

Pharmacokinetics Of Peg-Interferon Lambda (Peg-IFN-λ) In A Dose-Ranging Phase 1B Study In Hepatitis C Patients

ABSTRACT

Interferon Lambda-1 (IFN-λ1, IL-29) is a Type III interferon with potent antiviral activity against hepatitis C (HCV). The limited expression profile of the receptor for IFN-λ1 relative to the IFN-α receptor may lead to an improved therapeutic index for IFN-λ-based therapy. Therefore, Pegylated IFN-λ1 (Peg-IFN-λ) is under evaluation as a therapeutic agent for chronic HCV infection. Peg-IFN-λ pharmacokinetics were evaluated as part of a dose ranging Phase 1b study to assist in dose selection for subsequent studies.

HCV genotype 1 subjects received subcutaneous Peg-IFN-λ (0.5 - 3.0 µg/kg) with or without oral ribavirin for 4 weeks. Serum samples following the first dose and weekly trough samples were collected. Additionally, samples following the fourth dose were collected from a subset of subjects. AUC₀₋₄ and C_{max} increased with increasing dose. Median AUC₀₋₄ values ranged from 9.19 h*ng/mL at the 0.50 µg/kg dose to 116 h*ng/mL at the 3.0 µg/kg dose. Normalization of AUC₀₋₄ by dose (µg or µg/kg) appeared to remove the dose effect similarly across all dose levels. AUC₀₋₄ normalized by dose (µg) did not reveal any trend in exposure due to body weight. Following weekly dosing, the median accumulation index based on the Week 4 AUC₀₋₄ was 1.44. Median accumulation indices based on trough values ranged from 1.00 to 1.10.

Peg-IFN-λ exposure estimates increased with increasing dose in the dose range tested and showed evidence of modest accumulation with weekly dosing. Dose normalization analysis revealed that body weight did not appear to influence exposure. These findings suggest that weekly administration of fixed doses of Peg-IFN-λ is appropriate; this regimen is currently being evaluated in an on-going Phase 2 study.

* This value was originally reported as 10.5 h*ng/mL, based on preliminary analyses. Based on final analyses, it has been updated to 9.19 h*ng/mL.

BACKGROUND

Interferon Lambda-1 (IFN-λ1, also known as IL-29) is a Type III interferon with potent antiviral activity against hepatitis C (HCV) in vitro and in early clinical studies. The limited expression profile of the receptor for IFN-λ1 relative to the IFN-α receptor may lead to an improved therapeutic index for IFN-λ-based therapy compared to IFN-α, the current standard of care. Therefore, Pegylated IFN-λ1 (Peg-IFN-λ) is under evaluation as a new therapeutic agent for chronic HCV infection. Peg-IFN-λ pharmacokinetics (PK) were evaluated as part of a repeat dose, dose-ranging Phase 1b study to assist in interpretation of study findings related to safety and antiviral activity and to aid in dose selection for subsequent studies.

METHODS

A total of 56 subjects with HCV genotype 1 received Peg-IFN-λ via subcutaneous (SC) injection once every other week (Q2W) or once weekly (QW) over a 4-week period. Peg-IFN-λ was administered as either a single agent or in combination with daily administration of oral ribavirin (RBV; Copegus®). Subjects were assigned to 1 of 9 dose cohorts as shown in Table 1.

Table 1. Study Design

Cohort	Treatment	Dosing Schedule	n	Nominal PK Sampling Time Points
1	1.5 µg/kg Peg-IFN-λ	Q2W	6	First Dose: predose, 4, 24, 48 (optional), 72, and 168 h postdose
2	3.0 µg/kg Peg-IFN-λ	Q2W	6	
3	1.5 µg/kg Peg-IFN-λ	QW	6	
4	3.0 µg/kg Peg-IFN-λ	QW	6	Troughs: Days 8, 15, 22, and 29 (Weeks 1, 2, 3, and 4)
5	1.5 µg/kg Peg-IFN-λ + RBV	QW	7 ^b	
6	0.75 µg/kg Peg-IFN-λ + RBV	QW	6	
7	0.50 µg/kg Peg-IFN-λ + RBV	QW	6	
8	2.25 µg/kg Peg-IFN-λ + RBV	QW	6	Fourth Dose (subset of subjects): predose, 4, 24, 48, 72, and 168 h postdose
9 ^a	1.5 µg/kg Peg-IFN-λ + RBV	QW	7	

^aSubjects in Cohort 9 were treatment naive for HCV prior to receiving Peg-IFN-λ.

^bOne subject was not evaluated due to premature discontinuation of the study. Therefore, n = 6 evaluated for PK in Cohort 5.

PK serum samples were analyzed for Peg-IFN-λ with a validated Meso Scale Discovery (MSD; Gaithersburg, Maryland) electrochemiluminescent assay. The lower limit of quantification for this assay was 0.125 ng/mL.

The available concentration versus 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:

- C_{max} (maximum observed concentration)
- T_{max} (time at which maximal concentration was reached)
- AUC₀₋₄ (area under the concentration versus time curve from zero to the last measurable timepoint)

For all summaries:

- C_{max} values below the assay limit of quantification (LOQ) were imputed to be ½ of LOQ (½ of 0.125 ng/mL = 0.0625 ng/mL)
- AUC₀₋₄ values for subjects that were not estimated due to a lack of quantifiable data were imputed to be ½ of the lowest reported AUC₀₋₄ (½ of 6.78 h*ng/mL = 3.39 h*ng/mL)

Accumulation indices (AI) based on C_{max} and AUC₀₋₄ (Week 4 vs. Week 1) were calculated as follows:

- AI_{C_{max}} = C_{max, Day 22} / C_{max, Day 1}
- AI_{AUC} = AUC_{0-4, Day 22} / AUC_{0-4, Day 1}

Accumulation indices based on weekly trough values were calculated by dividing the trough Peg-IFN-λ concentration on each respective week by the trough value following dosing on Day 1 (i.e., the Peg-IFN-λ concentration at 168 h postdose).

Since ribavirin did not appear to affect Peg-IFN-λ exposure (Table 2), monotherapy and combination therapy cohorts were evaluated collectively.

Table 2. Dose-Normalized Peg-IFN-λ Exposure Without and With Ribavirin in HCV Subjects Following a Single SC Dose

C _{max} /dose [(ng/mL)/(µg/kg)]	n	Without Ribavirin (Cohorts 1-4)		With Ribavirin (Cohorts 5-9)	
		mean (SD)	median (range)	mean (SD)	median (range)
AUC ₀₋₄ /dose [(h*ng/mL)/(µg/kg)]	24	0.542 (0.383)	0.418 (0.0907, 1.24)	0.794 (0.957)	0.530 (0.0417, 4.84)
	30	48.9 (38.6)	38.2 (4.80, 129)	53.2 (68.5)	32.4 (2.26, 343)

EFFECT OF DOSE ON PEG-IFN-λ EXPOSURE

Following the first dose, mean Peg-IFN-λ serum levels were detectable out to 1 week at dose levels ≥ 1.5 µg/kg (see Figure 1).

Pharmacokinetic parameters, grouped by dose level, are summarized in Table 3.

- The average T_{max} was approximately 24 hours postdose, with a range of 4 to 78 hours
- AUC₀₋₄ and C_{max} increased with increasing dose (see Figure 2)
- Median C_{max} values ranged from 0.145 ng/mL (0.50 µg/kg dose) to 1.26 ng/mL (3.0 µg/kg dose)
- Median AUC₀₋₄ values ranged from 9.19 h*ng/mL (0.50 µg/kg dose) to 116 h*ng/mL (3.0 µg/kg dose)

Figure 1. Mean Peg-IFN-λ Concentration Versus Time Profiles by Dose Level (Following Dosing on Day 1)

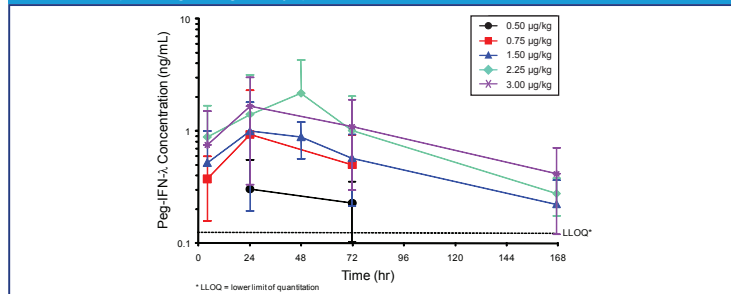


Table 3. Summary of Peg-IFN-λ PK Parameters in HCV Subjects Following a Single SC Dose (Day 1 Dosing; By Dose Level)

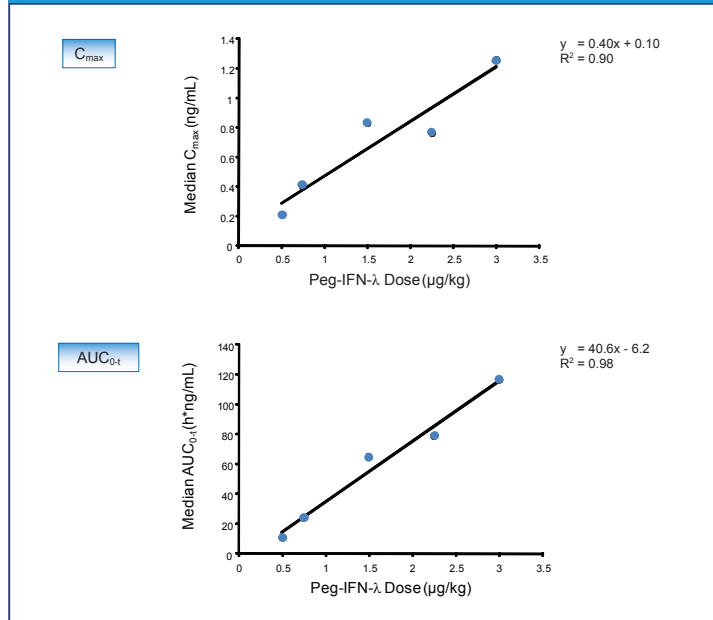
Peg-IFN-λ Dose Level	n	Parameter (Units)		
		C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₄ (h*ng/mL)
0.50 µg/kg (Cohort 7)	5	0.255 (0.238)	36.9 (27.4)	11.6 (7.85)
	mean (SD)	0.145 (0.0625 ^a , 0.659)	24.3 (21.1, 77.8)	9.19 (3.39 ^b , 24.5)
	median (range)	93.2	74.3	67.8
	% CV	6	6	6
0.75 µg/kg (Cohort 6)	6	0.927 (1.33)	29.3 (19.3)	59.6 (97.2)
	mean (SD)	0.400 (0.188, 3.63)	22.3 (17.8, 68.5)	22.7 (3.39 ^b , 257)
	median (range)	144	66.0	163
	% CV	25	24	25
1.50 µg/kg (Cohorts 1, 3, 5, & 9)	25	0.978 (0.810)	29.1 (17.5)	74.1 (60.6)
	mean (SD)	0.813 (0.0625 ^a , 3.49)	23.0 (4.13, 71.3)	62.5 (3.39 ^b , 225)
	median (range)	82.8	60.1	81.8
	% CV	6	6	6
2.25 µg/kg (Cohort 8)	6	1.42 (1.68)	30.7 (12.5)	131 (139)
	mean (SD)	0.759 (0.478, 4.83)	23.4 (21.6, 47.1)	78.7 (57.6, 414)
	median (range)	118	40.9	106
	% CV	12	12	12
3.00 µg/kg (Cohorts 2 & 4)	12	1.69 (1.31)	22.4 (9.5)	148 (122)
	mean (SD)	1.26 (0.272, 3.71)	23.0 (3.83, 46.9)	116 (14.4, 387)
	median (range)	77.8	42.7	82.3
	% CV			

Day 1 data from all cohorts at a given dose level, regardless of dosing frequency and ribavirin status, were combined for these analyses; Number of evaluable subjects: n = 5 (0.50 µg/kg), n = 6 (0.75 µg/kg and 2.25 µg/kg), n = 25 (1.50 µg/kg), and n = 12 (3.00 µg/kg).

^aC_{max} values below the assay limit of quantification (LOQ) were imputed to be ½ of LOQ (0.0625 ng/mL), and AUC₀₋₄ values for subjects that were not estimated due to lack of quantifiable data were imputed to be ½ of the lowest reported AUC₀₋₄ (6.78 h*ng/mL, ½ = 3.39 h*ng/mL).

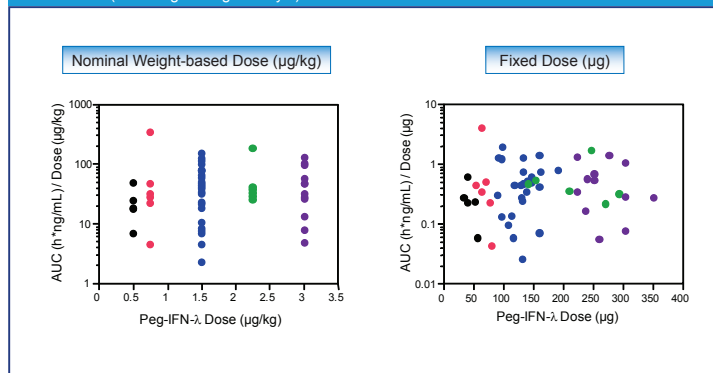
RESULTS

Figure 2. Median C_{max} and AUC₀₋₄ Values Versus Peg-IFN-λ Dose Level (Following Dosing on Day 1)



Normalization of AUC₀₋₄ values by dose (µg or µg/kg) appeared to remove the dose effect similarly across all dose levels (see Figure 3), suggesting that the effect of dose on exposure was consistent over the dose range tested.

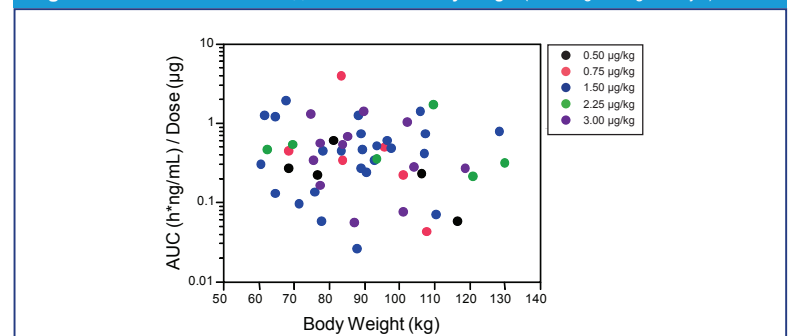
Figure 3. Dose-Normalized AUC₀₋₄ Values Versus Peg-IFN-λ Dose Level (Following Dosing on Day 1)



EFFECT OF BODY WEIGHT ON PEG-IFN-λ EXPOSURE

Subject body weights ranged from 60.5 kg to 130 kg. To explore the effect of body weight on exposure, subject AUC₀₋₄/dose (µg) estimates were compared to subject body weight (see Figure 4). No trend is apparent, given the limited data, suggesting that subject body weight may not be a significant determinant of exposure.

Figure 4. Dose-Normalized AUC₀₋₄ Values Versus Body Weight (Following Dosing on Day 1)



PEG-IFN-λ ACCUMULATION WITH REPEAT DOSING

Accumulation indices based on C_{max}, AUC₀₋₄, and weekly trough values are shown in Table 4. Following weekly dosing, Peg-IFN-λ demonstrated slight accumulation, confirming that Peg-IFN-λ exposure is maintained between weekly doses.

- Median Week 4 accumulation indices based on C_{max} and AUC₀₋₄ were 0.831 and 1.44, respectively
- Median accumulation indices based on weekly trough values ranged from 1.00 to 1.10

Table 4. Summary of Peg-IFN-λ Accumulation Indices in Subjects that Received Weekly Doses of Peg-IFN-λ (Day 1 Dosing; By Dose Level)

n	AI _{C_{max}} ^a	AI _{AUC} ^a	Trough ^b	Trough ^{b,c}	Trough ^{b,d}
	Week 4: Week 1	Week 4: Week 1	Week 2: Week 1	Week 3: Week 1	Week 4: Week 1
11	11	40	38	36	
mean (SD)	1.12 (0.75)	1.34 (0.68)	1.44 (0.89)	1.88 (1.67)	1.74 (1.14)
median	0.831	1.44	1.00	1.06	1.10
(range)	(0.445 - 3.15)	(0.174 - 2.27)	(0.425 - 4.08)	(0.451 - 10.0)	(0.214 - 4.65)

^aC_{max} values below the assay limit of quantification (LOQ) were imputed to be ½ of LOQ (0.0625 ng/mL), and AUC₀₋₄ values for subjects that were not estimated due to lack of quantifiable data were imputed to be ½ of the lowest reported AUC₀₋₄ (6.78 h*ng/mL, ½ = 3.39 h*ng/mL).

^bPeg-IFN-λ concentration values below the assay limit of quantification (LOQ) were estimated as ½ of LOQ (0.0625 ng/mL).

^cTwo subjects were excluded due to missed third dose.

^dFour subjects were excluded due to missed third or fourth dose.

CONCLUSIONS

Exposure data supports weekly dosing of Peg-IFN-λ.

- Serum levels were detectable out to 1 week postdose at dose levels ≥ 1.5 µg/kg
- Exposure estimates (C_{max} and AUC₀₋₄) increased with increasing dose in the dose range tested
- Peg-IFN-λ showed evidence of modest accumulation with weekly dosing, confirming that Peg-IFN-λ exposure is maintained between weekly doses

Normalization of exposure data by body weight supports the evaluation of fixed (non-weight-based) dosing of Peg-IFN-λ.

- No trend was observed following normalization of AUC₀₋₄/dose values by subject body weight, suggesting body weight does not substantially influence Peg-IFN-λ exposure. This will need to be confirmed in subjects administered fixed doses of Peg-IFN-λ.

The pharmacokinetic findings in this Phase 1b study suggest that weekly administration of fixed doses of Peg-IFN-λ is appropriate; this regimen is currently being evaluated in an on-going Phase 2 study.