CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

Updates on Current Status of HCV Therapy

K. Rajender Reddy, MD

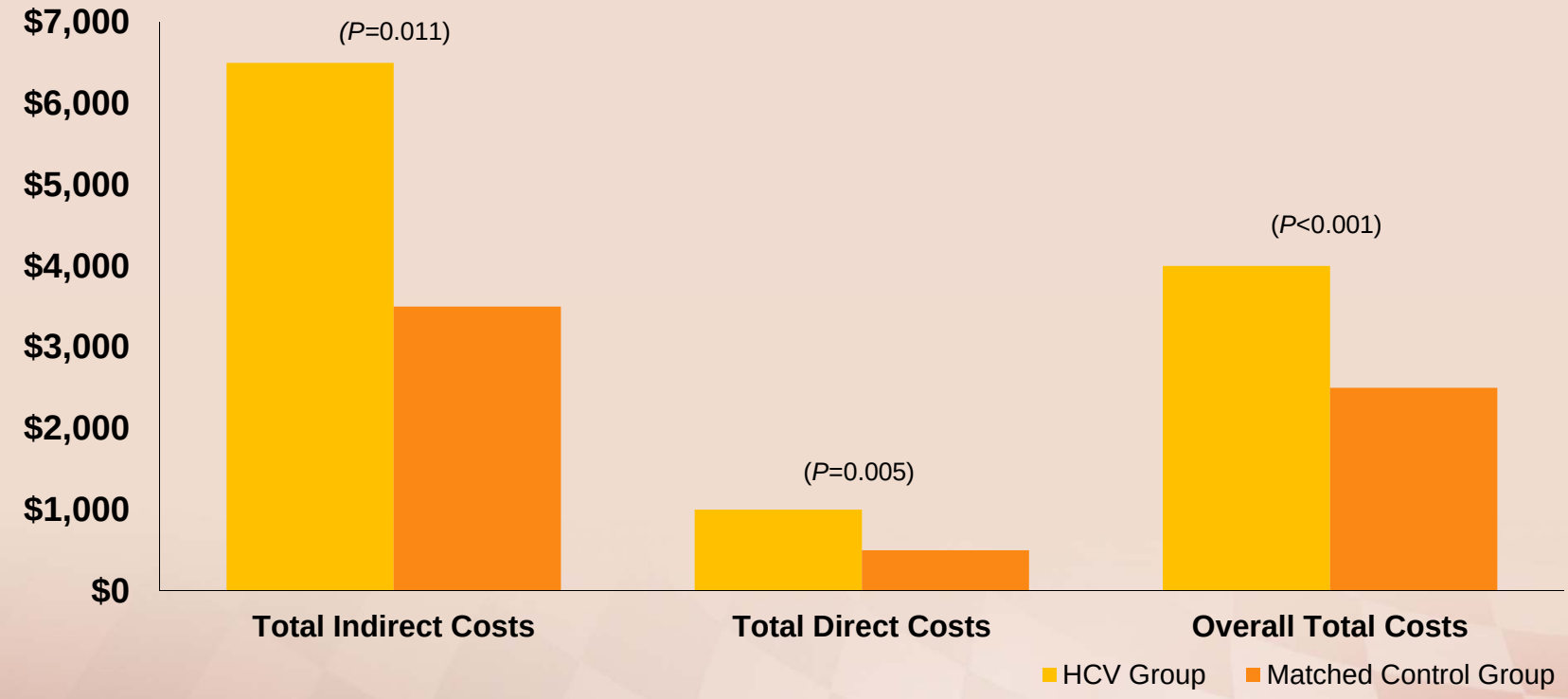
Professor of Medicine, Professor of Medicine in Surgery,
Director of Hepatology
Medical Director of Liver Transplantation
University of Pennsylvania
Philadelphia, Pennsylvania

Burden of Illness in Treatment Naïve Hepatitis C (HCV) Patients in the EU

- Background:
  - This study assessed productivity loss, healthcare resource utilization, and health related quality of life (HRQoL) in treatment naive HCV patients in the EU.
- Methods:
  - Adult subjects without HBV or HIV infection in the 2010 wave of the EU National Health and Wellness Survey, conducted by Kantar Health, were analyzed.
  - 57,172 survey respondents, 139 reported HCV infection, 139 matched controls
  - Propensity score was used to match untreated physician diagnosed HCV patients with individuals without HCV.
  - work productivity [percentage of work time missed (absenteeism) and percentage of impairment experienced while at work (presenteeism) because of one´s health in past seven days] and activity impairment; indirect costs [annual lost wages due to absenteeism and presenteeism]; healthcare resource utilization [outpatient and ER visits, hospitalization in past 6 months]; and HRQoL [MOS-SF12v2 based Physical and Mental Component Summary (PCS and MCS), and Health Utility score].

El Khoury AC et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 886.

Estimated costs in untreated HCV infected patients and matched subjects without HCV infection



- Average direct costs are reported for all patients (n=139); Average indirect costs are reported for only employed respondents (65 HCV infected patients and 65 matched controls); Indirect costs for unemployed respondents are included as zero for the calculation of overall total costs; p values based on Mann-Whitney U test.

Lower PCS 44 Vs.46 P=0.048 . Trends in poorer MCS and not statistically siginficant

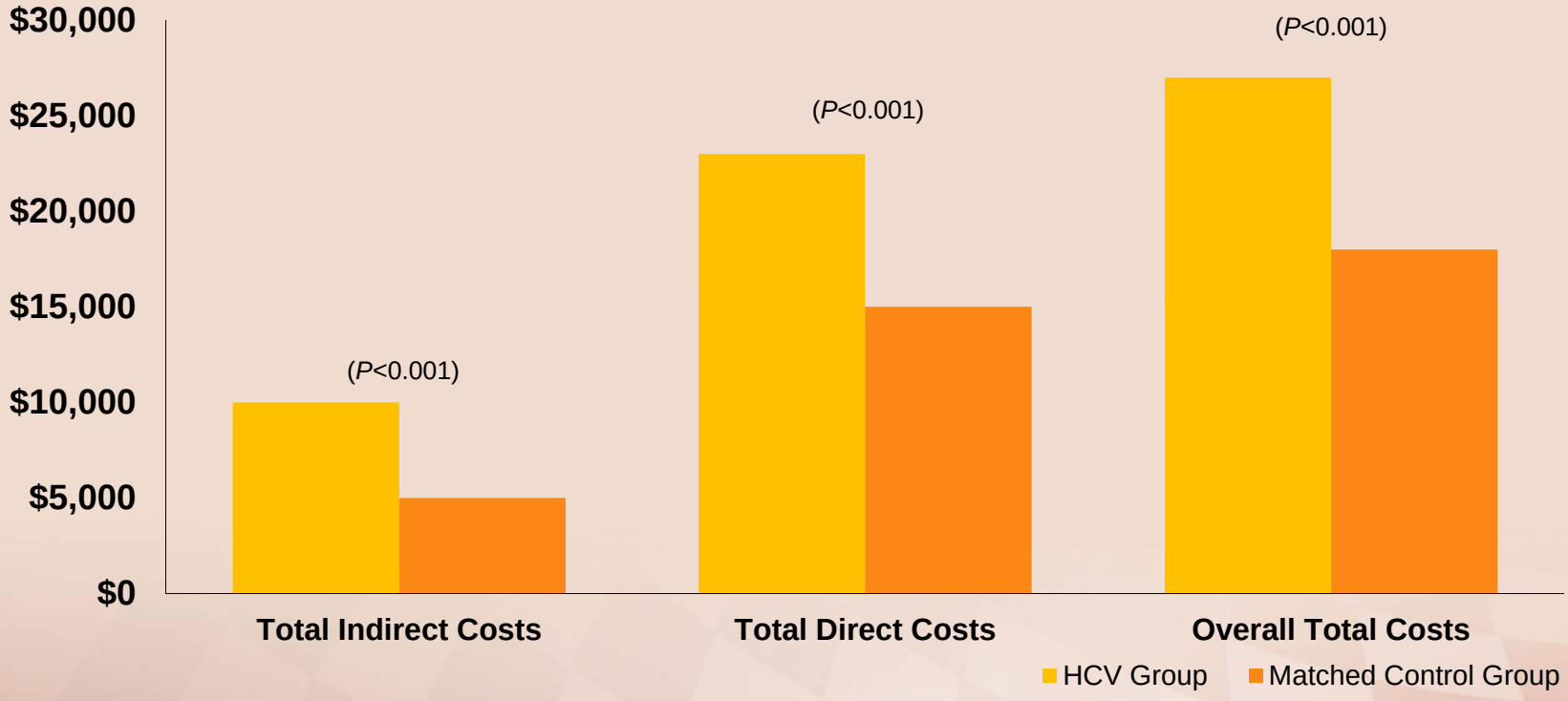
El Khoury AC et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 886.

Burden of Illness in Treatment Naïve Hepatitis C (HCV) Patients in the US

- Background:
  - The objective of study was to assess productivity loss, healthcare resource utilization, and health related quality of life (HRQoL) in treatment naive HCV patients in the US.
- Methods:
  - Data were analyzed from 2010 wave of US National Health and Wellness Survey (NHWS) conducted by Kantar Health.
  - 74,149 eligible subjects in database, 306 treatment naïve HCV and 306 matched non-HCV controls
  - Among patients´ ≥18 years without HBV or HIV infection, treatment naïve HCV patients were matched using propensity score matching methodology with those without HCV.
  - Work productivity [percentage of work time missed (absenteeism) and percentage of impairment experienced while at work (presenteeism) because of one´s health in past seven days] and activity impairment; indirect costs [annual lost wages due to absenteeism and presenteeism]; healthcare resource utilization [outpatient and ER visits, hospitalization] and related direct costs; and HRQoL [Medical Outcomes Study 12-Item Short Form Survey based Physical and Mental Component Summary (PCS and MCS), and Health Utility score].

El Khoury AC et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 887.

Estimated costs in untreated HCV infected patients and matched subjects without HCV infection



- Average direct costs are reported for all patients (n=306); Average indirect costs are reported for only employed respondents (121 HCV infected patients and 141 matched controls); Indirect costs for unemployed respondents are included as zero for the calculation of overall total costs; *P* values based on Mann-Whitney U test.

El Khoury AC et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 887.

Prospective Multisite Randomized Trial of Integrated Care (IC) vs.Usual Care (UC) for Improving Access to anti-viral Therapy for High Risk Patients with chronic HCV

- Three VA Hospitals
  (San Diego, CA, Bronx, NY, Palo Alto, CA)
- Patients attending HCV Clinics between 5/2009-2/2011
- Screened with routine psychiatric and substance abuse instruments
- Mid level mental health practitioner placed in each clinic and provided mental health interventions and case management according to an IC protocol

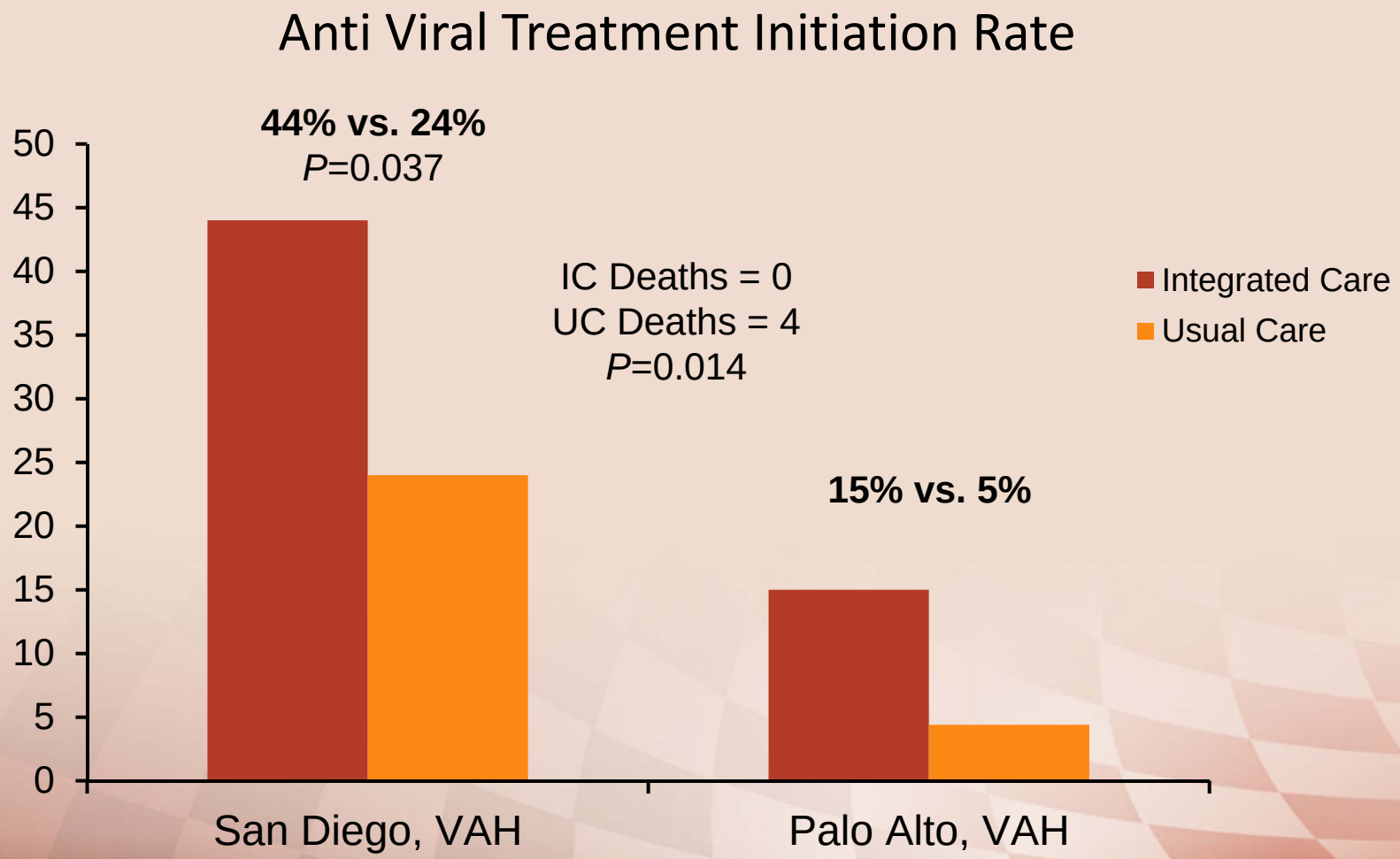
Ho SB et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 988.

IC vs. UC Study: Study Design

- 1752 screened; 763 (43%) were “high risk” screen positive and eligible for antiviral treatment
- 358 randomized to IC or UC
- 63% non-white (39% African-American, 18% Hispanic); 51% homeless in prior 5 years
- 80% genotype 1; 28% active alcohol use; 31% active major depression
- Mean follow up of 16 months-increase in number of patients that initiated anti-viral treatment 26.9% (49/182) IC vs. 15.4% (28/182) (15.4%) for UC (*P*=0.01)

Ho SB et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 988.

IC vs. UC Study: Anti Viral Treatment Initiation Rate



Ho SB et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 988.

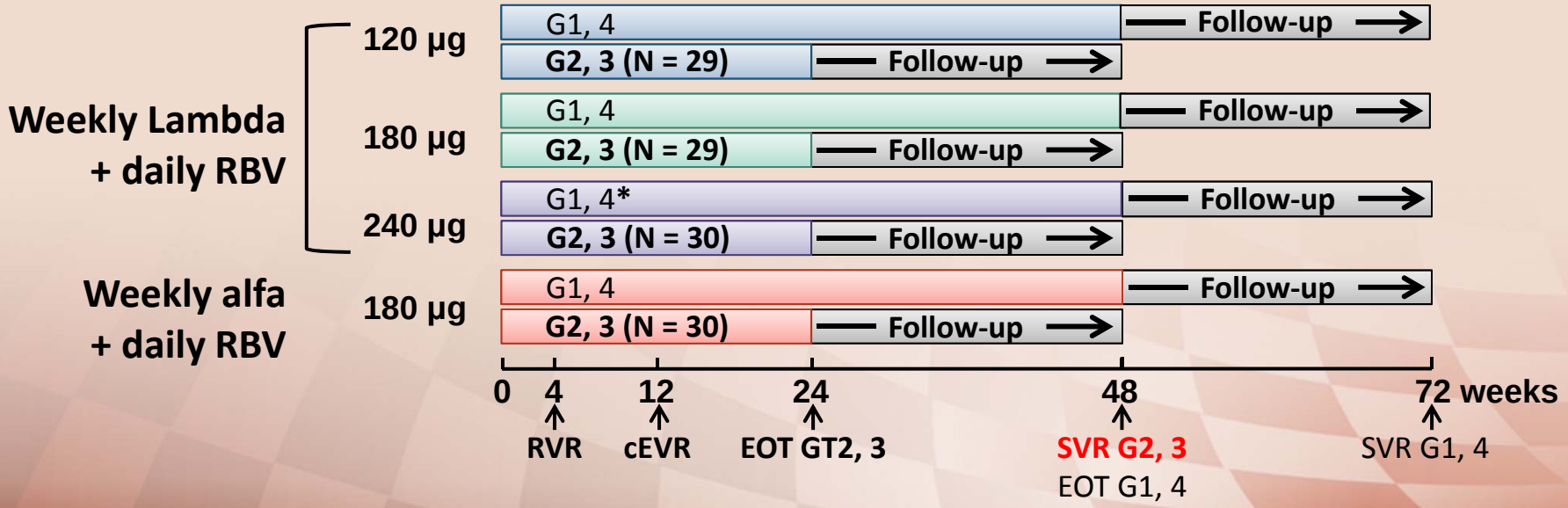
Peginterferon lambda-1a(Lambda) in HCV: EMERGE Phase IIB Results

- Peginterferon lambda-1a (Lambda) is a type III interferon with marked anti-HCV activity, and a restricted distribution of tissue receptors
- The EMERGE study is an ongoing phase 2b study comparing the efficacy and safety of Lambda with peginterferon alfa-2a (alfa), each combined with RBV, in treatment-naive patients with chronic hepatitis C
- Results through Week 48 (24 weeks following completion of treatment) in patients with HCV genotypes (G) 2 or 3 were reported at the meeting

Zeuzem S et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1435.

EMERGE Study: Study Design

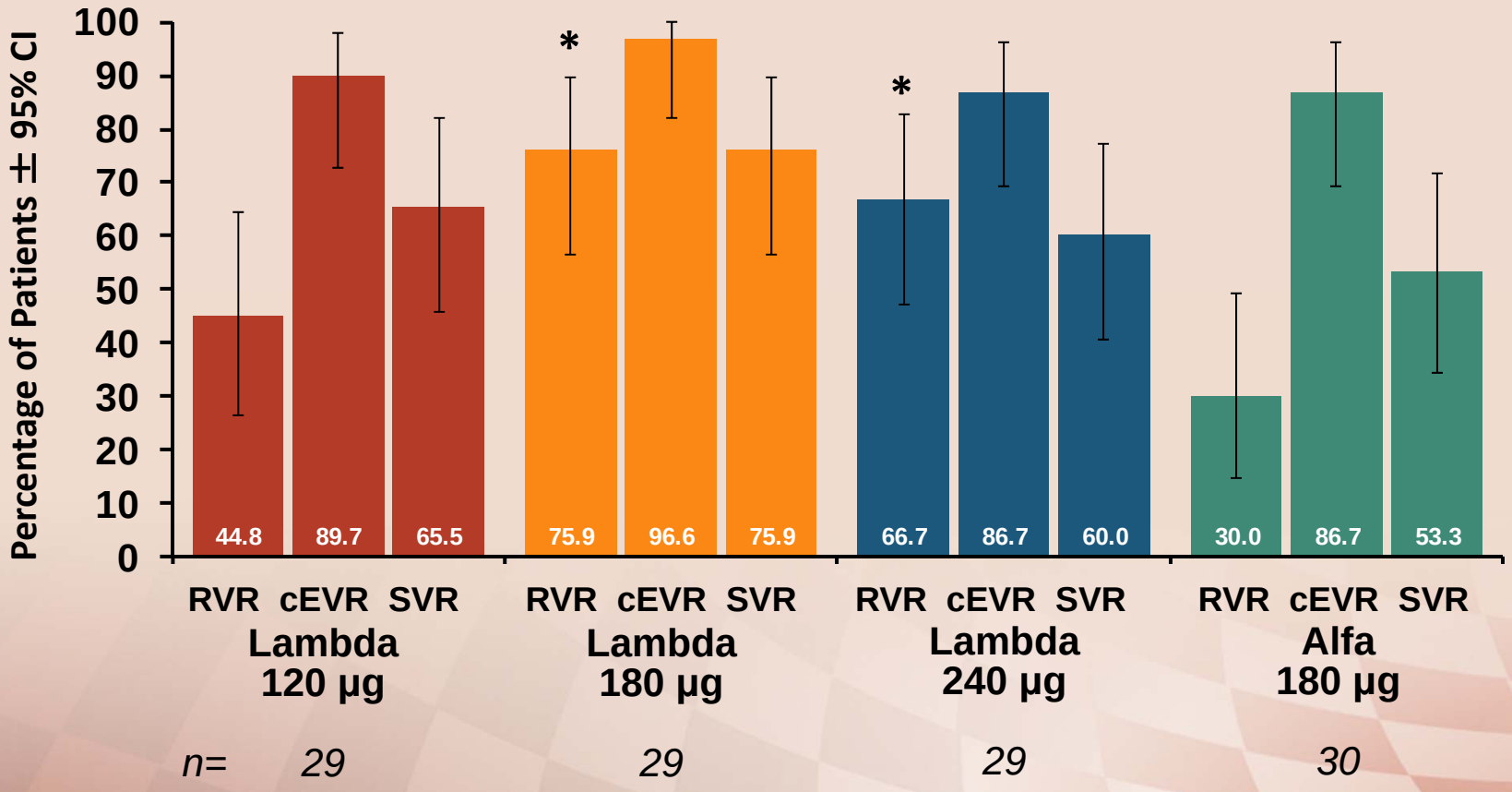
- Blinded and randomized study of 526 noncirrhotic treatment-naive adults aged 18–70 years
- 118 chronically infected with HCV G2 or G3
- HCV RNA ≥ 100,000 IU/mL
- HCV RNA assessed
- On-treatment at Weeks 4 (RVR), 12 (cEVR), 24 (EOT)
- Post-treatment at Weeks 28 (SVR4), 32 (SVR12), 48 (SVR24)
- Virologic response defined as HCV RNA undetectable with Roche COBAS® TaqMan® HCV Test v2.0
- Safety assessed through Week 48



* G1, 4 240 µg dose reduced to 180 µg (April 2011); G2, 3 patients unaffected.

Zeuzem S et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1435.

EMERGE Study: Undetectable HCV RNA at Week 4 (RVR), Week 12 (cEVR), and Week 48 (SVR_{24})



* *P*<0.05 vs alfa

Zeuzem S et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1435.

EMERGE Study: Adverse Events (Any Grade) Occurring in ≥ 20% of Patients in Any Treatment Group

	Lambda			alfa
Preferred Term	**120 µg (N=29)**	**180 µg (N=29)**	**240 µg (N=30)**	**180 µg (N=30)**
AE (any grade), %	96.6	**96.6**	93.3	96.7
Fatigue	41.4	**27.6**	50	53.3
Nausea	44.8	**27.6**	60	36.7
Headache	24.1	**20.7**	23.3	33.3
Myalgia	17.2	**10.3**	10	33.3
Arthralgia	10.3	**13.8**	10	33.3
Pyrexia	10.3	**17.2**	20	23.3
Insomnia	27.6	**27.6**	30	20
Chills	3.4	**6.9**	0	20
Irritability	13.8	**27.6**	13.3	13.3
Pruritus	27.6	**20.7**	26.7	10
Rash	10.3	**6.9**	20	6.7

Zeuzem S et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1435.

EMERGE Study: Treatment-Emergent Liver-Related Laboratory Abnormalities

		Lambda			Alfa
Lab Toxicity	**Severity**	**120 µg (N=29)**	**180 µg (N=29)**	**240 µg (N=30)**	**180 µg (N=30)**
ALT and/or AST high, %	> 5.0–10 × ULN	3.4	**6.9**	13.3	**13.3**
	> 10 × ULN	0	**0**	3.3	**0**
Total bilirubin high, %	1.6–2.5 × ULN	10.3	**3.4**	16.7	**6.9**
	2.6–5.0 × ULN	6.9	**0**	0	**0**
	> 5.0 × ULN	0	**0**	6.7	**0**
PegIFN dose reductions due to liver-related lab abnormality, %		0	**3.4**	6.7	**0**
PegIFN discontinuations due to liver-related lab abnormality, % - Both due to elevated bilirubin - Neither met criteria for pDILI[a] - Both resolved following DC		3.4	**0**	3.3	**0**

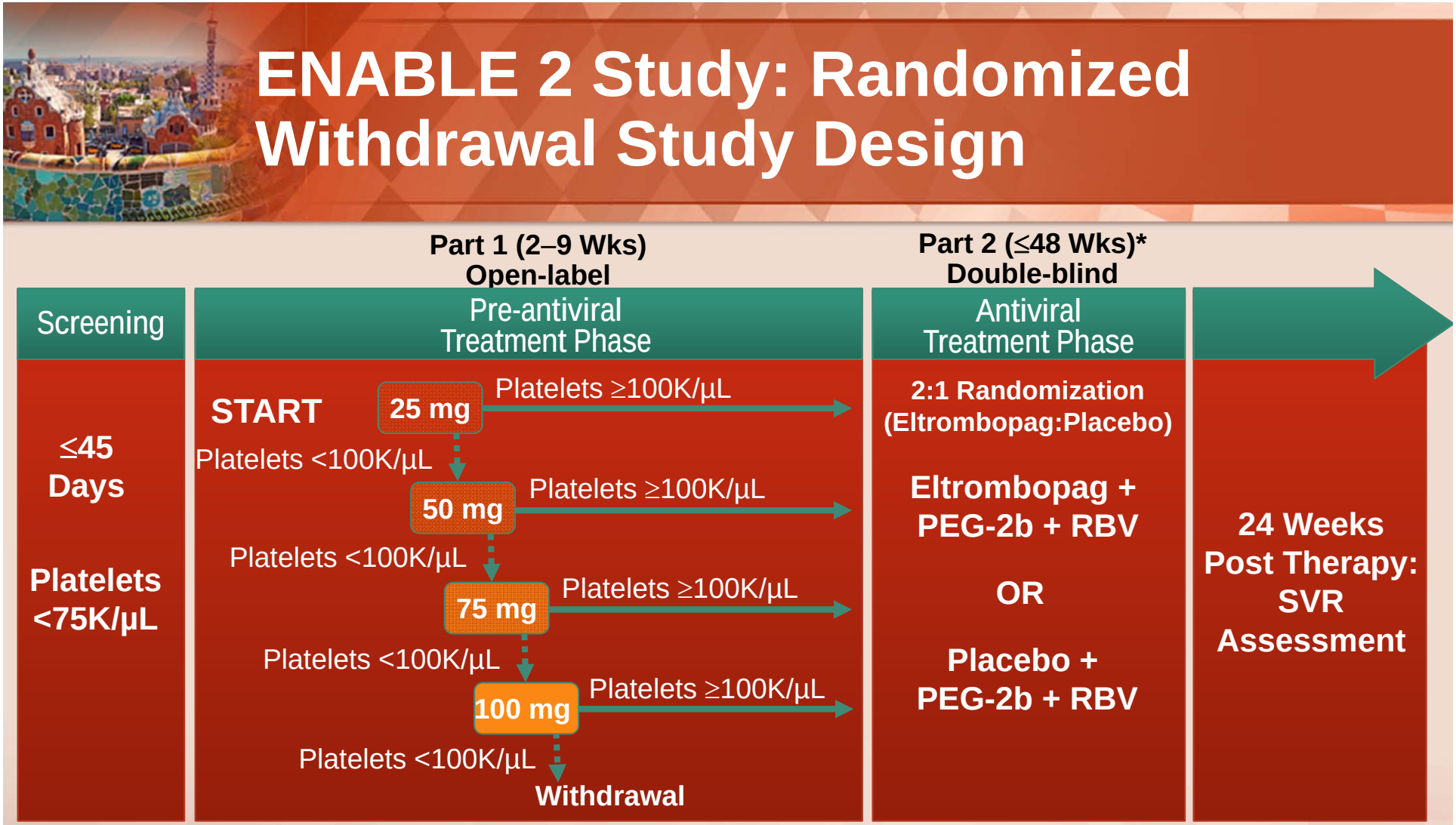
Zeuzem S et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1435.

EMERGE Study: Conclusions

At the 180-µg dose selected for phase 3, Lambda compared with Alfa was associated with:	
Efficacy	• Numerically greater SVR_{24} rate in patients with HCV G2, 3
	• More rapid time to virologic response
	• Suggestion of more favorable response in the more difficult-to-treat HCV G3 patients
Safety	• Reduced RBV and IFN dose-reduction rate
	• Less fatigue and few musculoskeletal and flu-like symptoms
	• Fewer hematologic abnormalities
	• Less elevation of ALT

Zeuzem S et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1435.

ENABLE 2 Study: Randomized Withdrawal Study Design

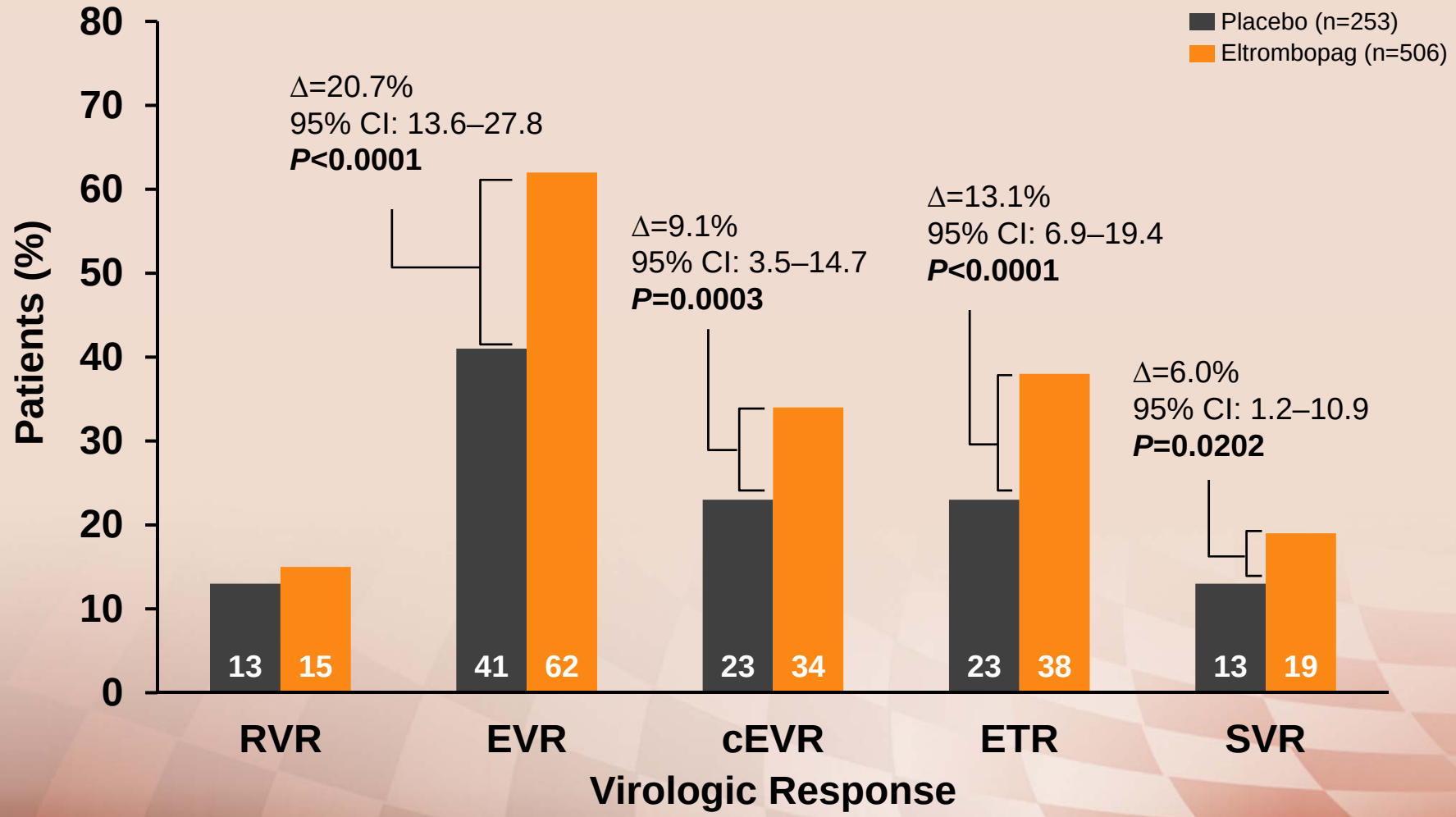


- Growth factor support allowed for anemia and neutropenia
- PEG-2b reduced or discontinued for TCP
- Eltrombopag/matched placebo could be titrated during Part 2 to maintain platelets 100K–200K/µL

*24 weeks if HCV genotype 2/3, otherwise 48 weeks.

Dusheiko G et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 279.

ENABLE 2 Study: Virologic Responses (ITT)



Dusheiko G et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 279.

ENABLE 2 Study: Adverse Events of Special Interest

AE Type, No. of Patients (%)*	Placebo (n=252)	Eltrombopag (n=506)
Thromboembolic	1 (<1)	20 (4)
Portal vein thrombosis	0	7 (2)
Hepatobiliary		
Events suggestive of progressive liver disease**	20 (8)	74 (15)
ALT >3x ULN	49(19)	76 (15)
Malignancies***		
Hepatocellular carcinoma	11 (4)	28 (6)
Other	1 (<1)	3 (<1)
Non-variceal bleeding	45 (18)	80 (16)
Ocular		
AEs	30 (12)	74 (15)
Progression of pre-existing cataract***	8 (3)	15 (3)
Incident cataract***	8 (3)	21 (4)

*Double-blind safety population. AEs on treatment + 30 days follow-up are reported except as noted.
**Events include ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis, hepatocellular carcinoma, and death.
**On treatment + 6 months follow-up.

Dusheiko G et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 279.

ENABLE 2 Study: Conclusions

- Eltrombopag elevated platelet counts to a level enabling introduction of antiviral therapy in 94% of patients
- Eltrombopag group showed statistically significant and clinically meaningful improvement in SVR vs placebo
  - Probably by delaying and reducing the number of PEG-2b dose reductions, particularly in the early phase of treatment
- Unexplained higher rate of thromboembolic events in the eltrombopag arm (vs ENABLE 1)
  - Requires evaluation of risk-benefit in patients at risk of disease progression
- SVR rates remain constrained by lack of interferon efficacy in patients with advanced disease

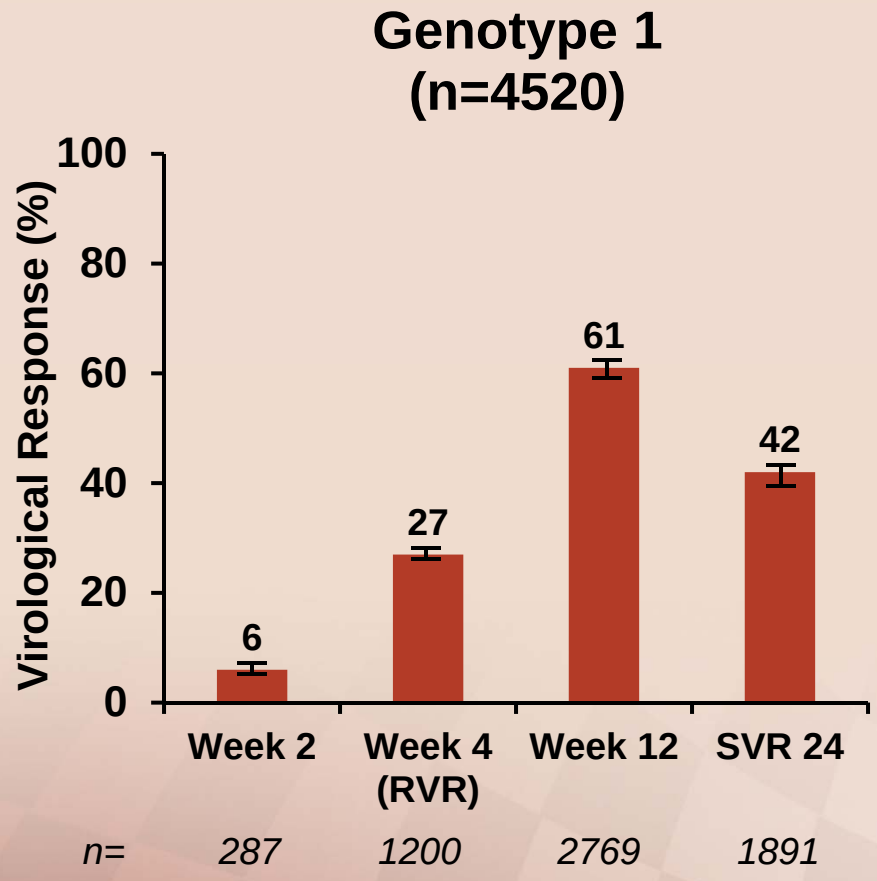
Dusheiko G et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 279.

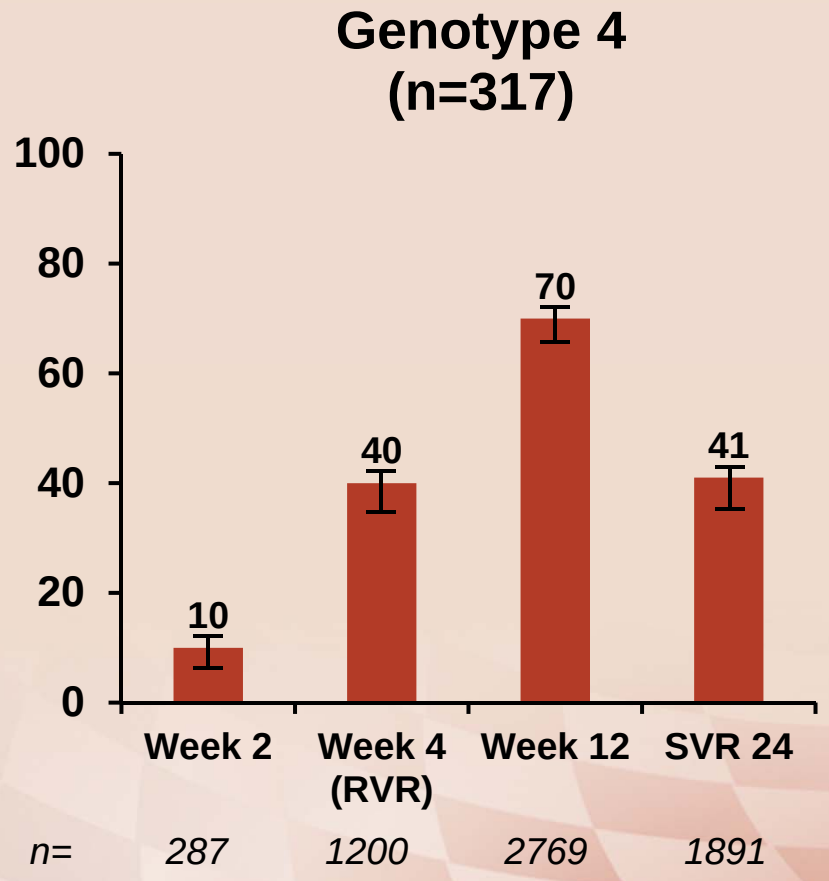
PROPHESYS Study: Worldwide Study Sites

Europe	North/South America	Africa
Austria, Belgium	Brazil	Morocco
Croatia, France	Canada	
Hungary, Ireland	Mexico	
Italy, Macedonia	USA	
Poland, Romania		
Serbia, Slovenia		
Sweden		
United Kingdom		

Marcellin P et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 73

PROPHESYS Study: Virological Response Varied by Genotype: G1 and G4

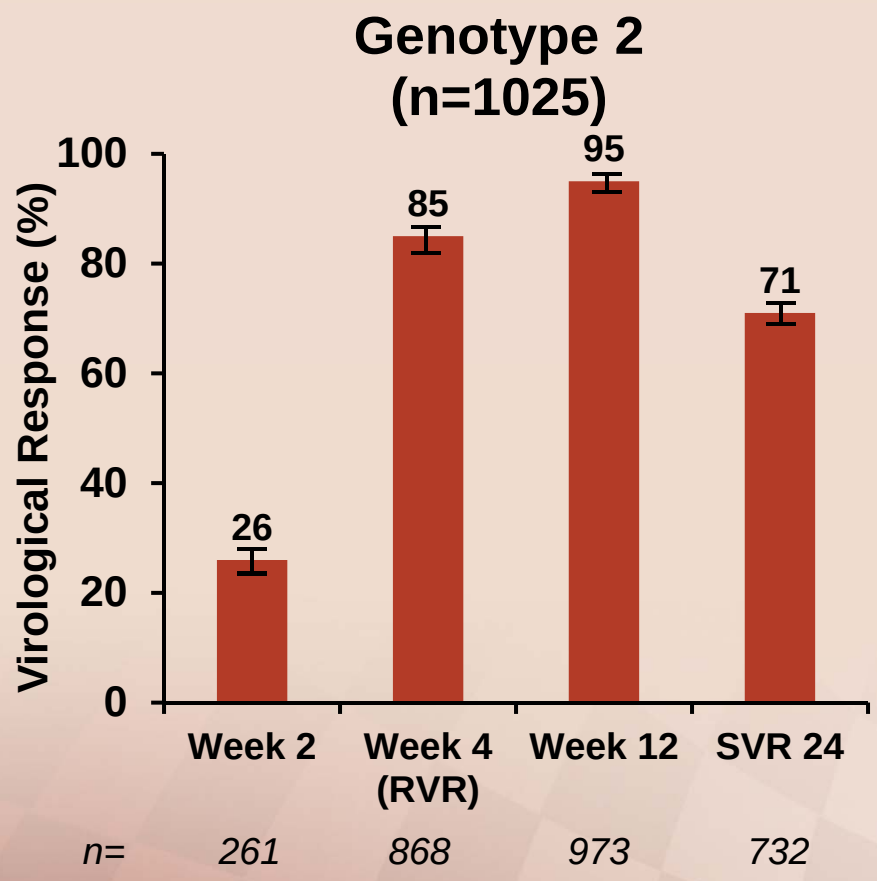


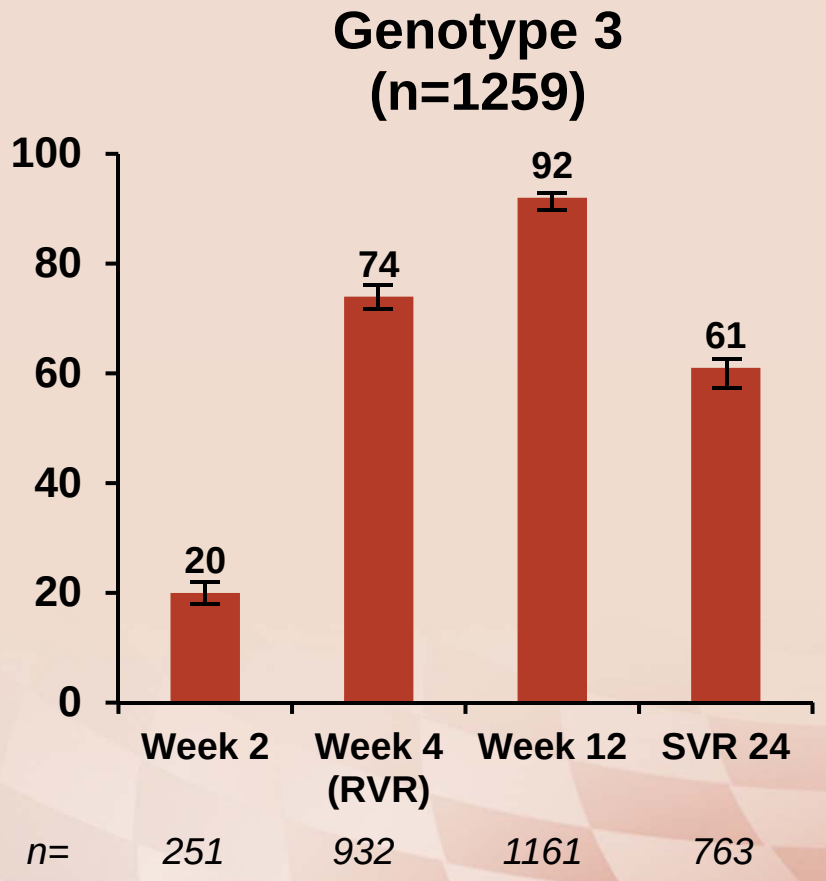


The error bars correspond to the 95% confidence intervals
Virological response defined as: HCV RNA <50 IU/mL

Marcellin P et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 73

PROPHESYS Study: Virological Response Varied by Genotype: G2 and G3





The error bars correspond to the 95% confidence intervals
Virological response defined as: HCV RNA <50 IU/mL

Marcellin P et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 73

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

Discussion

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

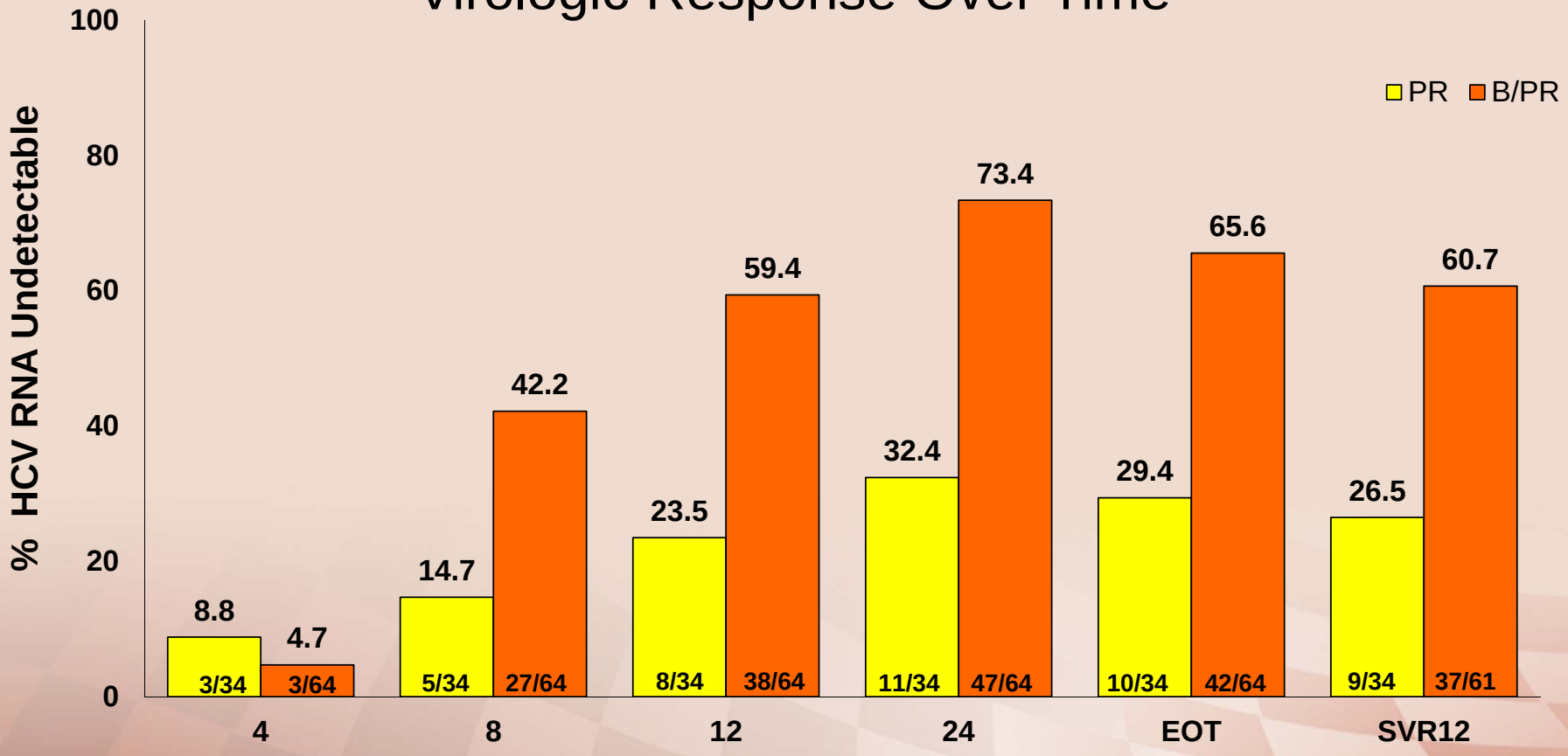
Boceprevir and Telaprevir

Fred Poordad, MD

Chief, Hepatology
Cedars-Sinai Medical Center
Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

BOCEPREVIR PLUS PEGINTERFERON/RIBAVIRIN FOR THE TREATMENT OF HCV/HIV CO-INFECTED PATIENTS: END OF TREATMENT (WEEK 48) INTERIM RESULTS

Virologic Response Over Time†

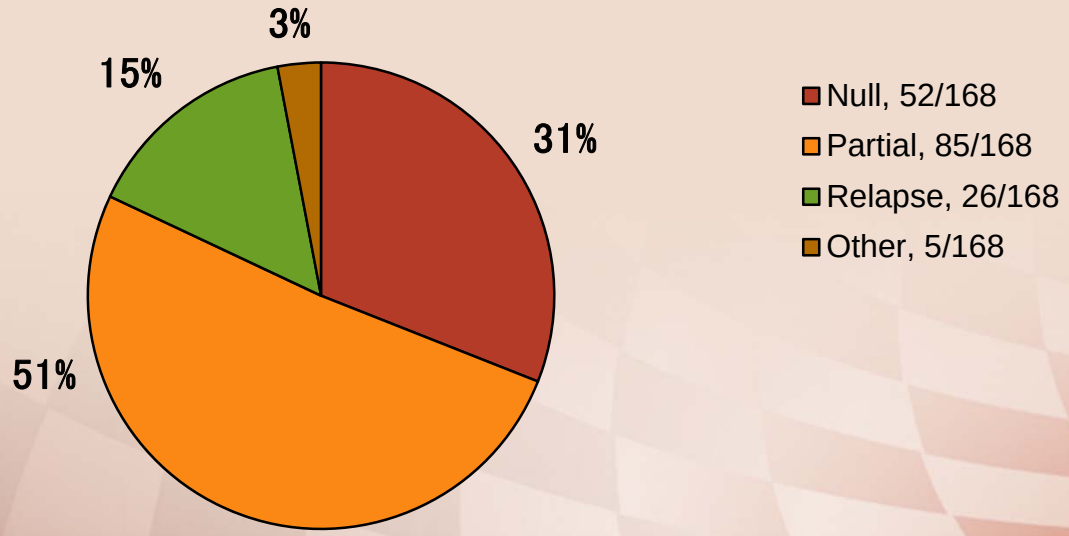


† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

Mollolas J, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 50.

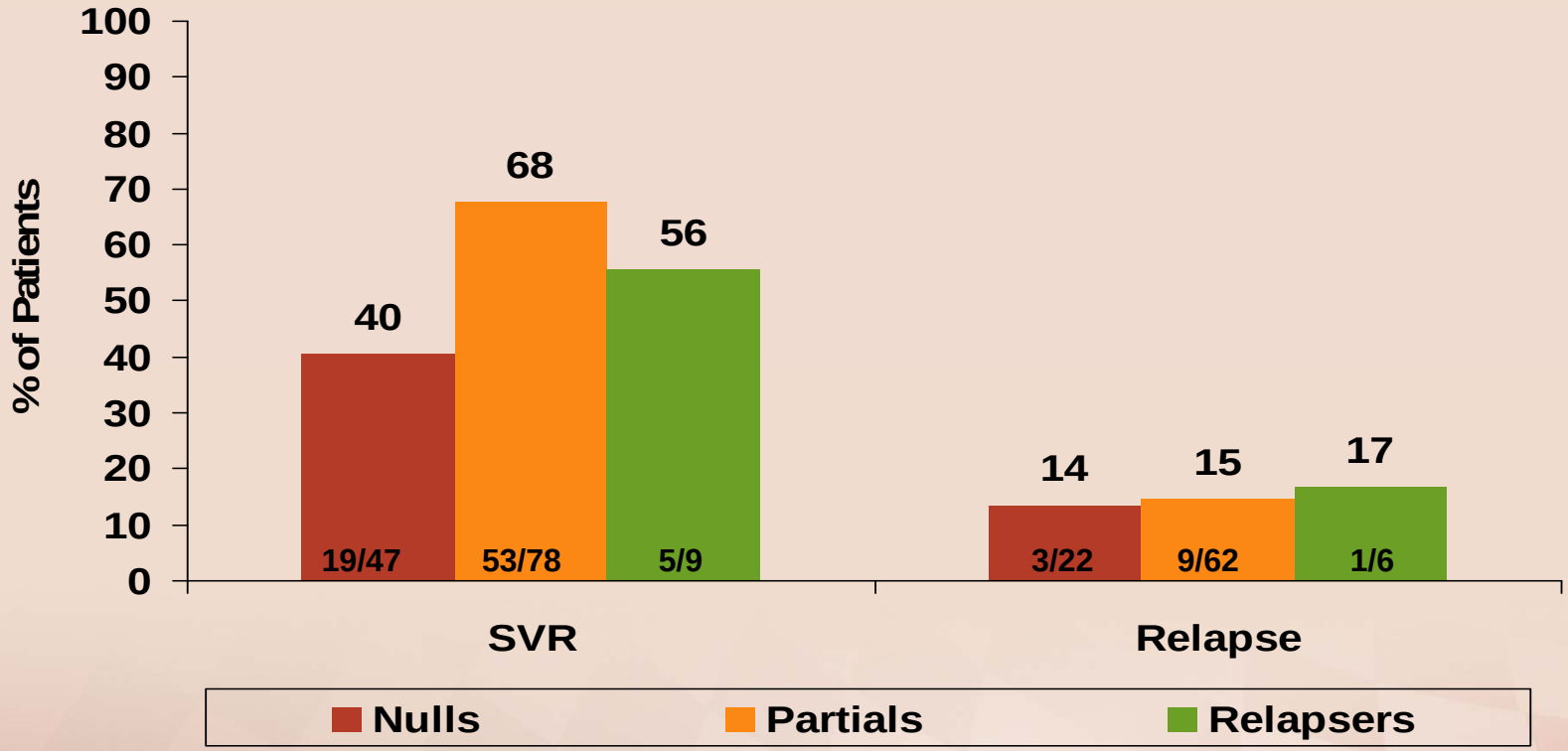
PROVIDE Study: Response to PR Treatment in Prior Study

Null response	<2 log decrease in HCV RNA at TW12 of PEG/RBV
Partial response	≥2 log decrease in HCV RNA by TW12 and detectable HCV RNA at end of treatment
Relapse	undetectable HCV RNA at end of prior treatment and detectable HCV RNA at end of follow-up
Other	not in the above categories of prior treatment failure



Bronowicki JP, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 11.

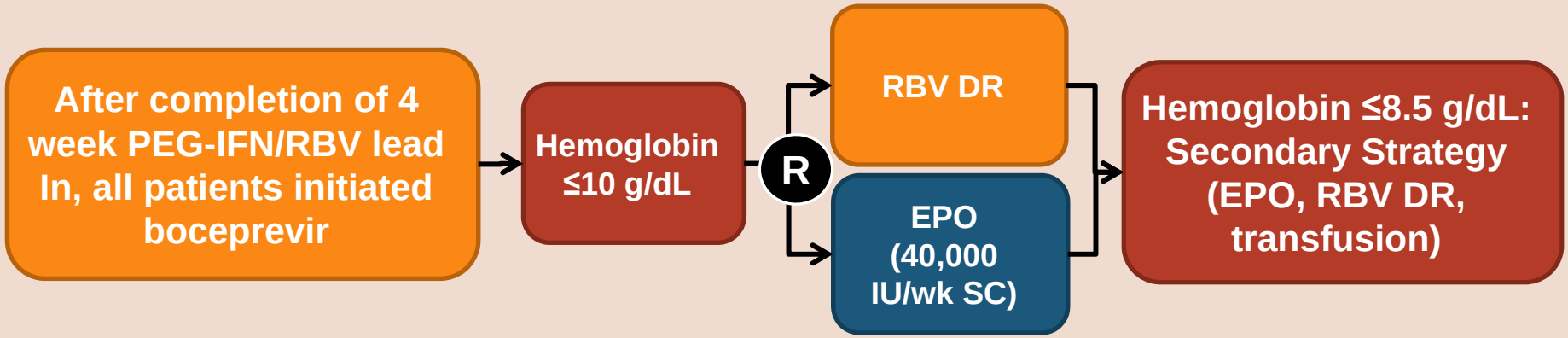
PROVIDE Study: SVR and Relapse Rates, by Prior Treatment Response



- SVR was also achieved in all 4 patients with ‘other’ prior non-response
- Overall, 81 of 138 patients (59%) achieved SVR

Bronowicki JP, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 11.

Anemia Management: Erythropoietin vs Ribavirin Dose Reduction - Methods



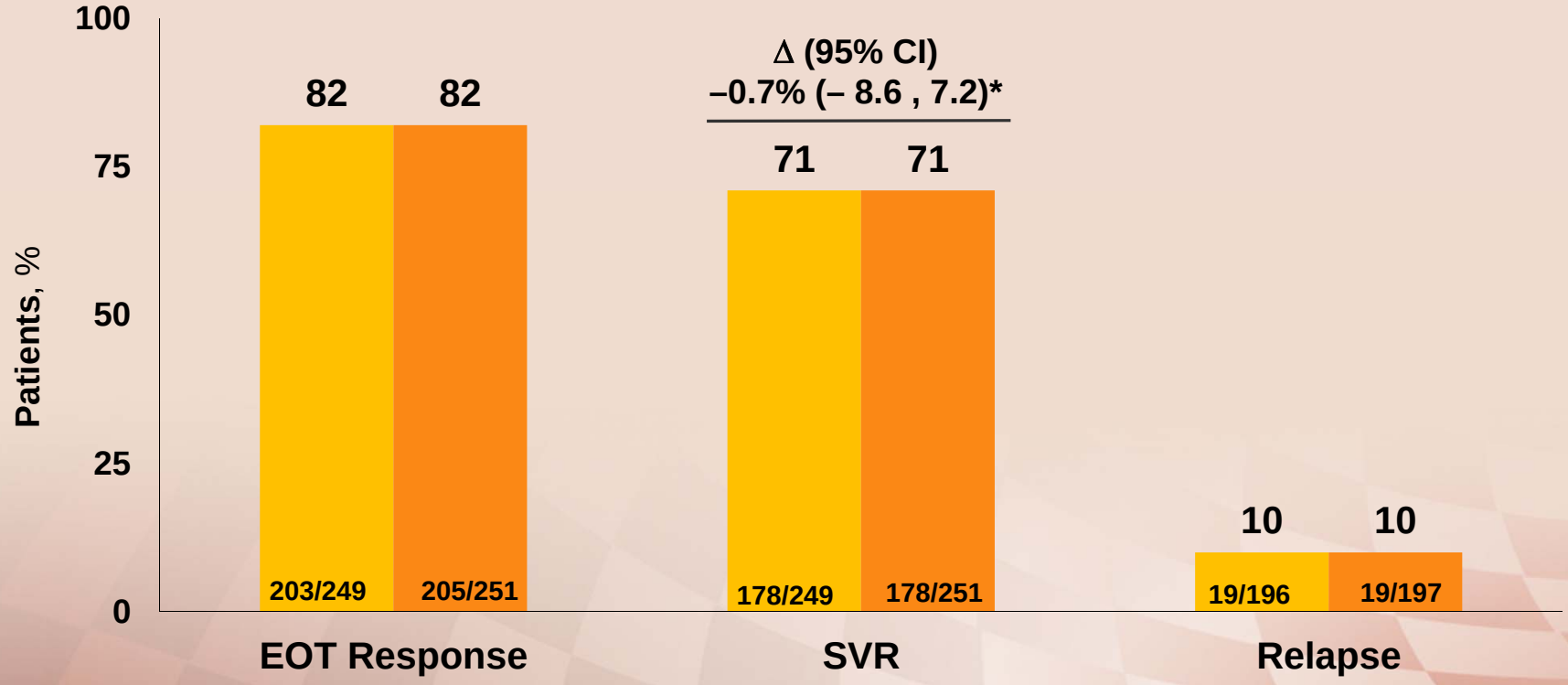
R = randomization

DR, dose reduction; EPO, erythropoietin; PEG-IFN, peginterferon; RBV, ribavirin; SC, subcutaneously.

Poordad F et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1419.

Anemia Management: Erythropoietin vs Ribavirin Dose Reduction - Primary and Key Efficacy End Points

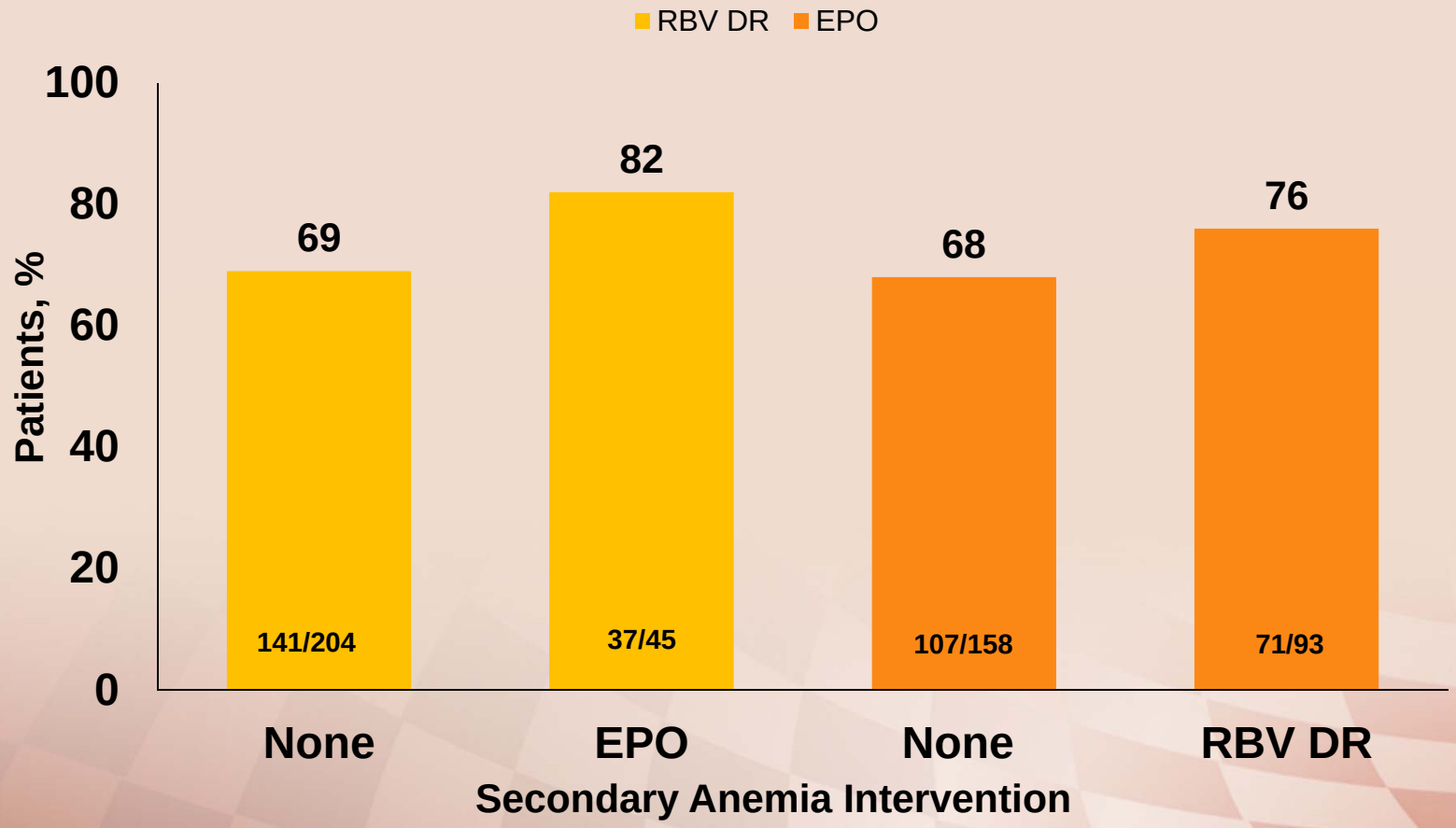
- End-of-treatment response, relapse, and SVR were comparable between RBV DR and EPO arms



CI, confidence interval; DR, dose reduction; EOT, end of treatment; EPO, erythropoietin; RBV, ribavirin; SVR, sustained virologic response.
*The stratum-adjusted difference (EPO vs RBV DR) in SVR rates, adjusted for stratification factors and protocol cohort.

Poordad F et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1419.

Anemia Management: Erythropoietin vs Ribavirin Dose Reduction - SVR by Secondary Anemia Intervention

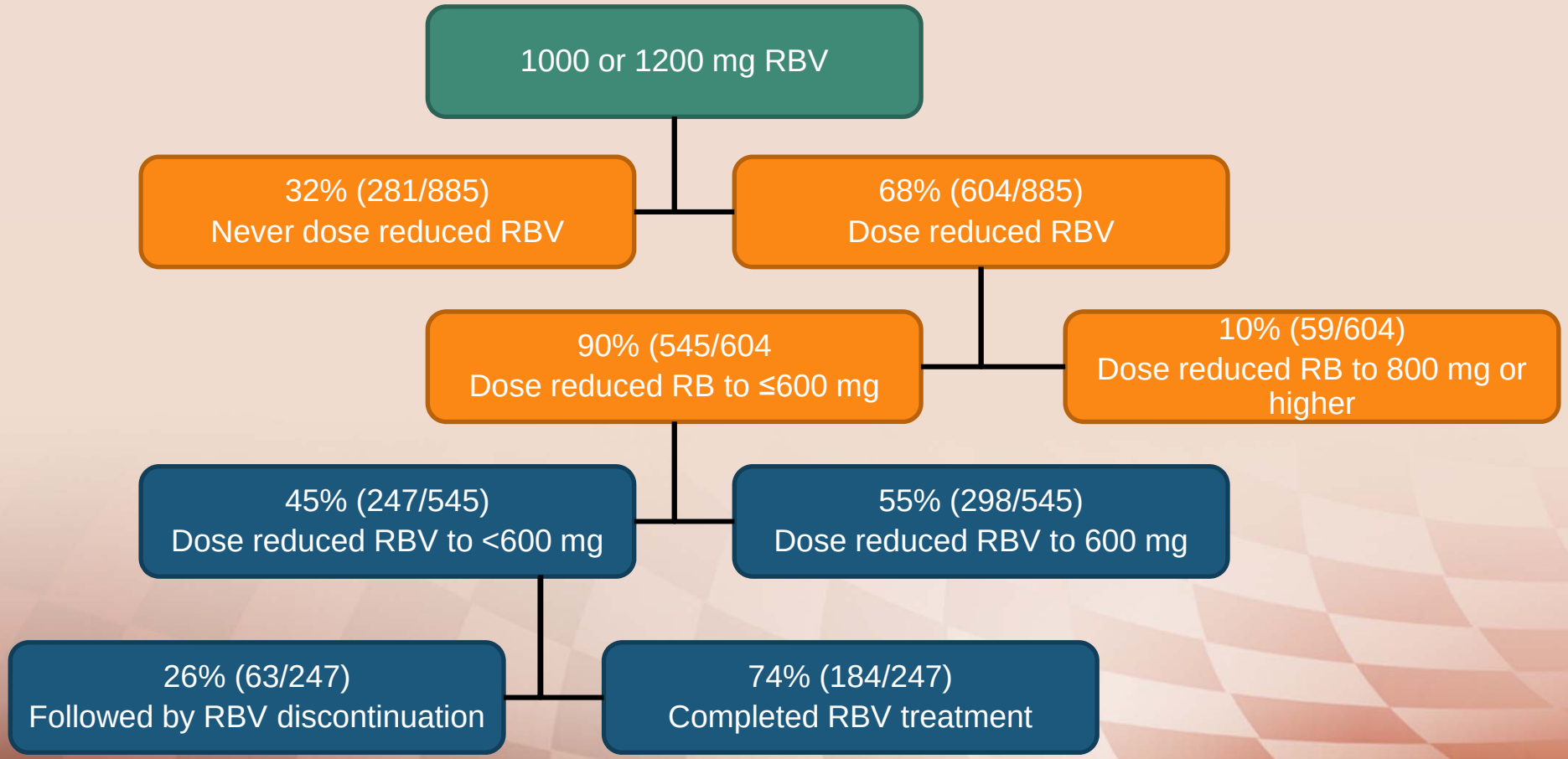


DR, dose reduction; EPO, erythropoietin; RBV, ribavirin; SVR, sustained virologic response.

Poordad F et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1419.

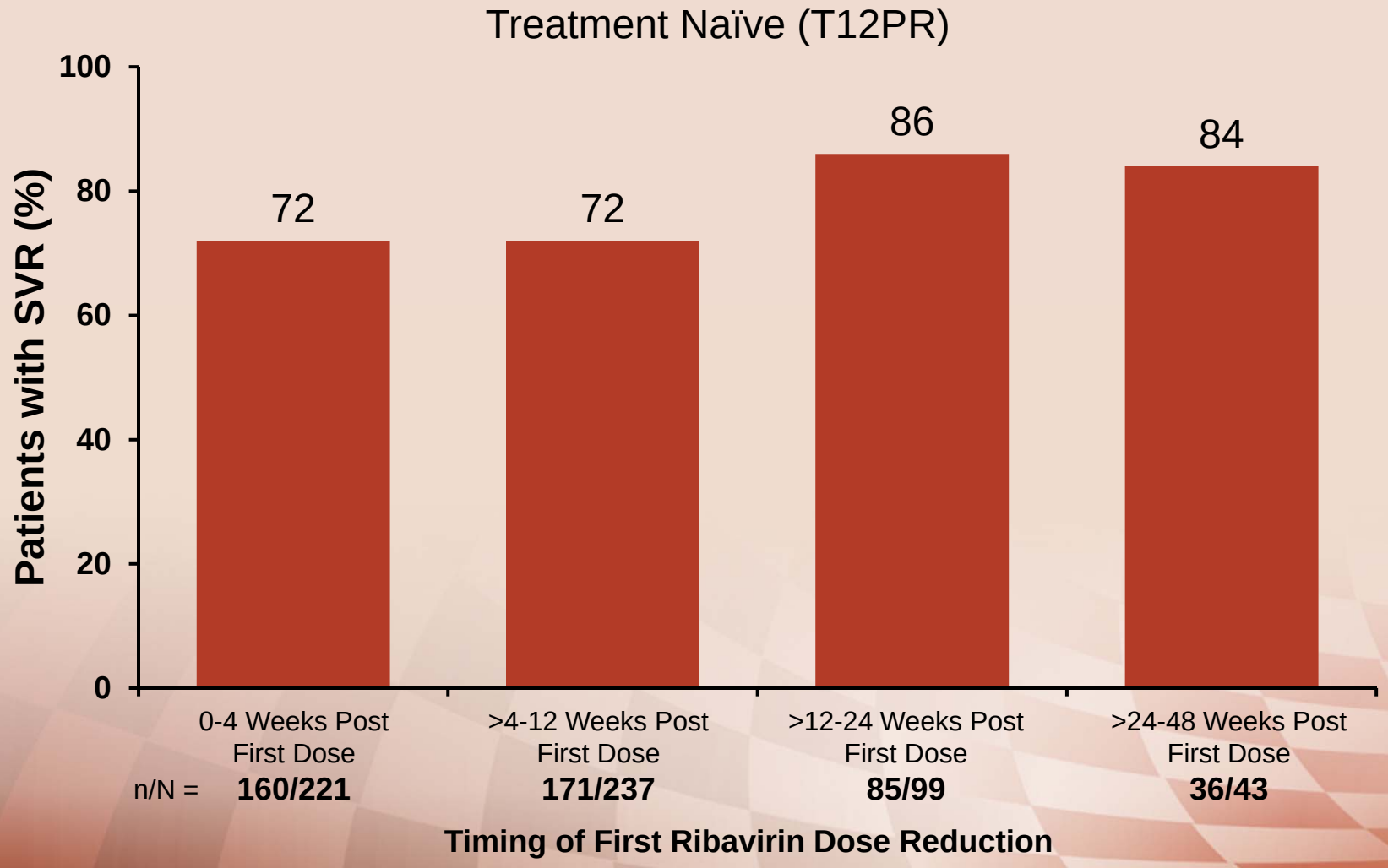
Ribavirin dose reduction: Telaprevir Phase 3 Studies

ADVANCE and ILLUMINATE (T12PR, N=885)



Sulkowski M et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1162.

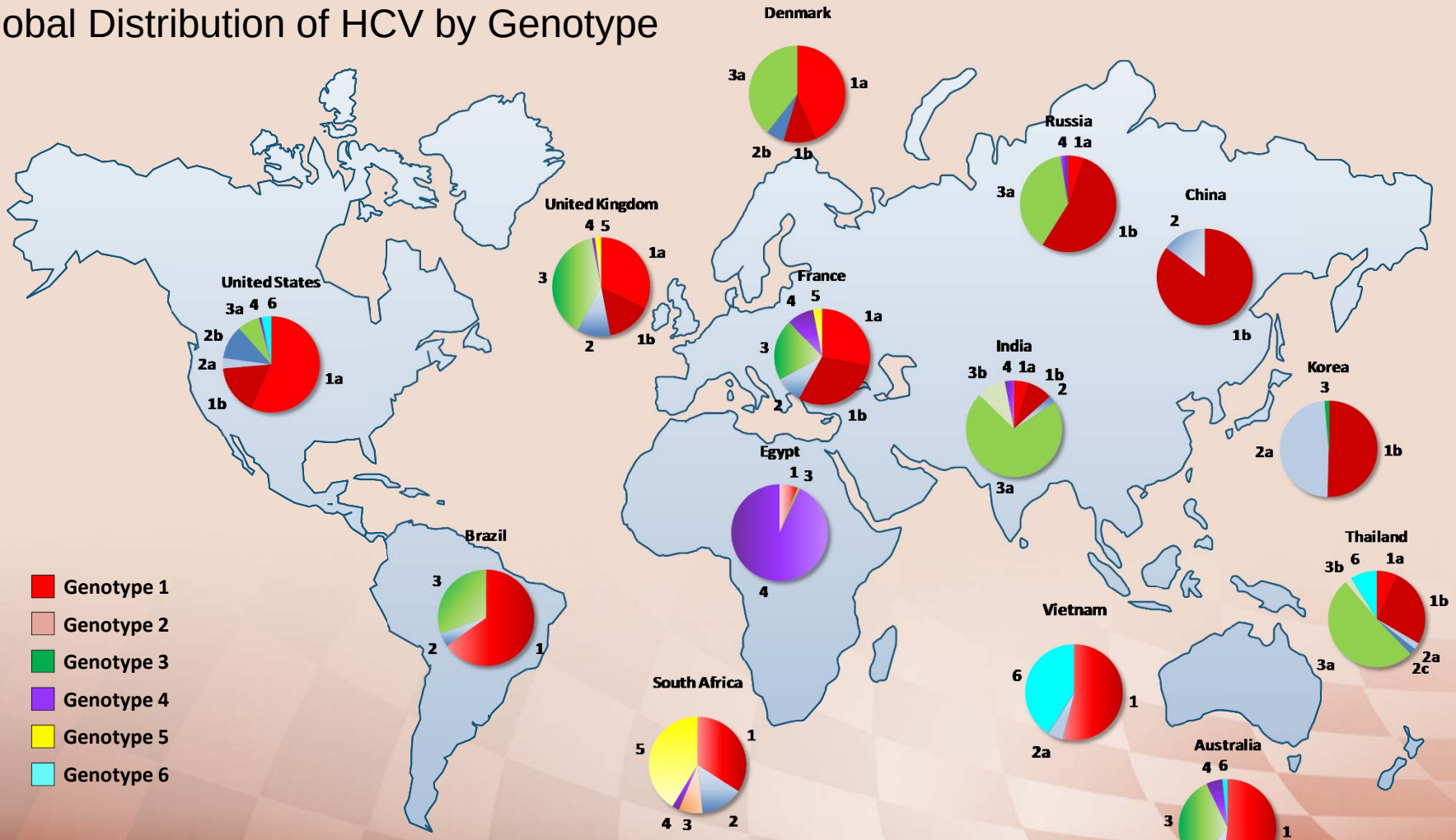
Ribavirin dose reduction: Proportion of Patients who Achieved SVR



Sulkowski M et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1162.

IN VITRO Characterization of the Pan-Genotype Activity of Boceprevir and Telaprevir

Global Distribution of HCV by Genotype



Source: MSD Internal Data. Epidemiology study by the International Conquer C Coalition (I-C3), Kromite

Howe JA et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 844.

Pan-Genotype of BOC and TVR: NS3/A PI Activity Against NS3/4A from HCV Infected Patients

	Average IC_{50}=nM (fold-shift over G1a)							
Genotype (n=samples)	1a (n=9)	1b (n=7)	2a (n=2)	2b (n=5)	3a (n=6)	4a (n=2)	5a (n=5)	6a (n=1)
Boceprevir	368 (1)	356 (1)	385 (1.1)	750 (2.0)	803 (2.2)	1180 (3.2)	956 (2.6)	205 (0.6)
Telaprevir	413 (1)	653 (1.6)	649 (1.6)	1119 (2.7)	3312 (8.0)	2466 (5.9)	1252 (3.0)	25 (1.3)

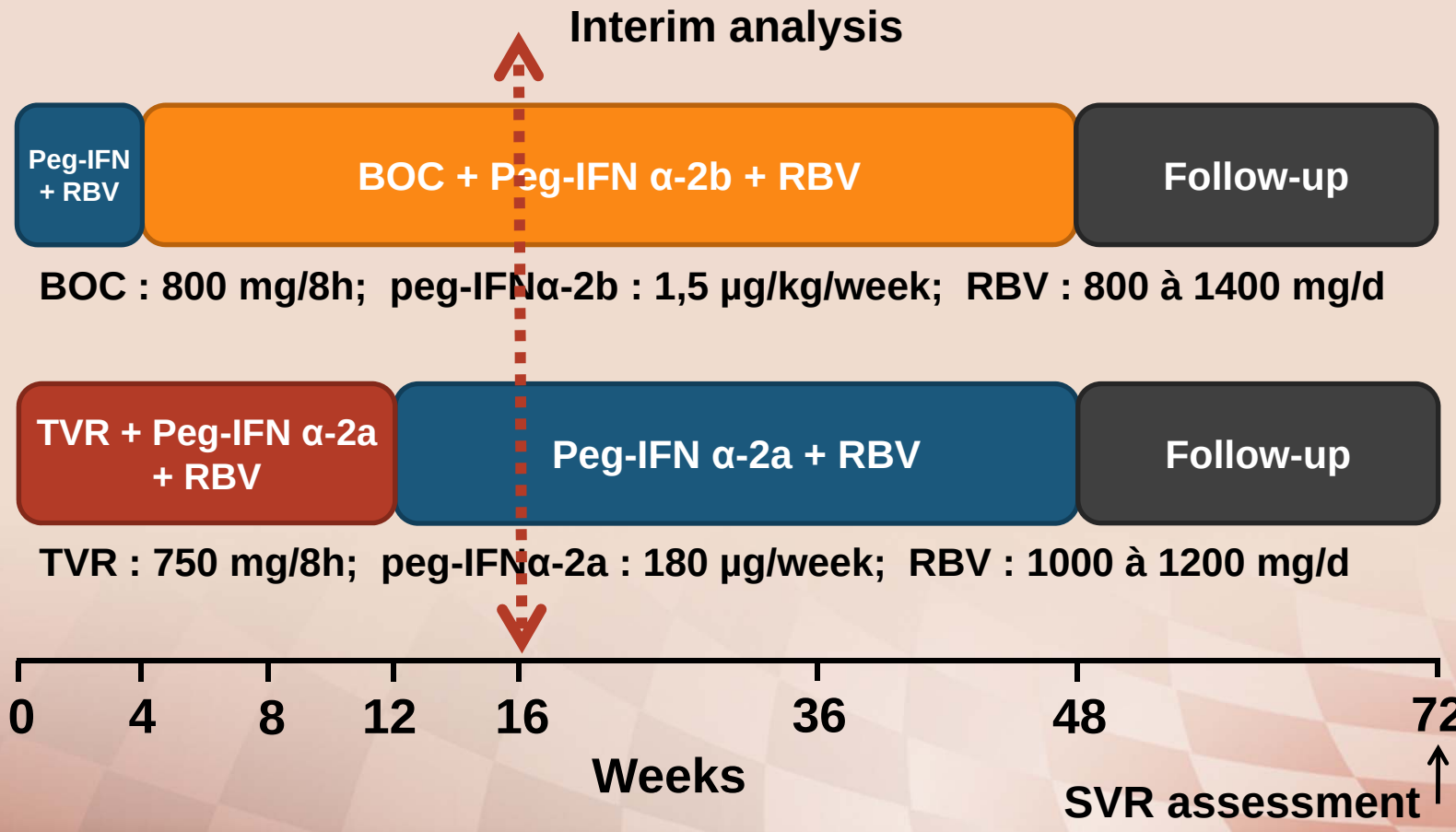
Howe JA et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 844.

Pan-Genotype of BOC and TVR: Summary

- Boceprevir and telaprevir were active across genotype 1-6 in NS3/4A enzymes *in vitro* and in a cell-based assays and against G1a, G1b, G2a, G2b, G3a and G5a replicons
  - Fold shift for boceprevir (compared to 1a) against patient samples in the cell-based assay was 2.2 for G3a and 3.2-fold for G4a
  - Fold shift for telaprevir (compared to 1a) against patient samples in the cell-based assay was 8.0 for G3a and 5.9-fold for G4a

Howe JA et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 844.

CUPIC: Treatment Regimen



Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CUPIC: Patients Characteristics (1)

	Telaprevir n=296	Boceprevir n=159
Male (%)	68	67.5
Mean age (years)	57.0	56.8
Median follow-up duration (days)	140	168
Median telaprevir duration (days)	84.0	140
Mean Neutrophils (10^9/mm^3)	3.3	3.2
Mean Hemoglobin (g/dl)	14.4	14.8
Mean Platelets (/mm^3)	150 000	150 000

Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CUPIC:
Patients Characteristics

	Telaprevir n=296	Boceprevir n=159
Genotype 1b / 1a (%)	61 / 39	60 / 40
Mean Baseline HCV RNA (log_{10} IU/mL)	6.5	6.5
Mean Prothrombin Time (ratio)	88	88
Mean Total Bilirubin (µmol/L)	15	15
Mean Albumin (g/dL)	40	41
Esophageal varices (%)	15	16
Previous treatment response (%)		
Partial responders	52	49
Relapsers	40	48
Nulls responders	8	3
Patients with Realize exclusion criteria (%)	34	26

Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CUPIC: Preliminary Safety Findings (1)

Patients, n (% patients with at least one event)	Telaprevir n=296	Boceprevir n=159
Serious adverse events (%)	48.6	38.4
Premature discontinuation	26.0	23.9
Due to SAEs (%)	14.5	7.4
Death (%)	2.0	1.3
Infection (Grade 3/4) (%)	8.8	2.5
Asthenia (Grade 3/4) (%)	4.7	5.7
Rash		
Grade 3 (%)	6.8	0
Grade 4 (SCAR) (%)	0.7	0
Pruritus (Grade 3/4) (%)	3.7	0.6
Hepatic decompensation (%)	4.4	4.4

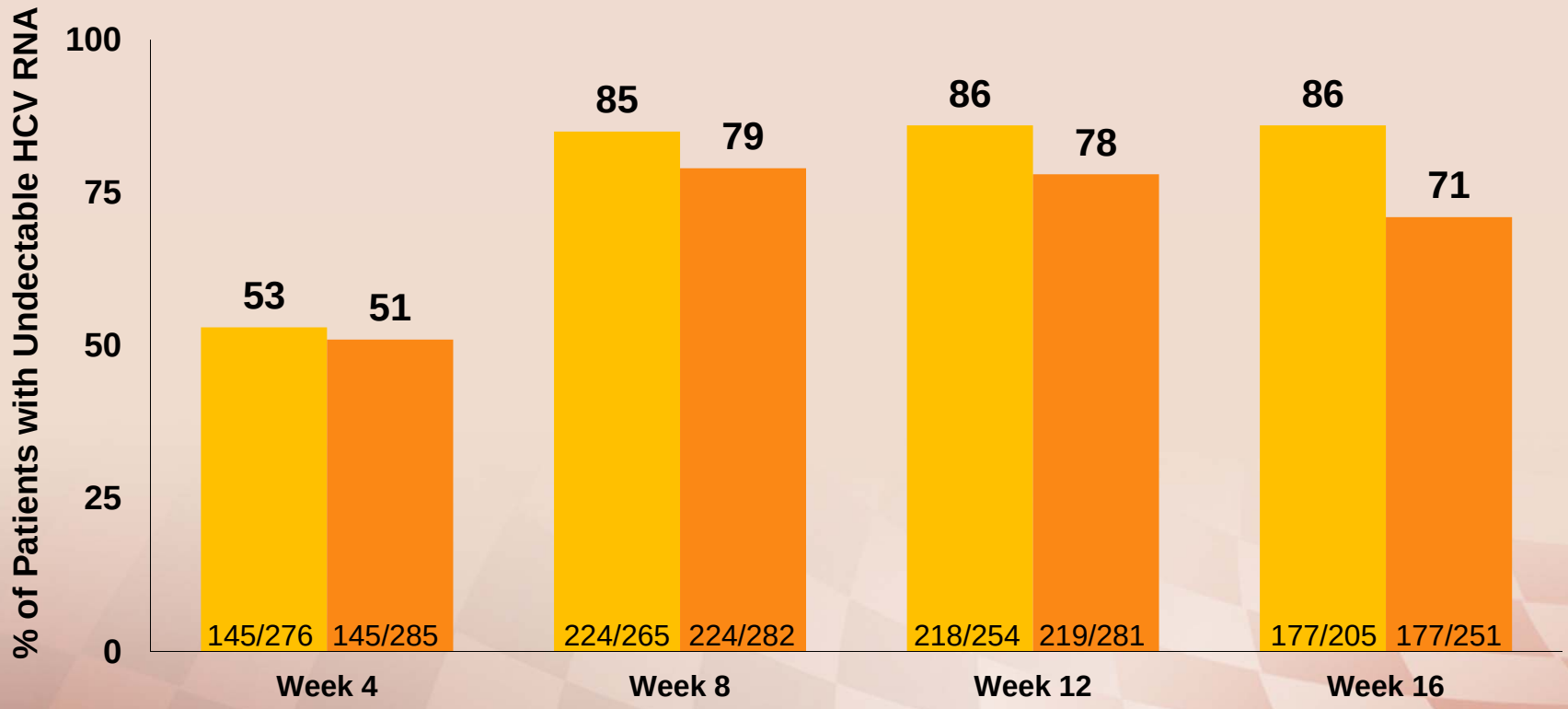
Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CUPIC: Preliminary Safety Findings

Patients, n (% patients with at least one event)	Telaprevir (n=296)	Boceprevir (n=159)
Anemia (%)		
Grade 2 (8.0 – <10.0 g/dL)	19.6	22.6
Grade 3/4 (<8,0 g/dL)	10.1	10.1
EPO use	56.8	66.0
Blood transfusion	15.2	10.7
Neutropenia (%)		
Grade 3 (500 – <1000/mm^3)	4.0	4.4
Grade 4 (<500/mm^3)	0.7	0.6
G-CSF use	2.4	3.8
Thrombopenia (%)		
Grade 3 (25 000 – <50 000)	11.8	6.3
Grade 4 (<25 000)	1.3	0.6
Thrombopoïetin Use	1.7	1.9

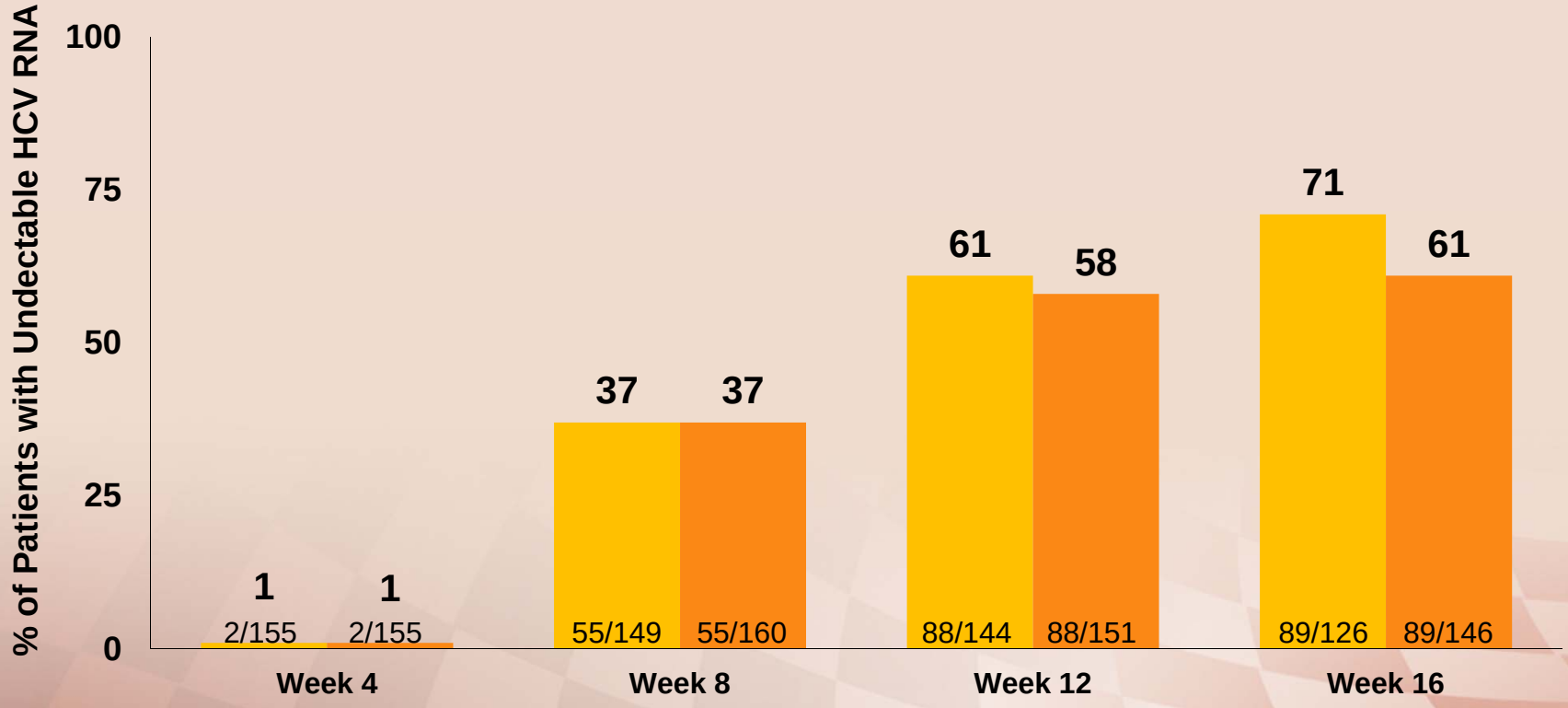
Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CUPIC:
Telaprevir Preliminary Efficacy Data



Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CUPIC:
Boceprevir Preliminary Efficacy Data



Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

Discussion

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

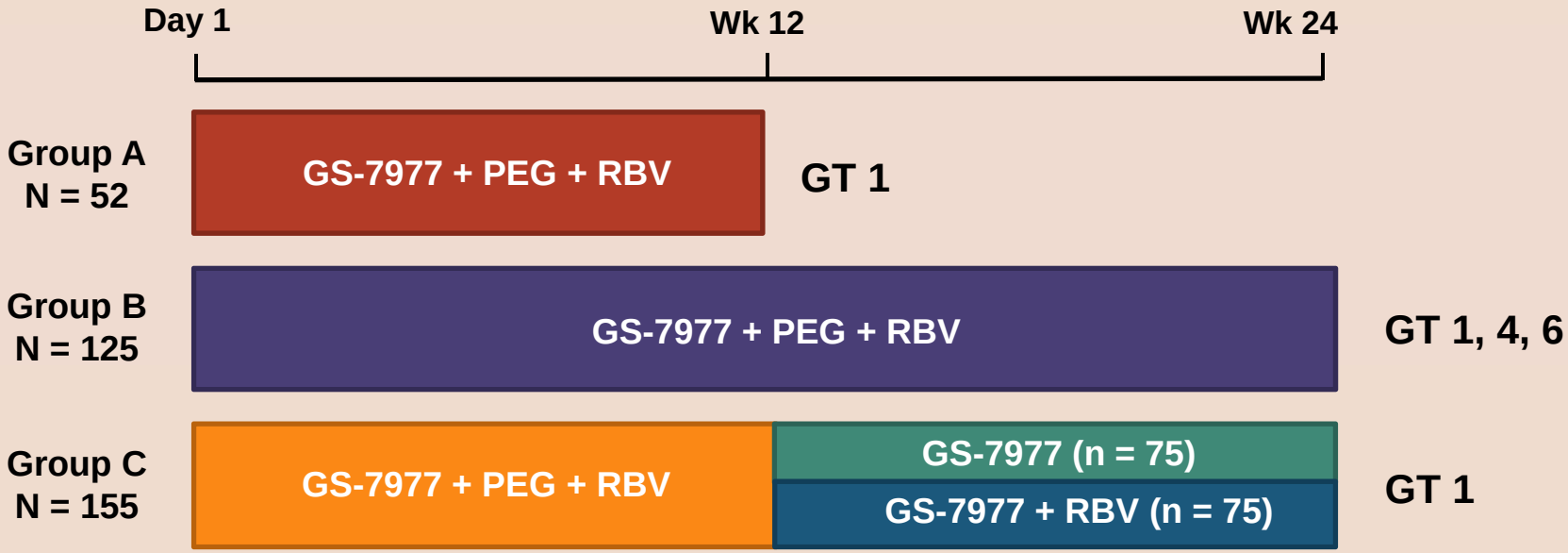
Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

Novel Therapies and Strategies

Nezam H. Afdhal, MD

Director of Hepatology
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Atomic Study: Treatment with GS-7977



- HCV genotype 1 randomized 1:2:3 into 1 of 3 open-label arms
- Stratified by:
  - *IL28B* genotype (CC vs non-CC)
  - HCV RNA at screening (≤ vs >800,000 IU/mL)

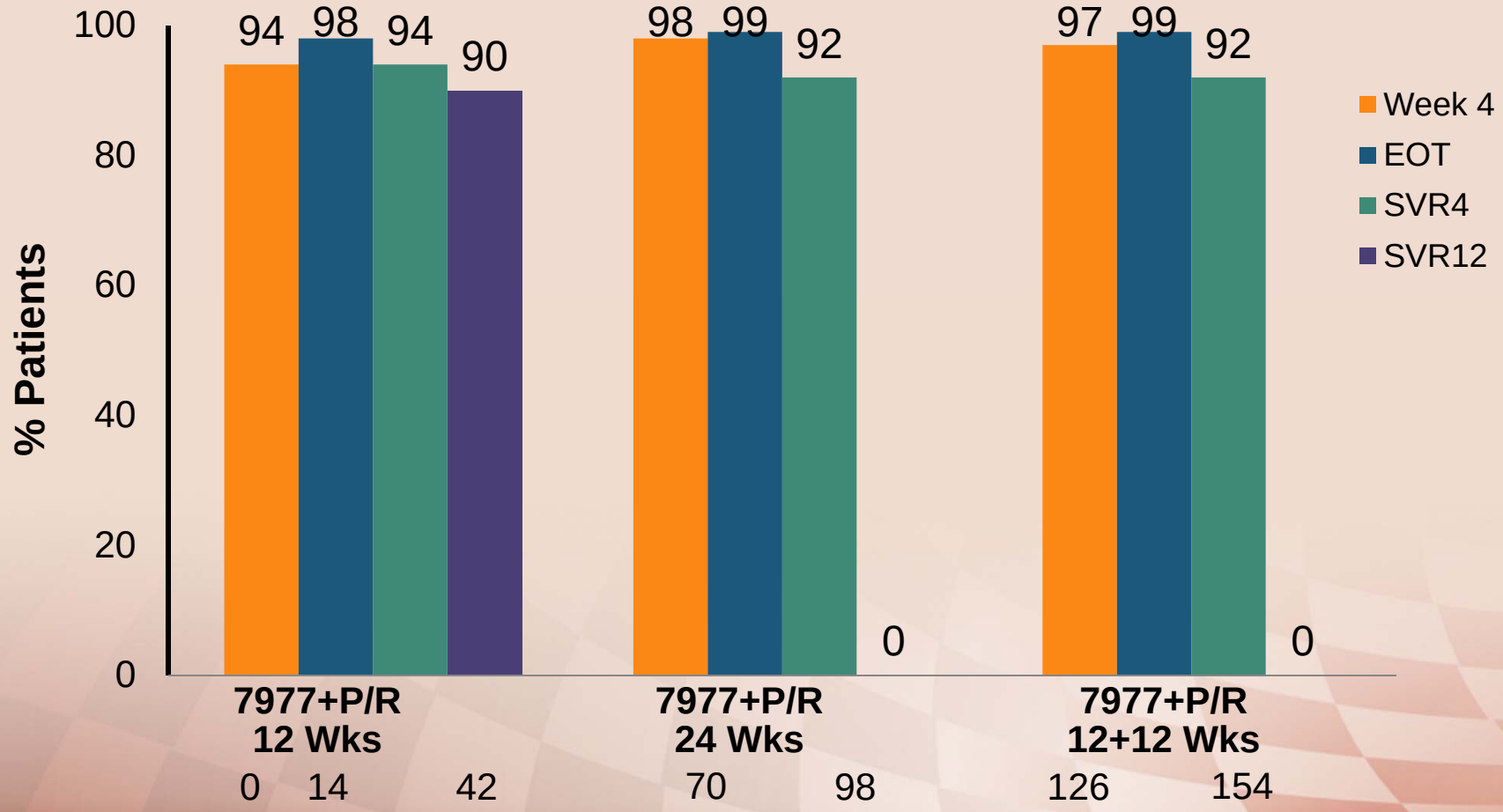
Kowdley K, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1.

Atomic Study: Baseline Demographics

	Arm A 7977/PR 12 wks N=52	Arm B 7977/PR 24 wks N=125	Arm C 7977/PR 12 + 12 wks N=155
Mean age (range)	50.8 (24, 63)	50.3 (19, 72)	49.7 (18, 74)
Male	67%	58%	68%
Caucasian	92%	79%	87%
Mean BMI (range)	27.15 (18.1, 46.7)	27.59 (18.3, 42.2)	28.27 (20, 46.4)
Non-CC *IL28B* genotype	77%	71%	72%
Genotype 1a	75%	68%	73%
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.51 (5.1, 7.7)	6.33 (4.3, 7.8)	6.41 (1.5, 7.7)

Kowdley K, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1.

Atomic Study: SVR12



For patients who received 12 weeks of GS-7977 + PEG/RBV treatment, 96% were <LOD at their last follow-up visit

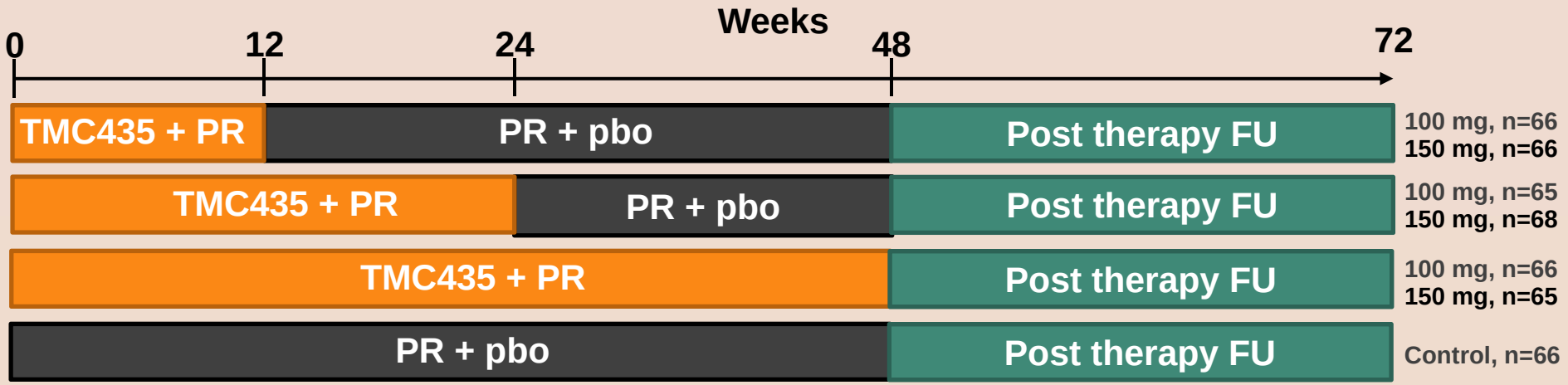
Kowdley K, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1.

Atomic Study: Conclusions

- GS-7977 + PEG/RBV provided rapid viral suppression with 97% RVR and no virologic breakthrough in treatment-naïve genotype 1 HCV patients
- SVR4 rates ≥92% were observed in genotype 1 patients receiving 12 to 24 weeks of treatment with GS-7977 + PEG/RBV
- 12 weeks of a GS-7977 + PEG/RBV regimen resulted in a SVR12 rate of 90% (ITT)
- GS-7977 + PEG/RBV was safe and well tolerated for up to 24 weeks
- To date, no S282T resistance mutation has been detected

Kowdley K, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1.

ASPIRE Study: Treatment with TMC435



- TMC435 either 100 or 150 mg QD

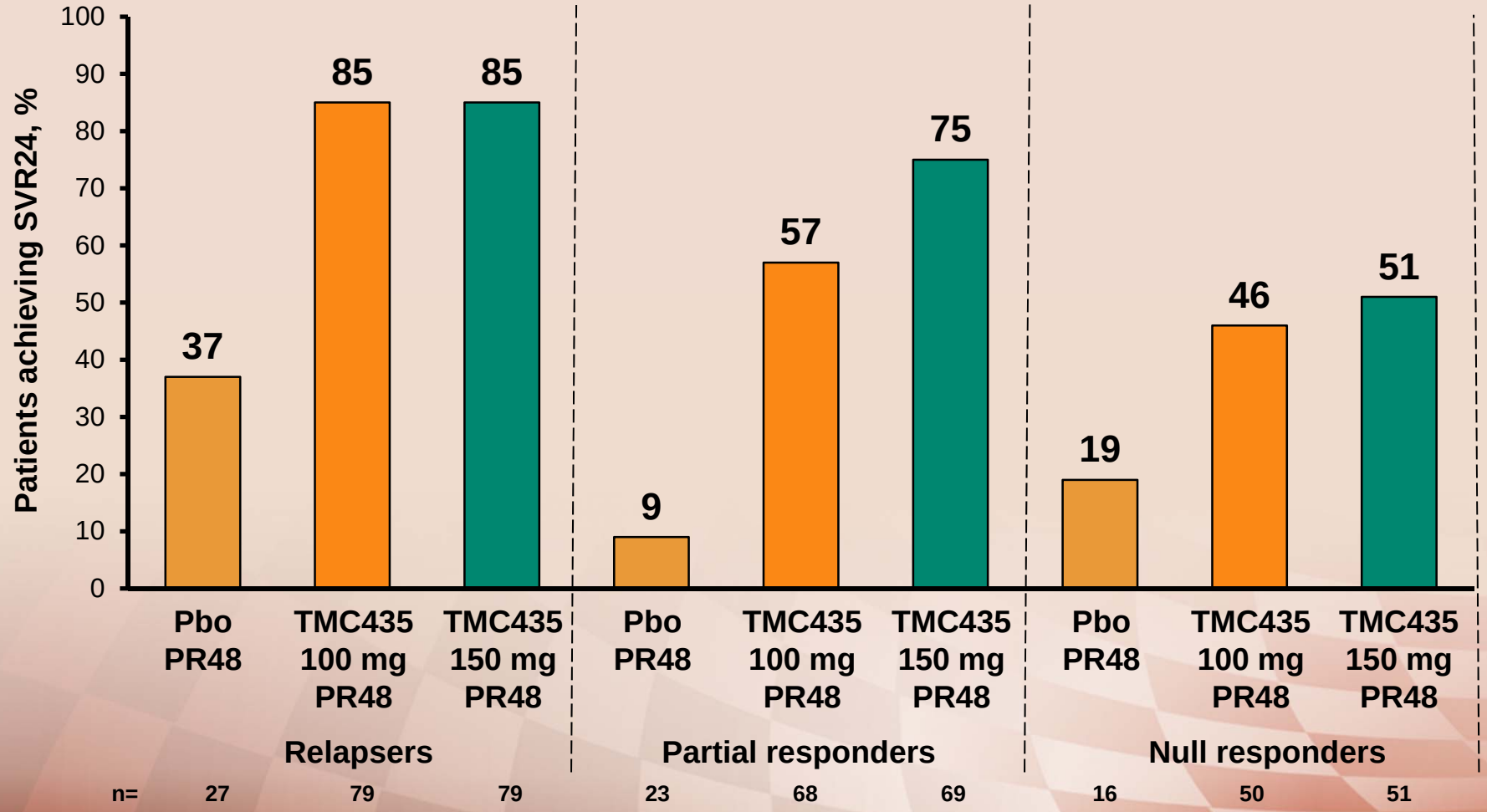
Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 2.

ASPIRE Study: Baseline Demographics and Disease Characteristics

	TMC435 100 mg PR48 n=197	TMC435 150 mg PR48 n=199	Pbo PR48 n=66
Patient Demographics			
Male, %	68	68	64
Race, white, %	92	93	94
Age, years, median (range)	50.0 (20-69)	50.0 (20-69)	50.5 (22-66)
Body weight, kg, median (range)	80.0 (43-138)	80.5 (50-125)	84.8 (53-112)
IL28B genotype CC[†], %	17 (n=136)	17 (n=142)	22 (n=50)
Disease Characteristics			
HCV subtype (NS5B) 1a[‡], %	41	42	41
HCV RNA ≥800 000 IU/mL at baseline[§], %	89	85	83
Metavir score, F3 / F4, %	23 / 18	15 / 20	20 / 16
Prior Response to PegIFN/RBV			
Relapser, %	40	40	41
Partial responder, %	35	35	35
Null responder, %	25	26	24

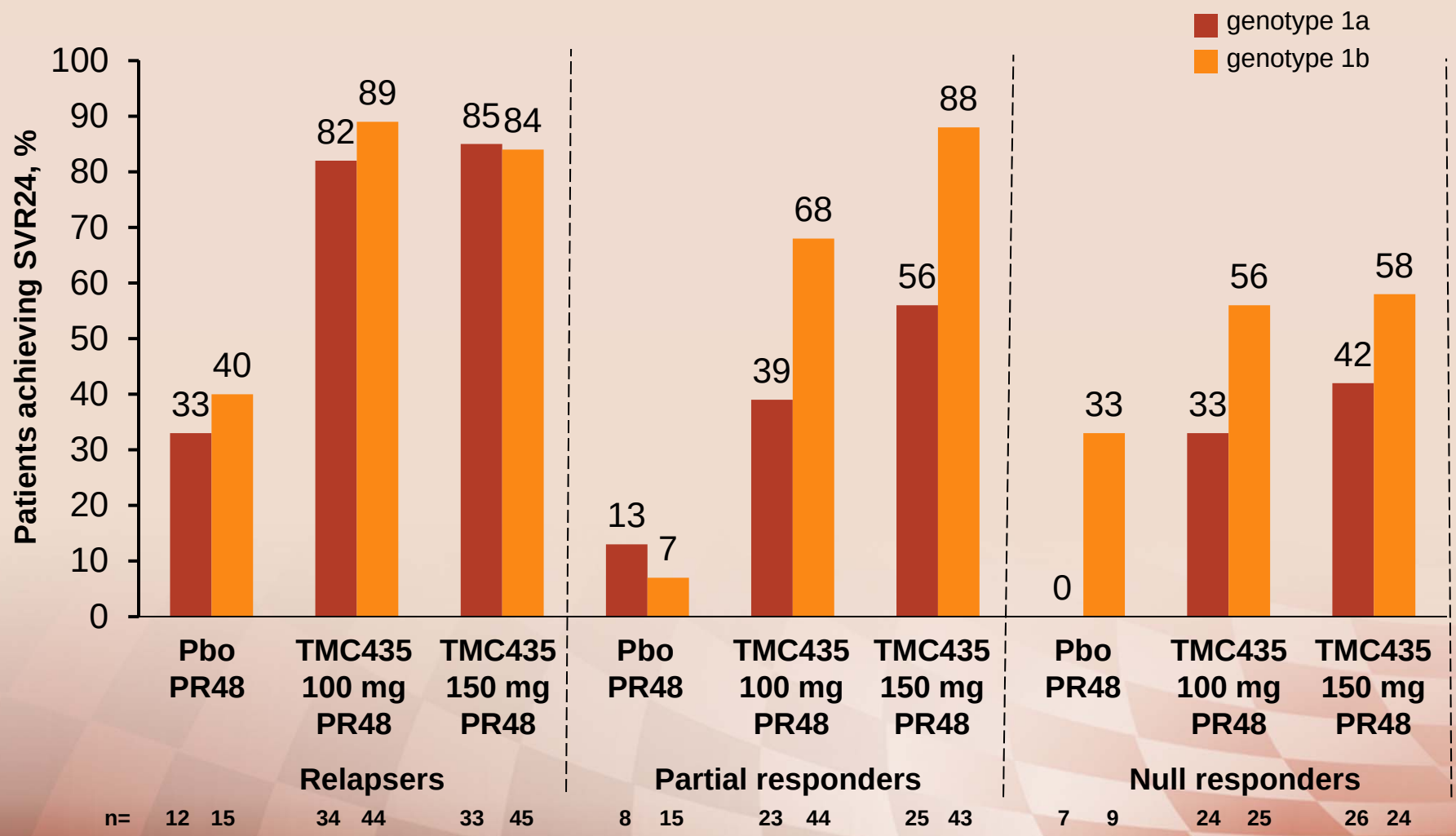
Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 2.

ASPIRE Study: Proportion of Patients Achieving SVR24 by Prior Response



Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 2.

ASPIRE Study: SVR24 by Prior Response and HCV Genotype Subtype



Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 2.

ASPIRE Study: Summary

- In HCV genotype 1 patients who previously failed PegIFN/RBV treatment, once-daily TMC435 administered with PegIFN/RBV was significantly more effective than PegIFN/RBV/placebo
- With TMC435 150 mg in combination with PegIFN/RBV:
  - 85% of prior relapsers achieved SVR24
  - 75% of prior partial responders achieved SVR24
  - 51% of prior null responders achieved SVR24
  - 31-82% in patients with cirrhosis
- Once-daily TMC435 was well tolerated in this population
- 12 weeks of potent PI adequate
- Phase III clinical trials for TMC435 150 mg are ongoing

PegIFN/RBV, peginterferon α-2a + ribavirin; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after planned end of treatment

Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 2.

Co-Pilot (M12-746) Study: ABT-450/r + ABT-333 Treatment

12 Weeks (On Treatment) → **Follow Up Period**

Arm 1
Treatment-naïve (N=19)
ABT-450/r 250/100 mg QD + ABT-333 400 mg BID + RBV

Arm 2
Treatment-naïve (N=14)
ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV

Arm 3
Prior P/R non-responders (N=17)
ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV

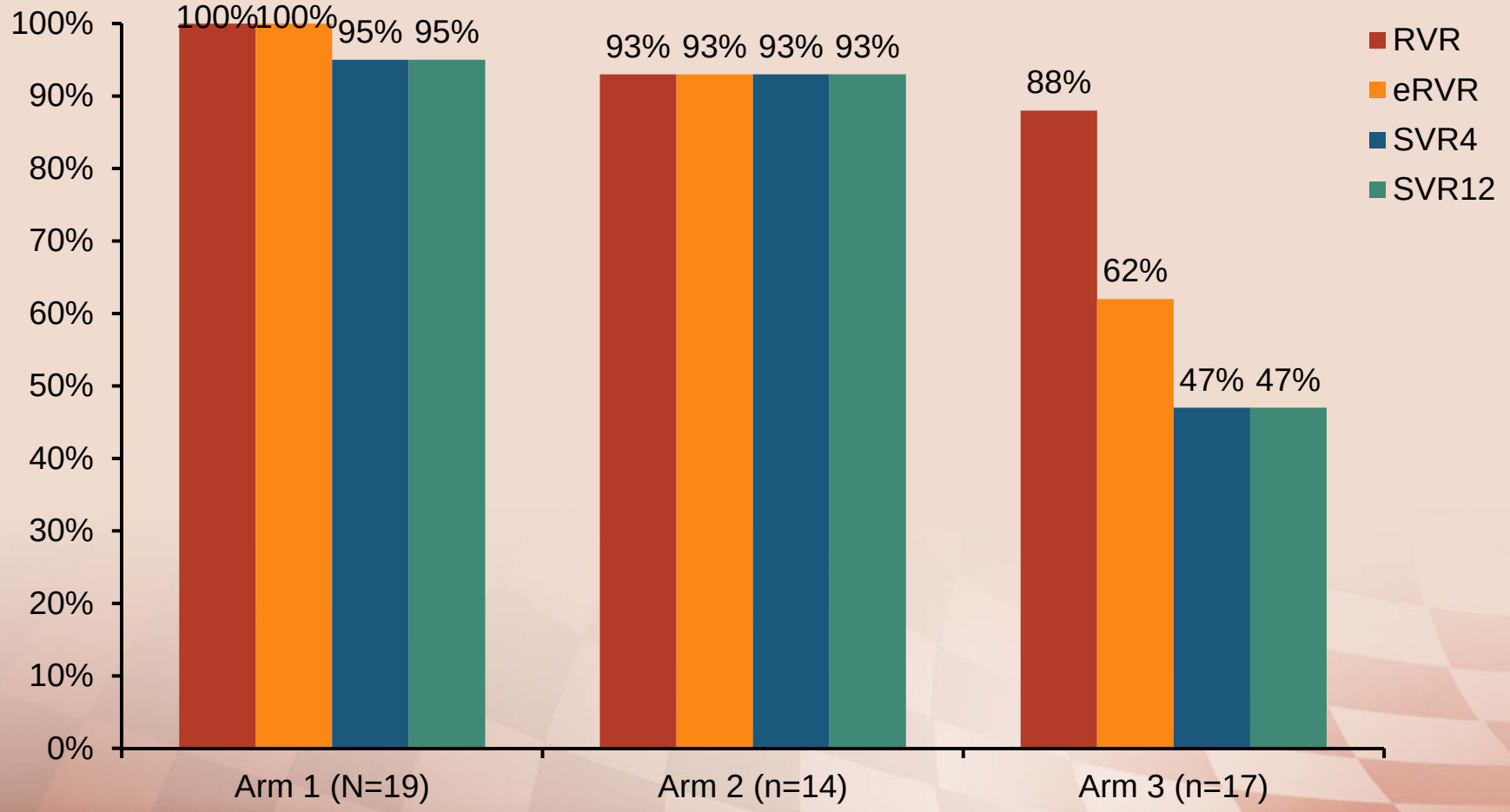
Poordad F, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1399.

Co-Pilot Study: Demographics and Baseline Characteristics

	Arm 1 N=19	Arm 2 N=14	Arm 3 N=17
Male, n (%)	10 (52.6)	14 (100)	11 (64.7)
White, n (%)	15 (78.9)	12 (85.7)	13 (76.5)
Hispanic/Latino, n (%)	3 (15.8)	0	4 (23.5)
Mean Age ± SD (years)	53.6 ± 9.78	50.9 ± 10.45	52.3 ± 9.03
Mean BMI ± SD (kg/m^2)	27.3 ± 3.84	24.6 ± 3.08	27.6 ± 4.65
IL28 genotype , n (%)			
CC	10 (52.6)	5 (35.7)	0
CT	7 (36.8)	7 (50.0)	12 (70.6)
TT	2 (10.5)	2 (14.3)	5 (26.3)
HCV genotype, n (%)			
1a	17 (89.5)	11 (78.6)	16 (94.1)
1b	2 (10.5)	3 (21.4)	1 (5.9)
HCV RNA			
Mean ± SD (log_{10} IU/mL)	6.25 ± 0.80	6.44 ± 1.15	6.93 ± 0.47
>800,000 IU/mL, n (%)	14 (73.7)	11 (78.6)	17 (100)
Non-responder status			
Partial responder	-	-	11 (64.7)
Null responder			6 (35.3)

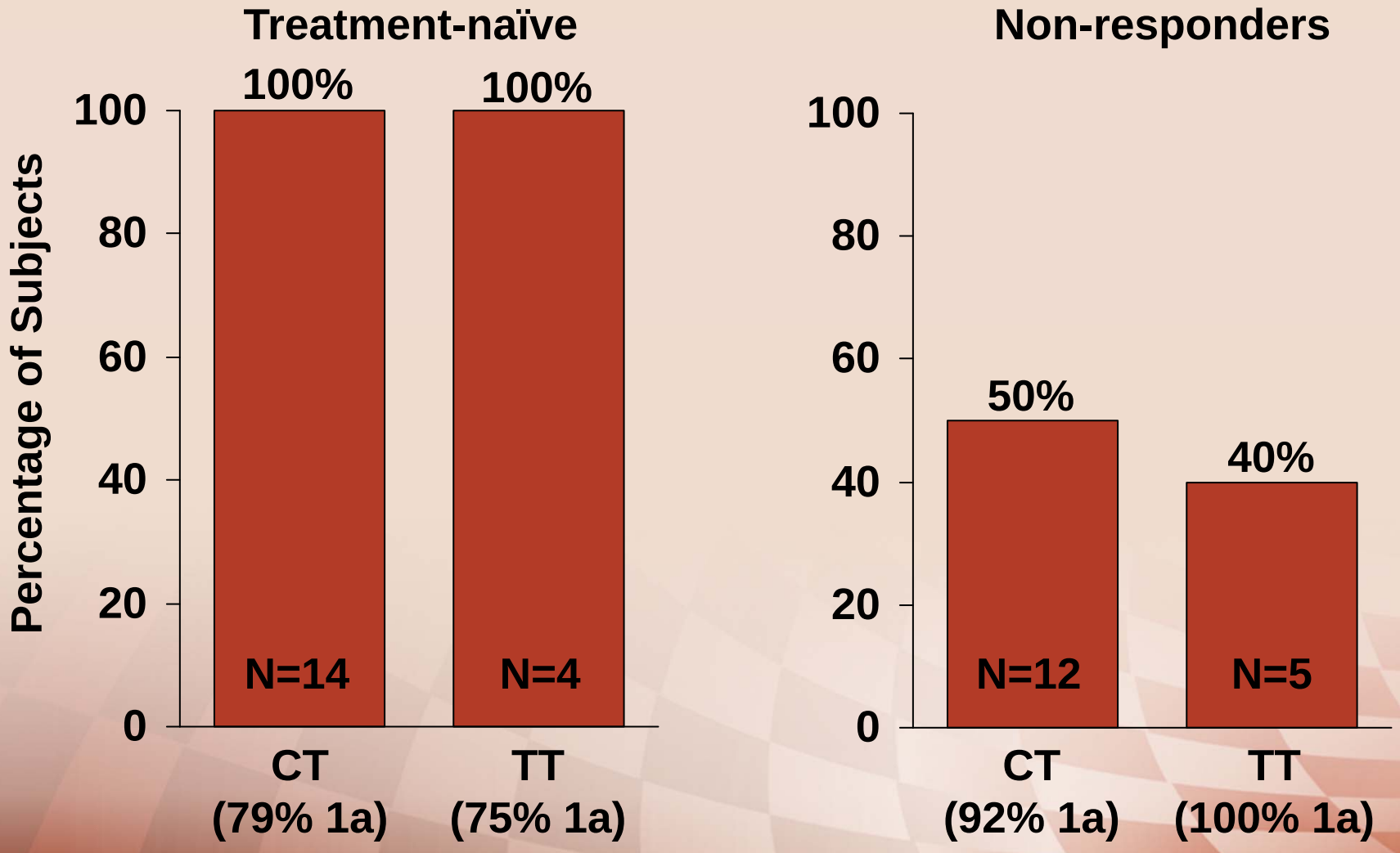
Poordad F, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1399.

Co-Pilot Study: Virologic Results



Poordad F, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1399.

No Impact of IL28B on SVR_{12}



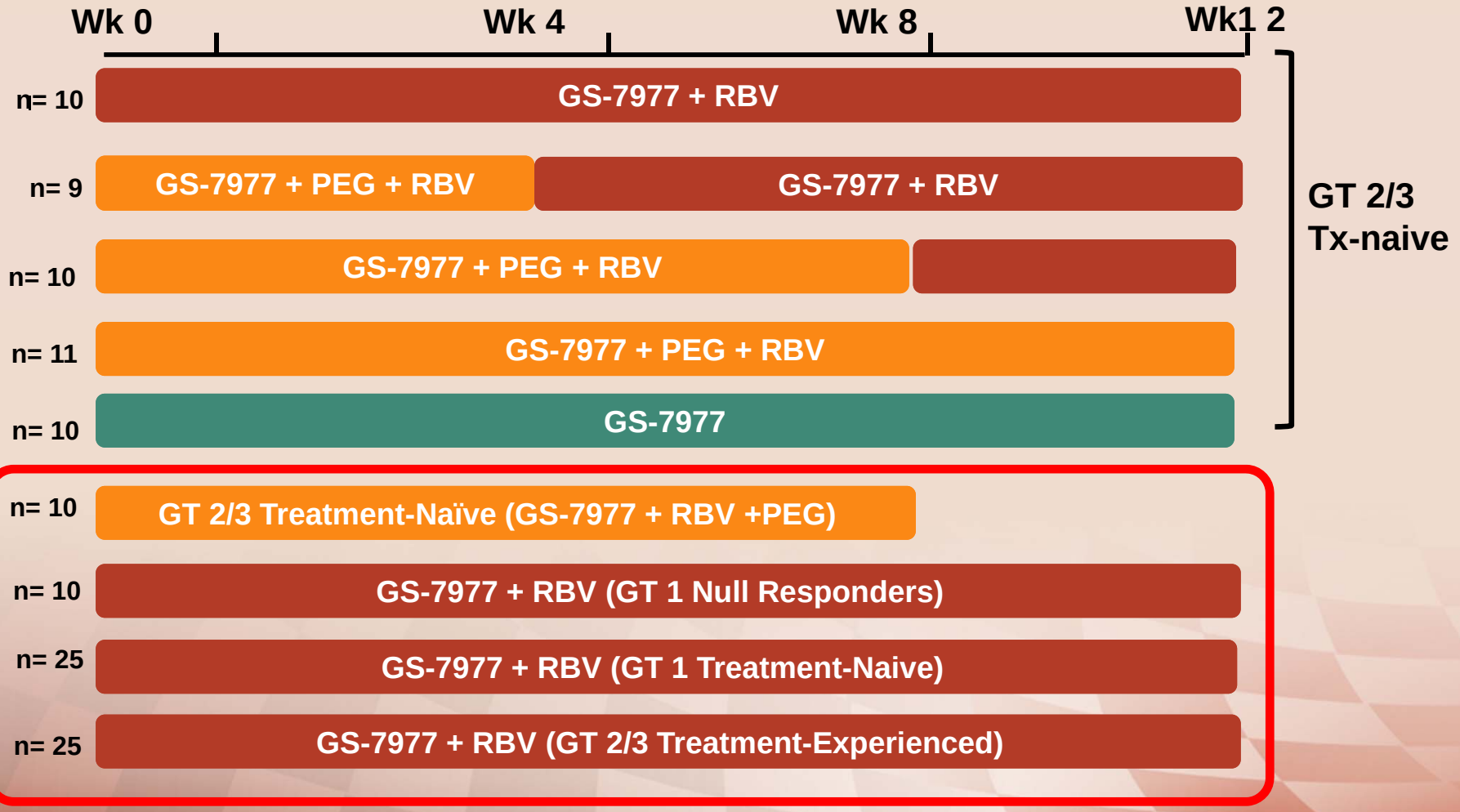
Poordad F, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1399.

Conclusions: Efficacy

- Overall, 93-95% of treatment-naïve subjects infected with HCV genotype 1 achieved SVR_{12} after 12 weeks of treatment
  - 100% (18 of 18) of IL28B “non-CC” subjects achieved SVR_{24}
  - No virologic failures occurred among treatment-naïve subjects who completed study drug treatment
- ABT-450/r 250/100 mg and 150/100 mg doses showed comparable response rates in treatment-naïve subjects
- 47% of previous non-responders achieved SVR_{12} after 12 weeks of treatment (50% in null responders and 45% in partial responders)
- ABT-450/r + ABT-333 + RBV for 12 weeks has the potential to achieve SVR in a high proportion of subjects without interferon

Poordad F, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1399.

Electron Study: Treatment of GS-7977



Gane E, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1113.

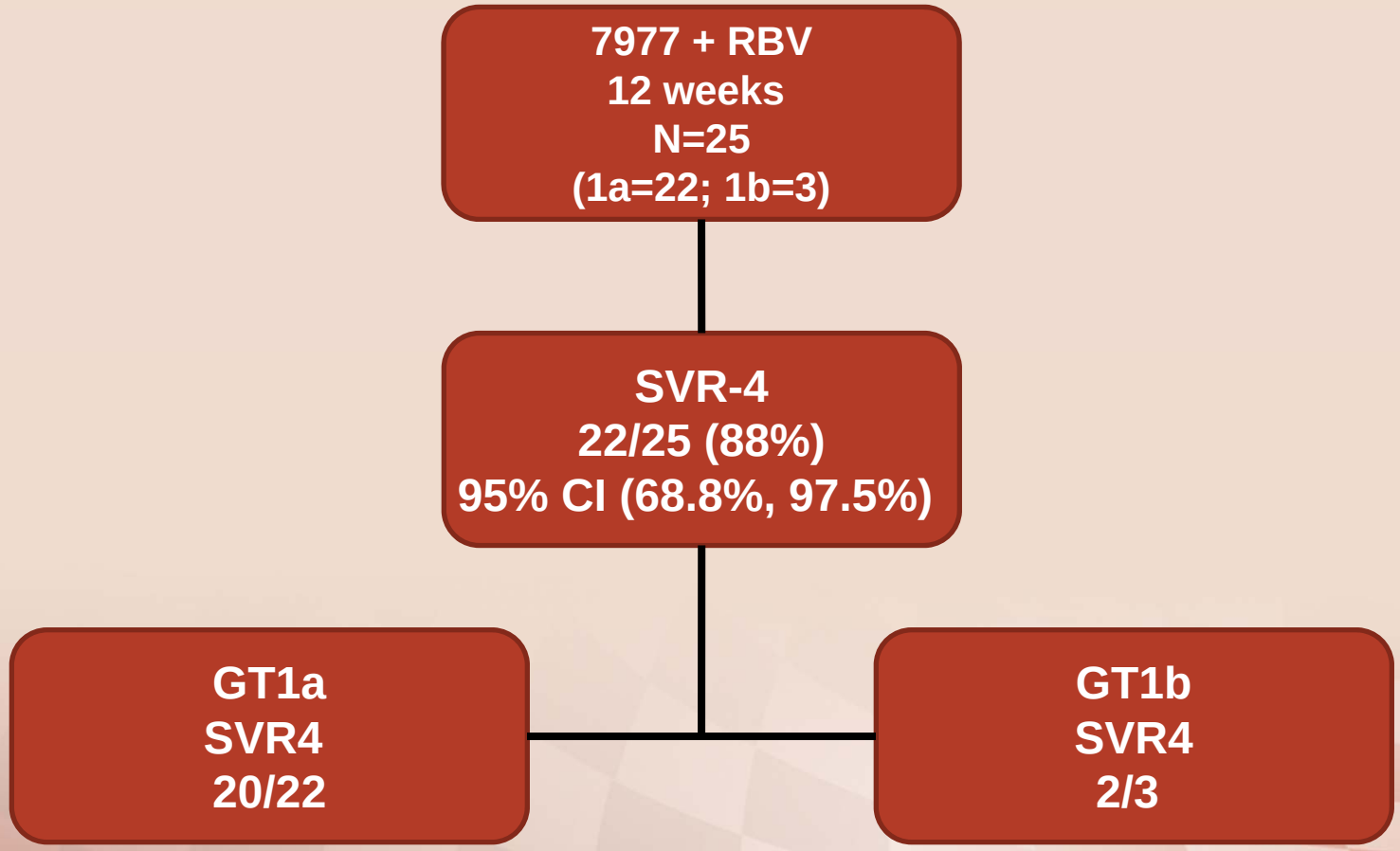
Electron Study: Virologic Response

Patients with HCV RNA <LOD Over Time, n/N (%)

	GT 2/3 Treatment-naïve 8 wks (N=10)	GT 1 Null Responders 12 wks (N=10)	GT 1 Treatment-naïve 12 wks (N=25)	GT 2/3 Treatment-experienced 12 wks (N=25)
Week 1	6/10 (60)	1/10 (10)	7/25 (29)	8/25 (32)
Week 2	10/10 (100)	7/10 (70)	17/24 (71)	21/25 (84)
Week 4	10/10 (100)	10/10 (100)	25/25 (100)	25/25 (100)
EOT	10/10 (100)	9/9 (100)	25/25 (100)	21/21 (100)
SVR 4	10/10 (100)	1/9 (11)	22/25 (88)	12/15 (80)
SVR 8	10/10 (100)	1/9 (11)	-	
SVR 12	10/10 (100)	-	-	-

Gane E, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1113.

Electron Study:
SVR 4 = 88% in GT1 Naive



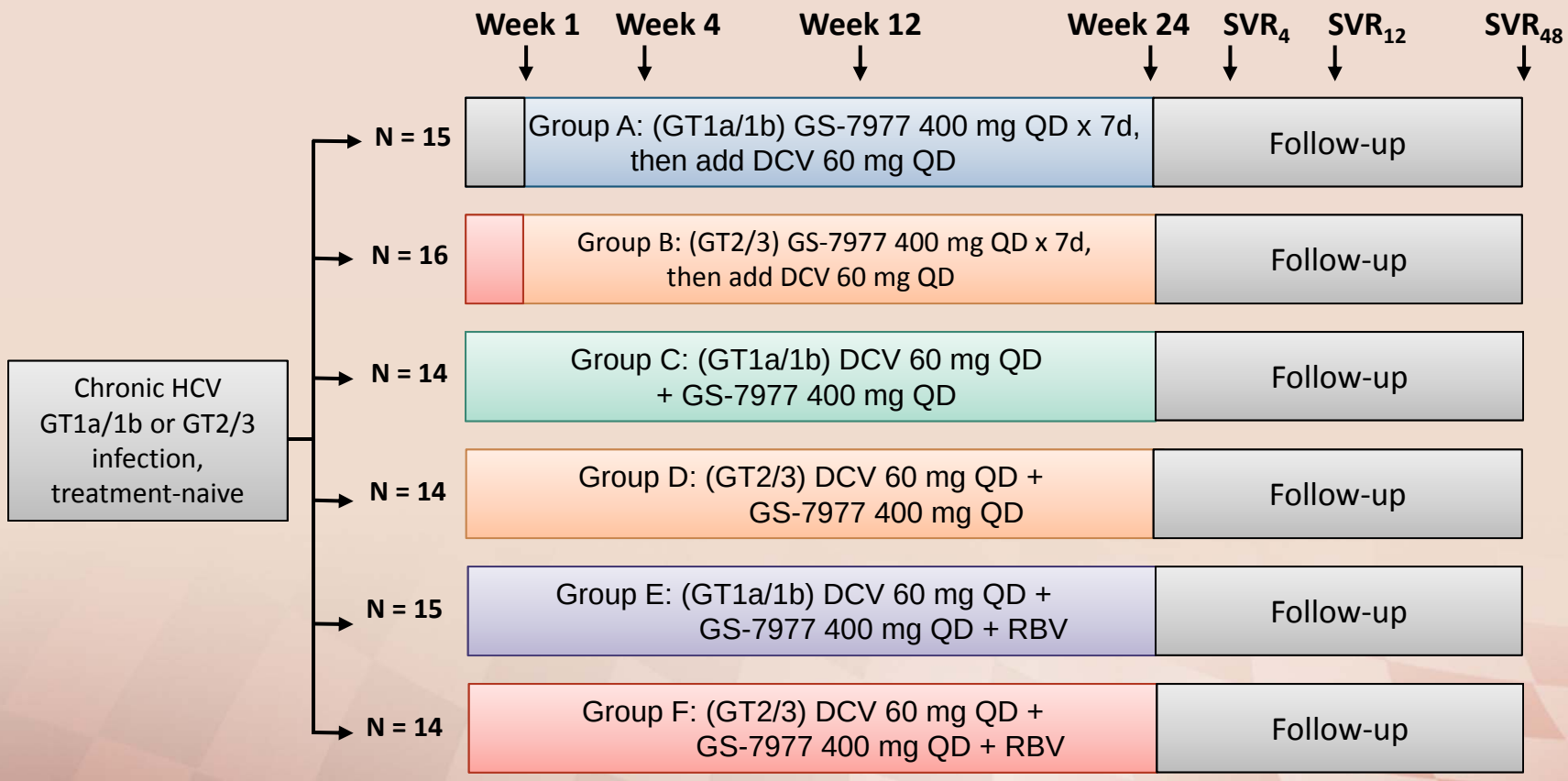
Gane E, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1113.

Electron Study: Conclusions

- 88% of treatment-naïve GT 1 patients achieved SVR4 following 12 weeks of therapy with GS-7977 + RBV
  - This result suggests that 12 weeks of GS-7977 + RBV can potentially provide higher rates of SVR in treatment-naïve GT1 patients than those achieved with longer durations of PI + PEG/RBV
- The combination of GS-7977 + RBV was well tolerated in all genotypes regardless of prior treatment history
- No virologic breakthrough occurred in any arm, suggesting a high barrier to resistance
  - To date, the S282T mutation has not been seen in any GS-7977/RBV regimen
- These results demonstrate the utility of GS-7977 across a broad spectrum of HCV disease treatment

Gane E, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1113.

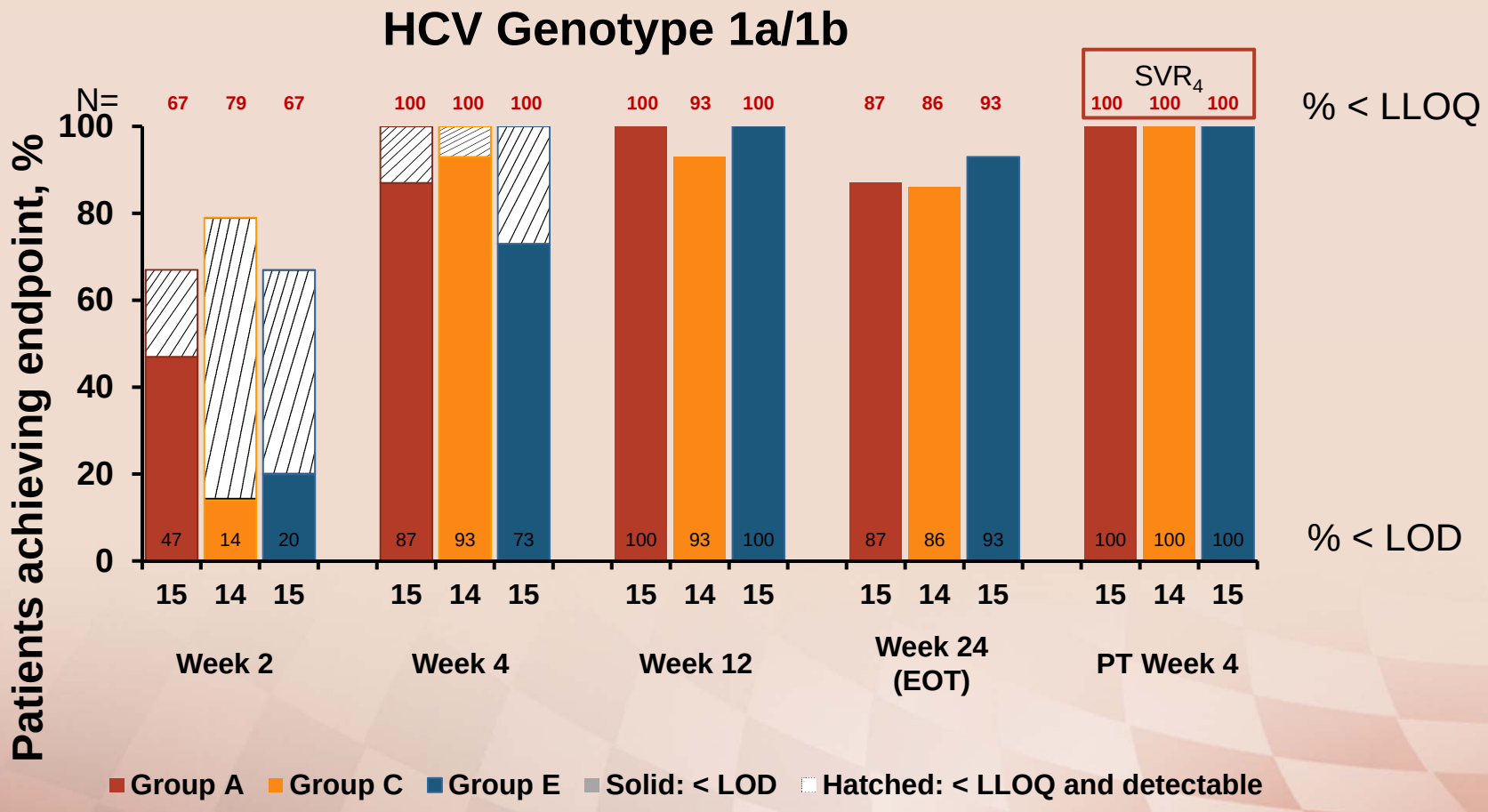
Study AI444-040: Treatment with GS-7977 + BMS-790052



RBV: 1000-1200 mg daily according to body weight for GT1 patients ; 800 mg daily for GT2/3 patients

Sulkowski M, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1422.

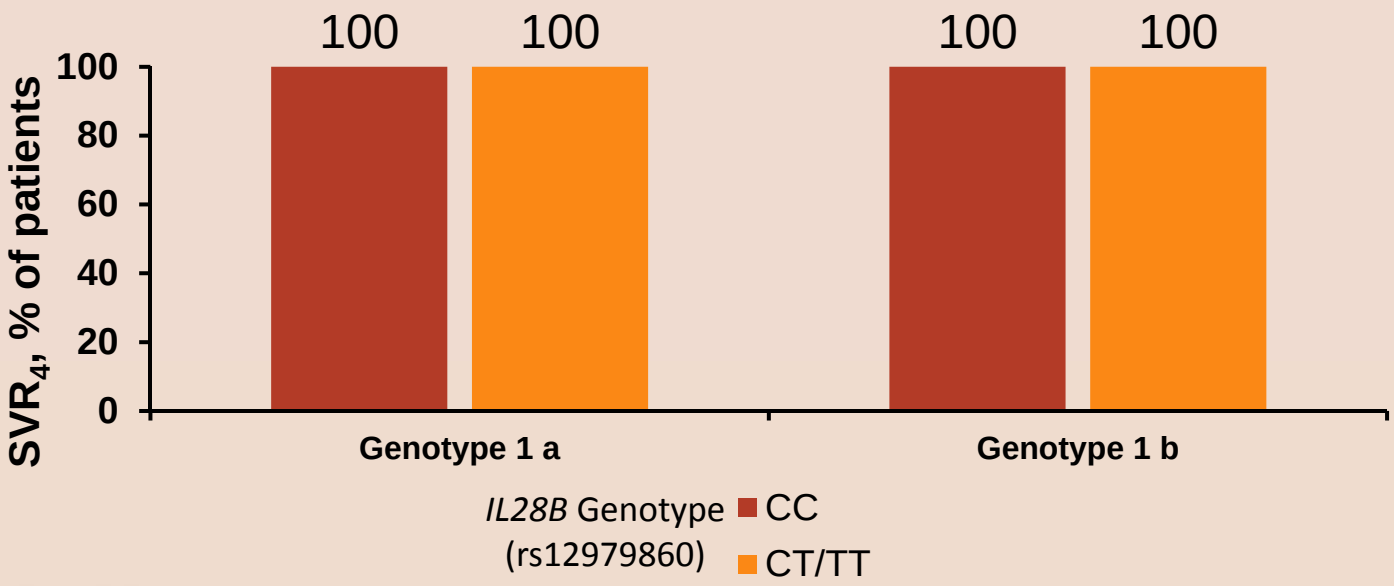
Study AI444-040: Key Results



mITT analysis, bars not reaching 100% after Week 4 reflect missing values.
PT, post treatment

Sulkowski M, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1422.

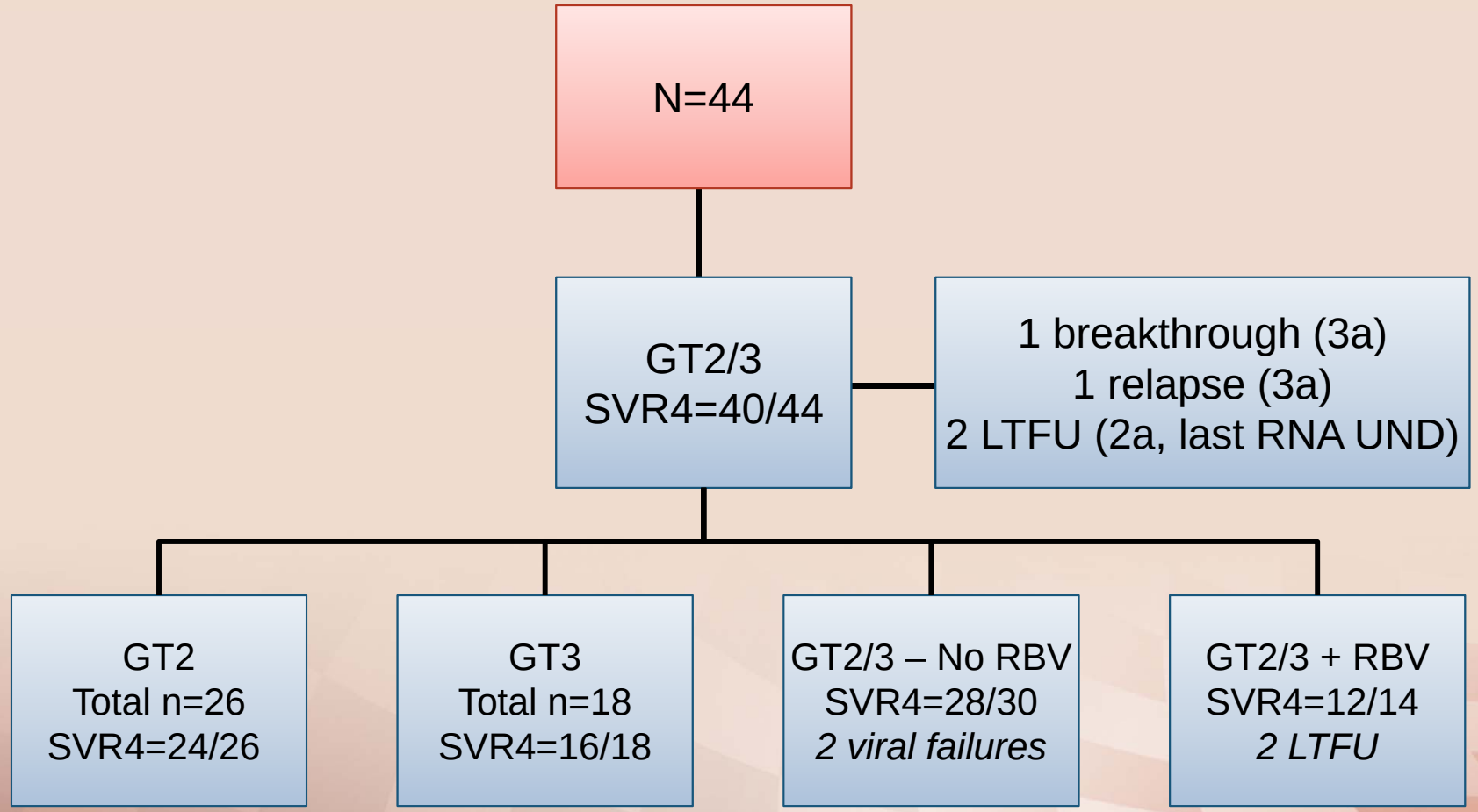
Study AI444-040: Key Results



- Overall SVR4 – 95.5% across GT 1,2 & 3
- GT1: 100% of patients (44/44) achieved SVR4
- No difference in SVR4 by HCV GT1 subtype or *IL28B* genotype
- Ribavirin did not increase the magnitude of HCV RNA decline or influence SVR

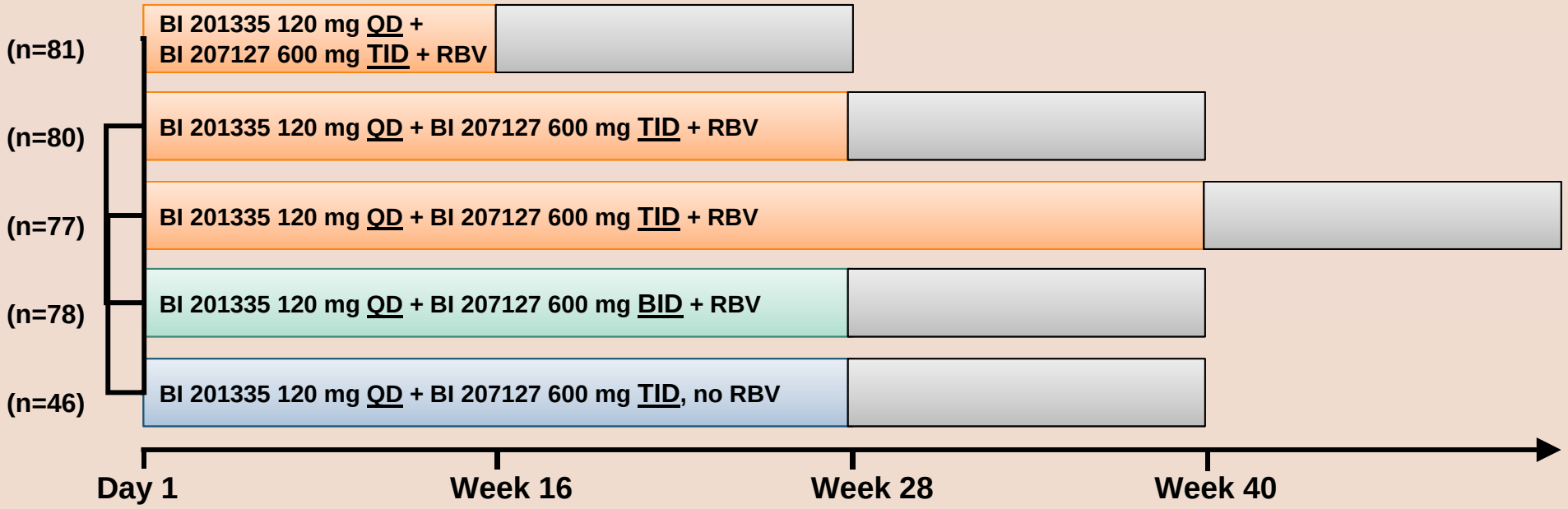
Sulkowski M, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1422.

Study AI444-040: GT2/3 Naïve



Sulkowski M, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1422.

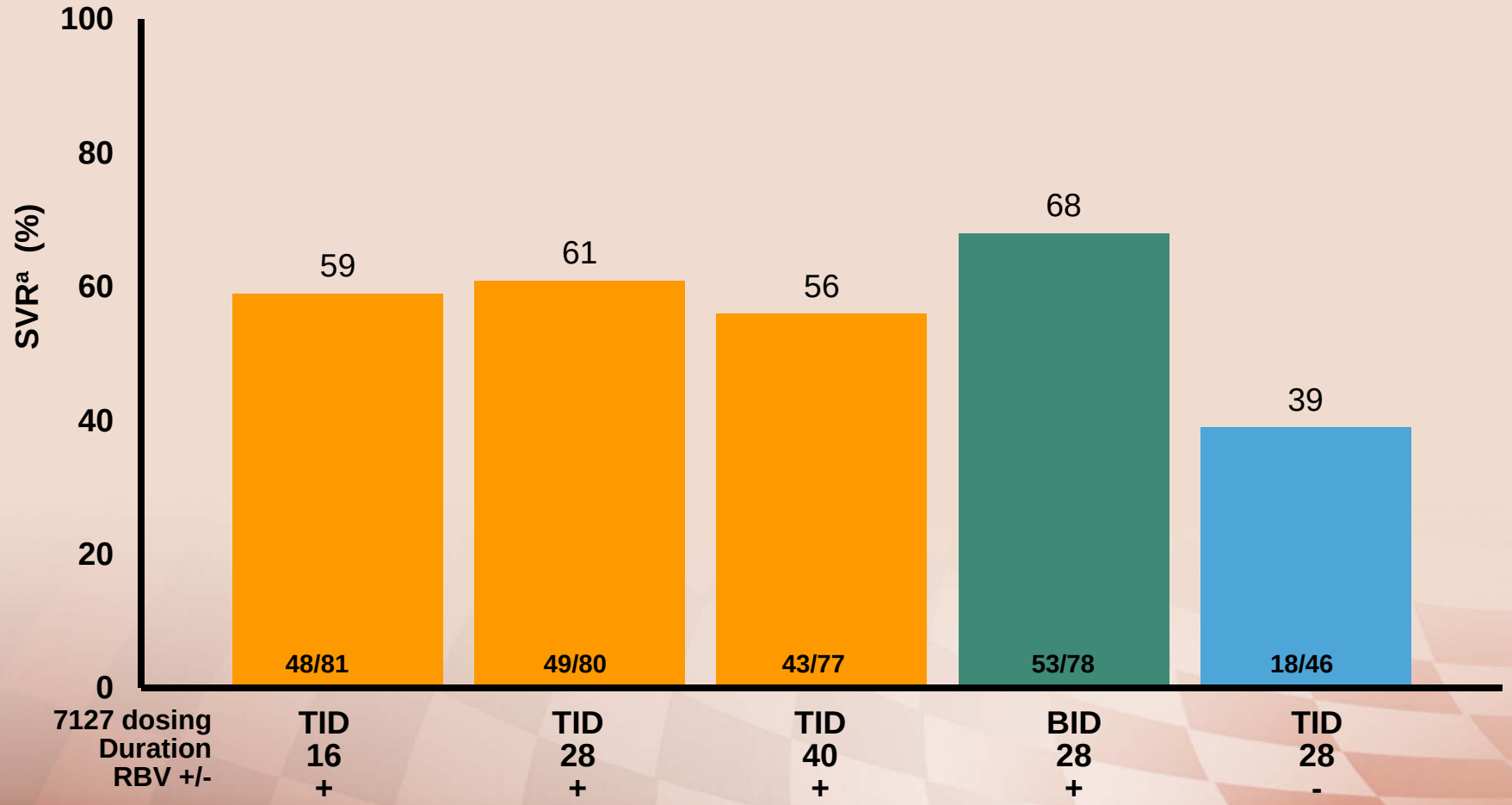
SOUND-C2 Study: BI 201335 (PI) AND BI 207127 (NNI)



- Phase IIb, multi-centre, open-label, randomised (1:1:1:1:1)
  - Treatment-naïve patients with chronic HCV GT-1
- Stratified by GT-1 subtype (1a vs 1b) and *IL28B* genotype (CC vs non-CC)
- Compensated cirrhosis allowed; 18–75 years of age, HCV RNA >100,000 IU/mL
- Primary endpoint: SVR 12
- All analyses are ITT

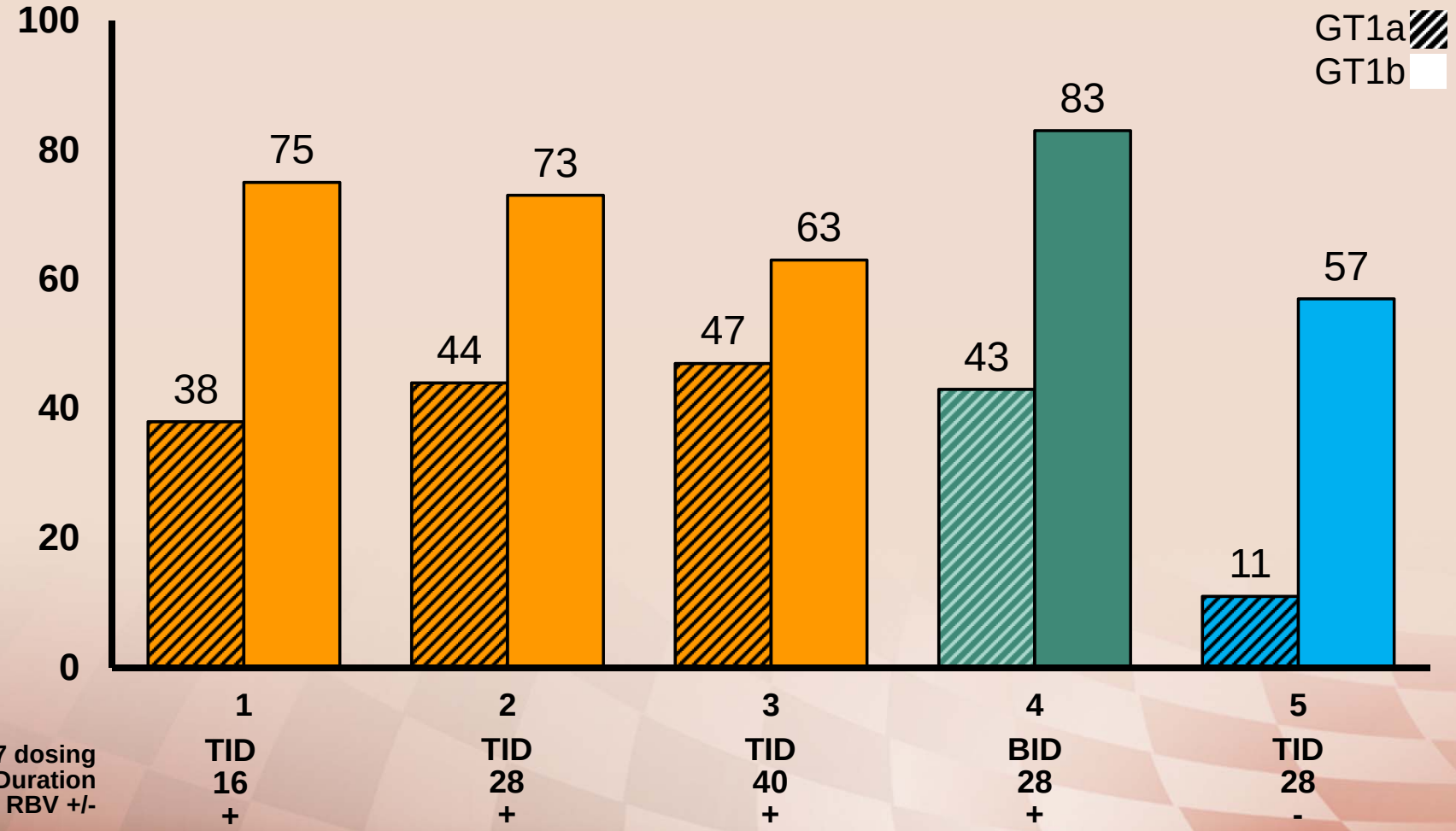
Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 101.

SOUND-C2 Study: Primary Endpoint: Sustained Virological Response (ITT)



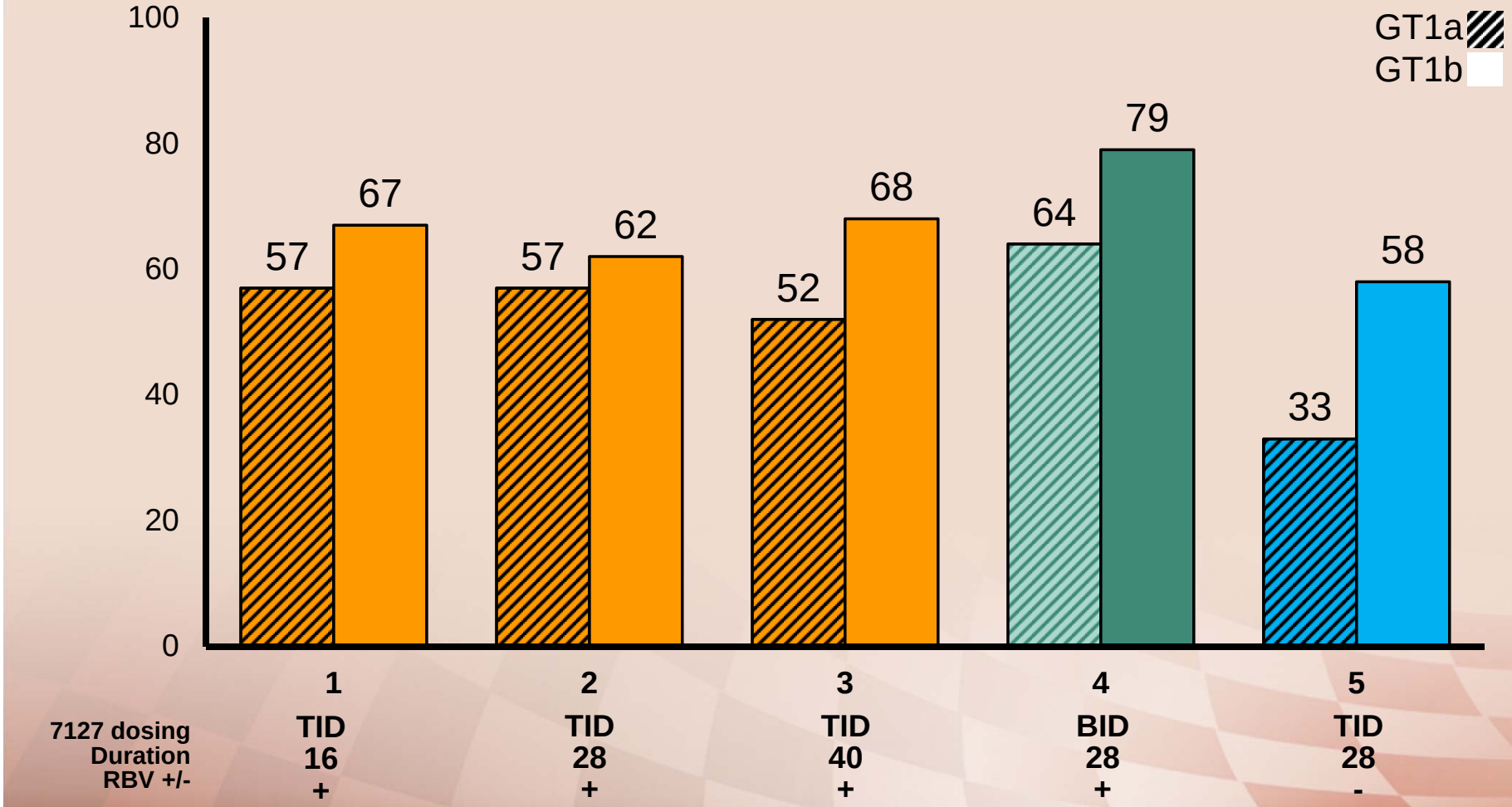
Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 101.

SOUND-C2 Study: SVR According to Subtype (GT-1a and GT 1b) (ITT)



Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 101.

SOUND-C2 Study: SVR According to *IL28B* GT (CC vs non-CC) (ITT)



Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 101.

SOUND-C2 Study: Conclusions

- The IFN-free combination of BI 201335 + BI 207127 + RBV demonstrated high efficacy and a good safety profile
  - Combination with ribavirin remains necessary
  - The BID (for BI 207127) regimen demonstrated the most favourable safety and tolerability profile with a low rate
  - 48% overall SVR in cirrhosis

Zeuzem S, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 101.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

Discussion

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ADVANCES IN CHRONIC HEPATITIS C MANAGEMENT AND TREATMENT

Reporting from

The 47th Annual Meeting of the
European Association for the Study of the Liver (EASL)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC