

# Interferon-Free Combination Therapies in Development

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SCSG 2011  
Post-AASLD  
Symposium

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# RBV Antiviral Mechanisms

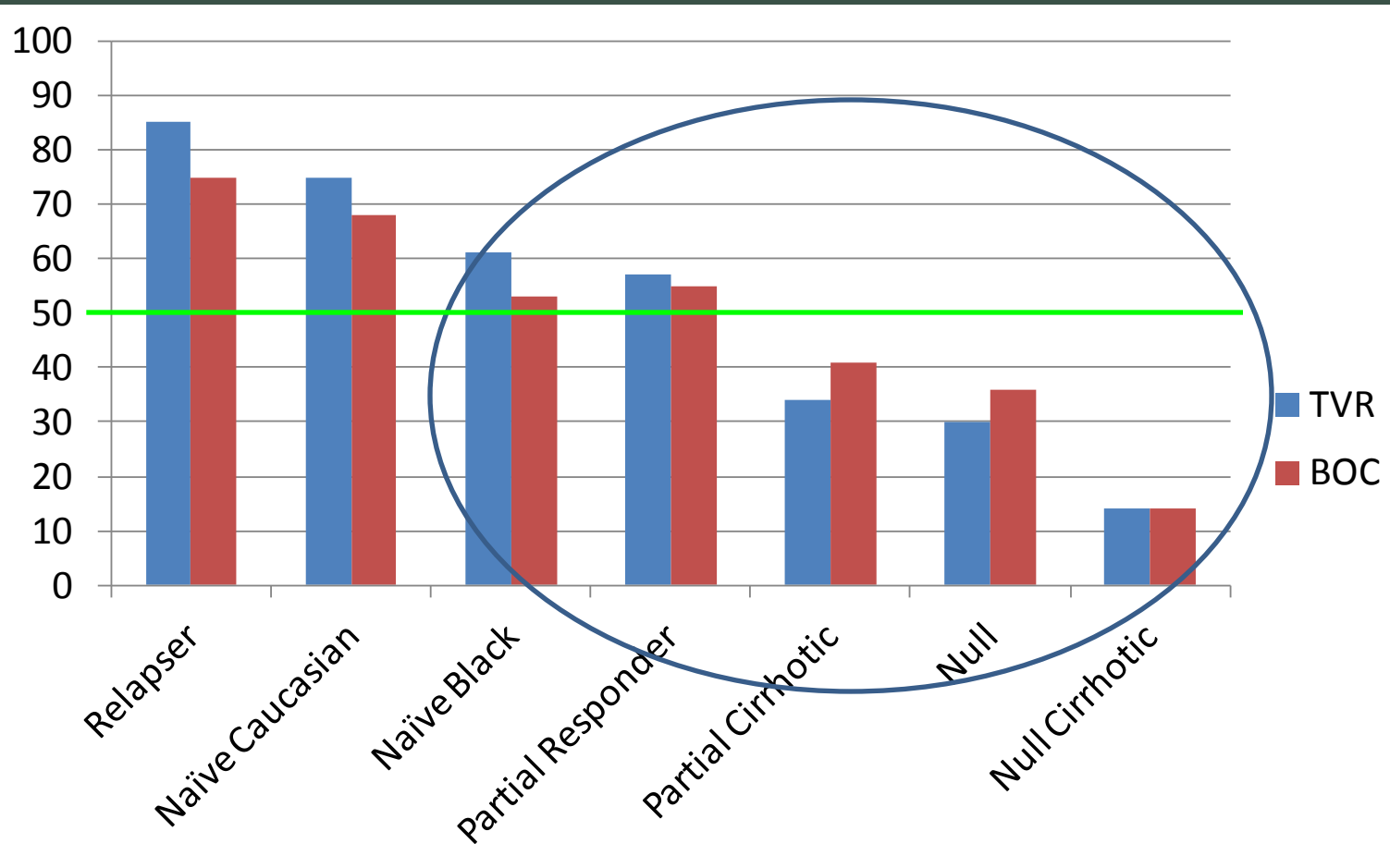
- Direct antiviral mechanisms of action
  - Depletion of GTP stores
  - Other possible mechanisms include RBV substitutions in the mRNA 5' cap structure and mismatch mutations in viral RNA which impairs translation of viral RNA
- Indirect mechanisms of action
  - T-helper cell modulation, natural killer cell activation, and a robust Th-1 response
  - Potential NS5B mutagenic activity
- The addition of RBV to peg-IFN took the SVR in genotype 1 from 21% to 46%. Hence, RBV has had much more of an impact on the treatment of HCV than pegylation of interferon

# HCV Inhibits the Host Immune System

- Envelope protein E2, NS3, and NS5A have inhibitory effects on the host immune system
- Varies by host factors
  - Age
  - Immune competence
  - Endogenous interferon production
    - IL28B region polymorphisms affect response to interferon
- Subtype 1a vs 1b differences?

# TVR and BOC SVR by Patient Type

% SVR



# Impact of Developing DAAs on Telaprevir and Boceprevir Use

	Naïve	Relapser	Partial Responder	Null Responder
Early Tenure of TVR and BOC	+++	+++	++	++
As other compounds show promise in phase 2	++	+++	+	+

# Who is Treating HCV?

	Academic Hepatologist	Community GI	Community ID	Internist	Family Practice
2011	✓	✓✓			
2012	✓	✓✓	✓		
2015-2020	✓	✓✓	✓	✓✓	✓

## Variables

- Ease of treatment regimens
- Reimbursement for competing priorities
- Access to specialty care in remote areas

# Emerging Therapies

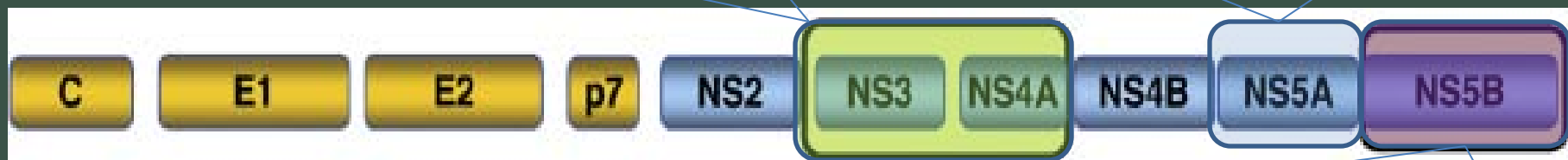
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# DAA Agents Overview

Mod to High potency  
+/-Multi-genotypic coverage  
Intermediate barrier to resistance

High potency  
Multi-genotypic coverage  
Low barrier to resistance



**NS5B Non Nucleoside Inhibitors (NNI)**

Low potency  
Limited-genotypic coverage  
Low barrier to resistance

**NS5B Nucleoside Inhibitors (NI)**

Intermediate to high potency  
Pan genotypic coverage  
High barrier to resistance

# NS3/4A Protease Inhibitors

Protease Inhibitors		
Drug	Company	Phase
Telaprevir	Vertex and J and J	Approved
Boceprevir	Merck	Approved
TMC-435	Janssen/Medivir/J and J	3
BI-201335	Boehringer Ingelheim	3
Vaniprevir	Merck	Halted
Narlaprevir	Merck	Halted
Danoprevir	Genentech	2
BMS-850032	Bristol-Myers Squibb	1
ACH-1625	Achillion	2
GS-9256	Gilead	2
ABT-450	Abbott/Enanta	2
IDX-320	Idenix	Halted
GS-9451	Gilead	2
ACH-2684	Achillion	1
MK-5172	Merck	2

# NS5B Compounds

## Nucleoside Polymerase Inhibitors

Drug	Company	Phase
R7128	Pharmasset and Genentech	2b
IDX-184	Idenix	2a
PSI-7977	Pharmasset	2b
PSI-938	Pharmasset	2b
INX-189	Inhibitex	1a

## Non-nucleoside Polymerase Inhibitors

Drug	Company	Phase
GS-9190	Gilead	2b
Filibuvir	Pfizer	Halted
ANA-598	Anadys	2b
ABT-333	Abbott	2b
ABT-072	Abbott	2b
IDX-375	Idenix	1

# NS5A/Cyclophilin Compounds

## NS5A Compounds

Drug	Company	Phase
ABT-267	Abbott	2
BMS-790052	BMS	2
GS-5885	Gilead	2
ACH-2928	Achillion	1
BMS 824393	BMS	1
PPI-461	Presidio	1

## Cyclophilin Inhibitors

Drug	Company	Phase
NIM 811	Novartis	HALTED
Deb025	Novartis	3

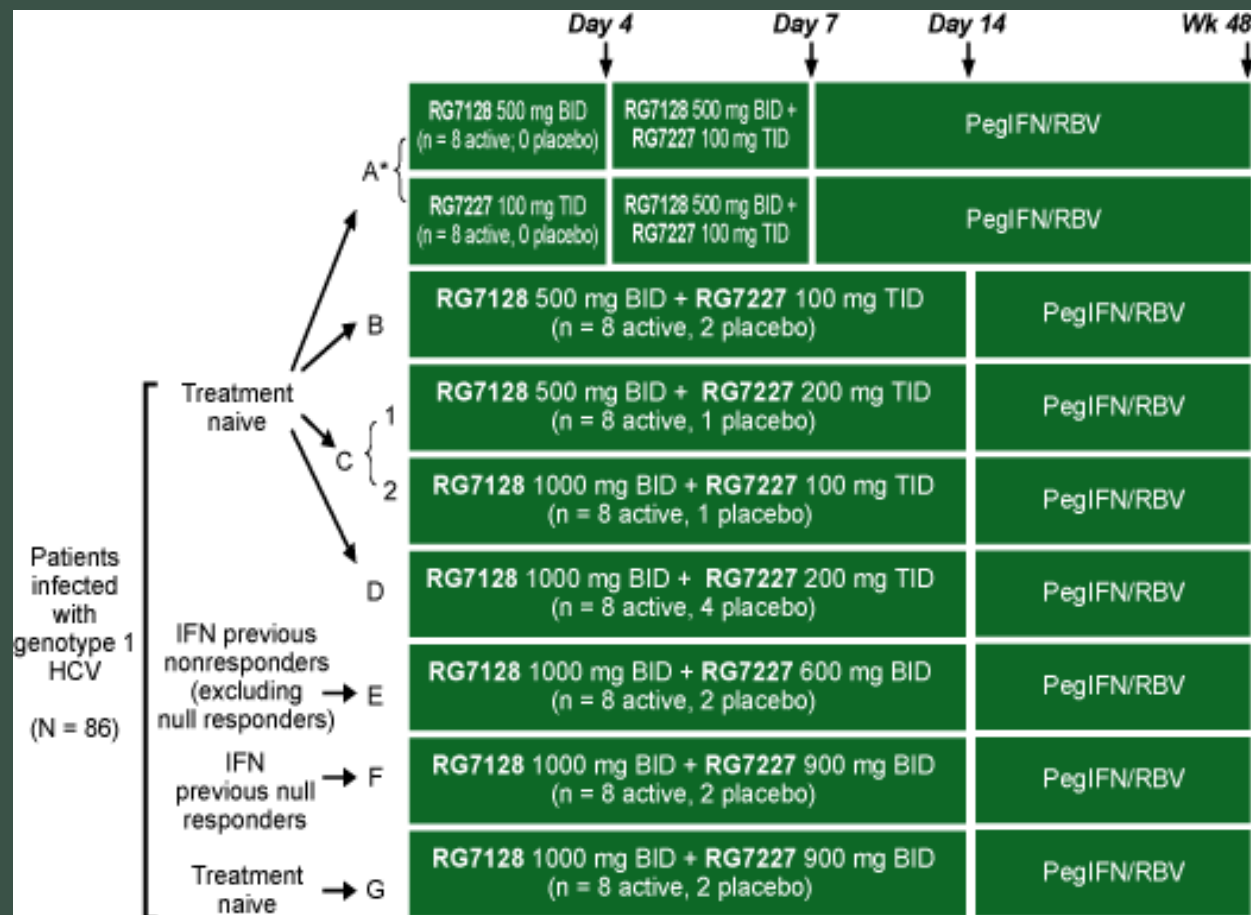
Will 2 DAAs Alone Be Sufficient?

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# INFORM-1: Safety and Efficacy of Combination of PI + Nucleoside analog

- R7128 – nucleoside analog
- R7227 – Protease Inhibitor



BID, twice daily; IFN, interferon; pegIFN, peginterferon alfa-2a 180 µg/wk; RBV, ribavirin 1000-1200 mg/day; TID, 3 times daily.

\*Not included in current analysis.

# INFORM-1: Safety and Tolerability

- Main findings

Adverse Events,* n	Placebo (n = 14)	Treatment Naive					Treatment Experienced	
		Arm B (n = 8)	Arm C1 (n = 8)	Arm C2 (n = 8 <sup>+</sup> )	Arm D (n = 8)	Arm G (n = 8)	Arm E (n = 8)	Arm F (n = 8)
Headache	4	1	1	4	3	1	4	3
Nausea	1	1	0	0	0	1	0	3
Diarrhea	0	1	1	0	0	0	0	2
Dysgeusia	0	0	1	1	0	0	1	0
Rash	0	1	0	0	1	1	1	0
Dry eyes	0	1	0	2	0	0	0	0

- R7128 and R227 were well tolerated at all doses tested
- Safety and tolerability profiles are similar to the profiles observed when administered as single agents
- NO SAEs, treatment-related discontinuations, or grade3/4 treatment-related abnormalities

# Protease Inhibitor and NS5A Inhibitor ± PegIFN/RBV (Null Responders)

## Study Design

Group A

BMS-790052 + BMS-650032 (n=11)

Group B

BMS-790052 + BMS-650032 + pegIFN/RBV  
(n=10)

Follow-up:  
up to 48 weeks  
post treatment

24-week duration of therapy

Null responders to PegIFN/RBV defined as  $< 2 \log_{10}$  decline after 12 weeks of therapy

BMS-790052 (NS5A inhibitor) 60 mg PO QD

BMS-550032 (NS3 protease inhibitor) 600 mg PO BID

Peg/IFN8-2a 180 µg SC once weekly

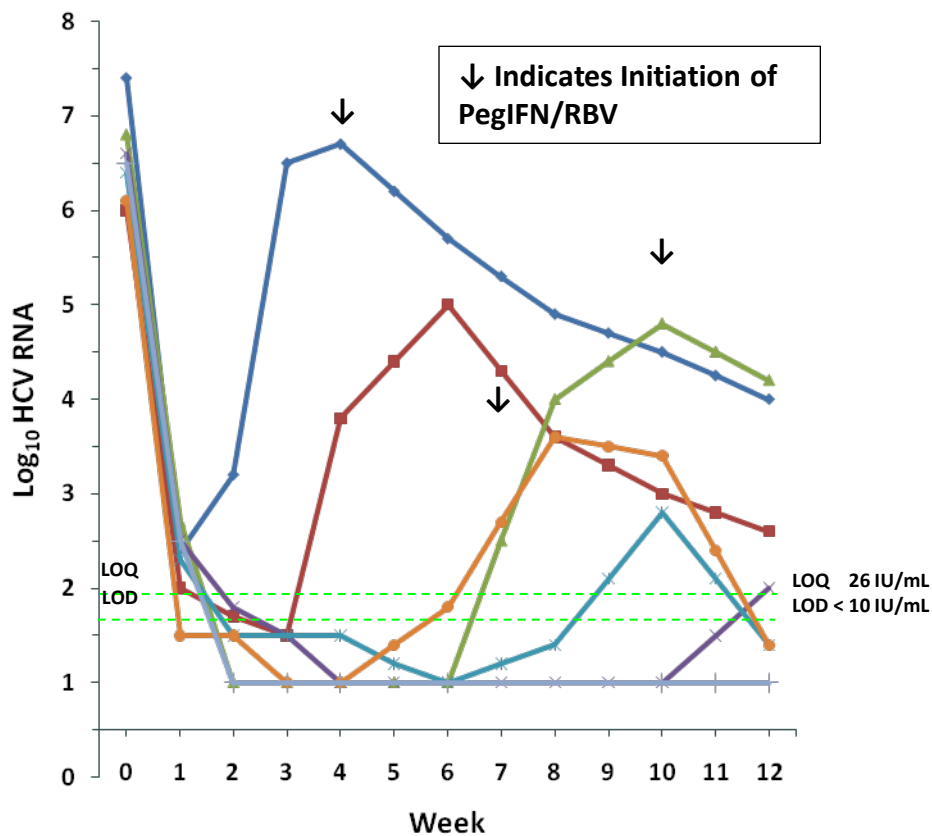
RBV 1000-1200 mg daily in 2 divided doses, according to body weight

# Virologic Response

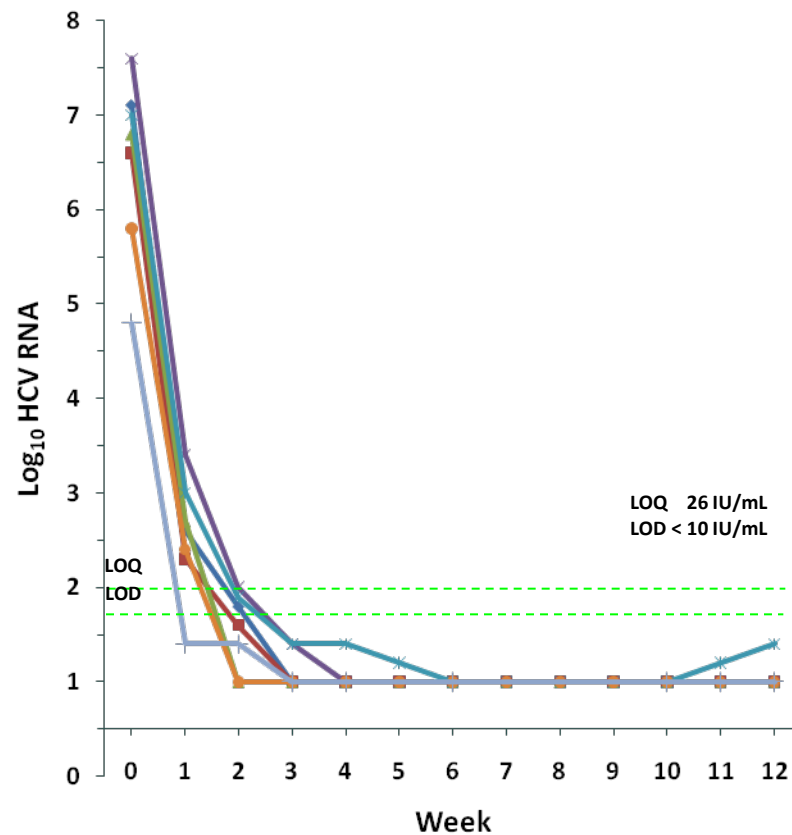
	Group A n =11 (%)	Group B n =10 (%)
Median HCV RNA decline at week 2 (log <sub>10</sub> IU/mL)	-5.1	-5.3
RVR n (%)	7 (64)	6 (60)
eRVR n(%)	4 (36)	6 (60)
SVR n(%)	4 (36)	9 (90)
Viral breakthrough	6/11 (55)	0

# Viral Kinetics According To Treatment Group

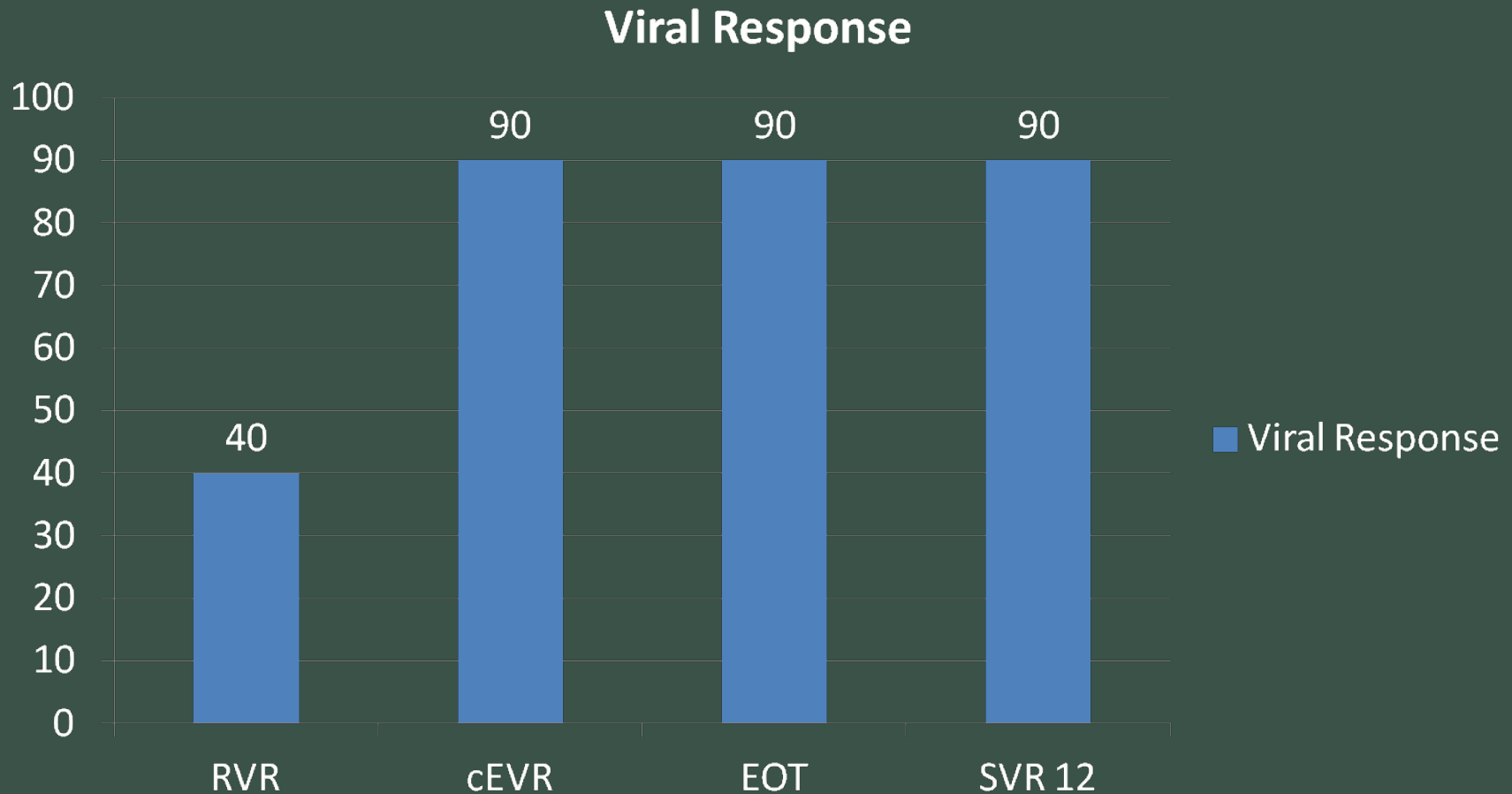
## HCV RNA Decline by subject : Group A



## HCV RNA Decline by subject : Group B



# Dual Therapy With BMS-052 + BMS-032 in a Null Responder Population



One patient dropped out at week 2, but achieved SVR and was excluded

# BMS-790052 + PegIFN Alpha-2b and RBV in Treatment-Naïve and Nonresponder Patients

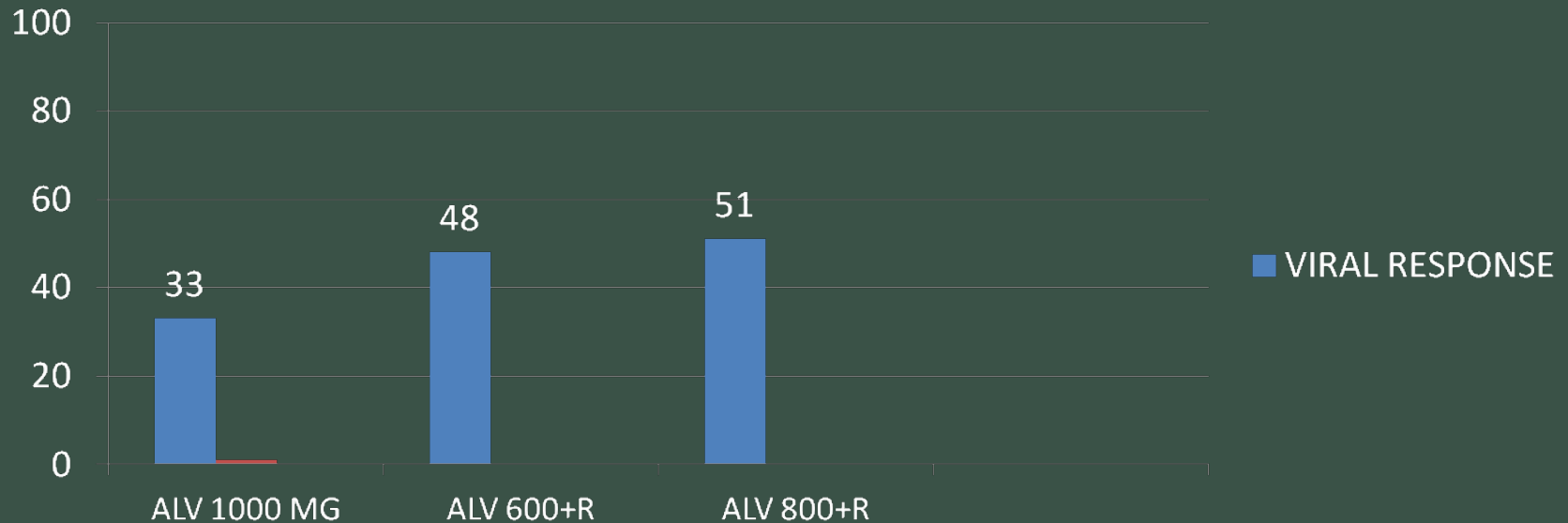
BMS-790052, an NS5A Replication Complex Inhibitor, in Combination with Peginterferon Alpha-2b and Ribavirin in Japanese Treatment-Naïve and Nonresponder Patients with Chronic HCV Genotype 1 Infection

n (%)	Treatment-naïve (N = 27)			Nonresponders (N = 18)	
	10mg QD + PEG2b/R n = 9	60mg QD + PEG2b/R n = 10	Placebo + PEG2b/R n = 8	10mg QD + PEG2b/R n = 9	60mg QD + PEG2b/R n = 9
eRVR	6 (67)	8 (80)	0	5 (56)	2 (22)
RVR	7 (78)	8 (80)	0	5 (56)	3 (33)
cEVR	7 (78)	10 (100)	5 (63)	5 (56)	5 (56)
PDR	7 (78)	10 (100)	0	5 (56)	3 (33)
Subjects who achieved PDR and received 24 weeks' treatment and 24 weeks' follow-up:					
SVR	6/7 (86)	9/10 (90)	NA	2/5 (40)	2/3 (67)

# Alisporivir QD IFN-Free Therapy in GT-2/3 Patients

- **334 G2/3 treatment-naïve patients**
- **5 treatment arms, 24-week study**
  - ALV 1000mg QD monotherapy (ALV1000, n=82)
  - ALV 600mg QD+ribavirin (R) (ALV600R, n=84)
  - ALV 800mg QD+R (ALV800R, n=94)
  - ALV 600 mg QD+PegIFN (P) (ALV+P, n=39)
  - PR, n=35

# Alisporivir QD IFN-Free Therapy in GT-2/3 Patients: RESULTS



–Adding PR to ALV from Week 6 to Week 8 for patients with detectable HCVRNA at Week 4 (ie, 2 weeks of ALV + PR)

- Week 8 undetectable: 86% ALV600R, 89% ALV800R, and 85% ALV1000

–Week 8 undetectable: 92% ALV+P and 100% PR

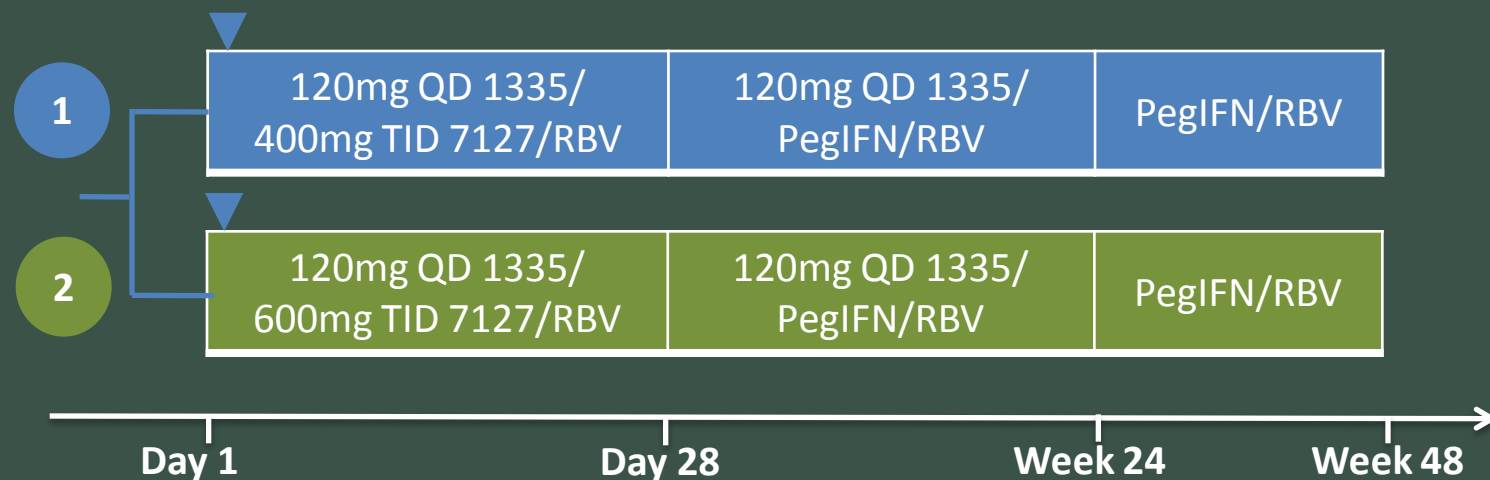
What about 3 DAAs?

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# SOUND-C1 Trial: PI (1335) + Non-Nucleoside Polymerase (7127) + RBV

- 32 HCV genotype-1, treatment naïve



- Mild GI effects; No SAE; No discontinuation for AE

# SOUND C-1: Virologic Response

	Day 8	Day 15	Day 22	Day 29	SVR
<b>Group 1:</b> 7127 (400 mg TID) + 1335 + RBV (N=15)	27%	40%	67%	73%	75%
<b>Group 2:</b> 7127 (600 mg TID) + 1335 + RBV (N=17)	18%	82%	100%	100%	100%

HCV RNA < 25 IU/mL, undetectable

Two genotype 1a patients in the low dose group had viral rebound during treatment

Virologic response to an interferon-free regimen of BI201335 and BI207127, with and without ribavirin, in treatment-naive patients with chronic genotype-1 HCV infection: Week 12 interim results of the SOUND-C2 study

**Methods:** A total of 362 TN HCV GT-1 patients were treated and randomized into 5 treatment arms: (1) 120 mg QD BI201335 (1335) combined with 600 mg TID BI207127 (7127<sub>TID</sub>) and RBV for 16 weeks; (2) 1335 + 7127<sub>TID</sub> + RBV for 28 weeks; (3) 1335 + 7127<sub>TID</sub> + RBV for 40 weeks; (4) 1335 + 600 mg BID BI207127 (7127<sub>BID</sub>) + RBV for 28 weeks; (5) 1335 + 7127<sub>TID</sub> for 28 weeks. This is a planned interim analysis performed after all patients completed 12 weeks of treatment. Randomization was stratified by HCV subtype (1a vs. 1b) and IL28B GT (rs12979860 CC vs. non-CC).

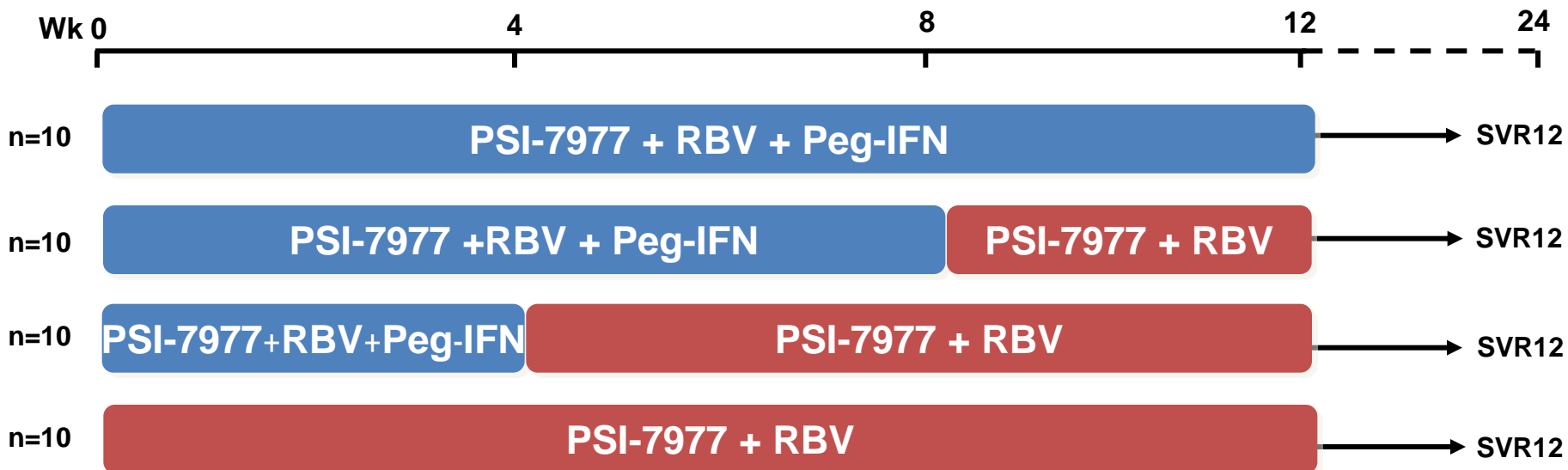
	1335 + 7127 <sub>TID</sub> + RBV Arms 1, 2 and 3 N=238	1335 + 7127 <sub>BID</sub> + RBV Arm 4 N=78	1335 + 7127 <sub>TID</sub> Arm 5 N=46
HCV RNA < LLOQ* at Week 4,	210 (88)	68 (87)	33 (72)
HCV RNA < LLOQ* at Week 12,	167 (70)	59 (76)	26 (57)
Lack of HCV RNA < LLOD* at Week 6 and 8	5 (2)	1 (1)	2 (4)
Breakthrough until Week 12	32 (13)	16 (21)	15 (33)

# ABT-450/R + RBV + ABT-072 or ABT-333

- Ritonavir-boosted PI + RBV + 1 of 2 NNRTIs
- Phase 2 study with treatment-naïve GT-1 patients
- 12 weeks of IFN-Free therapy
  - 42/44 patients have completed 12 weeks of treatment with all achieving undetectable virus at Week 12
  - 10 patients have reached SVR/cure assessment, with **9/10 achieving SVR**
  - No viral rebound
- Detailed data spring 2012 (EASL)

# PSI-7977 ELECTRON: Study Design for HCV GT2/3

- Treatment-naïve, non-cirrhotic, age  $\geq 18$  years
- HCV RNA  $>50,000$  IU/mL
- Allowed concurrent methadone use
- Stratified by HCV genotype and IL28B genotype
- Randomized 1:1:1:1 into IFN-sparing or IFN-free



# PSI-7977 ELECTRON Results

Time Wk	PSI-7977 RBV 12 weeks PEG	PSI-7977 RBV 8 weeks PEG	PSI-7977 RBV 4 weeks PEG	PSI-7977 RBV NO PEG
	n=11    %<LOD	n=10    %<LOD	n=9    %<LOD	n=10    %<LOD

# PSI-7977 ELECTRON

## IFN-free PSI-7977/RBV ➔ 100% RVR

Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
2	9/11	82	7/8	88	8/9	89	8/10	80
4	11/11	100	10/10	100	9/9	100	10/10	100

# PSI-7977 ELECTRON

## IFN-free PSI-7977/RBV ➔ 100% EOTR

Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
2	9/11	82	7/8	88	8/9	89	8/10	80
4	11/11	100	10/10	100	9/9	100	10/10	100
8	11/11	100	10/10	100	9/9	100	10/10	100
12	11/11	100	10/10	100	9/9	100	10/10	100

# PSI-7977 ELECTRON

IFN-free PSI-7977/RBV ➔ 100% SVR12

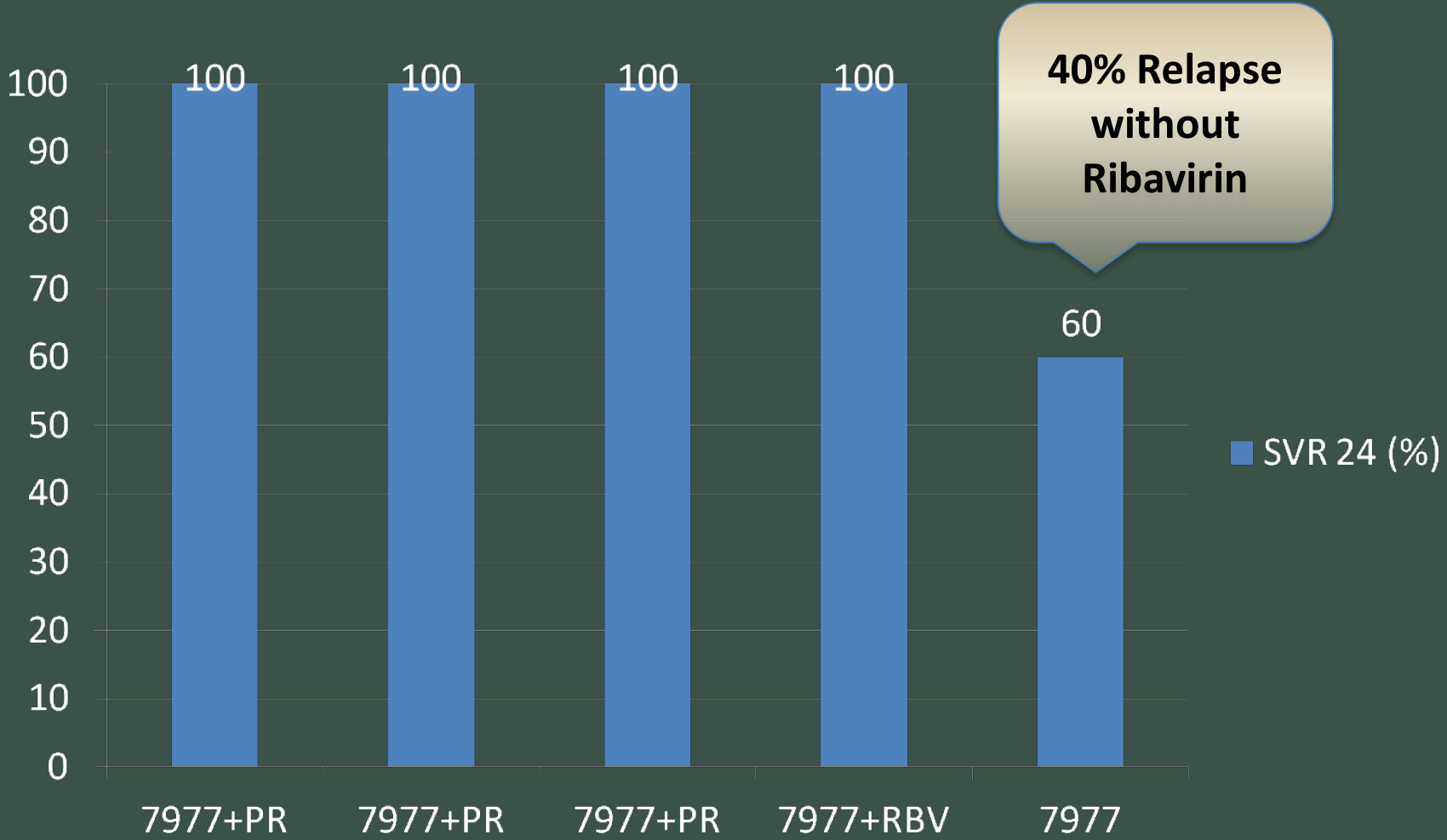
Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
<b>2</b>	9/11	82	7/8	88	8/9	89	8/10	80
<b>4</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>8</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>12</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>SVR4</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>SVR8</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>SVR12</b>	11/11	100	10/10	100	9/9	100	10/10	100

# PSI-7977 ELECTRON

## 100% concordance of SVR12 with SVR24

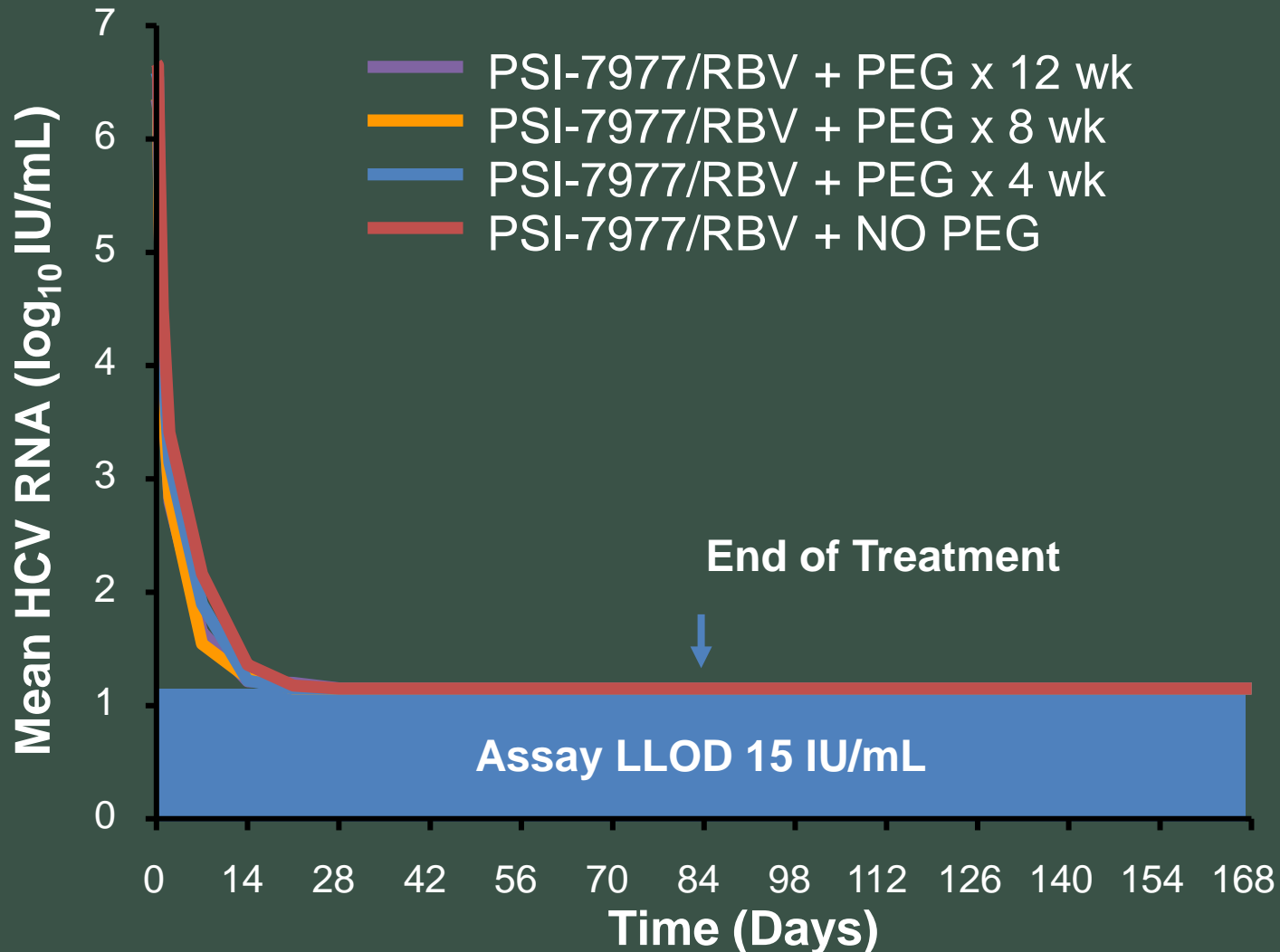
Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
<b>2</b>	9/11	82	7/8	88	8/9	89	8/10	80
<b>4</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>8</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>12</b>	11/11	<b>100</b>	10/10	<b>100</b>	9/9	<b>100</b>	10/10	<b>100</b>
<b>SVR4</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>SVR8</b>	11/11	100	10/10	100	9/9	100	10/10	100
<b>SVR12</b>	11/11	<b>100</b>	10/10	<b>100</b>	9/9	<b>100</b>	10/10	<b>100</b>
<b>SVR24</b>	6/6	<b>100</b>	5/5	<b>100</b>	5/5	<b>100</b>	4/4	<b>100</b>

# ELECTRON: SVR 24 in Genotype 2/3 Non-cirrhotics



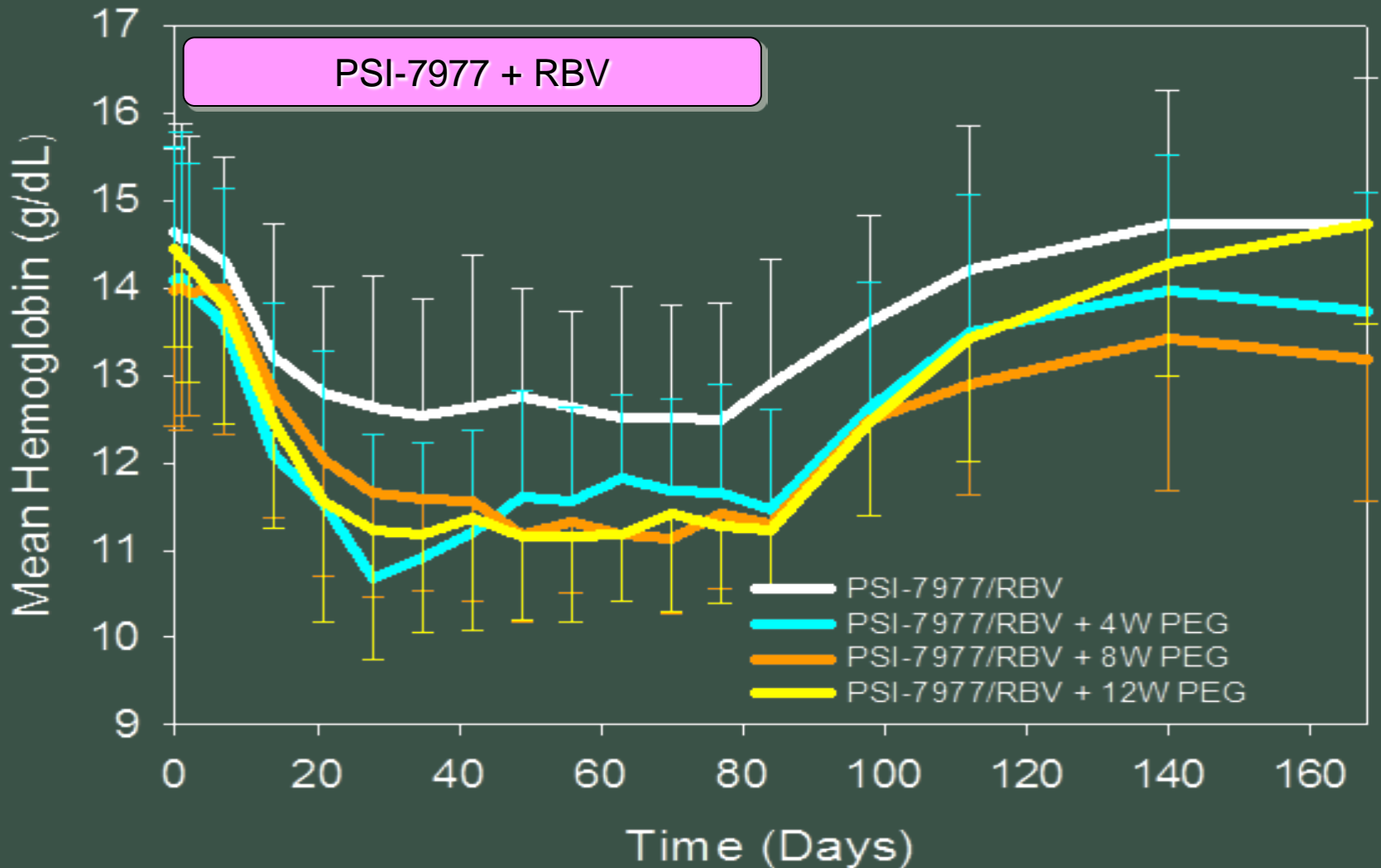
# PSI-7977 ELECTRON

## Rapid Viral Suppression with or without IFN



# PSI-7977 ELECTRON

## Less Impact on Hemoglobin in IFN-free PSI-977/RBV



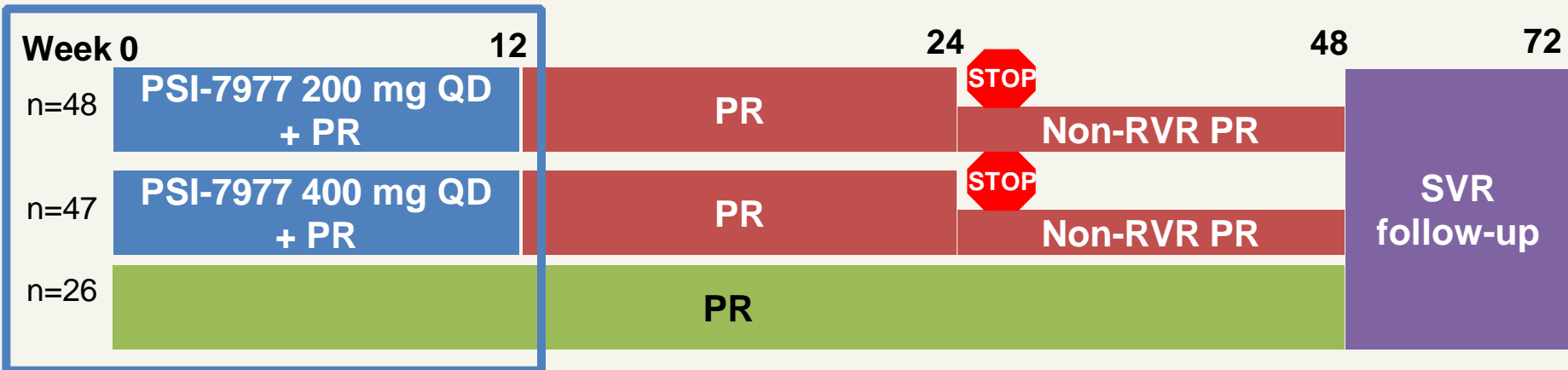
# PSI-7977 ELECTRON

Significant improvements in safety and tolerability with IFN-free PSI-7977/RBV

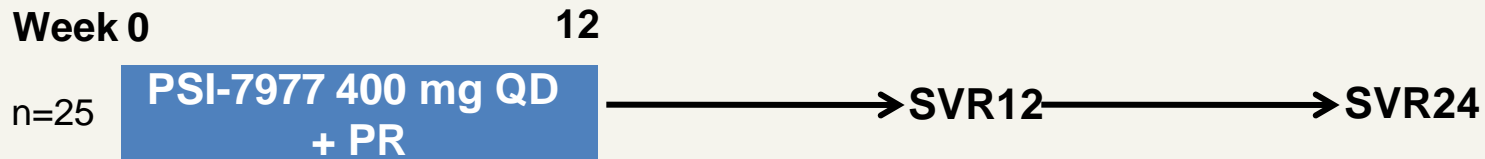
	PSI-7977 RBV 12 wks PEG n=11	PSI-7977 RBV 8 wks PEG n=10	PSI-7977 RBV 4 wks PEG n=9	PSI-7977 RBV NO PEG n=10
<b>SAE</b>	0	0	0	0
<b>&gt;1 AE: n (%)</b>	8 (72)	5 (50)	6 (67)	4 (40)
<b>Headache</b>	2 (18)	2 (20)	1 (11)	1 (10)
<b>Fatigue</b>	-	1 (10)	1 (11)	1 (10)
<b>Depression</b>	3 (27)	-	-	-
<b>Insomnia</b>	1 (9)	-	2 (22)	-
<b>Anxiety</b>	1 (9)	-	1 (11)	-
<b>Irritability</b>	2 (18)	-	-	-
<b>Myalgia</b>	1 (9)	-	-	1 (10)
<b>Upper RTI</b>	1 (9)	-	1 (11)	-

# PROTON: Once Daily PSI-7977 + PEG-IFN + RBV in HCV Treatment-Naïve Patients with G1 (and G2/G3)

## HCV G1 (N=121 treatment-naïve patients)



## HCV G2/G3 (N=25 treatment-naïve patients)

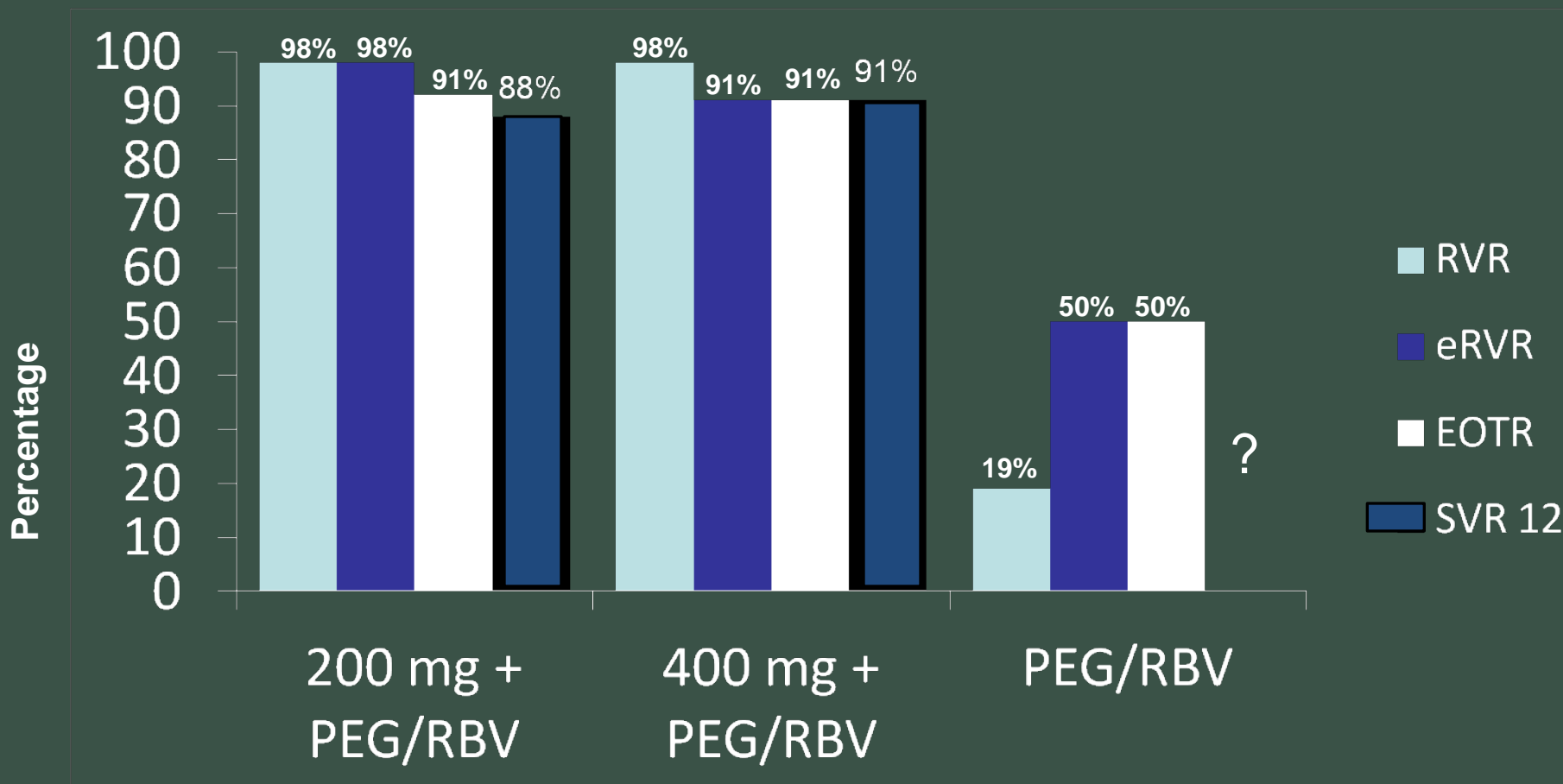


Nelson DR, et al. Poster presented at: EASL: The International Liver Congress 2011; March 30-April 3, 2011; Berlin, Germany. Poster LB1372.

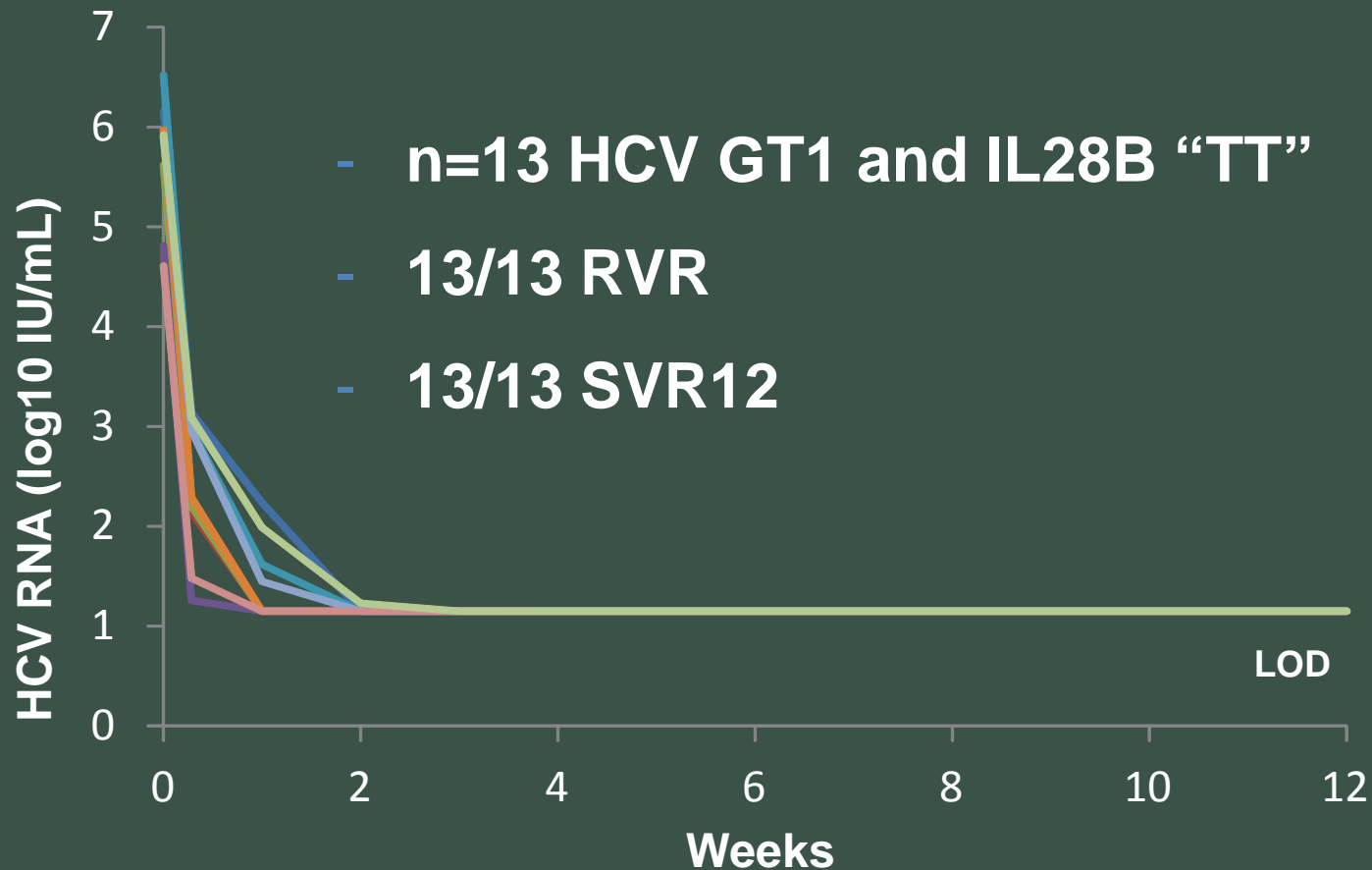
Lalezari J, et al. Presented at: EASL: The International Liver Congress 2011; March 30-April 3, 2011; Berlin, Germany. Oral Presentation 61.

Lawitz E, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 225.

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



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



# PSI-7977 Phase III Program

	<b>FISSION</b>	<b>POSITRON</b>	<b>NEUTRINO</b>
Planned Initiation	Year-end 2011	Early 2012	Mid-2012
Genotypes	2/3*	2/3	All
Patient Type	Treatment-naive	Cannot take INF	Cannot take INF
Control Arm	P/R-24 weeks	Placebo-12 weeks	Placebo-12 weeks
Total patient #	500	225	280
Randomization	1:1	2:1	3:1
Patient # PSI-7977+R	250	150	210
Duration of therapy	12 weeks	12 weeks	12 weeks
Primary endpoint	SVR12	SVR12	SVR12
*Plan to enroll 1 to 3 between genotypes Source: Pharmasset, Inc.			

# IFN-Free Clinical Studies SVR Summary

DRUG COMBINATIONS	CLASS	COMPANY	PHASE	DURATION (WEEKS)	SVR
BMS-032+052	PI+NS5A	BMS	2A	24	90% in 1b
DANOPREVIR (RG7227)+RG7128	PI+NPI	GENENTECH	2B	24	-
GS-9190+GS-92568	PI+NNPI	GILEAD	2A	24	-
BI-201335+BI-207127	PI+NNPI	BOEHRINGER INGELHEIM	2A	16, 28, 40	-
PSI-938+PSI-7977	NPI+NPI	PHARMASSET	2A	2	-
PSI-7977+RBV	NPI	PHARMASSET	2A	12	100% in G2/3
ABT-450/R+ RBV + ABT-072 or ABT-333	PI+NNPI	ABBOTT	2A	12	90% in G1 IL28CC
ALV + RBV	Cycl Inh	NOVARTIS	3	24	-

PI=PROTEASE INHIBITOR; NPI=NUCLEOSIDE POLYMERASE INHIBITOR;  
 NNPI=NON-NUCLEOSIDE POLYMERASE INHIBITOR

# Beyond 2015

