

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

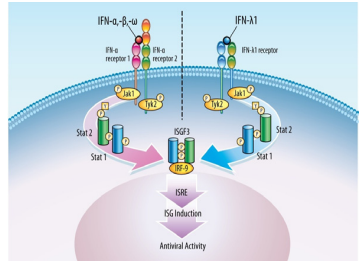
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INTRODUCTION

- PegIFNλ is in development as a new treatment for chronic hepatitis C virus (HCV)
- PegIFNλ, a member of the type III/λ 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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST), with or without increased bilirubin levels
- Here we report the safety, tolerability, and antiviral activity through 12 weeks on combination therapy in a phase 2a study evaluating fixed doses of pegIFNλ and a control, pegylated interferon alfa-2a (pegIFNα-2a, Pegasys) given in combination with RBV for treatment of chronic HCV for up to 24 (HCV genotypes 2/3) or 48 (HCV genotypes 1/4) weeks

Figure 1. IFNα and Type 1 Interferons Share Intracellular Signaling Pathways

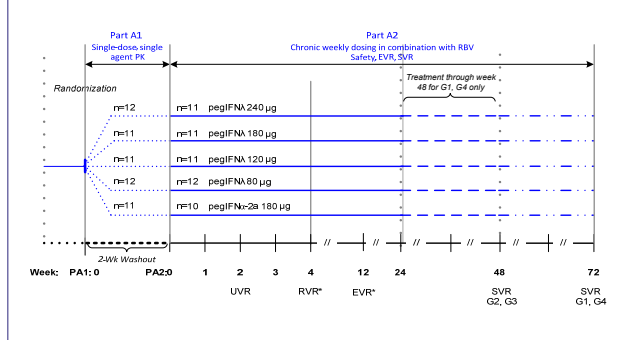


METHODS

- Two-part, dose-ranging, randomized, controlled, multicenter phase 2 study of treatment of chronic hepatitis C genotypes 1, 2, 3, and 4 in patients naive to prior therapy
- Part A: open-label, ongoing (n=57)
 - A1: Pharmacokinetics (PK) over 2 weeks following a single administration of 1 of 4 fixed dose levels of pegIFNλ or pegIFNα-2a
 - A2: Safety, efficacy, and PK with up to 24 (HCV G2/3) or 48 (HCV G1/4) weeks of treatment with 1 of 4 fixed dose levels of pegIFNλ or pegIFNα-2a administered in combination with RBV. First dose in Part A2 was administered 2 weeks after the single dose in Part A1
- Part B: blinded, ongoing (n=570)
 - Safety, efficacy, and PK with up to 24 (HCV G2/3) or 48 (HCV G1/4) weeks of treatment with 1 of 3 fixed dose levels of pegIFNλ or pegIFNα-2a administered in combination with RBV
- Treatments – Part A
 - PegIFNλ at 1 of 4 dose levels (80, 120, 180, or 240 μg) or pegIFNα-2a at 180 μg subcutaneously (SC) weekly for up to 24 (HCV G2/3) or 48 (HCV G1/4) weeks
 - RBV administered daily at doses of 1200 mg (HCV G1/4 patients ≥75 kg), 1000 mg (HCV G1/4 patients <75 kg), or 800 mg (HCV G2/3)
- Dose adjustments and discontinuation
 - Adjustments for defined elevations in AST/ALT
 - AST or ALT >10x ULN, or >5x ULN and >3x baseline
 - Patients with grade 2 elevation in INR or bilirubin (predominantly conjugated): discontinue study drug
 - Otherwise, hold study drug for up to 2 weeks; restart at next lower dose when AST/ALT improves
 - AST or ALT >15x ULN: discontinue study drug
 - Adjustments for hematologic parameters, depression, or other grade 3 adverse events, consistent with pegIFNα-2a label
 - Adjustments in RBV dose should be consistent with RBV label
- Enrollment Criteria
 - HCV genotype 1, 2, 3, or 4 with HCV RNA ≥100,000 IU/mL at screening
 - Naive to prior IFN therapy
 - ALT, AST ≤5.0x ULN; INR ≤1.2; bilirubin ≤1.5 mg/dL; albumin ≥3.5 g/L
 - No evidence of decompensated liver disease or cirrhosis
- Study Assessments
 - Antiviral activity
 - HCV RNA (Roche COBAS® TaqMan® HCV test, v2.0, with LOQ = 25 IU/mL)
 - Safety
 - Adverse event reports
 - Clinical laboratory evaluations
 - Pharmacogenomics
 - IL28B genotype determined at rs12979860 (CC, CT, or TT) using custom TaqMan-based assay in consenting patients (subset of study population)

ULN = upper limit of normal; INR = international normalized ratio; LOQ = lower limit of quantitation.

STUDY DESIGN



*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 virologic 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 log₁₀ reduction in HCV RNA from baseline at 12 weeks; SVR = sustained virologic response, HCV RNA undetectable 24 weeks following end of treatment.

RESULTS

- Enrollment
 - 57 patients enrolled at 8 sites in Canada and US, including Puerto Rico
 - 55 patients entered Part A2, combination treatment
 - Part A2 is ongoing; all subjects will complete treatment by January 2011
- Disposition of 55 subjects in Part A2 through week 12
 - 51 patients completed 4 weeks of treatment
 - 45 patients completed 12 weeks of treatment
 - Discontinuations prior to week 12
 - 3/10 (30%) patients treated with pegIFNα-2a
 - 1 related serious adverse event
 - 1 elevated creatinine, not related
 - 1 withdrawn consent
 - 7/45 (16%) patients treated with pegIFNλ
 - 1 related serious adverse event
 - 4 protocol violations
 - 2 withdrawn consents

Table 1. Demographics: Patients Receiving Combination Treatment in Part A2

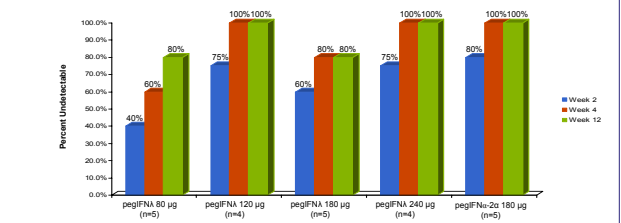
Parameter	Category / Statistic	pegIFNα-2a 180 μg n=10 (%)	pegIFNλ 240 μg n=11 (%)	pegIFNλ 180 μg n=11 (%)	pegIFNλ 120 μg n=11 (%)	pegIFNλ 80 μg n=12 (%)
Age (y)	Mean (SD)	43.6 (11.8)	45.1 (11.6)	44.1 (14.1)	42.9 (10.8)	51.3 (11.7)
Gender, n (%)	F	4 (40.0)	3 (27.3)	5 (45.5)	4 (36.4)	1 (8.3)
	M	6 (60.0)	8 (72.7)	6 (54.5)	7 (63.6)	11 (91.7)
Race, n (%)	Black or African American	1 (10.0)	4 (36.4)	2 (18.2)	2 (18.2)	2 (16.7)
	Other	0	0	0	1 (9.1)	0
	White	9 (90.0)	7 (63.0)	9 (81.8)	8 (72.7)	10 (83.3)
BMI (kg/m ²)	Mean (SD)	30.12 (5.87)	30.10 (3.45)	27.98 (6.05)	29.65 (4.04)	26.17 (3.45)
Baseline viral load (log ₁₀ IU/mL)	Mean (SD)	6.65 (0.58)	6.63 (0.51)	6.67 (0.63)	6.13 (0.72)	6.72 (0.72)

BMI = body mass index; SD = standard deviation.

RESULTS (cont'd)

EFFICACY RESULTS

Figure 2. Proportion of HCV Genotypes 2/3 Not Detectable (<LOQ of 25 IU/mL) at Weeks 2, 4*, and 12* (ITT Analysis)



*Not comparable to published RVR and cEVR rates due to extra dose 2 weeks prior to start of Part A2. ITT = intent-to-treat.

Figure 3. Mean (SE) Log₁₀ HCV RNA Over Time (Observed) in HCV Genotypes 2/3 (Observed only; data for discontinued subjects not included)

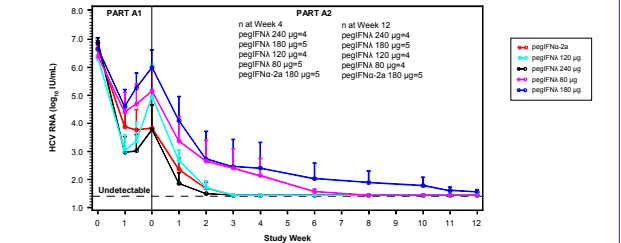
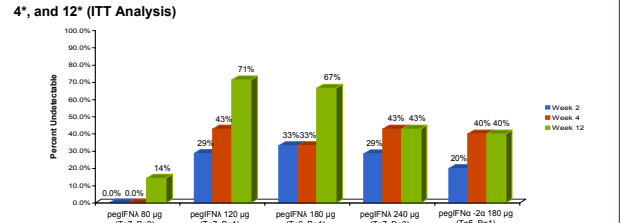


Figure 4. Proportion of HCV Genotypes 1/4 Not Detectable (<LOQ of 25 IU/mL) at Weeks 2, 4*, and 12* (ITT Analysis)



*Not comparable to published RVR and cEVR rates due to extra dose 2 weeks prior to start of Part A2. T = total number of patients; B = black or of African descent.

Figure 5. Mean (SE) Log₁₀ HCV RNA Over Time (Observed) in HCV Genotypes 1/4 (Observed only; data for discontinued subjects not included)

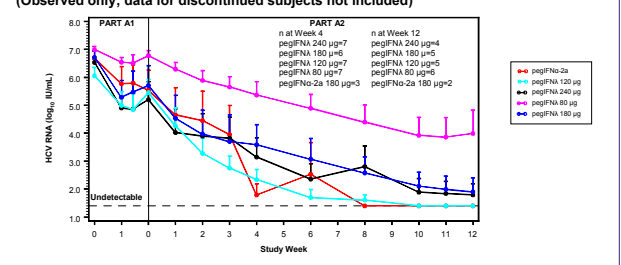
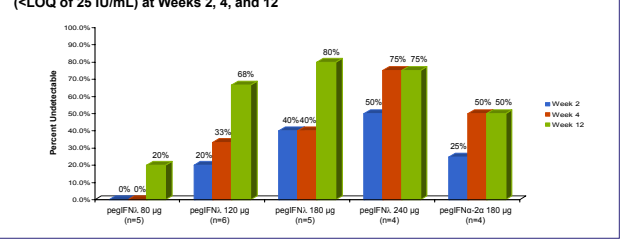


Figure 6. Impact of Race: Non-Black Patients, HCV Genotypes 1/4 Not Detectable (<LOQ of 25 IU/mL) at Weeks 2, 4, and 12



RESULTS (cont'd)

Table 2. Impact of Host IL28B Genotype: Virologic Among Patients With HCV Genotypes 1/4

Virologic Response*	pegIFNλ ^{a,c} (combined for doses of 120-240 μg)		Published Data ^b	
	CC n=7	Non-CC n=12	CC	Non-CC
Virologic response at week 2	71%	8%	12%	2%
Virologic response at week 4	71%	25%	28%	5%
Virologic response at week 12	86%	50%	84%	33%

*Virologic response = HCV RNA below LOQ (25 IU/mL); ITT analysis.
^aIncluding 2 patients with HCV G4. HCV RNA of 1 of the 2 HCV G4 patients became undetectable by Week 12.
^bHCV G1 only, from Thompson AJ, et al. *Gastroenterology*. 2001;119(1):120-9.e18. Study results are not directly comparable to published results due to extra IFN dose 2 weeks prior to initiation of combination therapy and possible differences in definition of virologic response.
^cData for pegIFNα-2a subjects (n=2) and for patients with HCV genotypes 2/3 (n=2 CC) were not sufficient for analysis.

SUMMARY: VIROLOGIC RESPONSE

- Robust antiviral activity was observed at all dose levels
 - Less activity at lowest dose (80 μg)
 - Virologic response, defined as HCV RNA LOQ (<25 IU/mL) at 2, 4, or 12 weeks*, was influenced by HCV genotype and race
 - Response rates higher for HCV G2/3 than for HCV G1/4
 - Response rates lower in patients who were black or of African descent
 - Racial imbalance may have influenced observed differences in responses across groups
 - Virologic response was influenced by host genotype at rs12979860, a single nucleotide polymorphism linked to the IL28B gene
 - Homozygosity for C (CC) was associated with a greater proportion with virologic response at 2, 4, and 12 weeks
- *Viral response at 4 and 12 weeks was not directly comparable to published RVR and cEVR rates, due to extra dose of study drug for PK analysis 2 weeks prior to starting combination therapy.

SAFETY RESULTS

Table 3. Safety Overview Through Week 12

	pegIFNα-2a 180 μg n=10 (%)	pegIFNλ				Total N=45 (%)	
		240 μg n=11 (%)	180 μg n=11 (%)	120 μg n=11 (%)	80 μg n=12 (%)		
Death	0	0	0	0	0	0	
Dose-limiting toxicity	0	0	0	0	0	0	
Dose reductions	1 ^a (10)	3 ^b (27)	1 ^b (9)	0	0	4 (9)	
Discontinuations due to related AEs	1 (10)	0	0	1 (9)	1 (8)	2 (4)	
SAEs	All	1 (10)	0	0	3 (27)	2 (17)	5 (11)
	Related	1 ^c (10)	0	0	0	2 ^d (17)	2 (4)

AEs = adverse events; SAEs = serious adverse events.
^aDose reduced x2 due to depression, then discontinued.
^bDose held, then reduced due to patients meeting protocol-defined criteria of AST/ALT >5x ULN and >3x baseline. Laboratory abnormalities resolved after single held dose, and treatment was restarted at next lower dose.
^cDepression and suicidal ideation.
^dSuicidal ideation; pneumonitis.

Table 4. Adverse Events Through Week 12

Most Common Adverse Events ^a	pegIFNα-2a 180 μg n=10 (%)	pegIFNλ				pegIFNλ groups Combined ^b N=45
		240 μg n=11 (%)	180 μg n=11 (%)	120 μg n=11 (%)	80 μg n=12 (%)	
Myalgia	4 (40)	0	0	6 (55)	0	6 (13)
Fatigue	3 (30)	2 (18)	5 (46)	2 (18)	1 (8)	10 (22)
Headache	3 (30)	3 (27)	2 (18)	4 (36)	1 (8)	10 (22)
Nausea	3 (30)	4 (36)	1 (9)	2 (18)	3 (25)	10 (22)
Injection site reaction	3 (30)	3 (27)	1 (9)	4 (36)	1 (8)	9 (20)
Depression	2 (20)	1 (9)	2 (18)	1 (9)	2 (17)	6 (13)
Pruritus	1 (10)	3 (27)	0	2 (18)	0	5 (11)
Vomiting	1 (10)	1 (9)	0	3 (27)	1 (8)	5 (11)
Irritability	1 (10)	2 (18)	3 (27)	3 (27)	3 (25)	11 (24)
Insomnia	0	2 (18)	2 (18)	4 (36)	3 (25)	11 (24)

^aReported in at least 10% of patients for pegIFNλ groups combined.
^bMajority were mild to moderate in severity.

RESULTS (cont'd)

Figure 7. Mean (SE) Hemoglobin Over Time, All Genotypes

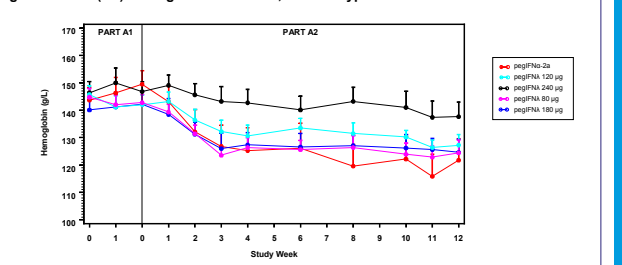


Figure 8. Mean (SE) Total Neutrophils Over Time, All Genotypes

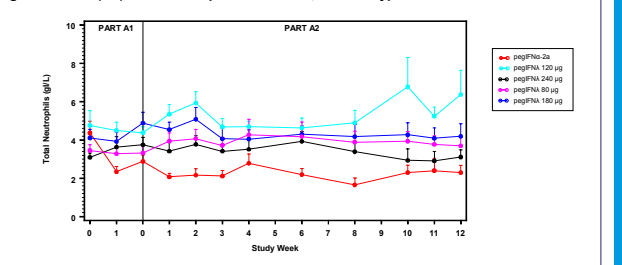
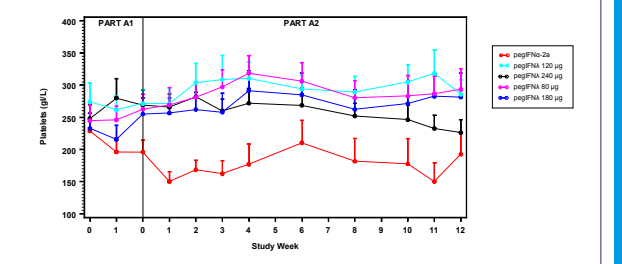


Figure 9. Mean (SE) Platelets Over Time, All Genotypes



SUMMARY: SAFETY

- PegIFNλ was generally well-tolerated at all doses tested, with the majority of adverse events and laboratory abnormalities mild (grade 1) or moderate (grade 2) in severity
- PegIFNλ was associated with minimal changes in hematologic laboratory parameters compared with pegIFNα-2a
- Four pegIFNλ patients (3 on 240 μg, 1 on 180 μg) met protocol-defined criteria for dose reduction based on elevated AST or ALT. All were readily managed by holding dose for 1 week, then were restarted at the next lower dose

CONCLUSIONS

- PegIFNλ shows promise across a broad range of doses and viral genotypes, and in difficult-to-treat host genotypes
- At the highest 3 doses of pegIFNλ
 - Virologic response at 4 and 12 weeks was similar to, or greater than, that observed and reported with type 1 interferon-based regimens
 - PegIFNλ in combination with RBV was associated with rapid virologic response
- Virologic response was influenced by race, viral genotype, and host genotype at rs12979860
 - Non-CC patients treated with pegIFNλ achieved promising virologic responses
- Treatment with pegIFNλ was generally well-tolerated through 12 weeks
 - Adverse events were mild to moderate and led to few treatment discontinuations
 - Minimal hematologic effects observed
 - Elevations in ALT or AST were readily managed by dose adjustment
- Study is ongoing; all patients will have reached end of treatment by January 2011 and SVR will be assessable after July 2011

DISCLOSURE

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