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## ABSTRACT

**Background:** Pegylated interferon lambda (pegIFN $\lambda$ ) exerts antiviral effects through a unique receptor with limited distribution and is anticipated to have an improved safety profile compared to alpha interferons. PegIFN $\lambda$  is currently under development as a therapeutic agent for chronic hepatitis C virus (HCV) infection. Pharmacokinetic data from a previous phase 1b study suggested that weekly administration of fixed pegIFN $\lambda$  doses may be appropriate; however, the drug was administered on a weight basis in that study. This report describes data from an ongoing phase 2a study, the first part of which was designed to evaluate the pharmacokinetics of pegIFN $\lambda$  over a broad range of fixed doses.

**Methods:** Treatment-naive HCV subjects (genotypes 1, 2, 3, or 4) received a single subcutaneous (SC) fixed dose of pegIFN $\lambda$  (80, 120, 180, or 240  $\mu$ g; 1-12 subjects/dose group). Serial serum samples were collected over a 2-week period postdose. Samples were analyzed by validated Meso Scale Discovery (MSD) electrochemiluminescent assay. Noncompartmental and compartmental analyses were performed to estimate pharmacokinetic parameters and allow simulation of multiple-dose pharmacokinetics. The relationship of several covariates, including dose level and body weight, to pegIFN $\lambda$  exposure was examined graphically.

**Results:** The mean pegIFN $\lambda$  elimination half-life ( $t_{1/2}$ ) ranged from 37 to 52 hours. Estimated CL/F and V<sub>d</sub>/F values were relatively consistent across the 120-, 180-, and 240- $\mu$ g dose groups (approximately 2 L/h and 100 L, respectively); CL/F and V<sub>d</sub>/F were lower in the 80- $\mu$ g dose group at 1.04 L/h and 46 L, respectively. The mean  $T_{max}$  was approximately 24 hours, with a range of 4 to 73 hours. Mean  $AUC_{0-168h}$  and  $C_{max}$  increased in a dose-dependent manner. Based on the single-dose data, steady state is predicted to be reached after 2 to 3 weeks of once-weekly dosing. There was no apparent effect of body weight on pegIFN $\lambda$  exposure. Other covariates, such as HCV genotype, host IL28B genotype, and other subject characteristics (age, race, sex, and body mass index), do not appear to affect pegIFN $\lambda$  exposure.

**Conclusions:** Based on the data from this study, pegIFN $\lambda$  elimination  $t_{1/2}$  is approximately 2 days. There appears to be little influence of common baseline demographics, such as age, race, sex, body weight, or body mass index, or of disease-specific parameters, such as HCV genotype or host IL28B genotype, on the pharmacokinetic properties of pegIFN $\lambda$ . Collectively, the data on demographics and time to steady state support the use of fixed SC doses of pegIFN $\lambda$ , on a once-weekly schedule.

## INTRODUCTION

PegIFN $\lambda$  is in development as a new treatment for chronic HCV

— PegIFN $\lambda$ , a member of the type III interferon family, binds to a unique receptor with more restricted distribution than the receptor for type I $\alpha$  interferons, and thus has the potential for comparable efficacy to other interferons with a more favorable tolerability and side effect profile

— A phase 1b study of pegIFN $\lambda$  at several weight-based dose levels administered for 4 weeks in combination with ribavirin (RBV) showed robust antiviral activity, with minimal constitutional symptoms or hematologic effects. The primary dose-limiting toxicity was reversible elevations in ALT or AST, with or without increased bilirubin levels

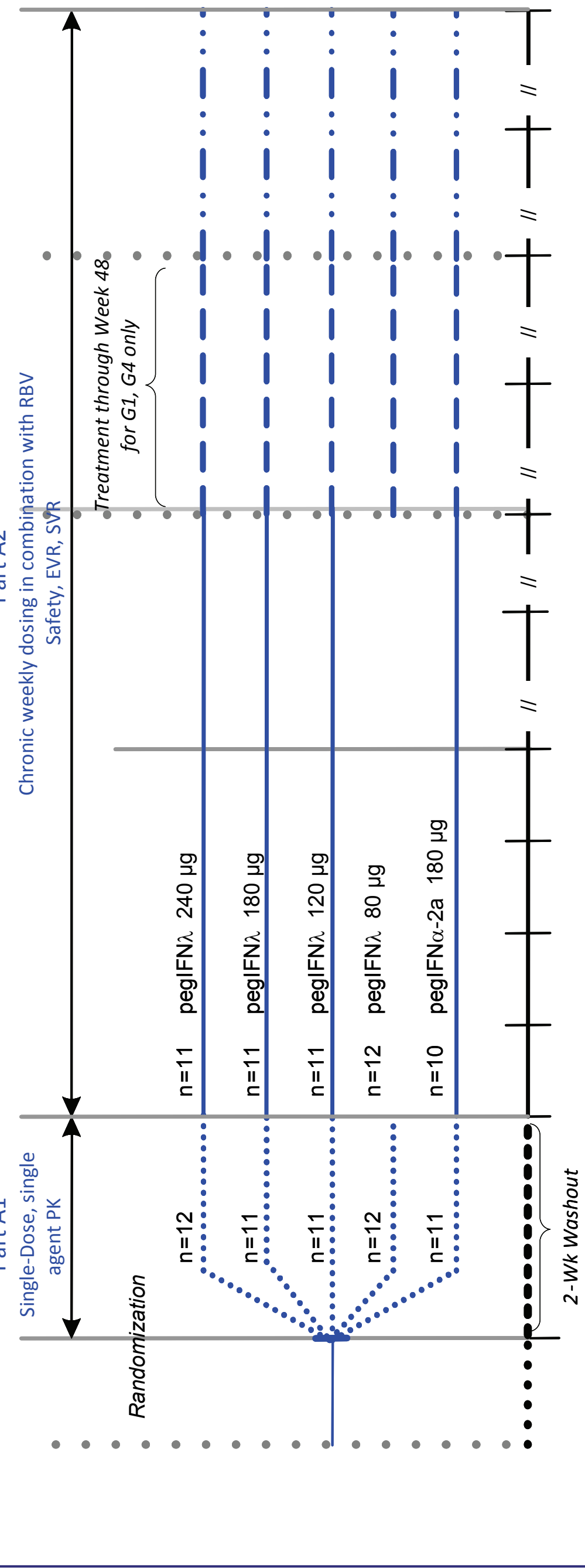
— Pharmacokinetic (PK) data from a previous phase 1b study suggested that weekly administration of fixed pegIFN $\lambda$  doses may be appropriate; however, the drug was administered on a weight basis in that study<sup>1</sup>

— This report describes data from a phase 2a study, the first part of which (Part A1) was designed to evaluate the pharmacokinetics of pegIFN $\lambda$  over a broad range of fixed doses

## METHODS

### Study Design

— Treatment-naive HCV subjects (genotype 1, 2, 3, or 4) received a single SC injection of pegIFN $\lambda$  in a dose of either 80, 120, 180, or 240  $\mu$ g (11-12 subjects/dose group)



**PK Evaluation**

— Serial serum samples were collected over a 2-week period at the following time points: predose, and 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, and 336 hours postdose. PK serum samples were analyzed for pegIFN $\lambda$  with a validated MSD (Gaithersburg, Maryland) electrochemiluminescent assay (see Figure 1). The lower limit of quantification (LLOQ) for this assay was 0.125 ng/mL

— The concentration vs time profiles for each subject were evaluated by noncompartmental analysis using WinNonlin v5.2.1 software (Pharsight Corporation, Cary, NC). The reported PK parameters were as follows:

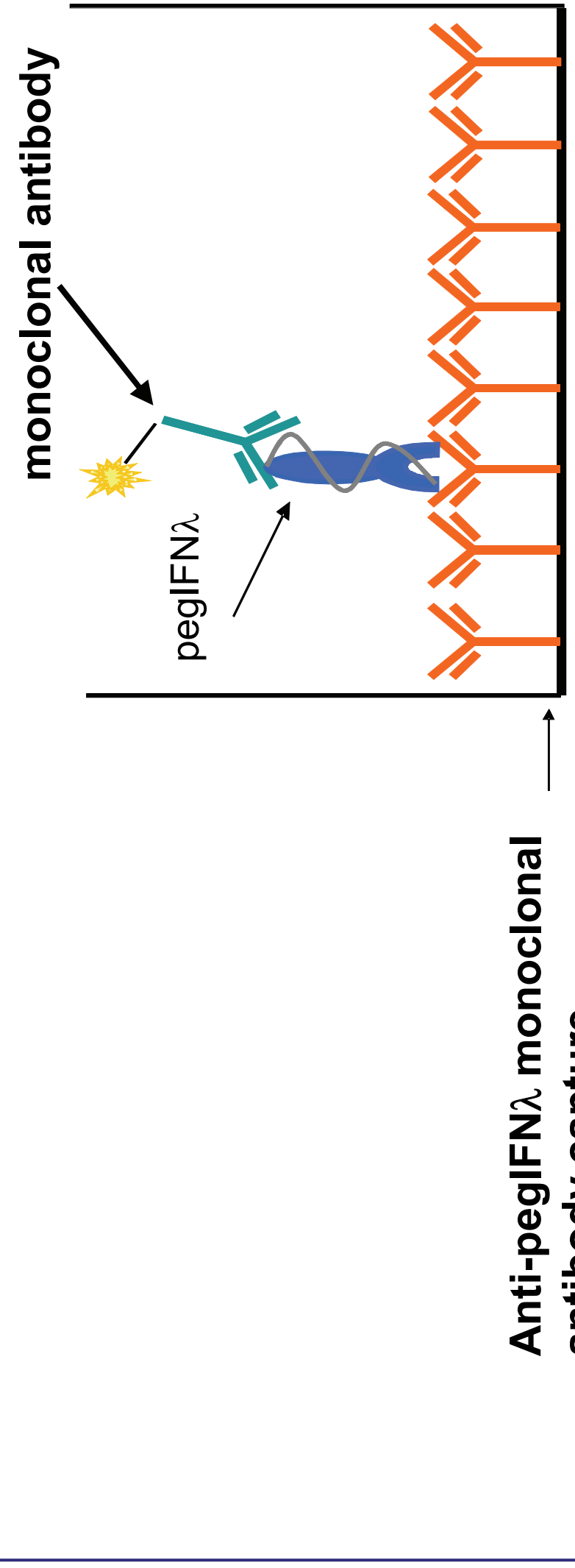
- $C_{max}$  (maximum observed concentration)
- $T_{max}$  (time at which maximal concentration was reached)
- $AUC_{0-168h}$  (area under concentration vs time curve from zero to 168 hours postdose)
- $AUC_{0-\infty}$  (area under concentration vs time curve from zero extrapolated to time infinity)
- $t_{1/2}$  (terminal half-life)
- CL/F (clearance divided by bioavailable fraction)
- V<sub>d</sub>/F (volume of distribution divided by bioavailable fraction)
- For summary statistics:
  - $C_{50}$  values below the assay LLOQ were imputed to be one half of LLOQ (one half of 0.125 ng/mL = 0.0625 ng/mL)
  - $AUC_{0-168h}$  values for subjects that were not estimated due to a lack of quantifiable data were imputed to be one half of the lowest theoretically possible  $AUC_{0-168h}$  (one half of 0.814 h $\cdot$ ng/mL = 0.407 h $\cdot$ ng/mL)

## METHODS (cont'd)

— The concentration vs time profiles for each subject were also evaluated by compartmental methods. The data were best described by a 1-compartment extravascular model with a 1 $\gamma^2$  weighting scheme (see Figure 2). The resulting mean volume of distribution divided by the bioavailable fraction (V<sub>d</sub>/F), absorption rate constant (k<sub>01</sub>), and elimination rate constant (k<sub>10</sub>) were then used to simulate pegIFN $\lambda$  concentration vs time profiles following multiple doses of 80, 120, 180, or 240  $\mu$ g

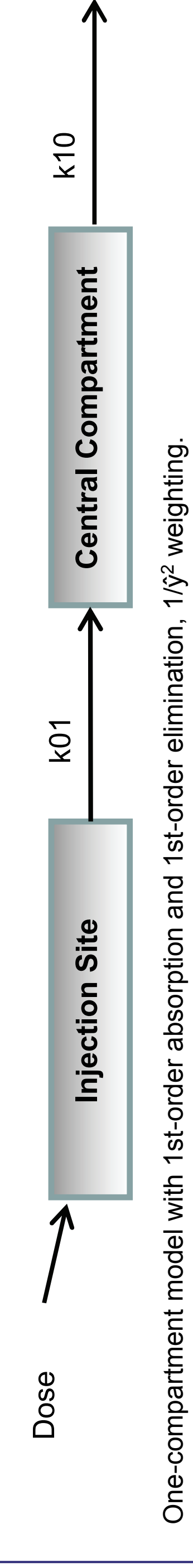
—  $AUC_{0-168h}$  was used to graphically examine the relationship between exposure and pegIFN $\lambda$  dose, as well as the relationship between exposure and subject body weight. The relationship between pegIFN $\lambda$  exposure and other covariates (HCV genotype, host IL28B genotype, age, race, gender, and body mass index [BMI]) were also examined

Figure 1. Meso Scale Discovery (MSD) Platform Used for PegIFN $\lambda$  Quantitation



This method utilizes MSD technology in which carbon electrodes integrated into the bottom of an assay plate excite a ruthenium label, emitting light at 620 nm, which is then read by the MSD Sector Imager. A murine anti-pegIFN $\lambda$  monoclonal antibody was used to capture pegIFN $\lambda$  present in the serum samples and a second ruthenium-labeled murine anti-pegIFN $\lambda$  monoclonal antibody was used for detection of captured drug.

Figure 2. Compartmental Model Used for Simulation of Multiple-Dose Pharmacokinetic Profiles



## RESULTS

The noncompartmental pharmacokinetic parameters for pegIFN $\lambda$ , grouped by dose level, are shown in Table 1.

- The mean  $T_{max}$  was approximately 24 hours postdose, with a range of 4 to 73 hours
- Exposure ( $C_{max}$  and  $AUC_{0-168h}$ ) increased in a dose-proportional manner (see Figure 3)
- Estimated CL/F and V<sub>d</sub>/F values were relatively consistent across the 120-, 180-, and 240- $\mu$ g dose groups (approximately 2 L/h and 100 L, respectively); CL/F and V<sub>d</sub>/F were lower in the 80- $\mu$ g dose group (1.04 L/h and 46 L, respectively)
- The discrepancy in the parameters from the 80- $\mu$ g dose cohort is likely due to the low pegIFN $\lambda$  concentrations following this dose, and sensitivity limitations of the assay
- The mean  $t_{1/2}$  ranged from 37 to 52 hours
- The compartmental pharmacokinetic parameters for pegIFN $\lambda$  were averaged across all dose groups to allow simulation of concentration vs time profiles from an ‘average’ subject:
  - V<sub>d</sub>/F = 133 L
  - k<sub>01</sub> = 0.115 1/h
  - k<sub>10</sub> = 0.0172 1/h

Steady state is expected to be reached after 2 to 3 weeks of once-weekly dosing. The predicted multiple-dose pegIFN $\lambda$  serum concentrations based on the single-dose parameters are shown in Figure 4

Table 1. Pharmacokinetic Parameters Following a Single Subcutaneous PegIFN $\lambda$  Dose

PK Parameter	PegIFN $\lambda$ Dose Cohort					
	80 $\mu$ g (n=12)	120 $\mu$ g (n=11)	180 $\mu$ g (n=11)	240 $\mu$ g (n=12) <sup>a</sup>	Mean (SD)	% CV
$C_{max}$ (ng/mL)	12	11	11	11	0.88 (0.41)	46.8
$T_{max}$ (h)	12	11	11	11	1.49 (1.52)	102
$AUC_{0-168h}$ (ng $\cdot$ h/mL)	12	11	11	11	53.7 (43.1)	80.4
$t_{1/2}$ (h)	11	11	11	11	45.9	61.0
$AUC_{0-\infty}$ (ng $\cdot$ h/mL)	32.8 (12.0, 49.8)	20.3 (8.0, 48.0)	24.9 (8.1, 73.1)	28.0 (4.0, 72.0)	24.9 (8.1, 73.1)	72.6
$t_{1/2}$ (h)	46.5	71.2	76.3	72.6	76.3	42.9
$AUC_{0-168h}$ (ng $\cdot$ h/mL)	12	11	11	11	53.7 (43.1)	80.4
$t_{1/2}$ (h)	11	11	11	11	45.9	61.0
$AUC_{0-\infty}$ (ng $\cdot$ h/mL)	37.0 (26.3)	47.4 (15.2)	52.0 (22.3)	41.9 (17.4)	47.4	41.6
$t_{1/2}$ (h)	70.9	32.0	42.9	32.0	42.9	32.0
$AUC_{0-168h}$ (ng $\cdot$ h/mL)	11	11	11	11	53.7 (43.1)	80.4
$t_{1/2}$ (h)	11	11	11	11	45.9	61.0
$AUC_{0-\infty}$ (ng $\cdot$ h/mL)	93.5 (43.4)	81.0 (40.9)	143 (104)	173 (102)	93.5 (43.4)	46.4
$t_{1/2}$ (h)	70.9	32.0	42.9	32.0	42.9	32.0
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