# 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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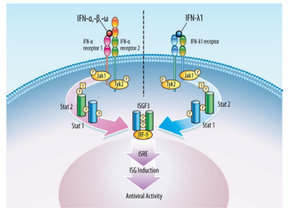
## INTRODUCTION

- 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. IFNλ and Type 1 Interferons Share Intracellular Signaling Pathways**

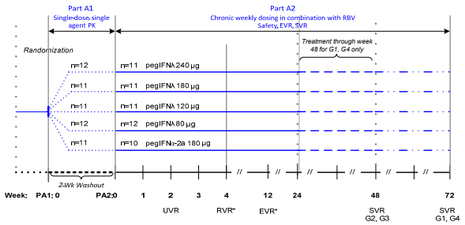



## METHODS

- 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 ≤ULN
  - 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 log$_{10}$ 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 | | peglFNα-2a 180 µg n=10 (%) | peglFNλ 240 µg n=11 (%) | peglFNλ 180 µg n=11 (%) | peglFNλ 120 µg n=11 (%) | peglFNλ 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) |

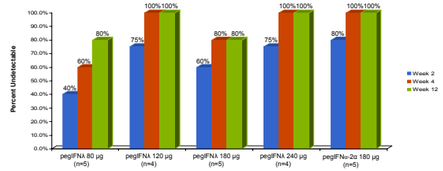
BMI = body mass index; SD = standard deviation.

## RESULTS (cont'd)

### EFFICACY RESULTS

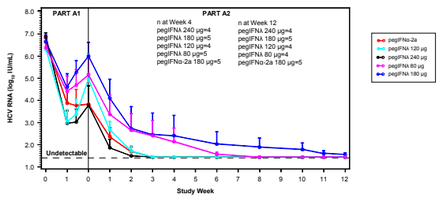
#### Virologic Response, Genotypes 2/3

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



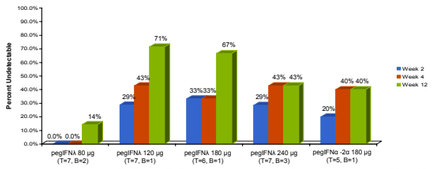

*Not comparable to published RVR and cEVR rates due to extra dose 2 weeks prior to start of Part A2.
ITT = intent-to-treat.

**Figure 3. Mean (SE) Log$_{10}$ HCV RNA Over Time (Observed) in HCV Genotypes 2/3 (Observed only; data for discontinued subjects not included)**



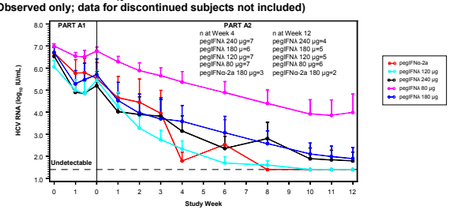

#### Virologic Response, Genotypes 1/4

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



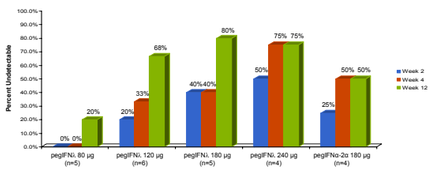

*Not comparable to published RVR and cEVR rates due to extra dose 2 weeks prior to start of Part A2.
T = total number of patients; B = black or of African descent.

**Figure 5. Mean (SE) Log$_{10}$ HCV RNA Over Time (Observed) in HCV Genotypes 1/4 (Observed only; data for discontinued subjects not included)**




#### Virologic Response, Genotypes 1/4: Non-Black Patients

**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* | peglFNλ[a,c] (combined for doses of 120-240 µg) | | Published Data[b] | |
|---|---|---|---|---|
| Host Genotype at rs12979860 | 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.
[a]Including 2 patients with HCV G4. HCV RNA of 1 of the 2 HCV G4 patients became undetectable by Week 12.
[b]HCV G1 only, from Thompson AJ, et al. *Gastroenterology*. 2001;139(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.
[c]Data 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**

| | | peglFNα-2a 180 µg n=10 (%) | peglFNλ 240 µg n=11 (%) | peglFNλ 180 µg n=11 (%) | peglFNλ 120 µg n=11 (%) | peglFNλ 80 µg n=12 (%) | peglFNλ Total N=45 (%) |
|---|---|---|---|---|---|---|---|
| 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.
[a]Dose reduced x2 due to depression, then discontinued.
[b]Dose 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.
[c]Depression and suicidal ideation.
[d]Suicidal ideation; pneumonitis.

**Table 4. Adverse Events Through Week 12**

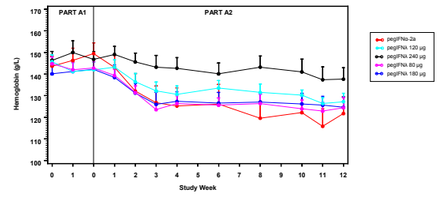
| Most Common Adverse Events[a] | peglFNα-2a 180 µg n=10 (%) | peglFNλ 240 µg n=11 (%) | peglFNλ 180 µg n=11 (%) | peglFNλ 120 µg n=11 (%) | peglFNλ 80 µg n=12 (%) | peglFNλ groups Combined[b] N=45 |
|---|---|---|---|---|---|---|
| Myalgia | 4 (40) | 0 | 0 | 6 (55) | 0 | 6 (13) |
| Fatigue | 3 (30) | 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) |

[a]Reported in at least 10% of patients for peglFNλ groups combined.
[b]Majority were mild to moderate in severity.

## RESULTS (cont'd)

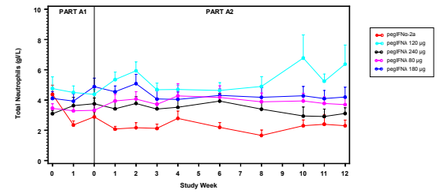
#### Mean Hemoglobin by Treatment Arm

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



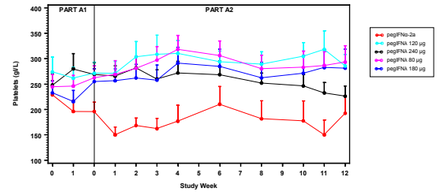

#### Mean Absolute Neutrophil Count by Treatment Arm

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




#### Mean Platelets by Treatment Arm

**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 peglFNα-2a
- Four peglFNλ 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 peglFNλ
  - 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 peglFNλ achieved promising virologic responses
- Treatment with peglFNλ 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



ZymoGenetics

Bristol-Myers Squibb