

HCV: Wave 2

Interferon based therapy

SCSG 2011  
Post-AASLD  
Symposium

SOUTHERN  
CALIFORNIA  
SOCIETY OF  
GASTROENTEROLOGY

HCV Treatment

“V 2.2”

Interferon based therapy

Wave of the future?

Thing of the past?

Robert G. Gish MD

Professor of Clinical Medicine

Medical Director:

Center for Hepatobiliary Disease and  
Abdominal Transplantation

SCSG 2011  
Post-AASLD  
Symposium

SOUTHERN  
CALIFORNIA  
SOCIETY OF  
GASTROENTEROLOGY

**UC San Diego**  
HEALTH SYSTEM

**Center for Hepatobiliary  
& Abdominal Transplant**

# Disclosures

- I have consulting, research and advisory board relationships with
  - Merck
  - J and J Tibotec
  - Vertex
  - Gilead
  - BMS
  - BI



# Notes

- Authorships and locations of study data
  - NATAP website
  - AASLD abstracts
    - [AASLD.org](http://AASLD.org)

# Listen up

## Valve Job

- A mechanic was removing a cylinder head from the motor of a Harley motorcycle when he spotted a well-known heart surgeon in his shop.
- The surgeon was there waiting for the service manager to come take a look at his bike.
- The mechanic shouted across the garage, "Hey, Doc, can I ask you a question?"
- The surgeon, a bit surprised, walked over to the mechanic working on the motorcycle. The mechanic straightened up, wiped his hands on a rag and asked, "So Doc, look at this engine. I open its heart, take valves out, fix 'em, put 'em back in, and when I finish, it works just like new.
- So how come I get such a small salary and you get the really big bucks, when you and I are doing basically the same work?"
- The surgeon paused, smiled and leaned over, and whispered to the mechanic..."

...**"TRY DOING IT WITH THE ENGINE  
RUNNING."**

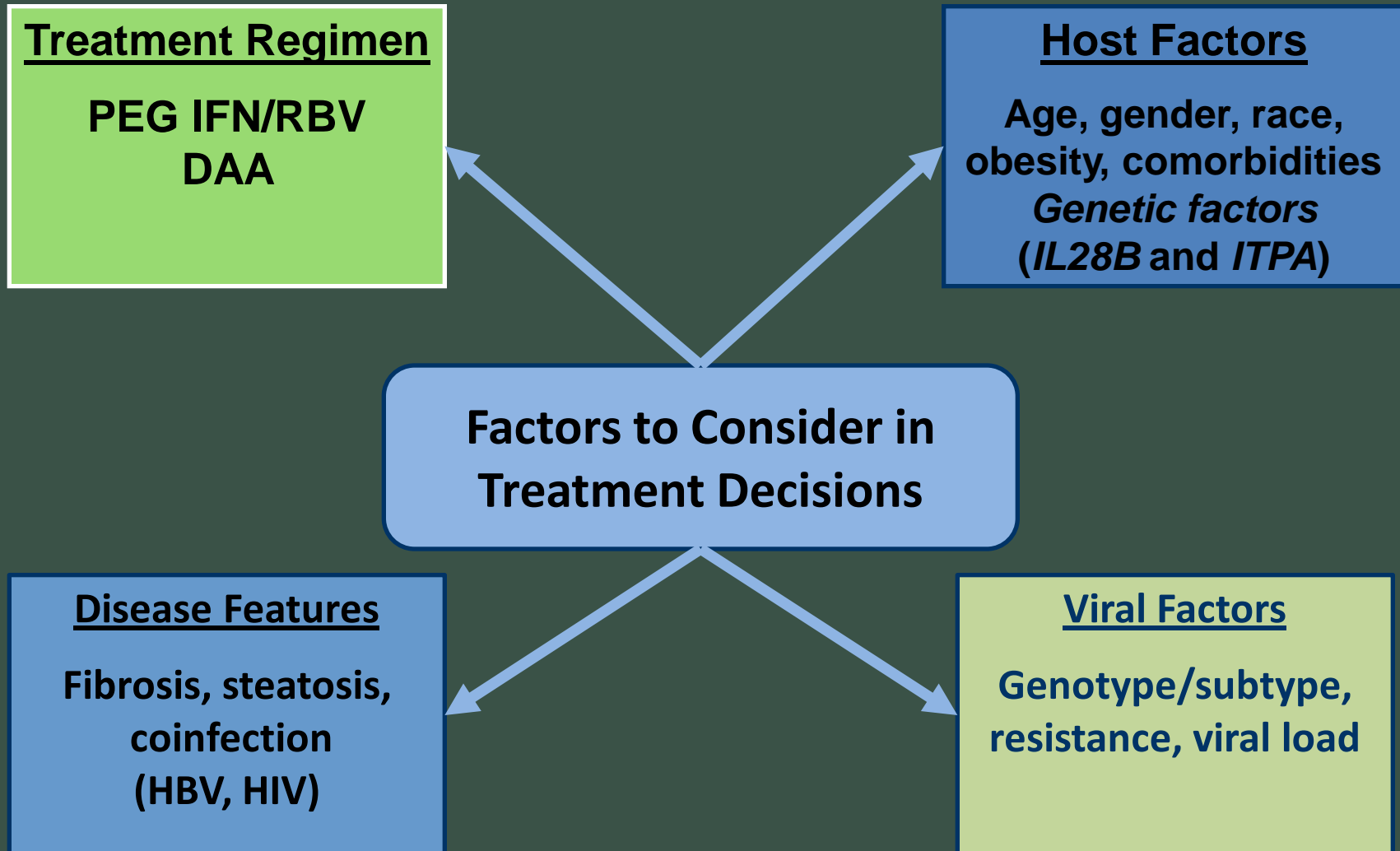
# Health care cost and utilization statistical models adjusted for demographics and co-morbidities

- Patients with CC and ESLD were estimated to have incremental cost ratios that were 1.40-fold (95% CI, 1.31–1.49,  $P < .001$ ) and 3.33-fold (95% CI, 3.12–3.56,  $P < .001$ ) greater than those for patients with NCD, respectively.
- The covariate adjusted analyses showed that, when compared with patients with NCD, individuals with CC are predicted to make 1.18-fold (95% CI, 1.15–1.21,  $P < .001$ ) more ambulatory visits. The predicted number of emergency room visits for patients with NCD and CC was similar (0.0795 vs 0.0775 PPPM, respectively), as was the predicted number of inpatient visits (0.0225 vs 0.0217 PPPM, respectively).
- The covariate adjusted analyses showed that patients with ESLD were predicted to make 1.55-fold (95% CI, 1.52–1.59,  $P < .001$ ) more ambulatory visits compared with patients with NCD. Patients with ESLD were predicted to make 1.76 times more emergency room visits than patients with NCD (0.1397 vs 0.0795 PPPM, respectively) and 3.88 times more inpatient visits (0.0872 vs 0.0225 PPPM, respectively).

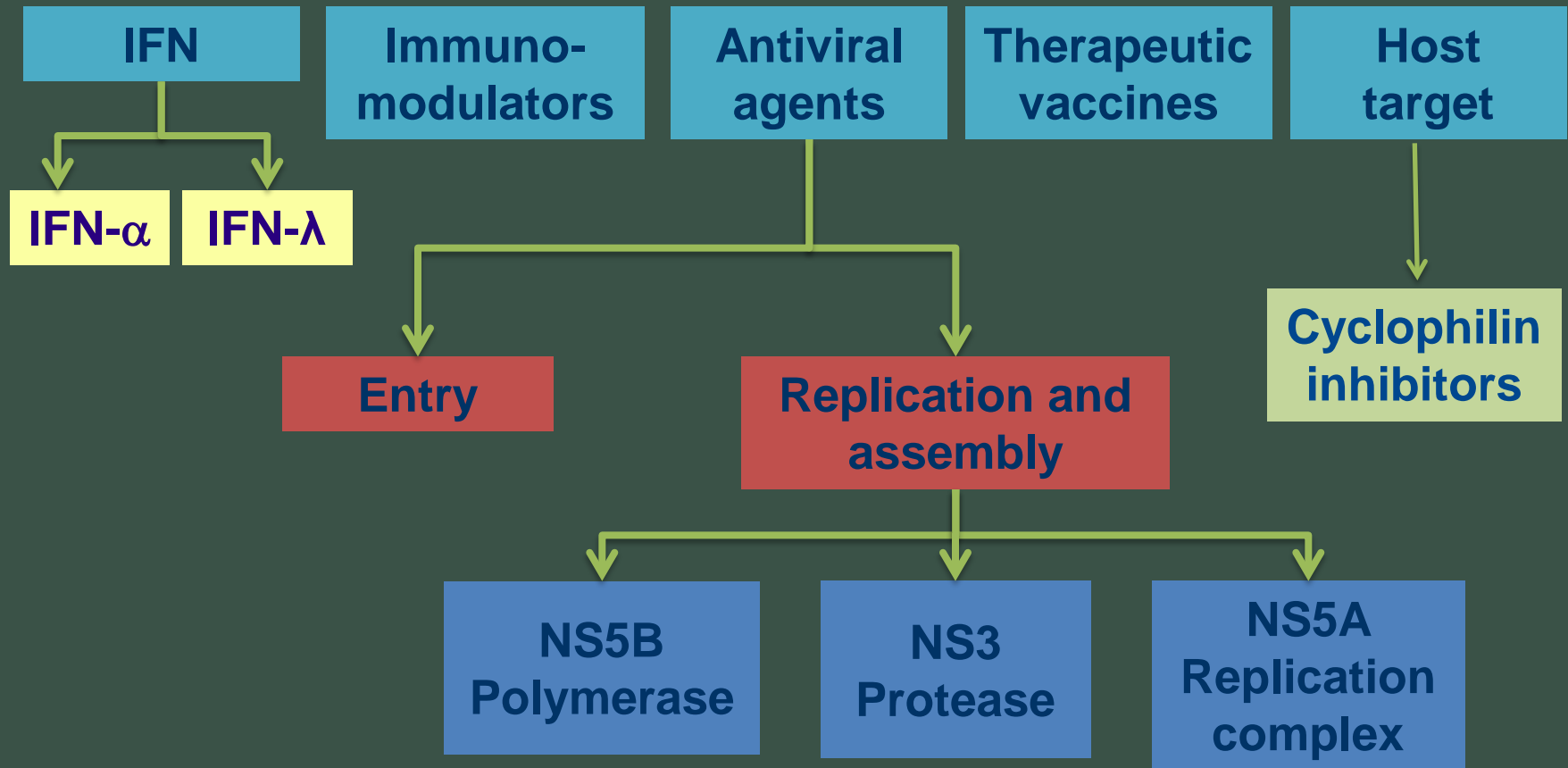
# Annual cost estimates

- Under the assumption that follow-up time was not associated with disease severity; PPPM all-cause cost measures can be roughly translated into annual cost estimates by multiplying the PPPM estimates by 12.167.
- Using this formula, annual all-cause health care costs were estimated to be \$24,176 for patients with chronic HCV infection. When stratified by cohort, average annual costs were estimated to be \$17,277 among patients with NCD, \$22,752 among patients with CC, and \$59,995 among patients with ESLD.

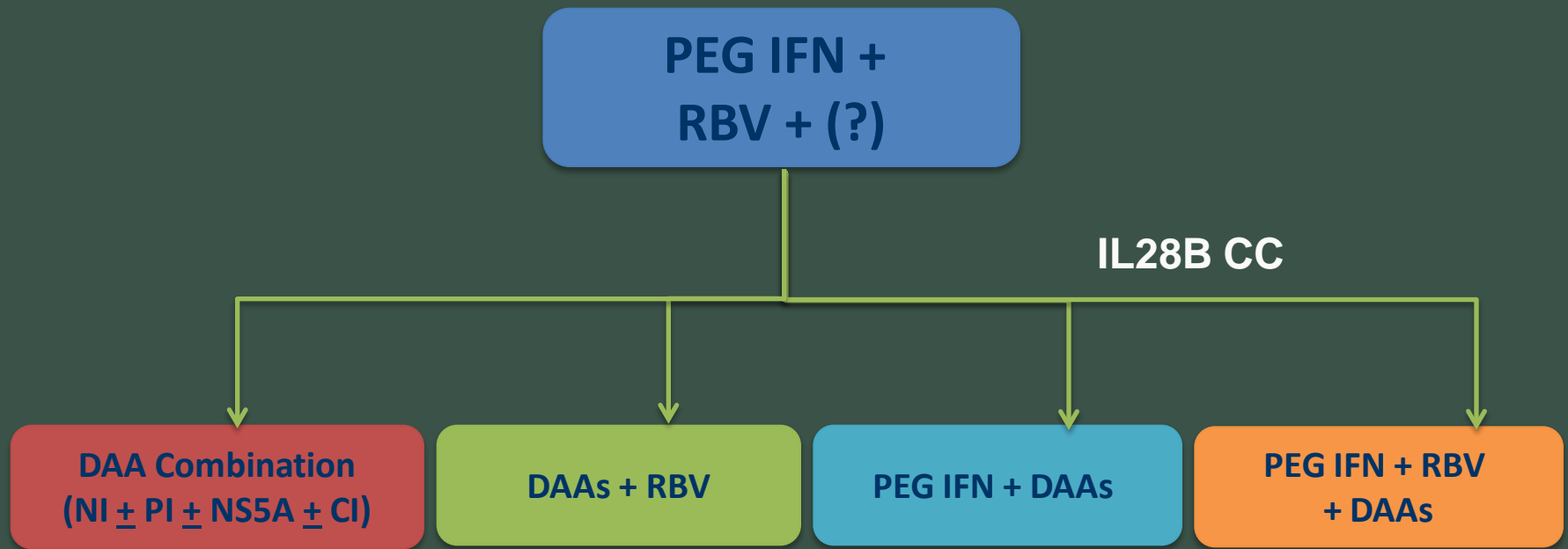
# Identifying Candidates For Triple or Quad Therapy



# Antiviral Targets and Approaches for the Future



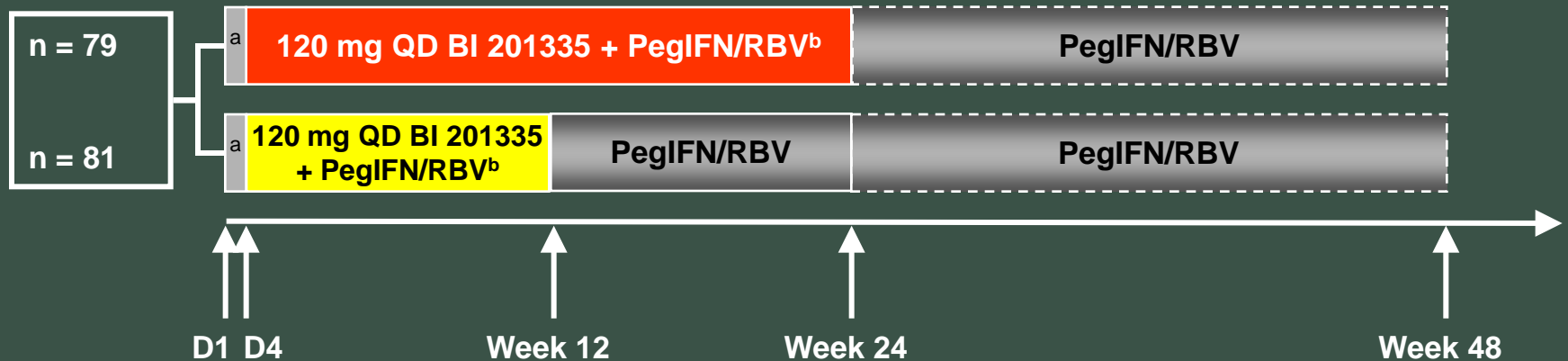
# Towards a Future of Personalized Medicine



Abbreviations: CI, cyclophilin inhibitor; DAA, direct-acting antiviral; NI, nucleoside inhibitor; PEG IFN, peginterferon; PI, protease inhibitor; RBV, ribavirin. Graphic courtesy of Dr. David R. Nelson.

# SILEN-C3 trial

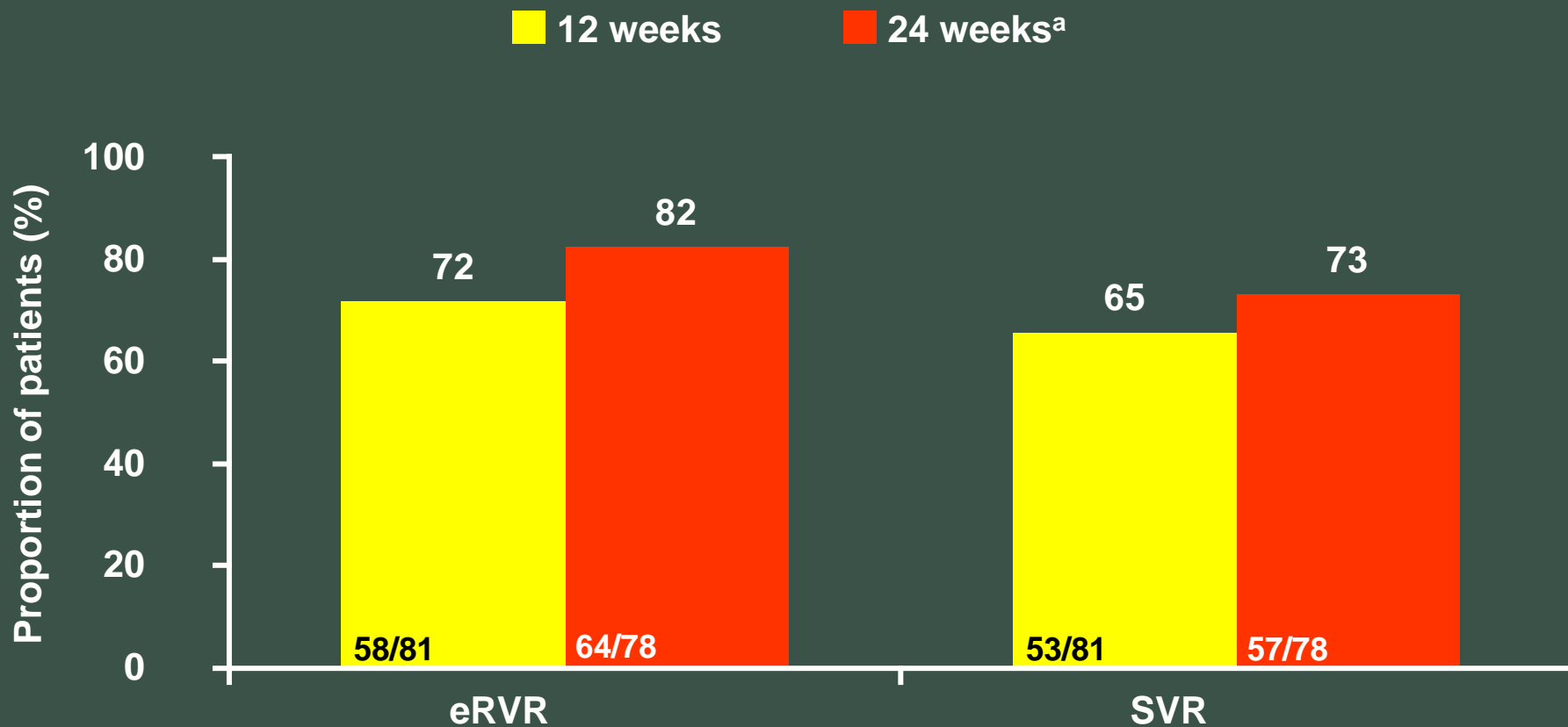
Open-label phase IIb study in treatment-naïve, hepatitis C virus (HCV) genotype-1 (GT-1) patients



<sup>a</sup>3-day lead-in period (LI) of Peg-interferon (IFN) alfa 2a (180 µg/week) plus ribavirin (RBV) (1,000 mg or 1,200 mg/day);

<sup>b</sup>Patients without extended rapid virologic response (eRVR, HCV RNA < lower limit of quantification [LLOQ] Week 4 and < lower limit of detection [LLOD] Weeks 8 to 18), continued PegIFN/RBV up to Week 48 QD, once daily

# Virological response



<sup>a</sup>One patient excluded who discontinued PegIFN prior to BI 201335 for bone pain

eRVR: HCV RNA < LLOQ at Week 4 and < LLOD at Weeks 8 to 18; SVR, sustained virologic response

# HIGH RAPID VIROLOGIC RESPONSE (RVR) WITH ACH-1625 DAILY DOSING PLUS PEGIFN-ALPHA 2A/RBV IN A 28-DAY PHASE 2A TRIAL

## BACKGROUND

- HCV NS3 serine protease is a prime target of new therapies that have the potential to improve SVR rates and/or reduce adverse events in patients with chronic hepatitis C when combined with peginterferon alfa-2a plus ribavirin (PR)
- ACH-1625 is a potent, linear, noncovalent inhibitor of HCV NS3 protease<sup>1,2</sup>
  - It binds to NS3 protease slowly and tightly with an inhibition constant at steady state ( $K_i^*$ ) of 0.06 nM (eg, for genotype 1b [GT-1b])
  - It inhibits NS3 proteases of all genotypes with similar potency, except GT-3
- The mean  $EC_{50}$  value in a cell line harboring the GT-1b/Con-1 subgenomic replicon is 11 nM (or 8.8 ng/mL no salt)
- ACH-1625 distributes rapidly and selectively to liver, partly due to transporter-mediated uptake<sup>3</sup>
- Subsequent analyses on individual PK curves and antiviral efficacy collected in a phase 1 trial in GT-1 patients yielded an  $EC_{50}$  of 0.41 ng/mL
- Phase 1 trial data demonstrated the safety and tolerability of ACH-1625 monotherapy up to 1200 mg/day for 5 days in patients with HCV<sup>4</sup>
- Pharmacokinetic (PK) and viral kinetics profiles support QD dosing and the potential to combine ACH-1625 in an all direct-acting antiviral (DAA) combination<sup>4,5</sup>
- This presentation describes Week 4 RVR data after administration of ACH-1625/placebo in combination with PR for 28 days

## RESULTS

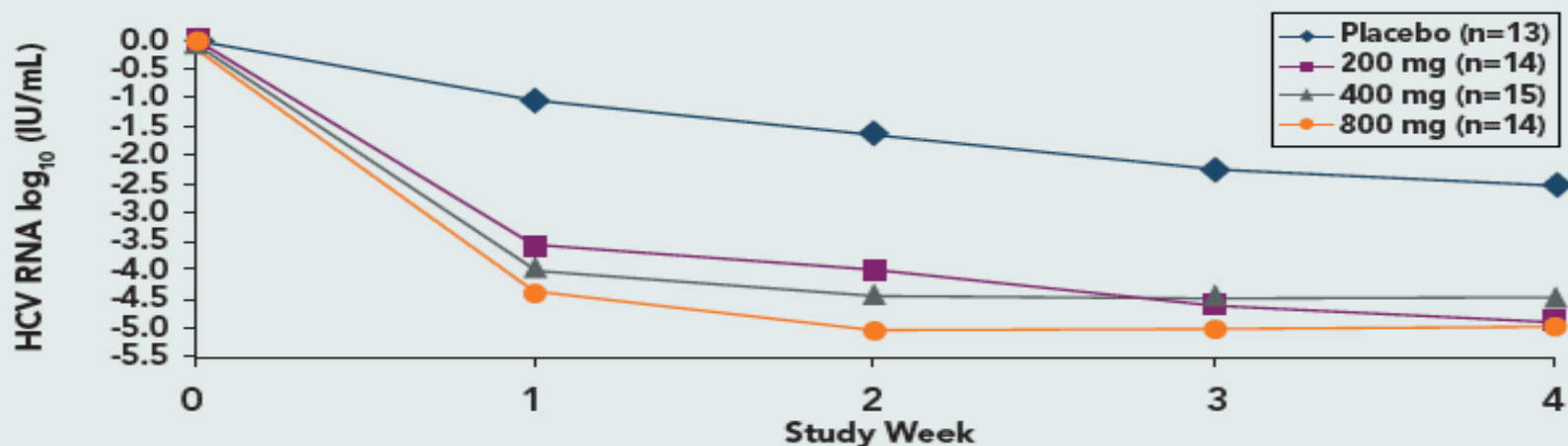
### Patient Demographics

- 12 US sites enrolled 64 patients infected with HCV GT-1a (73%), GT-1b (25%), GT-1 (2%)
- Baseline demographics were similar across groups
- 47 (73%) were male; 38 (59%) Caucasian, 21 (33%) African American, 5 (8%) other
- Mean age: 50
- Mean BMI: 27.6
- 83% of patients enrolled were IL28B CT/TT and 17% were CC

### Viral Response

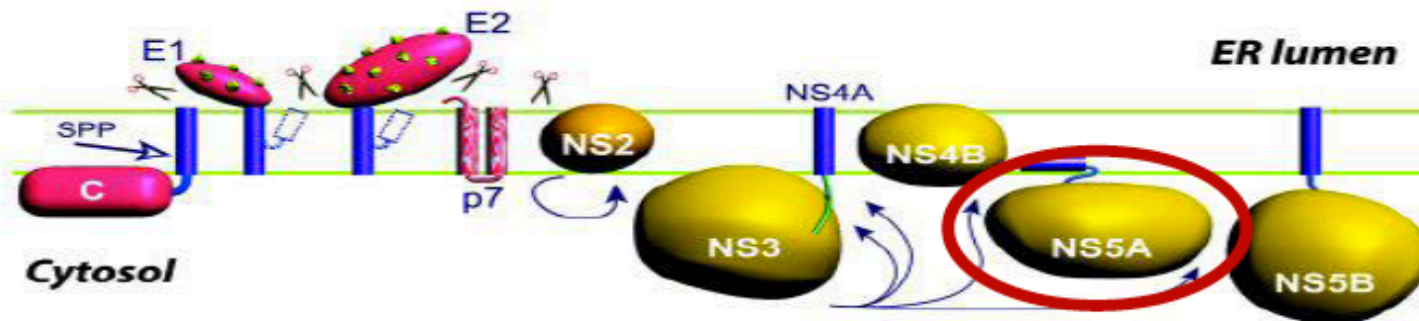
- Administration of 800 mg QD dose for 28 days in combination with PR resulted in a 5 log<sub>10</sub> maximum reduction in HCV RNA (Figure 1 and Table 1)
- 400 mg QD dose with PR resulted in a 4.6 log<sub>10</sub> maximum reduction
- 200 mg QD dose with PR resulted in a 4.9 log<sub>10</sub> maximum reduction
- The results demonstrate similar response rates across dose groups

Figure 1. Viral Load Decay Through Week 4



## Background

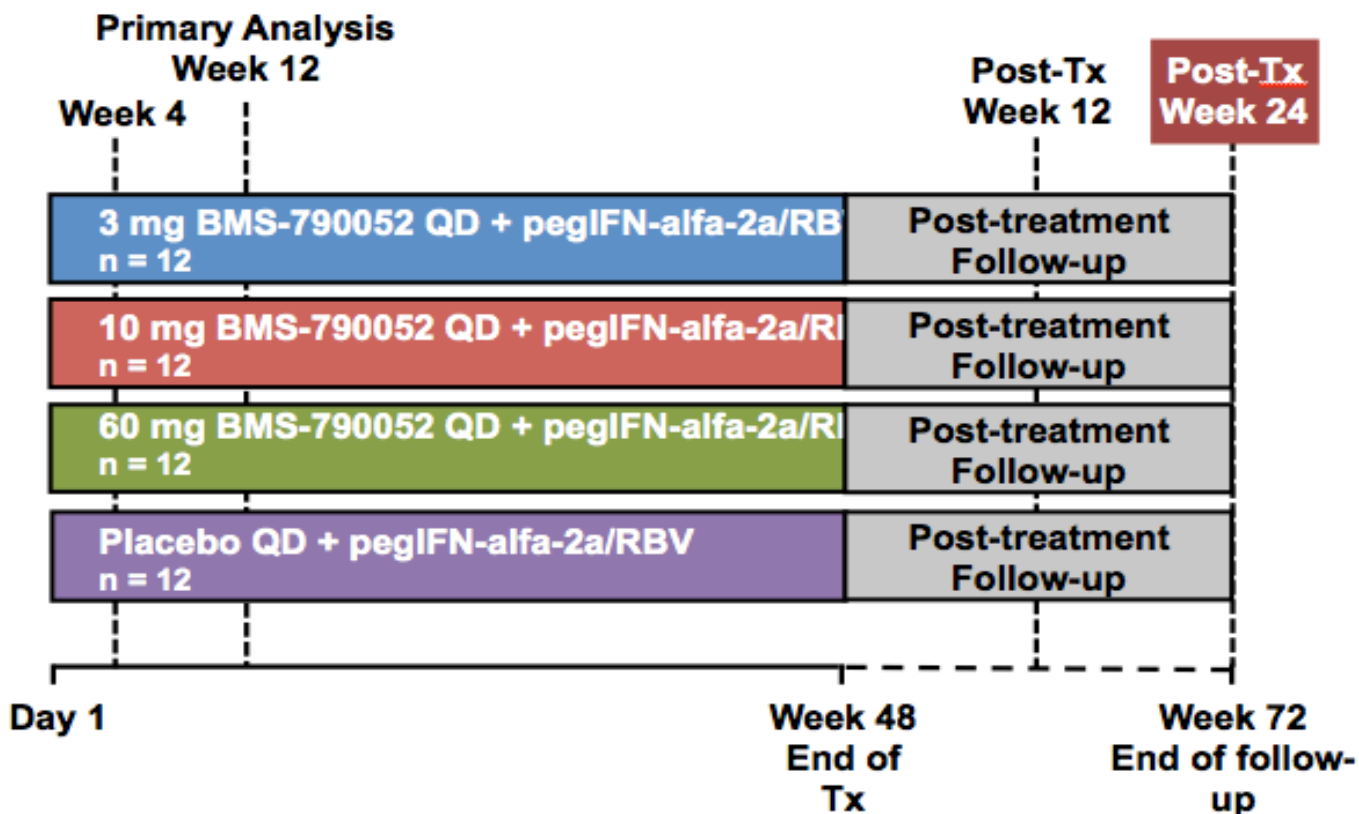
- Daclatasvir (DCV; BMS-790052) is a highly selective, first-in-class HCV NS5A replication complex inhibitor with picomolar potency, broad genotypic coverage *in vitro*, and a PK profile supportive of once-daily administration
- Daclatasvir combined with pegylated interferon-alfa-2a (peg-alfa) and ribavirin (RBV) has shown high rates of SVR in several phase 2a studies
  - See Izumi *et al.* (LB-20) and Suzuki *et al.* (LB-22) at this conference



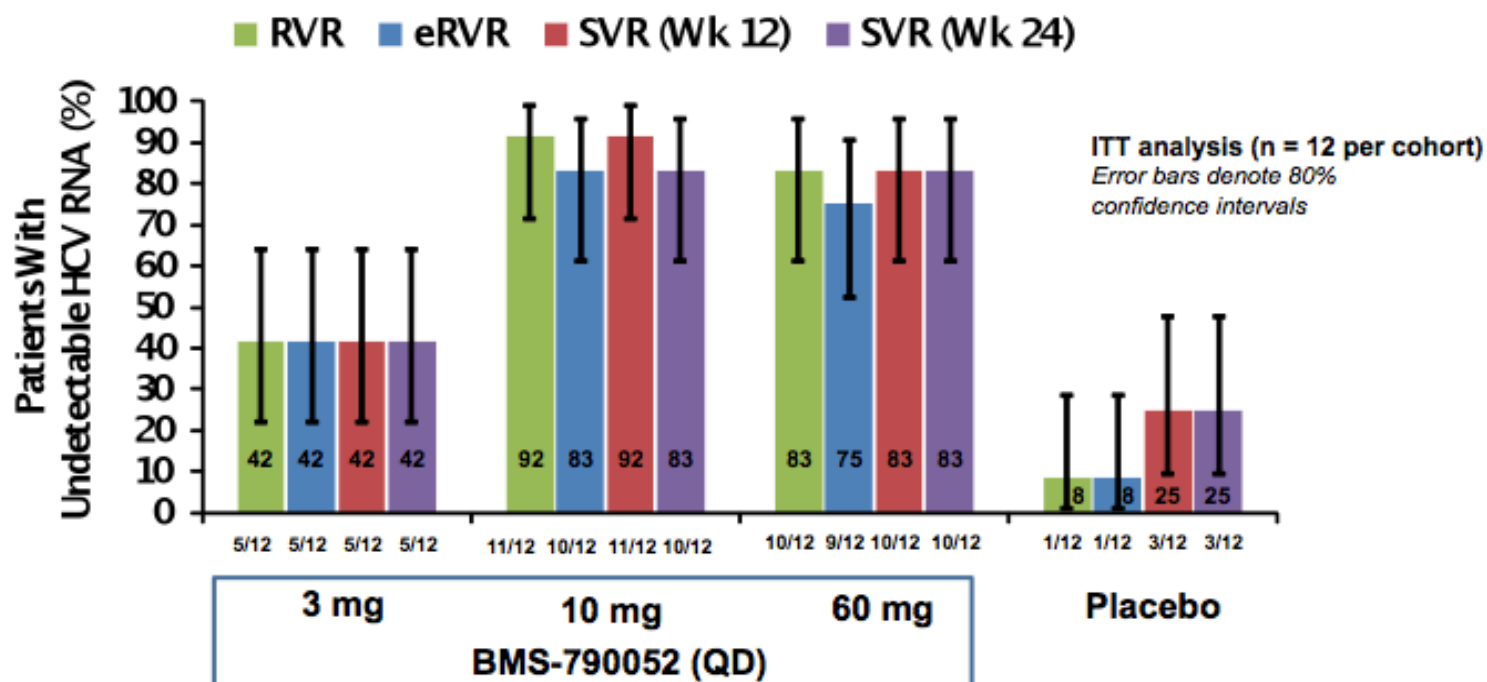
# BMS NS5a Triple therapy

## Study Design

Study AI444-014



## Virologic Responses During and After Treatment

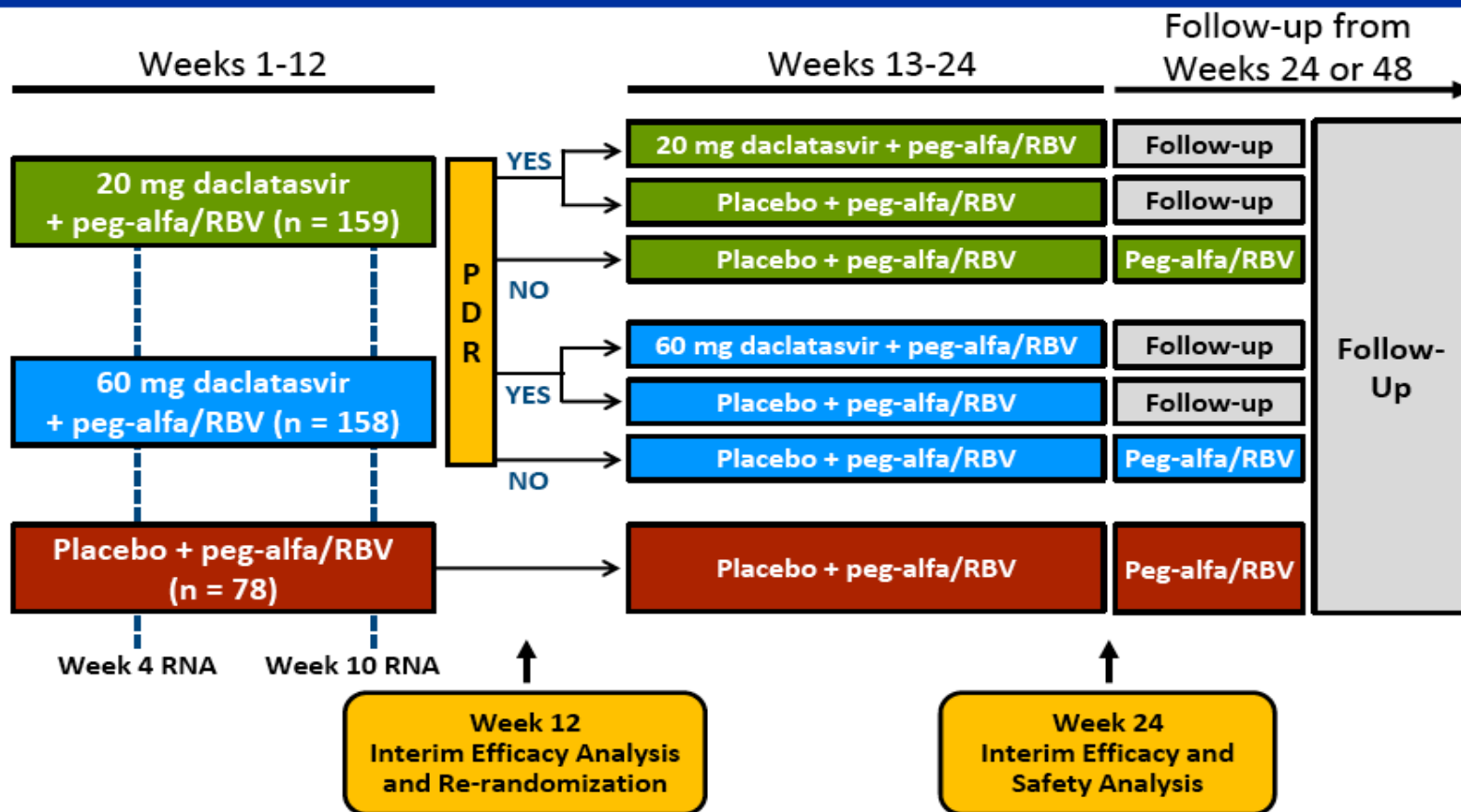


Assay lower limit of quantitation (LLQ) = 25 IU/mL (Roche COBAS® TaqMan® High Pure v2.0)

RVR, undetectable (< 10 IU/mL) HCV RNA at week 4; eRVR, undetectable HCV RNA at weeks 4 and 12 on treatment; SVR (weeks 12, 24), undetectable HCV RNA at post-treatment week 12, 24; ITT, intent to treat

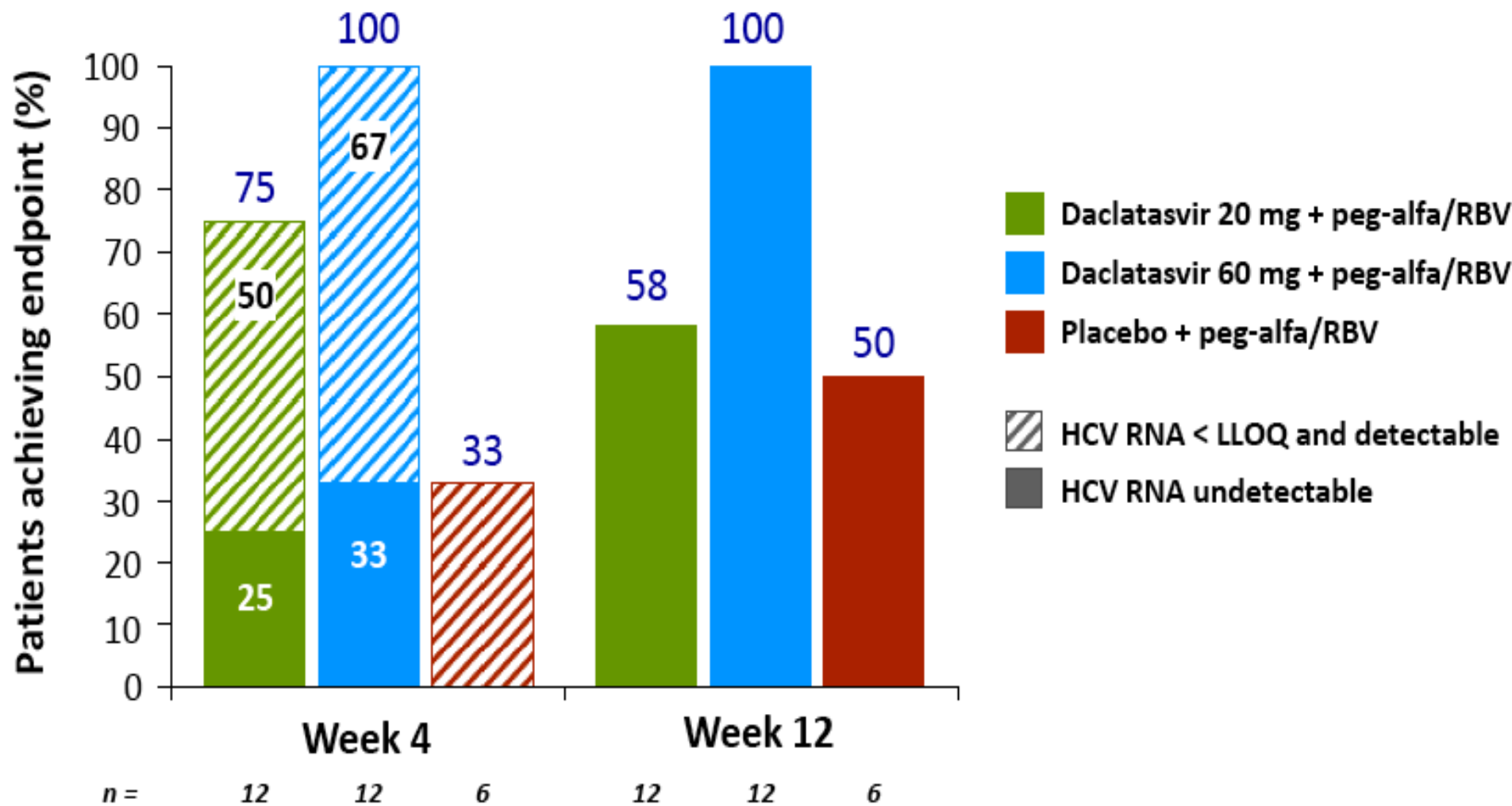
# Daclatasvir (DCV; BMS-790052), an NS5A Replication Complex Inhibitor, Combined With Peginterferon-Alfa-2a and Ribavirin in Treatment-Naive HCV-Genotype 1 or 4 Subjects: Phase 2b COMMAND-1 Study Interim Week 24 Results

## Study Design



PDR, protocol-defined response: HCV RNA < LLOQ (25 IU/mL) at week 4 and undetectable (< 10 IU/mL) at week 10.

# Virologic Responses Through Week 12: HCV Genotype 4



# Grade 3/4 Hematologic and Laboratory Abnormalities Through Week 24

Event, %	Daclatasvir 20 mg + peg-alfa/RBV (n = 159)		Daclatasvir 60 mg + peg-alfa/RBV (n = 158)		Placebo + peg-alfa/RBV (n = 78)	
<b>Hematologic Laboratory Abnormalities</b>						
Neutropenia	25		27		24	
Lymphopenia	11		13		5	
Anemia	6		6		5	
Thrombocytopenia	1		3		3	
<b>Hepatic Laboratory Abnormalities</b>						
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Increased total bilirubin	1	0	0	0	1	0
Elevated ALT*	0	0	4	0	1	0

\* There were no patients with grade 3/4 elevations of both ALT and bilirubin

Neutropenia: grade 3, 500-749/mm<sup>3</sup>; grade 4, < 500/mm<sup>3</sup>

Lymphopenia: grade 3, 350-499/mm<sup>3</sup>; grade 4, < 350/mm<sup>3</sup>

Anemia: grade 3, hemoglobin 7-8.9 g/dL; grade 4, < 7.0 g/dL

Thrombocytopenia: grade 3, 25,000-49,999/mm<sup>3</sup>; grade 4, < 25,000/mm<sup>3</sup>

ALT elevations: grade 3, 5.1-10 x ULN; grade 4, > 10 x ULN

Bilirubin elevations: grade 3, 2.6-5 x ULN; grade 4, > 5 x ULN

# Vertex: what is next?

## INTRODUCTION

- VX-222 is a selective, noncompetitive inhibitor of the hepatitis C virus (HCV) NS5B polymerase.<sup>1</sup> Telaprevir (TVR) is a specific, reversible, covalent, tight- and slow-binding HCV NS3/4A protease inhibitor<sup>2,3</sup> that in combination with peginterferon and ribavirin (PR) improved sustained viral response (SVR) rates compared with PR.<sup>4-9</sup>
- The combination of 2 direct-acting antiviral (DAA) compounds, such as VX-222 and TVR should:
  - inhibit 2 different, essential enzymes for viral replication
  - increase the barrier to resistance compared with each inhibitor alone
  - increase the antiviral potency of the treatment regimen, additively or synergistically.
- The ZENITH study is investigating the safety, tolerability, pharmacokinetics, and antiviral activity of combination treatment with 2 dose levels of VX-222 and a fixed dose of TVR administered with and without peginterferon alfa-2a and/or ribavirin for 12 to 24 weeks in treatment-naïve patients with genotype 1 chronic hepatitis C infection.
- The results of the interim analysis of virologic data of all patients from arms C and D through Week 36, and safety and tolerability summary during the QUAD (TVR + VX-222 + Peg-IFN + RBV) phase (12 weeks of treatment) are presented here.

# Antiviral activity

## Table 3: Key Virologic Endpoints

n (%)		All Patients	
		C 100 mg VX-222 (N=29)	D 400 mg VX-222 (N=30)
Week 2	HCV RNA undetectable	11 (38)	17 (57)
	HCV RNA <25 IU/mL	27 (93)	26 (87)
Week 4 (RVR)	HCV RNA undetectable <sup>a</sup>	25 (86)	26 (87)
	HCV RNA <25 IU/mL	28 (97)	29 (97)
Weeks 2 and 8	HCV RNA undetectable <sup>a</sup>	11 (38)	15 (50)
	HCV RNA <25 IU/mL	25 (86)	24 (80)
Week 12 (cEVR)	HCV RNA undetectable <sup>a</sup>	24 (83)	27 (90)
	HCV RNA <25 IU/mL	24 (83)	27 (90)
EOT	HCV RNA <25 IU/mL	28 (97)	30 (100)
SVR12	HCV RNA undetectable <sup>a</sup>	24 (83)	27 (90)
Relapse <sup>b</sup>	HCV RNA >25 IU/mL after <25 IU/mL at EOT n/N (%)	2/28 (7)	2/30 (7) <sup>c</sup>
		<b>Patients eligible to receive 12 weeks total treatment</b>	
		<b>C (N=11)</b>	<b>D (N=15)</b>
EOT	HCV RNA <25 IU/mL	11 (100)	15 (100)
SVR12	HCV RNA undetectable <sup>a</sup>	9 (82)	14 (93)
SVR24	HCV RNA undetectable <sup>a</sup>	9 (82)	14 (93)
Relapse	HCV RNA >25 IU/mL after <25 IU/mL at EOT n/N (%)	2/11 (18)	1/15 (7) <sup>c</sup>
		<b>Patients eligible to receive 24 weeks total treatment</b>	
		<b>C (N=18)</b>	<b>D (N=15)</b>
EOT	HCV RNA <25 IU/mL	17 (94)	15 (100)
SVR12	HCV RNA undetectable <sup>a</sup>	15 (83)	13 (87)
Relapse <sup>b</sup>	HCV RNA >25 IU/mL after <25 IU/mL at EOT n/N (%)	0/17 (0)	1/15 (7)

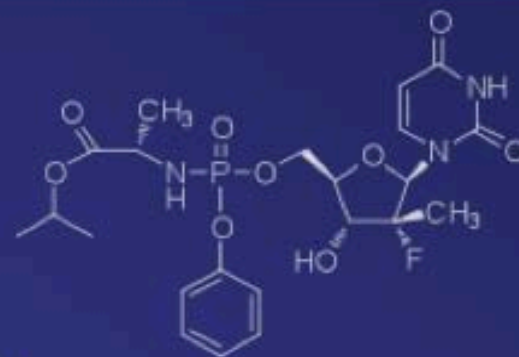
<sup>a</sup>HCV RNA <25 IU/mL and undetectable (ie, below LOD). <sup>b</sup>Additionally, 2 patients in arm C and 1 patient in arm D have missing value 12 weeks after EOT. <sup>c</sup>1 patient with relapse received only 1 week of treatment.

# Pharmasset: a great asset?

## Polymerase Inhibitor

### 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 #34, Nov 6<sup>th</sup>)**
  - **PROTON GT1 98% RVR (Nelson, EASL 2011)**
  - **PROTON GT2/3 94% SVR (Lalezari, EASL 2011)**
- **High barrier to resistance**





**PROTON**

## STUDY DESIGN: Dose ranging in GT1

### HCV GT1



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

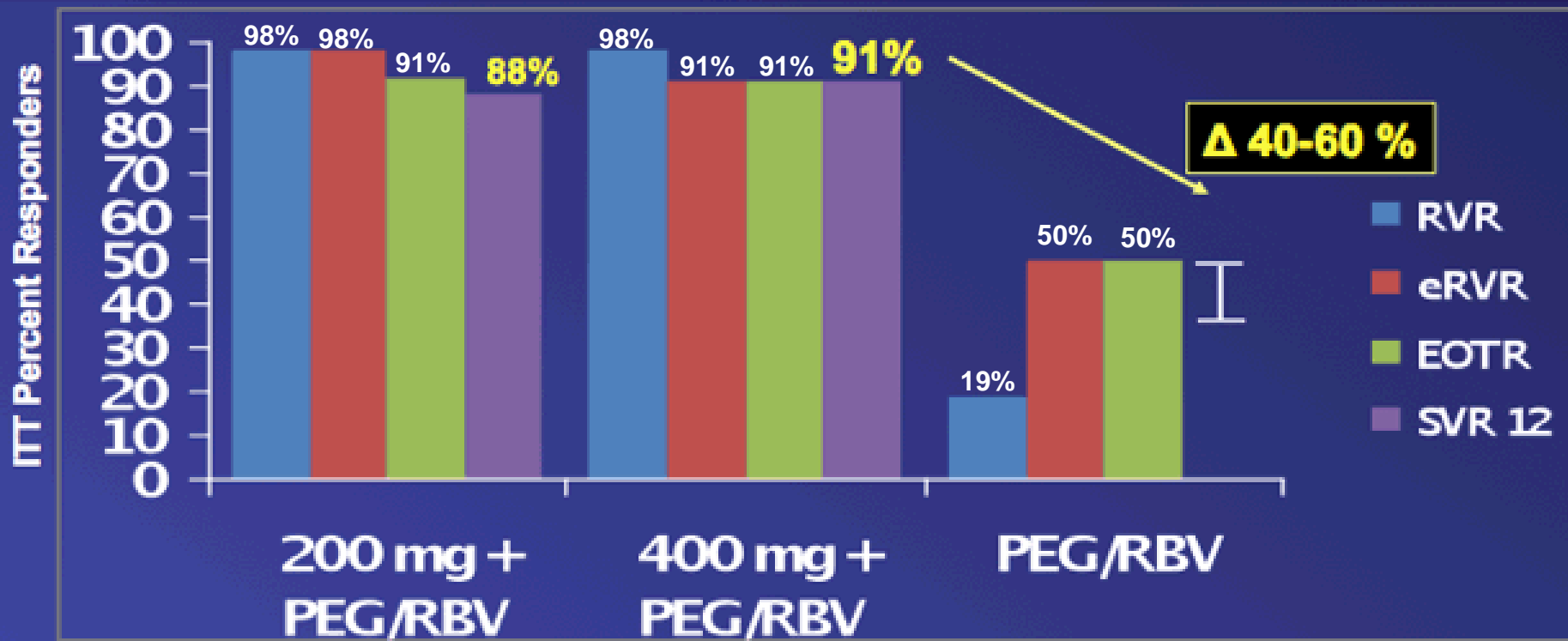
### HCV GT2 or GT3, open-label



- 25 treatment-naïve patients with HCV GT2 or GT3; one pt lost to F/U after Day 1
- 24/25 RVR, SVR 12 and SVR 24 (EASL 2011, Lalezari *et al.*)

## RESULTS:

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



# PILLAR Study (TMC435-C205):

## Objectives & Endpoints

### Study design

- International, Phase IIb, randomized, double-blind, placebo-controlled clinical trial

### Objective

- To assess efficacy and safety of HCV NS3/4A protease inhibitor TMC435 75 mg or 150 mg administered once-daily (QD) in combination with PegIFN/RBV in treatment-naïve patients infected with HCV genotype 1

### Primary efficacy endpoint

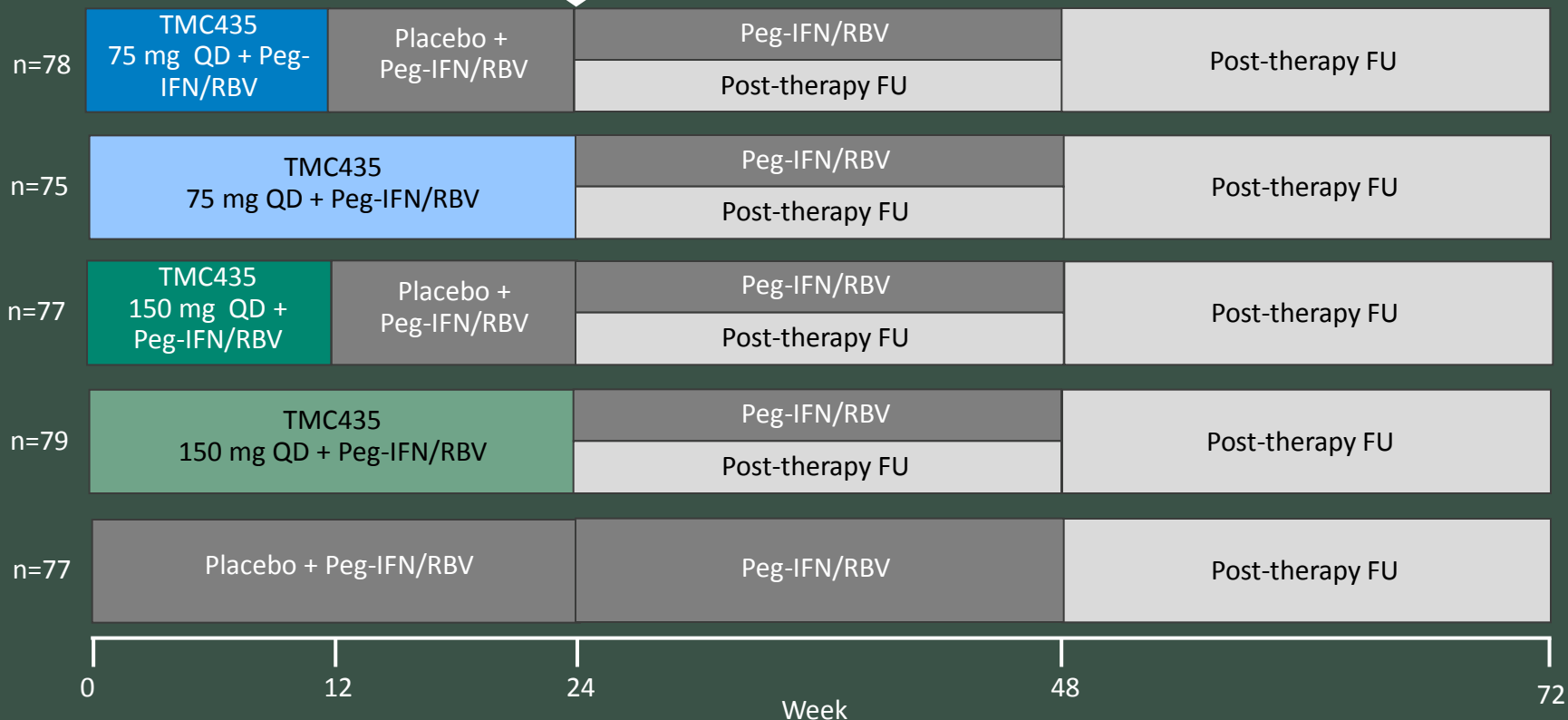
- Sustained virologic response at Week 72 (SVR Wk 72)

### Key secondary endpoints

- SVR 12 and 24 weeks after planned treatment end; viral breakthrough and relapse rates; safety and tolerability

# PILLAR Study: Design

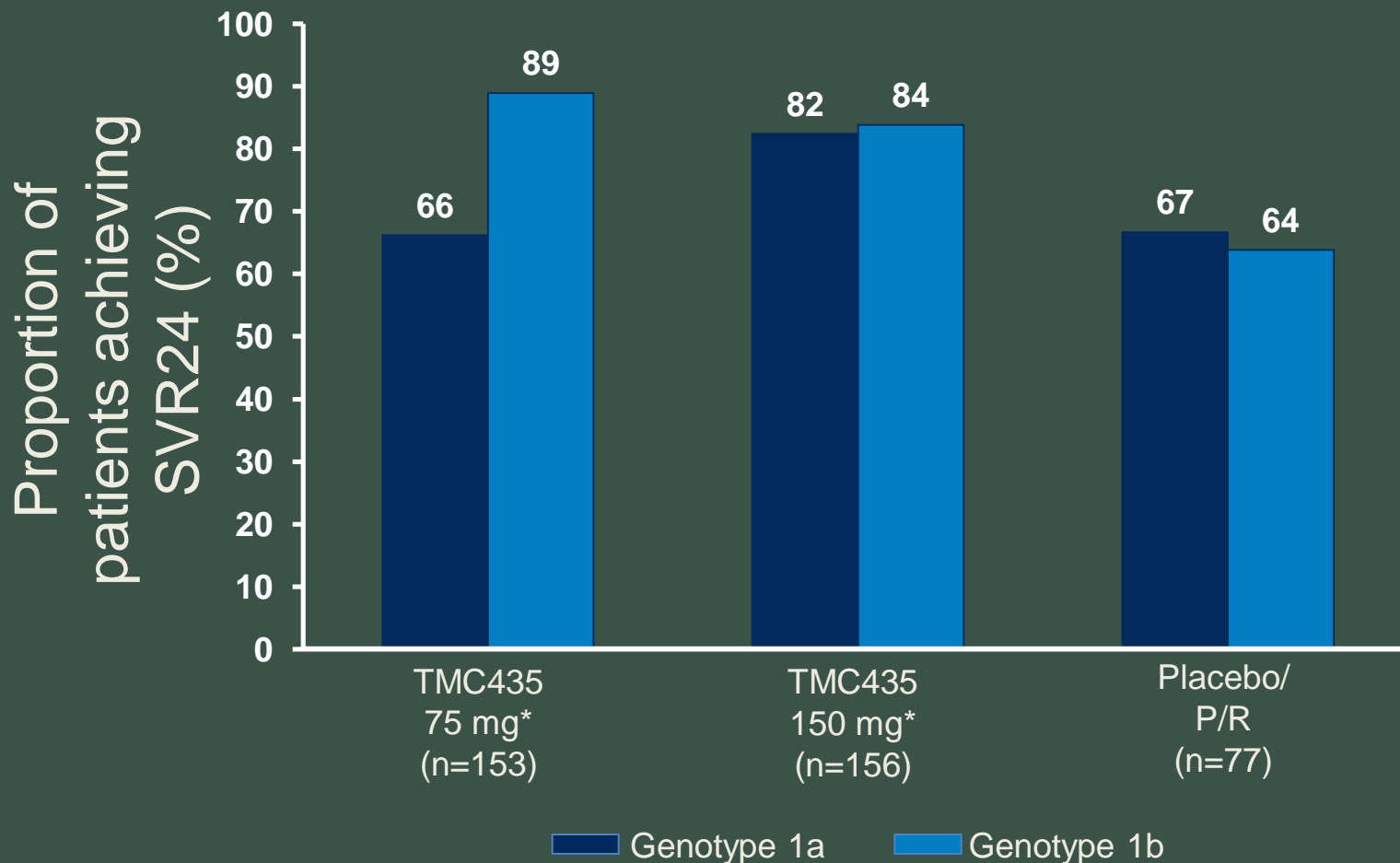
Response guided treatment (RGT); TMC435 arms only



- **RGT criteria in TMC435 arms:** End treatment at W24, if HCV RNA <25 IU/mL detectable/undetectable at W4 and <25 IU/mL undetectable at W12, W16, W20 (all other patients continued Peg-IFN/RBV up to W48)

# PILLAR Study:

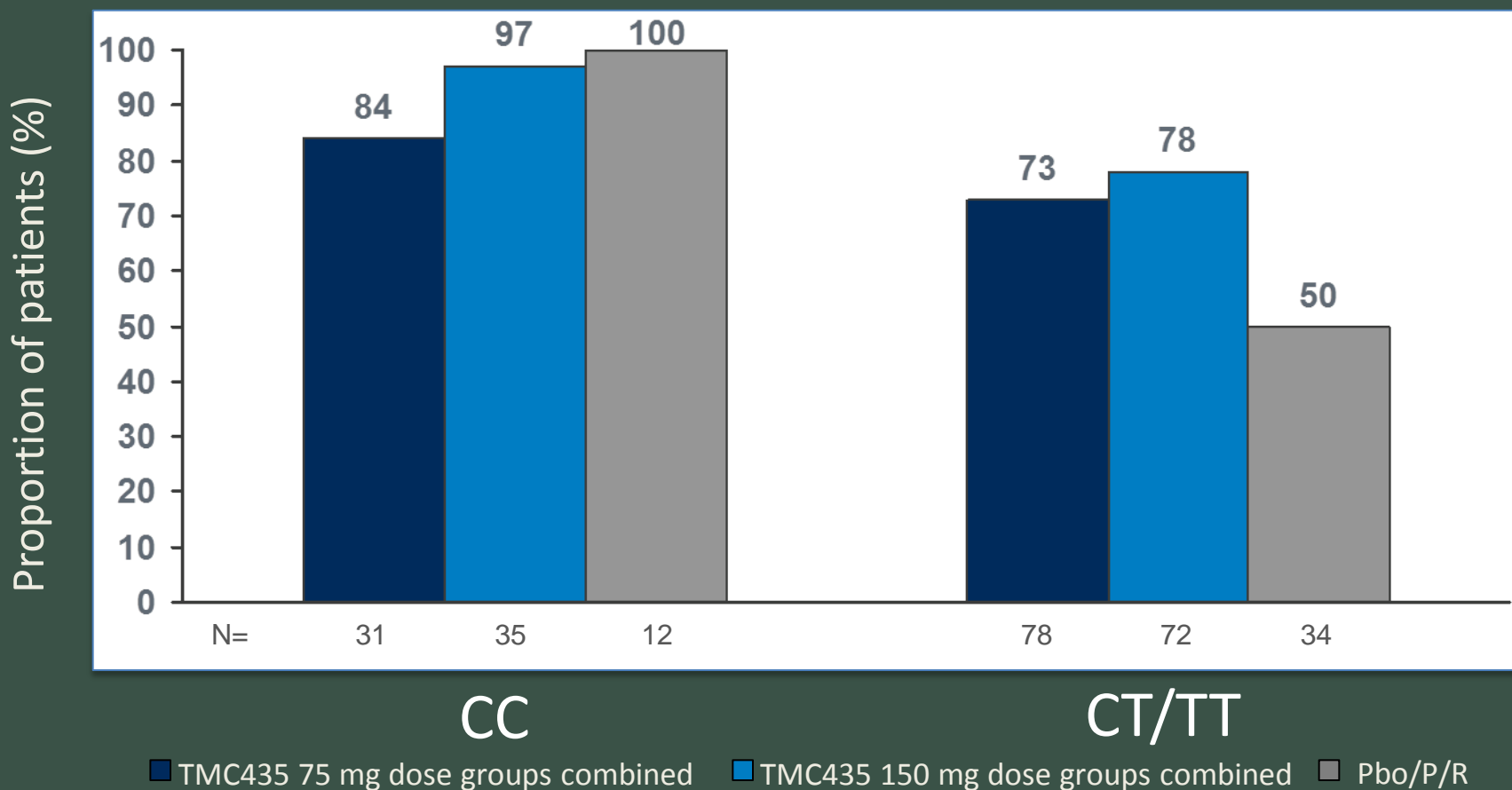
Proportion of Patients Achieving SVR24 by HCV Subtype and TMC435 dose (ITT)



\* TMC435 dose groups combined; ITT, intent-to-treat; P/R, peginterferon  $\alpha$ -2a + ribavirin; SVR, sustained virologic response

# PILLAR Study: SVR24 by *IL28B* Genotype

- In consenting patients (67.9%), distribution of *IL28B* genotype was 30% CC, 58% CT, and 12% TT



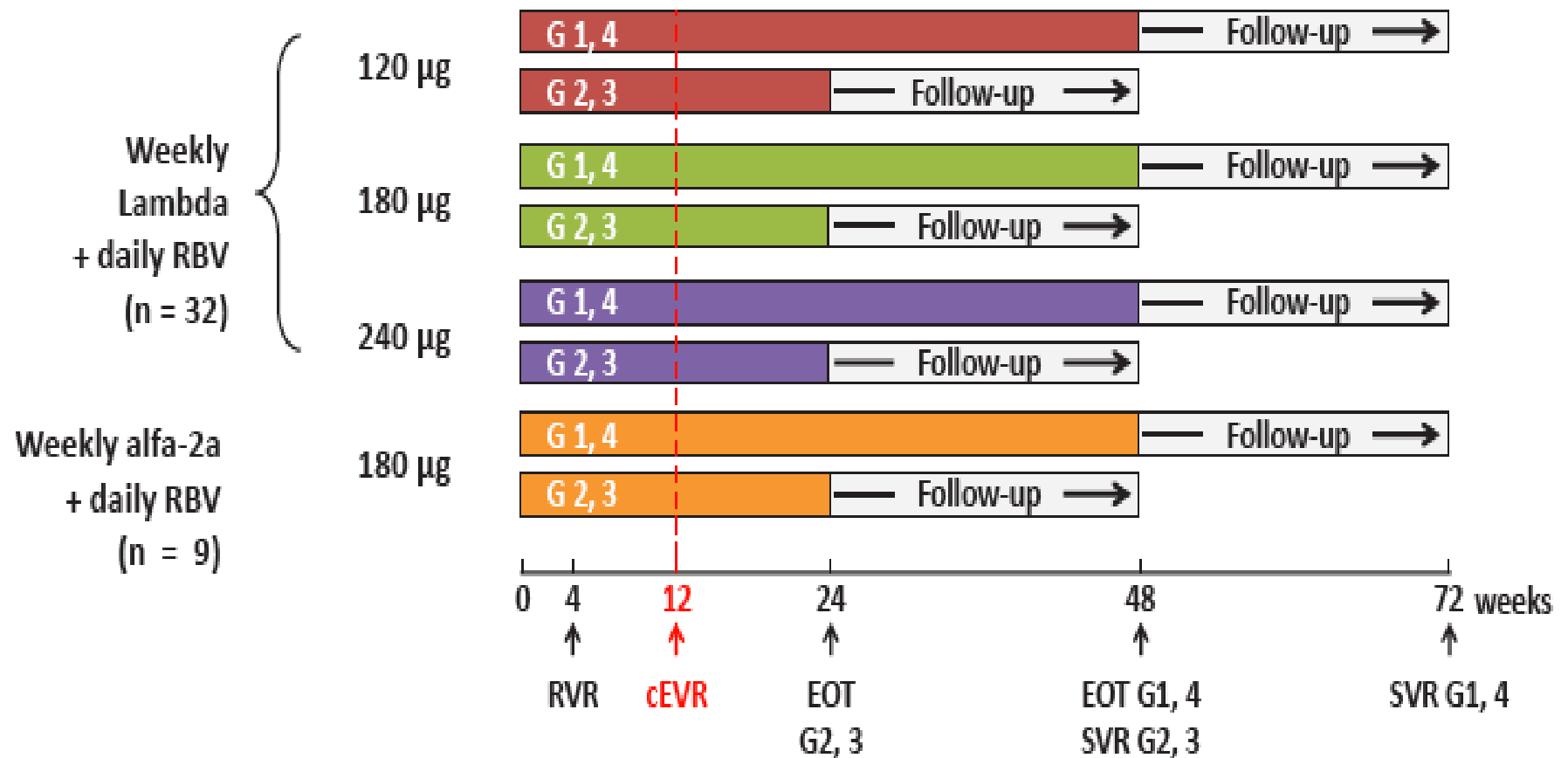
# Alpha, beta and now LAMBDA?

## BACKGROUND

- Current therapy of chronic hepatitis C virus (HCV) infection with the combination of pegylated interferon alfa (alfa) and ribavirin (RBV) is limited by hematologic toxicity, frequent adverse events, and suboptimal efficacy
- Interferon lambda is a type III interferon with many functional similarities to alfa interferons
- Peginterferon lambda-1a (Lambda) is currently under development for the treatment of chronic hepatitis C
  - Lambda exerts antiviral effects through a unique receptor with limited distribution outside the liver and is expected to have an improved profile vs alfa-2a
- The EMERGE study is an ongoing phase 2b study comparing the efficacy and safety of Lambda with alfa-2a, each combined with RBV, in treatment-naïve patients with chronic hepatitis C
- In 526 noncirrhotic patients, Lambda showed superior viral response vs alfa-2a through Week 12, with reduced cytopenias, arthralgias, myalgias, and flu-like symptoms, and fewer interferon and RBV dose reductions<sup>1</sup>
- Here we report safety and efficacy through Week 12 in cirrhotic patients

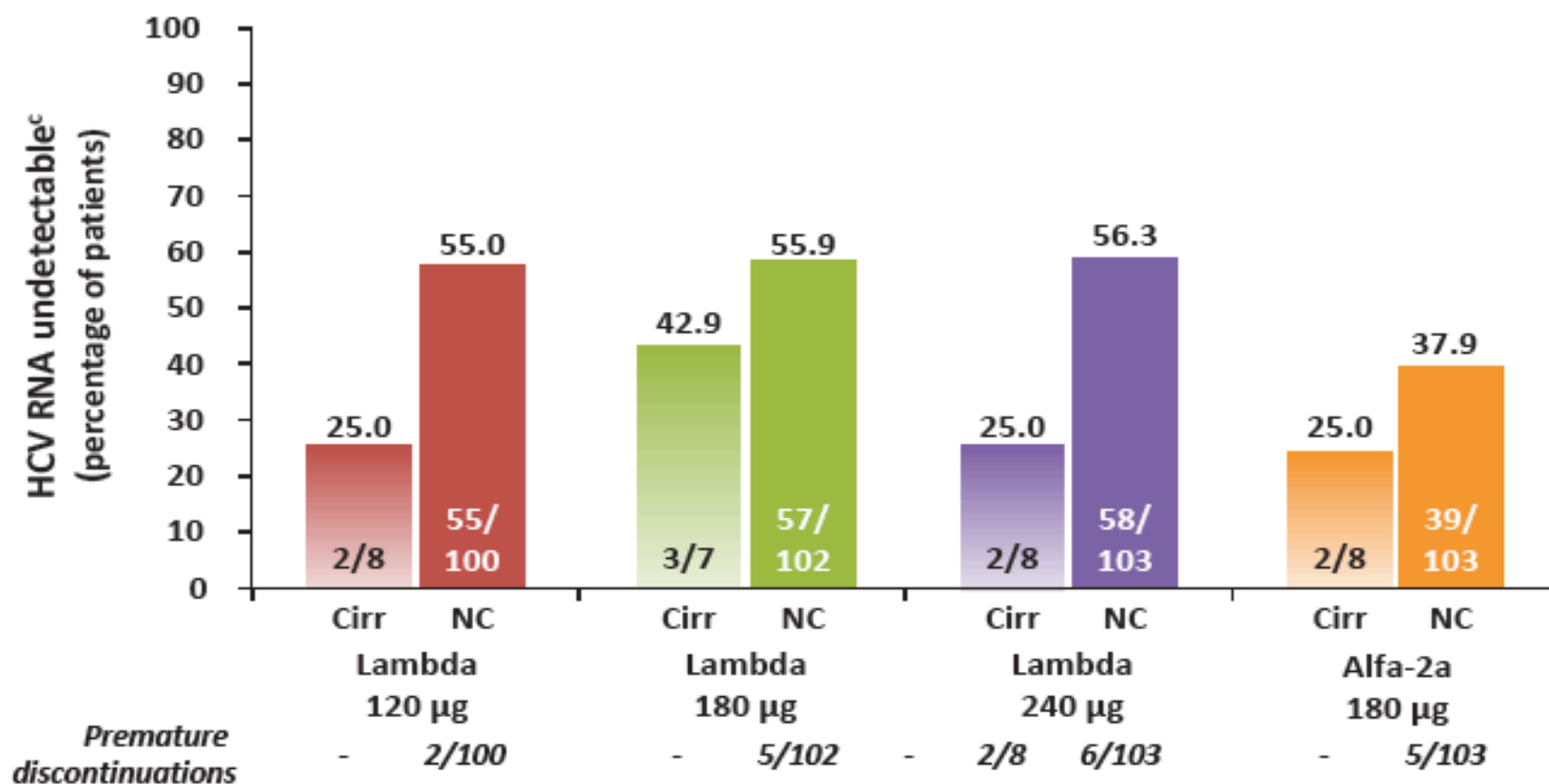
# METHODS

Figure 1. Study Design



cEVR, complete early virological response; EOT, end of treatment; G, genotype; RVR, rapid virological response; SVR, sustained virological response.

Figure 2. Undetectable HCV RNA at Week 12 (cEVR), Cirrhotics (Cirr) vs Noncirrhotics (NC)<sup>a</sup>, HCV G1/4<sup>b</sup> (mITT Analysis Set)

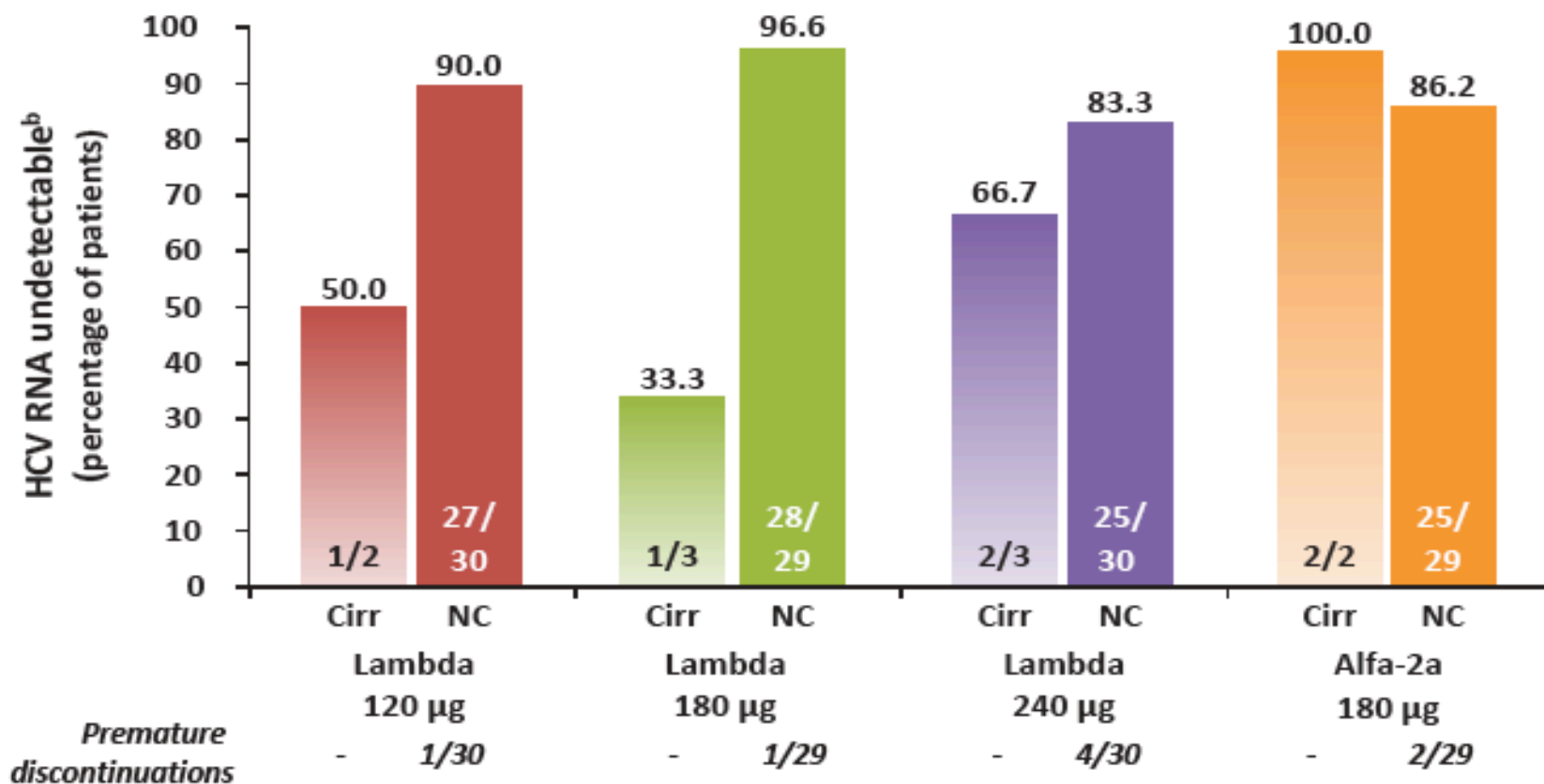


<sup>a</sup> Previously presented<sup>1</sup>.

<sup>b</sup> There were no patients with HCV G4 among patients with cirrhosis.

<sup>c</sup> HCV RNA not detected by Roche COBAS TaqMan HPS v2.0. Patients who discontinued treatment prior to Week 12 were classified as nonresponders.

Figure 3. Undetectable HCV RNA at Week 12 (cEVR), Cirrhotics (Cirr) vs Noncirrhotics (NC)<sup>a</sup>, HCV G2/3 (mITT Analysis Set)



<sup>a</sup> Previously presented<sup>1</sup>.

<sup>b</sup> HCV RNA not detected by Roche COBAS TaqMan HPS v2.0. Patients who discontinued treatment prior to Week 12 were classified as non-responders

**Table 5. Hematologic and Laboratory Abnormalities (Safety Analysis Set)**

Event, n (%)	Lambda				Alfa-2a
	120 µg n = 12	180 µg n = 10	240 µg n = 10	Total n = 32	180 µg n = 9
Hemoglobin < 10 g/dL and/or > 3.5 g/dL decline from baseline	0	2 (20.0)	3 (30.0)	5 (15.6)	7 (77.8)
Neutrophils < 1000/mm <sup>3</sup>	0	0	0	0	6 (66.6)
Platelets < 50,000/mm <sup>3</sup>	0	0	0	0	5 (55.6)
AST or ALT > 5 xULN	0	0	2 (20.0)	2 (6.3)	0
Direct bilirubin > 1.2 mg/dL	1 (8.3)	0	3 (30.0)	4 (12.5)	0

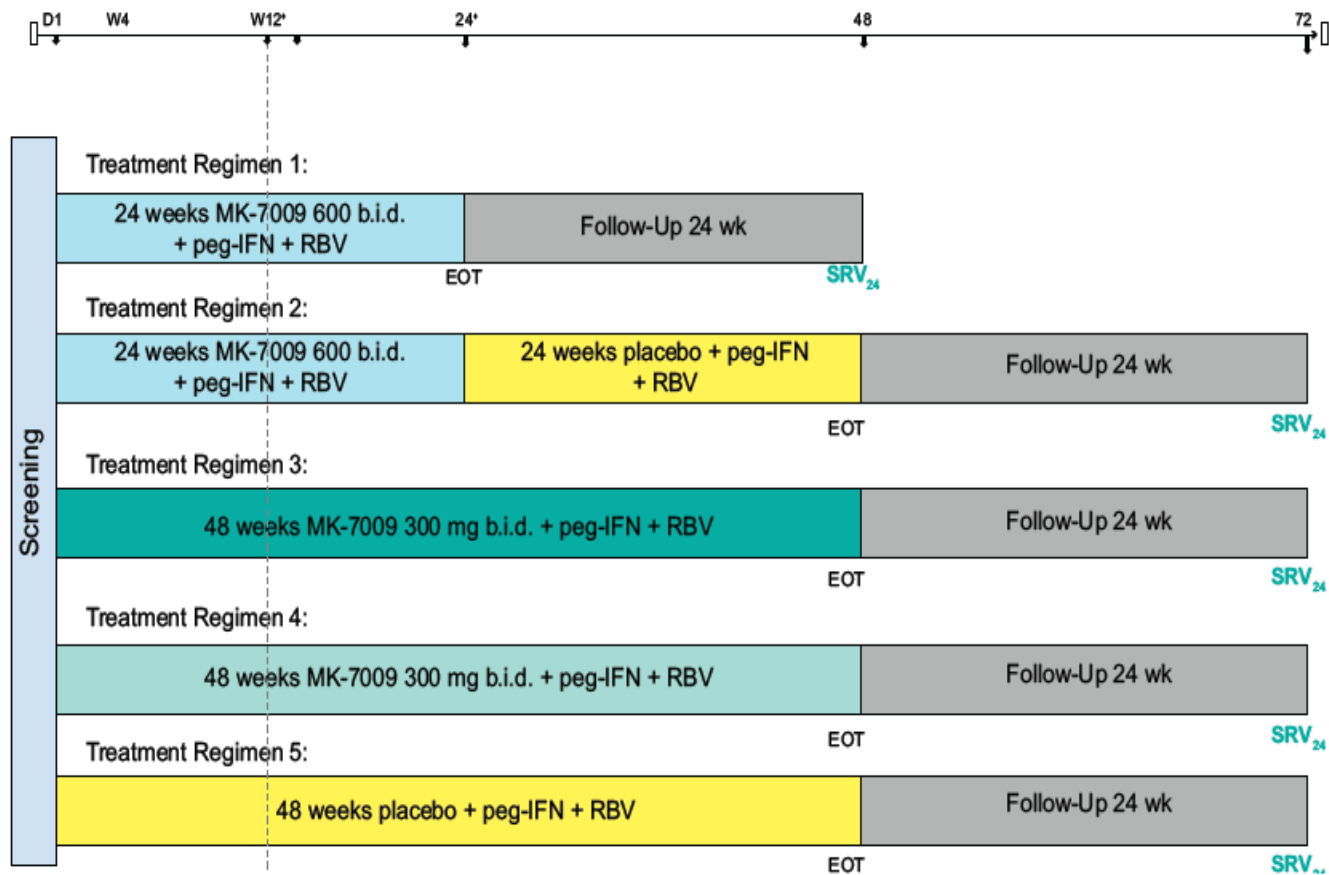
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

- Adverse events occurring in  $\geq 10\%$  of patients receiving Lambda (Table 3) were mostly low grade, self-limited, and unrelated to dose
- Dose reductions (both interferon and RBV) were more frequent in the alfa-2a group than in the Lambda groups (Table 4)
- Lambda was associated with fewer hematological abnormalities than alfa-2a (Table 5)
- ALT/AST and/or direct bilirubin rises were most frequent in patients receiving 240 µg Lambda (Table 5)
  - All resolved without sequelae after interferon dose modification and/or discontinuation

## Background

- MK-7009 (vaniprevir) is a non-covalent competitive inhibitor of the hepatitis C virus (HCV) NS3/4A protease
- MK-7009 has demonstrated safety and efficacy when administered as monotherapy for 8 days<sup>1</sup> and in combination with pegylated interferon (peg-IFN) and ribavirin (RBV) for 4 weeks in a global treatment naïve (TN) study<sup>2</sup> and a Japan study with patients who have relapsed<sup>3</sup>
- This poster presents the primary analysis results (safety and sustained viral response) of a Phase 2b study of MK-7009 given in combination with peginterferon alfa2a 180 µg weekly and RBV 1000-1200 mg/day for 24 to 48 weeks to non-cirrhotic patients who have failed previous peg-IFN and RBV treatment

# Study Design



# SVR 24 rate 40-100% depending on previous treatment response

## Conclusions

- MK-7009 when combined with Peg-IFN and RBV achieves significant improvement in SVR compared to Peg-IFN and RBV control in this population of GT 1 experienced patients and compares favorably with other first generation Protease Inhibitors
- Resistance associated amino acid variants (RAVs) were predominantly observed at positions R155, A156 and/or D168 in non-SVR patients
- MK-7009 at 300 mg b.i.d. and 600 mg b.i.d. is generally well tolerated for use for up to 48 weeks of therapy
- Patients in MK-7009 regimens had higher rates of gastrointestinal (GI) adverse events (AEs) as compared to control. Most GI AEs were mild to moderate
- There were no significant differences in rates of anemia and rash between the MK-7009 regimens and control
- The development of MK-7009 has advanced to Phase 3 in Japan

## Next steps?

- Oct 24 2011 Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the initiation of a Phase 3b study called CONCISE that will evaluate the potential for treatment with INCIVEK (telaprevir) combination therapy to be shortened to 12 weeks in people with genotype 1 chronic hepatitis C who have the 'CC' variation near the IL28B gene. INCIVEK (in-SEE-veck) is administered in combination with pegylated-interferon and ribavirin.

# DAA's in Combination with PEG-IFN/RBV in HCV Treatment

- Helpful data prior to initiating treatment :
  - HCV genotype 1a/1b vs other genotypes
  - Quantitative viral level
  - IL-28 genotype (treatment naïve)
  - Previous viral kinetics if non-responder
    - IL-28 not as helpful with accurate viral kinetics
  - Fibrosis assessment
  - CBC/Platelets (cirrhotics), CMP (creatinine)
  - Bilirubin
  - Concomitant medicines/Drug-Drug interaction query
  - Management plan for side effects
    - Rash, anemia, GI side effects
      - Identify Dermatologist

## What we need for v2.2

- No GI side effects
- No hyperbilirubinemia
- No Boosting

