

# PROTON: PSI-7977 400 mg with PEG/RBV Provides 93% SVR Across HCV GT 1, 2, 3

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**I have the following financial relationships to disclose relevant to my presentation:**

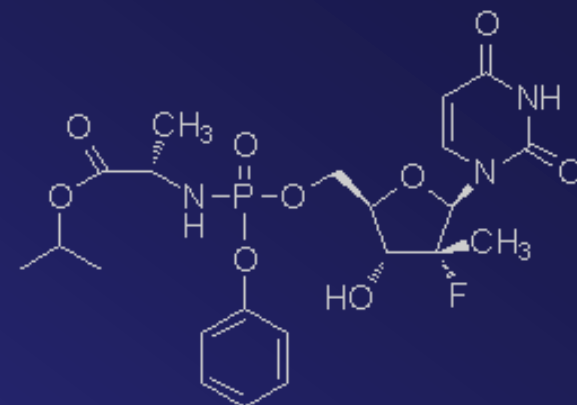
**Abbott Laboratories, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biorex Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Globelimmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Inhibitex Pharmaceuticals, Medarex, Medtronic, Merck & Co., Novartis, Pharmasset, Roche, Schering-Plough, Santaris Pharmaceuticals, Scynexis Pharmaceuticals, Tibotec, Vertex Pharmaceuticals, ViroChem Pharma, ZymoGenetics**

**AND**

**My presentation includes discussion of investigational use of PSI-7977**

# INTRODUCTION: PSI-7977

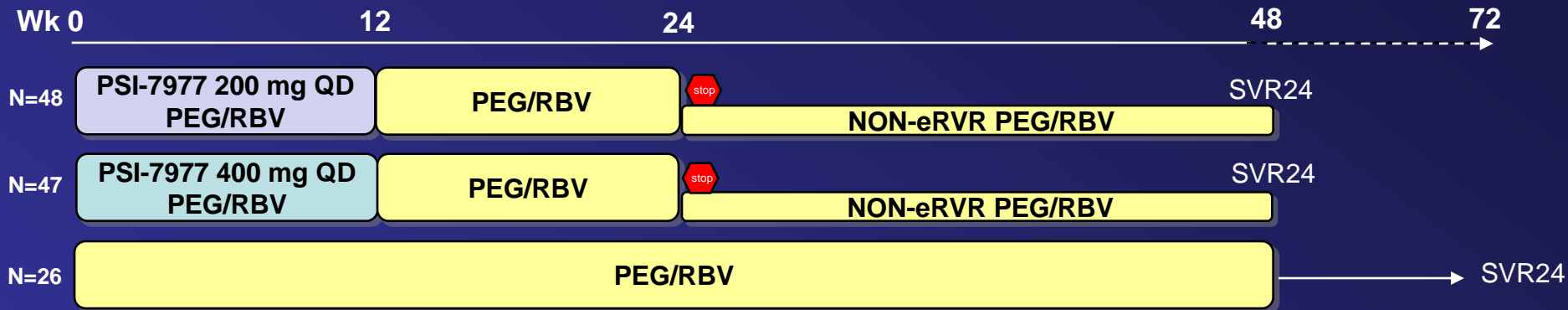
- **PSI-7977 is a potent, specific HCV nucleotide analog**
- **Safe and well-tolerated in clinical studies**
- **Once-daily, with or without food**
- **Excellent antiviral activity with broad HCV genotype coverage, with or without IFN**
  - **ELECTRON GT2/3 100% SVR (Gane, AASLD 2011)**
  - **PROTON GT1 91% SVR (Lawitz, AASLD 2011)**
  - **PROTON GT2/3 96% SVR (Lalezari, EASL 2011)**
- **High barrier to resistance**





# STUDY DESIGN: Dose ranging in GT1

## HCV GT1



- Double-blind, randomized, placebo-controlled
- 121 treatment-naïve patients with HCV GT1

## HCV GT2 or GT3



- Open label
- 25 treatment-naïve patients with HCV GT2 or GT3

# PROTON: Key Eligibility Criteria

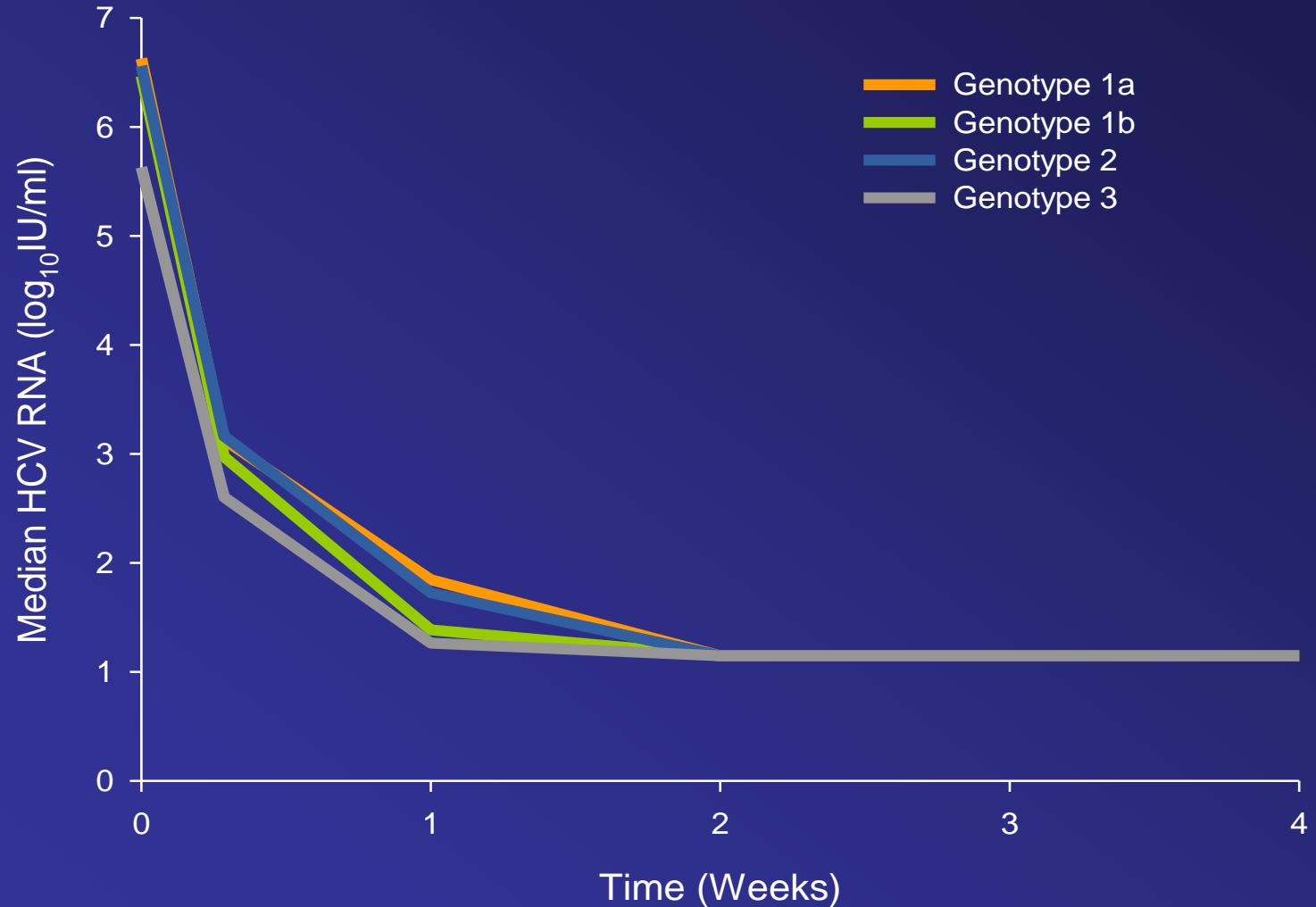
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- HCV Genotype 1, 2 and 3
- HCV RNA  $\geq 50,000$  IU/mL
- Treatment-Naïve, Non-cirrhotic
- $\geq 18$  years of age
- Laboratory Parameters:
  - Platelets  $> 90,000/\text{mm}^3$
  - Neutrophil  $\geq 1500/\text{mm}^3$  ( $\geq 1250$  cells/ $\text{mm}^3$  for African American/Black)
  - Hgb  $\geq 11$  g/dL in females;  $\geq 12$  g/dL in males

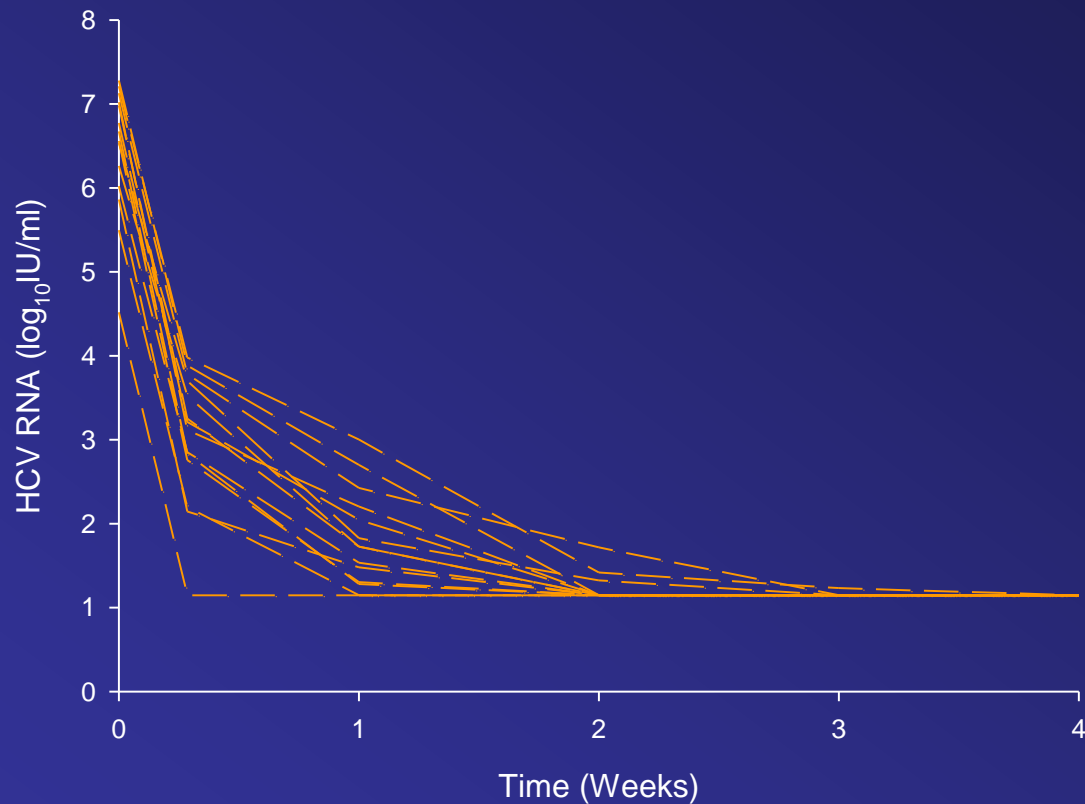
# Demographics and Baseline Characteristics Representative of US HCV+ Population

	PSI-7977 200 mg PEG/RBV n = 48	PSI-7977 400 mg PEG/RBV n = 47	PSI-7977 400 mg PEG/RBV n = 25	Placebo + PEG/RBV n = 26
Median HCV RNA log <sub>10</sub> IU/mL (range)	6.6 (5.2 - 7.8)	6.6 (3.8 - 7.4)	6.0 (4.5-7.3)	6.7 (4.6 - 7.4)
Male Gender, n (%)	33 (69)	21 (44)	16 (64)	19 (73)
HCV GT1a HCV GT2/3	37 (77) 0	35 (74) 0	0 25 (100)	20 (77) 0
Race/Ethnicity				
Black/African American	6 (13)	7 (15)	4 (16)	5 (19)
Hispanic	5 (10)	6 (13)	8 (32)	2 (8)
Median Age (range)	51 (24-65)	53 (24-66)	50 (23-64)	48 (25-64)
Median BMI (range)	27 (19-33)	26 (23-30)	28 (19-36)	29 (26-31)
IL28B C/C, n (%)	21 (44)	18 (38)	7 (28)	11 (42)
Fibrosis (F0-2)	46 (96)	46 (98)	25 (100)	24 (92)

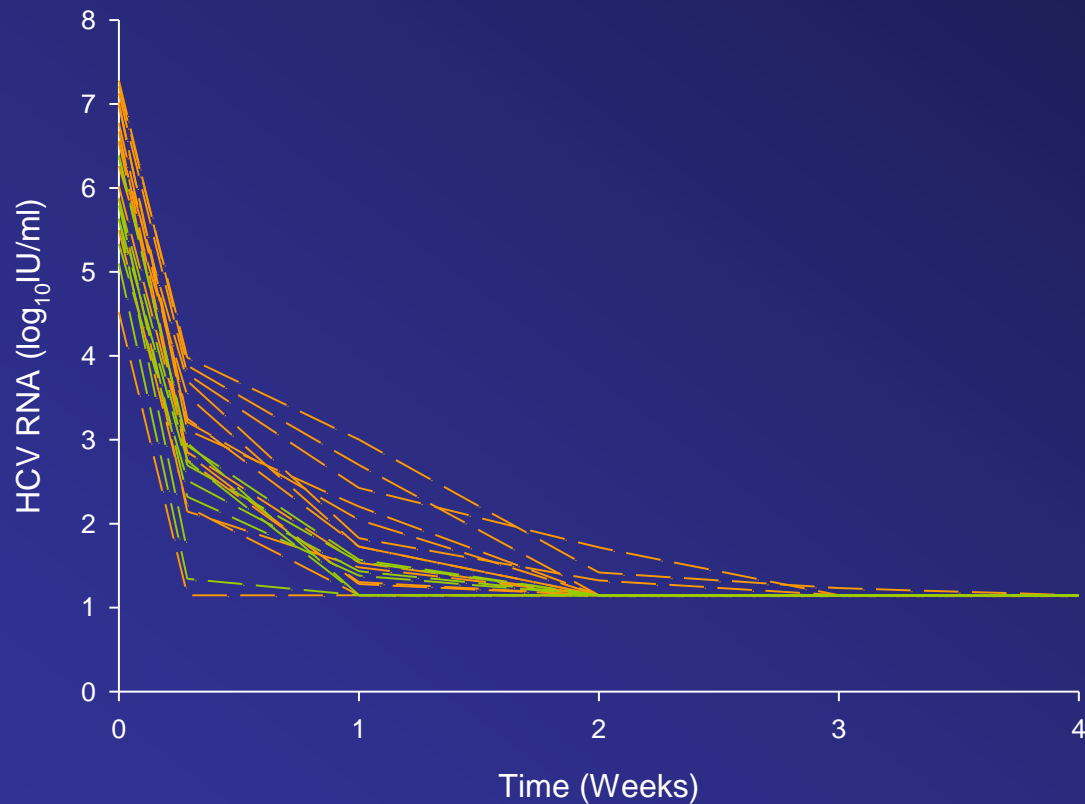
# Rapid HCV RNA Suppression in all Subjects Independent of HCV genotype on PSI-7977 400 mg QD + PEG/RBV



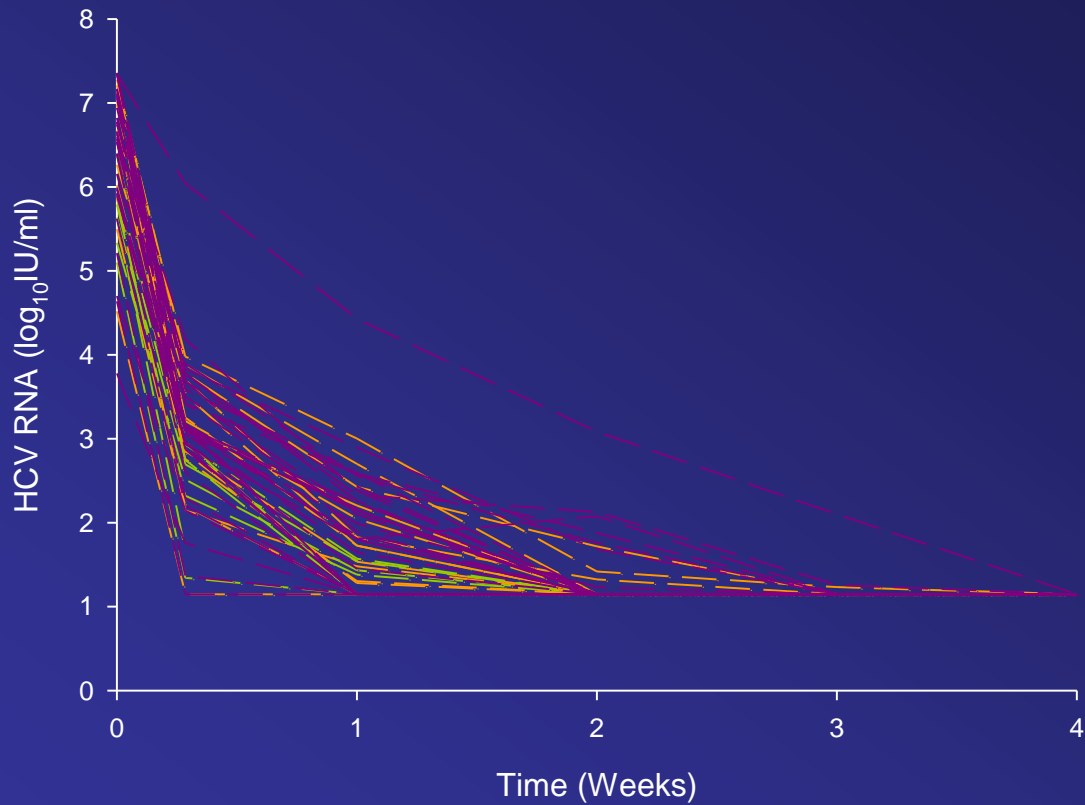
# HCV RNA Suppression of Individual Subjects on PSI-7977 400 mg QD + PEG/RBV: Genotype 2



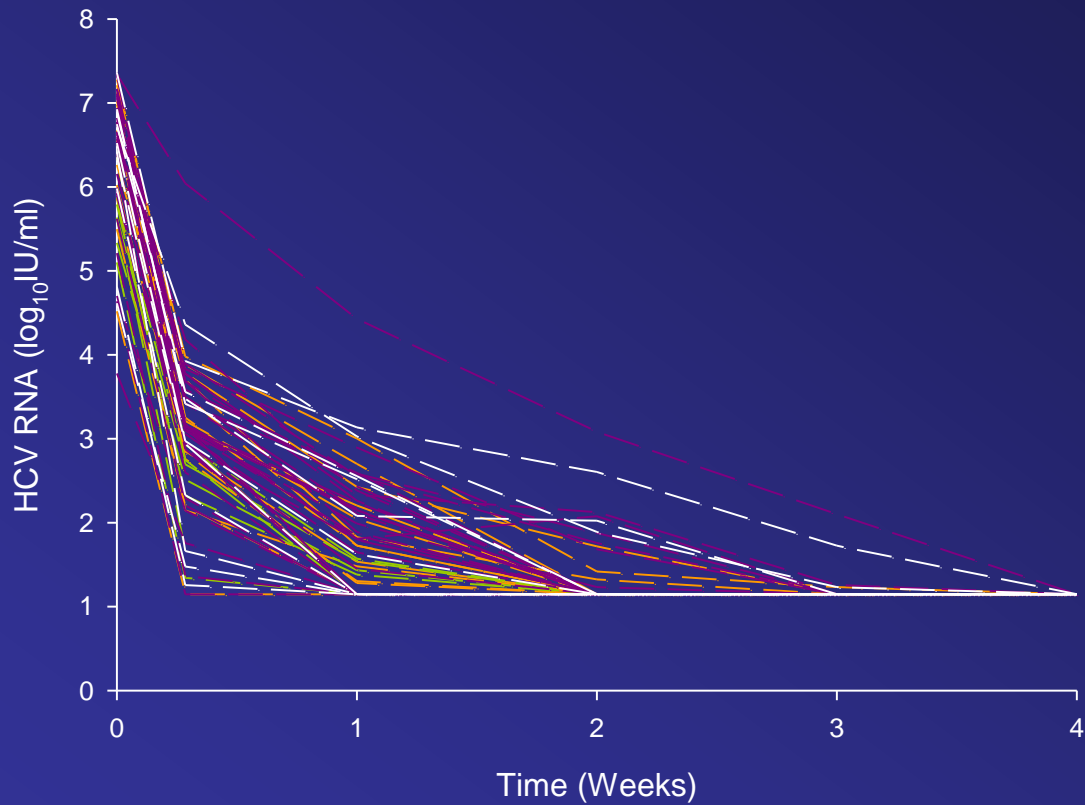
# HCV RNA Suppression of Individual Subjects on PSI-7977 400 mg QD + PEG/RBV: Genotype 2 & 3



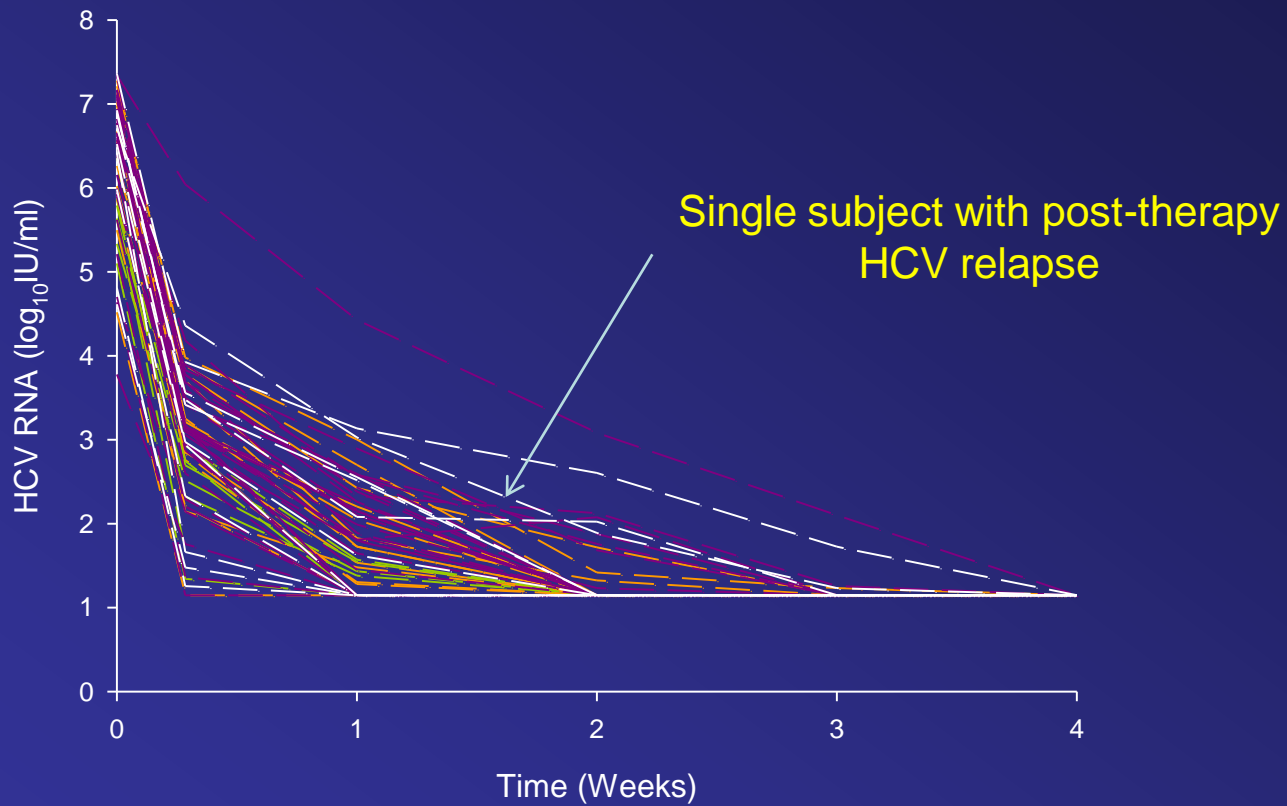
# HCV RNA Suppression of Individual Subjects on PSI-7977 400 mg QD + PEG/RBV: Genotype 2, 3, 1a



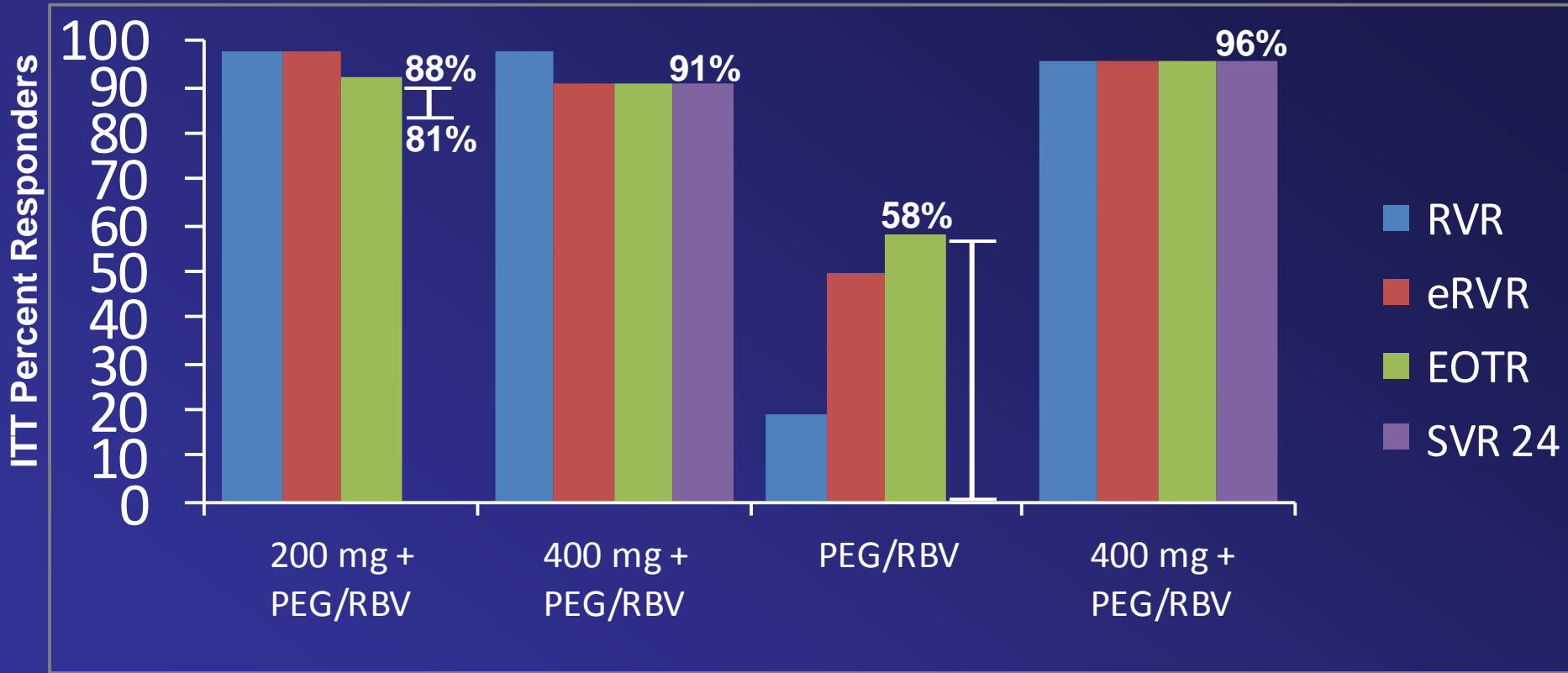
# HCV RNA Suppression of Individual Subjects on PSI-7977 400 mg QD + PEG/RBV: Genotype 2, 3, 1a &1b



# HCV RNA Suppression of Individual Subjects on PSI-7977 400 mg QD + PEG/RBV: Genotype 2, 3, 1a & 1b



# PSI-7977 400 mg QD + PEG/RBV 93% SVR24 Across GT 1, 2 & 3

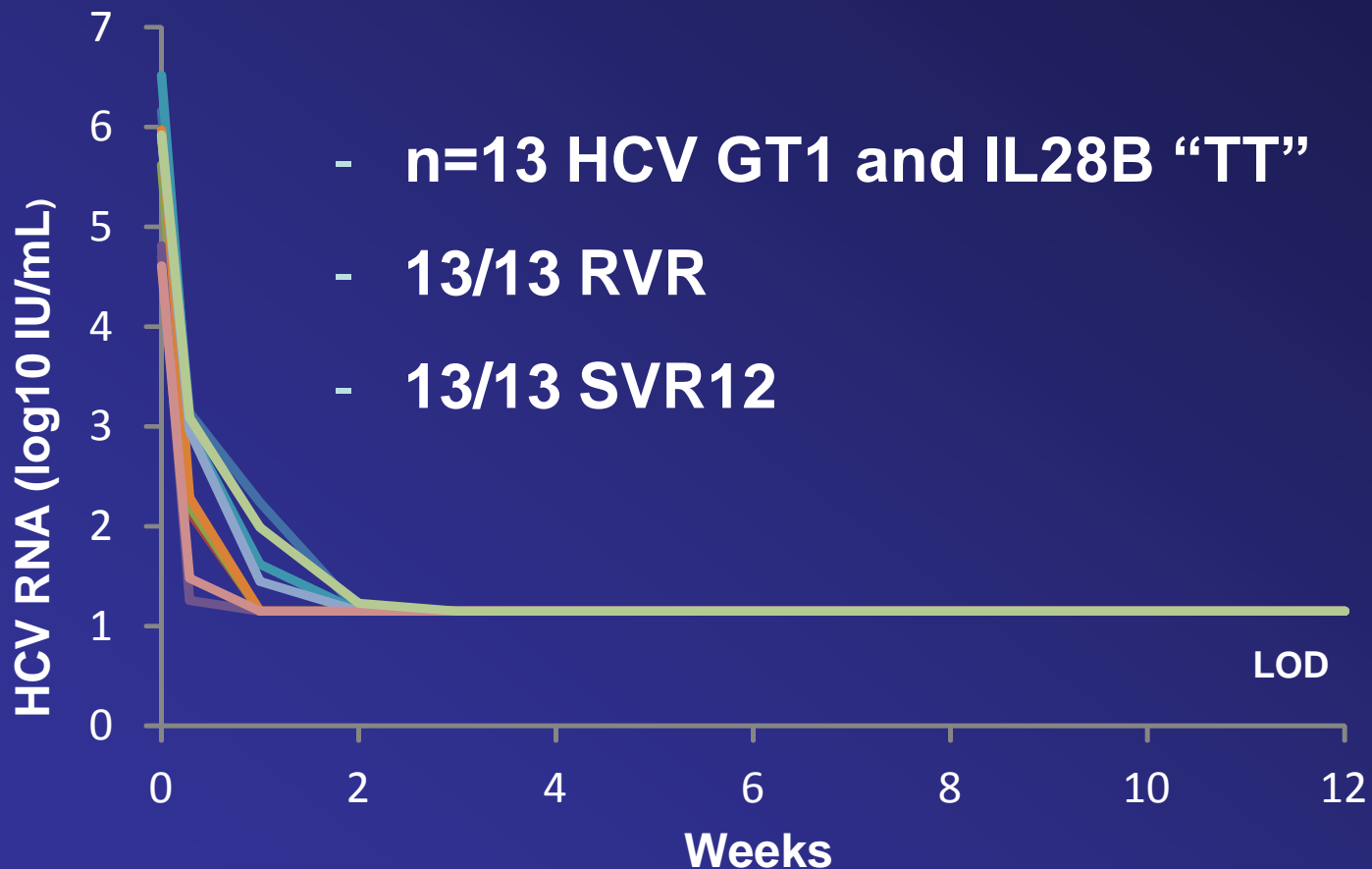


← Genotype 1 →

Genotype 2/3

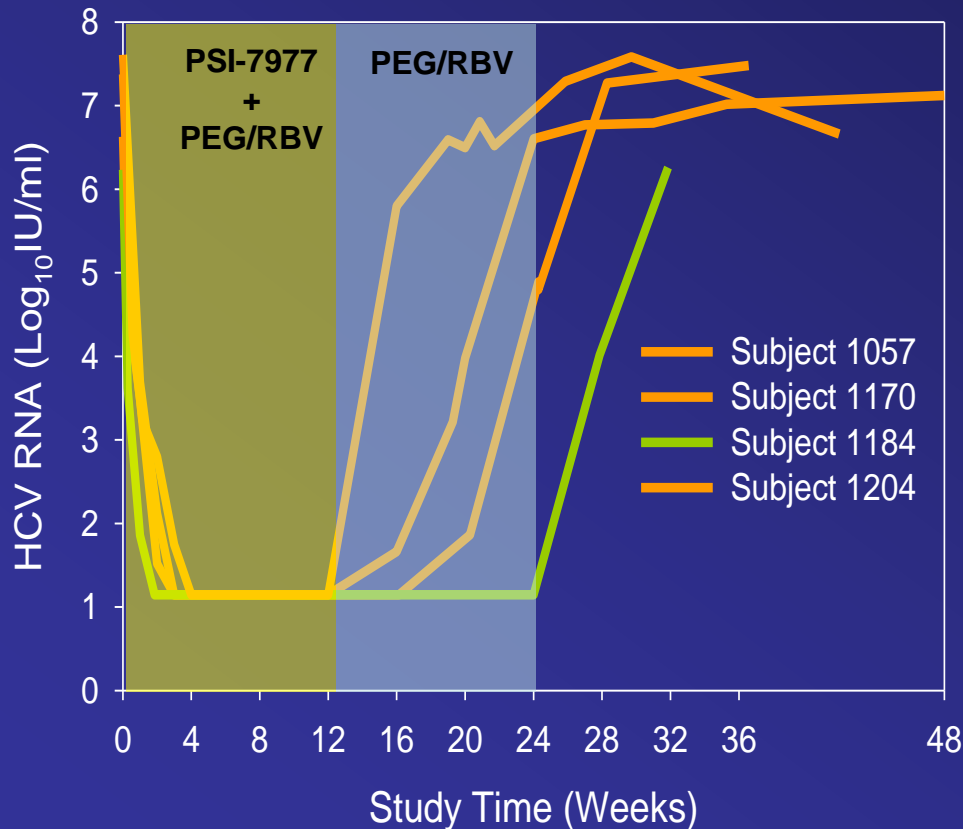
n	48	48	48	48	47	47	47	47	26	26	26	26	25	25	25	25
<LOD ITT	47	47	44	42	46	43	43	43	5	13	15*		24	24	24	24
% ITT	98	98	92	tbd	98	91	91	91	19	50	58		96	96	96	96

# RESULTS: SVR in 13 Subjects with HCV GT1 & Genetic Predictors of IFN “non-response”



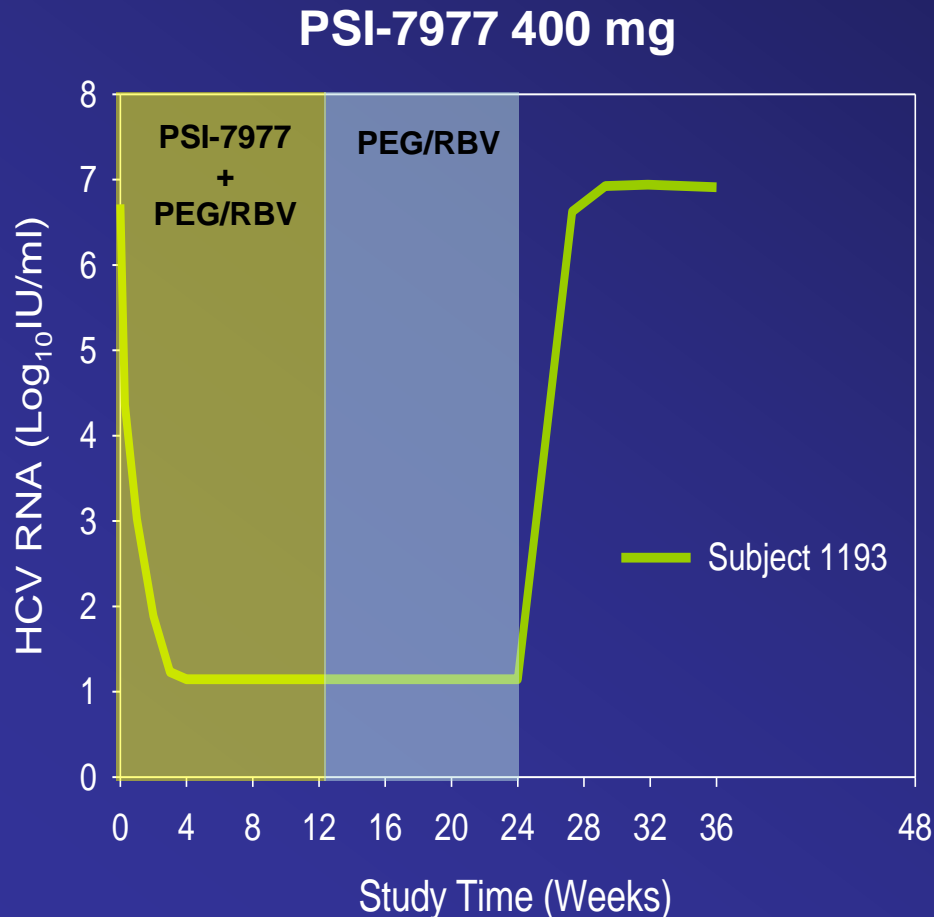
# No Virologic Breakthrough on PSI-7977 200 mg During PSI-7977 Therapy

PSI-7977 200 mg



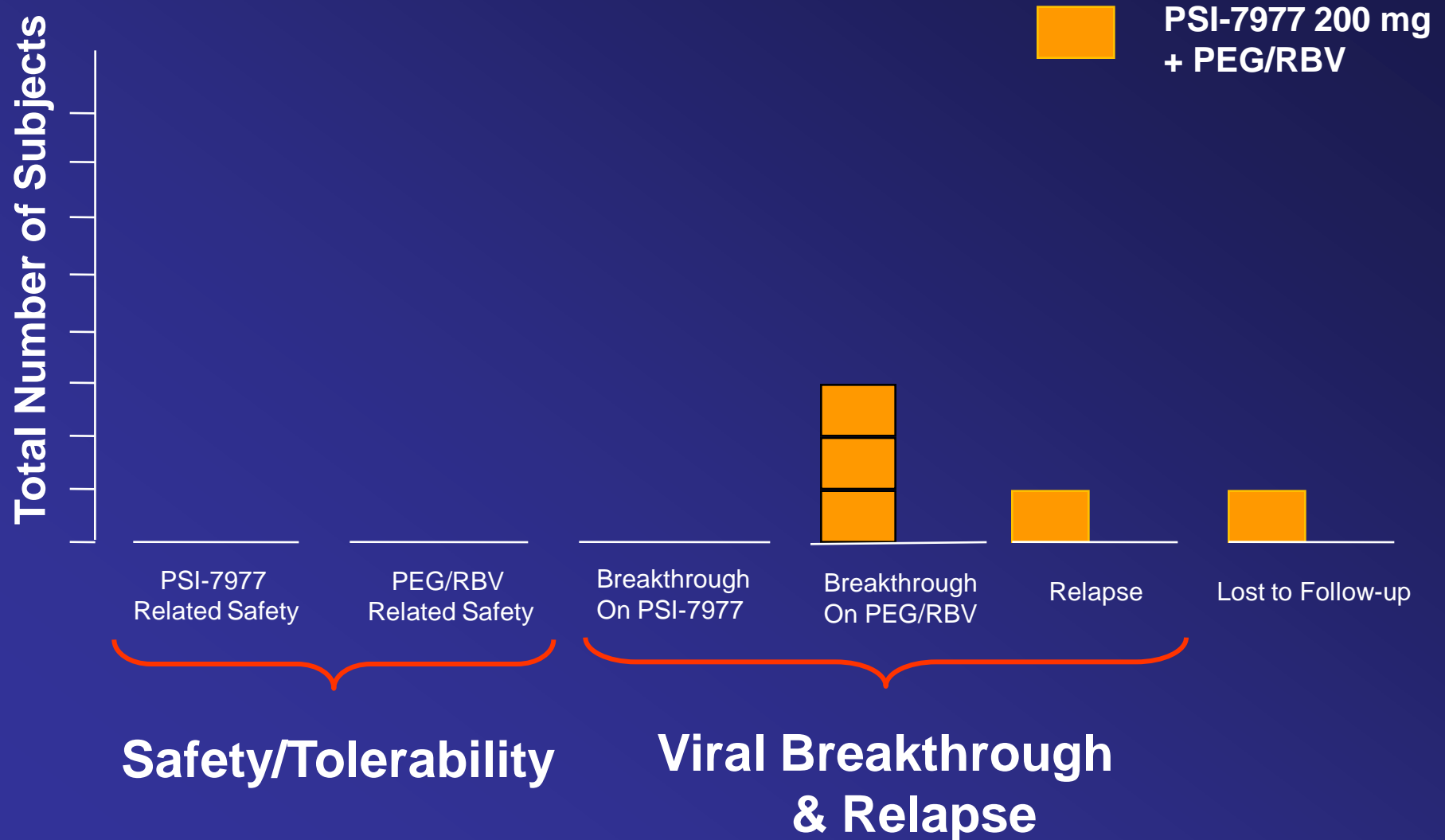
- PSI-7977 200 mg + PEG/RBV had NO breakthrough during PSI-7977 therapy
- 3 viral rebounds during PEG/RBV follow up
- 1 relapse before SVR4
- No S282T

# No Virologic Breakthrough on PSI-7977 400 mg During PSI-7977 Therapy or PEG/RBV follow-up

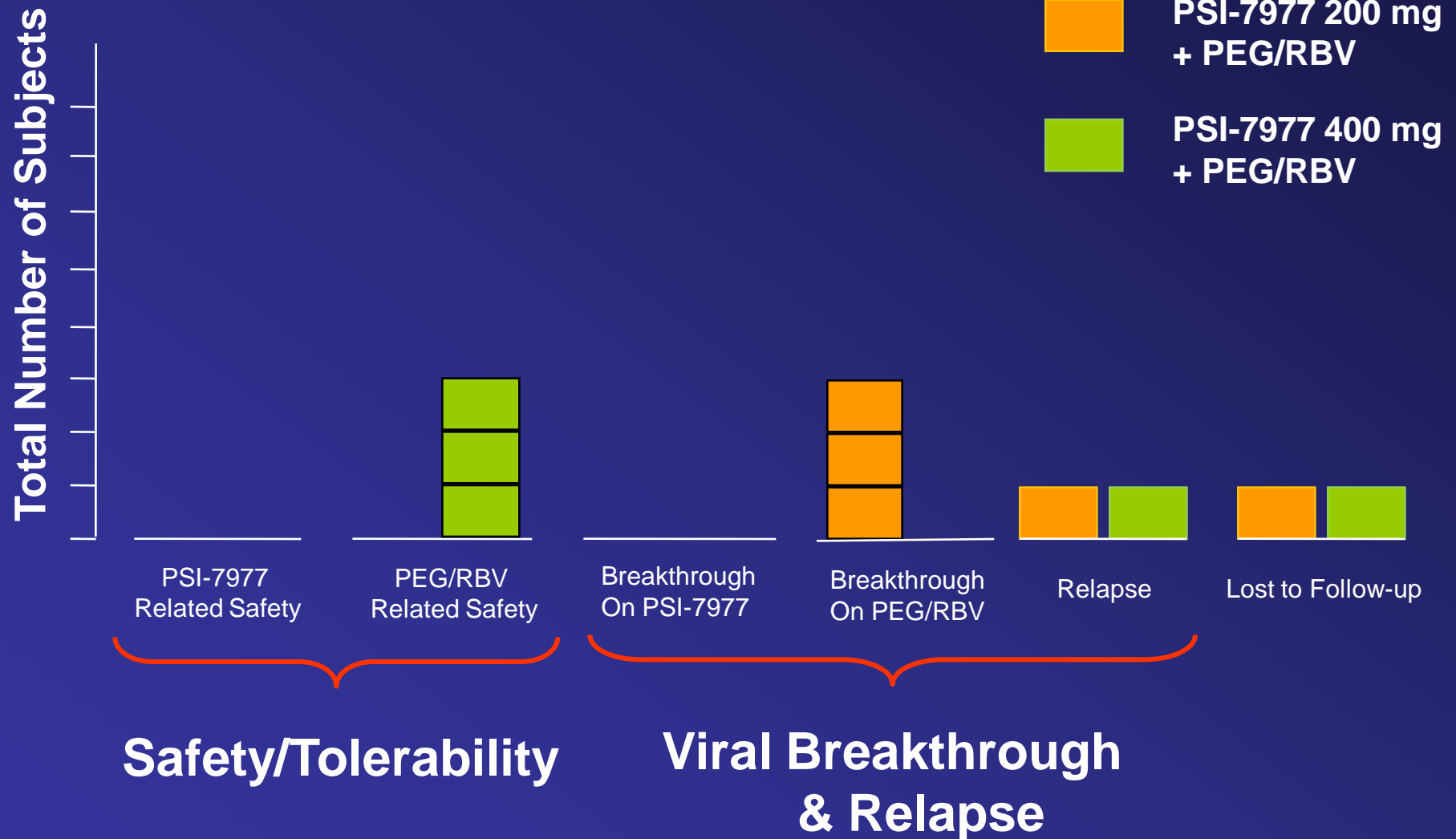


- PSI-7977 400 mg + PEG/RBV had no breakthrough during PSI-7977 therapy
- No breakthrough during PEG/RBV
- 1 relapse prior to SVR4
- No S282T

# PROTON HCV GT1: Low Study Discontinuations Reflects Safety and Tolerability, Antiviral Potency & High Barrier to Resistance



# PROTON HCV GT1: Low Study Discontinuations Reflects Safety and Tolerability, Antiviral Potency & High Barrier to Resistance



# PSI-7977 + PEG/RBV was Well Tolerated with an AE Profile Similar to Placebo + PEG/RBV\*

Number of Subjects with $\geq$ Grade 2 AE* N (%)	GT1 PSI-7977 200 mg + PEG/RBV n=48	GT1 PSI-7977 400 mg + PEG/RBV n=47	GT 2/3 PSI-7977 400 mg + PEG/RBV n=25	Placebo PEG/RBV n=26
Fatigue	6 (13)	6 (13)	0	6 (23)
Headache	3 (6)	3 (6)	0	6 (23)
Nausea	1 (2)	4 (9)	1 (4)	2 (8)
Chills	2 (4)	2 (4)	1 (4)	3 (12)
Pain	3 (6)	3 (6)	1 (4)	2 (8)
Insomnia	2 (4)	7 (15)	1 (4)	2 (8)
Neutropenia	5 (10)	8 (17)	5 (20)	3 (12)
Anemia	4 (8)	7 (15)	3 (12)	4 (15)
Pyrexia	3 (6)	0	0	0
Depression	1 (2)	3 (6)	0	2 (8)

\*Occurring in  $\geq$ 5% of subjects in any PSI-7977-containing treatment arm

# Safety Results: Grade 3/4 Heme Abnormalities Similar to Placebo + PEG/RBV\*

	GT1 PSI-7977 200 mg + PEG/RBV n=48	GT1 PSI-7977 400 mg + PEG/RBV n=47	GT2/3 PSI-7977 400 mg + PEG/RBV N=25	Placebo + PEG/RBV n=26
<b>Grade 3 n (%)</b>				
Hemoglobin	3 (6)	3 (6)	1 (4)	2 (8)
Lymphopenia	2 (4)	2 (4)	0	1 (4)
Neutropenia	11 (23)	14 (30)	6 (24)	6 (23)
<b>Grade 4 n (%)</b>				
Lymphopenia	2 (4)	0	1 (4)	0
Neutropenia	2 (4)	1 (2)	0	0

\*Over the first 12 weeks of treatment only

Hemoglobin Grade 3: 7.0 – 8.9 g/dL

Lymphopenia Grade 3: 350 – 499/mm<sup>3</sup> Grade 4: < 350/mm<sup>3</sup>

Neutropenia Grade 3: 500 – 749/mm<sup>3</sup> Grade 4: < 500/mm<sup>3</sup>

# **PROTON Summary:**

## **PSI-7977 400 mg QD + PEG/RBV**

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### **SAFETY:**

**PSI-7977 was very well tolerated with no attributable safety signal, and no discontinuations related to PSI-7977**

### **POTENCY:**

**By ITT analysis across HCV GT1, 2 and 3 achieved 93% SVR24. Subjects who received 8+ wks PSI-7977 achieved 99% SVR24.**

### **NO RESISTANCE:**

**No viral breakthrough has been observed on PSI-7977. No S282T in any subject with relapse**

# **PSI-7977 PROTON**

## **Conclusions**

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- **The high SVR in HCV GT1, 2 and 3 (93%) was independent of predictors of poor interferon response**
- **PSI-7977/RBV will be carried forward into Phase 3 across all HCV genotypes**
- **PSI-7977/RBV has the potential to dramatically impact the treatment paradigm for HCV of all genotypes and in all patients**

# ACKNOWLEDGEMENTS

## PATIENTS AND THEIR FAMILIES

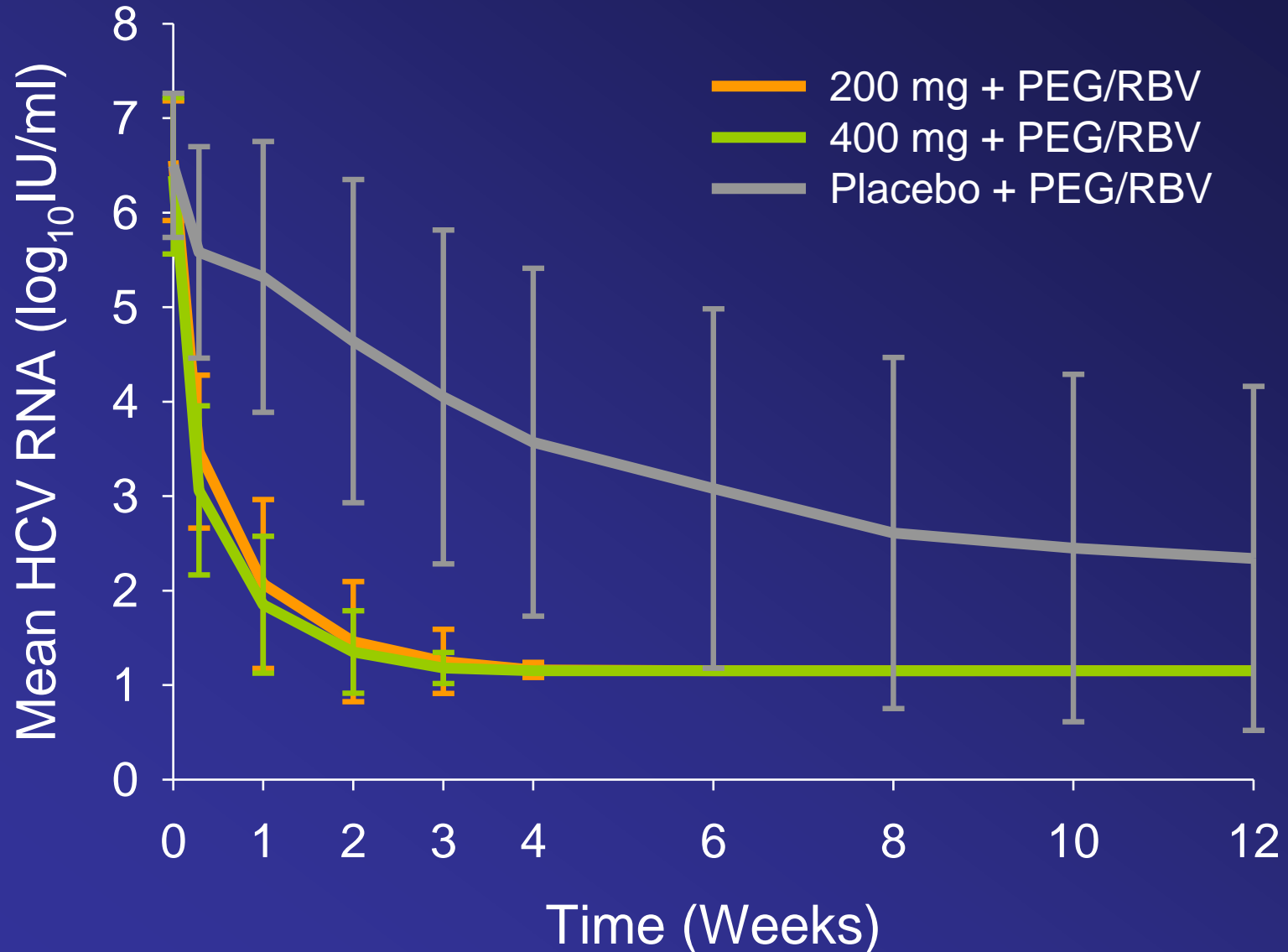
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- T Hassanein: SCLC, San Diego, CA
- K Kowdley: VMMC, Seattle, WA
- F Poordad: Cedars Sinai Med Ctr, Los Angeles, CA
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- N Adfhal: Beth Israel Deaconess, Boston, MA
- D Bernstein: North Shore University Hospital, Manhasset, NY
- E DeJesus: OIC, Orlando, FL
- B Freilich: Kansas City Gastroenterology, KS
- D Nelson: UFL, Gainesville, FL
- D Dieterich: Mount Sinai, New York, NY
- I Jacobson: Cornell University, New York, NY
- D Jensen: University of Chicago, Chicago, IL
- G Abrams: Alabama Liver and Digestive Specialists, Montgomery, AL
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- M Rodriguez-Torres: Fundacion de Investigacion, San Juan, PR
- K Reddy: University of Pennsylvania, Philadelphia, PA
- M Sulkowski: Johns Hopkins University, Lutherville, MD;
- N. H. Bzowej: California Pacific Medical Center, San Francisco, CA
- M DeMicco: ACRI, Anaheim, CA; <sup>22</sup>Columbia Gastroenterology, Columbia, SC
- J Strohecker: Columbia Gastroenterology, Columbia, SC
- Study Team at Pharmasset, Inc.
- DCRI, Pharstat, Inc., and Cenetron

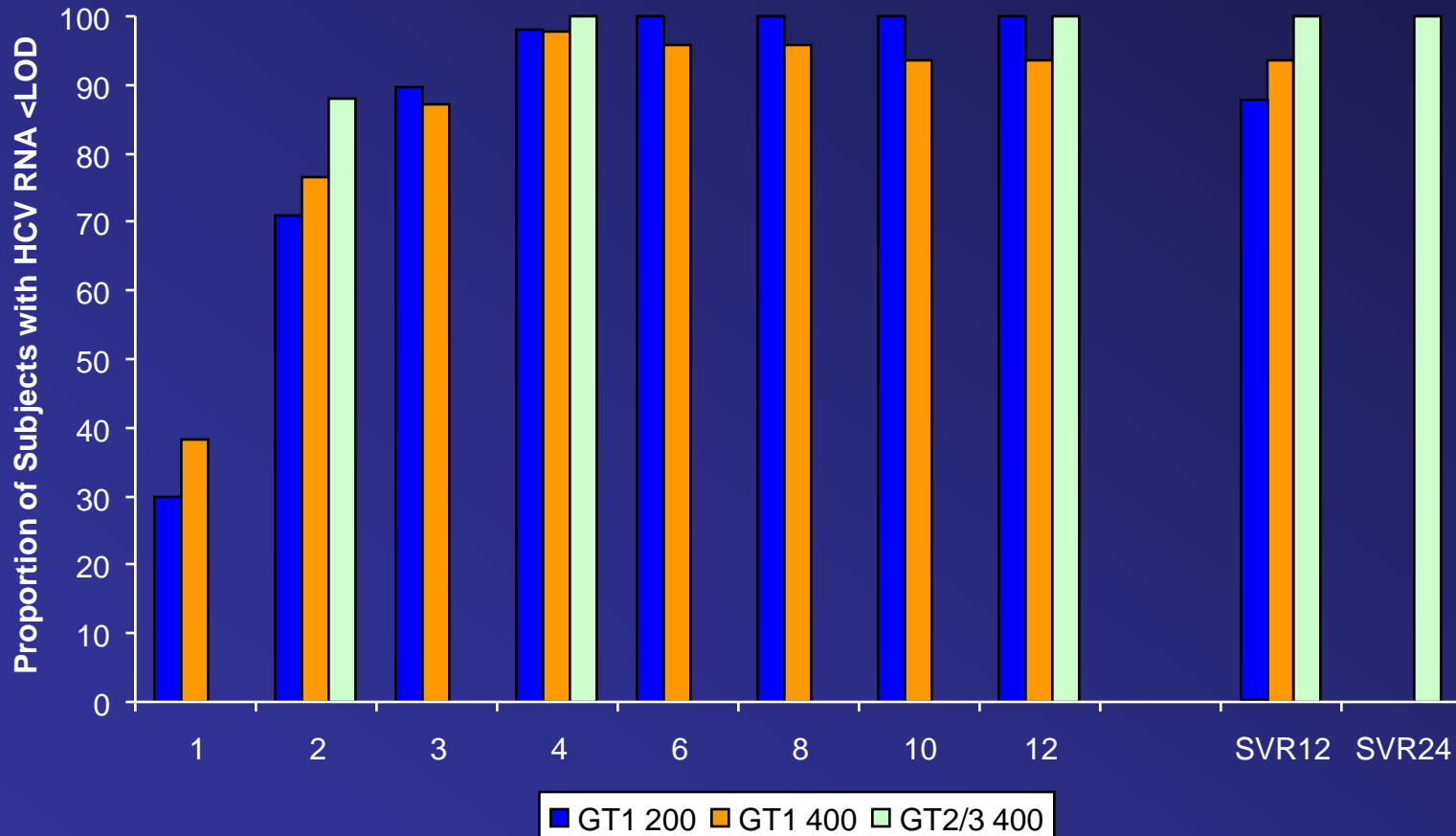
# BACKUP

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# Rapid HCV RNA Suppression in all 95 subjects with HCV GT1 on PSI-7977 200 or 400 mg QD + PEG/RBV

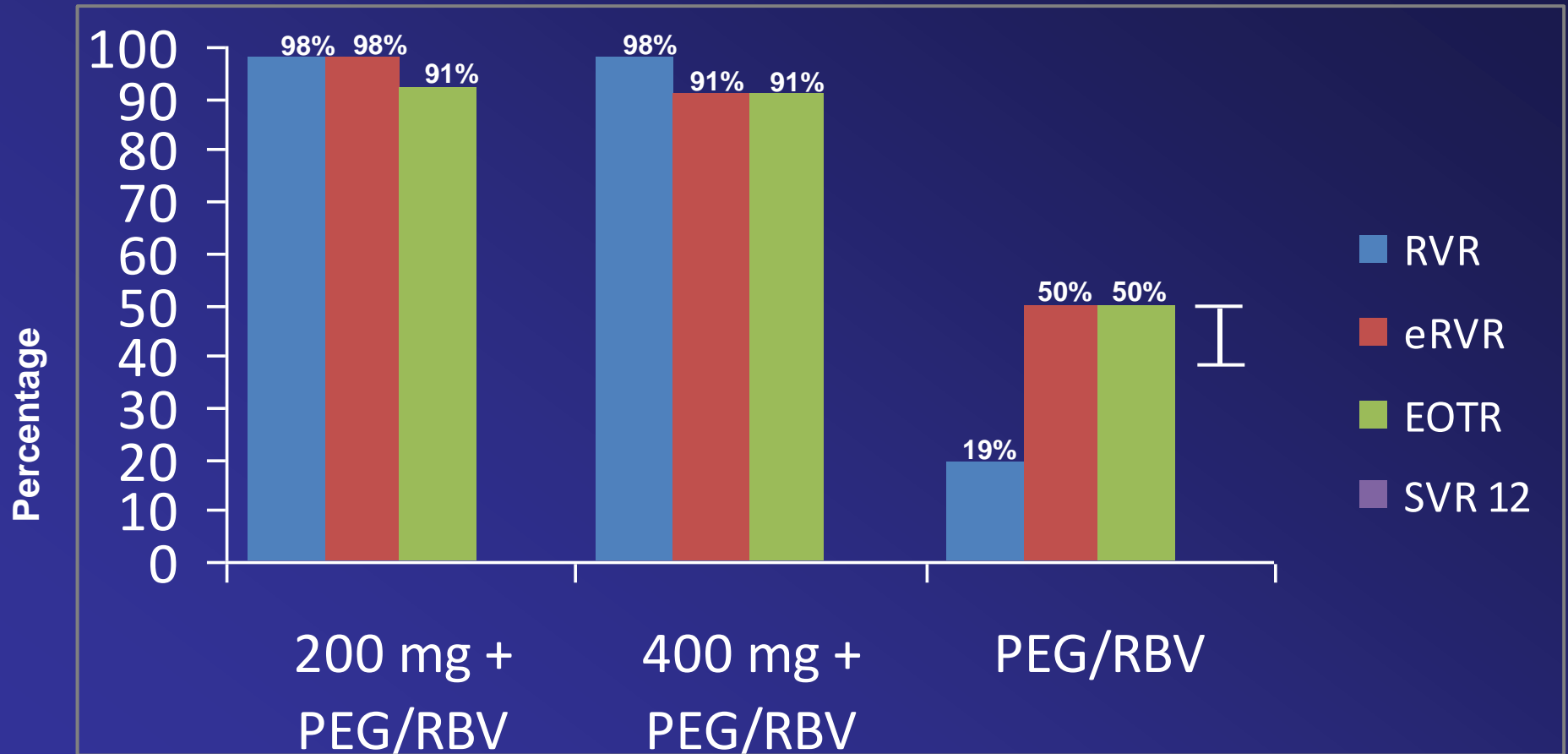


# 93% SVR12 Across Genotypes 1, 2 and 3 when treated with PSI-7977 400 mg QD + PEG/RBV

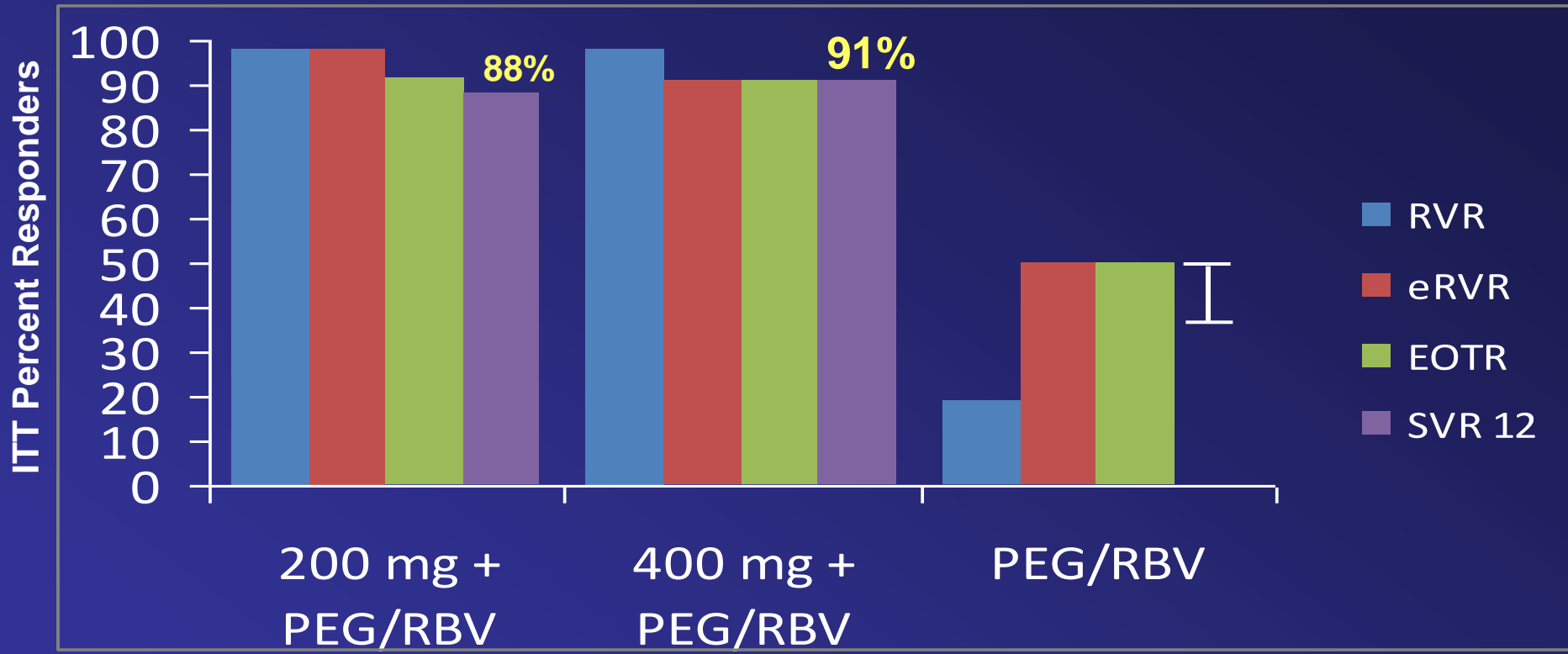


As treated: 99% of patients who received  $\geq 8$  wks PSI-7977 achieved SVR (GT 2/3=100% and for GT1=98%)

# RESULTS: PSI-7977 200 mg and 400 mg Cohorts >91% EOTR (through wk 24) vs ~50% Control



# PSI-7977 400 mg QD + PEG/RBV 91% SVR12 vs ~50% EOTR Control (SVR pending)

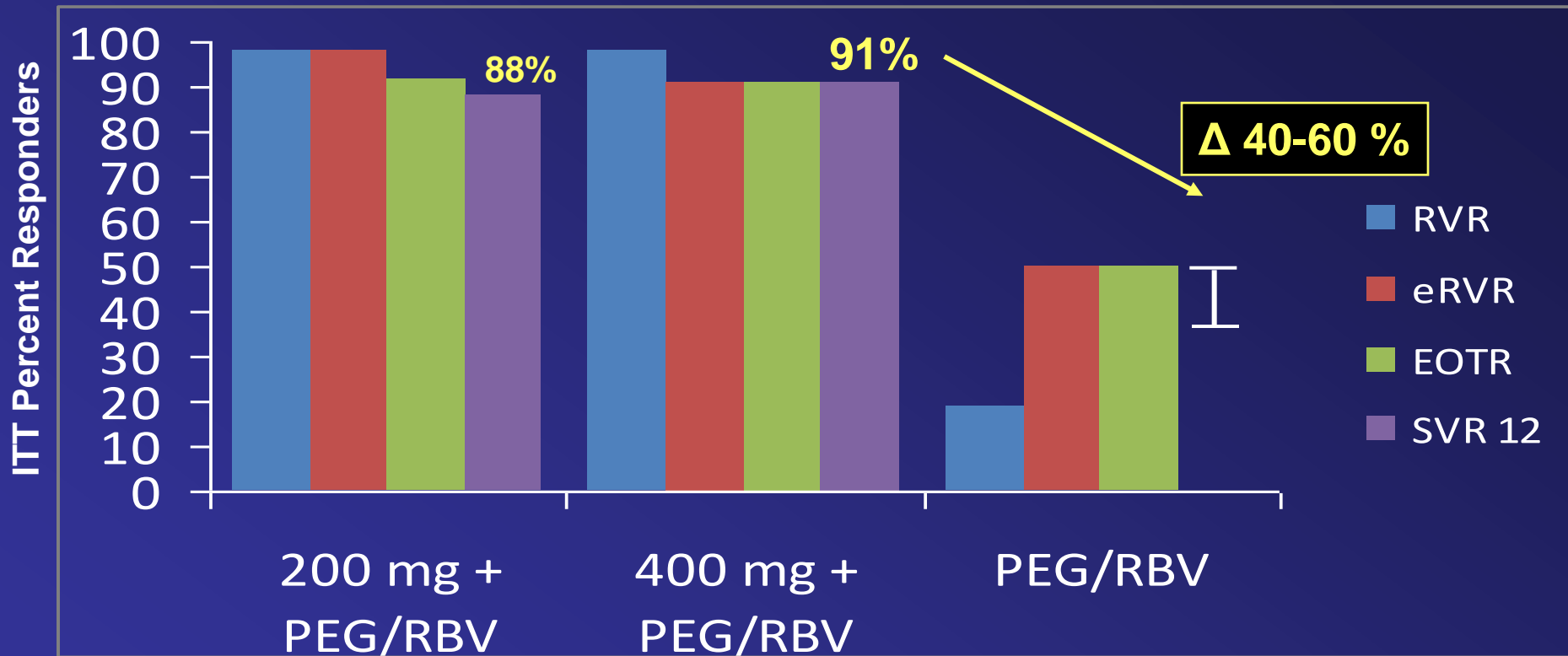


n	48	48	48	48	47	47	47	47	26	26	26	26
<LOD ITT	47	47	44	42	46	43	43	43	5	13	13*	
% ITT	98	98	92	88	98	91	91	91	19	50		

ITT = all dosed patients

# RESULTS:

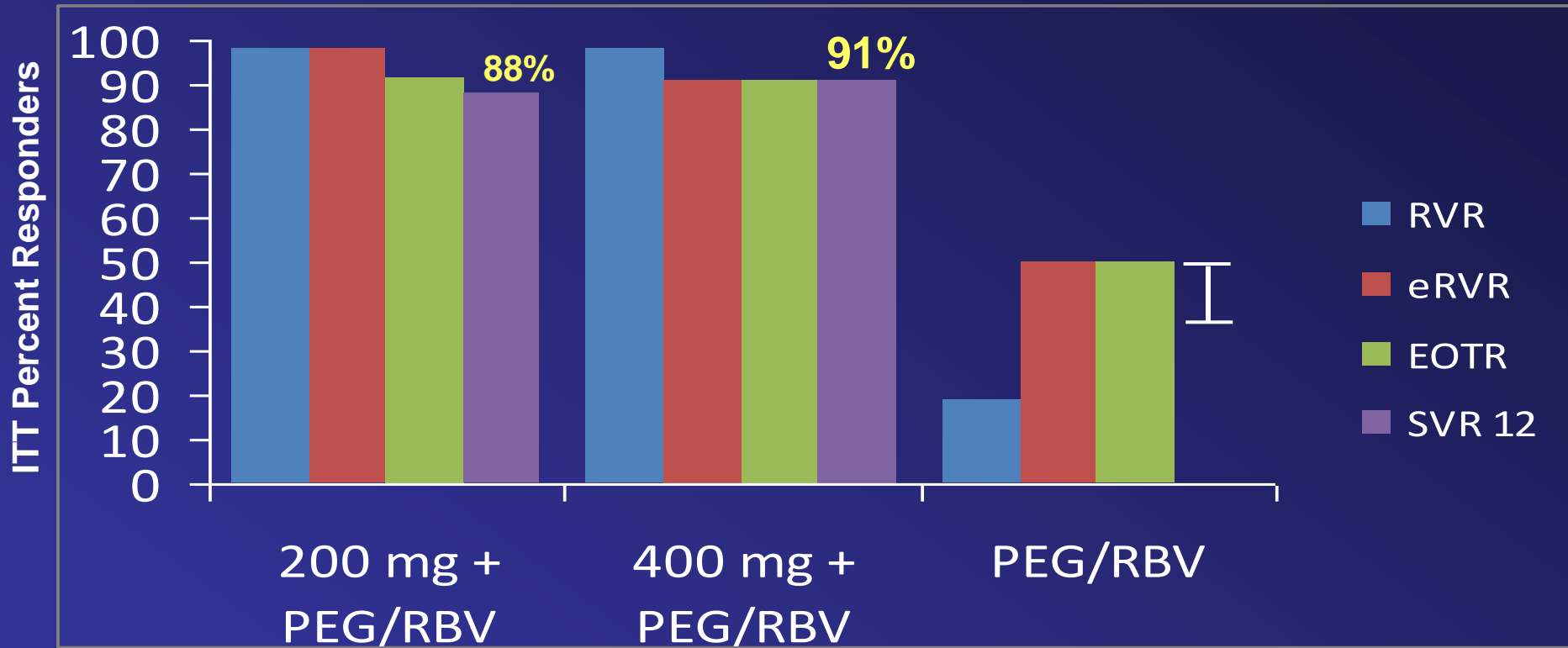
## PSI-7977 400 mg QD + PEG/RBV 91% SVR12



n	48	48	48	48	47	47	47	47	26	26	26	26
<LOD ITT	47	47	44	42	46	43	43	43	5	13	13	
% ITT	98	98	92	88	98	91	91	91	19	50	50	<50

ITT = all patients dosed

# RESULTS: 98% SVR in subjects who received at least 8 weeks of PSI-7977 400 mg QD + PEG/RBV



n	48	48	48	48	47	47	47	47	26	26	26	26
% AT*	98	98	98	88	100	100	100	98				

As treated: Patients who received  $\geq 8$  wks PSI-7977