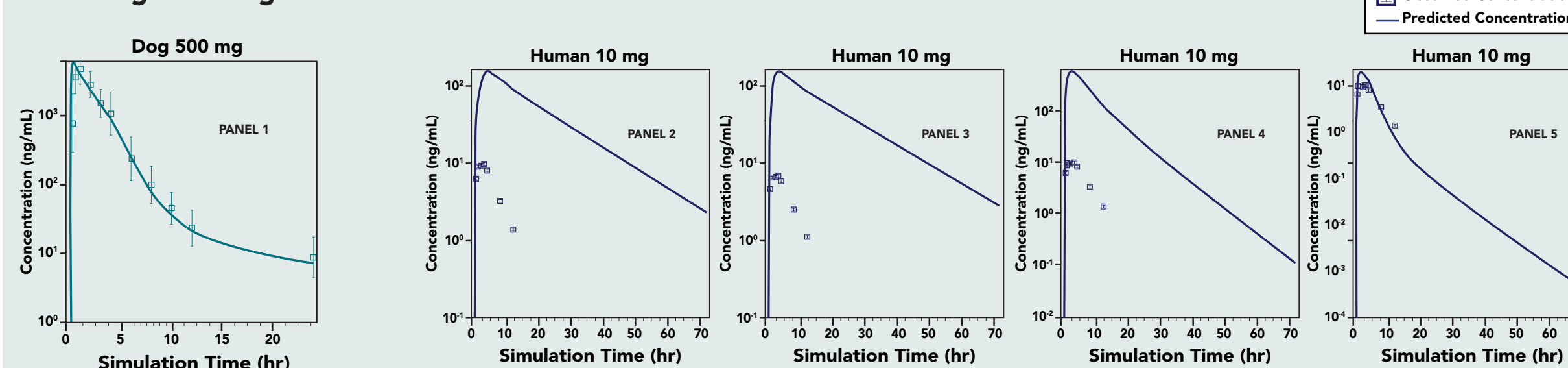
Figure 2. Uptake of ACH-2684 into Isolated Rat and Human Hepatocytes



- ACH-2684 demonstrated hepatoselective distribution in the rat and the dog, in which maximal liver-to-plasma ratios reached 6 to >500-fold in the dog and rat, respectively
- Additionally, active uptake of ACH-2684 was demonstrated in isolated rat and human hepatocytes. Saturation of uptake was suggested by the lower intrinsic clearance observed at 5 µM compared with 0.5 µM concentrations.

2 MODEL OPTIMIZATION

Figure 3. Predicted Versus Observed Plasma ACH-2684 Concentrations in the Dog Following a 500 mg Dose



- Panel 1:** Optimization of the dog plasma concentration profile was achieved with the ACAT model using ACH-2684 aqueous solubility and lower hepatic extraction based on dog liver:plasma values shown after intravenous dosing
- Panel 2:** Simulation of 10 mg dose with optimized ACAT parameters from dog simulations using human clearance and volume of distribution predicted by allometry
- Panel 3:** Input of improved ACH-2684 solubility in dilutions of SIF with clinical formulation than undiluted SIF
- Panel 4:** Clearance was modified to reflect the average of in vitro metabolic clearance and allometric predictions
- Panel 5:** The model was fit to observed data by predicting an hepatic extraction of 90% that was supported by the extensive active uptake into hepatocytes observed in vitro

Table 1. Final Model Inputs

Parameters	Value	Data Source
PKa	3.23, 6.88	Measured
Log D	5.6	In silico prediction
Aqueous solubility (pH 7.4)	6 µg/mL	Measured
Solubility (SIF diluted with clinical formulation)	0.04, 0.2, 0.8, 1.2, and 1.6 mg/mL at 10, 50, 200, 300, and 400 mg respectively 500 mg: 1.6 mg/mL	Dose (mg) / 250 (mL) ACH-2684 maximum solubility measurements of ~ 1.6 mg/mL in solutions of dose vehicle diluted into simulated intestinal fluid
Permeability (Human P _{eff})	1.12 X 10 ⁻⁴ cm/s	Measured in Caco-2 cells; conversion to P _{eff}
Vc	0.385	Allometric prediction
CL	0.166	Mean of in vitro metabolic CL and allometric prediction
Liver extraction	90% - 55%	Fitted to data (90%, 90%, 90%, 70%, 55%, and 55% at 10, 50, 200, 300, 400, and 500 mg, respectively)
Absorption scale factor c3	0.012147	Fitted to data
Absorption scale factor c4	0.046632	Fitted to data

3 SIMULATION RESULTS

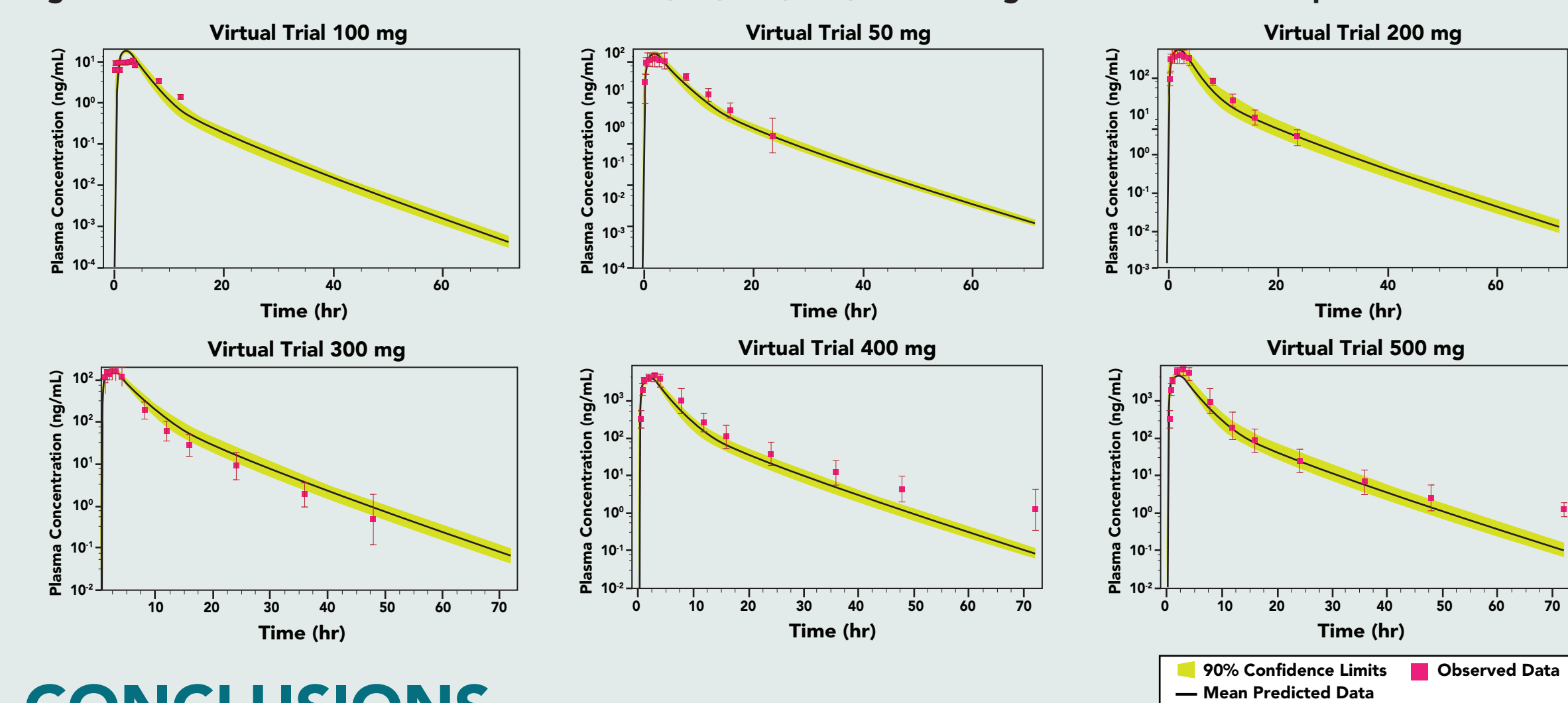
Table 2. Comparison of Predicted Mean (% CV) ACH-2684 Pharmacokinetic Parameters With Those Obtained From Human Volunteers After Oral Administration in Clinical Trial ACH684-001

PK Parameter	Unit(s)	Dose (mg)											
		10		50		200		300		400		500	
		Obs	Sim	Obs	Sim	Obs	Sim	Obs	Sim	Obs	Sim	Obs	Sim
C _{max}	ng/mL	10.4 (60)	18.6 (21)	80.2 (51)	101 (20)	632 (46)	580 (18)	1920 (53)	1870 (18)	5180 (31)	4650 (24)	4520 (39)	4098 (16)
T _{max}	hr	1.9 (42)	2.2 (11)	2.0 (35)	2.0 (8)	1.9 (37)	2.09 (12)	2.5 (32)	2.2 (11)	2.3 (17)	2.0 (24)	2.7 (30)	2.08 (12)
AUC _{0-∞}	ng-hr/mL	69.2 (56)	96 (44)	502 (47)	496 (35)	2940 (43)	3080 (46)	8810 (51)	10900 (43)	27600 (45)	22800 (65)	20200 (44)	19100 (45)

Obs: observed value
Sim: simulated value

- ACH-2684 was safe and well-tolerated during treatment
- Virtual trials predicted pharmacokinetic parameters (C_{max}, AUC, and T_{max}) that were within 2-fold of observed results
- ACH-2684 plasma concentrations were linear over the dose range of 10 and 50 mg ACH-2684. At higher doses, the pharmacokinetics were nonlinear showing an approximate 10-fold increase in exposure across a 2-fold (200-400 mg) dose range. The nonlinearity was modeled by the input of a decreased liver extraction in the nonlinear region.
- The highest dose, 500 mg, showed an apparent concentration plateau. Solubility experiments conducted with clinical formulations diluted in simulated intestinal fluid suggested that maximal solubility was attained at 1.6 mg/mL. Limiting the ACH-2684 solubility in the 500 mg simulation showed concurrence with observed values.

Figure 5. Virtual Trial Results of Simulations of 10, 50, 200, 300, and 400 mg ACH-2684 Dose Groups



CONCLUSIONS

- The pharmacokinetics of ACH-2684 in healthy volunteers was linear up to 50 mg. At dose levels between 200 and 400 mg, the exposure (AUC) increased approximately 10-fold with a 2-fold increase in dose. The highest dose, 500 mg, showed an apparent concentration plateau.
- A pharmacokinetic model was designed in GastroPlus using nonclinical in vitro and in vivo data. Liver uptake and formulation-enhanced drug solubility were key components used to optimize the model to fit the observed clinical data.
- Suspected lower gastrointestinal solubility of the drug at the 500 mg dose was captured by the model and showed good correlation with observed data
- As the model did not capture the apparent increase in terminal phase half-life noted at the 2 higher doses, this ACAT model serves as a starting point to refine into a physiologically based pharmacokinetic model as more data (in vivo and in vitro) become available
- Based on the favorable pharmacokinetic and safety properties observed in this study, ACH-2684 is moving forward into clinical trials with HCV-infected patients