The Effect of Treatment Group, HCV Genotype, and IL28B Genotype on Early HCV Viral Kinetics in a Phase 2a Study of PEG-Interferon Lambda (pegIFNλ) in Hepatitis C Patients

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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. The safety and efficacy of pegIFNλ is currently under investigation in a phase 2 study. This report describes an exploratory evaluation of early hepatitis C virus (HCV) kinetic data collected in the phase 2a portion of this study.

Methods: 57 treatment-naive patients infected with HCV genotype 1, 2, 3, or 4 were randomized to receive 80, 120, 180, or 240 µg pegIFNλ or 180 µg pegylated interferon alfa-2a (pegIFNα-2a). Early HCV viral kinetics (first- and second-phase slopes) and rapid and complete early virologic response (RVR and cEVR) were estimated from plasma HCV RNA measurements. IL28B genotype at rs12979860 was determined for all consenting subjects (n=48). The effect of HCV genotype, IL28B genotype, and treatment group on first- and second-phase slopes was evaluated using a multivariable linear regression model. The effect of HCV genotype and pegIFNλ dose on virologic response was evaluated using logistic regression.

Results: The multivariable linear regression analysis suggested that first- and second-phase slopes may be explained independently by HCV genotype, IL28B genotype, and treatment group. Independent of HCV genotype, HCV viral decline was faster in subjects with a CC IL28B genotype across all treatment groups. Across host and virus genotype, HCV decline increased in a pegIFNλ dose-dependent manner. The analysis suggests that the rates of viral decline were faster in subjects treated with 120, 180, or 240 µg pegIFNλ than in subjects treated with pegIFNα-2a, independent of host and virus genotype (first phase decline of 1.3 $\log_{10}$ HCV RNA/d for pegIFNλ compared with 0.87 $\log_{10}$ HCV RNA/d for pegIFNα -2a). Interestingly, the first- and second-phase slopes of pegIFNλ in subjects with a CT/TT IL28B genotype approached those achieved by pegIFNα-2a in subjects with a CC IL28B genotype. Logistic regression analysis of virologic response indicates that the probabilities of RVR and cEVR increase with increasing pegIFNλ dose. The probability of RVR at the 240-µg dose was estimated to be approximately 50% in subjects infected with HCV genotype 1.

Conclusions: The results of this analysis suggest that the rates of HCV RNA decline and virologic response in subjects treated with 120, 180, or 240 µg pegIFNλ may be equivalent to, or even exceed, those observed and reported for patients dosed with pegIFNα-2a. These results should be confirmed with data from additional studies of pegIFNλ.

INTRODUCTION

- PegIFNλ 1 (pegylated interferon lambda 1a, peglyatedIL-29, pegIFNλ) is in development as a new treatment for chronic hepatitis C virus (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 efficacy comparable to that of 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
- Here we report the HCV viral kinetics in patients treated with fixed doses of pegIFNλ or a control, pegylated interferon alfa-2a (pegIFNα-2a), given in combination with RBV for treatment of chronic HCV for up to 24 (genotypes 2 or 3; G 2/3) or 48 (genotypes 1 or 4; G 1/4) weeks

HCV Viral Kinetics

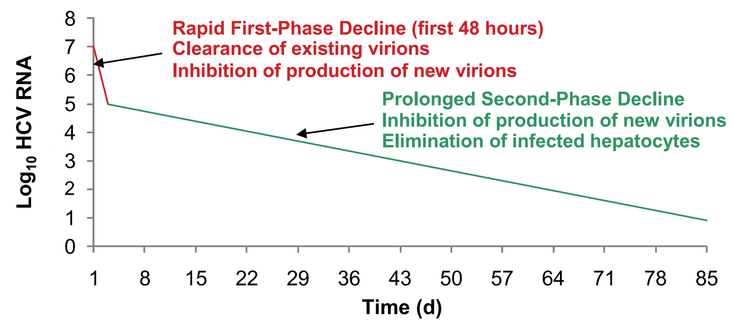
- Treatment of chronic HCV infection with interferon-based therapy typically leads to a biphasic decline in HCV RNA levels over time
  - The first phase
    - Is characterized by a rapid decline in HCV RNA levels over the first 2 days of treatment
    - Is believed to be a function of blockade of viral production
  - The second phase
    - Is a slower and more prolonged period of HCV RNA decline that may extend through the duration of treatment
    - Is believed to represent the loss and elimination of infected hepatocytes
    - When HCV RNA is represented as $\log_{10}$, the decline in HCV over time in the second phase is linear

Objectives

- To estimate first- and second-phase rate of HCV RNA decline in subjects treated with pegIFNλ or pegIFNα-2a
- To evaluate the potential impact of subject covariates, such as IL28B genotype, treatment group, age, gender, and HCV genotype, on slope estimates using linear regression analysis
- To estimate the probability of RVR and cEVR using logistic regression analysis

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RVR = rapid virologic response; cEVR = complete early virologic response.

Figure 1. Idealized HCV RNA Kinetics Upon Treatment With Interferon



METHODS

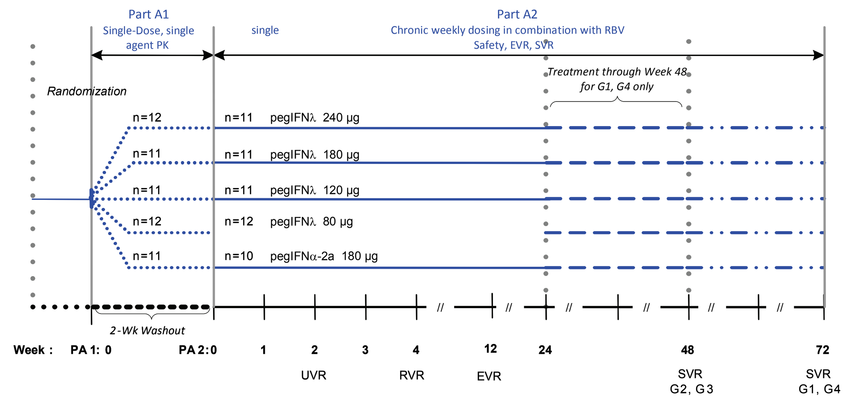
Study Overview

- Study Design
  - Open-label, ongoing phase 2a study (n=57)
  - Two-part, dose-ranging, randomized, controlled, multicenter phase 2 study of treatment of chronic hepatitis C genotypes 1, 2, 3, and 4 in treatment-naive patients
    - Part 1: Pharmacokinetics over 2 weeks following a single subcutaneous (SC) administration of 1 of 4 fixed-dose levels of pegIFNλ (80, 120, 180, or 240 µg), or pegIFNα-2a (180 µg)
    - Part 2: Safety, efficacy, and pharmacokinetics with up to 24 (HCV G 2/3) or 48 (HCV G 1/4) weeks of treatment with 1 of 4 fixed-dose levels of pegIFNλ or pegIFNα-2a administered in combination with RBV

METHODS (cont'd)

- IL28B SNP Genotype
  - IL28B genotype determined at rs12979860 (CC, CT, or TT) using custom TaqMan®-based assay in consenting subjects (subset of study population)
- HCV RNA Measurement
  - HCV RNA quantified at regular intervals through parts 1 and 2 using Roche COBAS® TaqMan® HCV test, v2.0 (lower limit of quantitation [LOQ] of 25 IU/mL)

Study Design[1]

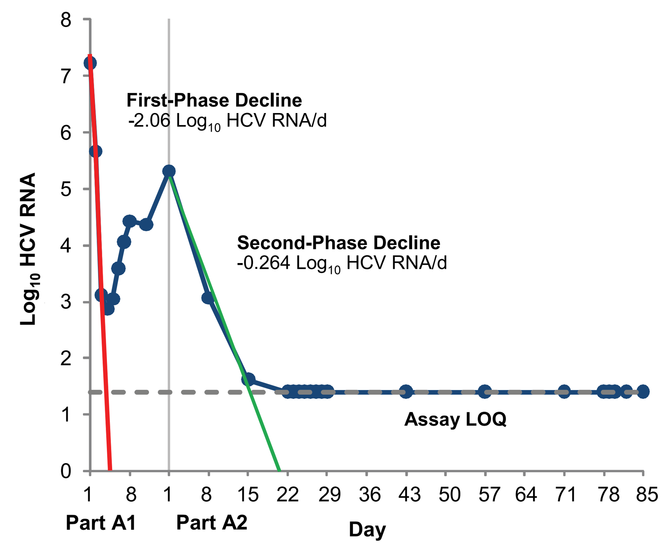


*Not comparable with published rates due to extra dose 2 weeks prior to start of Part A2.
UVR = ultra-rapid virologic response, HCV RNA not detectable (<LOQ of 25 IU/mL) at 2 weeks; RVR = rapid viral response, HCV RNA not detectable (LOQ) at 4 weeks; cEVR = complete early virologic response, HCV RNA not detectable (LOQ) at 12 weeks; EVR = early virologic response, ≤2 $\log_{10}$ reduction in HCV RNA from baseline at 12 weeks; SVR = sustained virologic response, HCV RNA undetectable 24 weeks following end of treatment.

Viral Kinetic Analysis

- The rate of decline in the first phase was determined using the $\log_{10}$ HCV RNA data collected on days 1 (predose), 2, and 3 of part A1
- The rate of decline in the second phase was determined using the $\log_{10}$ HCV RNA data collected on dosing days (prior to dosing) in Part A2 through week 12
  - Data were included only for the duration of intended therapy
  - The model included only quantifiable results. HCV RNA levels reported as below the LOQ (25 IU/mL) were excluded from analysis
- Rates of decline were estimated using WinNonlin® (Pharsight, Cary, NC) and JMP v7.0 (SAS Institute, Cary, NC)

Figure 2. Representative First- and Second-Phase Declines for a Subject in pegIFNλ 240-µg Group



Linear Regression Analysis

- Effect of subject covariates on first- and second-phase slope estimates were evaluated using multivariable linear regression
  - Evaluated covariates included HCV genotype (G 1/4 or G 2/3), treatment group, age, gender, race, weight, body mass index, and IL28B genotype (CC or CT/TT)
- Multivariable regression analysis conducted with all covariates using stepwise approach of forward addition and backward subtraction
  - Final models included only covariates with $P<0.05$
  - Interaction terms not evaluated due to limited sample size

Logistic Regression Analysis

- Probability of achieving not detectable HCV RNA after 4 weeks (RVR) and 12 weeks (cEVR) of treatment with pegIFNλ, in combination with RBV was evaluated using logistic regression
- Model for each endpoint included HCV genotype (1 or 4 vs 2 or 3) and pegIFNλ dose as a continuous variable
- Probabilities of achieving RVR and cEVR estimated for pegIFNλ dose range of 80 µg to 240 µg

RESULTS

First- and Second-Phase Slope Estimation

- Of 57 subjects enrolled in the study, first- and second-phase slopes were estimated for 56 and 44 subjects, respectively (see Table 1)
- Linear fits to the individual second-phase weekly HCV RNA measurements were acceptable (see Table 2)

Table 1. First- and Second-Phase Slope Sample Sizes

Effect	Category	Number of Individual First-Phase Slope Estimates	Number of Individual Second-Phase Slope Estimates
Treatment group	pegIFNλ 80 µg	12	11
	pegIFNλ 120 µg	10	10
	pegIFNλ 180 µg	11	10
	pegIFNλ 240 µg	12	6
	pegIFNα-2a	11	7
IL28B genotype	CC	15	12
	CT/TT	32	27
	Not determined	9	5
HCV genotype	1 or 4	33	29
	2 or 3	23	15

Table 2. Goodness of Fit for Second-Phase Slope Estimates

Treatment Group	Range of R^2 Estimates for Individual Second-Phase Fits
pegIFNλ 80 µg	0.927 – 0.995
pegIFNλ 120 µg	0.883 – 0.998
pegIFNλ 180 µg	0.968 – 0.999
pegIFNλ 240 µg	0.936 – 0.985
pegIFNα-2a	0.924 – 0.987

R^2 values estimated for second-phase fit with at least 3 data points and a second-phase slope less than -0.02 $\log_{10}$ HCV RNA/d.

Linear Regression Results

- The multivariable linear regression analysis suggests that first- and second-phase slopes may be explained by HCV genotype, IL28B genotype, and treatment group (See Tables 3-7)

Table 3. Multivariable Linear Regression Results

Effect	Significance of Effect (*P*)	
	First-Phase Slope	Second-Phase Slope
HCV genotype	0.0001	<0.0001
Treatment group	0.0077	0.0109
IL28B genotype	0.0028	0.0134

Table 4. IL28B Genotype Effect in Multivariable Models

IL28B Genotype	Least Squares Means From Multivariable Models	
	First-Phase Slope (Log_{10} HCV RNA/d)	Second-Phase Slope (Log_{10} HCV RNA/d)
CC	-1.33	-0.278
CT/TT	-0.879	-0.190

Relative standard error (standard error/estimate) ranged from 9% to 11%.

Table 5. HCV Genotype Effect in Multivariable Models

HCV Genotype	Least Squares Means From Multivariable Models	
	First-Phase Slope (Log_{10} HCV RNA/d)	Second-Phase Slope (Log_{10} HCV RNA/d)
1 or 4	-0.814	-0.138
2 or 3	-1.40	-0.331

Relative standard error ranged from 8% to 14%.

Table 6. Treatment Group Effect in Multivariable Models

Treatment Group	Least Squares Means From Multivariable Models	
	First-Phase Slope (Log_{10} HCV RNA/d)	Second-Phase Slope (Log_{10} HCV RNA/d)
pegIFNλ 80 µg	-0.777	-0.133
pegIFNλ 120 µg	-1.19	-0.277
pegIFNλ 180 µg	-1.22	-0.244
pegIFNλ 240 µg	-1.48	-0.289
pegIFNα-2a	-0.865	-0.230

Relative standard error ranged from 10% to 22%.

RESULTS (cont'd)

Table 7. Comparison of HCV Kinetics Across Test Articles and IL28B Genotype

Comparator Group	Least Squares Means From Multivariable Models	
	First-Phase Slope (Log_{10} HCV RNA/d)	Second-Phase Slope (Log_{10} HCV RNA/d)
pegIFNλ CC	-1.52	-0.314
pegIFNλ CT/TT	-1.07	-0.226
pegIFNα-2a CC	-1.08	-0.274
pegIFNα-2a CT/TT	-0.629	-0.186

Across all HCV genotypes (1-4).
pegIFNλ groups represent average of 120-, 180-, and 240-µg dose groups.

Logistic Regression Results

- Logistic regression analyses indicate that the probability of achieving RVR and cEVR increases with increasing pegIFNλ dose for all genotypes (1/4 and 2/3) (See Figures 3-4)

Figure 3. Estimated Probabilities of RVR by HCV Genotype

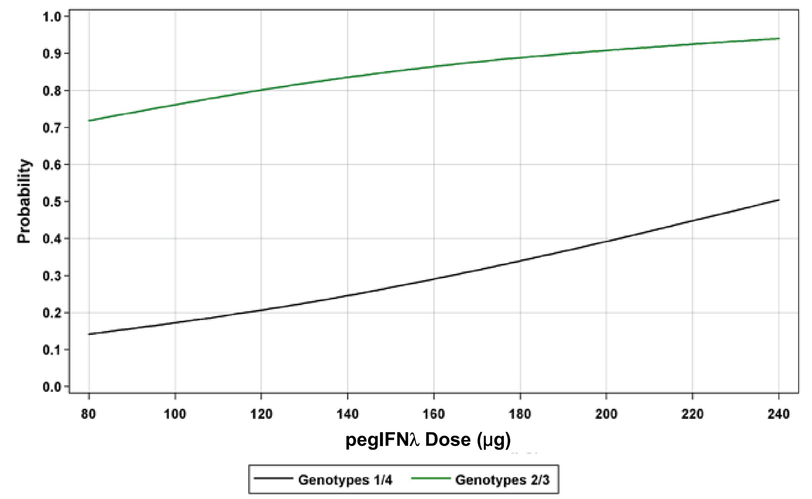
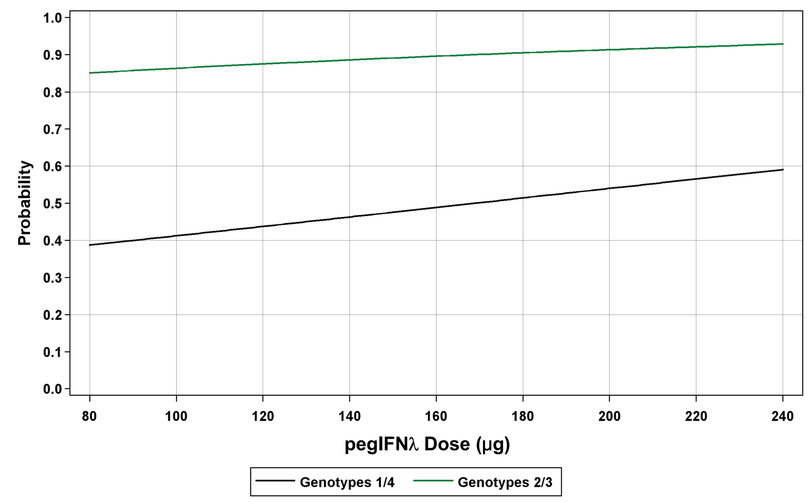


Figure 4. Estimated Probabilities of cEVR by HCV Genotype



CONCLUSIONS

- The rate of HCV RNA decline and virologic response in subjects treated with 120, 180, or 240 µg pegIFNλ may be equivalent to, or exceed, those observed and reported for patients treated with pegIFNα-2a
- The rate of HCV RNA decline upon treatment with pegIFNλ may be faster in subjects with an IL28B CC genotype than in subjects with an IL28B CT or TT genotype
- The rate of HCV RNA decline in subjects with an IL28B CT/TT genotype treated with pegIFNλ approached that observed in subjects with an IL28B CC genotype treated with pegIFNα-2a
- The relationship between early viral decline and sustained virologic response will be evaluated

REFERENCE

1. Muir AJ, Lawitz E, Ghalib R, et al. Pegylated interferon lambda (pegIFNl) 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.

DISCLOSURE

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

ZymoGenetics

FINAL Bristol-Myers Squibb