Pharmacokinetics of PEG-Interferon Lambda (pegIFNλ) Following Fixed Dosing in Treatment-Naive Hepatitis C Subjects (Single-Dose Interim Data From a Dose-Ranging Phase 2a Study)

830

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ABSTRACT

Background: Pegylated interferon lambda (pegIFNλ) exerts antiviral effects through a unique receptor with limited distribution and is anticipated to have an improved safety profile compared to alpha interferons. PegIFNλ 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 pegIFNλ 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 pegIFNλ 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 pegIFNλ (80, 120, 180, or 240 µg; 11-12 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 pegIFNλ exposure was examined graphically

Results: The mean pegIFNλ elimination half-life ($t_{1/2}$) ranged from 37 to 52 hours. Estimated CL/F and V_z/F values were relatively consistent across the 120-, 180-, and 240-µg dose groups (approximately 2 L/h and 100 L, respectively; CL/F and V_z/F were lower in the 80-µg 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 $AUC_{0\text{-}168h}$ 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 pegIFNλ 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 pegIFNλ exposure

Conclusions: Based on the data from this study, pegIFNλ 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 pegIFNλ . Collectively, the data on demographics and time to steady state support the use of fixed SC doses of pegIFNλ on a once-weekly schedule

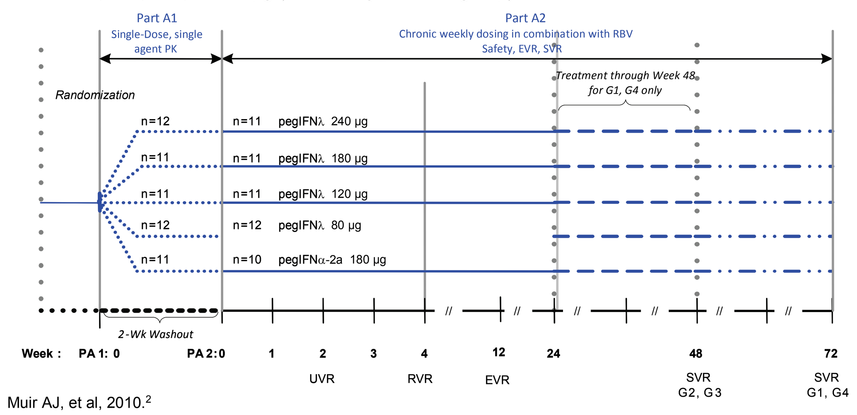
INTRODUCTION

- PegIFNλ is in development as a new treatment for chronic HCV
  - PegIFNλ, a member of the type III/interferon family, binds to a unique receptor with more restricted distribution than the receptor for type I/α 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 pegIFNλ 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 pegIFNλ doses may be appropriate; however, the drug was administered on a weight basis in that study[1]
- This report describes data from a phase 2a study, the first part of which (Part A1) was designed to evaluate the pharmacokinetics of pegIFNλ 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 pegIFNλ in a dose of either 80, 120, 180, or 240 µg (11-12 subjects/dose group)



Muir AJ, et al, 2010.[2]

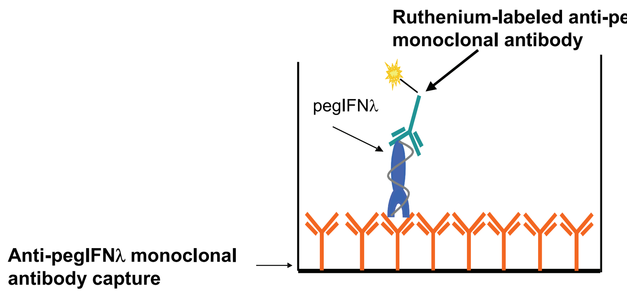
PK Evaluation

- 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 pegIFNλ 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)
  - $AUC_{0\text{-}168h}$ (area under concentration vs time curve from zero to 168 hours postdose)
  - AUC_{INF} (area under concentration vs time curve from zero extrapolated to time infinity)
  - $t_{1/2,\lambda z}$ (terminal half-life)
  - CL/F (clearance divided by bioavailable fraction)
  - V_z/F (volume of distribution divided by bioavailable fraction)
- For summary statistics:
  - C_{max} values below the assay LLOQ were imputed to be one half of LLOQ (one half of 0.125 ng/mL = 0.0625 ng/mL)
  - $AUC_{0\text{-}168h}$ 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 $AUC_{0\text{-}168h}$ (one half of 0.814 h*ng/mL = 0.407 h*ng/mL)

METHODS (cont'd)

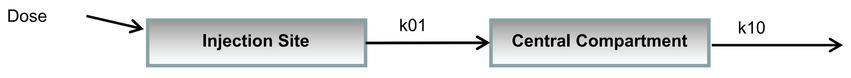
- The concentration vs time profiles for each subject were also evaluated by compartmental methods. The data were best described by a 1-compartment extravascular model with a $1/\hat{y}^2$ weighting scheme (see Figure 2). The resulting mean volume of distribution divided by the bioavailable fraction (V/F), absorption rate constant (k01), and elimination rate constant (k10) were then used to simulate pegIFNλ concentration vs time profiles following multiple doses of 80, 120, 180, or 240 µg
- $AUC_{0\text{-}168h}$ was used to graphically examine the relationship between exposure and pegIFNλ dose, as well as the relationship between exposure and subject body weight. The relationship between pegIFNλ 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 PegIFNλ 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-pegIFNλ monoclonal antibody was used to capture pegIFNλ present in the serum samples and a second ruthenium-labeled murine anti-pegIFNλ monoclonal antibody was used for detection of captured drug.

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



One-compartment model with 1st-order absorption and 1st-order elimination, $1/\hat{y}^2$ weighting.

RESULTS

The noncompartmental pharmacokinetic parameters for pegIFNλ, 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 $AUC_{0\text{-}168h}$) increased in a dose-proportional manner (see Figure 3)
- Estimated CL/F and V_z/F values were relatively consistent across the 120-, 180-, and 240-µg dose groups (approximately 2 L/h and 100 L, respectively); CL/F and V_z/F were lower in the 80-µg dose group (1.04 L/h and 46 L, respectively)
  - The discrepancy in the parameters from the 80-µg dose cohort is likely due to the low pegIFNλ concentrations following this dose, and sensitivity limitations of the assay
- The mean $t_{1/2,\lambda z}$ ranged from 37 to 52 hours
- The compartmental pharmacokinetic parameters for pegIFNλ were averaged across all dose groups to allow simulation of concentration vs time profiles from an "average" subject:
  - V/F = 133 L
  - k01 = 0.115 1/h
  - k10 = 0.0172 1/h
- Steady state is expected to be reached after 2 to 3 weeks of once-weekly dosing. The predicted multiple-dose pegIFNλ serum concentrations based on the single-dose parameters are shown in Figure 4

Table 1. Pharmacokinetic Parameters Following a Single Subcutaneous PegIFNλ Dose

PK Parameter		PegIFNλ Dose Cohort 80 µg (n=12)	120 µg (n=11)	180 µg (n=11)	240 µg (n=12)[a]
C_{max} (ng/mL)	n	12	11	11	11
	Mean (SD)	0.57 (0.47)	0.88 (0.41)	1.49 (1.52)	2.59 (2.76)
	% CV	82.4	46.8	102	106
T_{max} (h)	n	11	11	11	11
	Mean (range)	32.8 (12.0, 49.8)	20.3 (8.0, 48.0)	24.9 (8.1, 73.1)	28.0 (4.0, 72.0)
	% CV	46.5	71.2	78.3	72.6
$AUC_{0\text{-}168h}$ (ng*h/mL)	n	12	11	11	11
	Mean (SD)	53.7 (43.1)	70.1 (32.2)	122 (101)	154 (94)
	% CV	80.4	45.9	83.2	61.0
$t_{1/2,\lambda z}$ (h)	n	7[b]	11	11	11
	Mean (SD)	37.0 (26.3)	47.4 (15.2)	52.0 (22.3)	41.9 (17.4)
	% CV	70.9	32.0	42.9	41.6
AUC_{INF} (ng*h/mL)	n	7[b]	11	11	11
	Mean (SD)	93.5 (43.4)	81.0 (40.9)	143 (104)	173 (102)
	% CV	46.4	50.6	73.1	59.3
CL/F (L/h)	n	7[b]	11	11	11
	Mean (SD)	1.04 (0.52)	2.06 (1.56)	1.82 (1.01)	2.07 (1.83)
	% CV	49.9	75.4	55.5	88.3
V_z/F (L)	n	7[b]	11	11	11
	Mean (SD)	46 (18)	123 (73)	135 (80)	113 (80)
	% CV	39.3	59.5	59.4	71.0

[a] One subject discontinued the study and no samples for PK analysis were obtained past day 4; therefore, no parameters were generated for this subject.
[b] The terminal phase of the concentration vs time curves could not be defined in 5 of 12 subjects. Therefore, $t_{1/2,\lambda z}$, CL/F, V_z/F, and AUC_{INF} could not be estimated for these subjects.

RESULTS (cont'd)

Figure 3. Mean C_{max} and $AUC_{0\text{-}168h}$ Values vs PegIFNλ Dose Level

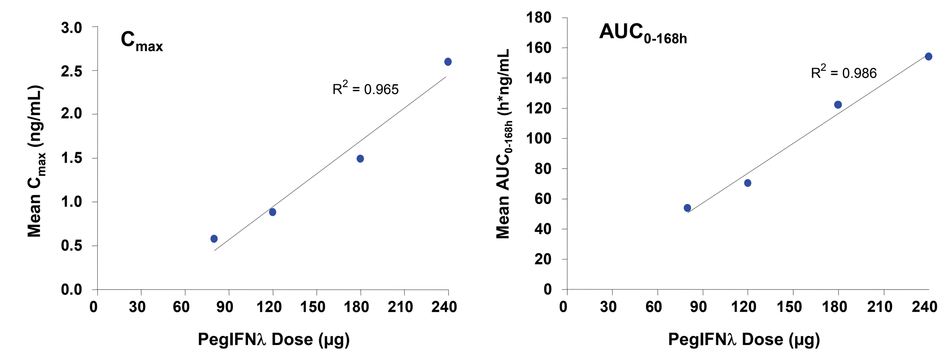
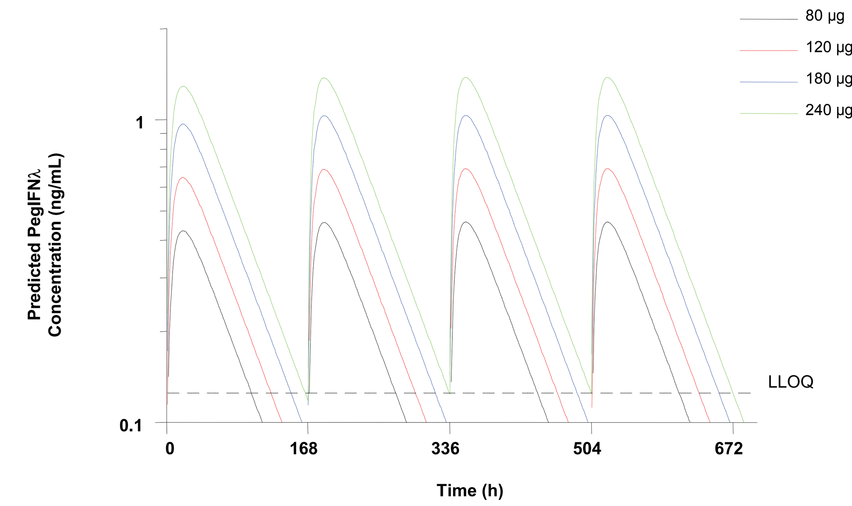


Figure 4. Simulated Multiple-Dose PegIFNλ Serum Concentration vs Time Profiles



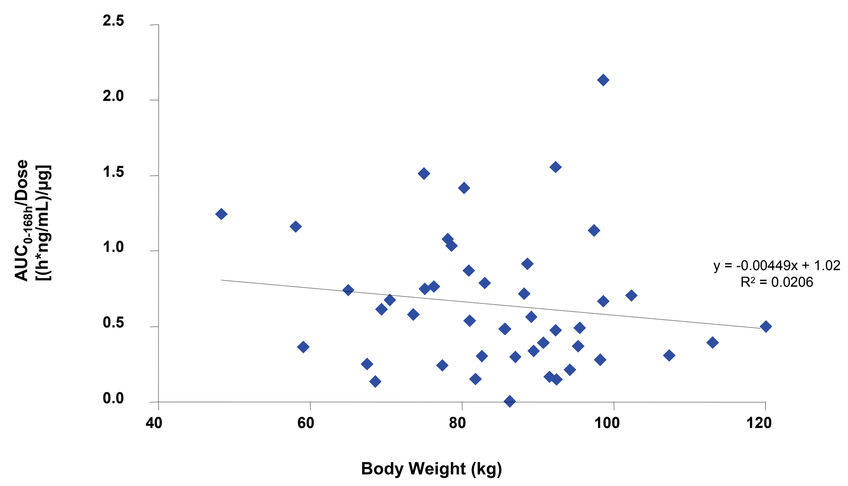
LLOQ = lower limit of quantitation (0.125 ng/mL).

Since pegIFNλ PK parameters were generally consistent across the dose levels, dose-normalized $AUC_{0\text{-}168h}$ was used to evaluate the effect of covariates on exposure across all dose cohorts.

Effect of Body Weight on PegIFNλ Exposure

- Subject body weights ranged from 48.3 kg to 120 kg
- To explore the effect of body weight on exposure, dose-normalized $AUC_{0\text{-}168h}$ values were compared to subject body weight (see Figure 5)
- No relationship was apparent, suggesting that subject body weight is not a significant determinant of exposure after administration of fixed doses of pegIFNλ

Figure 5. Dose-Normalized $AUC_{0\text{-}168h}$ Values vs Subject Body Weight

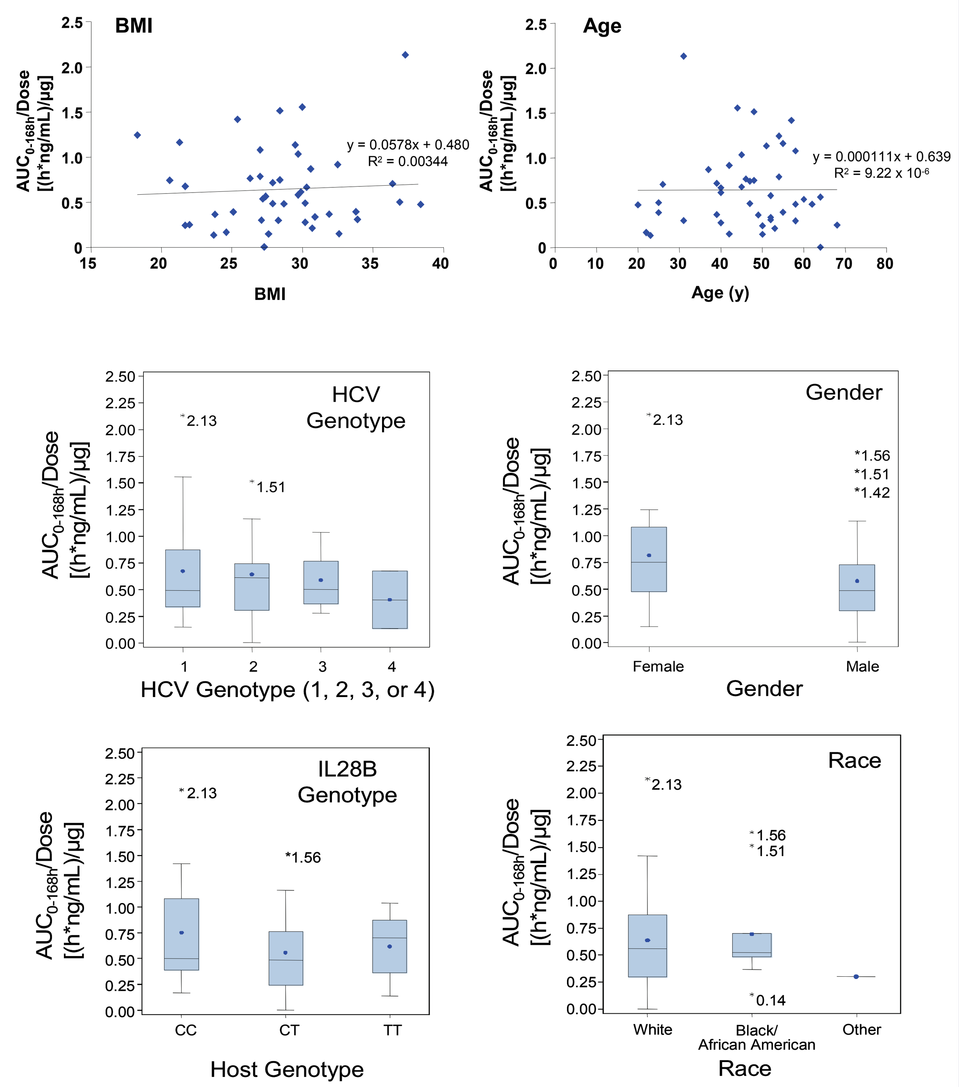


RESULTS (cont'd)

Effect of Other Subject Covariates on PegIFNλ Exposure

- Subject covariates examined were BMI, age, HCV genotype, host IL28B genotype, gender, and race
- To explore the effect of these covariates on exposure, dose-normalized $AUC_{0\text{-}168h}$ values were compared across the range of available values (see Figure 6)
- No relationship was apparent for any of these subject covariates, suggesting that they do not affect exposure of pegIFNλ

Figure 6. Dose-Normalized $AUC_{0\text{-}168h}$ Values vs Subject Covariates



*Indicates outliers.

CONCLUSIONS

- Based on the data from this study, the pegIFNλ T_{max} is approximately 1 day and the elimination half-life is approximately 2 days
- Exposure following fixed doses of 120, 180, or 240 µg pegIFNλ is consistent with that following weight-based dosing in the phase 1b study[1]
- There appears to be little influence of common baseline demographics, such as body weight, age, race, gender, or body mass index, or of disease-specific parameters, such as HCV genotype or host IL28B genotype, on the pharmacokinetic properties of pegIFNλ
- Collectively, these data support the use of fixed SC doses of pegIFNλ on a once-weekly schedule

REFERENCES

1. Byrnes-Blake KA, Freeman JA, Dodds MG, et al. Pharmacokinetics of peg-interferon lambda (peg-IFNλ) in a dose-ranging phase 1B study in hepatitis C patients. Presented at: Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria.
2. Muir AJ, Lawitz E, Ghalib R, et al. Pegylated interferon lambda (pegIFNλ) phase 2 dose-ranging, active-controlled study in combination with ribavirin (RBV) for treatment-naive HCV patients (genotypes 1, 2, 3, or 4): safety, viral response, and impact of IL28B host genotype through week 12. Presented at: 61st Annual Meeting of American Association for the Study of Liver Diseases; October 29–November 2, 2010; Boston, MA, USA.

DISCLOSURE

- Study sponsored by ZymoGenetics, Inc. and Bristol-Myers Squibb

ZymoGenetics

FINAL Bristol-Myers Squibb