Simeprevir (TMC435)

Antiviral Drugs Advisory Committee Meeting

October 24, 2013

janssen
PHARMACEUTICAL COMPANIES
OF Johnson & Johnson

Opening Remarks

Gaston Picchio, PhD
Hepatitis Disease Area Leader
Janssen

Proposed Indication for Simeprevir

- A HCV NS3/4A protease inhibitor indicated in combination with PR
  - For the treatment of GT 1 chronic HCV
  - In adult patients with compensated liver disease, including cirrhosis
  - Treatment-naïve, or
  - Previously treated with (Peg)IFN with or without RBV
    - Including prior null responders, partial responders and relapsers

HCV = hepatitis C virus
(Peg)IFN/±R = pegylated or non-pegylated interferon with or without ribavirin

Presentation Agenda

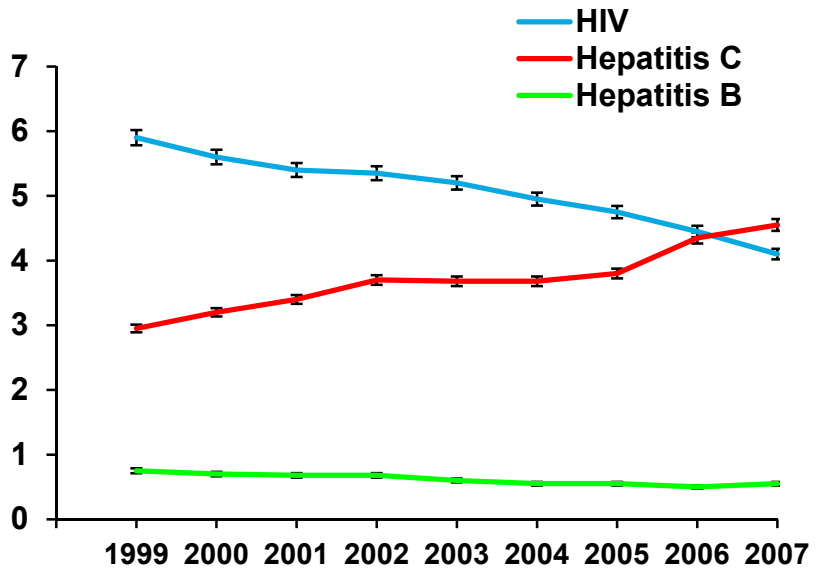
HCV Treatment	**Nezam H. Afdhal, MD** Professor of Medicine Harvard University Chief of Hepatology Director, Liver Center Beth Israel Deaconess Medical Center Boston, MA
Overview	**Katia Boven, MD** Medical Department Head Infectious Diseases and Vaccines
Efficacy	**Maria Beumont, MD** Senior Director Medical Team Lead SMV
Virology	**Oliver Lenz, PhD** Scientific Director Clinical Virology Lead SMV
Safety	**Wolfgang Jessner, MD** Medical Director, Clinical Development Trial Physician SMV
Treatment Management	**Gaston Picchio, PhD** Hepatitis Disease Area Leader

Evolving Risks and Benefits of HCV Treatment in the Era of Direct-acting Antivirals

Nezam H. Afdhal, MD
Chief of Hepatology
Director, Liver Center
Beth Israel Deaconess Medical Center
Boston, MA

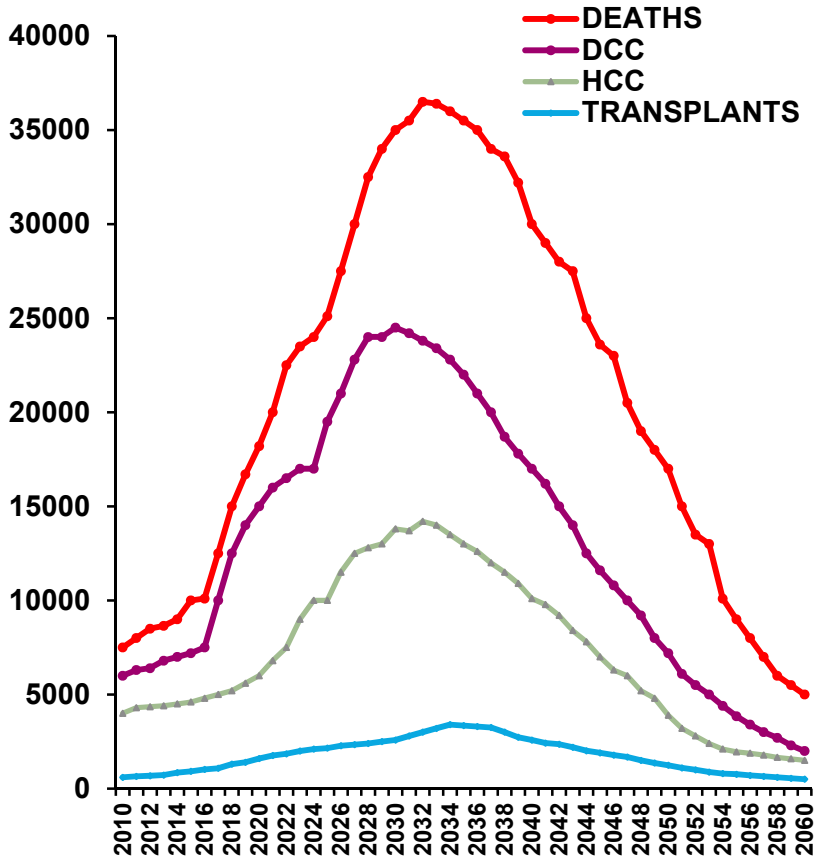
Over 5 Million Americans Living with HCV[1]: A Looming Healthcare Crisis…

Mortality Rates of HBV, HCV and HIV: United States, 1999-2007[2]



"2007 hepatitis C-associated deaths had overtaken HIV as a cause of mortality in the United States. To achieve declines in mortality similar to those seen with HIV will require new policy directions and commitment to detect and link infected persons to care and successful treatment."

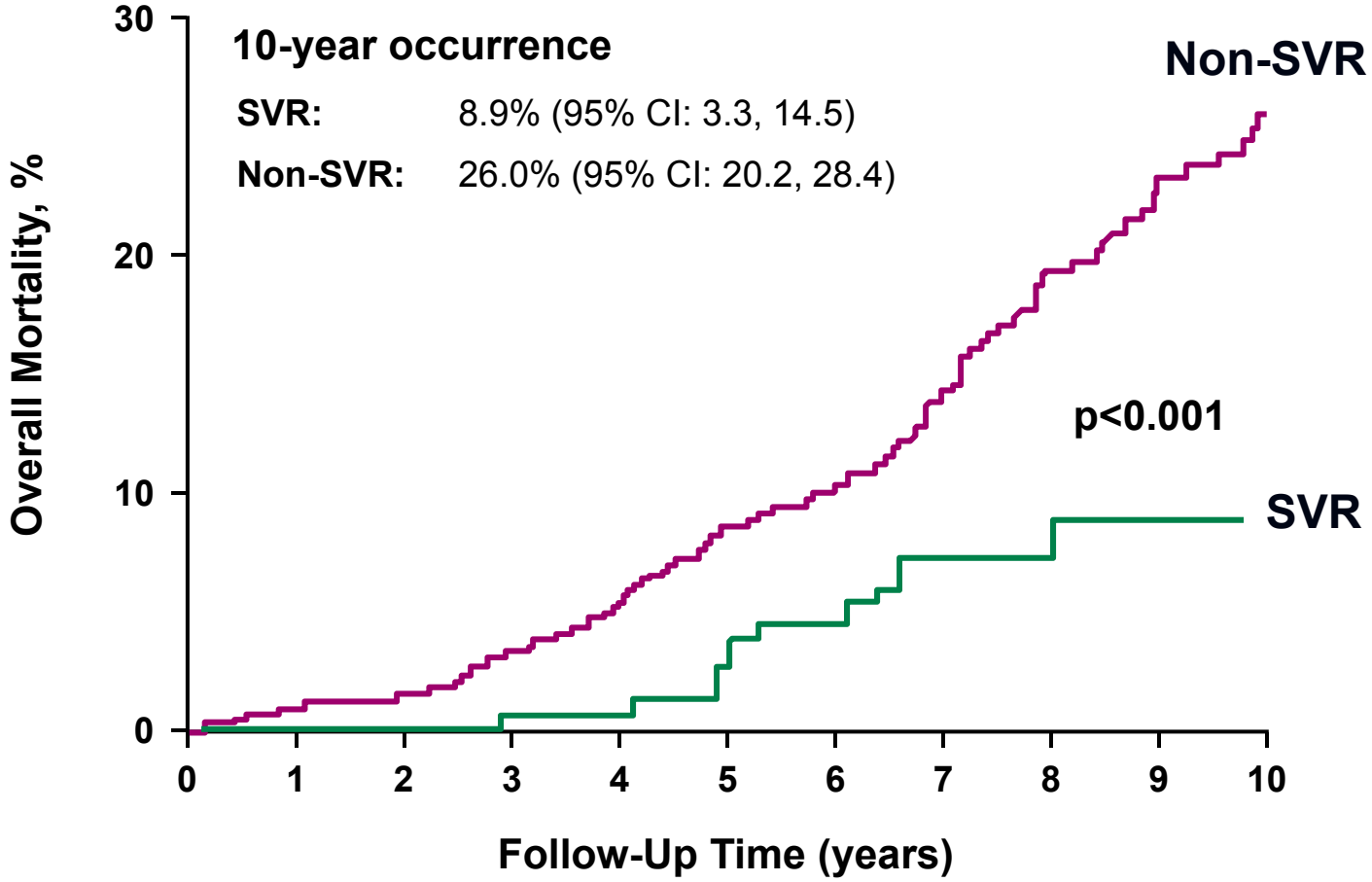
Morbidity and Mortality Predictions: United States[3]



1. Chak et al., *Liver International*. 2011; 1090-1101.
2. Adapted from Ly KN, et al. *Ann Intern Med.* 2012;156:271-278.
3. Adapted from Rein, RB et al. *Dig Liver Dis.* 2011;43:66-72.

SVR Saves Lives

Long-term follow-up of patients with cirrhosis post-treatment

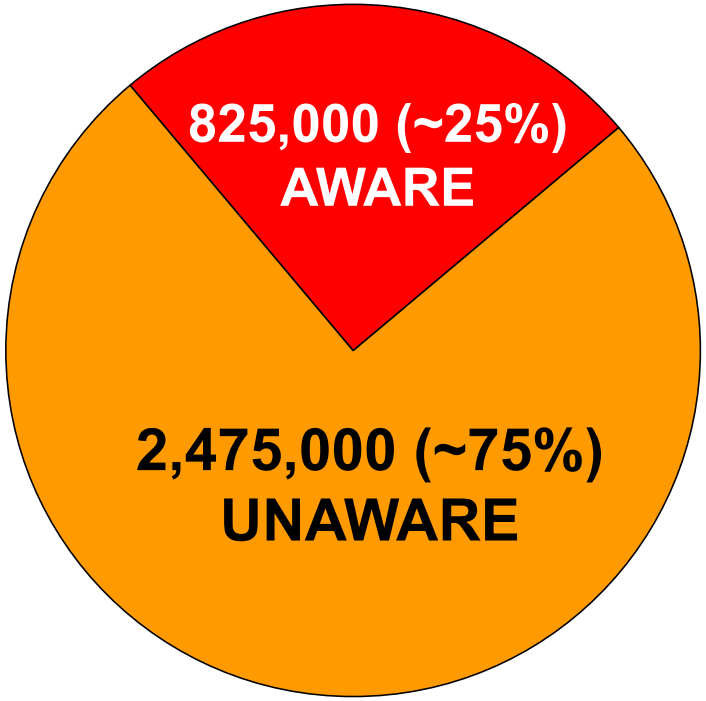


Van de Meer et al, JAMA 2012

Most Patients with Chronic Hepatitis C in the US are not Aware That They are Infected

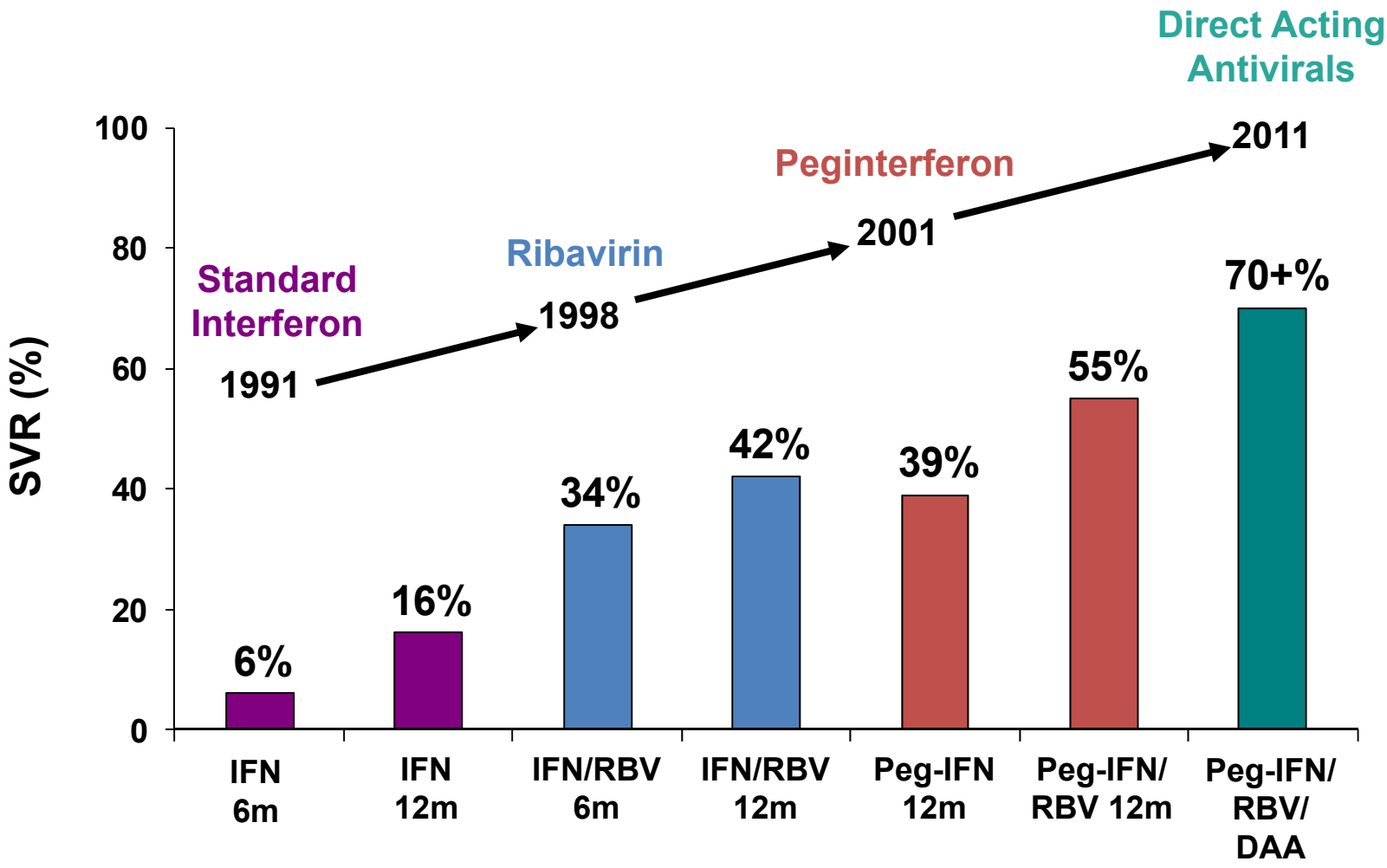
NHANES III Survey

Approximately 3,300,000 individuals are infected with the hepatitis C virus in the United States



Adapted from Colvin HM, Mitchell AE. Hepatitis and liver cancer: A national strategy for prevention and control of hepatitis B and C. Washington, DC: The National Academies Press; 2010.

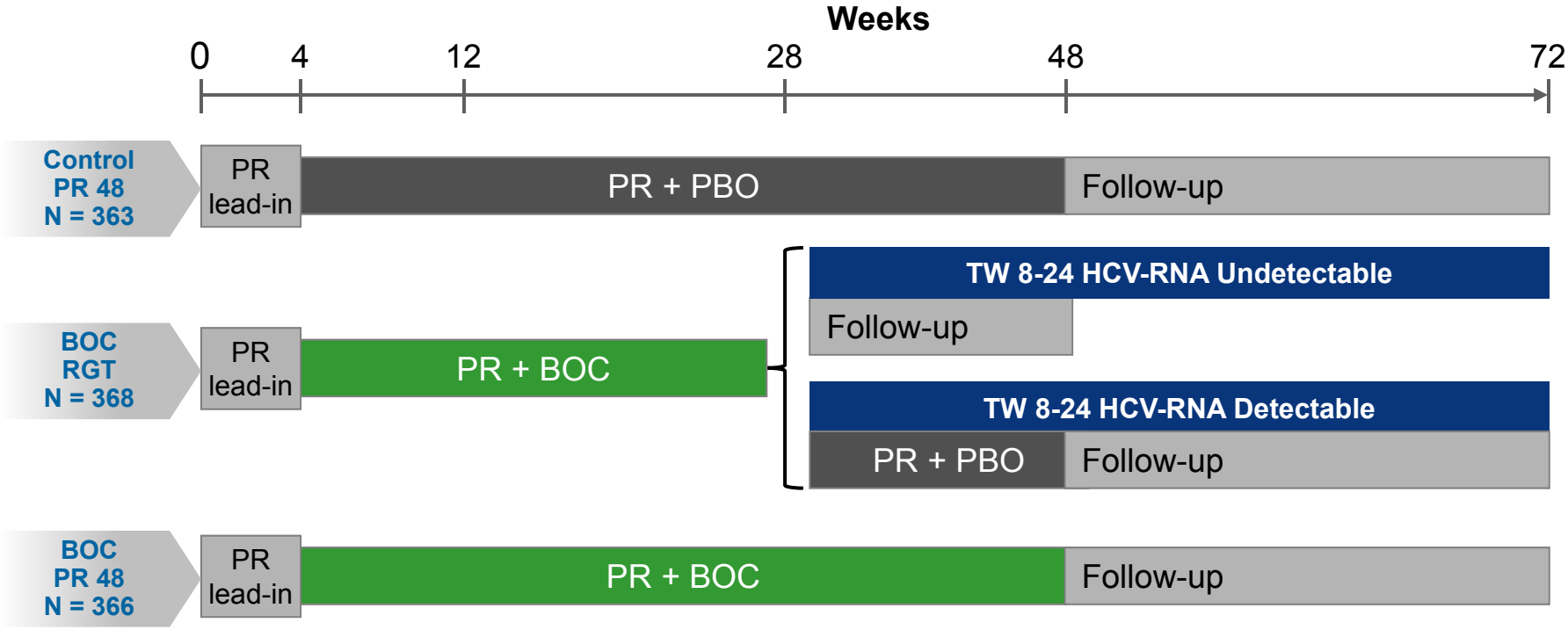
Milestones in Therapy of HCV: Average SVR Rates from Clinical Trials



Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.

SPRINT-2: Study Design

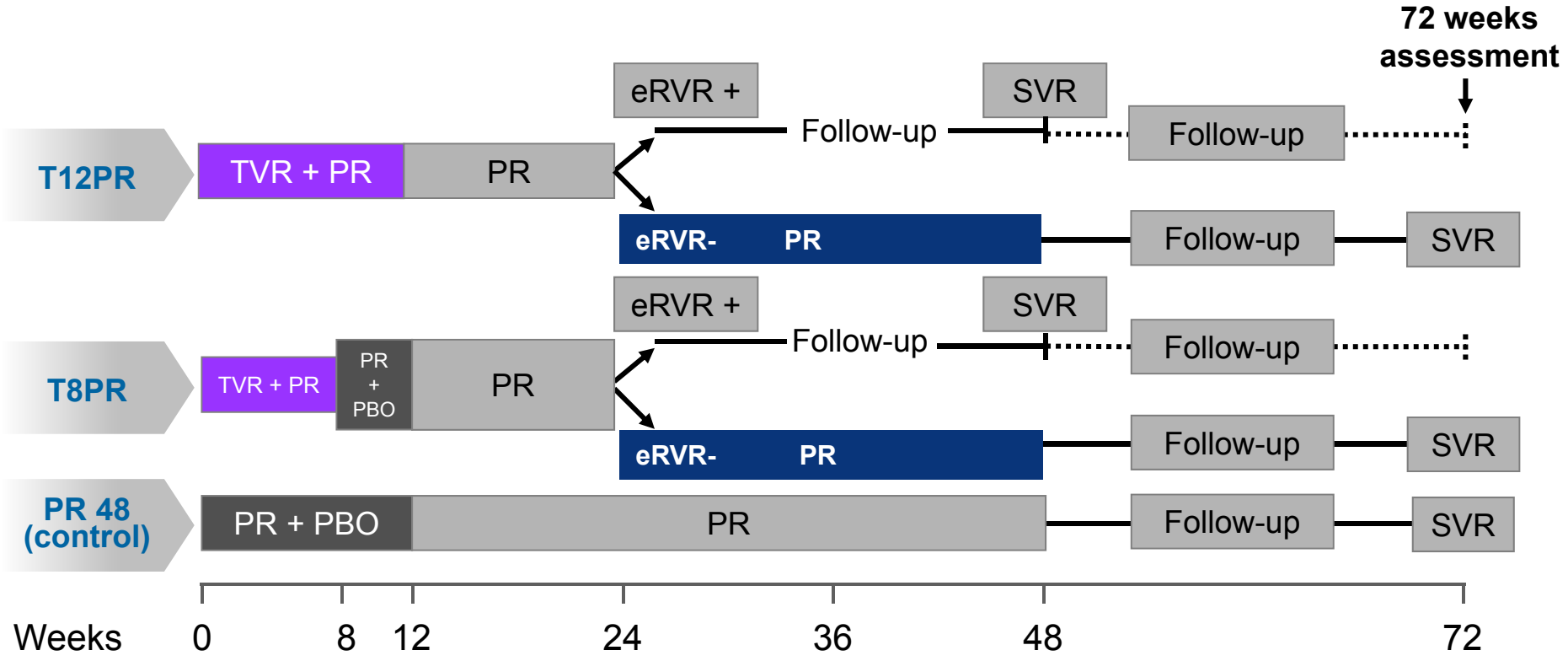
Study to compare safety/efficacy of two treatment strategies with boceprevir added to peginterferon/ribavirin (PR) versus PR alone in treatment naïve HCV genotype 1 patients



Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.

ADVANCE: Study Design

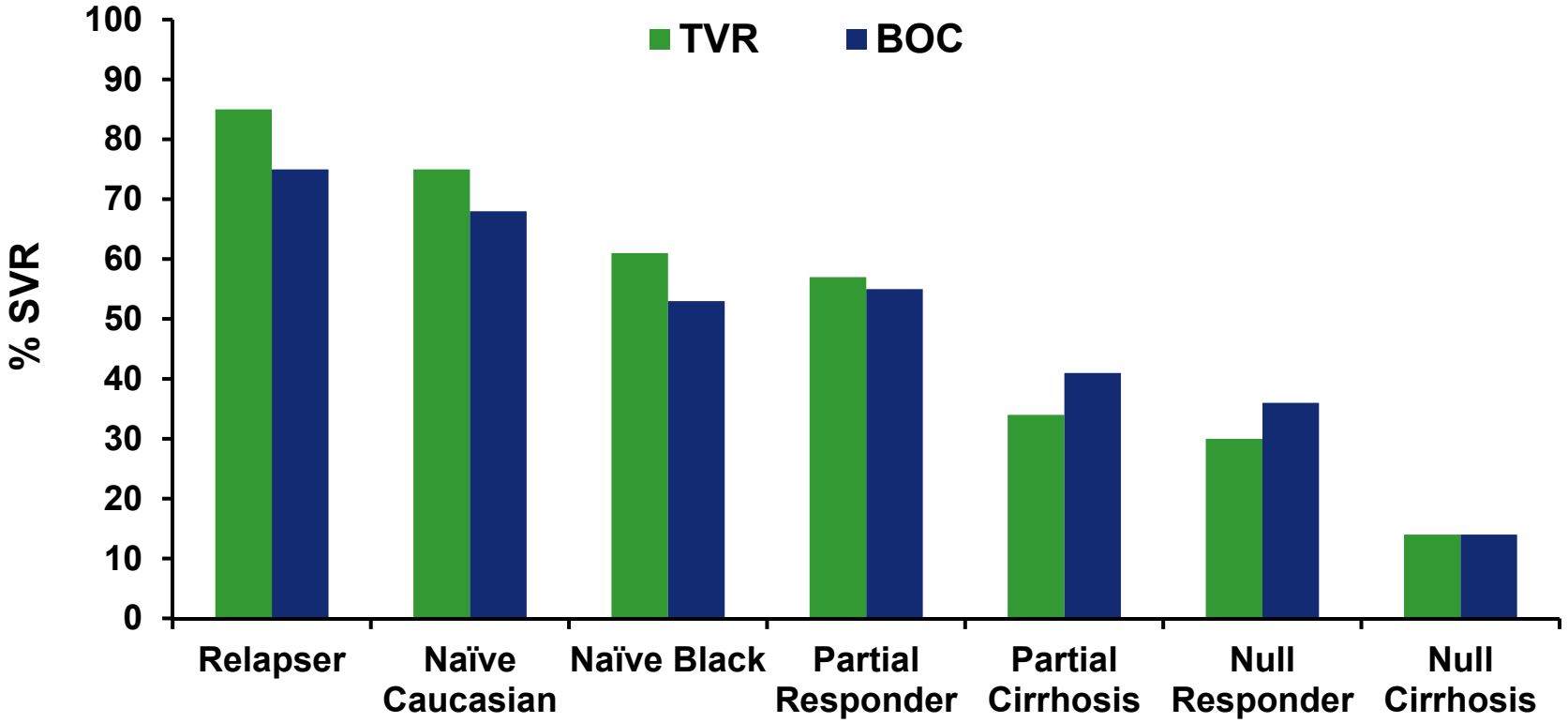
Study to compare efficacy/safety of 12 or 8 weeks of telaprevir in combination with 24 or 48 weeks of peginterferon alfa-2a/ribavirin in a response-guided regimen, with standard treatment for 48 weeks



(T) TVR = telaprevir 750 mg q8h; Pbo = Placebo; (P) Peg-IFN = pegylated interferon alfa-2a (40 kD) 180 µg/wk;
(R) RBV = ribavirin 1,000 or 1,200 mg/day

eRVR = HCV RNA undetectable at week 4 and week 12

Telaprevir and Boceprevir SVR24 by Patient Characteristics



Jacobson IM et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *NEJM*. 2011; 364: 2405-16.
Sherman KE et al. Response-Guided Telaprevir CombinationTreatment for Hepatitis C Virus Infection. *NEJM.* 2011; 365: 1014-24.
Zeuzem S et al. Telaprevir for Retreatment of HCV Infection. *NEJM*. 2011; 364: 2417-28.
Bacon BR et al. Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection. *NEJM*. 2011;364:1207-17.
Poordad F et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. *NEJM.* 2011;364:1195-206.

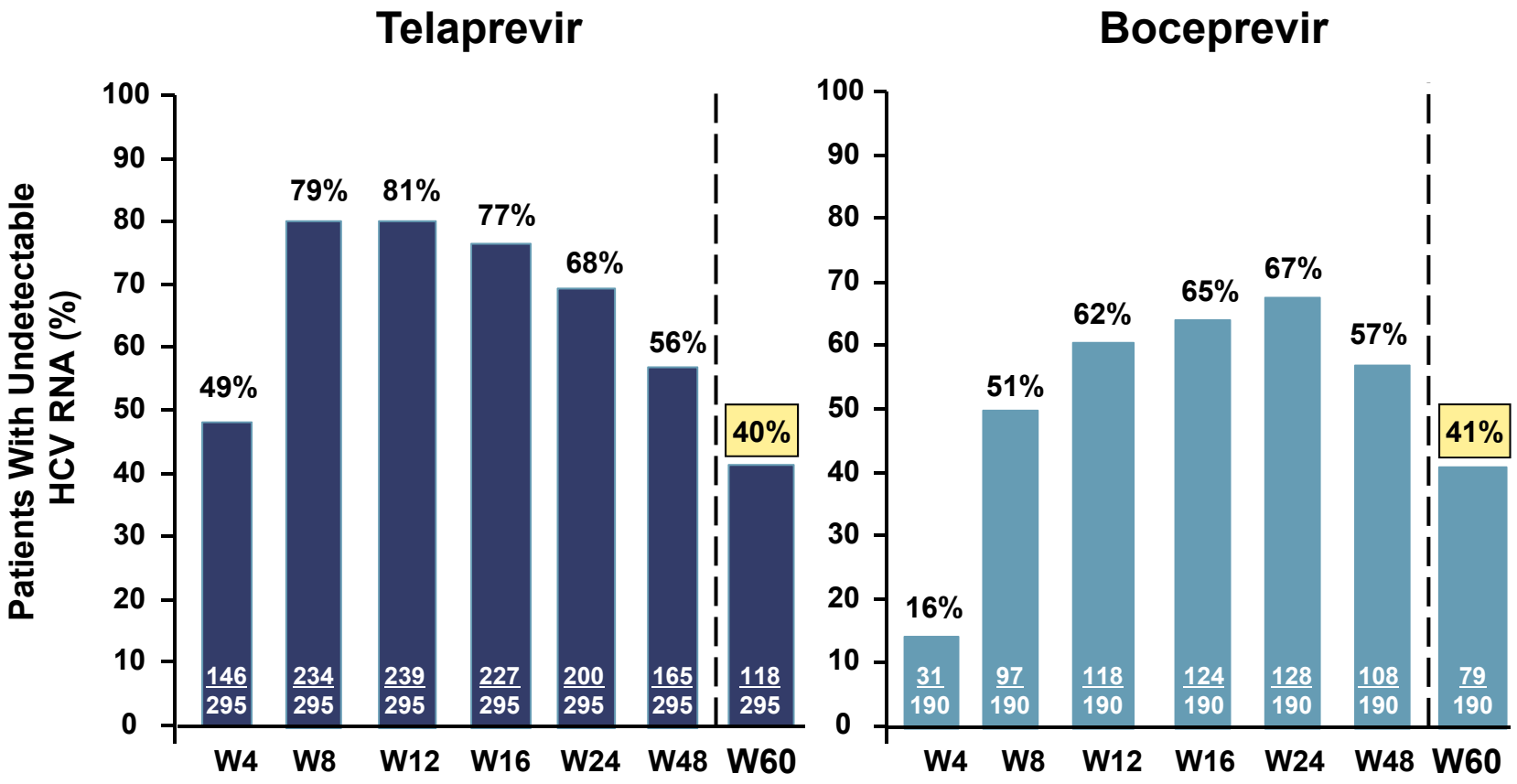
Telaprevir and Boceprevir DAA Related Adverse Events

- Telaprevir
  - Anemia
  - Anorectal disorders
  - Rash
  - Pruritus
- Boceprevir
  - Anemia
  - Neutropenia
  - Dysgeusia

One third of patients discontinued treatment before 24 weeks with TVR or BOC + PR*

* Belperio PS et al. *Clinical Gastroenterology and Hepatology* Available online 21 March 2013

Real Life Data – Patients with Cirrhosis
CUPIC: Virological Response (ITT) SVR12



Hezode,C et al, APASL 2013

Real Life Data – Patients with Cirrhosis

CUPIC: SVR12 Safety Findings

	Telaprevir W60 N=295 n (%)	Boceprevir W60 N=190 n (%)
Serious adverse events (SAEs)	535 in 160 patients (54.2)	321 in 97 patients (51.0)
Premature discontinuation / Due to SAEs	139 (47.1) / 63 (21.3)	80 (42.1) / 27 (14.2)
Death	7 (2.4)	3 (1.6)
Infection (Grade 3/4)	27 (9.1)	8 (4.2)
Hepatic decompensation (Grade 3/4)	15 (5.1)	9 (4.7)
Anemia (Grade 3/4: Hb < 8 g/dL)	38 (12.9)	19 (10)
Rash (Grade 3/SCAR)	16 (5.4) / 2 (0.6)	2 (1.0) / 0
EPO use / Blood transfusion	168 (57) / 53 (18)	119 (62.6) / 26 (13.7)
GCSF use	8 (2.7)	13 (6.8)
TPO use	6 (2)	3 (1.6)

SCAR: severe cutaneous adverse reaction

Fontaine H et al, EASL 2013

Currently Available HCV Protease Inhibitors: Pill Burden

Boceprevir

4 capsules x TID
(7 to 9 hours apart)

Medication Guide:
"Take VICTRELIS with food (a meal or light snack)."

Telaprevir

2 tablets x TID
(7 to 9 hours apart)

Medication Guide:
"Eat a meal or snack that contains about 20 grams of fat, within 30 minutes before you take each dose of INCIVEK."

Approved 1st-Generation Protease Inhibitors

Key Attributes	Challenges
Potent antiviral activity	Safety and tolerability concerns
Improved response rates in combination with IFN/RBV	Complicated treatment algorithm Pill burden & administration with high-fat food
Proven mechanism of action: • Prevents the proteolytic cleavage of the HCV polyprotein, a key step in viral replication	Low to modest SVR in GT1 prior null or partial responders to SOC
	Low barrier to resistance and limited pan-genotypic activity
	Drug-drug interactions

Second-generation PIs should be targeted towards an improved outcome in hard-to-treat populations, enhanced tolerability, and a simplified regimen

Abbreviations: IFN, interferon; PI, protease inhibitor; RBV, ribavirin; SOC, standard of care.

Poordad. *Journal of Viral Hepatitis* 2012;19,449–464; Schaefer EAK and Chung RT. *Gastroenterology* 2012;142(6):1340-1350.

The Future of HCV Therapy: Selected IFN-Free Regimens in Prior Null Responders

Trial	IFN-free Regimen	Treatment Duration	Patient Population
COSMOS[1]	simeprevir + sofosbuvir	12 weeks	Prior null responders non-cirrhotic
ELECTRON[2]	sofosbuvir + ledipasvir + ribavirin	12 weeks	Prior null responders non-cirrhotic
AVIATOR[3]	ABT-450/r + ABT-333 + ABT-267 + ribavirin	12 weeks	Prior null responders non-cirrhotic

[1]Lawitz E, et al. CROI 2013
[2]Gane E, et al. EASL 2013
[3]Kowdley K, et al. EASL 2013

Summary

- HCV is the most common chronic blood-borne infection in the United States and is a major preventable cause of morbidity and mortality
- Effective antiviral therapy leading to viral eradication improves survival
- First generation protease inhibitors
  - Increased treatment efficacy in some populations
  - Added treatment challenges
  - Had sub-optimal outcomes in many populations
- Simeprevir will provide an important step forward in the evolution of treatment for HCV

Overview

Katia Boven, MD

Medical Department Head
Infectious Diseases and Vaccines
Janssen

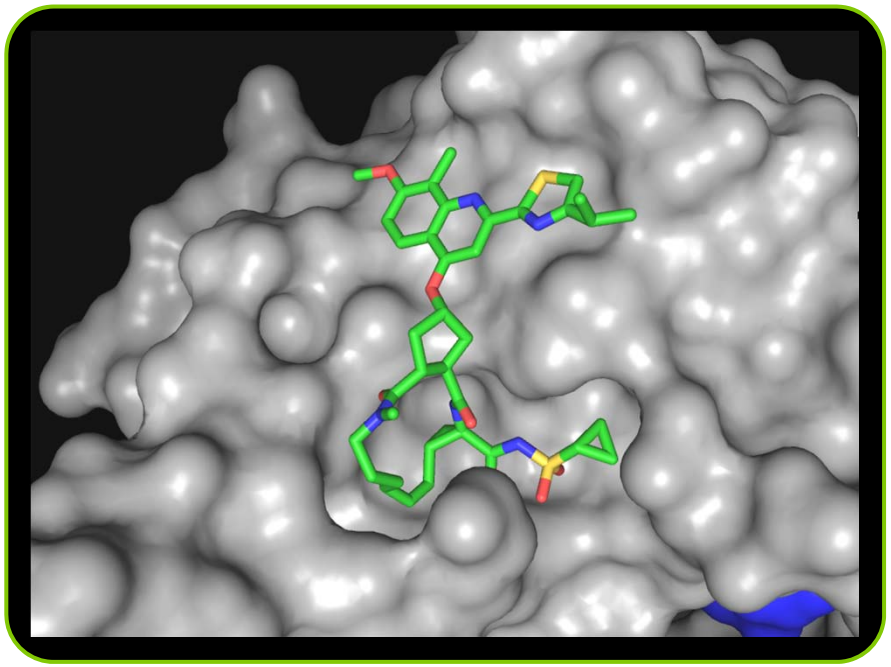
Important Goals for SMV Development Program

- Achieve high cure rates, also in difficult-to-cure patients (prior relapse and non-responder patients, patients with advanced fibrosis)
- Shorten treatment duration, with simplified treatment algorithm
- One pill, once daily regimen
- No major additional safety or tolerability issues

SMV = simeprevir

Simeprevir: An Oral Once Daily HCV Protease Inhibitor

- Non-covalent, macrocyclic HCV NS3/4A protease inhibitor
- Active in genotypes 1, 2, 4, 5, 6
- Potent in vitro activity:
  - EC_{50} = 28 nM in a genotype 1a replicon
  - EC_{50} = 9.4 nM in a genotype 1b replicon



EC_{50}, 50% effective concentration

Clinical Pharmacology of Simeprevir

- One pill, once-daily dosing
- Exposure increased by ~60% with any type of food
- Targeted to the liver, substrate of transporter OATP
- Excretion primarily via feces, minimal in urine (<1%)
- Metabolism primarily via CYP3A
  - SMV plasma exposure is modified by CYP3A inhibitors and inducers
- Well characterized drug-drug interaction profile
  - No interaction with oral contraceptives and immunosuppressants

OATP = organic anion transporter protein; CYP3A4 = cytochrome P450 3A4;

Selection of Optimal Dose and Duration of Simeprevir in Combination with PR (Phase 2)

Treatment-naïves (C205) and treatment-experienced (C206):

- Numerically higher SVR and lower viral relapse rate with SMV 150 mg QD compared to lower doses in some subgroups
- No consistent difference between SMV treatment duration groups of 12, 24 or 48 weeks, no additional benefit beyond 12 weeks

→ SMV 150 mg QD for 12 weeks selected for further development

PR = pegylated interferon and ribavirin
QD = once daily

Clinical Studies of Simeprevir with PR in Chronic HCV Patients: Phase 2

Study	Target Population	Study Type	Phase
C201 **OPERA-1**	HCV GT 1 Treatment Naïve and Experienced	Randomized placebo-controlled proof of concept	Phase IIa
C202	HCV GT 2-6 Treatment Naive		
C205 **PILLAR**	HCV GT 1 Treatment Naive	Randomized placebo-controlled dose finding	Phase IIb
C206 **ASPIRE**	HCV GT 1 Treatment Experienced		

Clinical Studies of Simeprevir with PR in Chronic HCV Patients: Phase 3

Study	Target Population	Study Type
C208 **QUEST-1**	HCV GT 1 Treatment Naïve Patients	Randomized placebo-controlled superiority
C216 **QUEST-2**		
HPC3007 **PROMISE**	HCV GT 1 Patients with Prior Relapse after PR	Randomized, placebo-controlled superiority

Efficacy

Maria Beumont, MD

Senior Director,
Medical Team Leader SMV
Janssen

Simeprevir Clinical Program

- **Objectives**

  Assess efficacy and safety of SMV in combination with PR for 24 or 48 weeks
- **Pivotal studies conducted in GT 1 HCV patients** evaluated SMV 150 mg during 12 weeks in combination with PR
  - Treatment-naïve patients
  - Prior PR treatment-experienced patients
  - All stages of liver fibrosis including compensated cirrhosis
- **Primary endpoint**: Sustained Virological Response (SVR) defined as:
  - Undetectable HCV RNA at end of treatment (EOT)
  - HCV RNA < 25 IU/mL 12 weeks after planned EOT

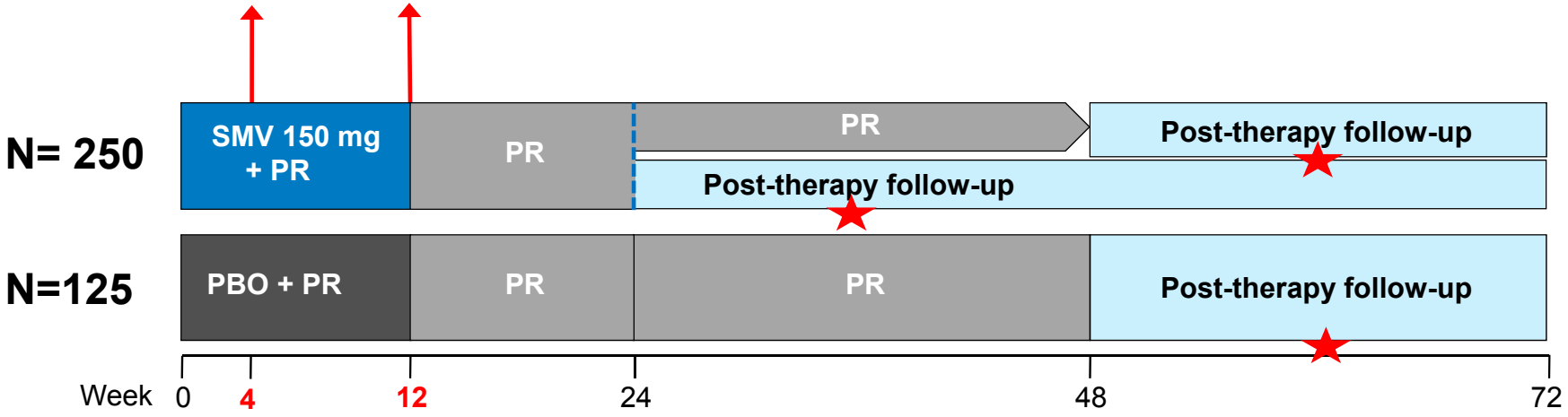
Simeprevir Clinical Studies

Study	Target Population	N	Study Type	Phase / Objectives
C208 **QUEST-1**	HCV GT 1 Naive	N=264 SMV + PR N=130 PBO + PR	Randomized Placebo controlled superiority	Phase III Confirm adequacy of RGT criteria Assess PegIFNα2b (C216)
C216 **QUEST-2**		N=257 SMV + PR N=134 PBO + PR		
HPC3007 **PROMISE**	HCV GT 1 Relapser	N=260 SMV + PR N=133 PBO + PR	Randomized Placebo controlled superiority	Phase III Assess RGT in Relapser patients
C206 **ASPIRE**	HCV GT 1 Treatment Experienced	N=396 SMV + PR N= 66 PBO + PR	Randomized Placebo controlled superiority	Phase IIb Dose selection

Phase 3 Trial Design
Studies C208/C216/3007

Response-Guided Therapy (RGT) criteria to guide PR treatment duration:

- HCV RNA <25 IU/mL at **Week 4** and HCV RNA undetectable at **Week 12** → **24 weeks**
- HCV RNA ≥25 IU/mL at **Week 4** or HCV RNA detectable at **Week 12** → **48 weeks**



- Stopping rules at week 4, 12, 24 and 36
- Patients stratified by HCV subtype and *IL28B*
- **Primary endpoint:** SVR12 ★ (12 weeks after planned end of treatment)

HCV RNA was assed using Roche COBAS Taqman HCV/HPS v 2.0 assay
RGT – Response-Guided treatment
PR - PegIFNα-2a: 180 µg once weekly and RBV 1000 or 1200 mg/day (weight dosed BID regimen)
- PegIFNα-2b: pre-filled pens per weight band, and RBV 800-1400 mg/day (weight dosed BID regimen) (C216 only)

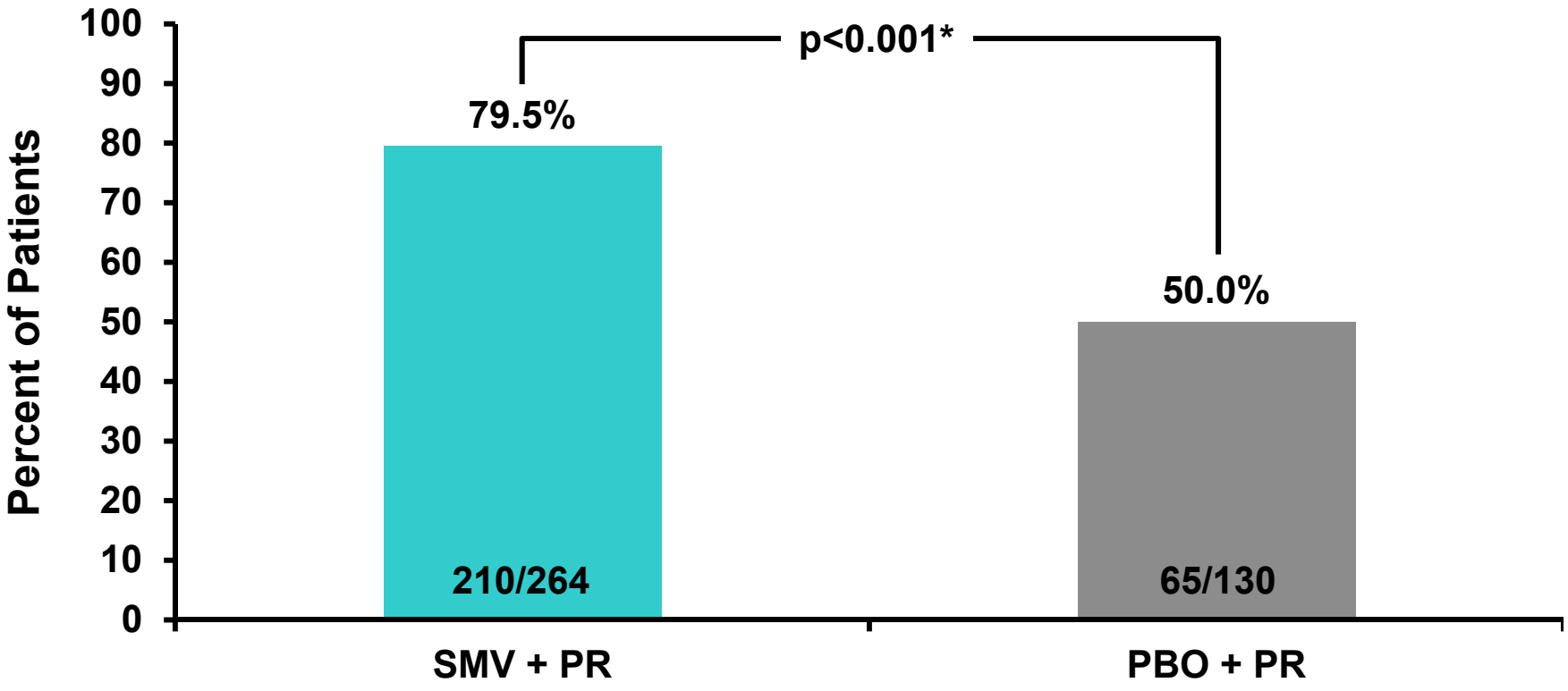
Key Baseline Demographics and Disease Characteristics
Studies C208/216 – Treatment Naive

		C208		C216	
		SMV + PR N=264 %	PBO + PR N=130 %	SMV + PR N=257 %	PBO + PR N=134 %
Gender	Female	44	43	46	43
Race	Caucasian	87	94	92	92
	Black or African American	10	3	6	7
Ethnicity	Hispanic or Latino	13	11	23	19
Age (years), Median		48	48	46	47
BMI (kg/m^2)	<25	36	36	43	42
	≥25 - <30	38	32	39	36
	≥30	26	32	18	21
Baseline HCV RNA category (IU/mL)	≤ 800,000	17	26	23	27
	>800,000	83	74	77	73
IL28B *	CC	29	28	29	31
	CT	57	58	55	53
	TT	14	13	16	16
HCV GT/subtype	1a	56	57	41	40
	1b	44	43	58	57
METAVIR score	F3 - F4	30	31	21	24

**IL28B*, polymorphism on chromosome 19 rs12979860

Proportion of Patients Achieving SVR12

Study C208 – Treatment Naive



Statistically superior SVR12 rates were observed with SMV vs PBO

* From the generalized CMH statistic controlling for stratification factors
SVR: HCV RNA undetectable at EOT and <25IU/mL 12 weeks after planned treatment end

RGT Duration and SVR12

Study C208 – Treatment Naive

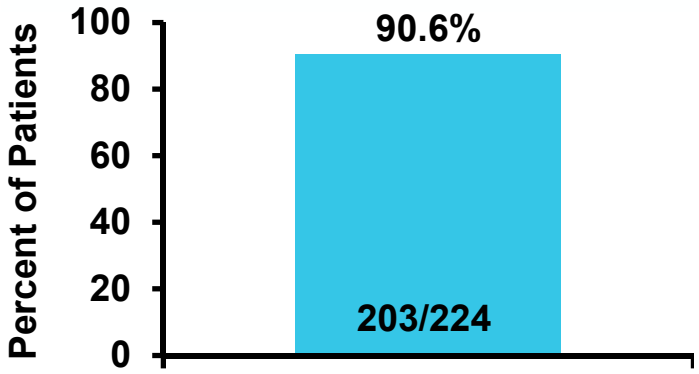
Patients treated with SMV + PR

Met RGT criteria:

84.8% (224/264) of patients

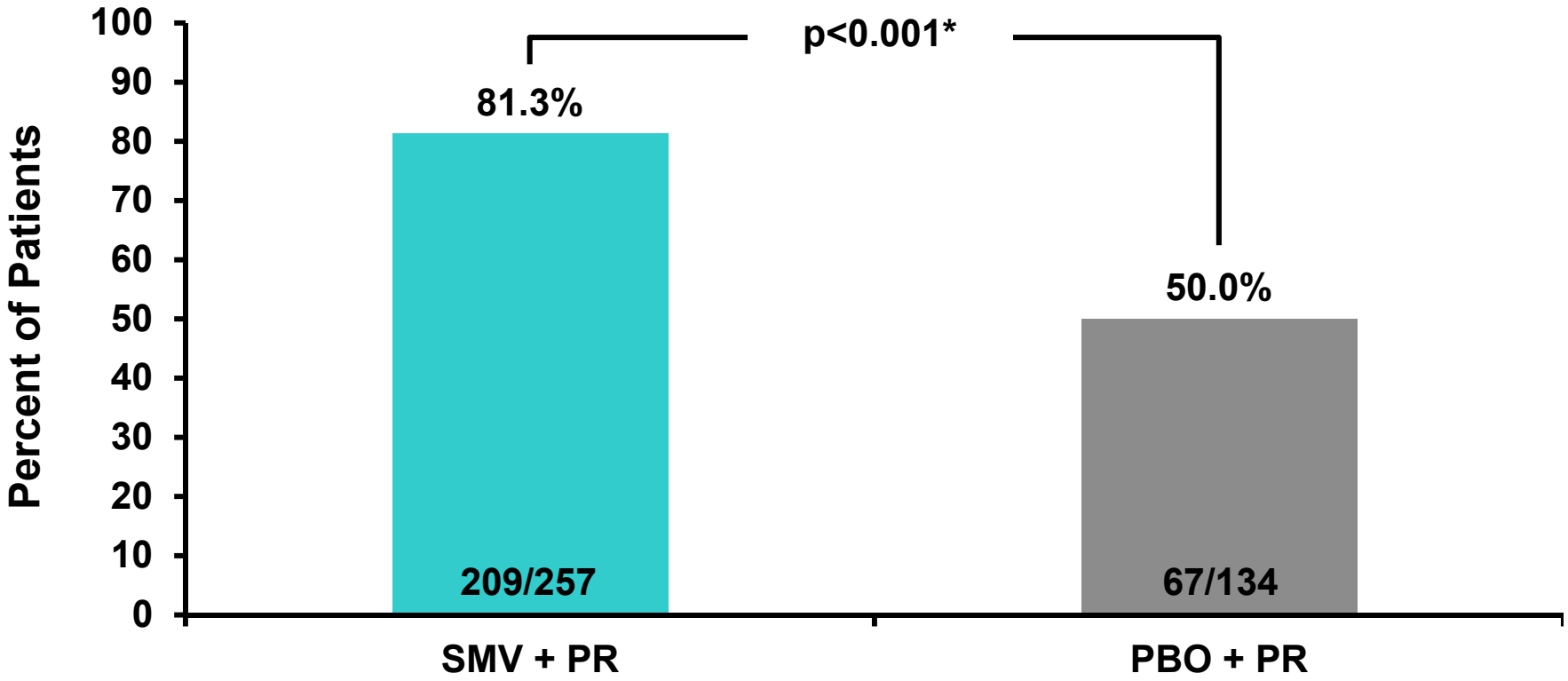
Eligible for 24 weeks of treatment

Proportion of patients achieving SVR12



Proportion of Patients Achieving SVR12

Study C216 – Treatment Naive



Statistically superior SVR12 rates were observed with SMV vs PBO

*Based on the generalized CMH test controlling for type of PR and stratification factors
SVR: HCV RNA undetectable at EOT and <25IU/mL 12 weeks after planned treatment end

RGT Duration and SVR12

Study C216 – Treatment Naive

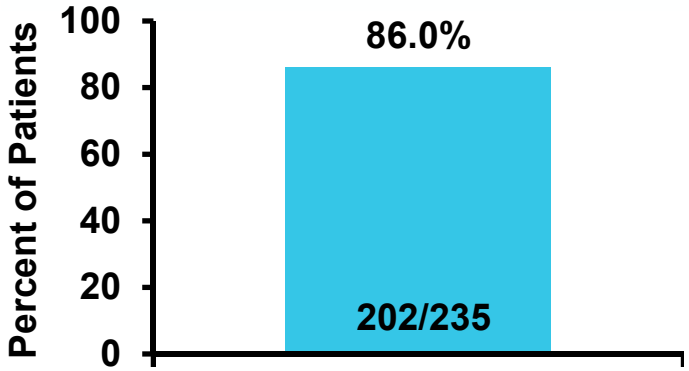
Patients treated with SMV + PR

Met RGT criteria:

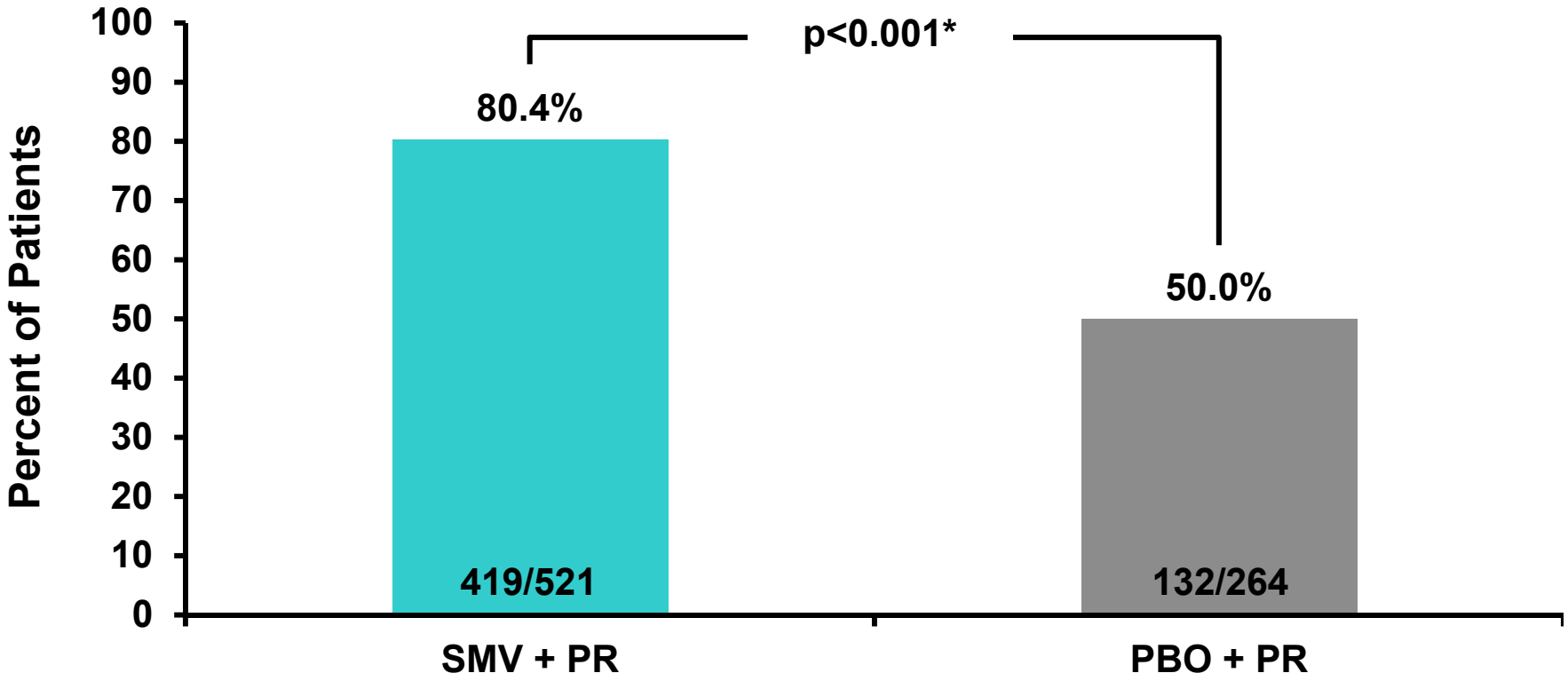
91.4% (235/257) of patients

Eligible for 24 weeks of treatment

Proportion of patients achieving SVR12



Primary Analysis Efficacy Pooling SVR12
Studies C208/216 – Treatment Naive

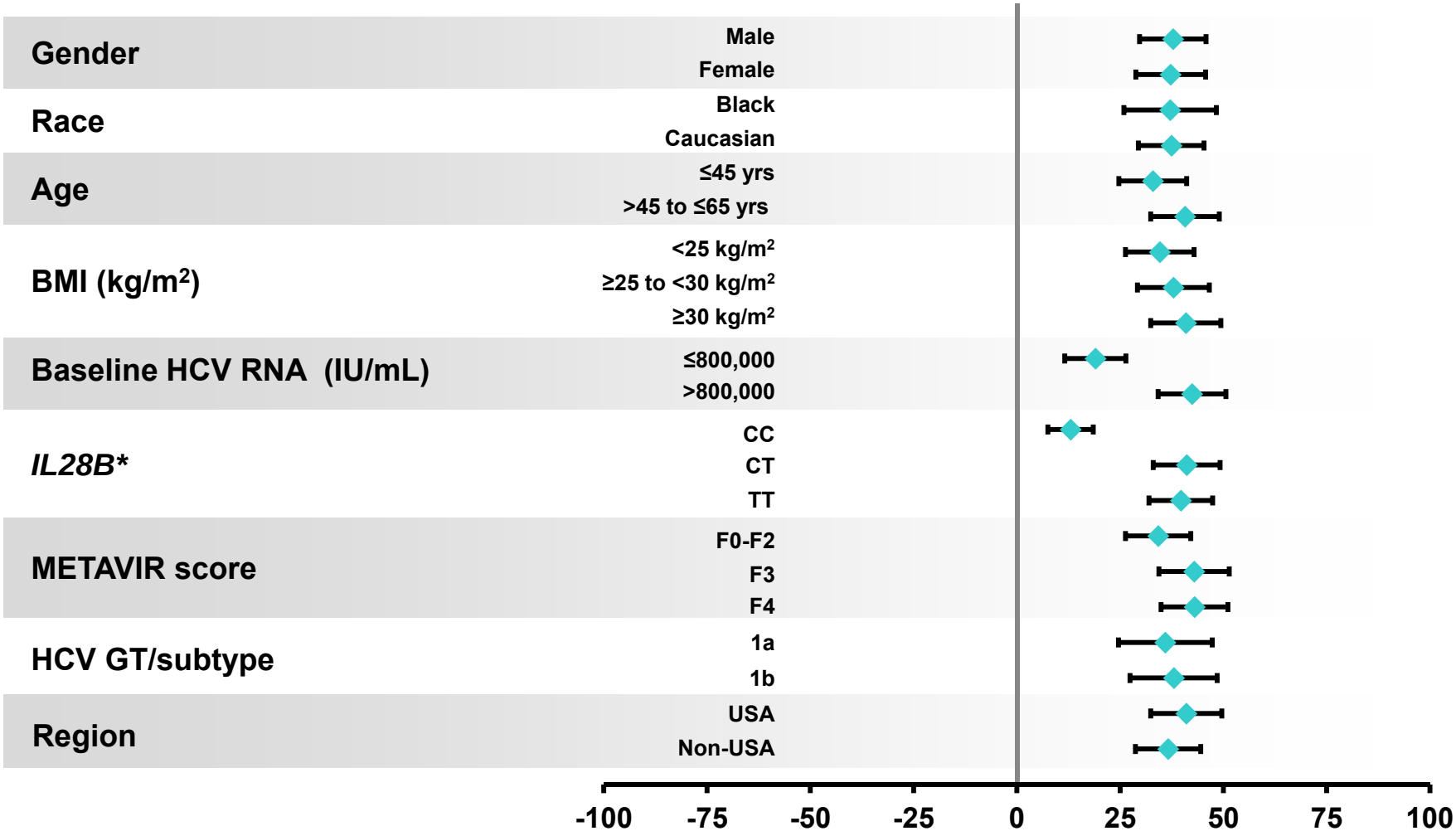


Statistically superior SVR12 rates were observed with SMV vs PBO

Phase 3 studies include C208 and C216
*From the generalized CMH test controlling for stratification factors and study .
SVR: HCV RNA undetectable at EOT and <25IU/mL 12 weeks after planned treatment end

SVR12 Differences Between Treatment Groups by Selected Baseline Characteristics

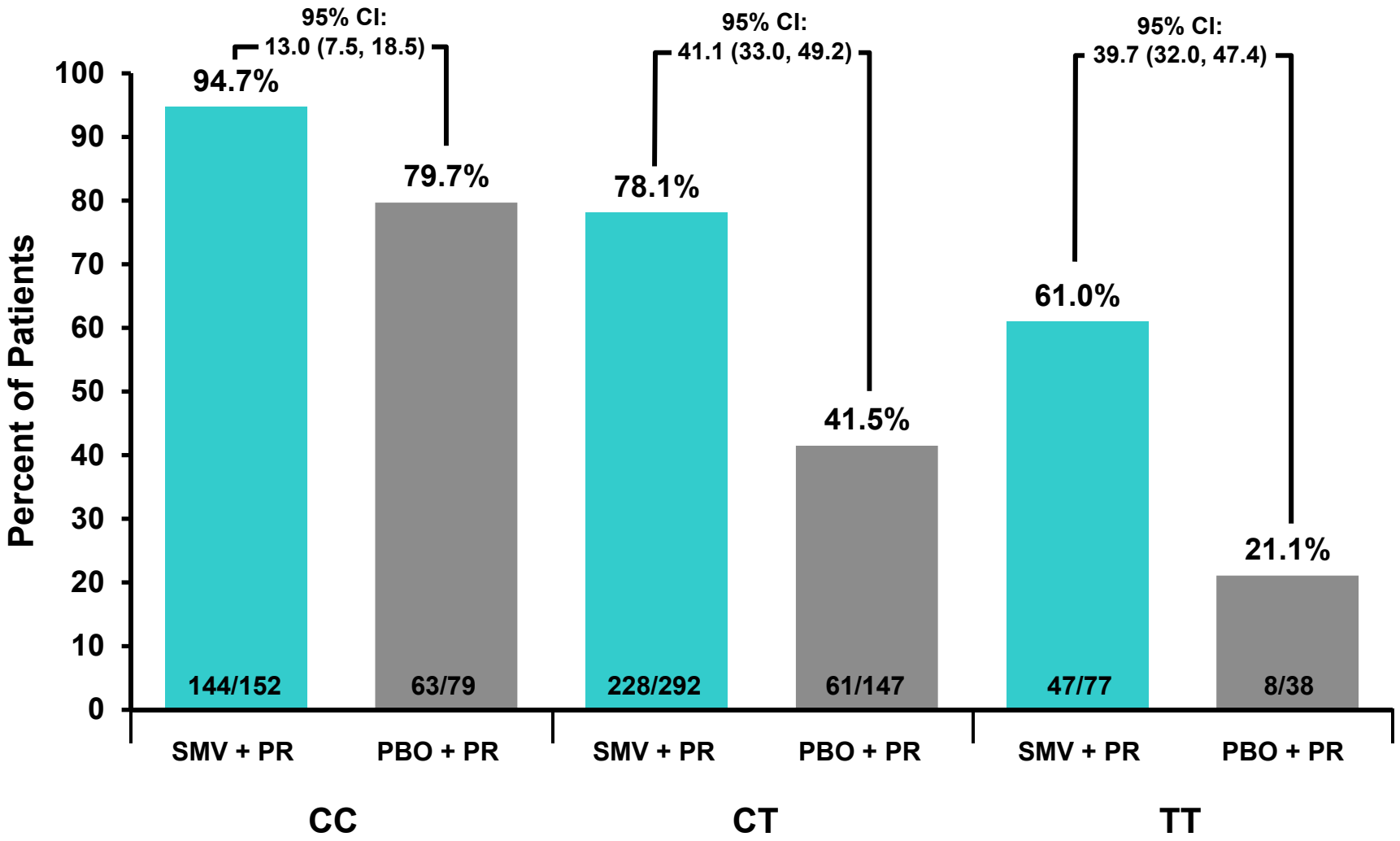
Studies C208/216 – Treatment Naive



Phase 3 studies include C208 and C216

**IL28B*, polymorphism on chromosome 19 rs12979860

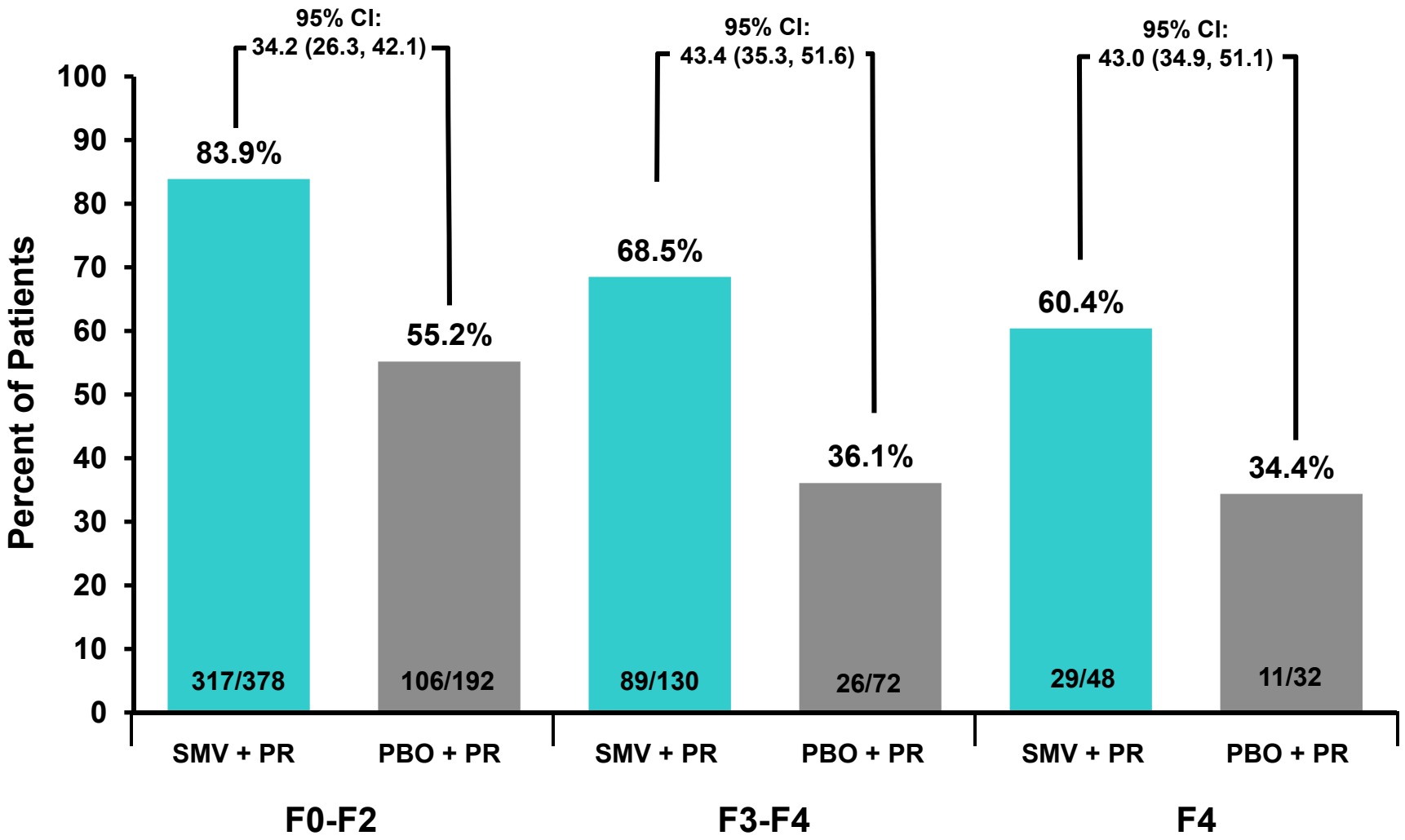
IL28B, Proportion of Patients with SVR12
Studies C208/216 – Treatment Naive



Phase 3 studies include C208 and C216

METAVIR Score, Proportion of Patients With SVR12

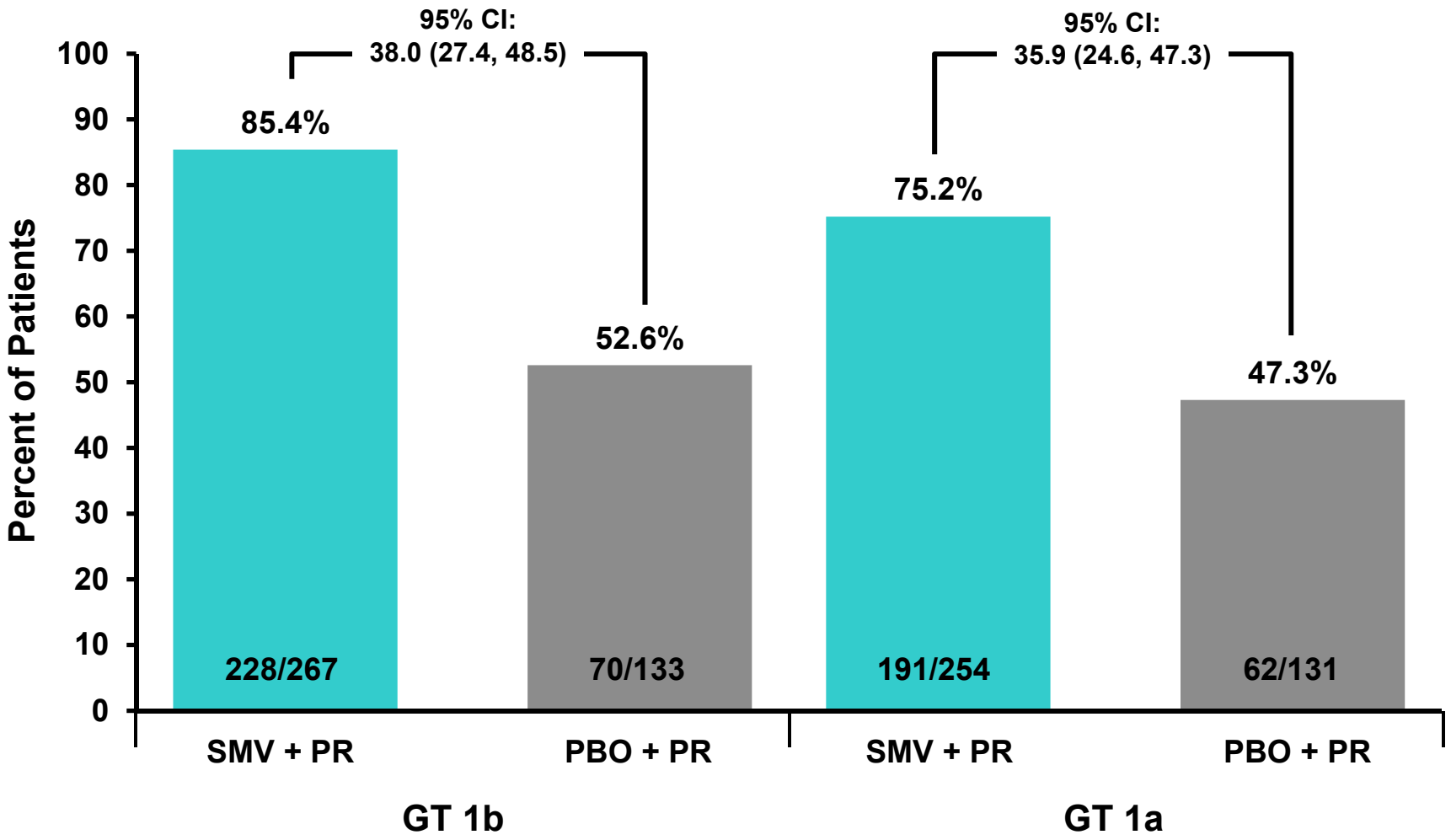
Studies C208/216 – Treatment Naive



Phase 3 studies include C208 and C216

Genotype 1a and 1b, Proportion of Patients With SVR12

Studies C208/216 – Treatment Naive



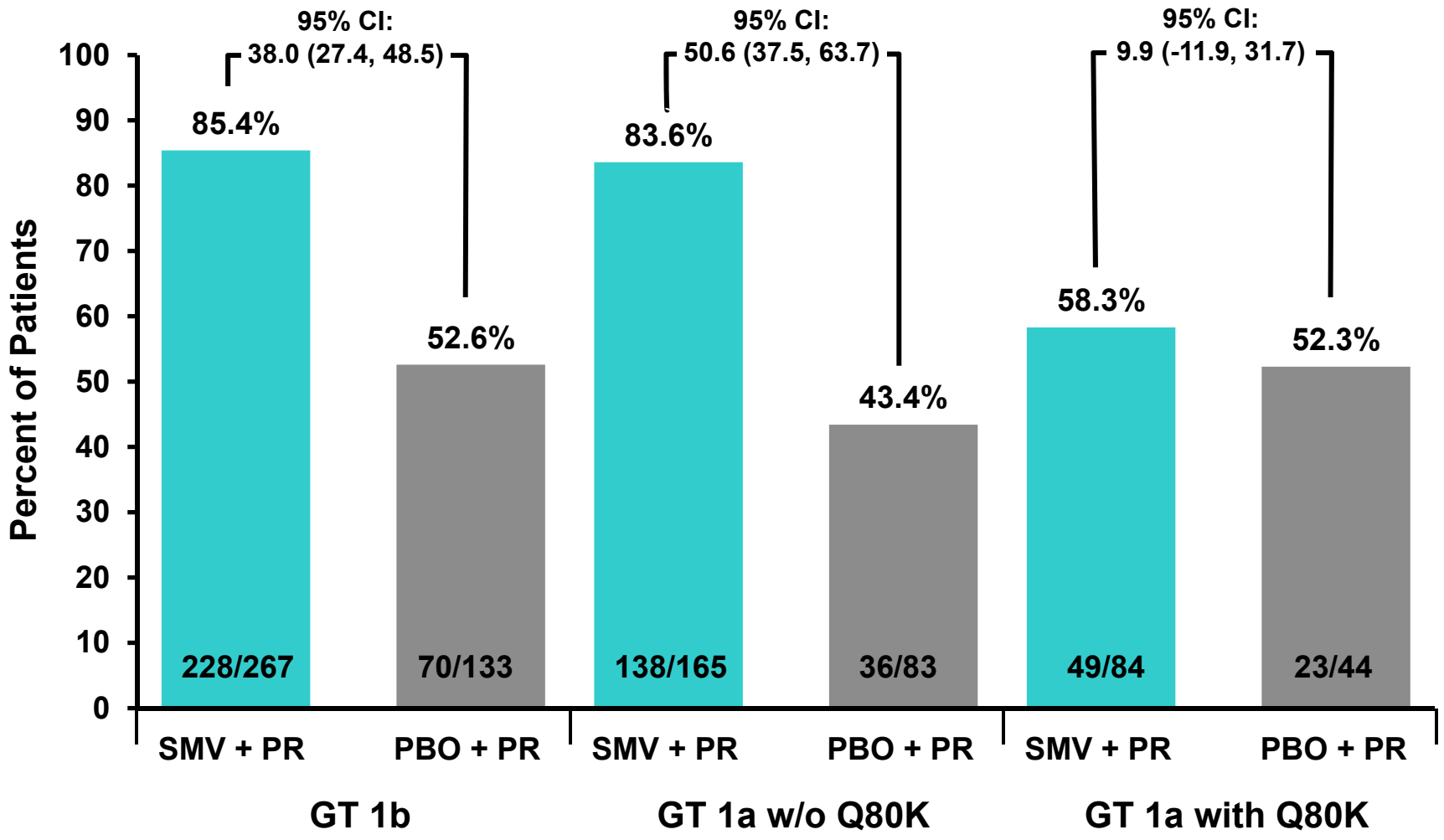
Phase 3 studies include C208 and C216

Q80K Polymorphism

- An additional factor was identified to have an influence on SVR12 among patients treated with SMV in combination with Peg-IFN/RBV.
- This factor is a naturally occurring aminoacid substitution in the viral NS3 region which confers low level resistance to SMV in vitro: Q80K.
- Q80K is primarily observed in HCV Subtype 1a
- The prevalence of the NS3 polymorphism in our Ph2b/3 studies was
  - 30% in GT 1a,
  - 0.5% in GT 1b
  - Resulting in an overall GT 1 prevalence of 14%.

Genotype 1b and 1a With and Without Q80K, Proportion of Patients With SVR12

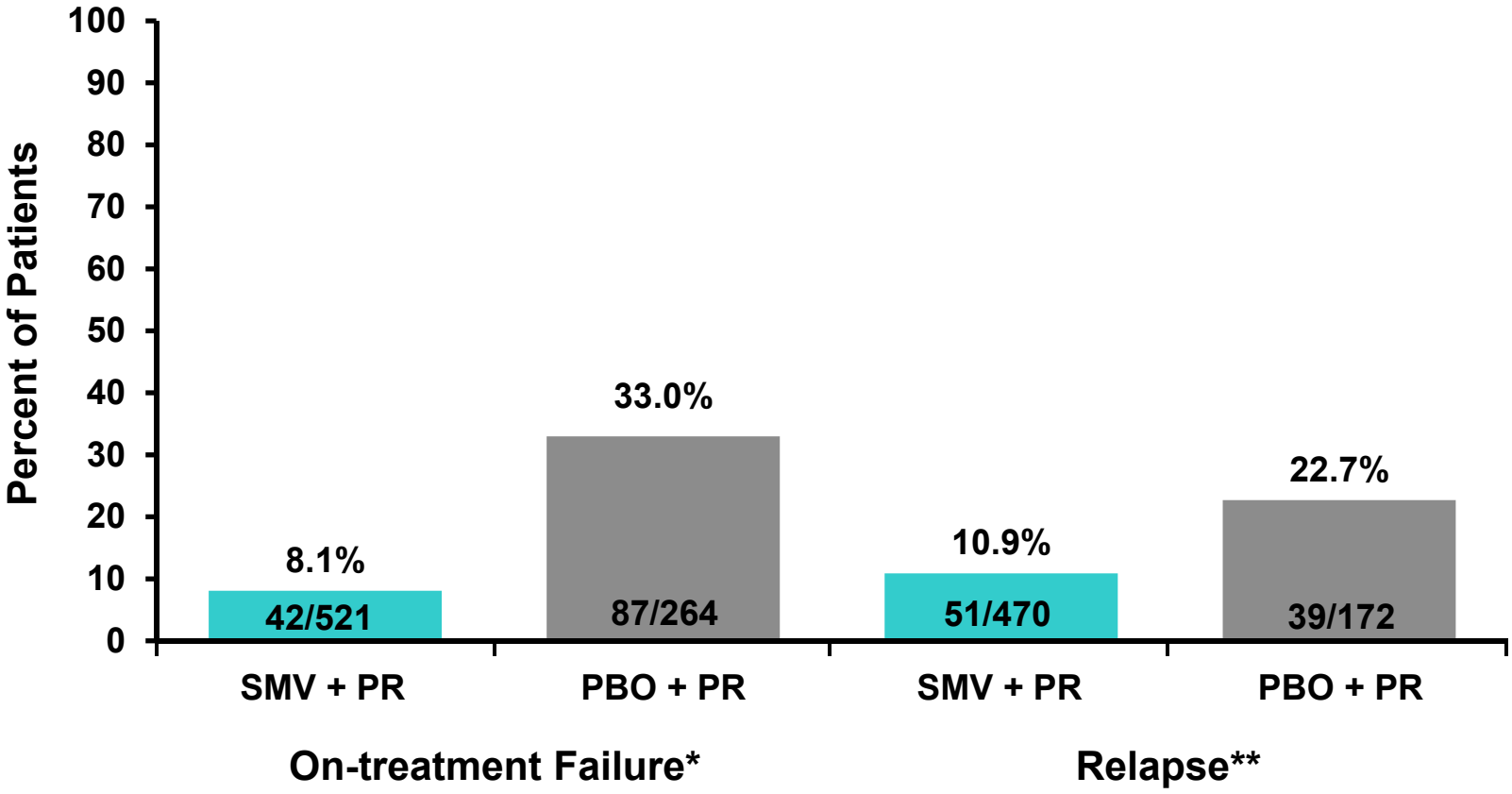
Studies C208/216 – Treatment Naive



Phase 3 studies include C208 and C216

Proportion of Patients Experiencing On-Treatment Failure or Viral Relapse

Studies C208/216 – Treatment Naive



Phase 3 studies include C208 and C216

* Defined as patients with detectable HCV RNA at actual end of treatment (EOT)

** Relapse was calculated amongst patients with undetectable HCV RNA at EOT

Simeprevir Clinical Studies

Study	Target Population	N	Study Type	Phase / Objectives
C208 **QUEST-1**	HCV GT 1 Naive	N=264 SMV + PR N=130 PBO + PR	Randomized Placebo controlled superiority	Phase III Confirm adequacy of RGT criteria Assess PegIFNα2b (C216)
C216 **QUEST-2**		N=257 SMV + PR N=134 PBO + PR		
HPC3007 **PROMISE**	HCV GT 1 Relapser	N=260 SMV + PR N=133 PBO + PR	Randomized Placebo controlled superiority	Phase III Assess RGT in Relapser patients
C206 **ASPIRE**	HCV GT 1 Relapser, Partial and Null Responders	N=396 SMV + PR N= 66 PBO + PR	Randomized Placebo controlled superiority	Phase IIb Dose selection

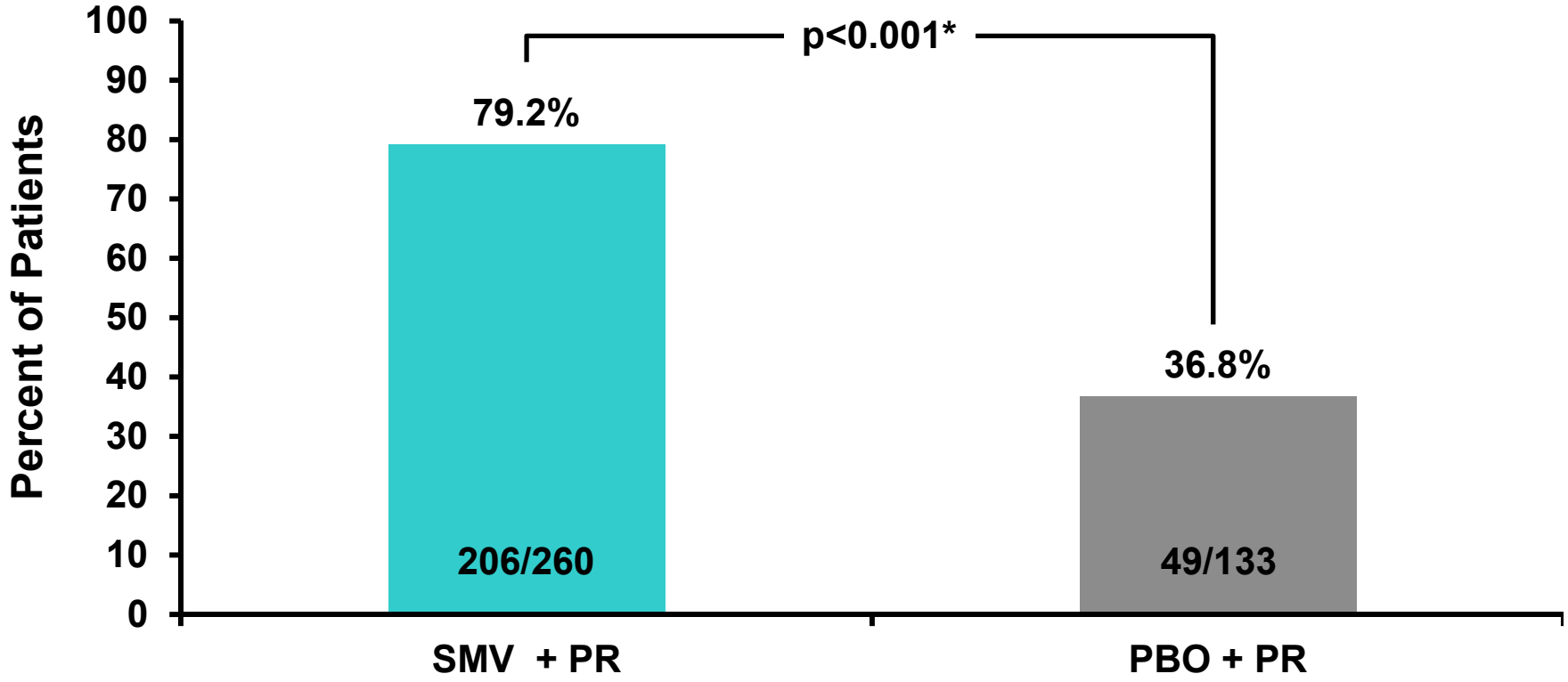
Key Baseline Demographics and Disease Characteristics
Study HPC3007 – Prior Relapser

		SMV 150 mg + PR N=260 %	PBO + PR N=133 %
Gender	Female	31	41
Race	Caucasian	93	96
	Black or African American	3	3
Ethnicity	Ethnicity (Hispanic or Latino)	8	5
Age (years), Median		52	52
BMI (kg/m^2)	<25	30	34
	≥25 - <30	45	39
	≥30	25	27
Baseline HCV RNA category (IU/mL)	≤ 800,000	16	17
	>800,000	84	83
IL28B*	CC	24	26
	CT	64	62
	TT	12	12
HCV GT/subtype	1a	42	41
	1b	57	59
METAVIR score	F3	18	11
	F4	16	14

**IL28B*, polymorphism on chromosome 19 rs12979860

Proportion of Patients Achieving SVR12

Study HPC3007 – Prior Relapser



Statistically superior SVR12 rates were observed with SMV vs PBO

* From the generalized CMH statistic controlling for stratification factors
SVR12, sustained virologic response (HCV RNA undetectable at EOT and <25IU/ml 12 weeks after planned treatment end.

Response-Guided Treatment Duration and SVR12
Study HPC3007 – Prior Relapser

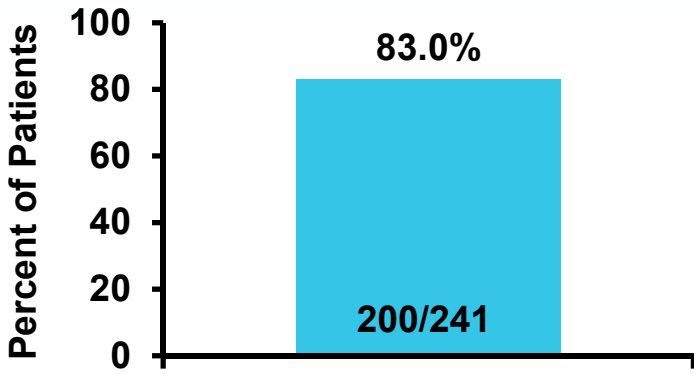
Patients treated with SMV + PR

Met RGT criteria:

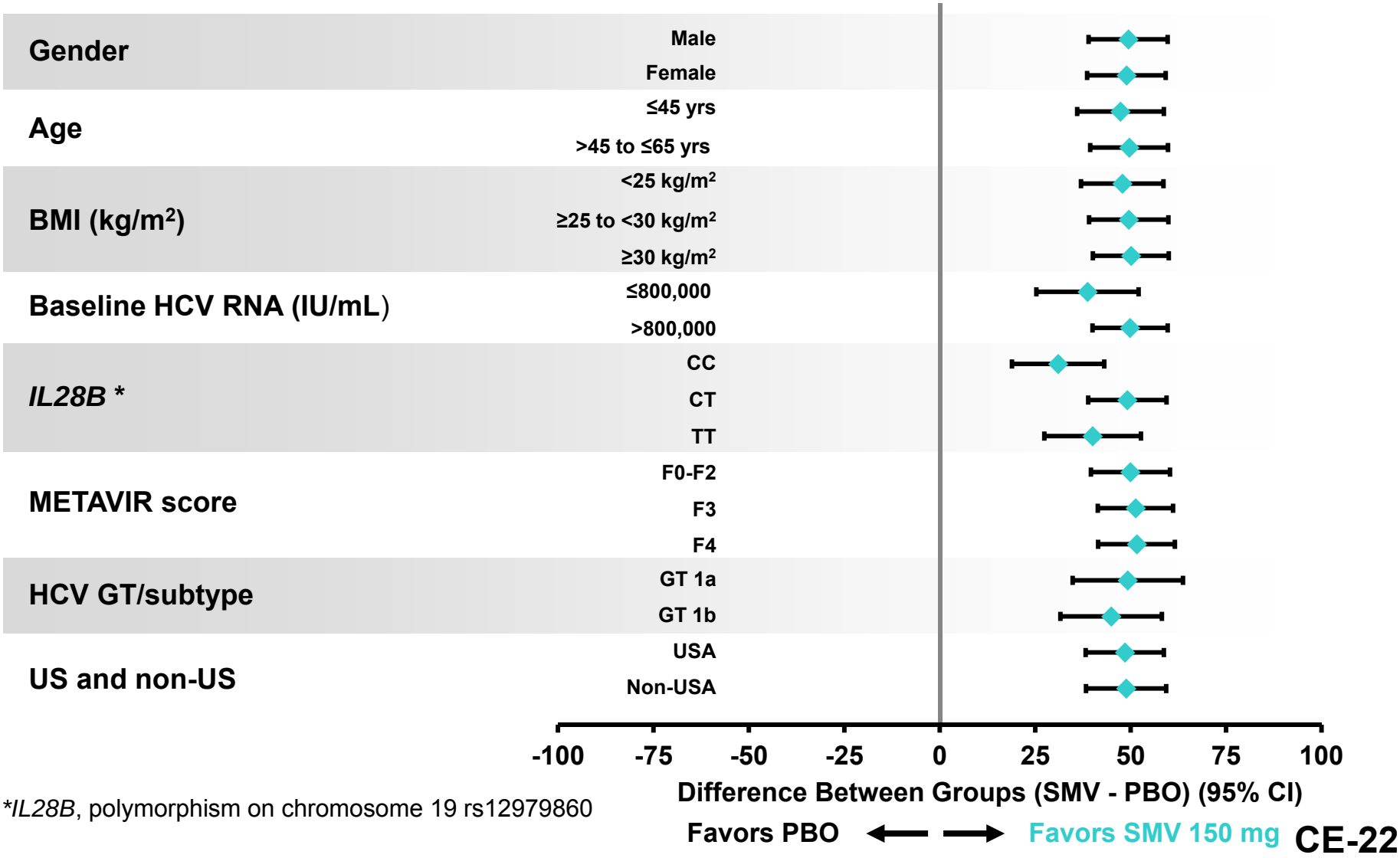
92.7% (241/260) of patients

Eligible for 24 weeks of treatment

Proportion of patients achieving SVR12



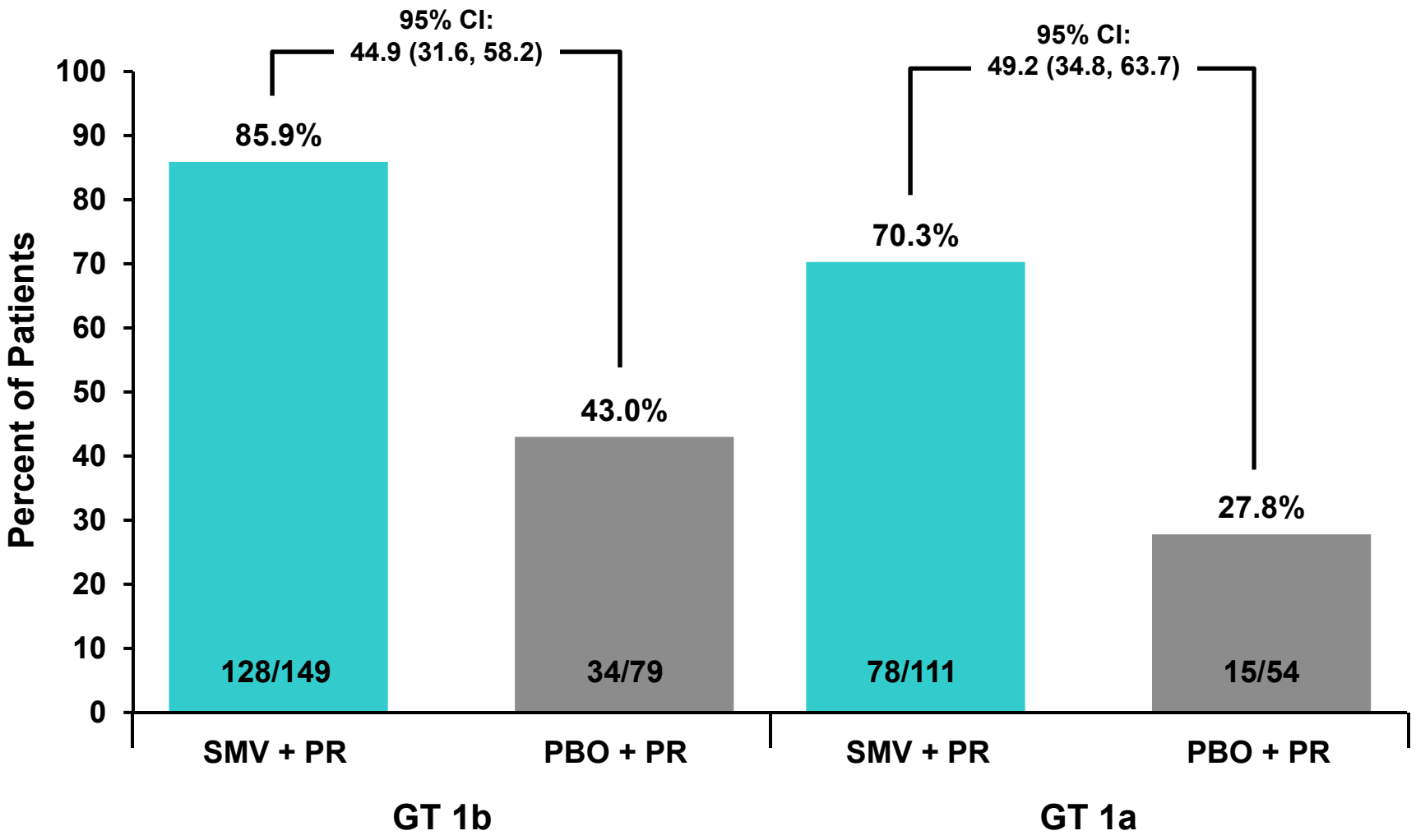
SVR12 by Selected Baseline and Demographic Characteristics
Study HPC3007 – Prior Relapser



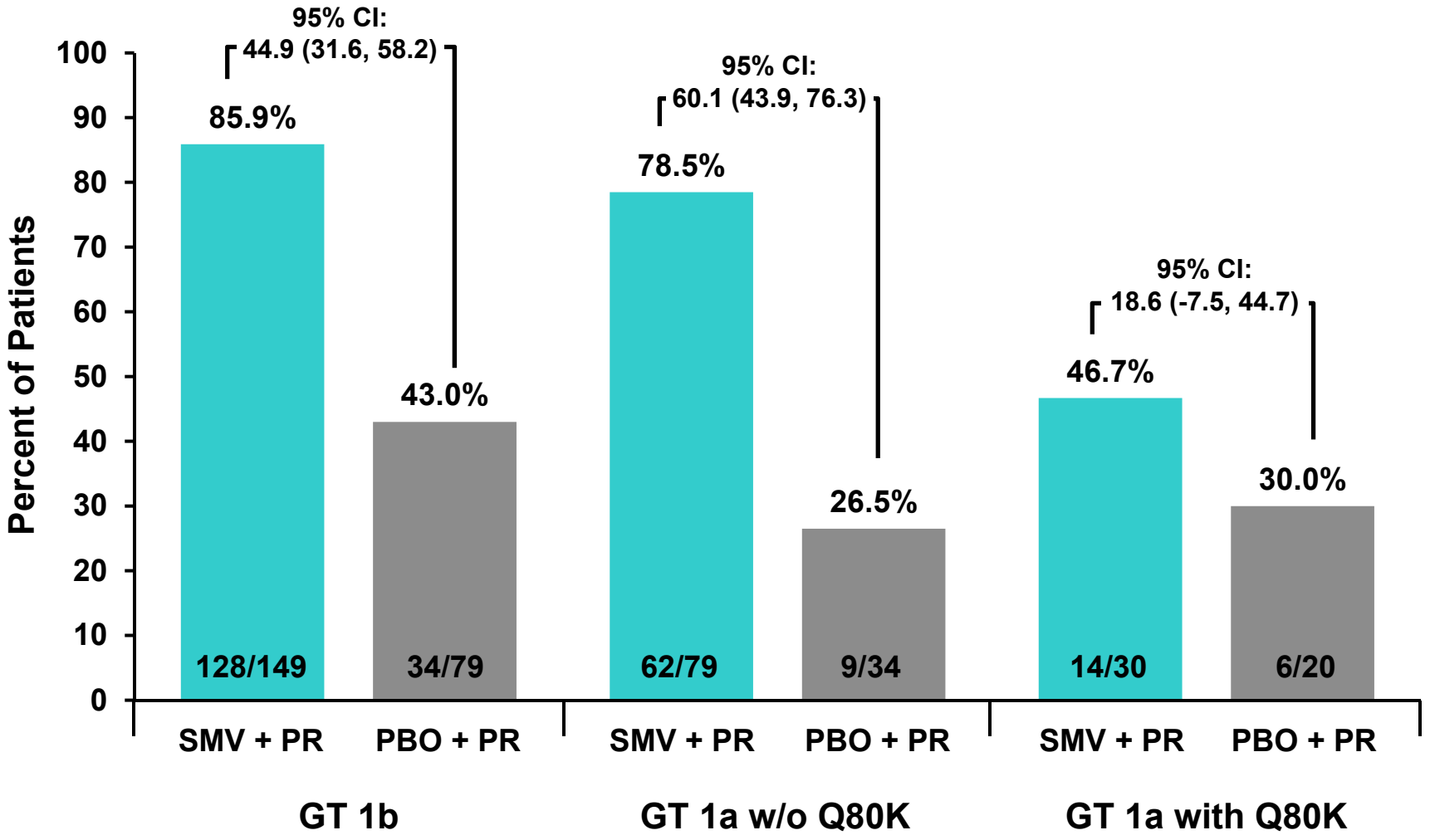
**IL28B*, polymorphism on chromosome 19 rs12979860

Genotype 1a and 1b, Proportion of Patients With SVR12

Study HPC3007 – Prior Relapser

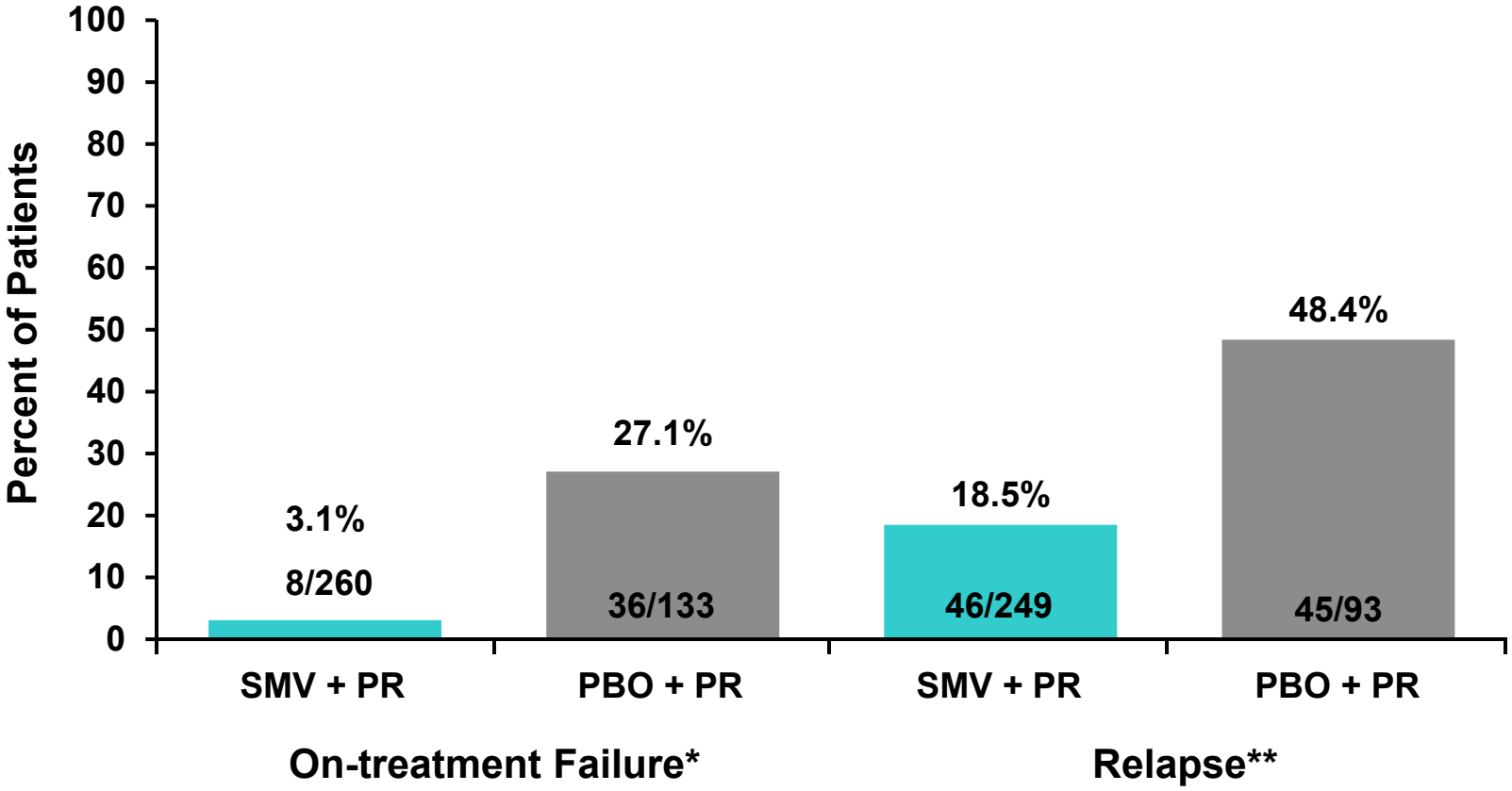


Genotype 1a and 1b With and Without Q80K
Proportion of Patients With SVR12
Study HPC3007 – Prior Relapser



Proportion of Patients Experiencing On-Treatment Failure or Relapse

Study HPC3007 – Prior Relapser



*Defined as confirmed detectable HCV RNA at actual end of treatment (EOT)

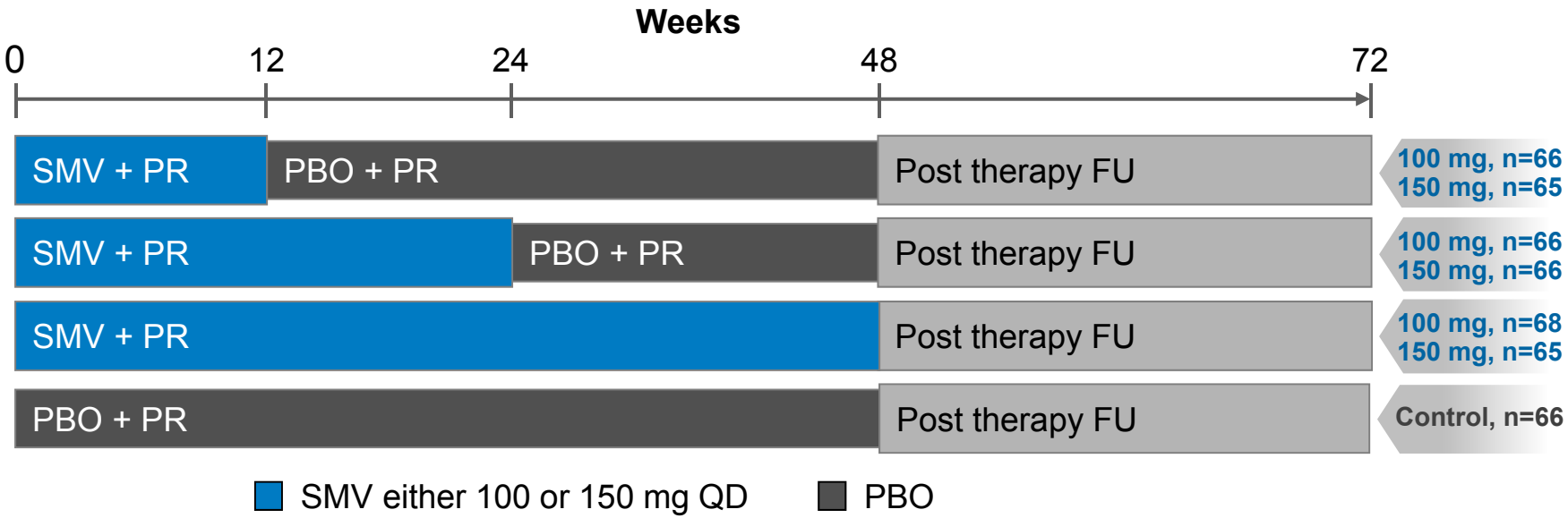
** Relapse was calculated amongst patients with undetectable HCV RNA at EOT

Simeprevir Clinical Studies

Study	Target Population	N	Study type	Phase / Objectives
C208 **QUEST-1**	HCV GT 1 Naive	N=264 SMV + PR N=130 PBO + PR	Randomized Placebo controlled superiority	Phase III Confirm adequacy of RGT criteria Assess PegIFNα2b (C216)
C216 **QUEST-2**		N=257 SMV + PR N=134 PBO + PR		
HPC3007 **PROMISE**	HCV GT 1 Relapser	N=260 SMV + PR N=133 PBO + PR	Randomized Placebo controlled superiority	Phase III Assess RGT in Relapser patients
C206 **ASPIRE**	HCV GT 1 Treatment Experienced	N=396 SMV + PR N= 66 PBO + PR	Randomized Placebo controlled superiority	Phase IIb Dose selection

Phase 2 Trial Study Design

Study C206 – Treatment Experienced



Primary endpoint	SVR24
Stratification factors	Prior Treatment Response and HCV GT(1a, 1b and other)

Prior treatment response

Null response	<2 log reduction in HCV RNA at Week 12
Partial response	≥2 log reduction in HCV RNA at Week 12 but not achieving undetectable at EOT

EOT, end of treatment; FU, follow-up; PBO, placebo;
PR, 180 µg PegIFN α-2a + 1000-1200 mg RBV; QD, once daily; W, week

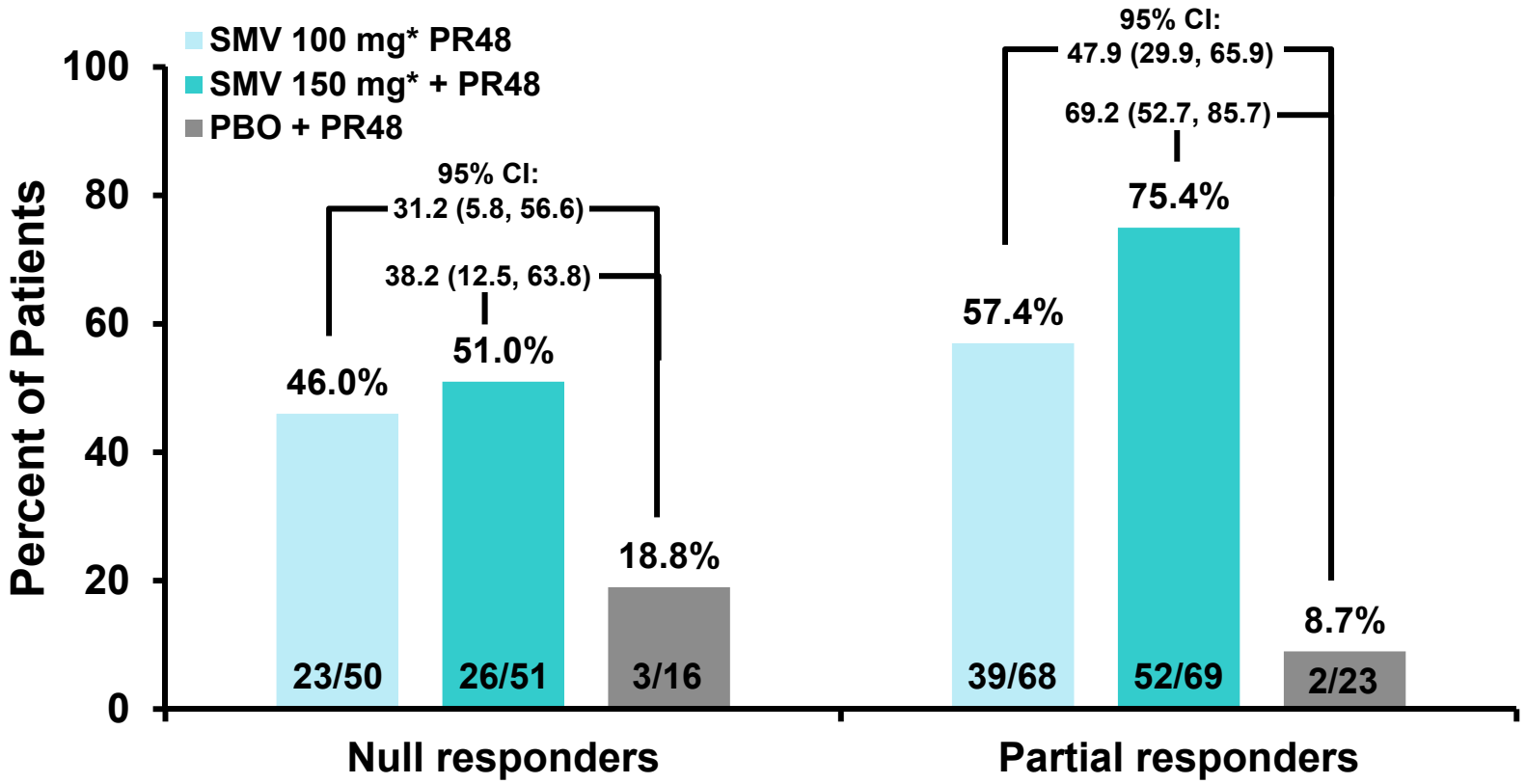
Key Baseline Demographics and Disease Characteristics
Study C206 – Prior Non Responders

		SMV 150 mg* Null Responders PR 48 N=51 %	SMV 150 mg* Partial Responders PR 48 N=69 %	PBO + PR 48 Null and Partial Responders N=39 %
Gender	**Female**	26	39	41
Race	**Caucasian**	92	93	100
	Black or African American	6	7	0
Ethnicity	**Hispanic or Latino**	4	4	5
Age (years), median		52	50	49
BMI (kg/m^2)	**<25**	33	38	23
	≥25 - <30	39	45	46
	≥30	28	17	31
Baseline HCV RNA category (IU/mL)	**≤800,000**	6	15	18
	>800,000	94	86	82
HCV GT/subtype	**1a**	51	36	39
	1b	47	62	62
METAVIR score	**F3**	16	15	24
	F4	26	16	11

*Same dose with all durations combined

Null and Partial Responders Dosed With Simeprevir 100 mg and 150 mg SVR24

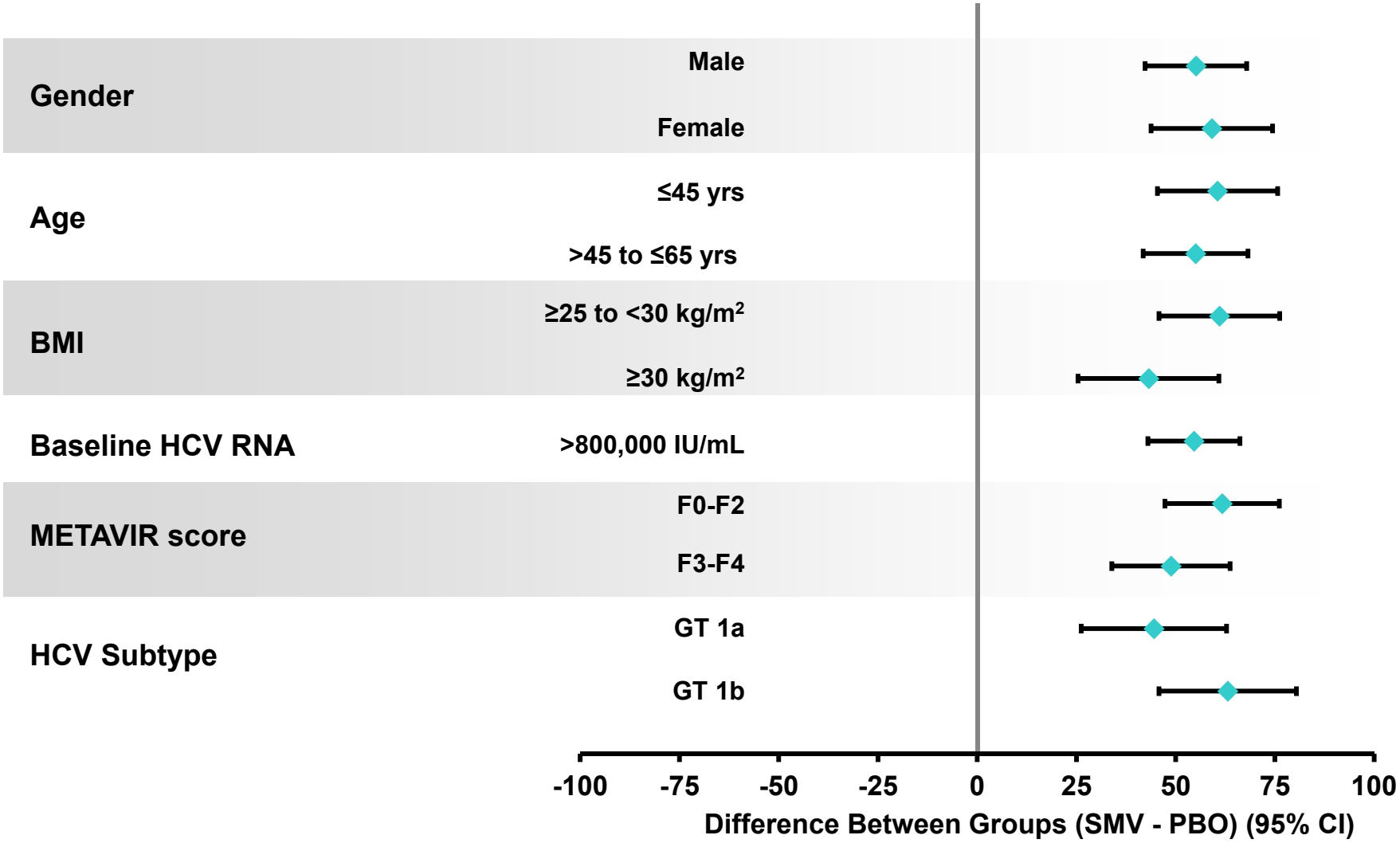
Study C206 – Prior Non Responders



* Same dose with all durations combined
SVR: HCV RNA undetectable at EOT and 24 weeks after planned treatment end

Null and Partial Responders Dosed with Simeprevir 150 mg SVR24 by Selected Baseline Characteristics

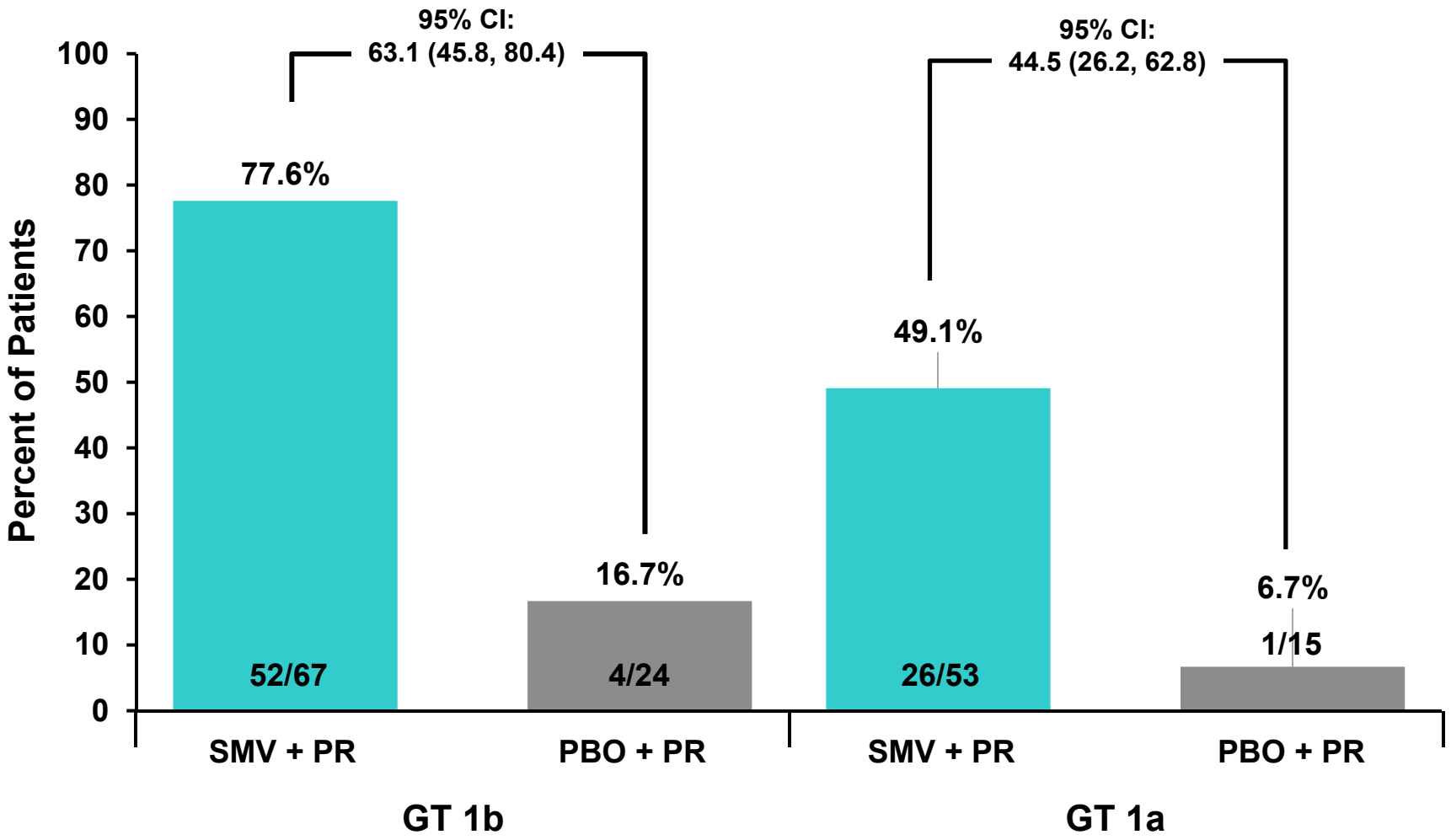
Study C206 – Prior Non Responders



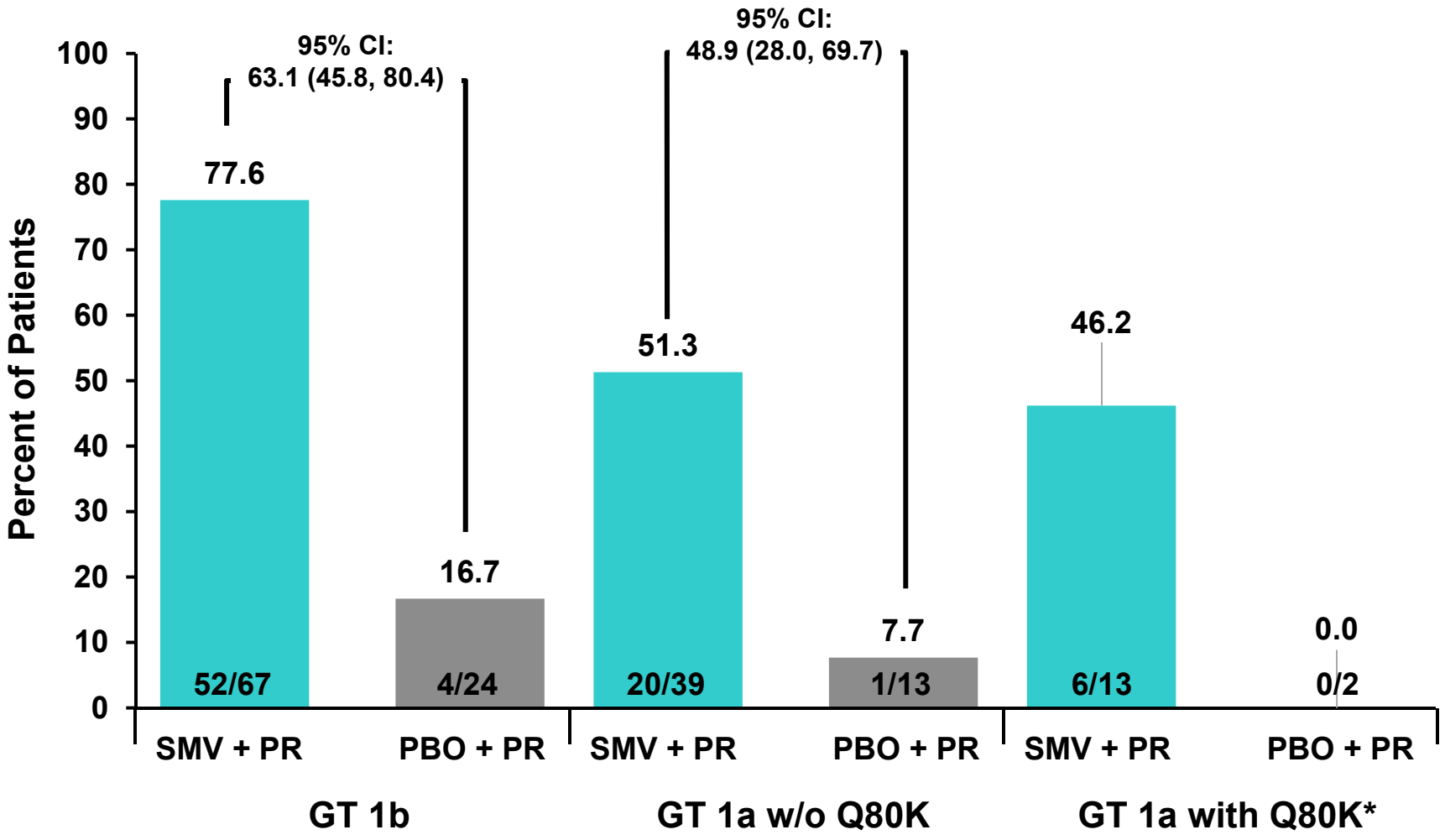
Some subgroups not displayed due to low subject numbers

Non-Responders Dosed With Simeprevir 150 mg SVR24 by Subtype

Study C206 – Prior Non Responders



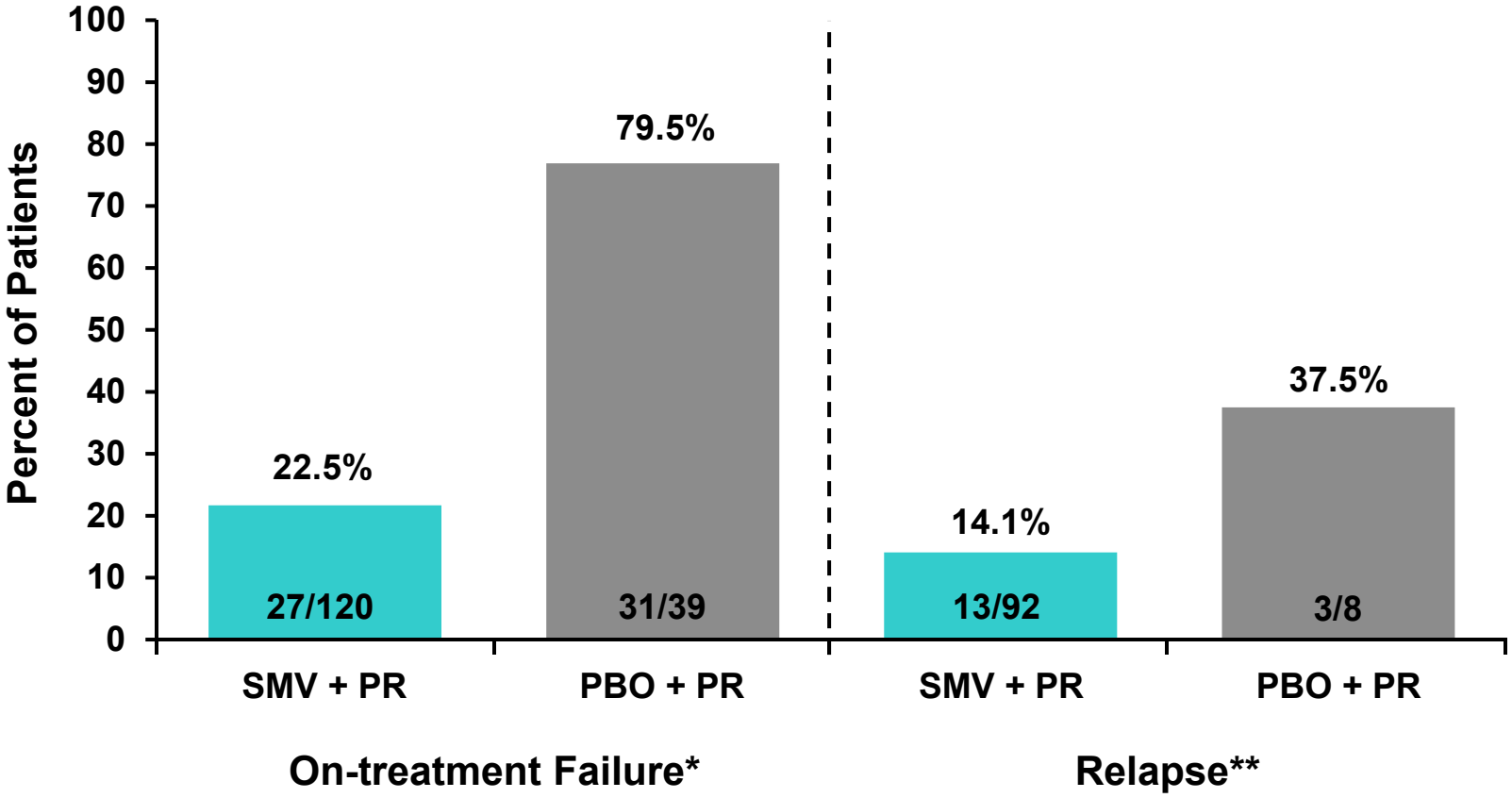
Non-Responders Dosed With Simeprevir 150 mg SVR24 by Genotype 1a and 1b With or Without Q80K
Study C206 – Prior Non Responders



*No analysis is available due to the low number of subjects

Non-Responders Dosed With Simeprevir 150 mg On-Treatment Failure or Viral Relapse

Study C206 – Prior Non Responders



*Defined as confirmed detectable HCV RNA at actual end of treatment;
** Relapse was calculated amongst patients with undetectable HCV RNA at EOT

Efficacy Conclusions

- SMV 150 mg in combination with PR was superior to treatment with PR alone in all populations studied
  - Treatment naive: 80% vs 50%
  - Prior Relapse: 79% vs 37%
  - Prior Partial Responder: 75% vs 9%
  - Prior Null Responders: 51% vs 19%
- Presence of baseline Q80K polymorphism was associated with lower SVR rates with SMV+PR
- 85-91% of treatment naïve and 93% of prior relapse patients treated with SMV+PR shortened treatment duration from 48 to 24 weeks using a pre-specified algorithm based on week-4 and week-12 response

Virology

Oliver Lenz, PhD

Scientific Director
Clinical Virology Lead SMV
Janssen

Virology Analyses

Baseline	Time of failure
Naturally occurring polymorphisms	Emerging mutations

Prevalence of Baseline Polymorphism Q80K
Phase 2b/3 Studies

	GT 1 (Overall)	GT 1a	GT 1b
Overall			
Patients with sequencing data	2007	911	1096
Q80K	274 (13.7%)	269 (29.5%)	5 (0.5%)
United States			
Patients with sequencing data	411	298	113
Q80K	143 (34.8%)	143 (48%)	0

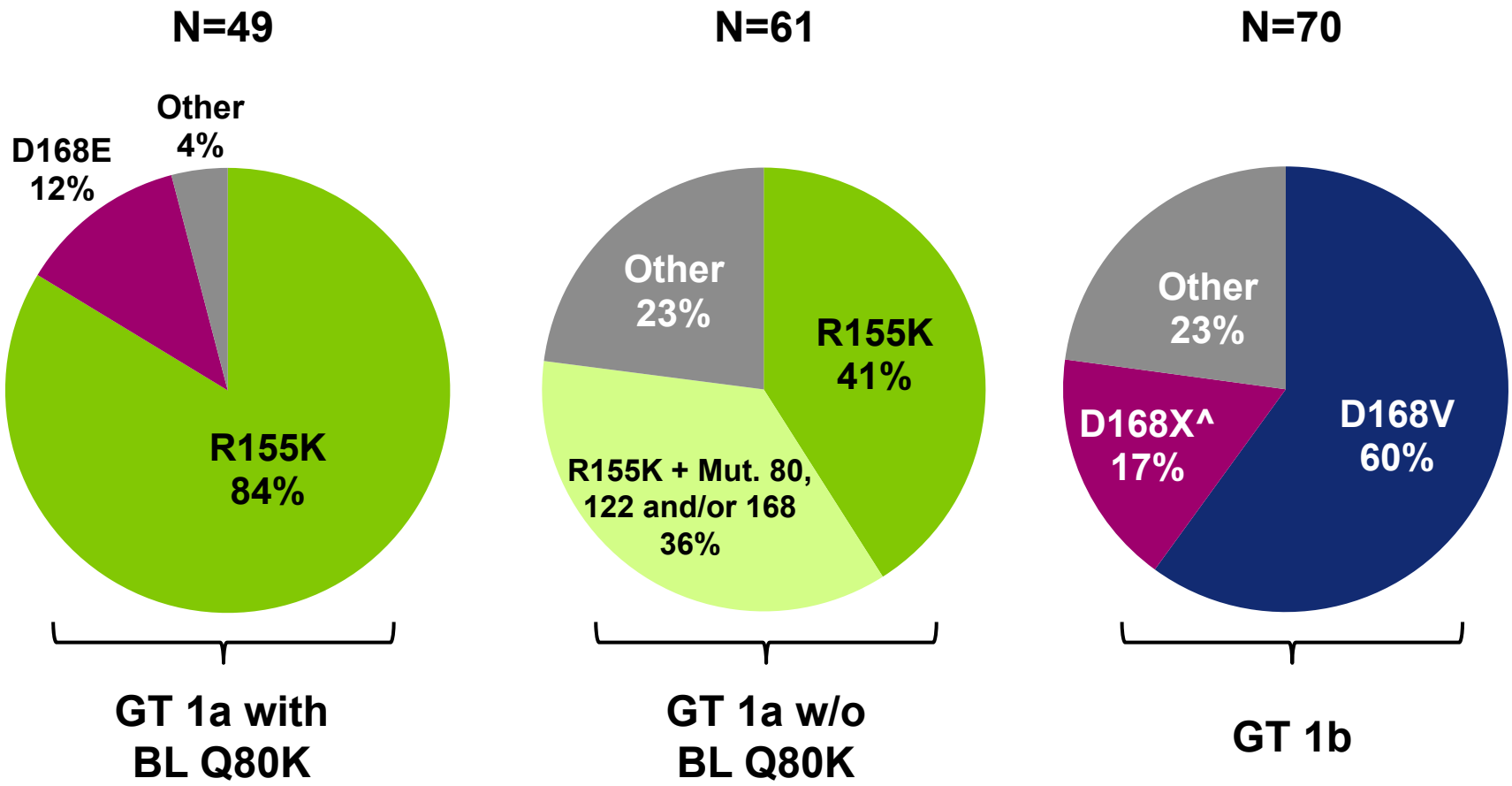
Q80K confers low level resistance to SMV *in vitro*
(median reduction in SMV activity of 11 fold)

Simeprevir Virology

- SMV 150 mg in combination with PR resulted in high SVR rates:
  - Treatment-naïve and Prior Relapse: 80% and 79%
  - Prior Partial Responder: 75%
  - Prior Null Responders: 51%
- Predictable and consistent resistance profile in patients who did not achieve SVR
  - High-level resistance mutations emerged in most patients who failed SMV + PR treatment
  - Different mutations emerged in GT 1a and 1b patients
  - Similar mutations emerged in patients with and without baseline Q80K
  - Emerging variants susceptible to anti-HCV agents with other mechanisms of action

Type and Frequency of Emerging Mutations* in Patients Not Achieving SVR by Subtype

Phase 2b/3 Studies



* Considering mutations at NS3 positions 43, 80, 122, 155, 156 and 168. ^X: represents amino acids A, E, H, T and A/V, E/V. SMV + PR treated patients receiving 150 mg QD SMV.

In vitro Cross-Resistance Between Simeprevir and DAA's With Other Mode of Actions

Resistant | Low-level resistant | Susceptible

Resistance to:		SMV	NS5A Inhibitor	NS5B NI	NS5B NNI*
SMV	Q80K	Low-level resistant	Susceptible	Susceptible	Susceptible
	R155K	Resistant	Susceptible	Susceptible	Susceptible
	D168A	Resistant	Susceptible	Susceptible	Susceptible
	D168E	Resistant	Susceptible	Susceptible	Susceptible
	D168H	Resistant	Susceptible	Susceptible	Susceptible
	D168V	Resistant	Susceptible	Susceptible	Susceptible
NS5A Inhibitor	Y93H	Susceptible	Resistant	Susceptible	Susceptible
NS5B NI*	S282T	Susceptible	Susceptible	Resistant	Susceptible
NS5B NNI*	C316Y	Susceptible	Susceptible	Susceptible	Resistant
	M414T	Susceptible	Susceptible	Susceptible	Resistant
	M423T	Susceptible	Susceptible	Susceptible	Resistant
	P495A	Susceptible	Susceptible	Susceptible	Resistant

*Multiple classes of NS5B NNIs are in development with different resistance profiles; NI: nucleoside inhibitors; NNI: non-nucleoside inhibitors

Simeprevir Virology

- Baseline polymorphism Q80K
  - Confers low-level resistance to SMV in vitro
  - Present in up to 50% of GT 1a patients in US and rarely found in GT 1b
- Predictable and consistent resistance profile
  - High-level resistance mutations emerged in most patients who failed SMV + PR treatment
  - Different mutations emerged in GT 1a and GT 1b patients
  - Similar mutations emerged in patients with and without baseline Q80K
  - Emerging variants are susceptible to anti-HCV agents with other mechanisms of action

Safety

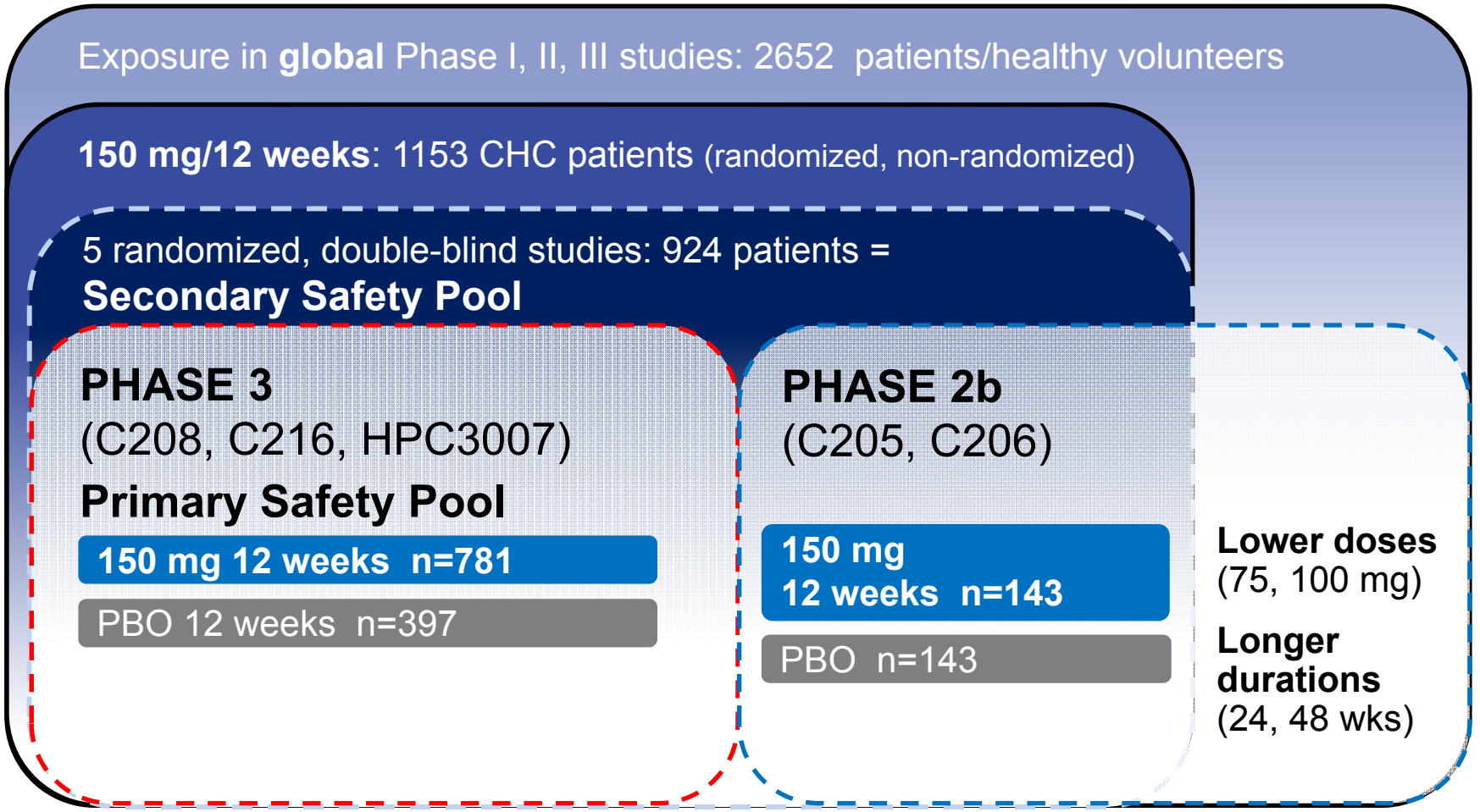
Wolfgang Jessner, MD

Medical Director, Clinical Development
Janssen

Synopsis

- Focus on comparison SMV/PR vs PBO/PR
  - Safety data pooled across Phase 3 studies
- PR associated with major side effects
- SMV characterized by a favorable safety profile
- Few adverse drug reactions
  - Low increases in incidence compared to PR
  - Mostly mild to moderate
- No hematologic side effects
- SMV safety not affected by liver cirrhosis

Safety Population



Overview on Patients with AEs
Phase 3 Studies

	First 12 Weeks	
	SMV 150 mg + PR N=781 n (%)	PBO + PR N=397 n (%)
Any AE	**744 (95.3)**	**376 (94.7)**
Worst grade 1 or 2	565 (72.3)	278 (70.0)
Worst grade 3 or 4	179 (22.9)	98 (24.7)
Any SAE	**16 (2.0)**	**10 (2.5)**

Phase 3 studies include C208, C216, and HPC3007

Treatment Discontinuation Summary
Phase 3 Studies

	SMV + PR N=781 n (%)	PBO + PR N=397 n (%)
During triple therapy (first 12 weeks)		
Discontinued SMV/PBO only due to an AE	6 (0.8)	2 (0.5)
Discontinued all therapy due to an AE	8 (1.0)	3 (0.8)
Discontinued PegIFN and/or RBV during the PR only phase (after week 12) due to an AE	13 (1.7)	21 (5.3)

Phase 3 studies include C208, C216, and HPC3007

AEs by Preferred Term in ≥ 10% of Patients
Phase 3 Studies

	First 12 Weeks	
	SMV 150 mg + PR N=781 n (%)	PBO + PR N=397 n (%)
Fatigue	278 (35.6)	157 (39.5)
Influenza like illness	203 (26.0)	84 (21.2)
Pyrexia	184 (23.6)	104 (26.2)
Asthenia	125 (16.0)	71 (17.9)
Pruritus	161 (20.6)	54 (13.6)
Rash	106 (13.6)	44 (11.1)
Nausea	173 (22.2)	70 (17.6)
Diarrhea	86 (11.0)	45 (11.3)
Headache	259 (33.2)	141 (35.5)
Insomnia	131 (16.8)	67 (16.9)
Myalgia	126 (16.1)	53 (13.4)
Neutropenia	109 (14.0)	50 (12.6)
Anemia	93 (11.9)	40 (10.1)
Decreased appetite	120 (15.4)	56 (14.1)

Phase 3 studies include C208, C216, and HPC3007

Subjects With SAEs Within First 12 Weeks
Phase 3 Studies

	First 12 Weeks	
	SMV 150 mg + PR N=781 n (%)	PBO + PR N=397 n (%)
Any SAE	**16 (2.0)**	**10 (2.5)**
Psychiatric	4 (0.5)	1 (0.3)
Infections and infestations	3 (0.4)	2 (0.5)
Hepatobiliary disorders	2 (0.3)	0
Nervous system disorders	2 (0.3)	3 (0.8)
Skin and subcutaneous tissue disorders	2 (0.3)	0
Eye disorders	1 (0.1)	0
Gastrointestinal disorders	1 (0.1)	0
Injury, poisoning and procedural complications	1 (0.1)	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0
Blood and lymphatic system disorders (Anemia)	0	2 (0.5)
Cardiac disorders	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)

Phase 3 studies include C208, C216, and HPC3007

Summary of AEs for First 12 Weeks
Study C206 – Prior Partial- and Null Responders

Analysis set: Intent-to-treat	First 12 Weeks		
	SMV 100 mg Pooled N = 118 n (%)	SMV 150 mg Pooled N = 120 n (%)	PBO N = 39 n (%)
Any AE	**114 (96.6)**	**117 (97.5)**	**37 (94.9)**
Worst grade 1 or 2 AE	**92 (78.0)**	**92 (76.7)**	**30 (76.9)**
Worst grade 3 or 4 AE	**22 (18.6)**	**25 (20.8)**	**7 (17.9)**
Worst grade 3	20 (16.9)	21 (17.5)	6 (15.4)
Worst grade 4	2 (1.7)	4 (3.3)	1 (2.6)
Treatment-related AE	**114 (96.6)**	**117 (97.5)**	**36 (92.3)**
At least possibly related to SMV/PBO	**88 (74.6)**	**89 (74.2)**	**22 (56.4)**
Any AE with fatal outcome	**0**	**0**	**0**
Any SAE	**5 (4.2)**	**1 (0.8)**	**0**
At least possibly related to SMV/PBO	0	1 (0.8)	0
AE leading to permanent stop[a]	**7 (5.9)**	**3 (2.5)**	**1 (2.6)**
SMV/PBO[b]	6 (5.1)	2 (1.7)	1 (2.6)
SMV/PBO only	1 (0.8)	0	0

[a] Permanent stop of at least one drug
[b] Without regard to PegIFN and RBV
Allocation of an AE that led to permanent stop of study drug(s) to a treatment phase is based on the onset date of the AE

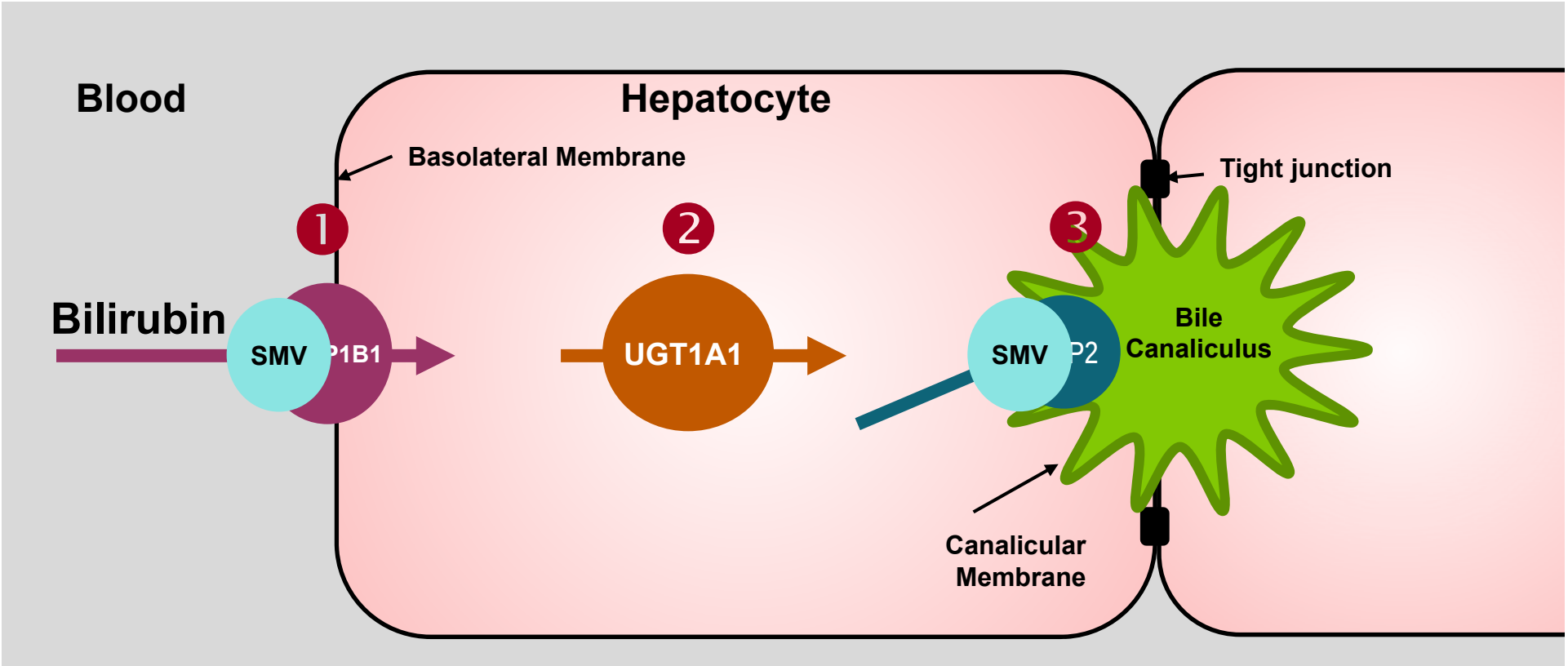
Patients With AEs of Interest
Phase 3 Studies (Grouped Terms)

	First 12 Weeks	
	SMV 150 mg + PR N=781 n (%)	PBO + PR N=397 n (%)
Anemia	105 (13.4)	43 (10.8)
Neutropenia	129 (16.5)	60 (15.1)
Rash (any type)	181 (23.2)	67 (16.9)
Photosensitivity conditions including sunburn	38 (4.9)	3 (0.8)
Pruritus	172 (22.0)	59 (14.9)
Increased Bilirubin	62 (7.9)	11 (2.8)
Dyspnea (any type)	92 (11.8)	30 (7.6)

Phase 3 studies include C208, C216, and HPC3007
Rash (any type) includes HLTs of Bullous conditions, Dermatitis ascribed to specific agent, Erythemas, Exfoliative conditions. Papulosquamous conditions, Photosensitivity conditions, Rashes, eruptions and exanthems NEC, Skin and subcutaneous tissue ulcerations, Skin vasculitides.
Dyspnea (any type) includes PTs: Acute respiratory distress syndrome, Dyspnoea, Dyspnoea exertional, Dyspnoea at rest, Hyperventilation, Orthopnoea.

Mechanism of Bilirubin Increase

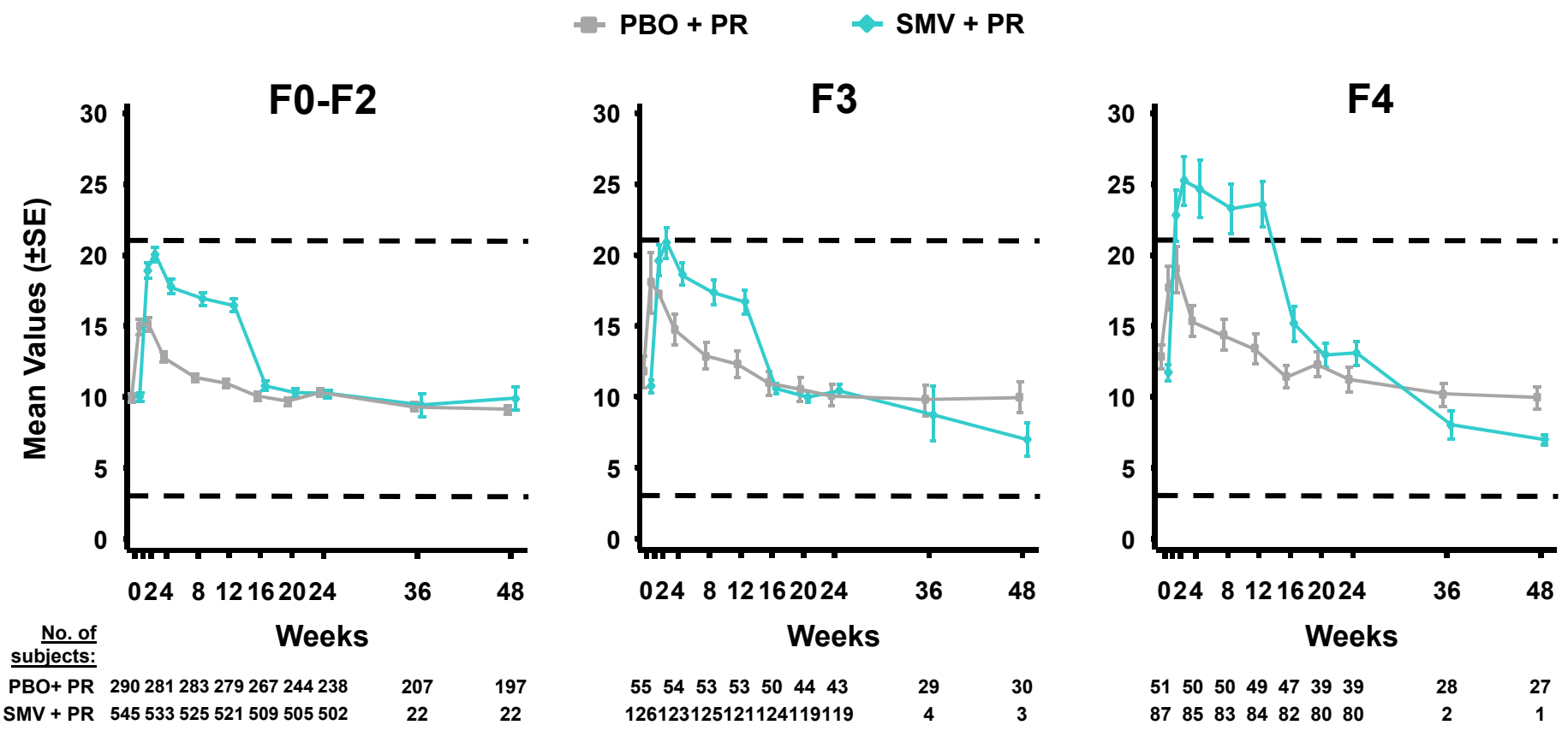
1. SMV inhibits OATP1B1: uptake of bilirubin and bilirubin conjugates into hepatocyte
2. SMV does not inhibit UGT1A1: bilirubin conjugation
3. SMV inhibits MRP2: transport of bilirubin conjugates into bile



Mean Total Bilirubin by Liver Disease Stage

Phase 3 Studies

Entire Treatment Phase



No. of subjects:									
PBO+ PR	290	281	283	279	267	244	238	207	197
SMV + PR	545	533	525	521	509	505	502	22	22

PBO+ PR	55	54	53	53	50	44	43	29	30
SMV + PR	126	123	125	121	124	119	119	4	3

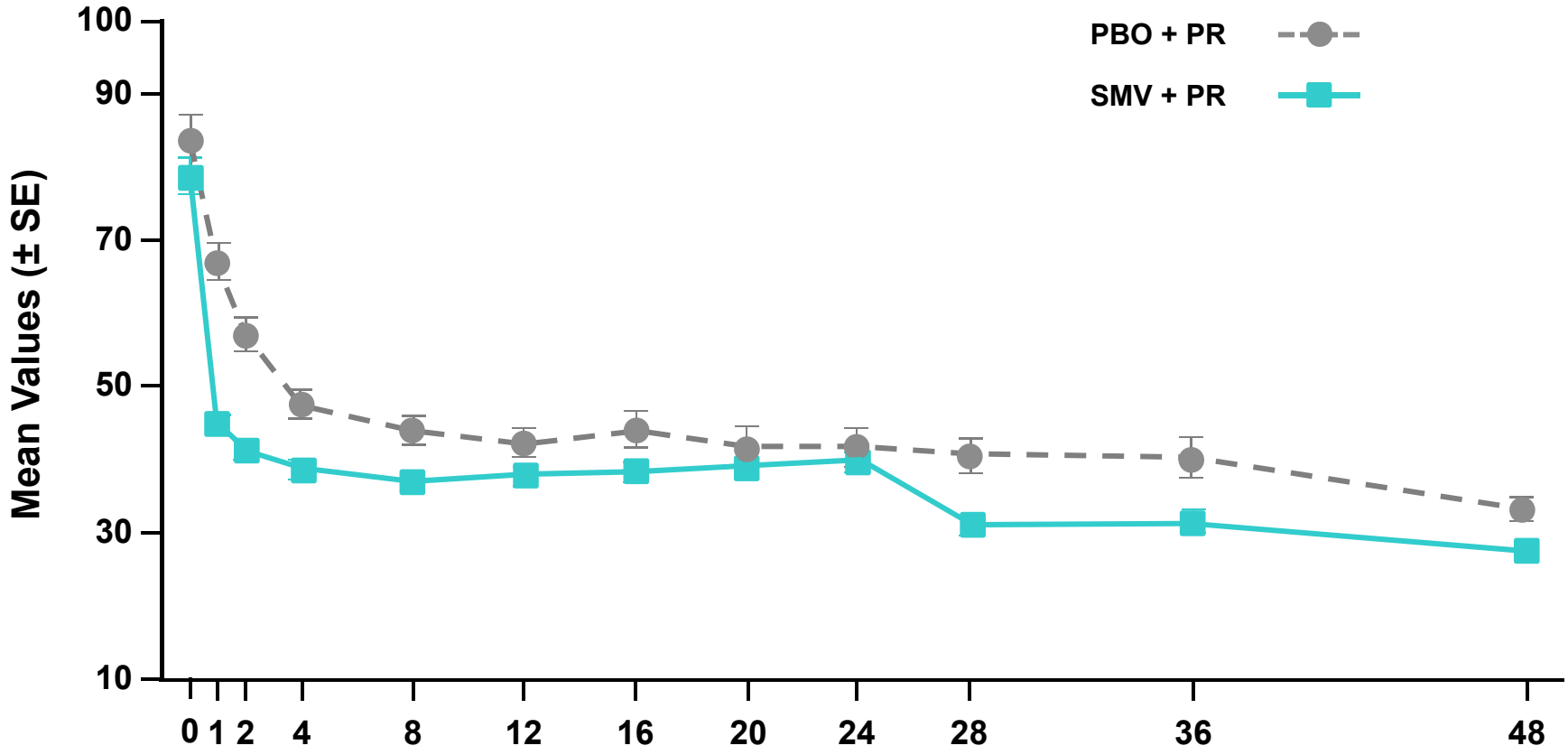
PBO+ PR	51	50	50	49	47	39	39	28	27
SMV + PR	87	85	83	84	82	80	80	2	1

Phase 3 include studies C208, C216, HPC3007

Mean ALT Over Time

72-Week Study Period

Phase 3 Studies



Number of Patients

PBO + PR	387	387	387	386	373	347	329	315	281	259
SMV + PR	764	764	757	753	742	734	724	706	681	669

Phase 3 studies include C208, C216, HPC3007

Liver Cirrhosis: Graded Bilirubin Abnormalities
Phase 3 Studies

Worst Treatment-Emergent WHO Toxicity	Entire Treatment Phase					
	No Cirrhosis			Cirrhosis		
	SMV 150 mg + PR N=670 n (%)	PBO + PR N=344 n (%)	Difference (%)	SMV 150 mg + PR N=87 n (%)	PBO + PR N=51 n (%)	Difference (%)
Grade 1	180 (26.9)	57 (16.6)	10.3	21 (24.1)	7 (13.7)	10.4
Grade 2	118 (17.6)	28 (8.1)	9.5	19 (21.8)	7 (13.7)	8.1
Grade 3	18 (2.7)	5 (1.5)	1.2	13 (14.9)	2 (3.9)	11.0
Grade 4	2 (0.3)	-	-	1 (1.1)	-	-

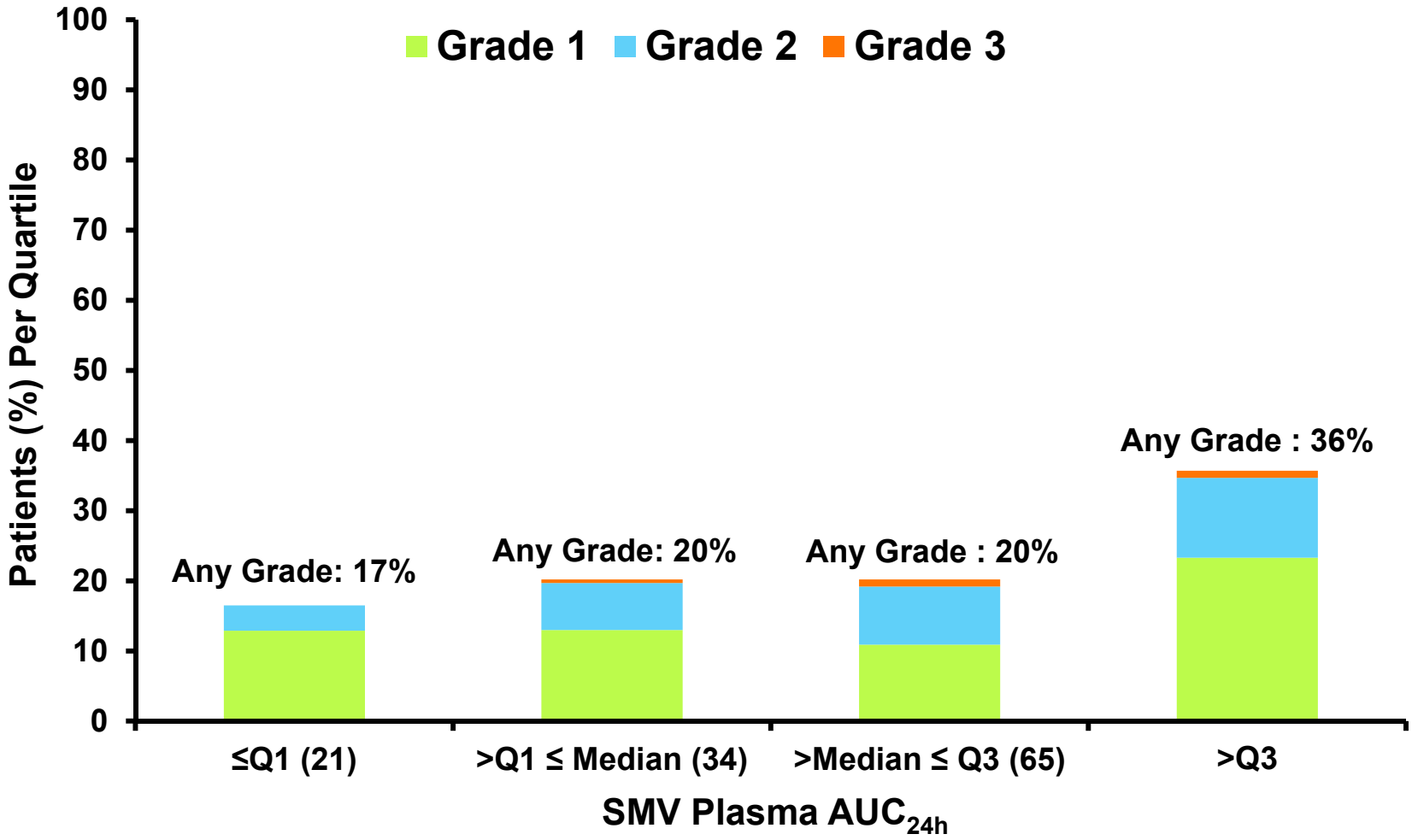
Phase 3 studies include C208, C216, and HPC3007

Skin Events
Phase 3 Studies

- Rash (any type)
  - First 12 wks incidence: 23.2% (SMV 150 mg + PR) vs 16.9% (PBO + PR)
  - Five (0.6%) SMV patients with Grade 3, no Grade 4
  - Discontinuation of SMV/PBO in 6 (0.8%) SMV and 1 (0.3%) PBO patients
- Photosensitivity Conditions or Sunburn
  - First 12 wks incidence: 4.9% (SMV 150 mg + PR) vs 0.8% (PBO + PR)
  - Five (0.6%) SMV patients with Grade 2, 1 (0.1%) SMV patient with Grade 3, no Grade 4; no Grade 2 – 4 on PBO
  - No study drug discontinuations
  - Two SAEs on SMV (hospitalization)
- Pruritus
  - First 12 wks incidence: 22.0% (SMV 150mg + PR) vs 14.9% (PBO + PR)
  - One (0.1%) SMV patient with Grade 3, no Grade 4; no Grade 3 or 4 on PBO
  - Discontinuation of study drugs in 1 (0.1%) SMV patient (Grade 2)
  - No SAEs
  - First 12 wks anal pruritus incidence in SMV 150mg: 0.3% (Grade 1 only)

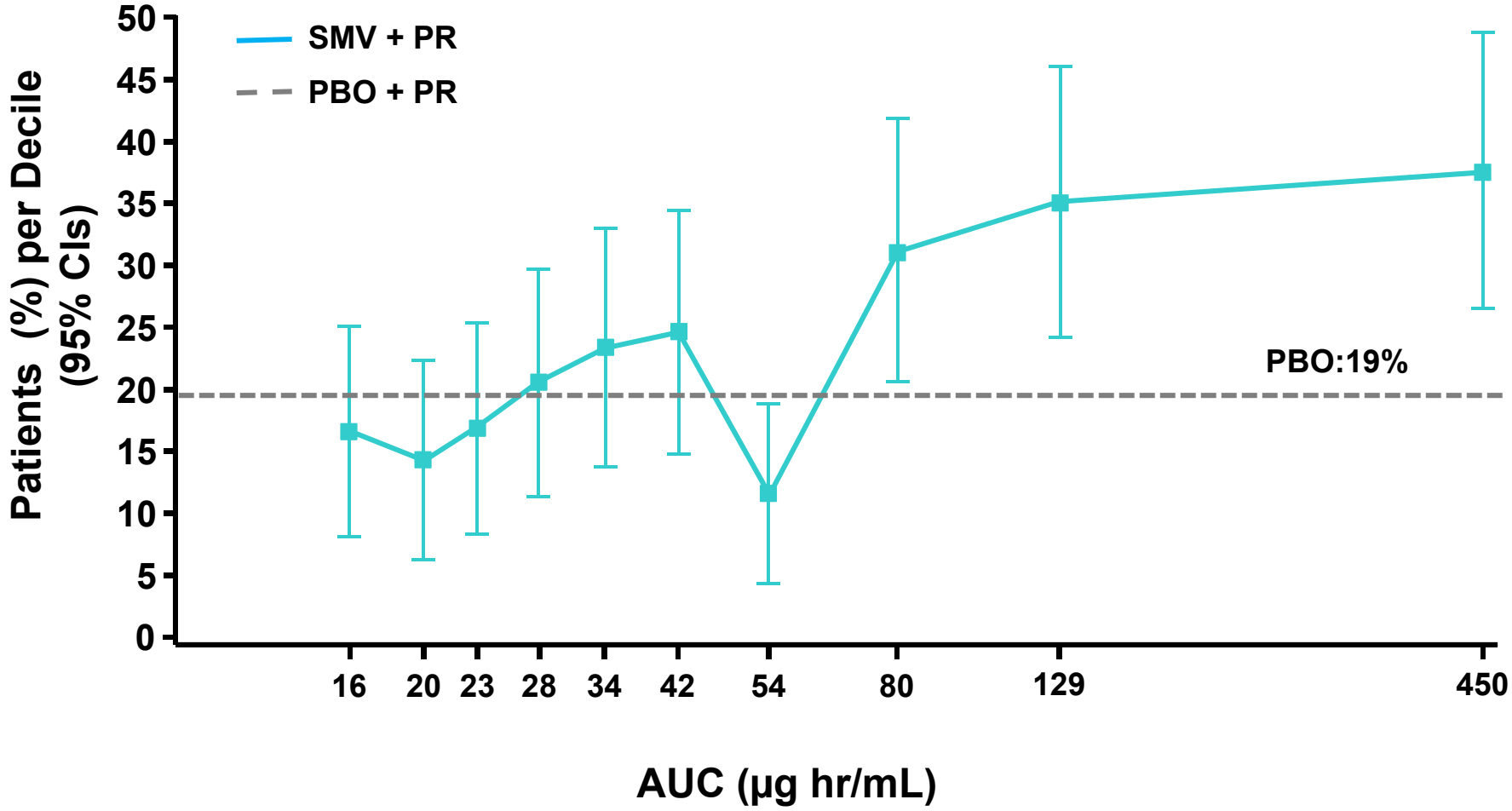
Phase 3 studies include C208, C216, and HPC3007

Rash (Any Type) by Worst Toxicity Grade by SMV Plasma AUC_{24h}
Phase 3 Studies



Phase 3 Studies include C208, C216, and HPC3007

Rash (Any Type) vs Simeprevir Plasma Exposure
Phase 3 Studies



Phase 3 Studies C208, C216, and HPC3007

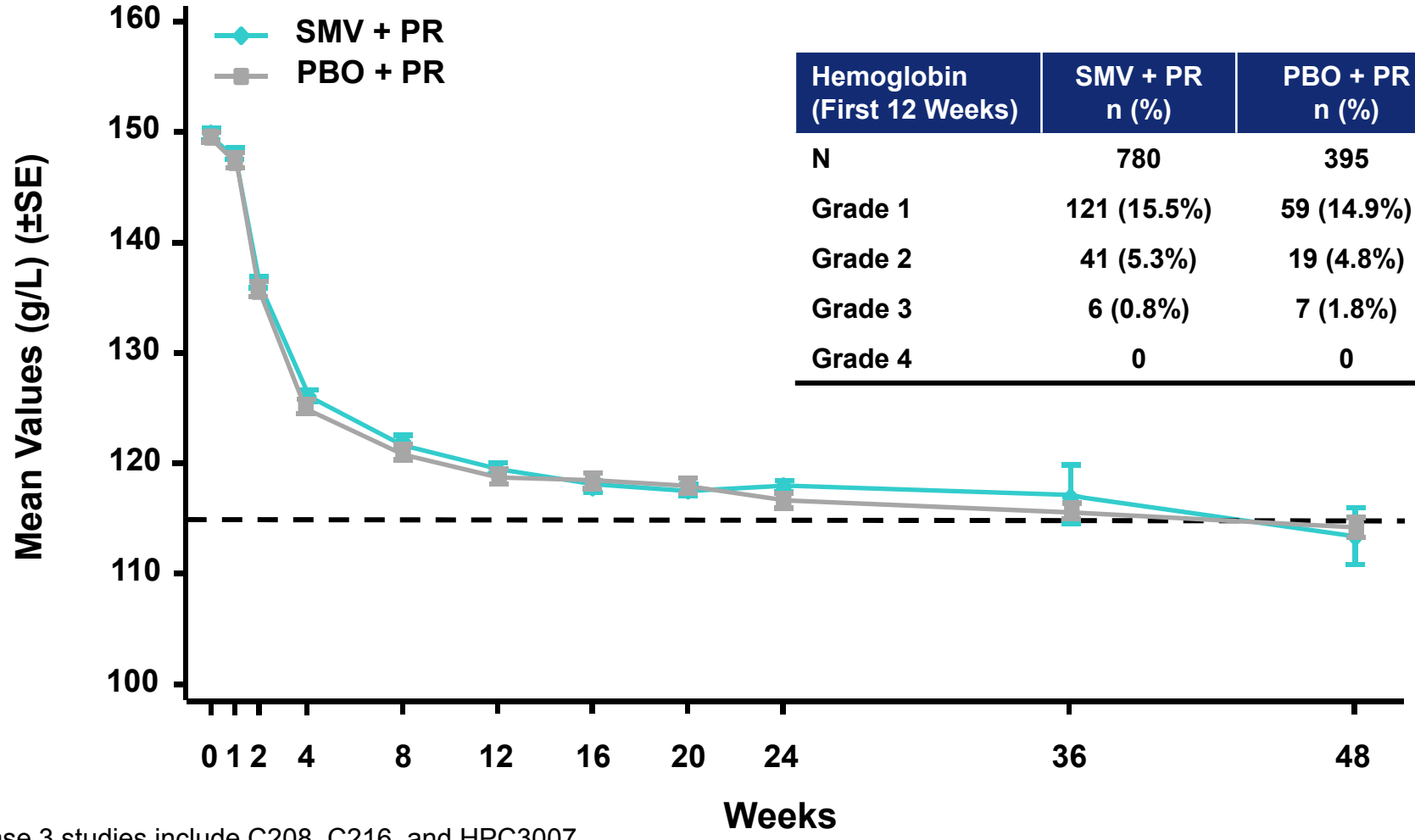
Rash and Pruritus in Liver Cirrhosis
Phase 3 Studies

AE of Special Interest	First 12 Weeks					
	No Cirrhosis			Cirrhosis		
	SMV 150 mg + PR N=671 n (%)	PBO + PR N=345 n (%)	Difference (%)	SMV 150 mg + PR N=87 n (%)	PBO + PR N=51 n (%)	Difference
Rash (Any Type)	150 (22.4)	55 (15.9)	6.5	26 (29.9)	12 (23.5)	6.4
Photosensitivity conditions including Sunburn	31 (4.6)	3 (0.9)	3.7	5 (5.7)	0	5.7
Pruritus	141 (21.0)	47 (13.6)	7.4	26 (29.9)	12 (23.5)	6.4

Phase 3 studies include C208, C216, and HPC3007

Mean Hemoglobin and Graded Abnormalities
Phase 3 Studies

Entire Treatment Phase – Hemoglobin (g/L)

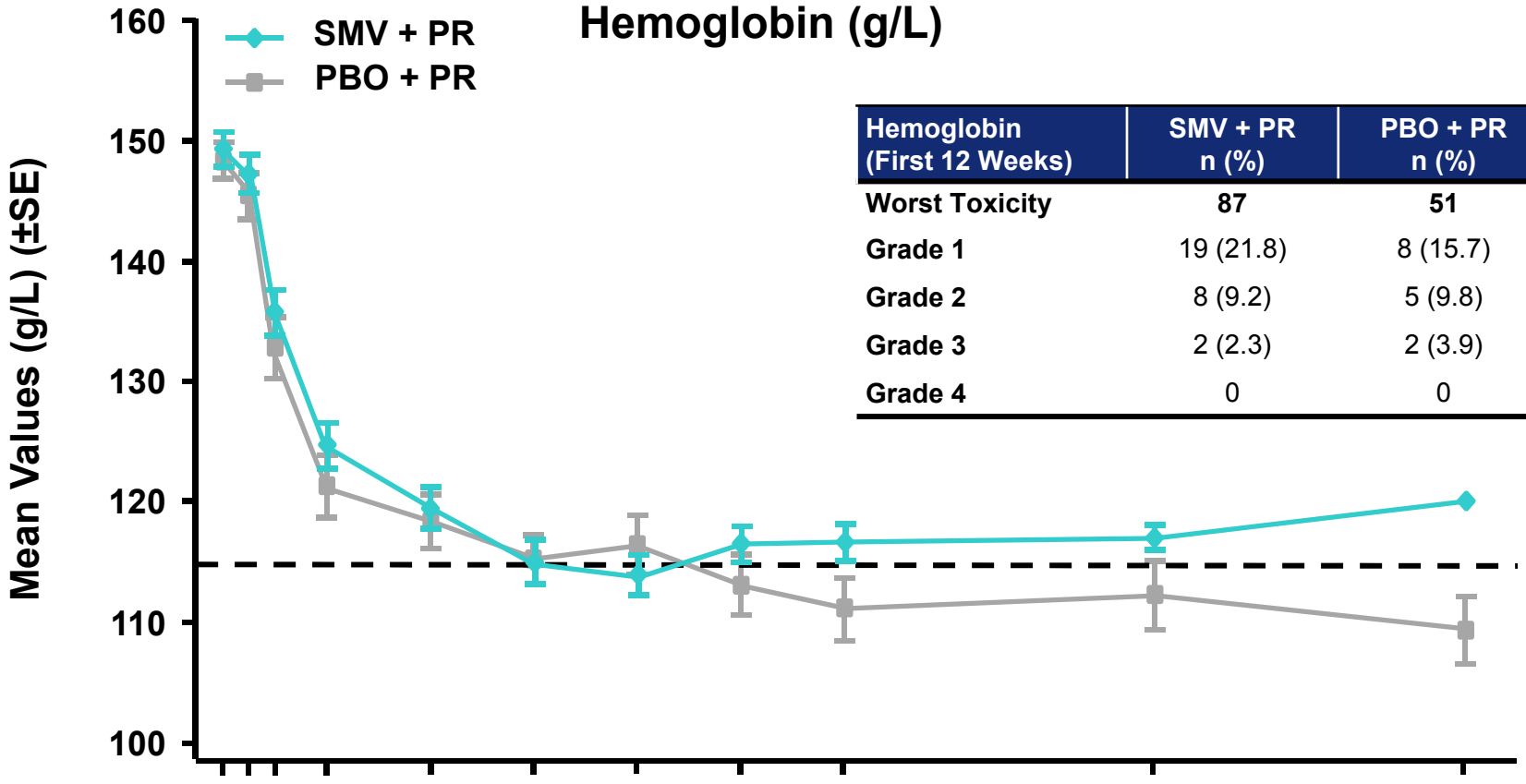


Hemoglobin (First 12 Weeks)	SMV + PR n (%)	PBO + PR n (%)
N	780	395
Grade 1	121 (15.5%)	59 (14.9%)
Grade 2	41 (5.3%)	19 (4.8%)
Grade 3	6 (0.8%)	7 (1.8%)
Grade 4	0	0

Phase 3 studies include C208, C216, and HPC3007

Hemoglobin in Patients With Metavir Fibrosis Stage 4 (Cirrhosis)

Phase 3 Studies



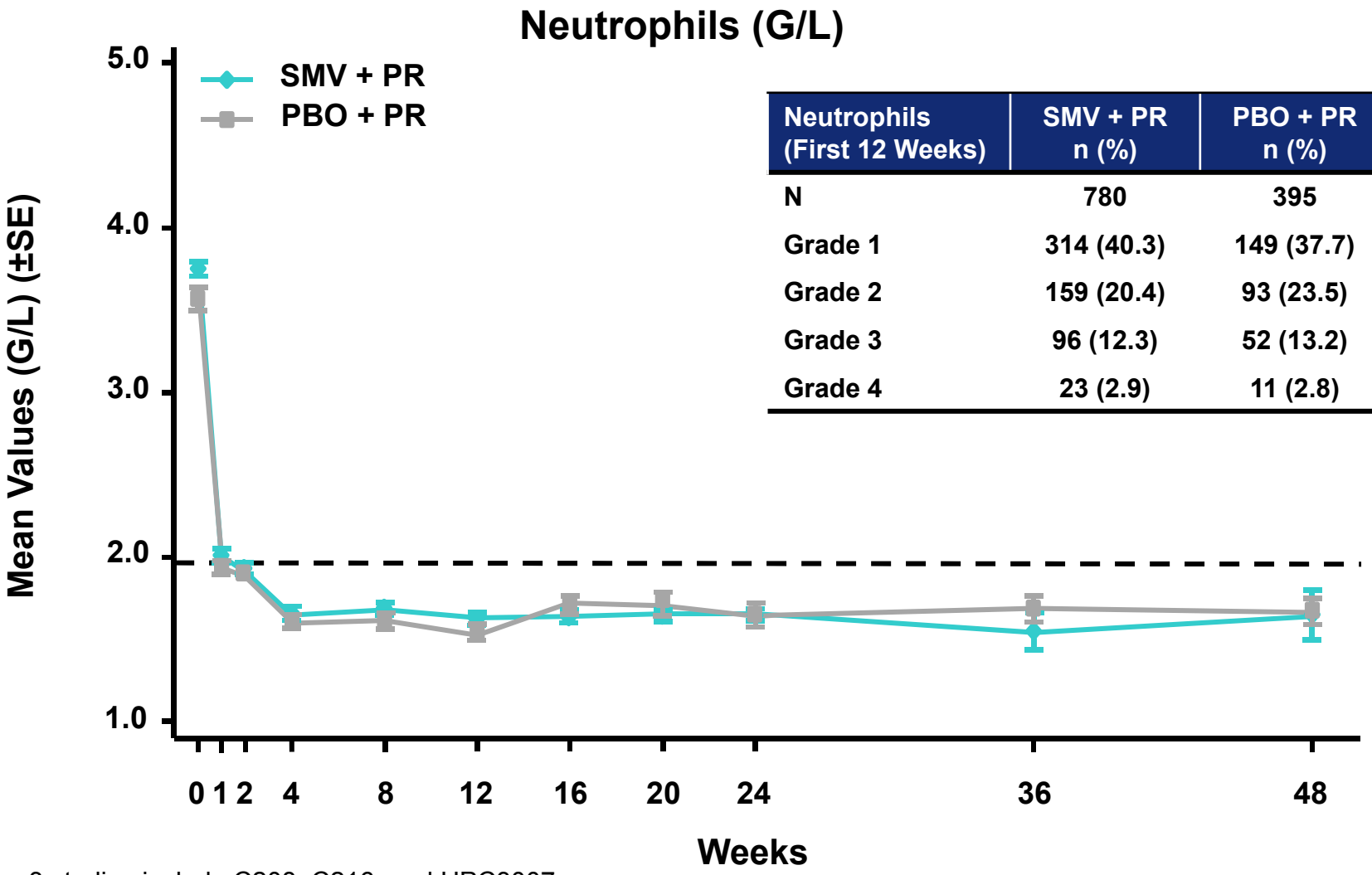
Hemoglobin (First 12 Weeks)	SMV + PR n (%)	PBO + PR n (%)
Worst Toxicity	**87**	**51**
Grade 1	19 (21.8)	8 (15.7)
Grade 2	8 (9.2)	5 (9.8)
Grade 3	2 (2.3)	2 (3.9)
Grade 4	0	0

Number of Patients

PBO + PR	51	50	50	48	46	38	39	28	27
SMV + PR	87	85	85	84	82	79	80	2	1

Phase 3 studies include C208, C216, and HPC3007

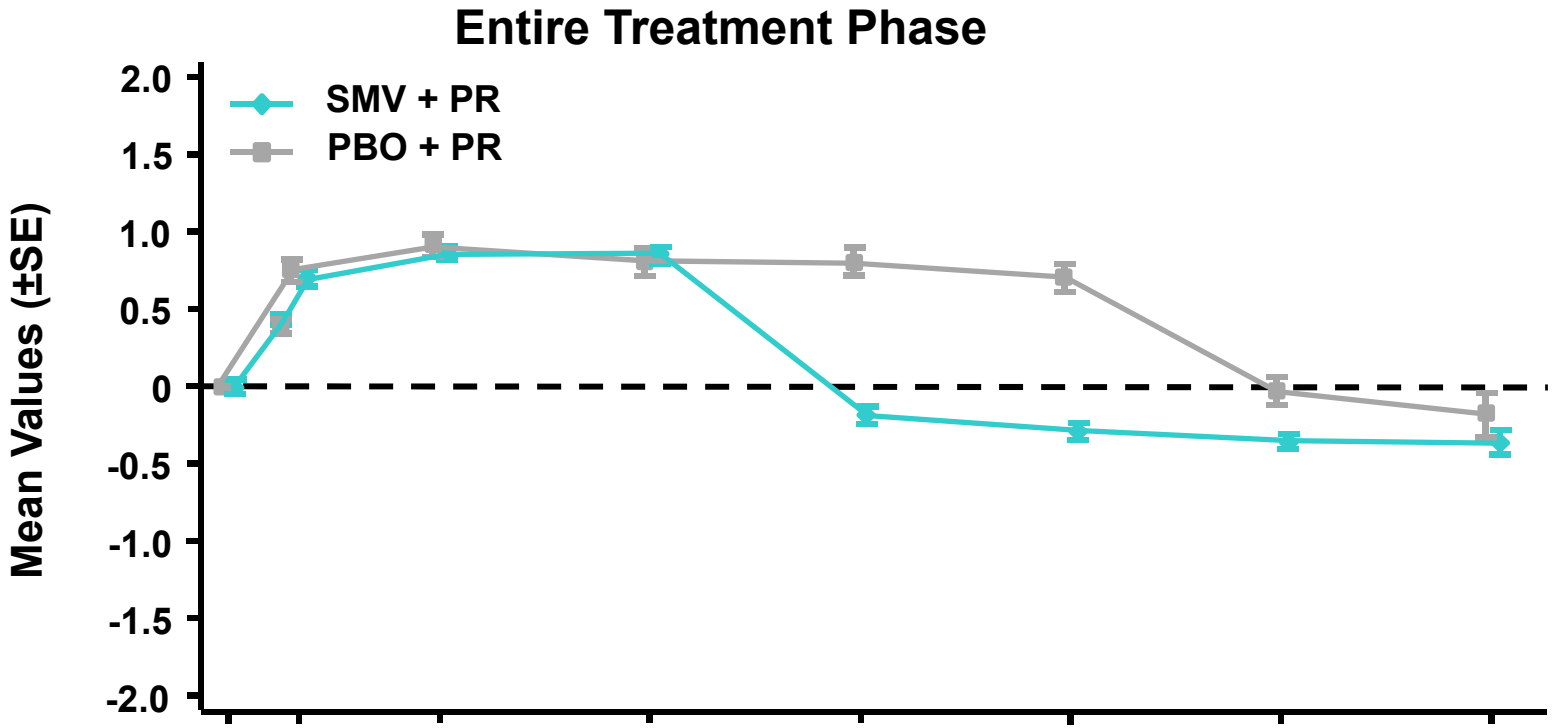
Mean Neutrophil Count and Graded Abnormalities
Phase 3 Studies



Neutrophils (First 12 Weeks)	SMV + PR n (%)	PBO + PR n (%)
N	780	395
Grade 1	314 (40.3)	149 (37.7)
Grade 2	159 (20.4)	93 (23.5)
Grade 3	96 (12.3)	52 (13.2)
Grade 4	23 (2.9)	11 (2.8)

Phase 3 studies include C208, C216, and HPC3007

Fatigue Severity Scale Scores
Phase 3 Studies



No. of patients:								
PBO + PR	393	387	377	361	340	342	346	132
SMV + PR	768	754	737	725	711	698	705	295

Phase 3 studies include C208, C216, and HPC3007
The FSS total score ranges from 1 to 7, with higher scores indicating worse outcome.

Safety and Subgroups
Phase 3 Studies

- **Age**: no consistent trend
- **Gender**: difference in rash SMV + PR/PBO higher in females (29.6 vs 19.2%) than males (18.8 vs 15.2%)
- **Race**: no consistent trend
- **BMI**: no consistent trend
- **Geographical Region**: no consistent trend

Phase 3 studies include C208, C216, and HPC3007

Simeprevir Safety Conclusions

- SMV generally safe and well tolerated
- Overall, similar AE rates of SMV + PR vs PBO
- Most Grade 1 or 2, no additional anemia
- More increased bilirubin events
  - Isolated (no Hy's Law Cases identified)
  - Completely reversible after SMV stop
  - Consistent with hepatic transporter inhibition
- Increased rate of photosensitivity reaction
- Small increase in rash incidence
  - Low rate of grade 3 rashes (0.6%)
- Safety consistent across subgroups including patients with liver cirrhosis

Recommendations for Treatment Management with Simeprevir and PR

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Simeprevir Efficacy Summary

- SVR rates were statistically significantly higher in HCV GT1 patients receiving SMV 150 mg + PR than in patients receiving PR alone.

- SVR rates were statistically significantly higher in GT 1a and GT 1b patients receiving SMV 150 mg + PR than in patients receiving PR alone

- SVR rates were reduced in GT 1a patients with Q80K compared to those without it

Treatment Management - Recommendations

- For GT 1a patients, alternative treatment options (other than SMV 150 mg + PR) should be considered in those with the Q80K polymorphism
- Simplified treatment strategy
- Well-defined, clear stopping rules are identified

Q80K Determination at Baseline

- The presence or absence of the Q80K polymorphism can be determined by genome sequencing of HCV present in plasma.
- At the present time in the United States, HCV NS3 sequencing is available from 2 commercial vendors
- Both available assays meet CLIA/CAP specifications

CLIA: Clinical Laboratory Improvement Amendments; CAP: College of American Pathologists

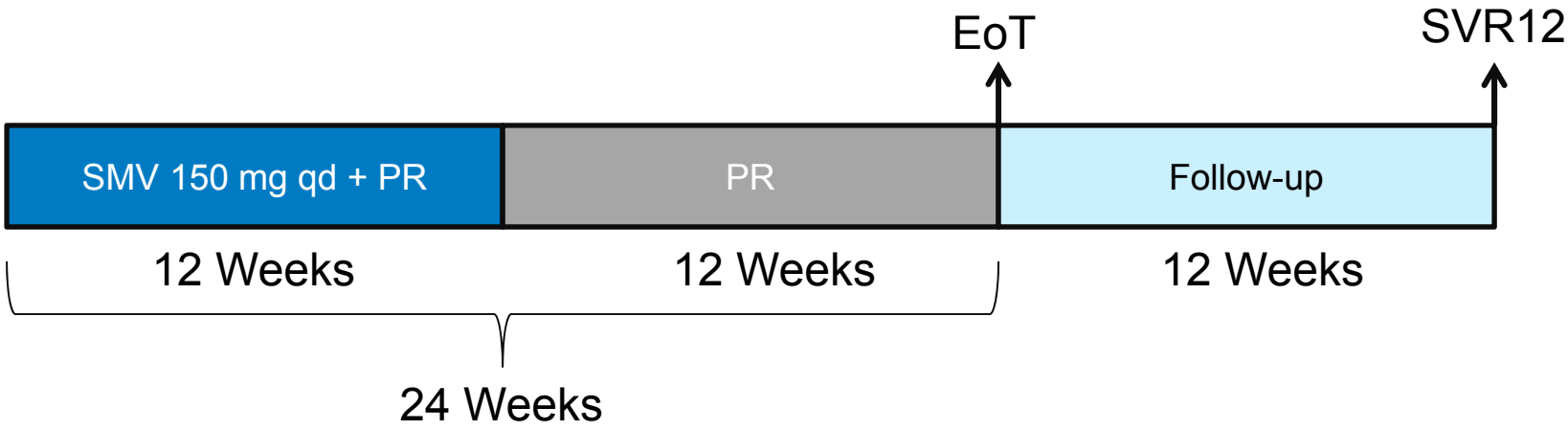
Treatment Duration in Treatment-naïve and Prior Relapser Patients

- In the Phase 3 studies, more than 85% of subjects qualified for 24-week total treatment duration and derived high SVR rates;
  - 88% of Treatment-naïves
  - 83% of Prior Relapsers

- Only 20% of treatment-naïve patients assigned to 48-week total duration derived a SVR

Treatment Duration in Treatment-naïve and Prior Relapser Patients (cont')

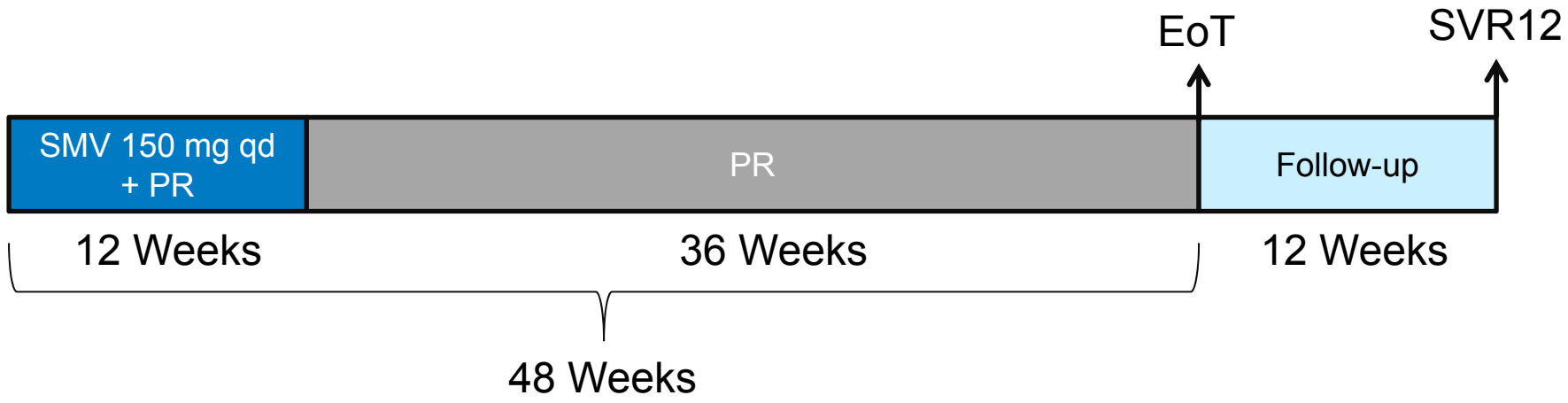
- The vast majority of treatment-naïve and prior relapser patients qualified for 24 weeks of total treatment duration
- Modest SVR rates were reported in those who were assigned to 48 weeks of treatment.
- A fixed total treatment duration of 24 weeks for all patients is recommended.



EoT: End of treatment

Treatment Duration in Prior Non-responders (Partial and Nulls)

- Prior non-responders (partial- and null-responders) should be treated for a total duration of 48 weeks



EoT: End of treatment

SVR by response at Week 4 in the context of Stopping Rules

Phase 3 Studies C208/C216

HCV RNA Week 4	Proportion of Patients n/N (%)	SVR12 n/N (%)	
<25 IU/mL	474/521 (91.0)	409/474 (86.3)	
≥25 - ≤100 IU/mL	7/521 (1.3)	1/7 (14.3)	7/35 (20%)
>100- ≤1,000 IU/mL	13/521 (2.5)	4/13 (30.8)	
>1,000 IU/mL	15/521 (2.9)	2/15 (13.3)	

note: For 12/521 (2.3%) HCV RNA assessment at week 4 was not available.

Simeprevir + PR Stopping Rules

Stopping rule	Treatment-naïve and Prior Relapsers	Prior Non-Responders
Week 4 HCV RNA ≥25IU/mL	STOP all therapy	STOP all therapy
Week 12 HCV RNA ≥25IU/mL	STOP all therapy	STOP all therapy
Week 24 HCV RNA ≥25IU/mL	NA	STOP all therapy

Simeprevir Meets Significant Unmet Medical Need

- High efficacy including difficult-to-treat patients
  - METAVIR scores F3/F4
  - *IL28B* CT/TT
  - Treatment-experienced (prior partial- and null-responders)
- Simplified treatment
  - One pill once-a-day dosing
  - 24-week total treatment duration for all treatment-naïve and prior relapser patients
  - Consistent stopping rules
- Favorable safety and tolerability profile
  - No added anemia
  - Very low discontinuation rates
  - Limited additional rash (<5% vs PBO), generally mild (0.6% grade 3 and no grade 4) and manageable
  - Photosensitivity (5%); well characterized and manageable
    - Sun protection measures recommended

Conclusions

Simeprevir represents a valuable new alternative for the treatment of HCV infection

- ✓ Efficacious in treatment naïve, prior relapser and non-responder patients
- ✓ Favorable safety profile
- ✓ Shorter and simpler regimen