

# Eric Lawitz, MD

## Alamo Medical Research, San Antonio, TX

I have financial relationships within the last 12 months relevant to my presentation with:

Abbott Laboratories, Anadys Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, GlobelImmune, Human Genome Sciences, Idenix Pharmaceuticals, Idera Pharmaceuticals, Intarcia Therapeutics, Medarex, Merck & Co., Novartis, Roche, Schering-Plough, Valeant Pharmaceuticals International, Vertex Pharmaceuticals, ViroChem Pharma, ZymoGenetics

My presentation does include discussion of investigational use of PEG-Interferon- $\lambda$  (PEG-rIL-29) in chronic Hepatitis C

# Phase 1b Dose-Escalation Study of PEG-Interferon- $\lambda$ (PEG-rIL-29) in Relapsed Chronic Hepatitis C Patients

***E. Lawitz<sup>1</sup>, A. Zaman<sup>2</sup>, A.J. Muir<sup>3</sup>, M.L. Shiffman<sup>4</sup>,  
B. Yoffe<sup>5</sup>, T. Zhang<sup>6</sup>, S. Souza<sup>6</sup>, D.F. Hausman<sup>6</sup>***

1. Alamo Medical Research, San Antonio, TX, USA.

2. Oregon Health & Science University, Portland, OR, USA.

3. Duke University, Durham, NC, USA.

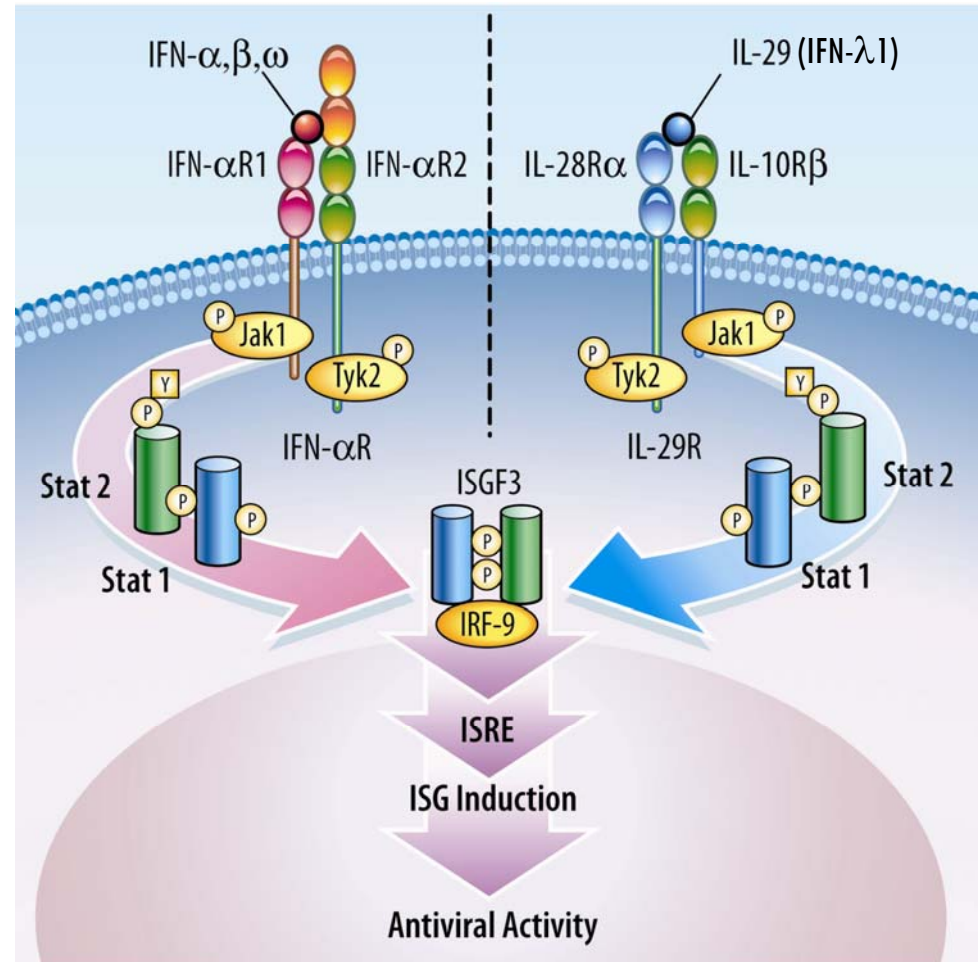
4. Virginia Commonwealth University Medical Center, Richmond, VA, USA.

5. Baylor College of Medicine/MEDVAMC, Houston, TX, USA.

6. ZymoGenetics Inc, Seattle, WA, USA.

# PEG-IFN- $\lambda$ : A More Targeted Interferon for HCV

- Novel PEGylated Type III IFN
  - ▶ Similar signaling pathway as IFN- $\alpha$
- Unique receptor
  - ▶ No cross-reactivity with IFN- $\alpha$  receptor
  - ▶ Expressed on hepatocytes
    - Limited expression on hematopoietic and neuronal cells
- Pharmacologic activity without typical IFN- $\alpha$  side effects in healthy volunteers



# Phase 1b Study in HCV Patients

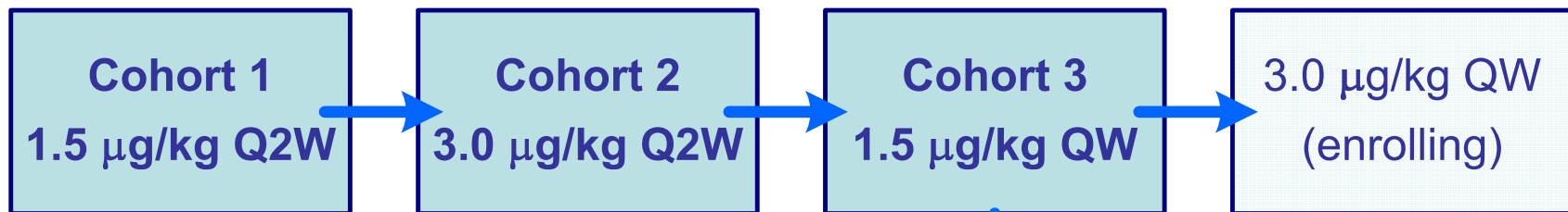
- Population
  - ▶ Genotype 1 HCV infection
  - ▶ Relapse after PEG-IFN- $\alpha$  + ribavirin
- Primary eligibility criteria
  - ▶ ALT and AST < 2.5 $\times$  ULN
  - ▶ Liver biopsy with Ishak score  $\leq$  4
  - ▶ No evidence of HBV or HIV infection
- Endpoints
  - ▶ Antiviral activity: > 1 Log decrease in HCV RNA
  - ▶ Safety: clinical events and laboratory abnormalities

# Phase 1b Dose and Schedule Escalation

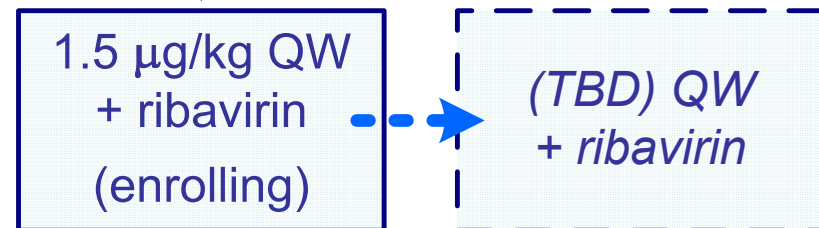
6 patients per cohort

Treatment: 4 weeks

## Part 1: Single-agent therapy



## Part 2: Combination therapy with ribavirin



*Ribavirin (Copegus): 1000 mg (< 75 kg) or 1200 mg (≥ 75 kg) daily*

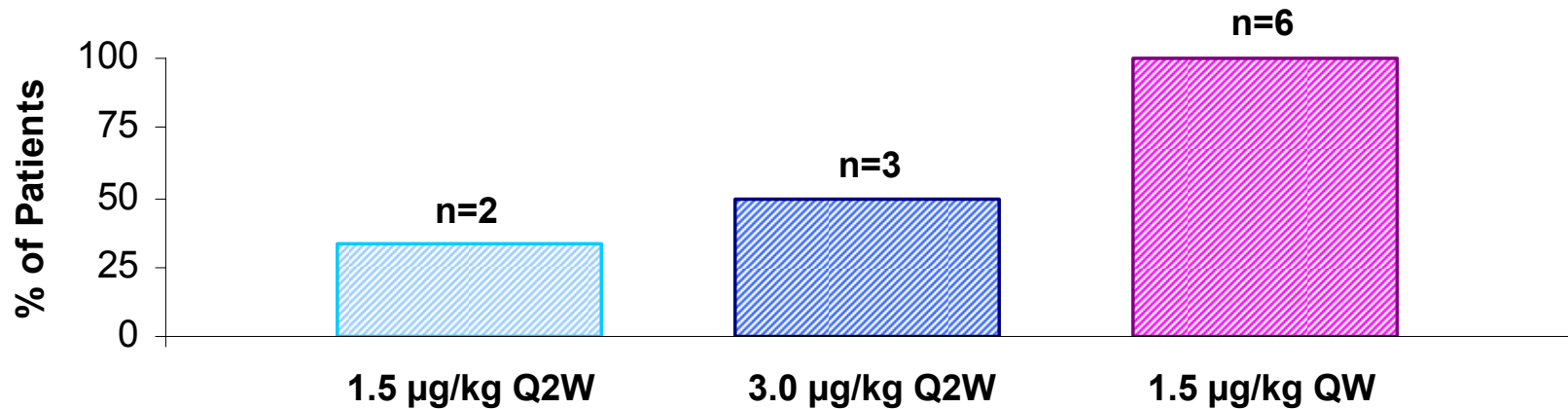
# Patient Characteristics

	----- Q2W -----		--- QW ---	Total (n=18)
	1.5 µg/kg (n=6)	3.0 µg/kg (n=6)	1.5 µg/kg (n=6)	
<b>Mean age</b>	53	49	56	53
<b>Race</b>				
<b>Black</b>	0	1	1	2
<b>Hispanic</b>	5	1	3	9
<b>White</b>	1	4	2	7
<b>Mean BMI (range)</b>	28 (25 - 30)	33 (25 - 49)	31 (24 - 40)	31
<b>Baseline Mean Log HCV RNA (range)</b>	7.3 (7.1 - 7.6)	6.5 (6.1 - 7.2)	6.6 (5.9 - 7.4)	6.8

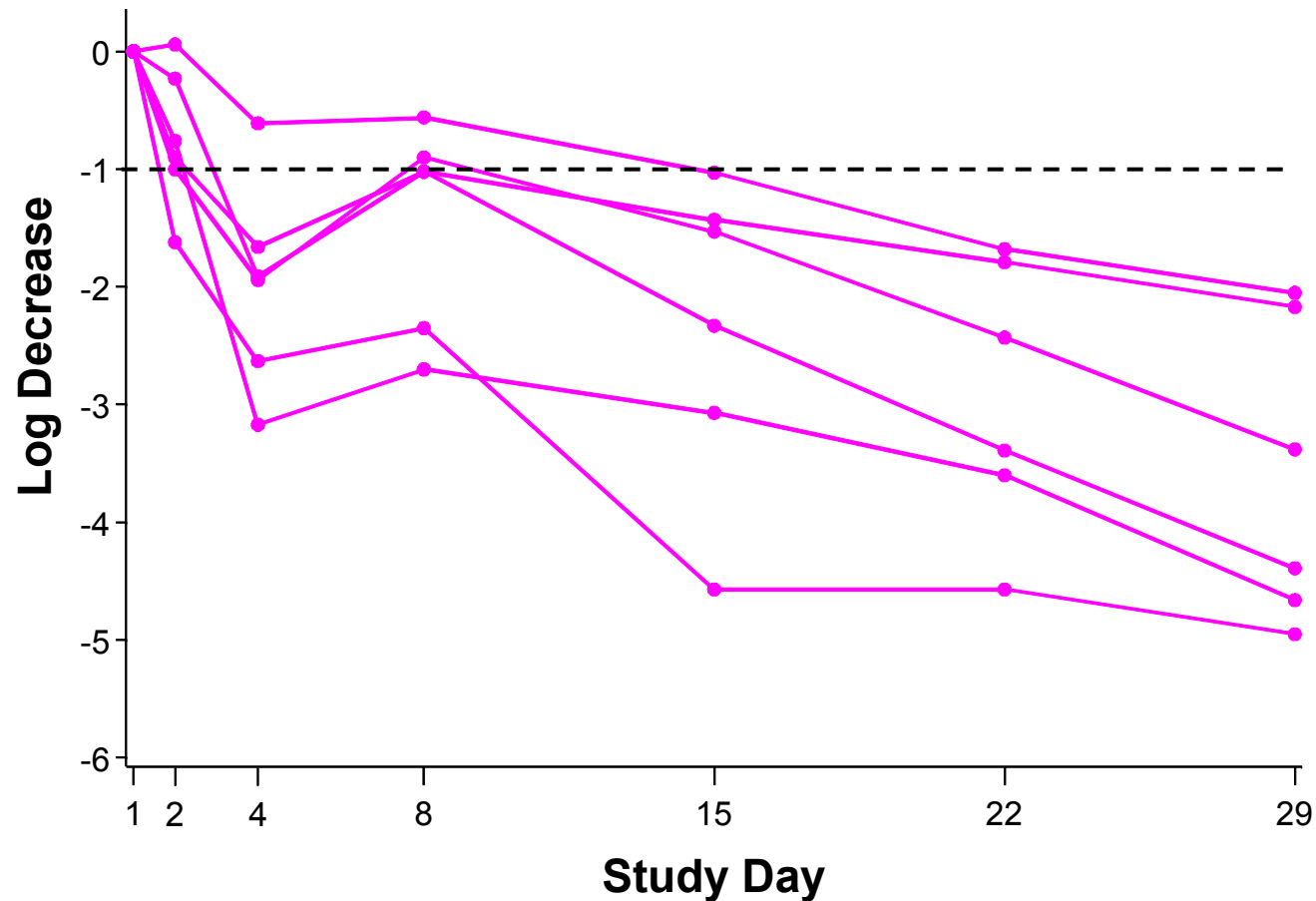
# Maximum Viral Load Reduction

	----- Q2W -----		--- QW ---
	1.5 µg/kg (n=6)	3 µg/kg (n=6)	1.5 µg/kg (n=6)
<b>Mean Decrease (Log)</b>	2.2	1.9	3.6
<b>95% CI</b>	0.42 – 3.88	0.96 - 2.82	2.27 - 4.93

Patients with > 2 Log Decrease in HCV RNA



# Viral Kinetics: 1.5 µg/kg QW Schedule



**4 of 6 patients with HCV RNA < 1000 IU/mL at Day 29**

# Clinical Adverse Events

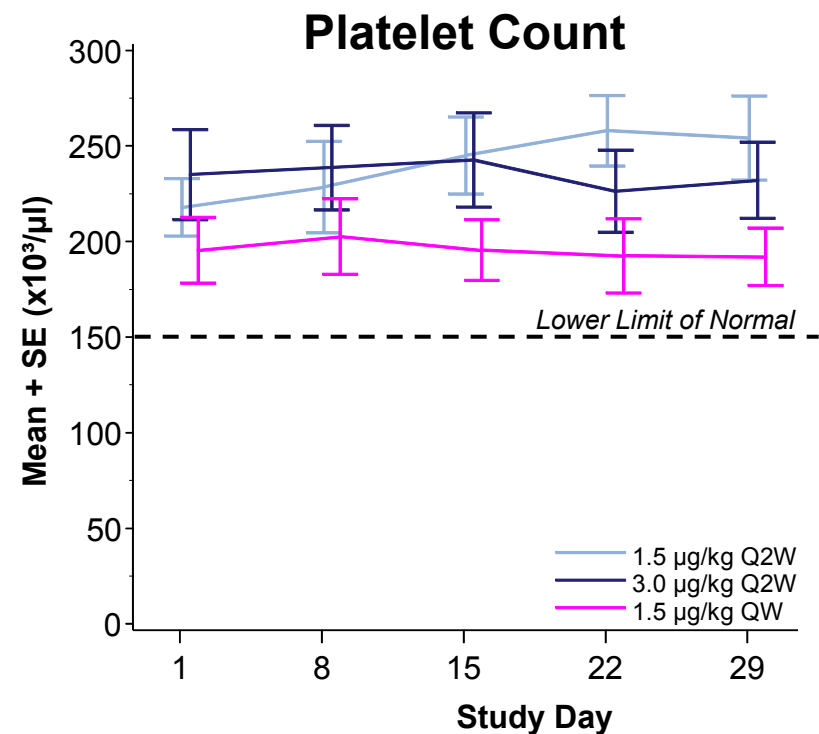
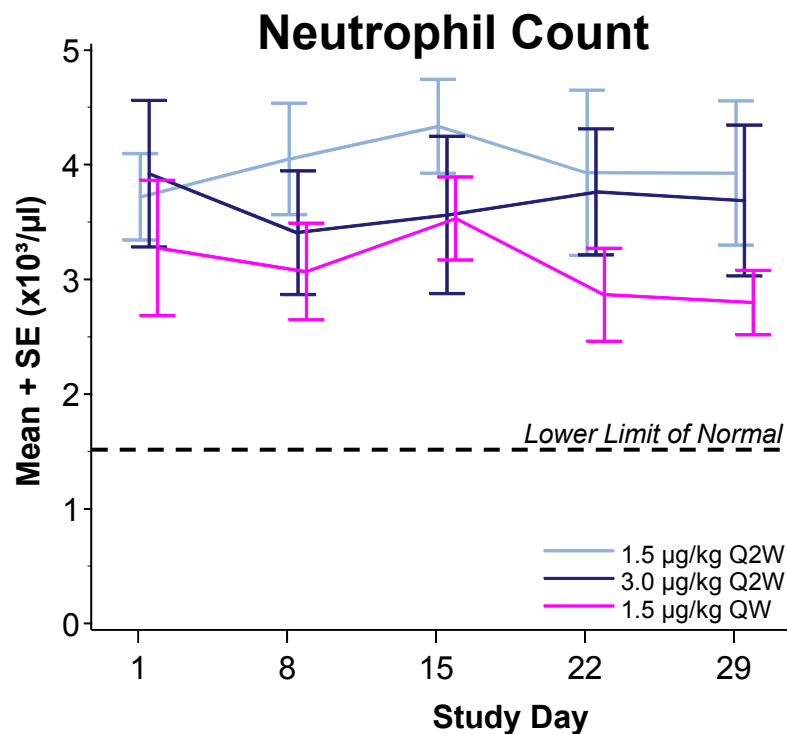
- **Well tolerated at all dose levels and schedules**
  - ▶ No discontinuation due to adverse events
  - ▶ No treatment-related fever
- **All adverse events Grade 1 or 2 in severity**

# Related Adverse Events

	----- Q2W -----		--- QW ---	
	1.5 µg/kg (n=6)	3.0 µg/kg (n=6)	1.5 µg/kg (n=6)	Total (n=18)
<b>Fatigue</b>	1 (17%)	1 (17%)	1 (17%)	3 (17%)
<b>Myalgia</b>	1 (17%)	--	1 (17%)	2 (11%)
<b>Anorexia</b>	-	1 (17%)	-	1 (6%)
<b>Dysgeusia</b>	-	1 (17%)	-	1 (6%)
<b>Flu-like symptoms</b>	-	1 (17%)	-	1 (6%)
<b>Injection site erythema</b>	-	-	1 (17%)	1 (6%)
<b>Irritability</b>	1 (17%)	-	-	1 (6%)
<b>Nausea</b>	-	1(17%)	-	1 (6%)

# Laboratory Values: Hematology

- No hematological toxicity
  - ▶ No neutropenia (ANC >  $1.5 \times 10^3/\mu\text{L}$  for all patients)
  - ▶ No thrombocytopenia
  - ▶ No anemia



# Laboratory Values: Transaminases

	Median ALT		
	----- Q2W -----		--- QW ---
	1.5 µg/kg (n=6)	3.0 µg/kg (n=6)	1.5 µg/kg (n=6)
<b>Baseline</b> (range)	<b>60</b> (29-96)	<b>52</b> (29-70)	<b>44</b> (26-122)
<b>Day 29</b> (range)	<b>47</b> (18-99)	<b>51</b> (19-100)	<b>58</b> (21-264)

- Reversible Gr 3 ALT or AST in 2 patients (< 7 days)
  - ▶ 3.0 µg/kg Q2W: Gr 3 AST (204 IU/L)
  - ▶ 1.5 µg/kg QW: Gr 3 ALT (264 IU/L)

# Summary

- Anti-viral activity
  - ▶ Demonstrated in all cohorts
  - ▶ Most vigorous response at 1.5 µg/kg QW
    - 6 of 6 patients experienced > 2-Log drop in HCV RNA
    - 4 of 6 patients with HCV RNA < 1000 IU/mL at Day 29
- Safety profile
  - ▶ Well tolerated over 4 week treatment
    - No neutropenia, thrombocytopenia, or anemia
    - No treatment-related fever
    - Minimal flu-like symptoms

# Conclusion

- PEG-IFN- $\lambda$  was well tolerated with no hematologic toxicity and limited constitutional symptoms
- Anti-viral efficacy was seen at all doses but most robust when dosed weekly
- Further trials are warranted in combination with ribavirin and other Hepatitis C therapies

# Acknowledgements

Steven Flamm, MD and Kim Sipich  
Northwestern University  
Chicago, IL

Andrew Muir, MD and Vicki Robertson  
Duke University Medical Center  
Durham, NC

Eric Lawitz, MD and Jessica Latham  
Alamo Medical Research  
San Antonio, TX

Mitchell Shiffman, MD and Marshall Jamerson  
McGuire Research Institute  
Richmond, VA

John Vierling, MD and Jana Lee  
St. Luke's Texas Liver Coalition  
Houston, TX

Russell Wiesner, MD  
Mayo Clinic  
Rochester, MN

Boris Yoffe, MD and Ketevan Garza Gasitashvili  
Baylor College of Medicine  
Houston, TX

Atif Zaman, MD and Suni Wilson  
Oregon Health and Science University  
Portland, OR

**THANK YOU to all the patients who participated in the trial**

# SUPPLEMENTAL SLIDES

# IFN- $\lambda$ 1 Receptor Distribution Is More Cell-type Specific than IFN- $\alpha$ Receptor

<b>Liver</b>	<b>IFN-<math>\lambda</math>1 Receptor<sup>1</sup></b>	<b>IFN-<math>\alpha</math> Receptor<sup>1</sup></b>
Hepatocytes	High	High
Endothelial cells	Not detected	High
Smooth muscle	Not detected	High
Fibroblasts	Not detected	High
<b>Hematopoietic</b>		
Bone Marrow Progenitors (CD 34+ cells)	Not detected	High
T and NK cells	Not detected	High
Monocytes	Not detected	High
B cells	High <sup>2</sup>	High

1. Based on levels of RNA expression

2. Protein levels are low