A CONTINUING MEDICAL EDUCATION ACTIVITY

THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Online Expert Poster Review and Discussion

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Pegylated Interferon-Lambda (PegIFN-λ) Shows Superior Viral Response With Improved Safety and Tolerability Versus PegIFN-α-2a in HCV Patients (G1/2/3/4): EMERGE Phase IIb Through Week 12

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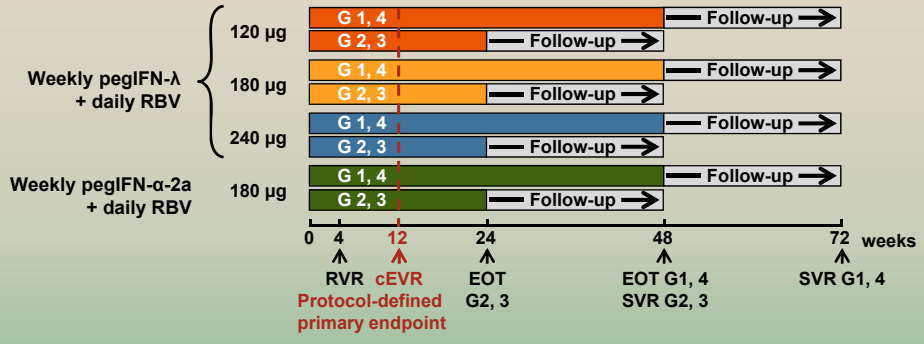
Abstract 1360

Background

- Current therapy of chronic hepatitis C is limited by hematologic toxicity, frequent adverse events (AEs), and suboptimal efficacy
- Interferon lambda-1 (IFN-λ1, IL-29) is a type III interferon with many functional similarities to alpha interferons (IFN-α)
  - Shared intracellular signal transduction pathways
  - Induction of interferon-sensitive genes
- Lambda and alpha interferons exert antiviral effects through different extracellular receptors
  - IFN-α receptors are widely distributed, contributing to AE frequency
  - IFN-λ receptors are expressed in hepatocytes; distribution is otherwise more limited than IFN-α receptors, with less expression in hematologic cells and in non-hepatocyte liver cells
- This ongoing phase 2b study compares the efficacy and safety of pegylated IFN-λ1 (pegIFN-λ) with pegylated interferon-alfa-2a (pegIFN-α-2a), each combined with ribavirin (RBV), in naïve patients with chronic hepatitis C

Study Design

- 526 non-cirrhotic treatment-naïve adults aged 18-70 years
- Chronic HCV infection ≥ 6 months, genotypes 1,2,3, or 4 (by Siemens TruGene® HCV 5'NC assay)
- HCV RNA ≥ 100,000 IU/mL
- ALT/AST ≤ 5 × ULN; no history or evidence of hepatic decompensation
- Safety assessed through week 12; HCV RNA assessed at weeks 4 (RVR) and 12 (cEVR)
- Defined as HCV RNA undetectable with Roche COBAS® TaqMan® HPS v2.0

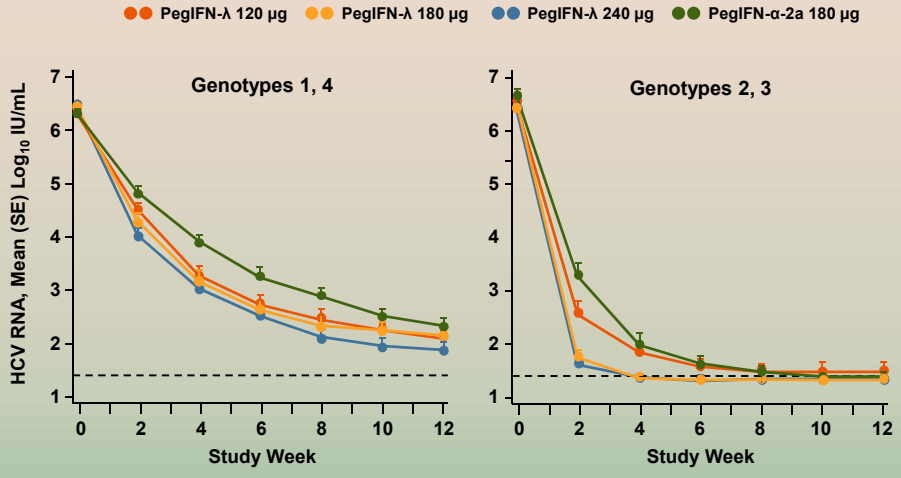


Baseline Demographic and Disease Characteristics

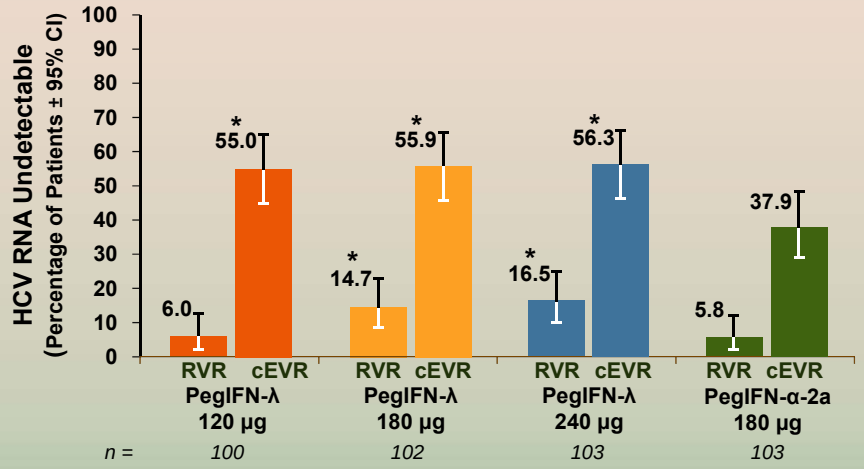
	PegIFN-λ				PegIFN-α-2a
Parameter	120 µg (N=128)	180 µg (N=131)	240 µg (N=134)	Total (N=393)	180 µg (N=133)
Age, mean years	45.6	46.1	47.8	46.5	47.5
Gender, % male	61.7	55.7	55.2	57.5	61.7
BMI, mean kg/m^2	26.8	27.3	27.2	27.1	27.1
Race, %					
White	82.0	84.0	84.3	83.5	87.2
Black or African American	9.4	9.2	11.2	9.9	5.3
Asian or Other	8.6	6.9	4.5	6.6	7.6
HCV RNA, mean $\log_{10}$ IU/mL	6.43	6.50	6.52	6.48	6.46
HCV genotype, %					
1	73.4	73.3	73.1	73.3	72.9
2	9.4	13.0	11.9	11.5	11.3
3	13.3	9.2	10.4	10.9	11.3
4	3.9	4.6	4.5	4.3	4.5
Fibrosis score, n*					
Ishak ≤3, Metavir ≤2, FibroTest <.58	111	116	114	341	114
Ishak 4, Metavir 3, FibroTest .58 to <.72	18	14	19	51	19
Ishak 5-6, Metavir 4, FibroTest ≥.72	0	1	1	2	0

* Based on biopsy within 2 years and/or FibroTest at screening; some patients had multiple fibrosis scores recorded

HCV RNA Concentration Over Time

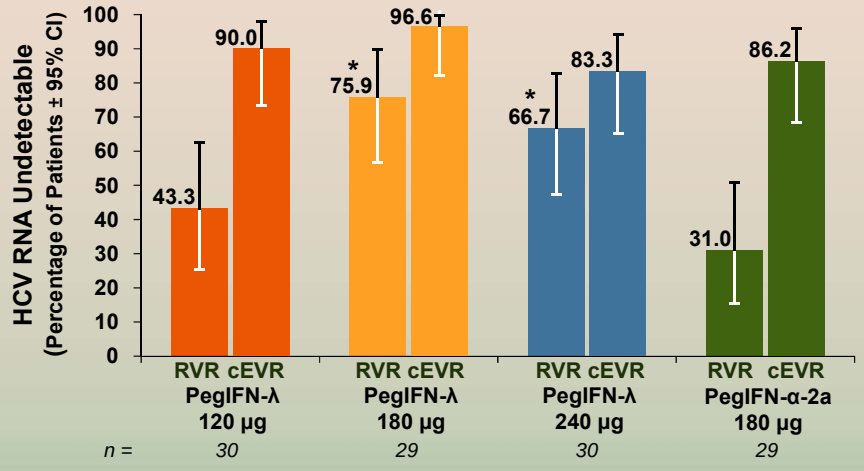


Undetectable HCV RNA at Week 4 (RVR) and Week 12 (cEVR): HCV Genotypes 1, 4



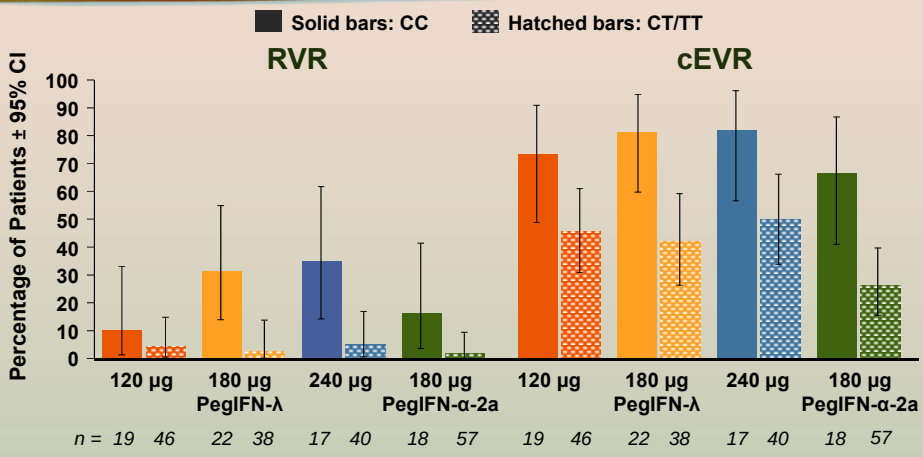
* $P < 0.05$ vs pegIFN-α-2a
Data indicate HCV RNA not detected by Roche COBAS TaqMan HPS v2.0

Undetectable HCV RNA at Week 4 (RVR) and Week 12 (cEVR): HCV Genotypes 2, 3



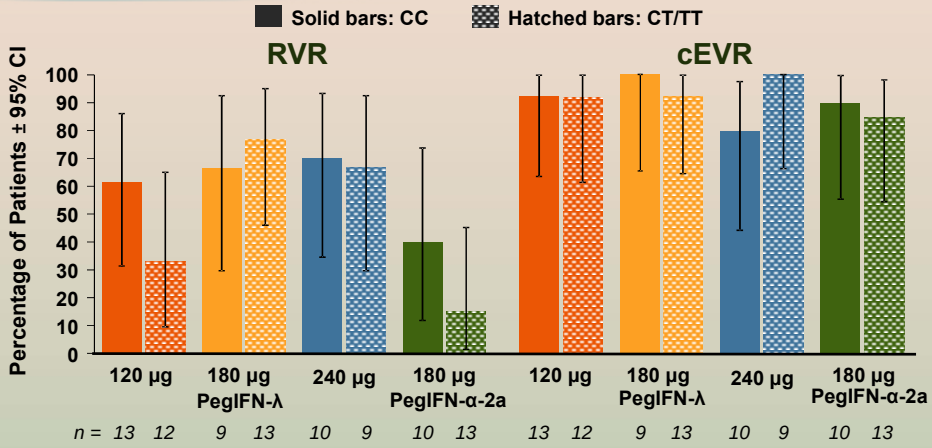
* $P < 0.05$ vs pegIFN-α-2a
Data indicate HCV RNA not detected by Roche COBAS TaqMan HPS v2.0

RVR and cEVR by IL28B Genotype* in Consenting Patients: HCV Genotypes 1, 4



*rs12979860: CC, favorable; CT/TT, unfavorable.
Data indicate HCV RNA not detected by Roche COBAS TaqMan HPS v2.0.

RVR and cEVR by IL28B Genotype* in Consenting Patients: HCV Genotypes 2, 3



*rs12979860: CC, favorable; CT/TT, unfavorable.
Data indicate HCV RNA not detected by Roche COBAS TaqMan HPS v2.0.

Adverse Events (Any Grade) Occurring in ≥ 10% of Patients in Any Treatment Group

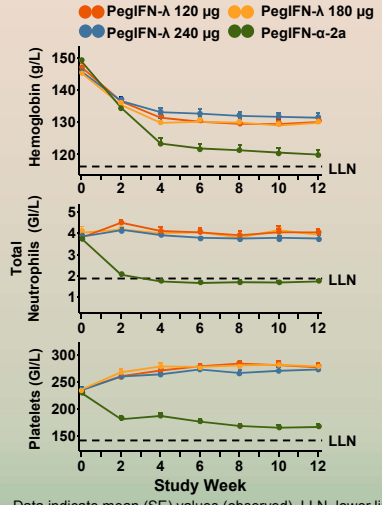
	PegIFN-λ				PegIFN-α-2a
Preferred Term	120 µg (N=128)	180 µg (N=131)	240 µg (N=134)	Total PegIFN-λ (N=393)	180 µg (N=133)
Any AE, %	85.9	86.3	88.1	86.8	95.5
Fatigue	34.4	38.2	36.6	36.4	42.9
Headache	25.0	23.7	23.1	23.9	33.1
Myalgia	10.9	6.1	9.0	8.7	30.1
Pyrexia	7.0	6.9	6.0	6.6	29.3
Nausea	27.3	19.1	35.8	27.5	27.1
Arthralgia	10.2	6.1	6.0	7.4	21.8
Chills	2.3	2.3	1.5	2.0	20.3
Insomnia	25.8	16.0	17.9	19.8	20.3
Rash	9.4	6.1	6.7	7.4	15.0
Pruritus	10.9	13.0	17.2	13.7	13.5
Diarrhea	11.7	5.3	10.4	9.2	11.3
Cough	6.3	8.4	6.7	7.1	11.3
Decreased appetite	10.9	7.6	11.2	9.9	10.5
Depression	10.9	3.8	6.7	7.1	9.8
Irritability	13.3	16.8	14.2	14.8	9.8

Listed by descending frequency on pegIFN-α-2a.
Shading indicates events with >2-fold difference in frequency, total pegIFN-λ vs pegIFN-α-2a.

Discontinuations, Dose Modifications, and Serious Adverse Events

	PegIFN-λ				PegIFNα-2a
	120 µg (N=128)	180 µg (N=131)	240 µg (N=134)	Total PegIFN-λ	180 µg (N=133)
Discontinuations, %	2.3	4.6	7.5	4.8	5.3
Related to treatment	1.6	2.3	3.0	2.3	3.8
Patients with any reduction in pegIFN dose, %	0.8	3.8	12.7	5.9	18.8
Patients with held and/or reduced RBV dose, %	10.2	4.6	11.2	8.7	20.3
Patients with any serious adverse events, %	1.6	2.3	5.2	3.1	2.3
Related to treatment	0.8	1.5	2.2	1.5	2.3

Changes in Hematologic Parameters Over Time and Hematology-Associated PegIFN and RBV Dose Reductions



Data indicate mean (SE) values (observed). LLN, lower limit of the reference range.

	PegIFN-λ			PegIFN α-2a
Lab Toxicity, %	120 µg (n=128)	180 µg (n=131)	240 µg (n=134)	180 µg (n=133)
Hemoglobin low	20.5	15.4	12.9	43.9
RBV dose reduction, % (due to Hgb abnormality)	**2.3**	**1.5**	**0.7**	**12.8**
Neutrophils low	0	0.8	0	15.2
Platelets low	0	0	0	1.5
PegIFN dose reduction, % (due to hematologic abnormality)	**0**	**0**	**0**	**17.3**

Hemoglobin low < 10 g/dL
Neutrophils low < 750/mm^3
Platelets low < 25,000/mm^3

Table summarizes patients' highest treatment-emergent toxicity in first 12 weeks of treatment.

Treatment-Emergent Liver-Related Laboratory Abnormalities

		PegIFN-λ			PegIFN-α-2a
Lab Toxicity, %	Severity	120 µg (N=128)	180 µg (N=131)	240 µg (N=134)	180 µg (N=133)
AST or ALT high	5.1-10 × ULN	0.8	2.3	14.4	7.6
	>10 × ULN	0	0	3.0	0
Direct bilirubin high	1.6-2.5 × ULN	4.7	4.6	12.1	1.5
	2.6-5.0 × ULN	0.8	3.1	6.1	0.8
	>5.0 × ULN	0	0.8	1.5	0
PegIFN dose reductions due to liver-related lab abnormality, %		0	1.5	7.5	0
• ALT, AST, bilirubin returned to acceptable range to restart treatment within 1-2 weeks					
PegIFN discontinuations due to liver-related lab abnormality, % (all due to hyperbilirubinemia)		0.8	0.8	1.5	0
• Direct bilirubin had recovered to < 2 x ULN in 3 patients and < 4 x ULN in 1 patient at the time of data analysis					

Conclusions

Compared to PegIFN-α-2a, PegIFN-λ was Associated with:	
Efficacy	• Superior cEVR rates at all doses in patients with HCV G1,4
	• Similar cEVR rates at all doses in patients with HCV G2,3
	• Superior RVR rates at 180 µg and 240 µg doses in HCV G1,4 and HCV G2,3
	• Increased virologic responses in favorable and unfavorable IL28B genotypes
Safety	• Reduced RBV and IFN dose reduction at all doses
	• Fewer adverse events of pyrexia, chills, arthralgia, myalgia and rash
	• Fewer hematologic abnormalities
	• At the 240 µg dose only, more elevations of AST and ALT with or without elevated bilirubin, managed with dose reduction
	• Four adverse events of hyperbilirubinemia led to discontinuation of treatment; all cases showed subsequent improvement