

**PEG-IFN-λ: Antiviral Activity and Safety Profile in a 4-Week Phase 1b Study in
Relapsed Genotype 1 Hepatitis C Infection**

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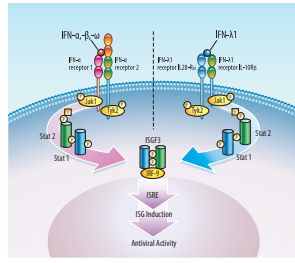
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Introduction

PEG-Interferon Lambda 1a (PEG-IFN-λ; PEG-rIL-29)

- PEGylated recombinant human interferon (IFN)-λ1
- Member of the Type III/λ IFN family^a
- Binds to a unique receptor with more restricted distribution than IFN-α/Type I IFN receptor
 - Receptor not detected in bone marrow CD34+ progenitor cells
- In development as new treatment for chronic hepatitis C virus (HCV) infection
 - Potential for more favorable side-effect profile than IFN-α and other Type I interferons, including decreased hematologic toxicity



PEG-IFN-λ and IFN-α activate a common antiviral response pathway

^a Kotelko, et al., Nature Immunology (2003) 4(1):69-77; Sheppard, et al., Nature Immunology (2003) 4(1):63-68

Study Design

Objectives: Safety and Antiviral Activity

- Part 1: Single agent PEG-IFN-λ (subcutaneous [SC])
- Part 2: PEG-IFN-λ (SC) in combination with ribavirin

Population

- Genotype 1 infection
- Relapsed after treatment with PEG-IFN-α + ribavirin
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN)
- No evidence or history of decompensated liver disease or cirrhosis

Treatment Regimen

- PEG-IFN-λ: Q2W (Days 1 and 15) or QW (Days 1, 8, 15, and 22)
 - No dose modification allowed
- Ribavirin (Copegus[®]): (Part 2 only) Daily (Days 1–28): 1000 mg (subjects <75 kg) or 1200 mg (subjects ≥75 kg)

On-Study Assessments

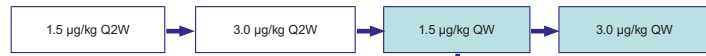
- Adverse events (AEs)
- Clinical laboratory evaluations
- HCV RNA
- Pharmacokinetics

Liver-Associated Dose-Limiting Toxicity (DLT) Criteria

- >5-fold increase in ALT/AST over baseline (≥ Grade 2), or
- >2-fold increase in ALT/AST (≥ Grade 2) with ≥ Grade 2 bilirubin

Dose and Schedule Escalation

Part 1: Single-agent therapy



Part 2: Combination therapy with ribavirin



This poster presents data for cohorts represented by shaded boxes. Data for the first two cohorts (1.5 and 3.0 µg/kg Q2W) were presented at AASLD, Nov 2008.

Results

Subject Characteristics (Weekly Cohorts)^a

	Single-agent PEG-IFN-λ		PEG-IFN-λ + ribavirin	
	1.5 µg/kg (N=6)	3.0 µg/kg (N=6)	0.75 µg/kg (N=3)	1.5 µg/kg (N=7)
Age	56	54	51	53
Race				
Black	1	1	0	1
Hispanic	3	0	2	0
White	2	5	1	6
BMI, mean (range)	31 (24–40)	27 (24–32)	31 (26–34)	31 (27–39)

^a Data cut-off 08 March 2009

Adverse Events and Laboratory Parameters

- Majority of AEs and laboratory changes Grade 1 or 2
- Most common AEs (regardless of dose level or cohort): fatigue (18%) and nausea (18%)
- No treatment-related fever in any subject
- 1 related Grade 3 liver event in Subject 0035 (see Table 2)

Table 1 Most Common Treatment-Emergent Adverse Events (Weekly Cohorts)^a

	Single-agent PEG-IFN-λ		PEG-IFN-λ + ribavirin		TOTAL (N=22) n (%)
	1.5 µg/kg (N=6) n	3.0 µg/kg (N=6) n	0.75 µg/kg (N=3) n	1.5 µg/kg (N=7) n	
Fatigue	1	0	0	3	4 (18)
Nausea	0	1	0	3	4 (18)
Insomnia	0	0	0	3	3 (14)
Flu-like illness	0	0	0	2	2 (9)
Chills	0	0	0	2	2 (9)
Cough	1	0	0	1	2 (9)

^a Reported in 2 or more subjects

Laboratory Parameters - Liver Function

- Dose-dependent, reversible increases in ALT and AST
- Majority <2-fold over baseline with no increase in bilirubin
- 4 subjects with elevations in ALT and/or AST that met DLT criteria

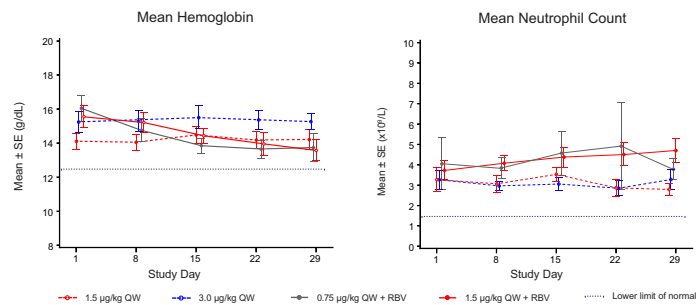
Table 2 ALT (U/L), AST (U/L), and Bilirubin (mg/dL) in Subjects with DLT (Weekly Cohorts)

	Single-agent PEG-IFN-λ						PEG-IFN-λ + ribavirin					
	1.5 µg/kg Subject 0032 ^a		3.0 µg/kg Subject 0061		3.0 µg/kg Subject 0065		1.5 µg/kg Subject 0035 ^a					
	ALT	AST	Bili	ALT	AST	Bili	ALT	AST	Bili			
Day 1	39	32	1.0	64	46	0.5	29	36	0.5	96	102	1.6
Day 8	105	89	0.9	115	104	2.8	56	41	0.5	88	103	1.6
Day 15	172	134	0.9	153	114	2.0	127	165	0.4	125	144	3.7
Day 22	179	182	1.6	91	70	1.0	173	180	0.5	528	847	11.6
Day 29	264	167	2.7	94	69	0.8	63	48	0.6	370	514	20.9
Day 59	53	37	0.7	-	-	-	-	-	-	116	148	3.8

^a Dosed in violation of protocol after meeting DLT criteria

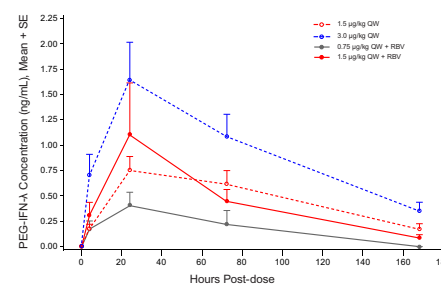
Laboratory Parameters - Hematology

- Decreases in hemoglobin only in ribavirin cohorts
- No neutropenia
- 1 subject in 3.0 µg/kg QW cohort with Grade 1 decrease in platelets 2 weeks after last dose



Pharmacokinetics

- No effect of ribavirin on PEG-IFN-λ pharmacokinetics
- Consistent with a PEGylated cytokine
- Dose-proportional exposure (as measured by area under the time vs. concentration curve [AUC])
- High degree of between-subject variability in exposure at a given dose level (>80% CV) by non-compartmental analysis



Antiviral Effects

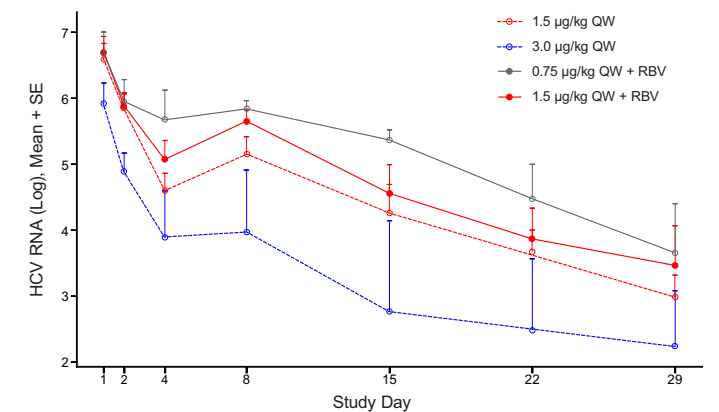
Table 3 Maximum Viral Load Reduction (Weekly Cohorts)

	Single-agent PEG-IFN-λ		PEG-IFN-λ + ribavirin	
	1.5 µg/kg (N=6)	3.0 µg/kg (N=6)	0.75 µg/kg (N=3)	1.5 µg/kg (N=7)
Log baseline HCV RNA, mean (range)	6.6 (6–7)	5.8 (4–7)	6.7 (6–7)	6.7 (6–8)
Maximum log decrease, mean (range)	3.6 (2.0–5.0)	3.4 (2.5–4.6)	3.0 (1.7–4.7)	3.2 (0.09–5.6)
>2-log decrease, n	6	6	2	5
HCV RNA <1000 IU/mL, n	4	4	1	2
HCV RNA <100 IU/mL, n	1	3	0	1
HCV RNA undetectable ^a , n	0	3 ^b	0	0

^a Lower limit of detection, 25 IU/mL

^b Baseline HCV RNA for these 3 subjects: 16,400, 213,000, and 1,000,000 IU/mL

Mean HCV RNA (Log) by Dose Level and Visit (Subjects who completed treatment)



Summary and Conclusions

- PEG-IFN-λ was associated with robust antiviral activity at all dose levels tested in subjects with relapsed HCV
 - 3 subjects with undetectable HCV RNA
- Dose-limiting toxicities were reversible elevations in ALT, AST, and bilirubin
 - Elevations anticipated to be manageable with dose modification
- Minimal constitutional symptoms and hematologic effects as single agent or with ribavirin

Data support moving to dose-ranging Phase 2 in treatment-naïve patients

Abstract

Background: PEG-interferon-λ1a (PEG-IFN-λ/PEG-rIL-29) is a Type III interferon that binds to a unique receptor with a more limited distribution than the Type I interferon receptor. In a Phase 1 healthy volunteer study, PEG-IFN-λ was pharmacologically active without flu-like symptoms or hematologic side-effects. This ongoing Phase 1b study is evaluating the safety and efficacy of PEG-IFN-λ in patients with relapsed genotype 1 hepatitis C virus (HCV) infection.

Methods: Cohorts of 6 subjects each received 4-week treatment with subcutaneous PEG-IFN-λ every other week (Q2W) or weekly (QW), alone or with daily ribavirin. Assessments included adverse events (AEs), laboratory abnormalities, and measurements of HCV RNA.

Results: 18 subjects with a mean baseline log₁₀ HCV RNA of 6.80 IU/L received PEG-IFN-λ alone (1.5 and 3.0-µg/kg Q2W, and 1.5-µg/kg QW). Antiviral activity (≥1-log₁₀ decrease in HCV RNA) was observed in all cohorts.

QW dosing was associated with the most robust response at Day 29: 6/6 subjects achieved > 2-log₁₀ decrease from baseline; 4/6 subjects had HCV RNA <1000 IU/L.

Treatment was well tolerated without hematologic toxicities or treatment-related fever. All AEs were Grade 1/2; the most common were fatigue (n=3) and myalgia (n=2). Most laboratory abnormalities were Grade 1/2; two subjects (1 each at 3.0-µg/kg Q2W and 1.5-µg/kg QW) experienced reversible Grade 3 aminotransferase elevations.

Conclusions: Repeated dosing with PEG-IFN-λ was well tolerated with minimal constitutional symptoms. In contrast to effects of Type I interferons, there were no significant decreases from baseline values in neutrophil or platelet counts. Maximal antiviral activity was achieved with weekly dosing. Results with single-agent PEG-IFN-λ support further study in combination with ribavirin or other antiviral agents. Updated results from the PEG-IFN-λ + ribavirin cohorts will be presented at the meeting.

	1.5 µg/kg Q2W (N=6)	3.0 µg/kg Q2W (N=6)	1.5 µg/kg QW (N=7)
Mean maximum log ₁₀ decrease HCV RNA (95% CI)	2.2 (0.4–3.9)	1.9 (1.0–2.8)	3.0 (2.3–4.3)
N with >2 log ₁₀ decrease in HCV RNA (any time on study)	2 (33%)	3 (50%)	6 (100%)
Mean baseline neutrophils × 10 ⁹ /L (range)	3.7 (2.6–5.0)	3.9 (2.1–5.6)	3.3 (1.9–5.2)
Mean Day 29 neutrophils × 10 ⁹ /L (range)	3.9 (2.7–6.9)	3.7 (2.2–6.1)	2.8 (1.8–3.8)
Mean baseline platelets × 10 ⁹ /L (range)	218 (173–270)	235 (165–316)	195 (140–259)
Mean Day 29 platelets × 10 ⁹ /L (range)	254 (171–323)	232 (182–300)	192 (149–255)