HEPATITIS WEB STUDY HEPATITIS C ONLINE

Simeprevir (*Olysio*)

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Last Updated: July 14, 2015

Hepatitis web study

SIMEPREVIR (*OLYSIO*)

Background and Dosing

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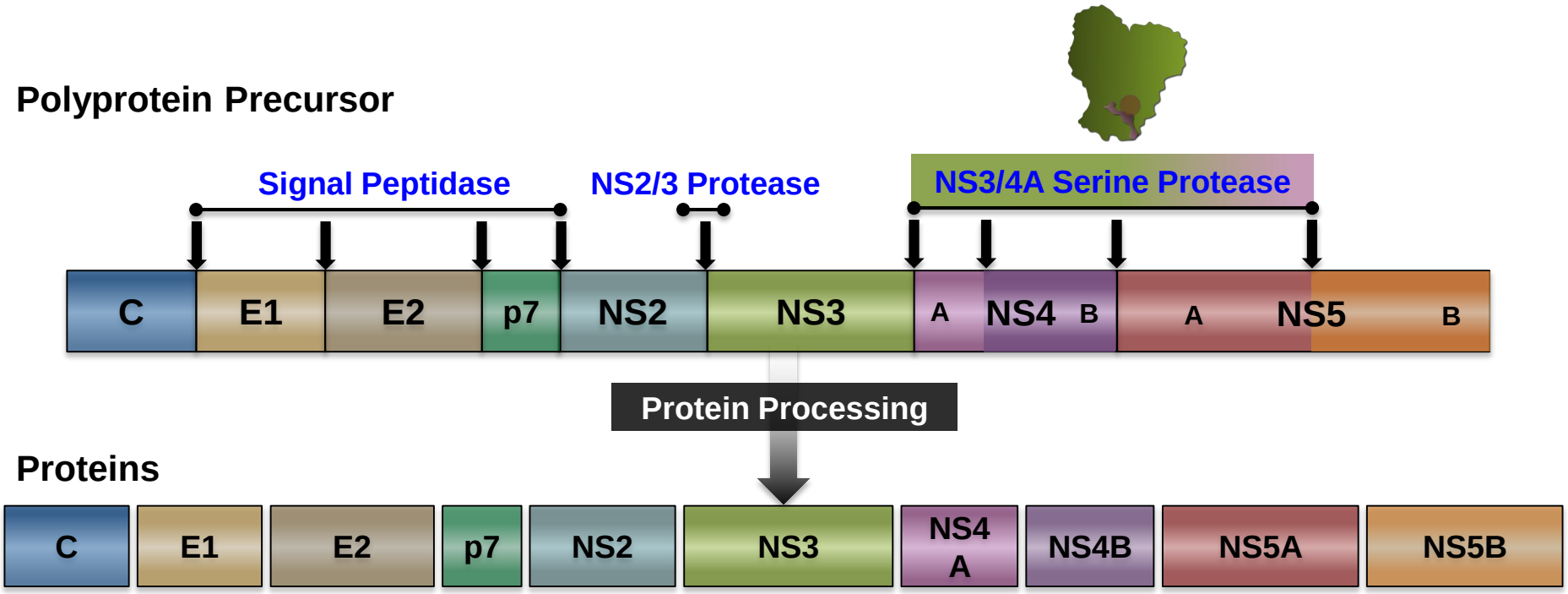
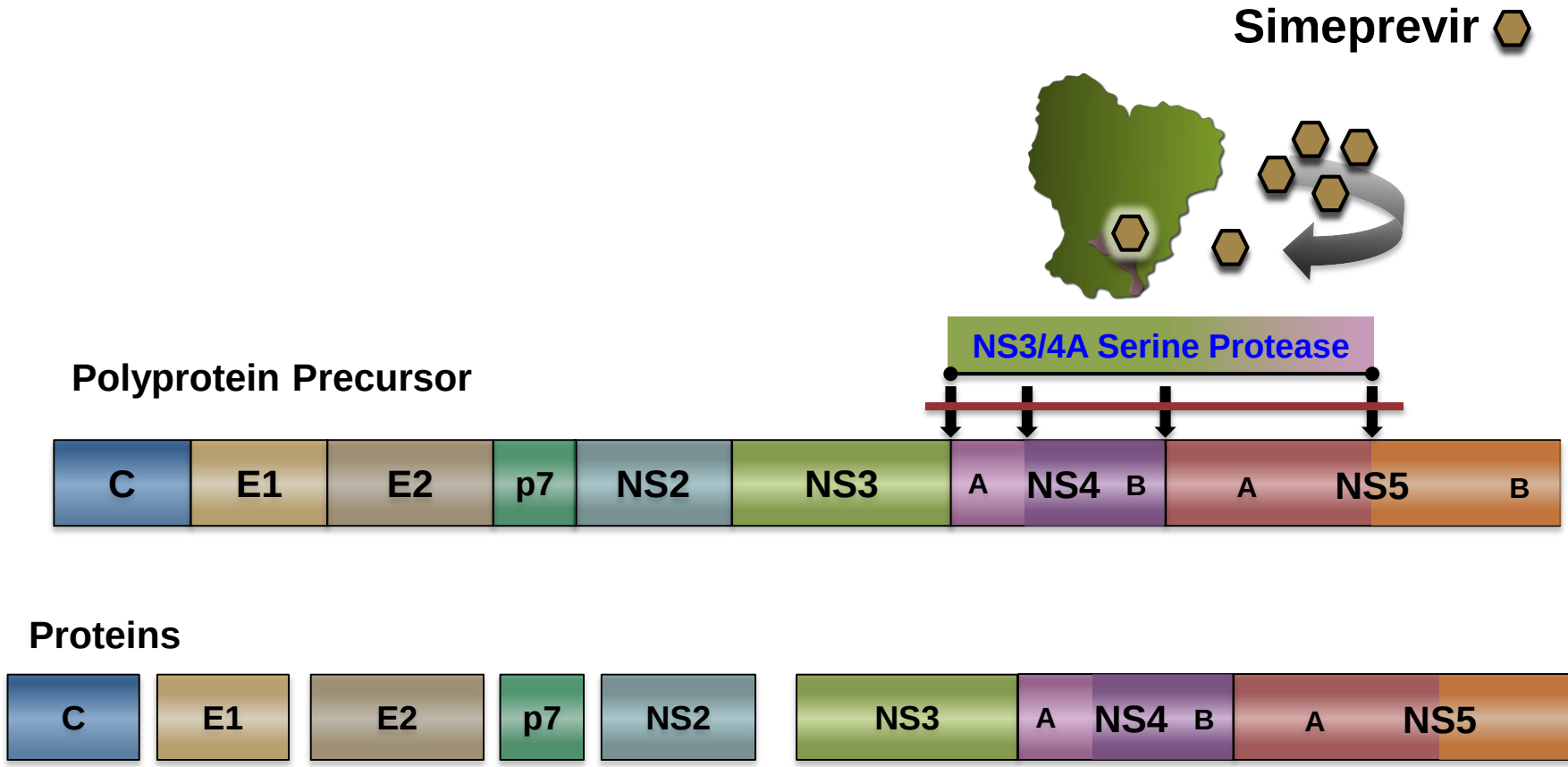
Simeprevir (*Olysio*) Summary

- **Approval Status**: FDA approved December 6, 2013
- **Indication for HCV Monoinfection**
  - GT 1: Simeprevir (12 weeks) + peginterferon + ribavirin (12 or 36 weeks)
  - Poor response to Simeprevir + Peginteferon + Ribavirin with GT1a and NS3 Q80K polymorphism at baseline
- **Class & Mechanism**
  - NS3/4A protease inhibitor
  - Activity against GT 1,2,4,5,6 (strongest activity against GT 1a, 1b)
- **Simeprevir Dosing**
  - 150 mg PO once daily with food
  - In combination with peginterferon + ribavirin (triple therapy)
- **Adverse Effects (AE) attributable to Simeprevir**
  - Rash (including a photosensitivity reaction), pruritus, and nausea
- **Wholesaler Acquisition Cost in United States**
  - 28 tablet bottle = $22,120; estimated 12-week cost = $66,360

HCV Protein Processing
Role of Role of NS3/4A Serine Protease



HCV Protein Processing
NS3/4A Serine Protease Inhibition



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SIMEPREVIR (*OLYSIO*)

Clinical Trials

Simeprevir: Summary of Key Studies

- **Phase 3 Trials in Treatment Naive**
  - **QUEST 1**: Simeprevir-PEG-RBV vs. PEG-RBV in GT1
  - **QUEST 2**: Simeprevir-PEG-RBV vs. PEG-RBV in GT1
- **Phase 3 Trials in Treatment Experienced**
  - **PROMISE**: Simeprevir-PEG-RBV vs. PEG-RBV in GT1, prior relapse
  - **ATTAIN**: Simeprevir vs. Telaprevir in prior null or partial responders
- **Phase 2 Trials in Treatment Experienced**
  - **ASPIRE**: Simeprevir + PR in GT1 treatment experienced

Simeprevir: Summary of Key Studies

- **Phase 3 Trials in Treatment Naïve and Experienced**
  - **RESTORE**: Simeprevir in HCV genotype 4 (naïve and experienced)
- **Simeprevir + Sofosbuvir**
  - **COSMOS**: Simeprevir + Sofosbuvir +/- RBV in GT1
  - **OPTIMIST-1**: Simeprevir + Sofosbuvir in GT1 without cirrhosis
  - **OPTIMIST-2**: Simeprevir + Sofosbuvir in GT1 with cirrhosis
- **HIV Coinfection**
  - **C212**: Simeprevir in HIV-HCV coinfected in GT1

Simeprevir in Treatment-Naïve Patients

Treatment Naïve

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1
QUEST-1 Trial

Jacobson IM, et al. Lancet. 2014;384:403-13.

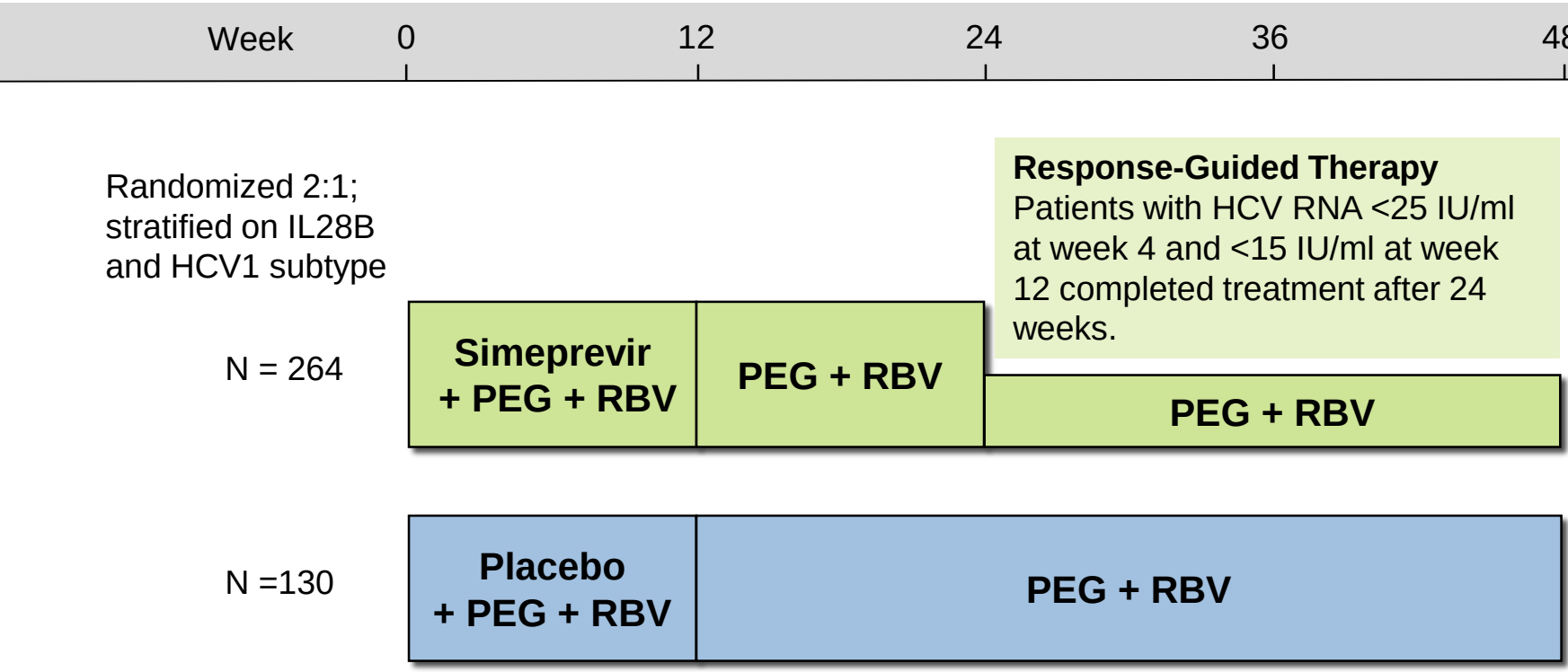
Simeprevir + PEG + Ribavirin for Treatment-Naïve HCV GT1 QUEST-1 Trial

QUEST-1 Trial: Features

- **Design**: Randomized, double-blind, placebo-controlled, phase 3 trial with simeprevir + PEG + RBV versus PEG + RBV in treatment-naïve GT 1
- **Setting**: Multicenter at 71 sites in 13 countries
- **Entry Criteria**
  - Treatment-naïve, chronic HCV monoinfection
  - HCV Genotype 1 (1a or 1b)
- **Patient Characteristics**
  - N = 394
  - HCV Genotype: 1a (56%); 1b (44%)
  - IL28B Genotype: 71% non-CC
  - Age: median age 48
  - Sex: 56% male
  - Race: 89% white, 8% black
  - Liver disease: F3 = 18%; F4 = 12%
- **Primary end-points**: Efficacy (SVR12) and safety

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Design



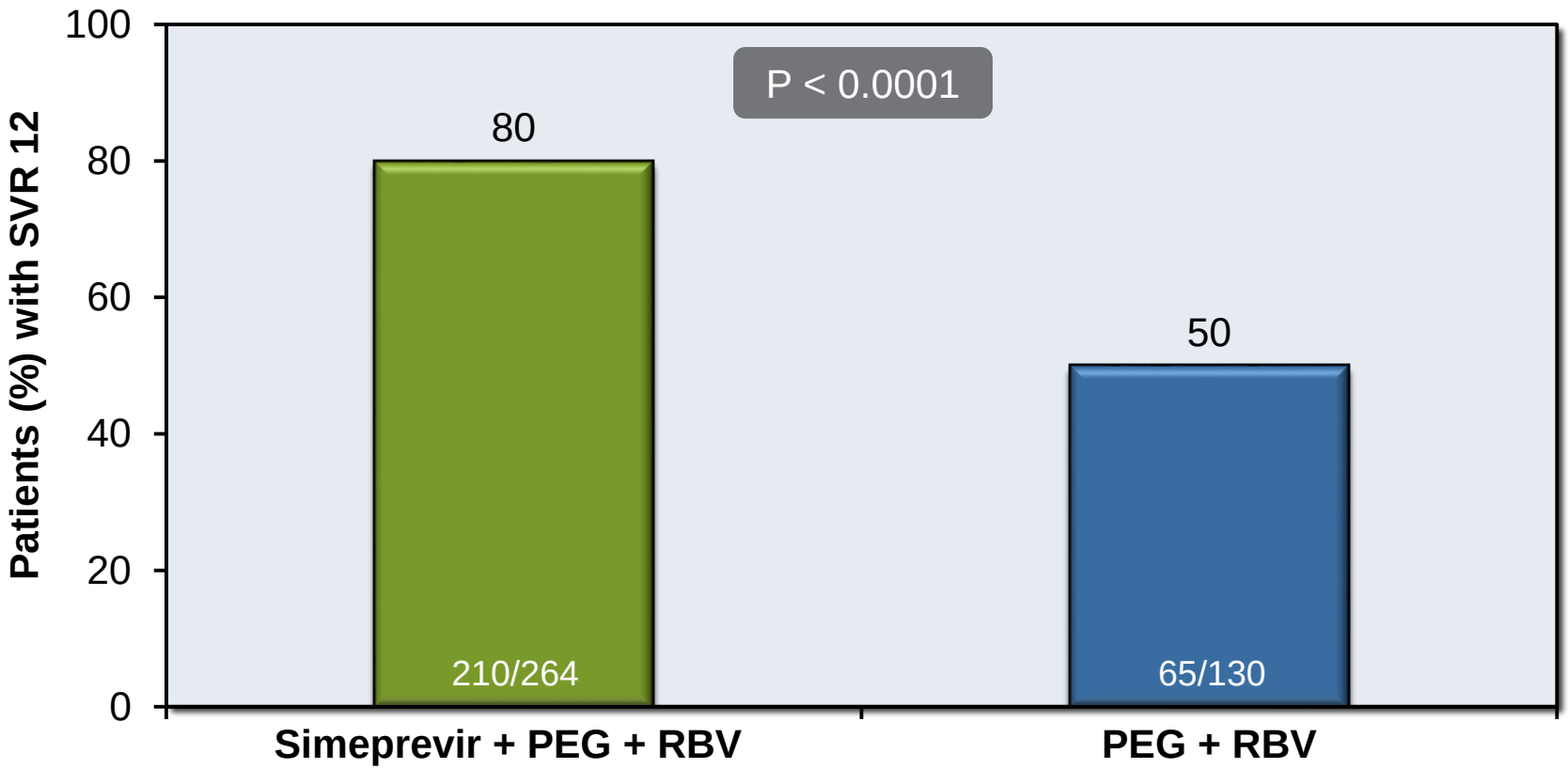
Response-Guided Therapy
Patients with HCV RNA <25 IU/ml at week 4 and <15 IU/ml at week 12 completed treatment after 24 weeks.

Drug Dosing
Simeprevir: 150 mg once daily
Peginterferon alfa-2a (PEG): 180 mcg/week
Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75kg

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST-1: Proportion of Patients with SVR12

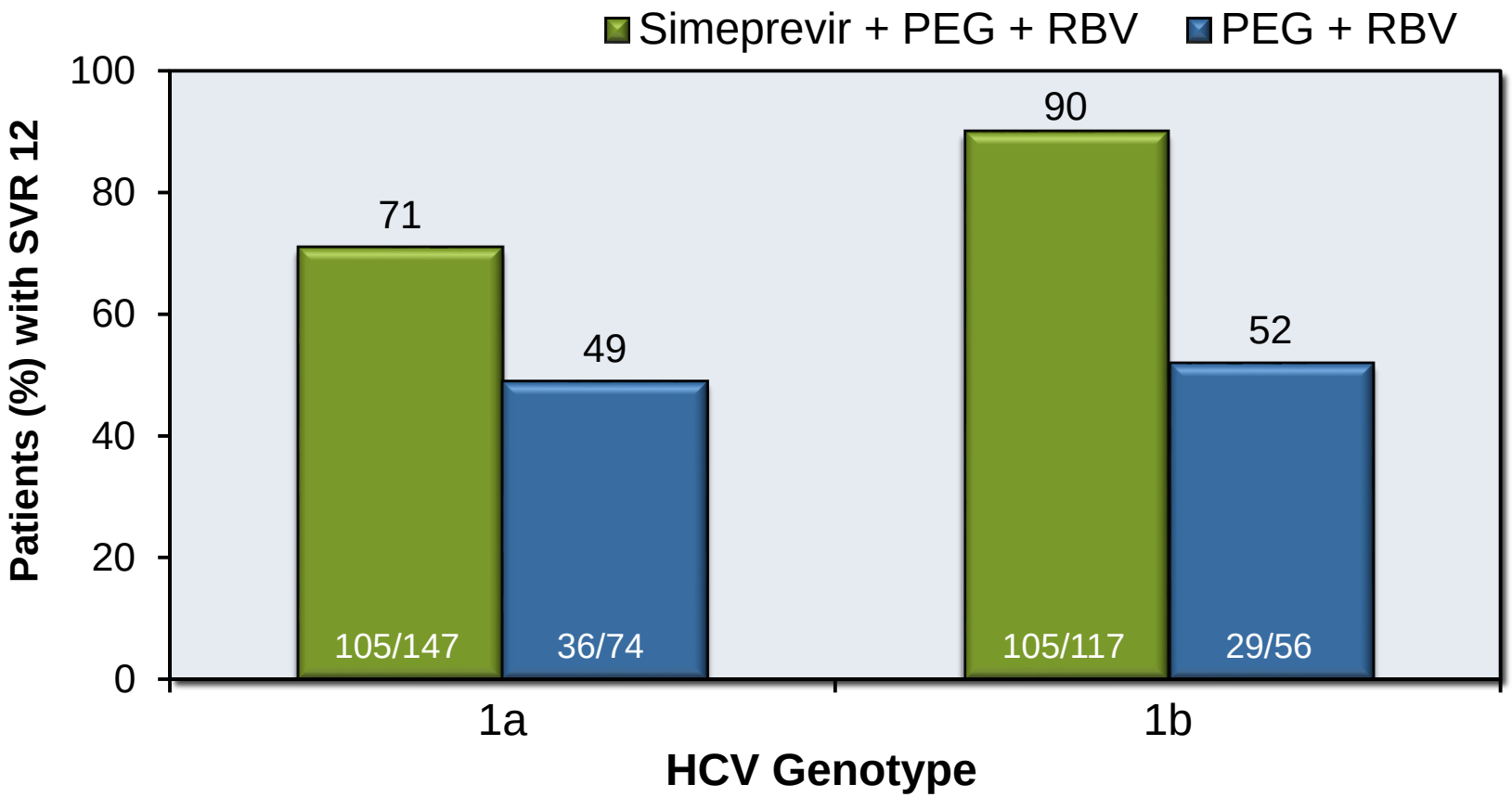


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

SVR12 by HCV Genotype 1 Subtype

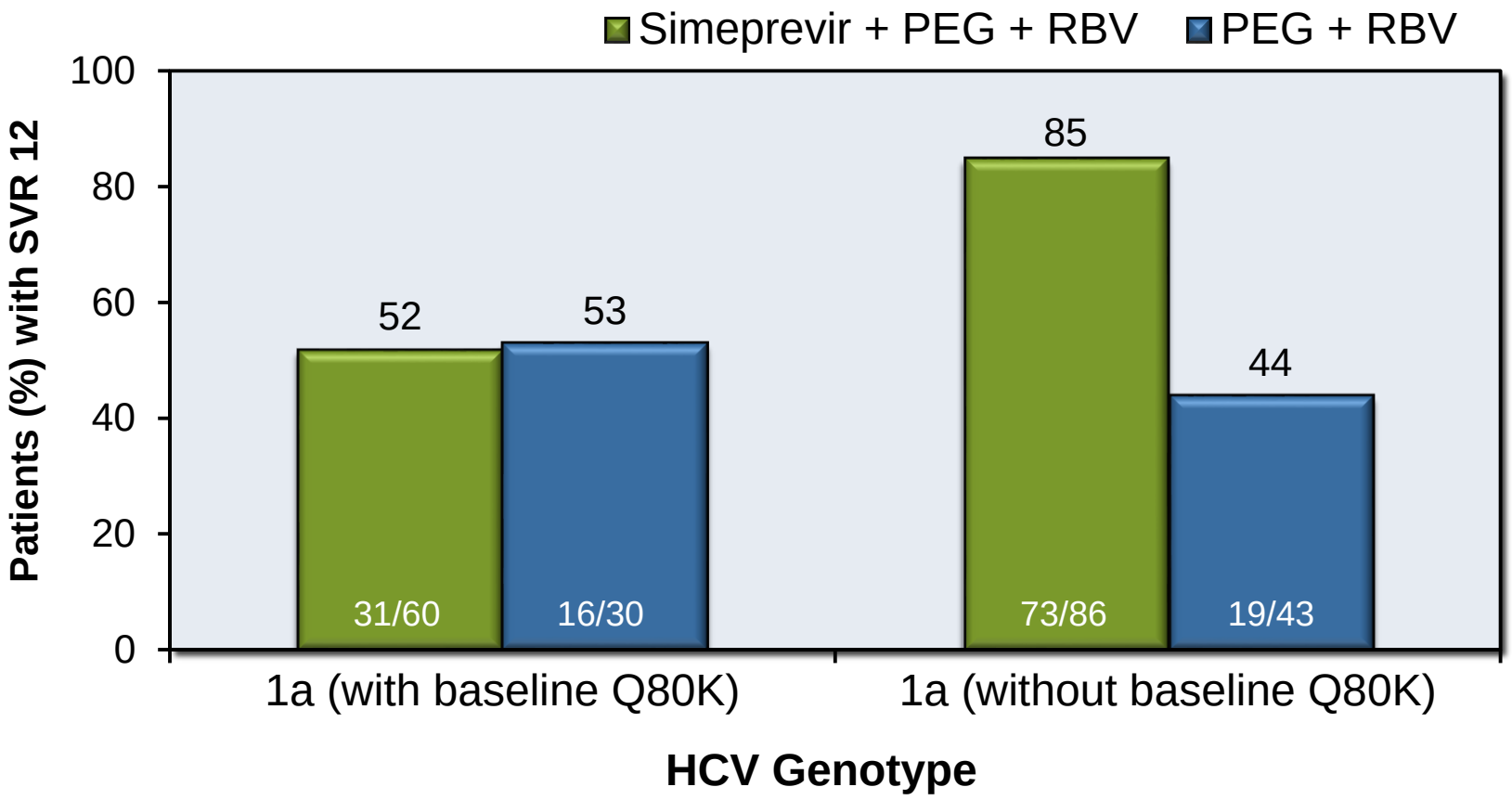


Abbreviations: PEG = Peginterferon; RBV = Ribavirin

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST 2: SVR12 for HCV 1a by Baseline Q80K Status



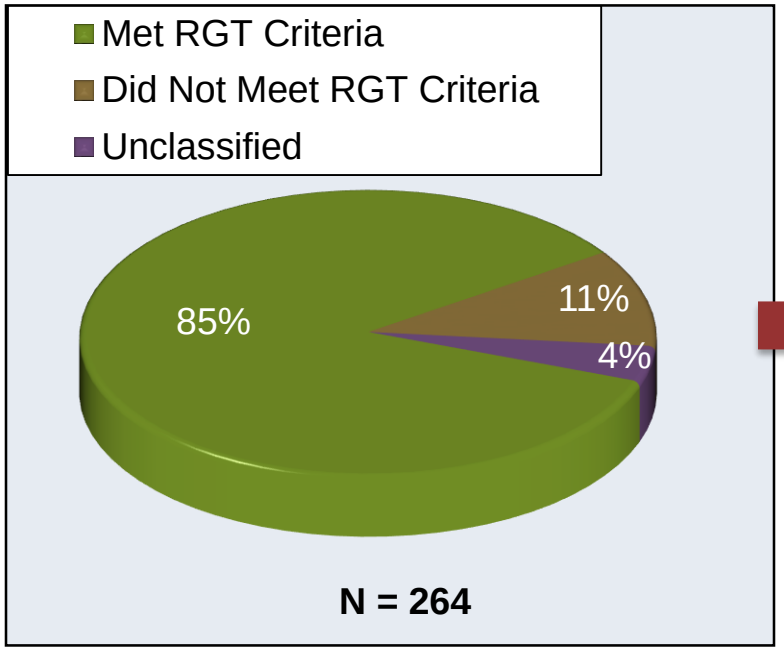
Abbreviations: PEG = Peginterferon; RBV = Ribavirin

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

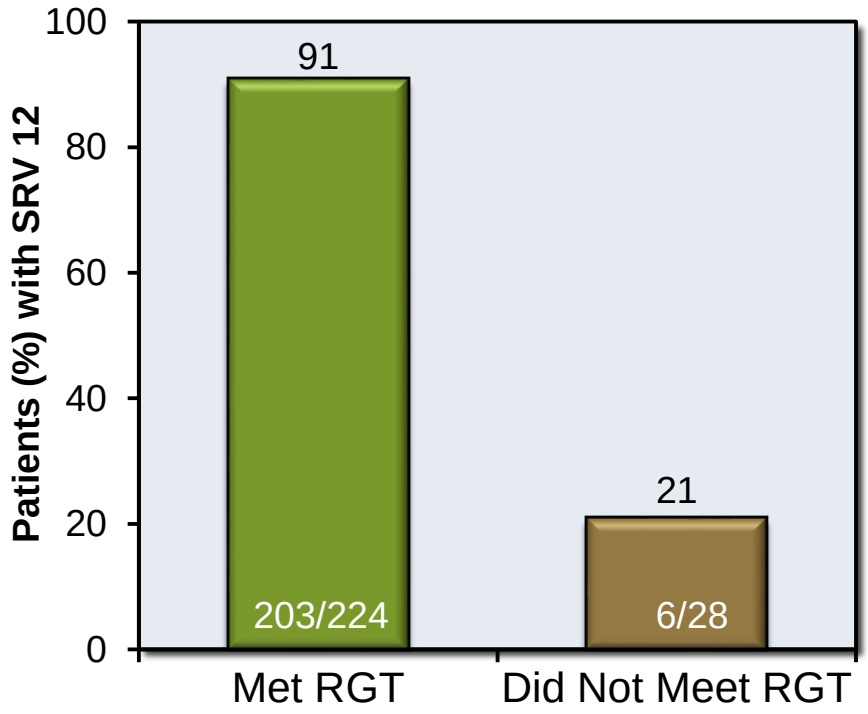
Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

SVR12 Response in Simeprevir Arm Based on Achievement of RGT Criteria

Patients (%) who Met RGT Criteria



SVR12 Based on Meeting RGT

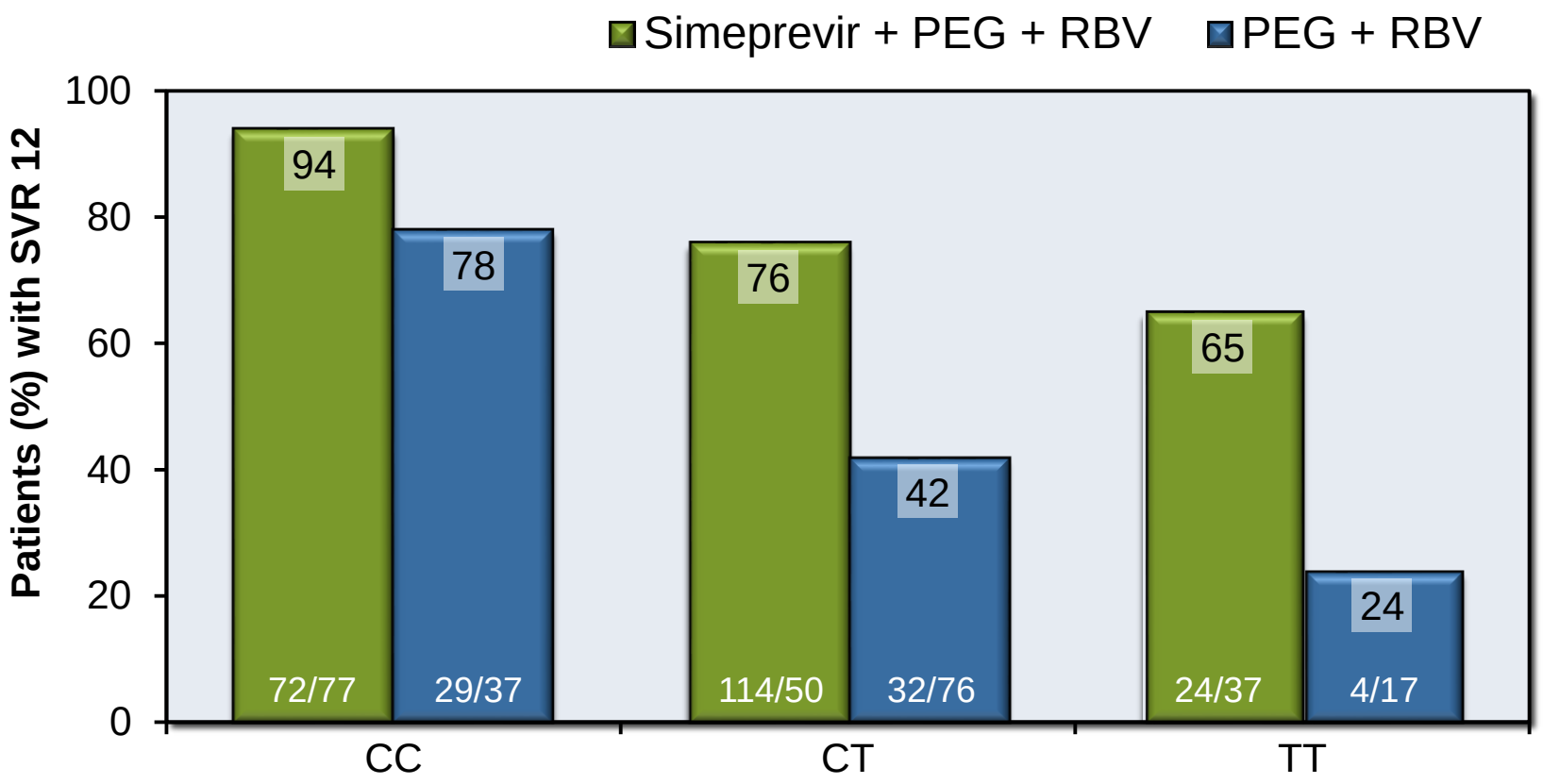


RGT= response-guided therapy: in simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST 1: SVR12 by Host *IL28B* Genotype

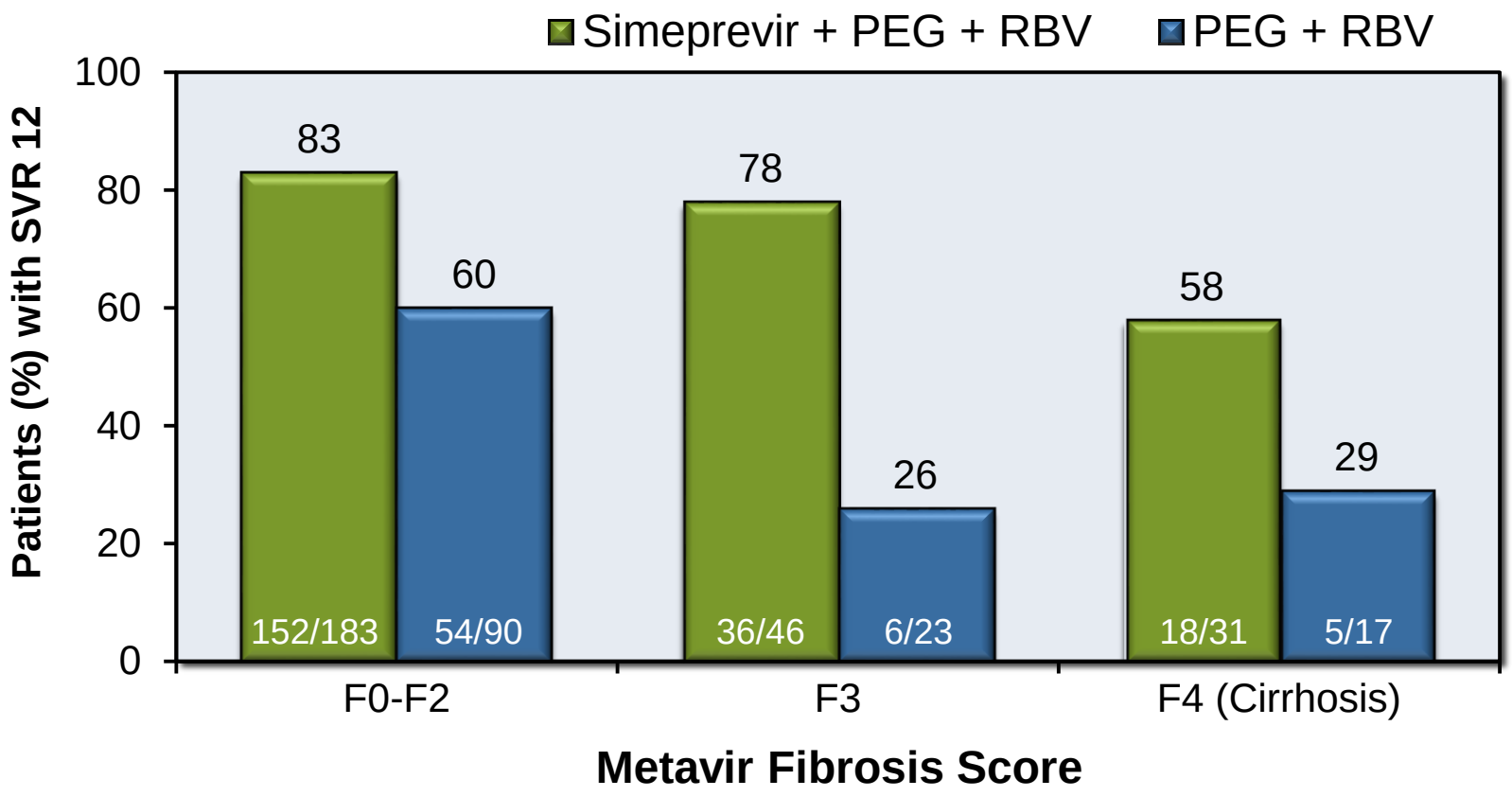


Abbreviations: PEG = Peginterferon; RBV = Ribavirin

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST 1: SVR12 by Liver Fibrosis (Metavir Score)



Abbreviations: PEG = Peginterferon ; RBV = Ribavirin

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

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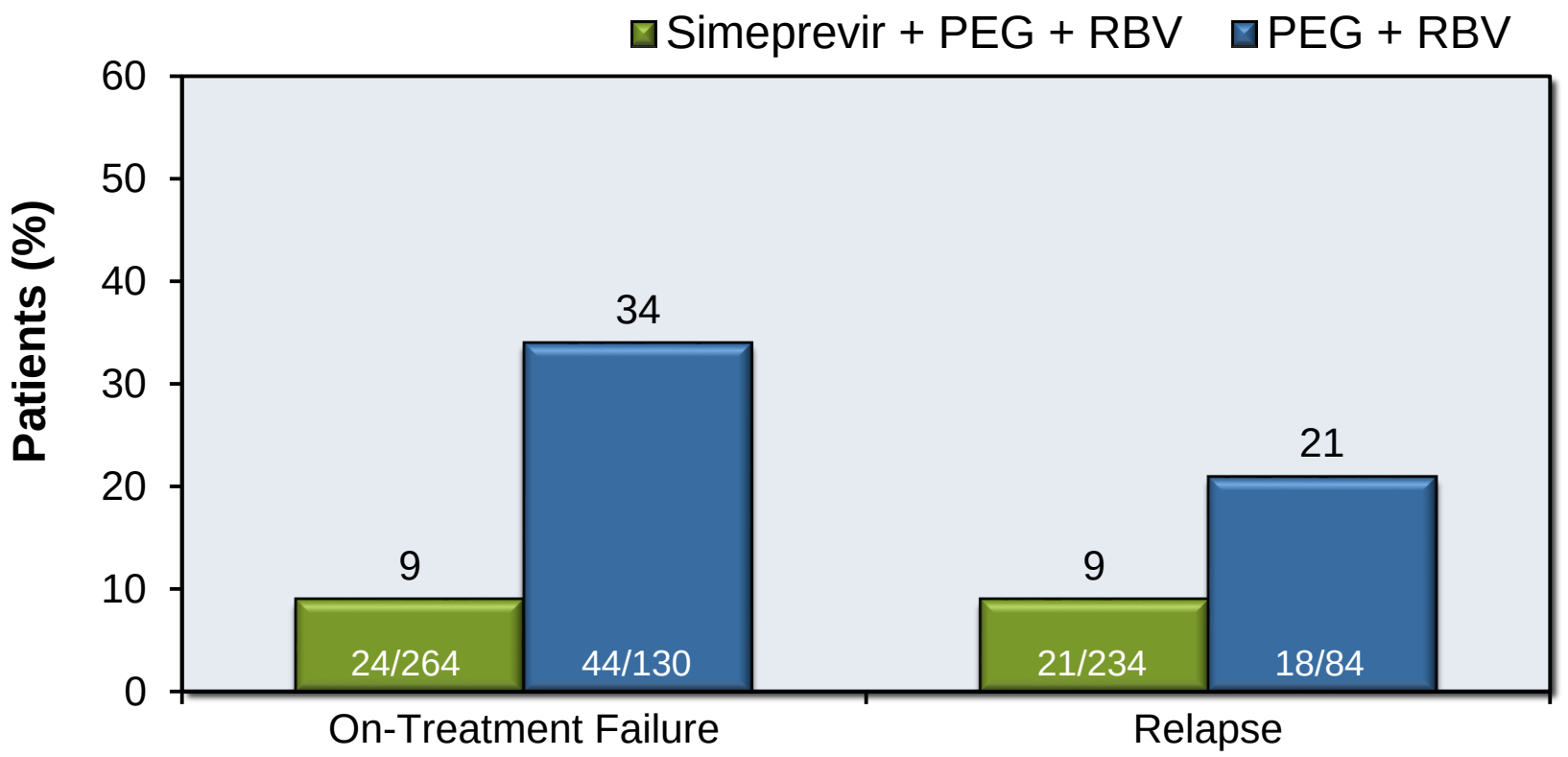
Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

On-Treatment Failure or Relapse



Stopping rules: (1) Stop simeprevir or placebo if HCV RNA>1000 at week 4; (2) Stop all therapy if HCV RNA < 2 $\log_{10}$ IU/mL reduction at week 12; (3) Stop all therapy if HCV RNA ≥25 IU/mL at week 24 or 36.
On-treatment failure: Detectable HCV RNA at end of treatment.

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

Emergent Protease Resistance in Patients who Failed to Achieve SVR12

- Among simeprevir-treated patients who failed to achieve SVR12, emergent mutations in NS3 protease domain detected in 35 (92%) of 38
- Genotype 1A: Most common mutation = R155K alone or in combination with mutations at codons 80 and/or 168
- Genotype 1B: Most common mutation = D168V

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1
QUEST-1 Trial: Adverse Effects

QUEST 1: Event	Simeprevir + PEG + RBV (n=264)	Placebo + PEG + RBV (n=130)
Discontinuation (due to adverse event)	3%	2%
Grade 3 adverse event	25%	33%
Grade 4 adverse event	3%	5%
Fatigue	42%	41%
Headache	33%	39%
Pruritus	30%	20%
Rash (any type)	34%	32%
Anemia	20%	21%
Photosensitivity condition	3%	<1%
Neutropenia	24%	18%
Bilirubin increase	9%	5%

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Conclusions

Interpretation: “Simeprevir once daily with peginterferon alfa 2a and ribavirin shortens therapy in treatment-naive patients with HCV genotype 1 infection without worsening the adverse event profiles associated with peginterferon alfa 2a plus ribavirin.”

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Treatment Naïve

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1
QUEST-2 Trial

Manns M, et al. Lancet. 2014;384:414-26.

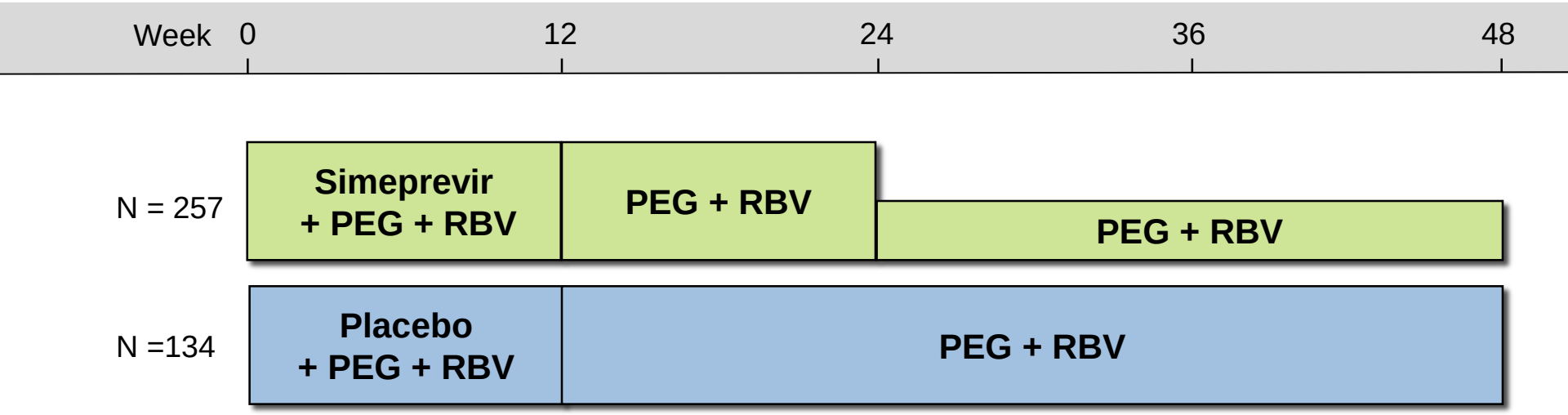
Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Background

QUEST-2 Trial: Features

- **Design**: Randomized, double-blind, placebo-controlled, phase 3 trial of simeprevir + PEG + RBV versus PEG + RBV in HCV GT1
- **Setting**: Multicenter at 76 sites in 14 countries
- **Entry Criteria**
  - Treatment-naïve, chronic HCV monoinfection
  - HCV Genotypes 1a or 1b
- **Patient Characteristics**
  - N = 391
  - HCV Subtype: 1a (41%); 1b (58%); other (<1%)
  - IL28B Genotype: 30% CC
  - Age and Sex: median age 46; 55% male
  - Race: 92% white
  - Liver disease: 14% with F3; 6% with F4
- **Primary end-points**: Efficacy (SVR12) and safety

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Design



Study Notes

- Randomized 2:1, stratified on IL28B and HCV subtype
- 63% in each arm randomized to receive PEG alfa-2a or PEG alfa-2b; remainder assigned PEG alfa-2a
- Response-guided therapy (RGT): In simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Drug Dosing

Simeprevir: 150 mg once daily

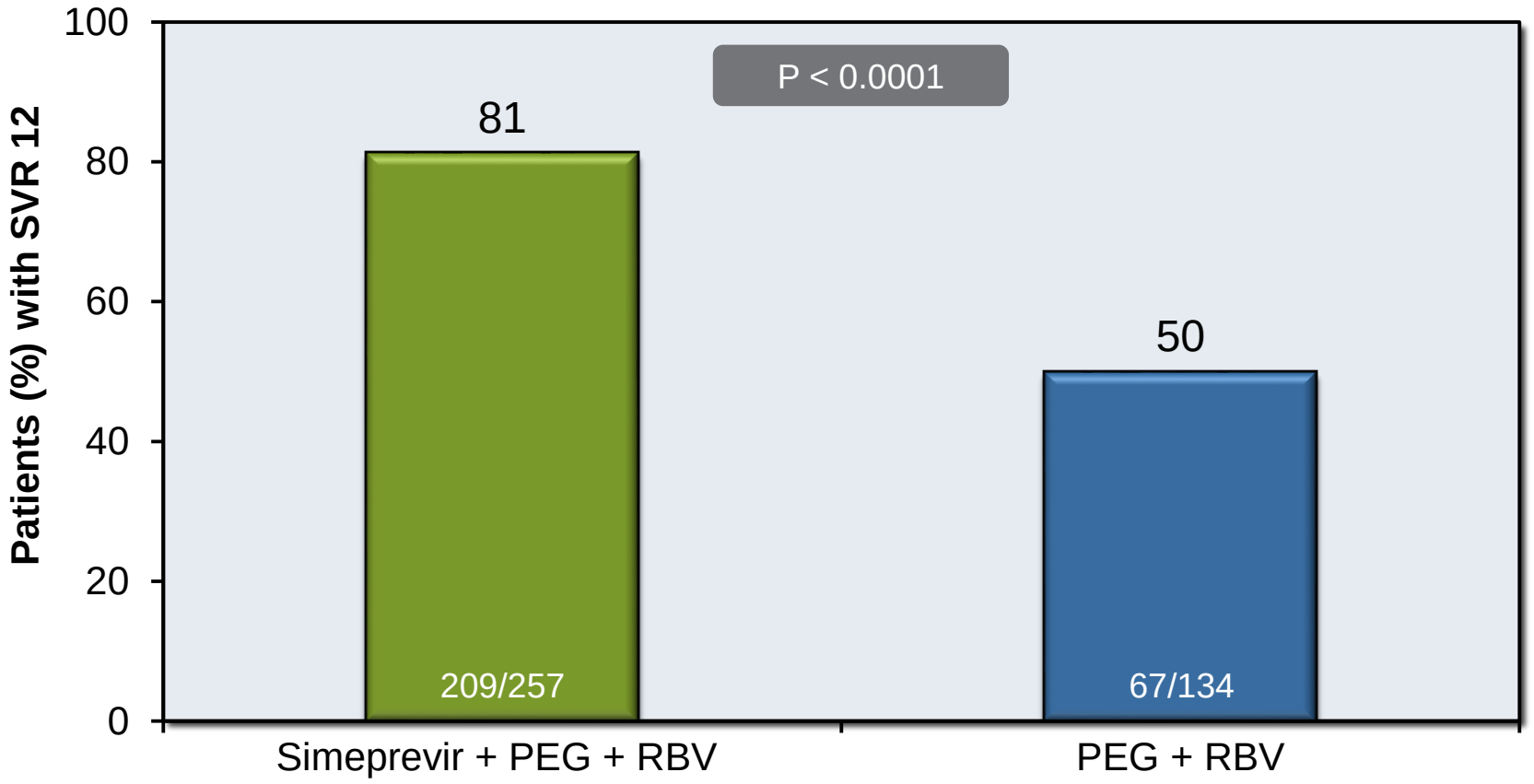
Peginterferon alfa-2a (PEG): 180 mcg/week OR Peginterferon alfa-2b: 1.5 mcg/kg/week

Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: Proportion of Patients with SVR12

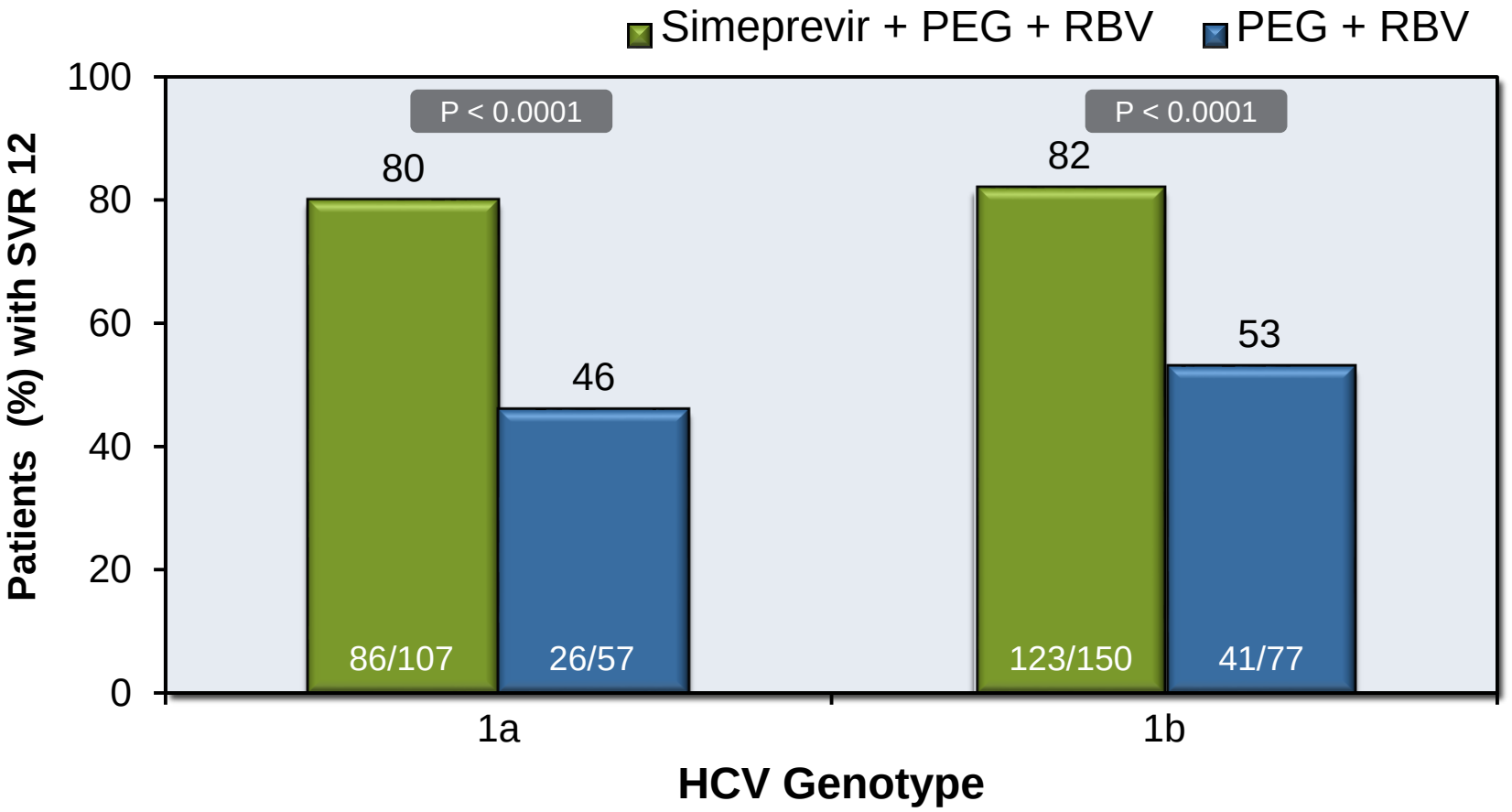


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: SVR12 by HCV Genotype 1 Subtype

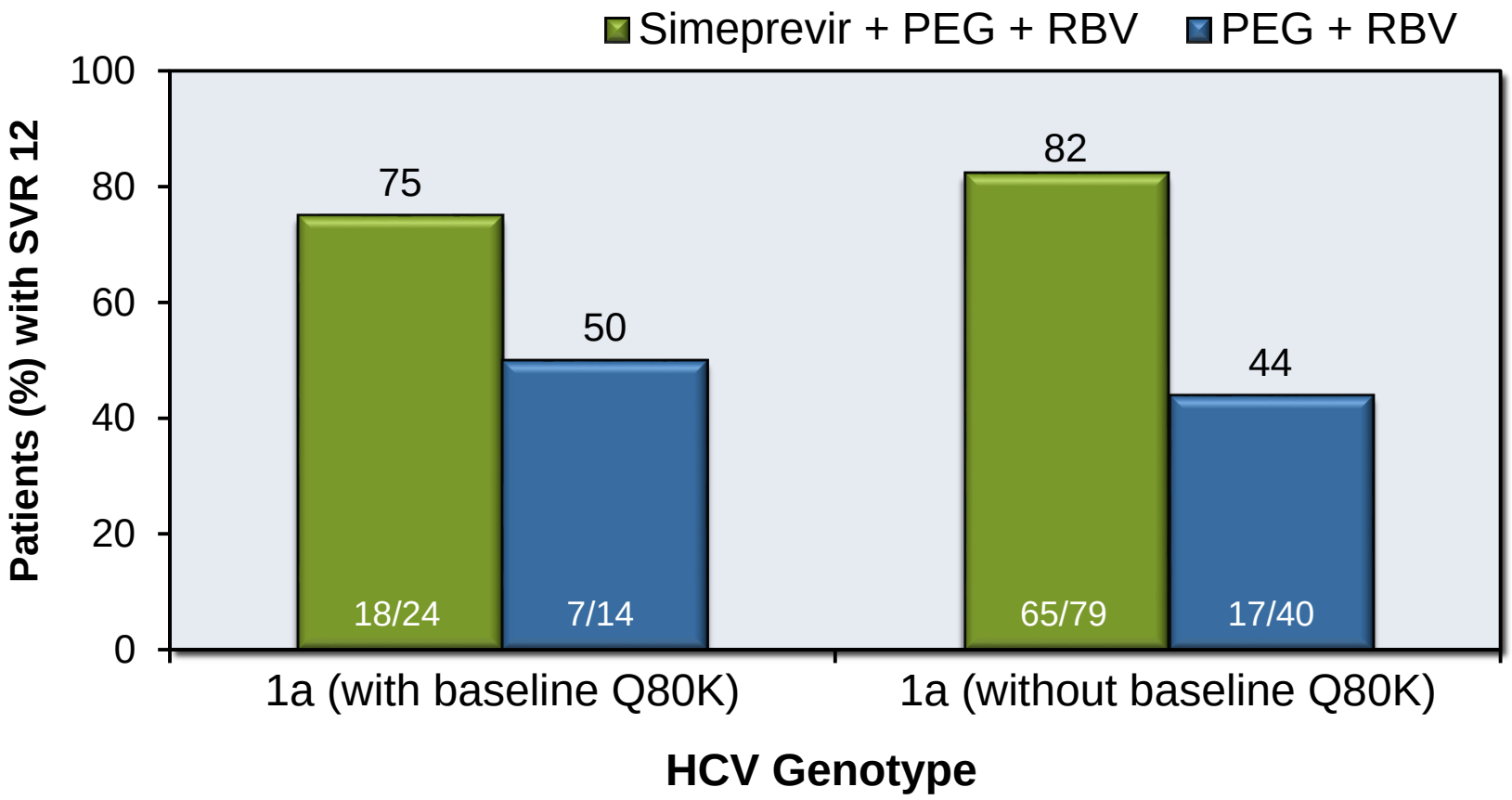


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: SVR12 for HCV 1a by Baseline Q80K Status



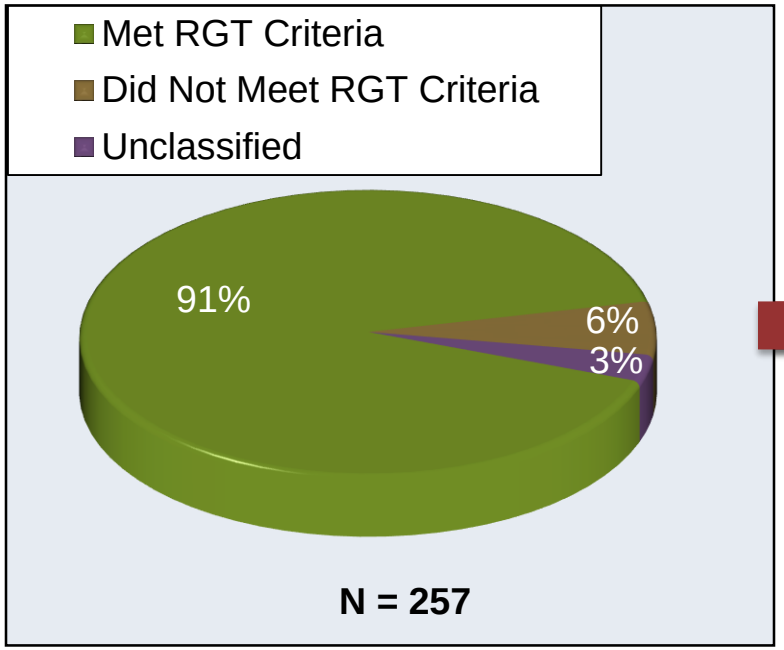
Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. Lancet. 2014;384:414-26.

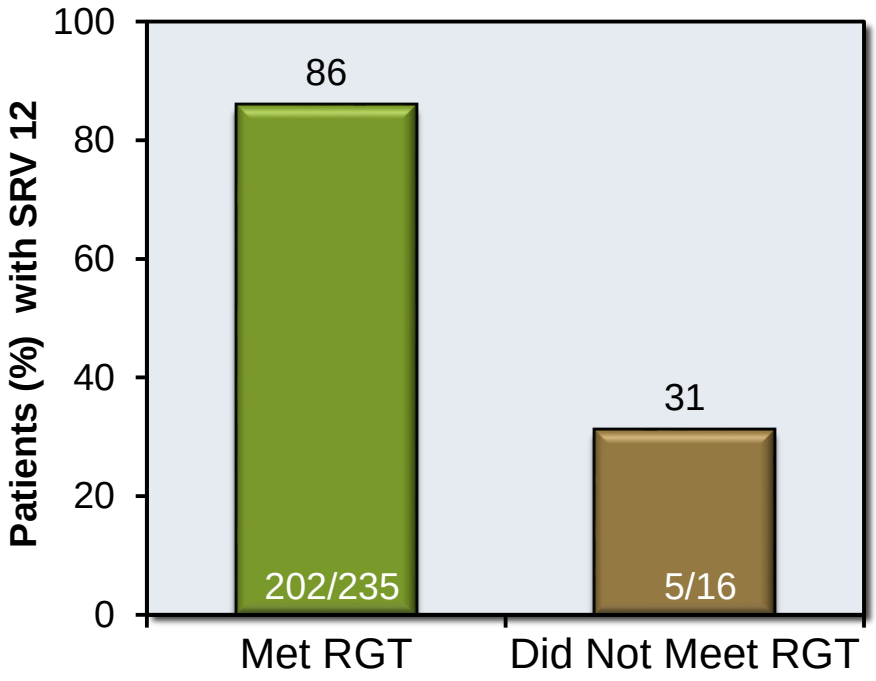
Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: SVR12 Response in Simeprevir Arm Based on RGT Criteria

Patients (%) who Met RGT Criteria



SVR 12 Based on Meeting RGT

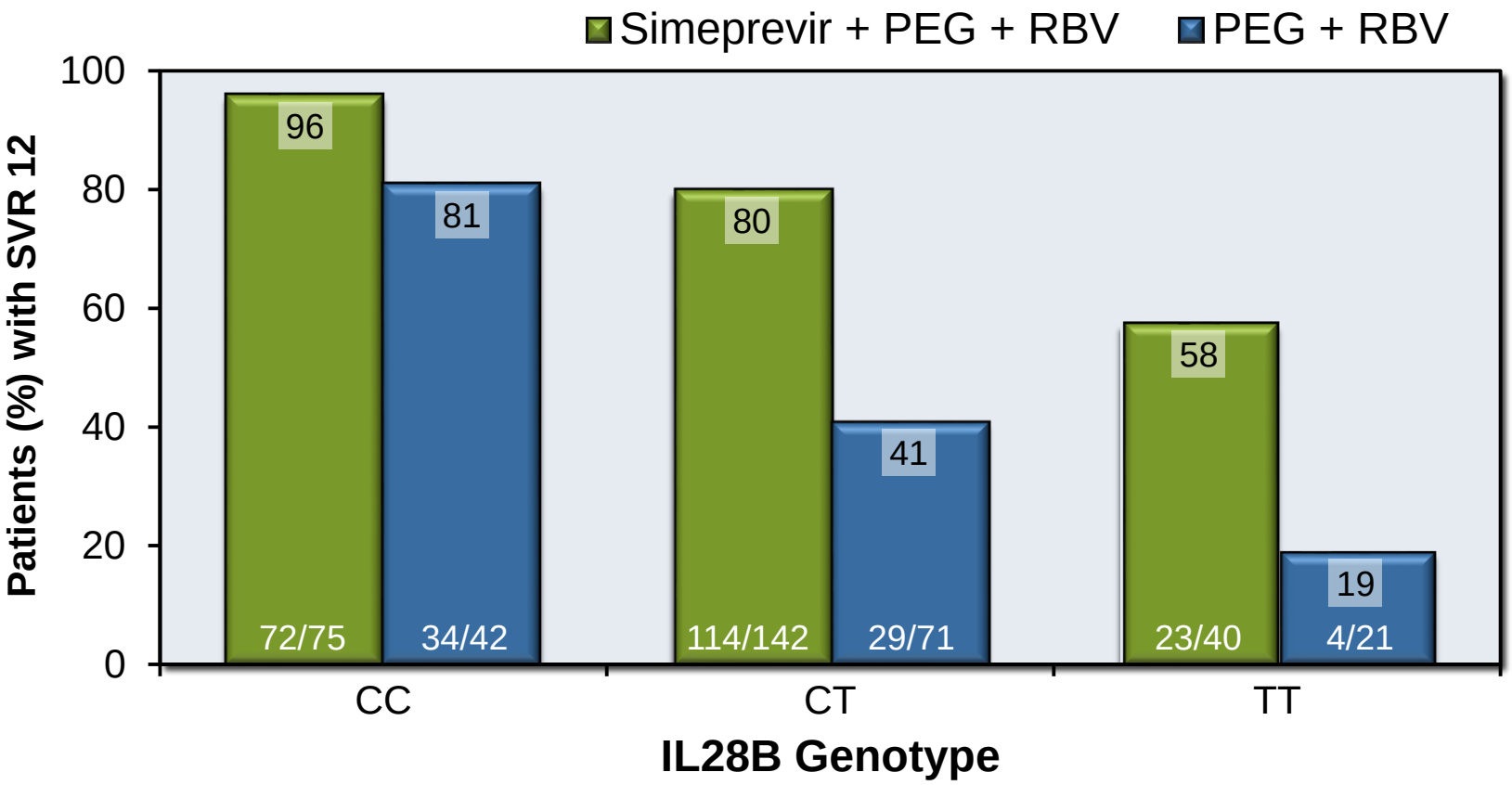


RGT= response-guided therapy: in simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: SVR12 by Host *IL28B* Genotype

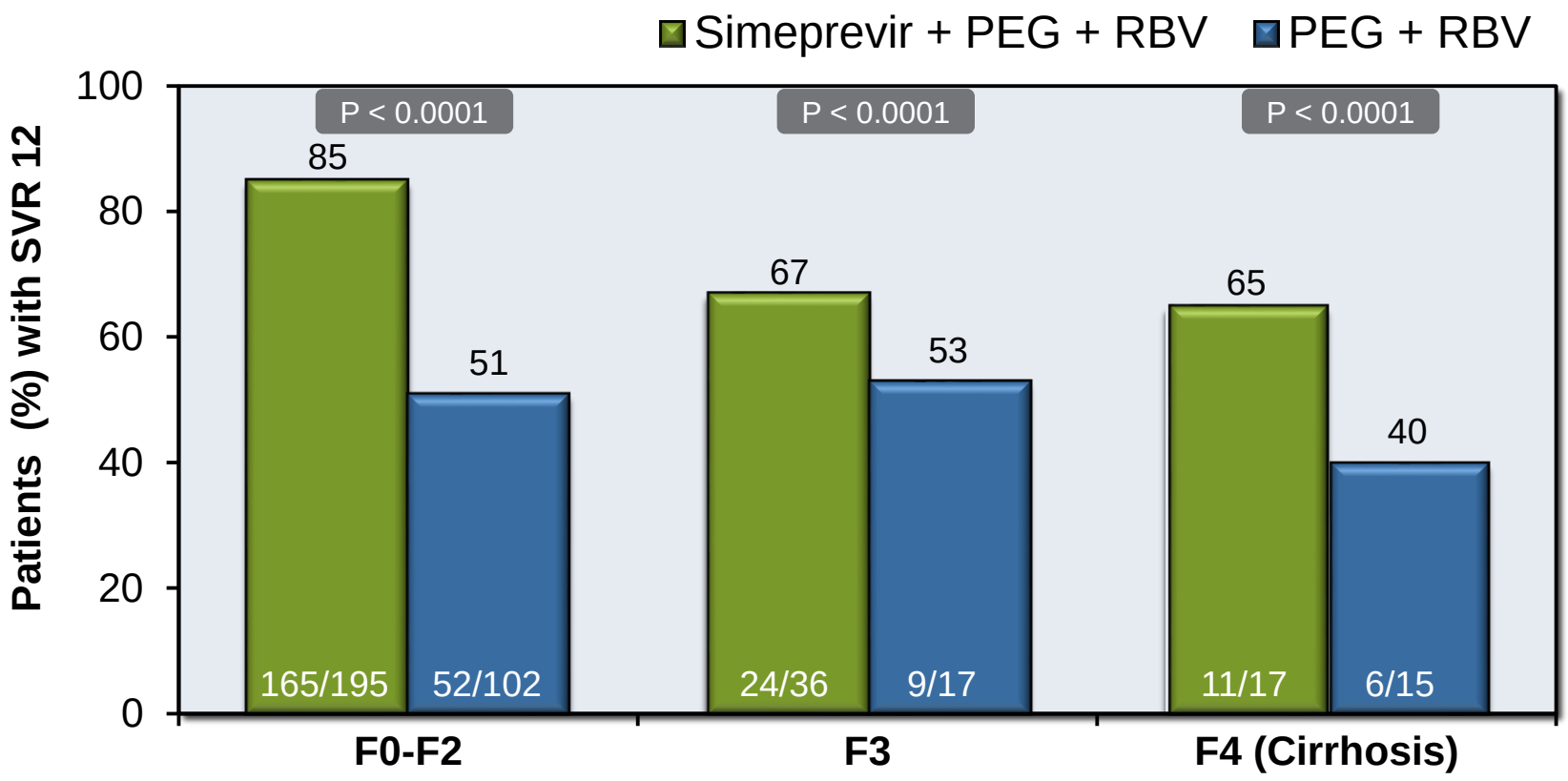


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: SVR12 by Liver Fibrosis (Metavir Score)

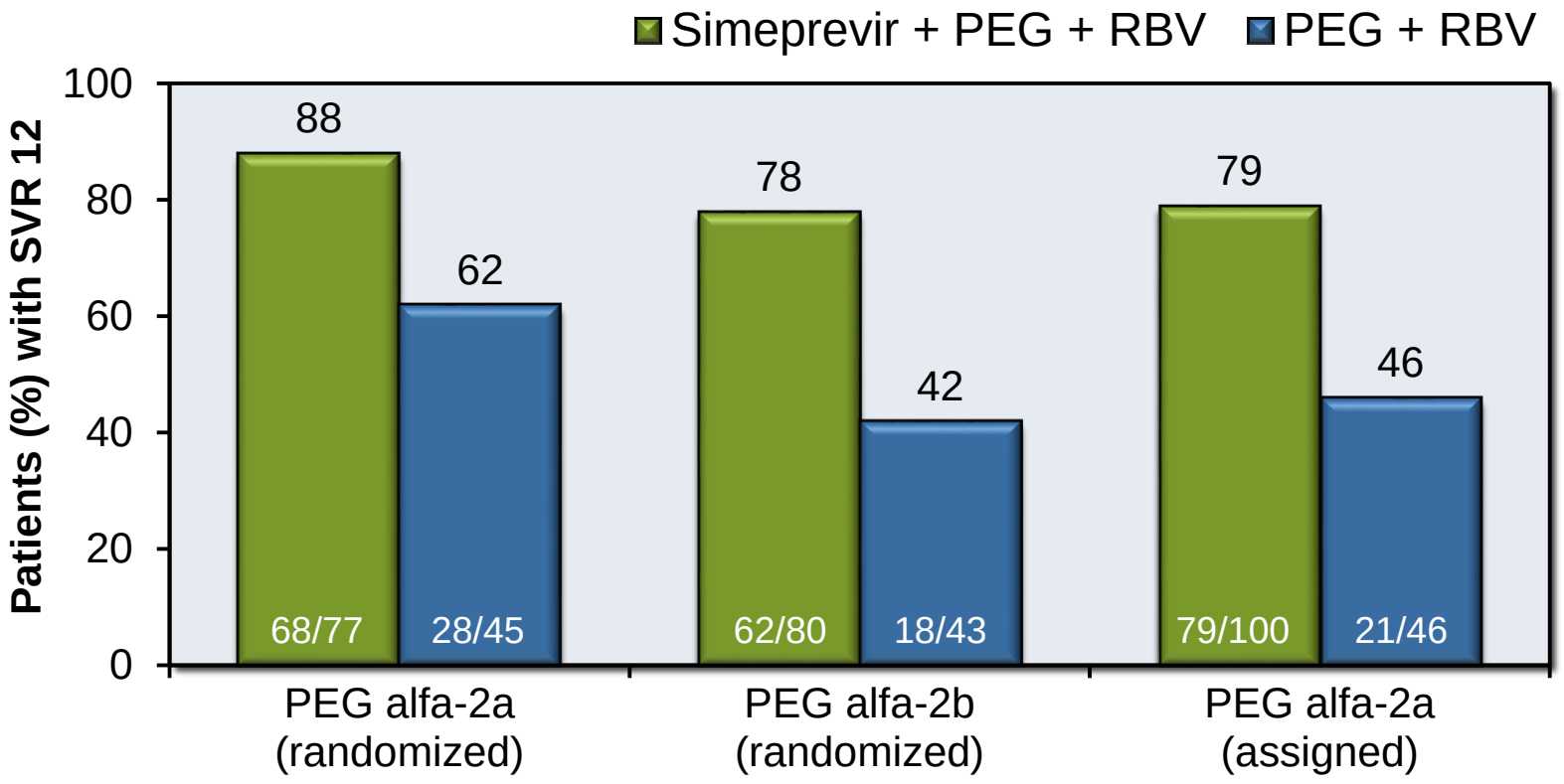


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

SVR12 by Type of Peginterferon

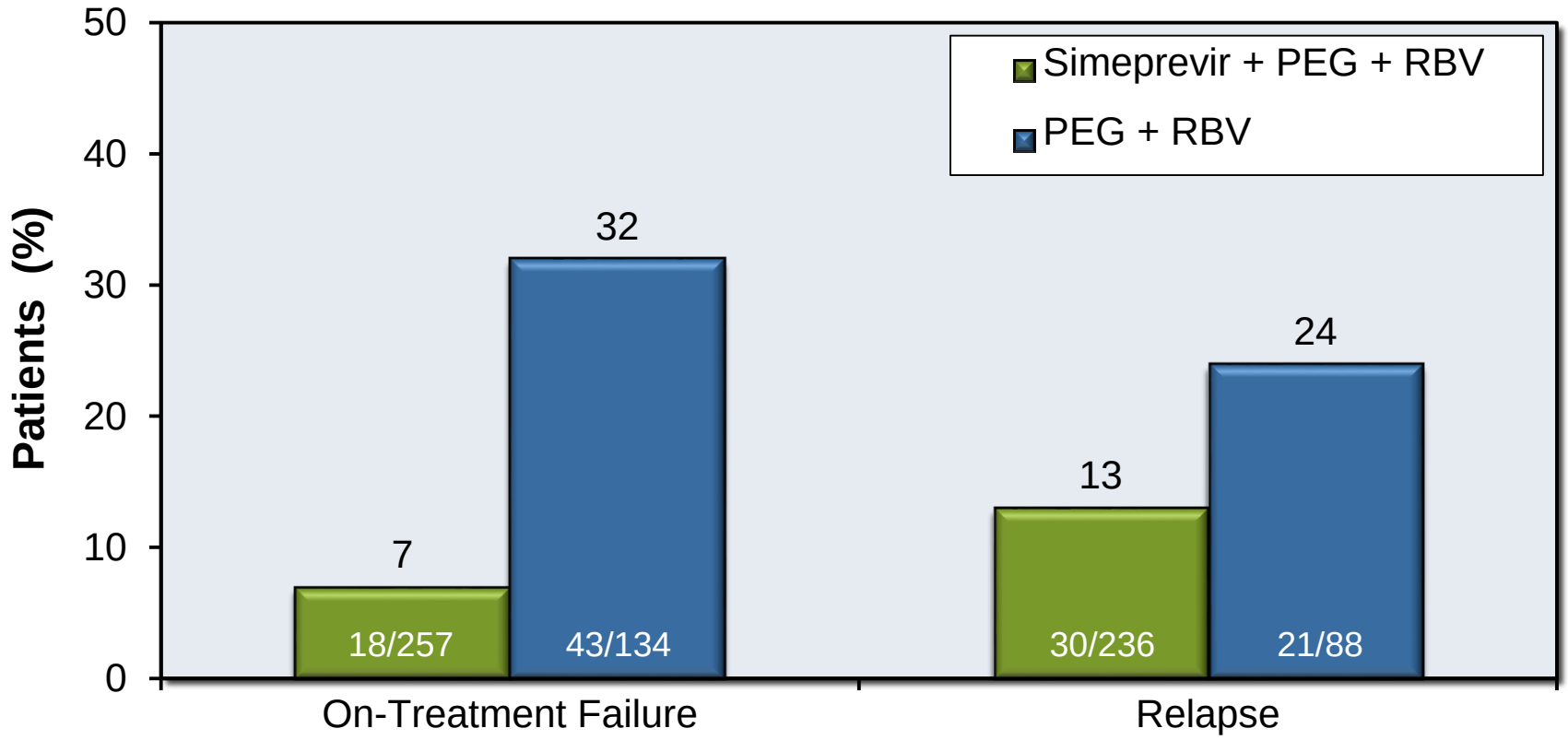


Type of PEG: 63% of patients randomized to receive PEG alfa-2a versus alfa-2b; remainder assigned PEG alfa-2a
Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: Patients Who Had On-Treatment Failure or Relapse



Abbreviations: PEG = Peginterferon; RBV = Ribavirin
On-Treatment Failure: Detectable HCV RNA at end of treatment.

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Adverse Effects

QUEST 2: Event	Simeprevir + PEG/RBV (n=257)	Placebo + PEG/RBV (n=134)
Discontinuation (due to adverse event)	<1%	<1%
Grade 3 adverse event	27%	31%
Grade 4 adverse event	6%	4%
Headache	39%	37%
Fatigue	37%	42%
Pyrexia	31%	40%
Influenza-like illness	26%	26%
Rash (any type)	27%	20%
Pruritus	26%	27%
Photosensitivity reactions	4%	<1%
Anemia	21%	28%
Neutropenia	21%	27%

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

QUEST 2: Emergent Resistance in Patients who Failed to Achieve SVR12

- Among simeprevir-treated patients who failed to achieve SVR12, emergent mutations in NS3 protease domain detected in 98%
- Genotype 1A: Most common mutation = R155K alone or in combination with mutations at codons 80 and/or 168
- Genotype 1B: Most common mutation = D168V and Q80R + D168E

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Conclusions

Interpretation: “Addition of simeprevir to either peginterferon alfa 2a or peginterferon alfa 2b plus ribavirin improved
SVR in treatment-naive patients with HCV genotype 1 infection, without worsening the known adverse events associated with peginterferon alfa plus ribavirin.”

Source: Manns M, et al. Lancet. 2014;384:414-26.

Simeprevir in Treatment-Experienced Patients

Treatment Experienced

Simeprevir in Genotype 1 (Viral Relapsers)
PROMISE Trial

Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

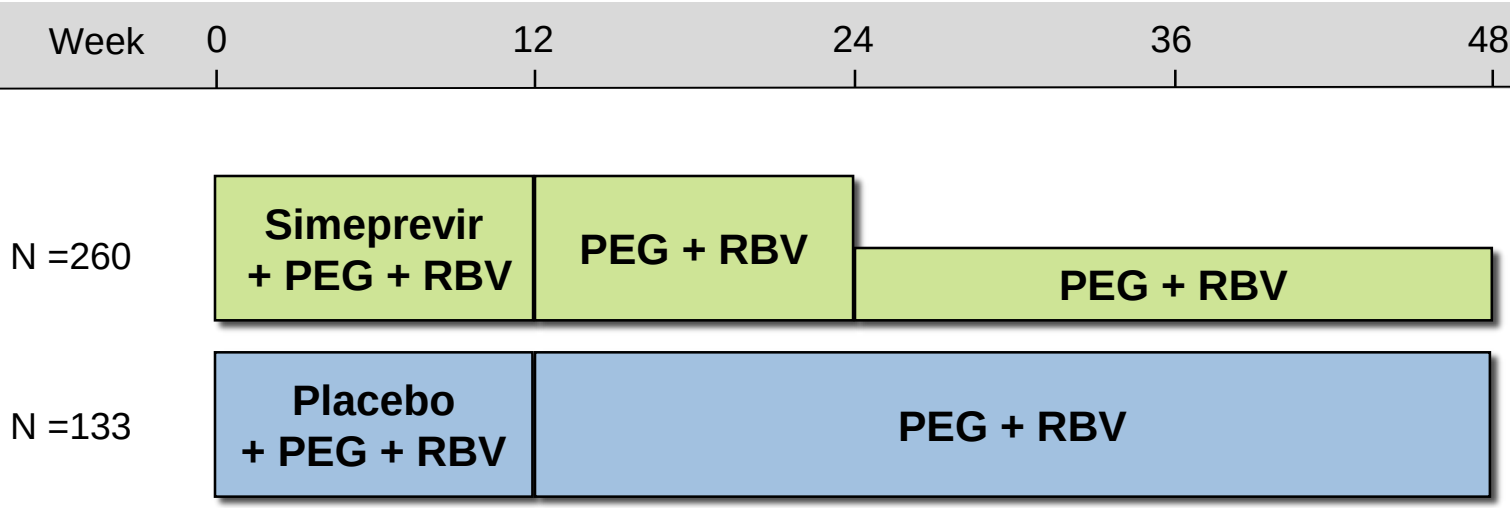
Simeprevir + PEG + Ribavirin for Chronic HCV
PROMISE Trial

PROMISE Trial: Study Features

- **Design**: Randomized, double-blind, placebo-controlled phase 3 trial of triple therapy with simeprevir, peginterferon alfa-2a, and ribavirin in treatment-experienced patients with HCV GT1 infection
- **Entry Criteria**
  - Treatment-experienced, chronic HCV monoinfection
  - Viral relapse with prior (≥ 24 weeks) of peginterferon-based therapy
  - HCV Genotype 1
- **Patient Characteristics**
  - N = 393
  - HCV Genotype: 1a (42%); 1b (58%)
  - IL28B Genotype: 76% non-CC
  - Age and Sex: median age 52; 66% male
  - Race: 94% white
  - Liver disease: 15% had METAVIR F3; 15% F4
- **Primary end-points**: Efficacy (SVR12)

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV PROMISE Trial: Design



Study Notes

- Randomized 2:1, stratified on IL28B and HCV subtype
- Response-guided therapy (RGT): In simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Drug Dosing

Simeprevir: 150 mg once daily

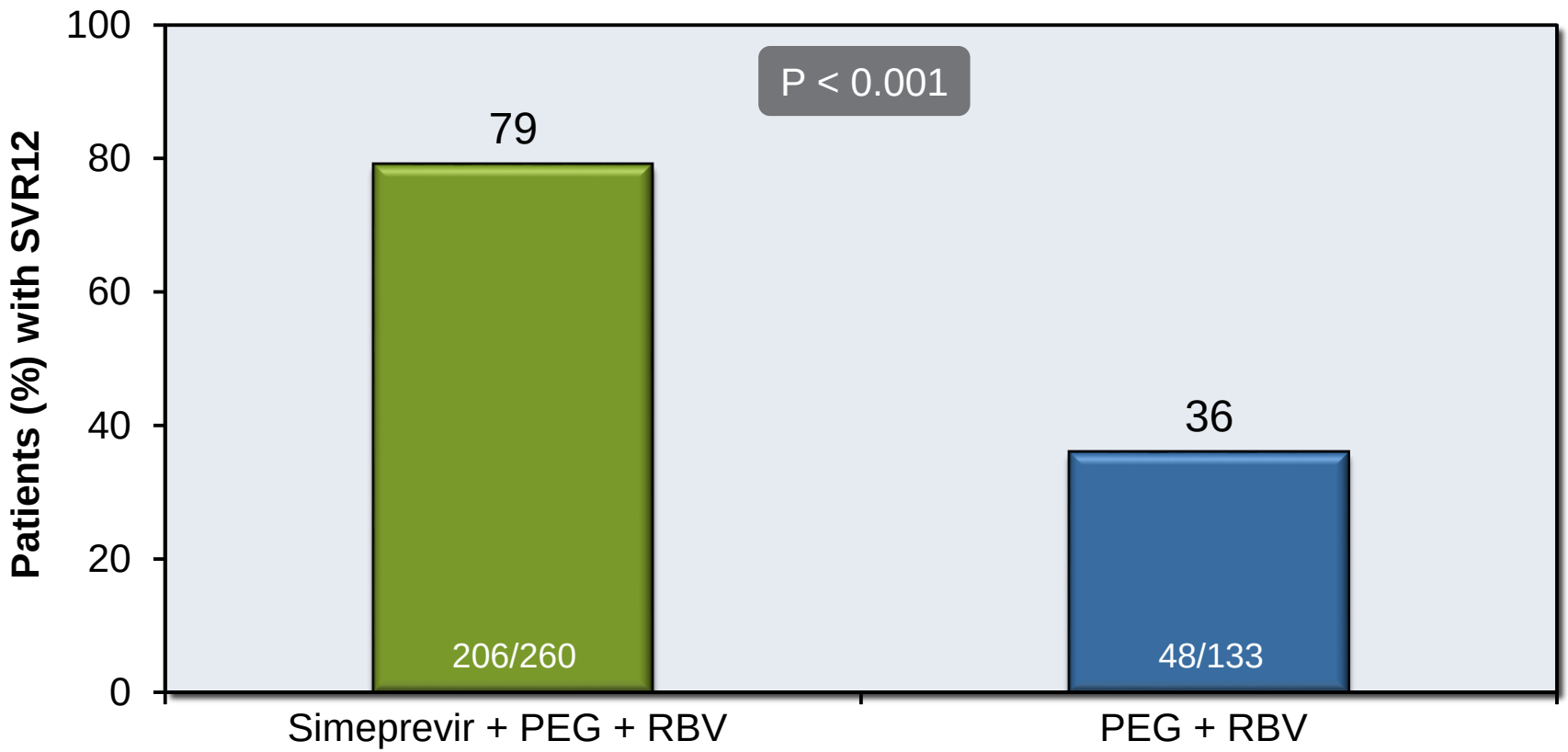
Peginterferon alfa-2a (PEG): 180 mcg/week

Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Trial: Results

PROMISE Trial: Proportion of Patients with SVR12

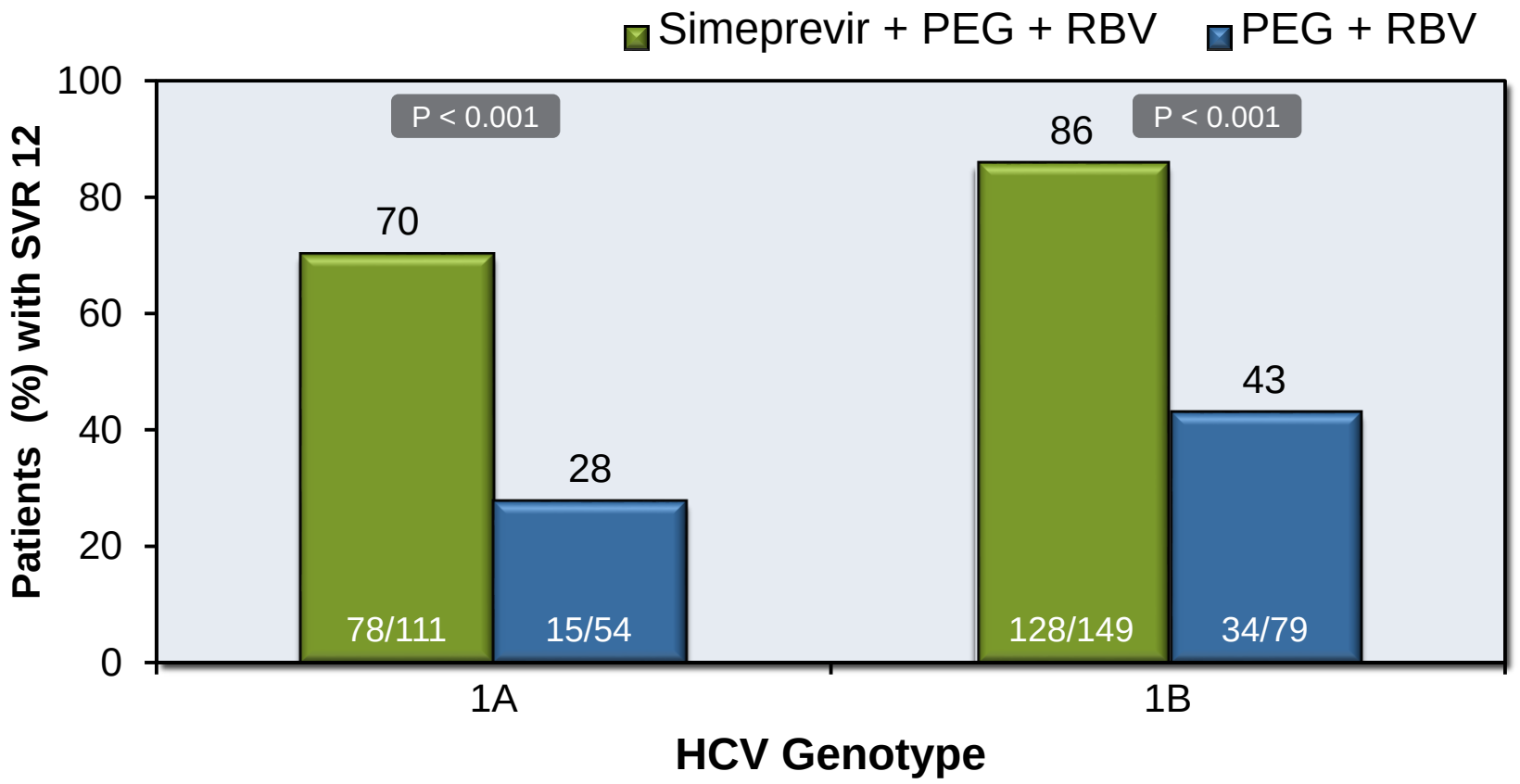


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Results

PROMISE Trial: SVR12 by HCV Genotype 1 Subtype



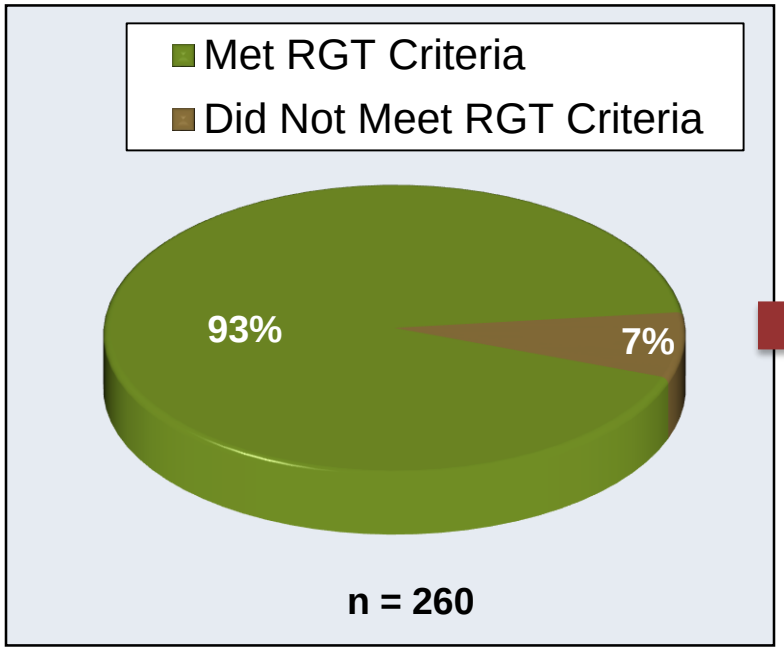
Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

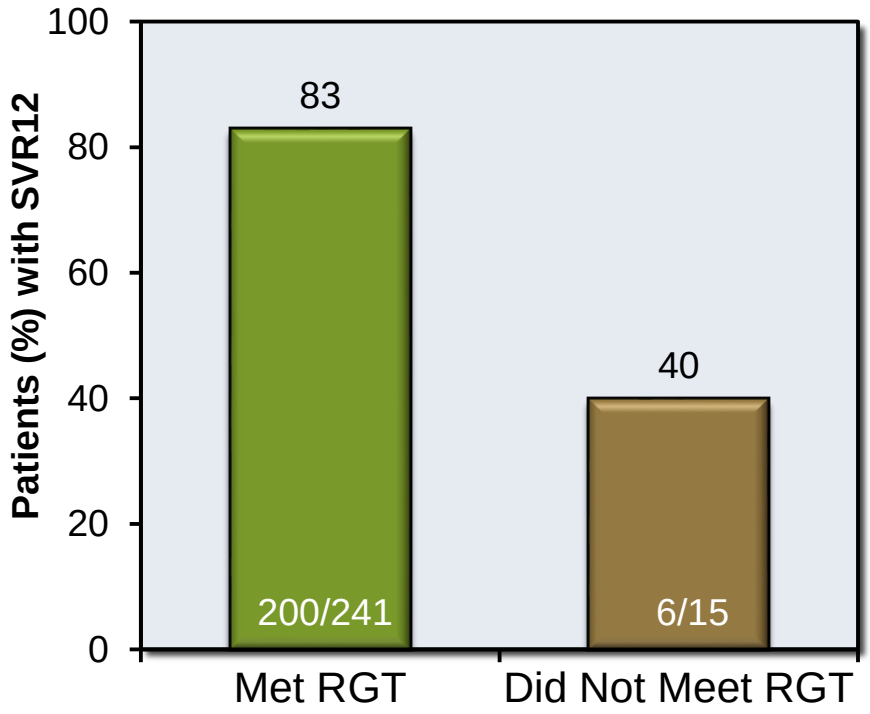
Simeprevir and Peginterferon plus Ribavirin for Chronic HCV PROMISE Results

PROMISE Trial: SVR12 Response in Simeprevir Arm Based on RGT Criteria

Patients (%) who Met RGT Criteria



Patient (%) with SVR 12 Response

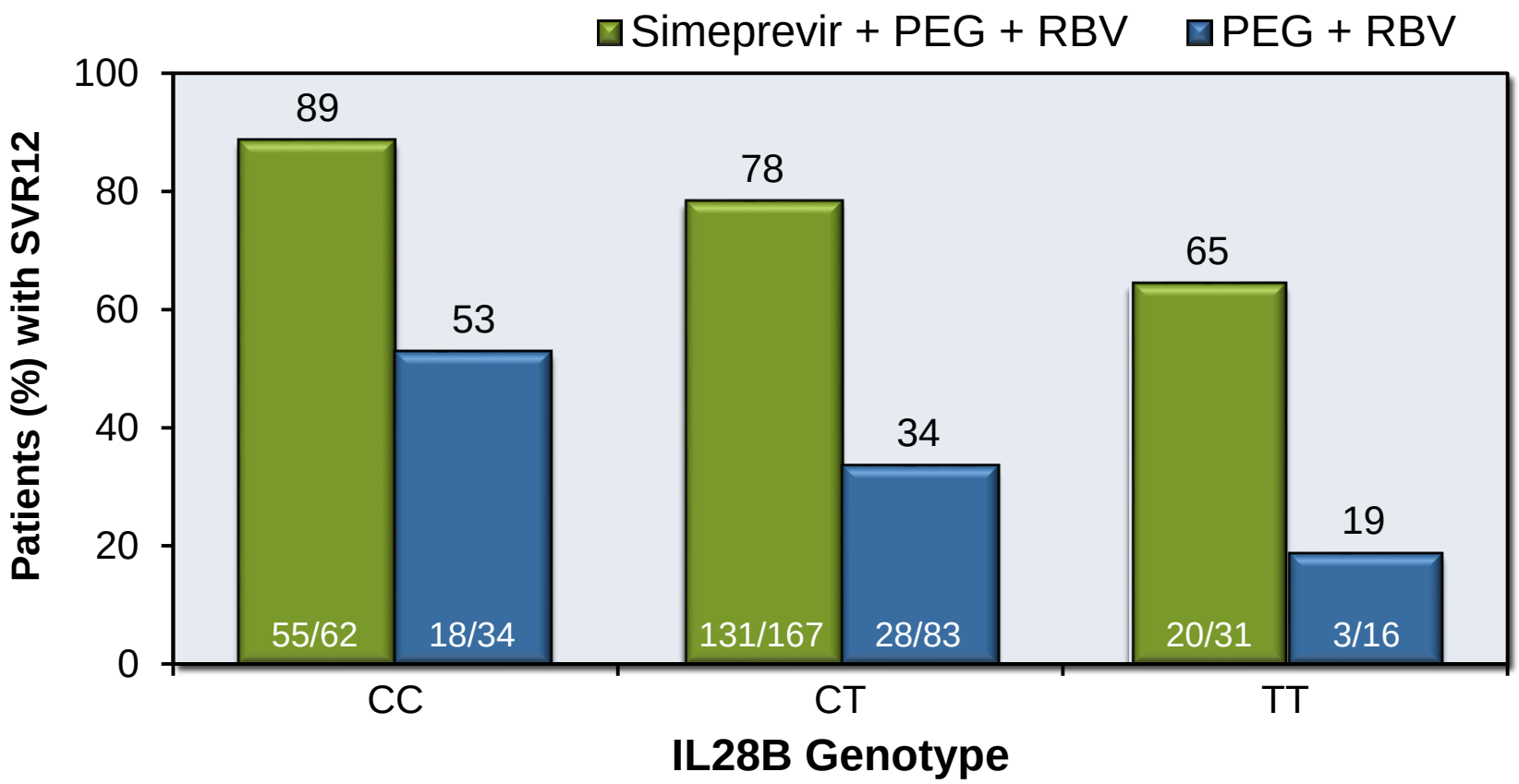


RGT= response-guided therapy: in simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Trial: Results

PROMISE TRIAL: SVR12 by Host *IL28B* Genotype

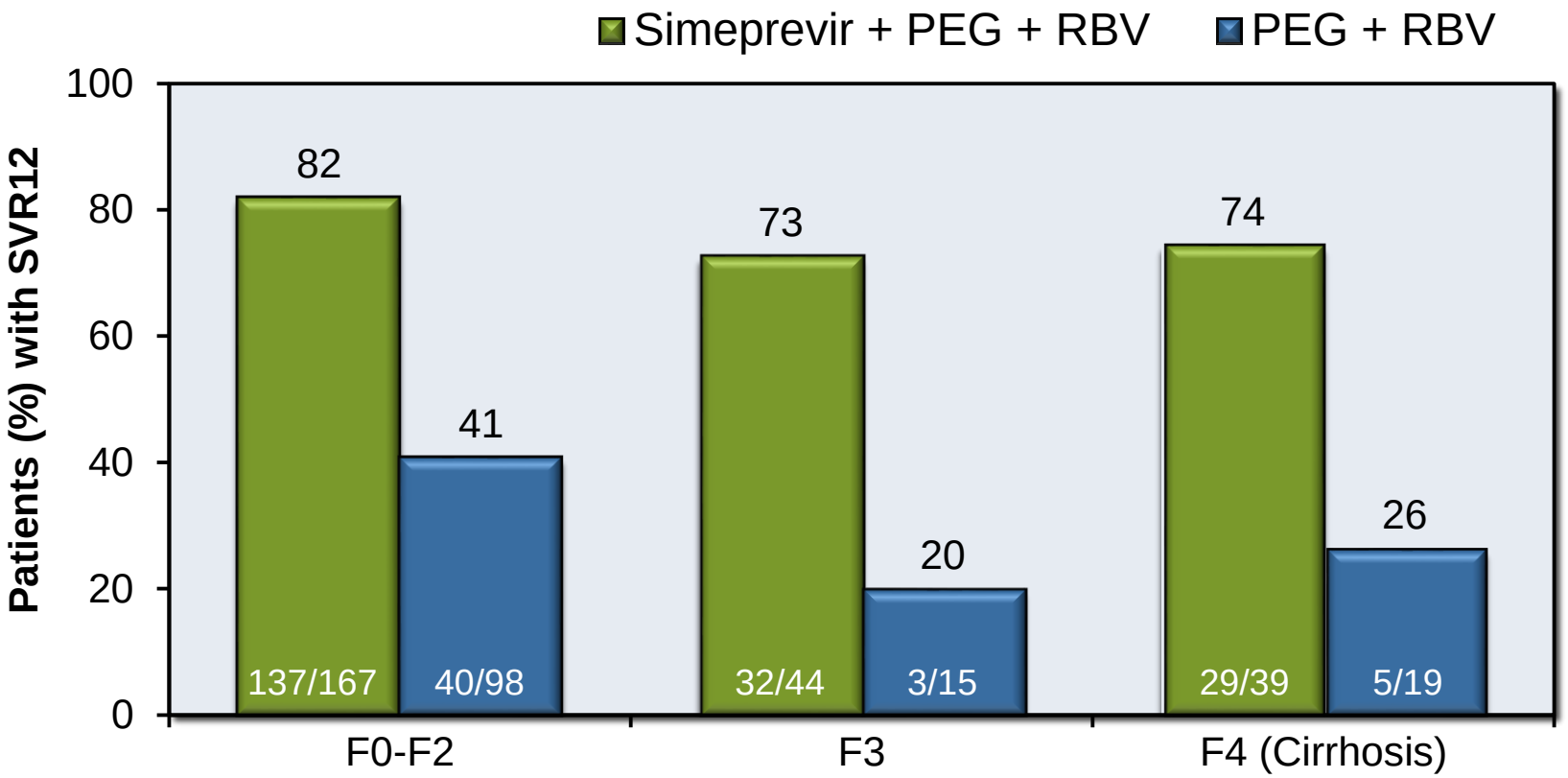


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Trial: Results

PROMISE Trial: SVR12 by Liver Fibrosis (METAVIR Fibrosis Score)



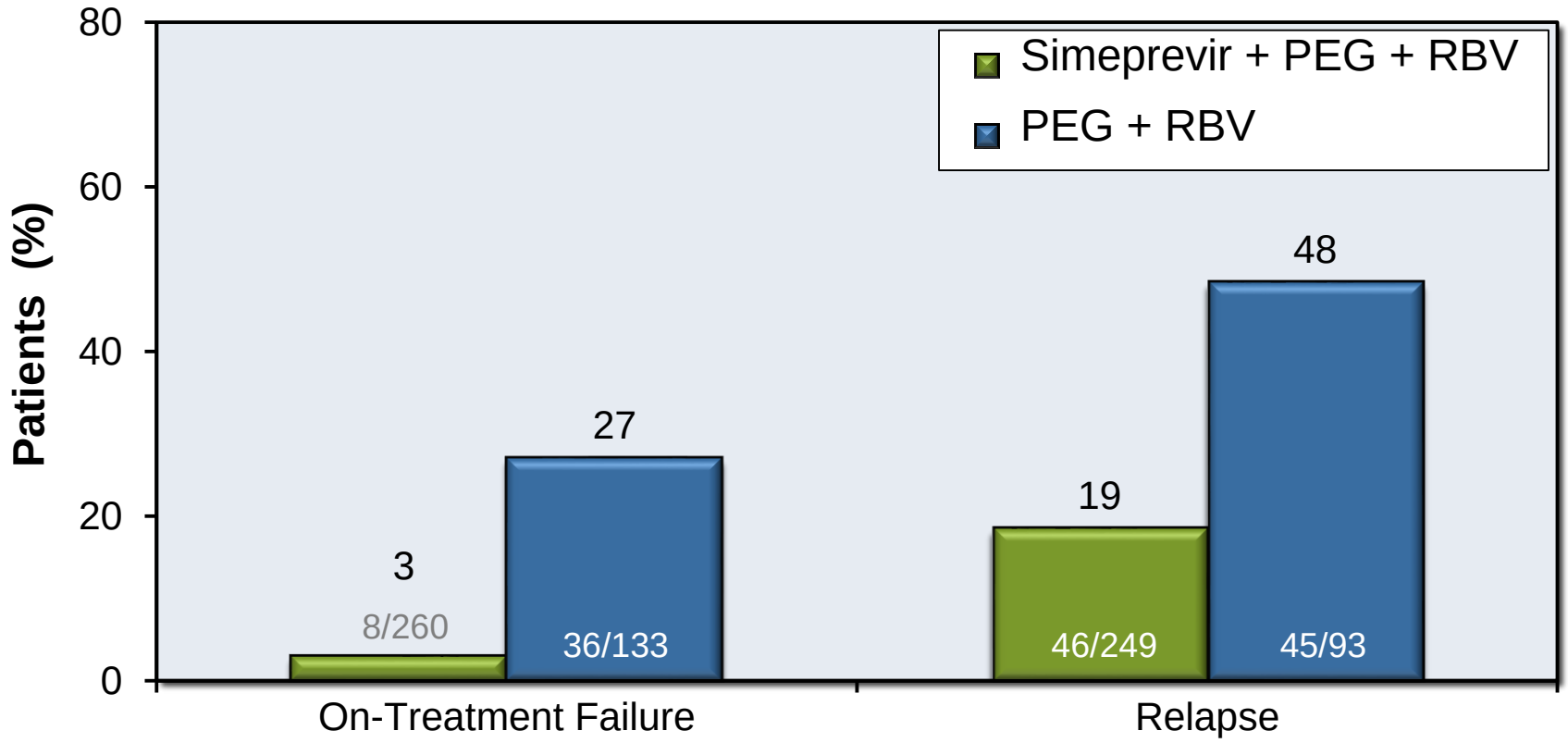
Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Hepatitis web study

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Results

Patients Who Had On-Treatment Failure or Relapse



Abbreviations: PEG = Peginterferon; RBV = Ribavirin
On-Treatment Failure: Detectable HCV RNA at end of treatment.

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir
Adverse Effects in PROMISE Trial

PROMISE Trial: Event	Simeprevir + PR (n=260)	Placebo + PR (n=133)	Simeprevir + PR (n=260)	Placebo + PR (n=133)
	First 12 Weeks		Entire Treatment Phase	
AE leading to permanent discontinuation of ≥ 1 drug	1.2%	1.5	2.3	5.3
Grade 3 event	18.1%	18.0%	24.2%	25.6%
Grade 4 event	1.9%	3.0%	3.5	4.5
Fatigue	31.9%	42.1%	32.3%	43.6%
Headache	31.9%	36.1%	33.1%	36.1%
Influenza-like illness	29.6%	20.3%	30.0%	20.3%
Rash (any type)	18.5%	14.3%	23.1%	22.6%
Pruritus	23.5%	16.5%	27.7%	27.8%
Neutropenia	14.6%	16.5%	17.7%	21.8%
Photosensitivity	3.5%	0%	3.5%	0%
Anemia	10.8%	6.0%	16.9%	20.3%

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV PROMISE Results

Emergent Protease Resistance in Patients who Failed to Achieve SVR12

- Most (90.4%) of simeprevir-treated patients who failed to achieve SVR12 developed emerging mutations in the NS3 protease domain
- Genotype 1A: Most common mutation = R155K or D168E, or combination of R155K and mutations at codons 80 and/or 168
- Genotype 1B: Most common mutations = D168V or D168A, E, T or E/V or the combinations Q80R + D168E/V, or Q80R + S122T + D168E

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV PROMISE Conclusions

Conclusions: “In a Phase 3 trial of patients who had relapsed following interferon-based therapy, addition of simeprevir to PR was generally well tolerated, with an SVR12 rate of 79.2%. Most patients (92.7%) receiving simeprevir were able to shorten therapy to 24 weeks.”

Source: Forns X, et al. Gastroenterology. 2014;146:1669-79.e3.

Treatment Experienced

Simeprevir versus Telaprevir with PR in GT1
ATTAIN Trial

Reddy KR, et al. Lancet Infect Dis. 2015;15:27-35.

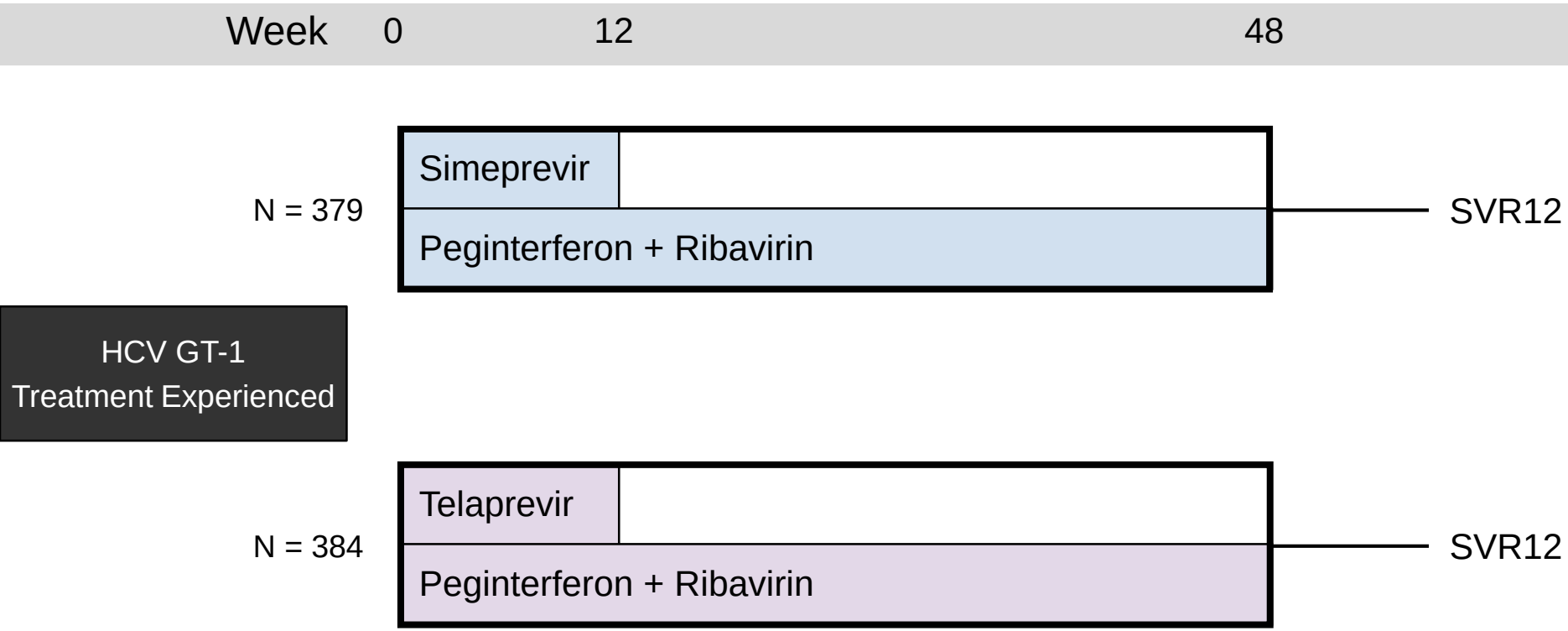
Simeprevir vs Telaprevir with Peginterferon + Ribavirin in GT1 ATTAIN: Study Features

ATTAIN Trial: Features

- **Design**: Randomized, double-blind, phase 3, study evaluating simeprevir versus telaprevir with peginterferon alfa-2a plus ribavirin for treatment-experienced patients with genotype 1 chronic HCV
- **Setting**: International at 169 sites in 24 countries
- **Entry Criteria**
  - Chronic HCV genotype 1
  - HCV RNA > 10,000 IU/mL
  - Adults ≥ 18
  - Prior null or partial responder with prior peginterferon + ribavirin
  - Compensated liver disease
- **Exclusion Criteria**
  - Non-HCV-related liver disease, including hepatocellular carcinoma
  - Prior HCV treatment with medication other than peginterferon + ribavirin
  - Coinfection with HAV, HBV, HIV, or non-genotype 1 HCV
- **Primary End-Points**: Efficacy (SVR12)

Source: Reddy KR, et al. Lancet Infect Dis. 2015;15:27-35.

Simeprevir vs Telaprevir with Peginterferon + Ribavirin in GT1 ATTAIN: Study Design



Drug Dosing

Simeprevir: 150 mg once daily

Telaprevir: 750 mg three times daily

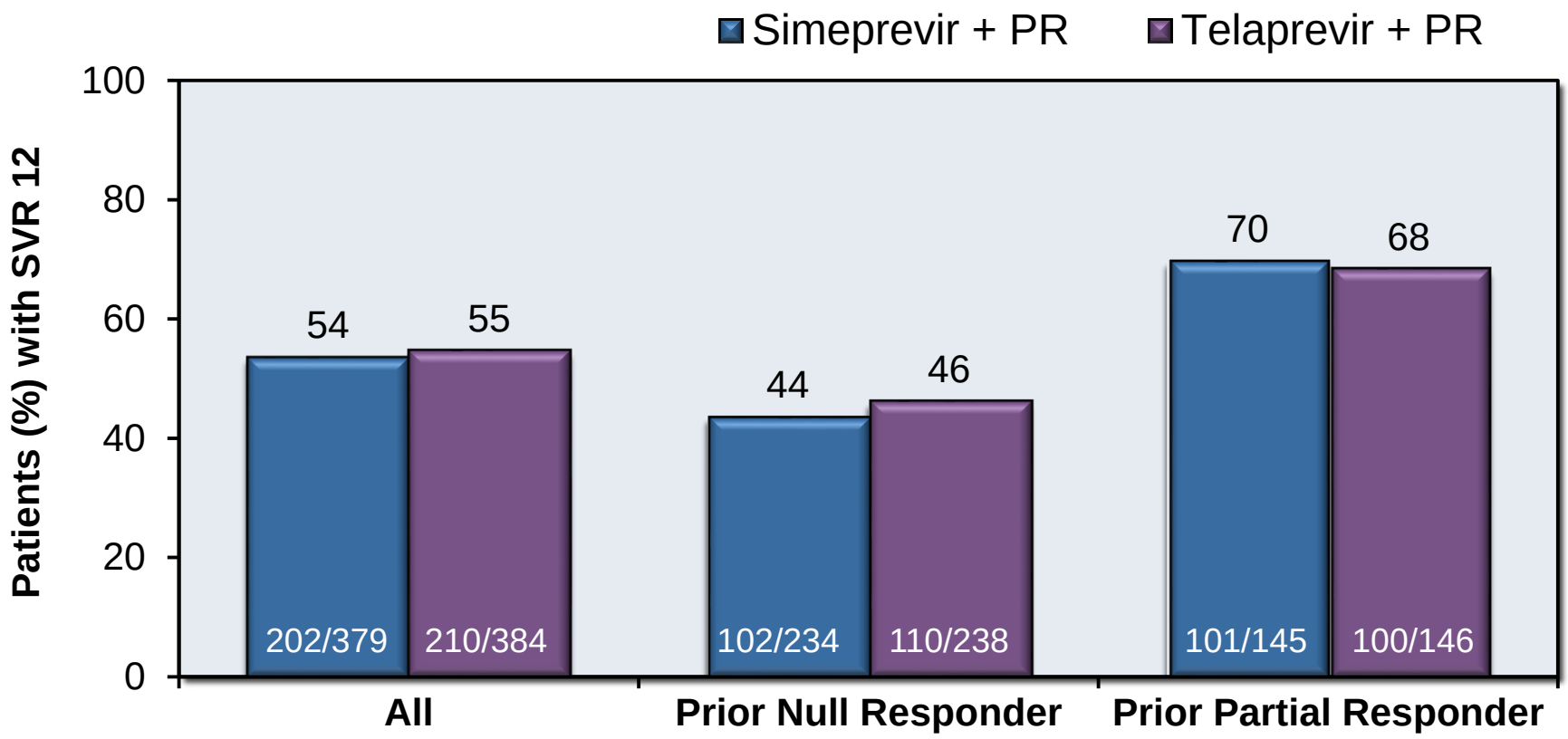
Peginterferon alfa-2a (PEG): 180 mcg/week

Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

Source: Reddy KR, et al. Lancet Infect Dis. 2015;15:27-35.

Simeprevir vs Telaprevir with Peginterferon + Ribavirin in GT1 ATTAIN: Results

ATTAIN: SVR12 by Prior Treatment Response



PR = peginterferon plus ribavirin

Source: Reddy KR, et al. Lancet Infect Dis. 2015;15:27-35.

Simeprevir vs Telaprevir with Peginterferon + Ribavirin in GT1 ATTAIN: Conclusions

Interpretation: “Simeprevir once a day with peginterferon alfa-2a and ribavirin was well tolerated in HCV genotype 1-infected previous non-responders and was non-inferior to telaprevir, thus providing an alternative treatment in areas of the world where all-oral HCV regimens are not available or accessible.”

Source: Reddy KR, et al. Lancet Infect Dis. 2015;15:27-35.

Treatment Experienced

Simeprevir in Treatment –Experienced Genotype 1 ASPIRE Trial

Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

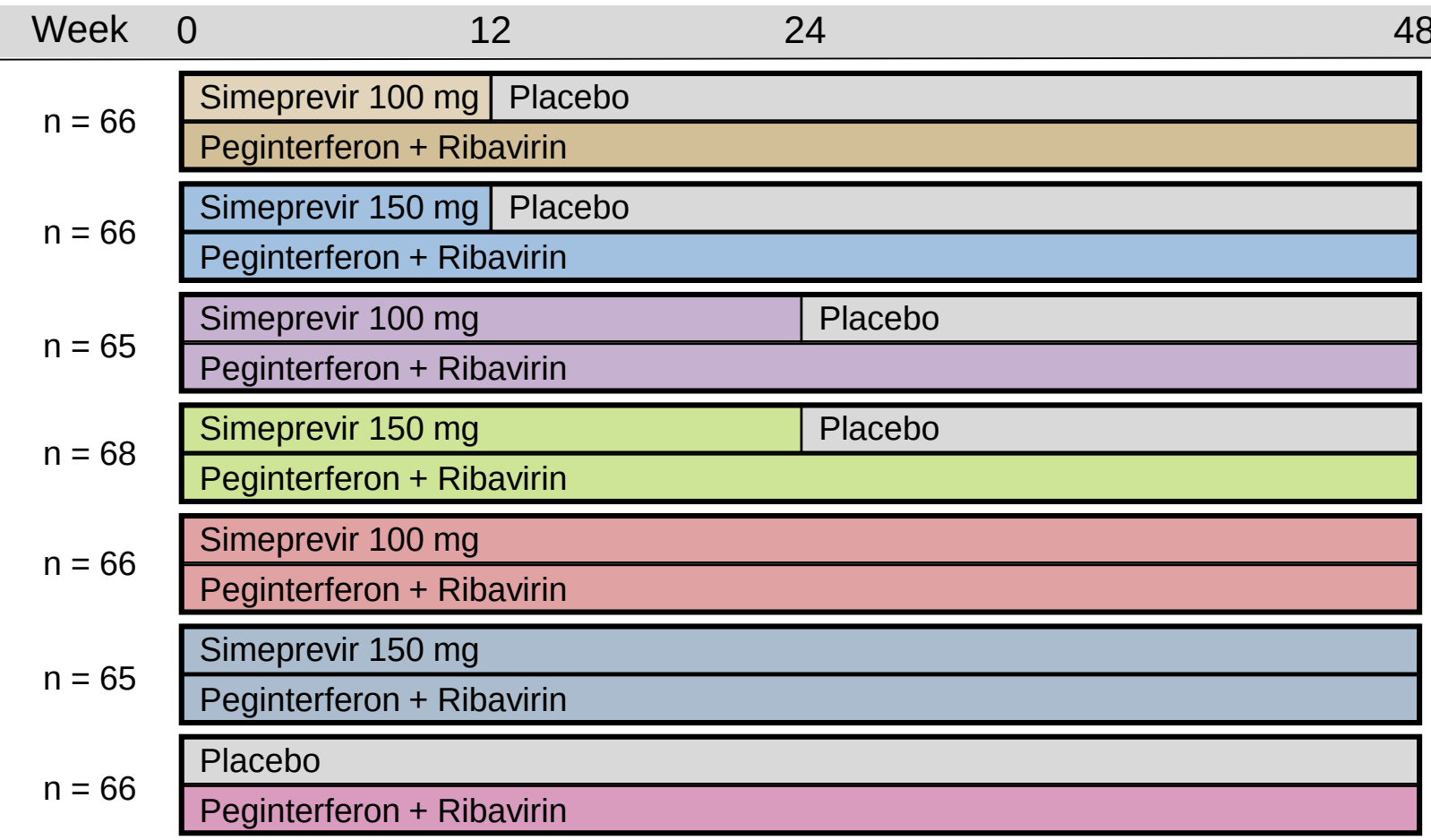
Simeprevir in Treatment Experienced Genotype 1 HCV
ASPIRE Trial: Features

ASPIRE Trial: Study Features

- **Design**: Randomized, double-blind, placebo-controlled, 7 arm, phase 2b trial of PEG and RBV with and without simeprevir in HCV GT1 for prior treatment failures with PEG and RBV
- **Setting**: Europe, North America, Australia, and New Zealand
- **Entry Criteria**
  - Treatment-experienced, chronic HCV GT-1 monoinfection
  - Prior failure with (≥ 12 weeks) of peginterferon-alfa plus ribavirin
  - HCV RNA > 10,000 IU/mL
- **Patient Characteristics**
  - N = 462
  - HCV Genotype: 1a (41%); 1b (58%); other (1%)
  - IL28B Genotype: 82% non-CC
  - Demographics: median age 50; 67% male; 93% white
  - Metavir Fibrosis: F3 = 19%; F4 = 18%
- **Primary end-points**: Efficacy (SVR24)

Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

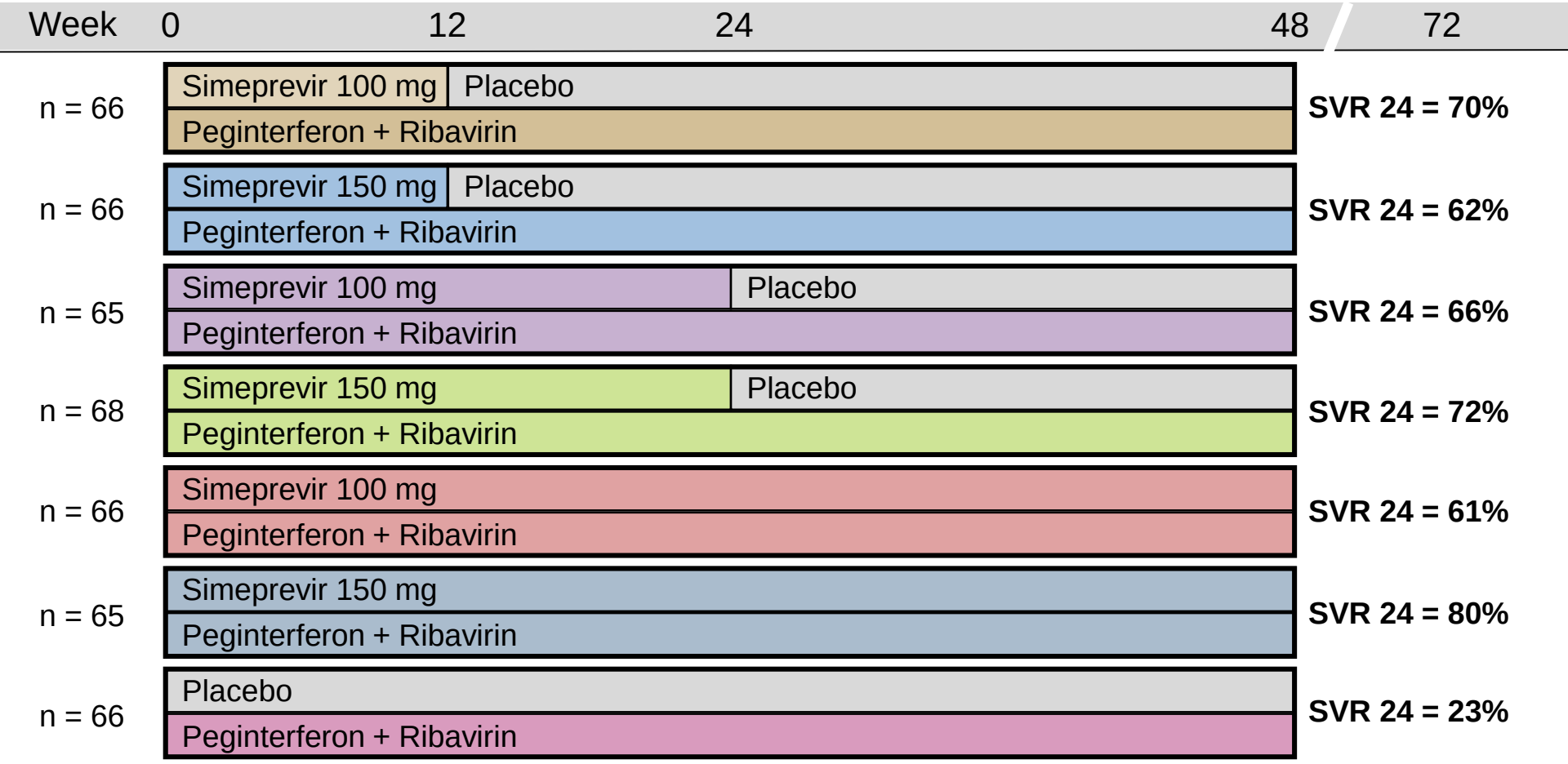
Simeprevir in Treatment Experienced Genotype 1 HCV
ASPIRE Trial: Design



Drug Dosing: Simeprevir: 100 or 150 mg once daily; Peginterferon alfa-2a (PEG): 180 mcg/week
Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

Simeprevir in Treatment Experienced Genotype 1 HCV
ASPIRE Trial: Results

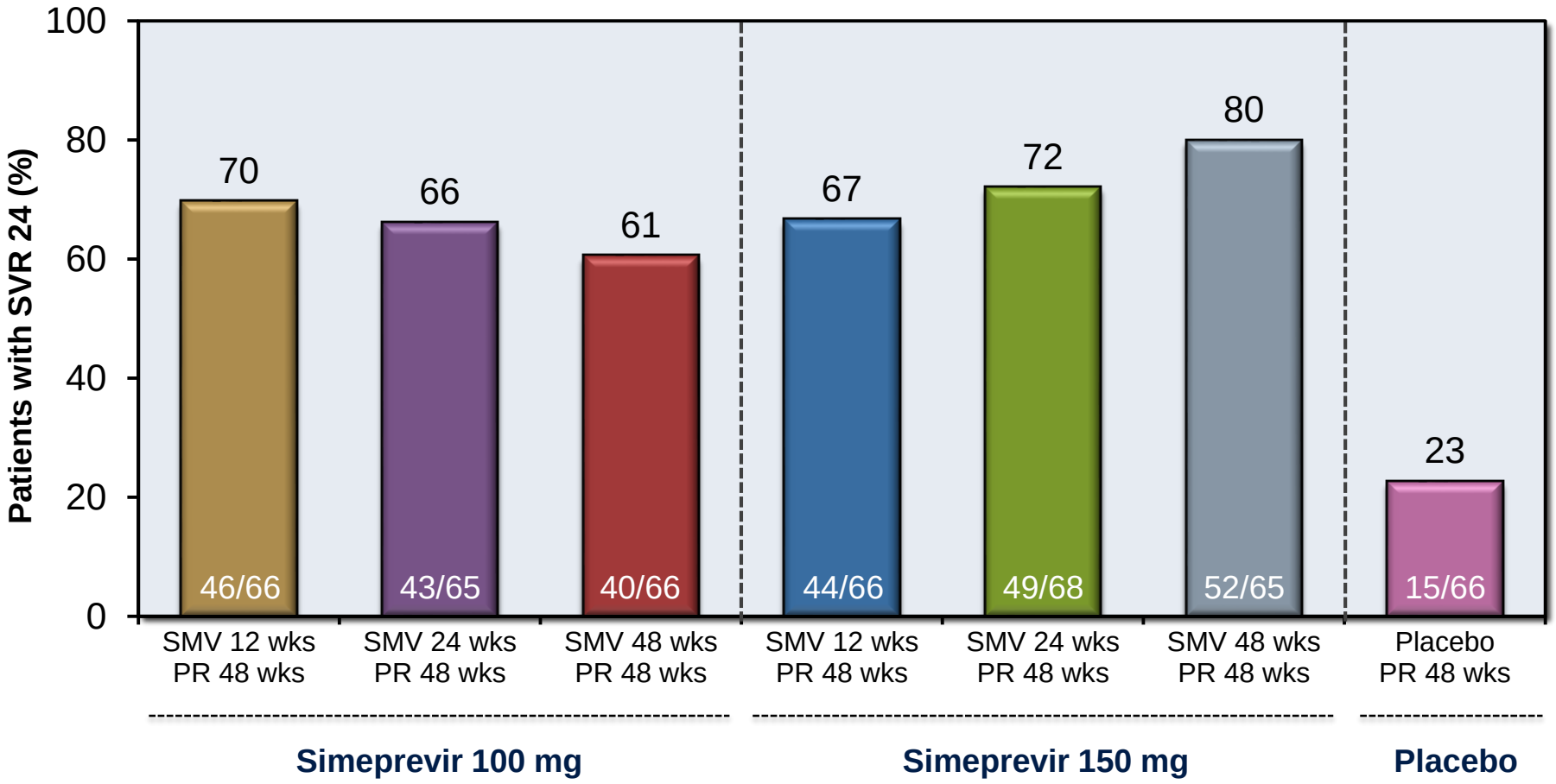


Drug Dosing: Simeprevir: 100 or 150 mg once daily; Peginterferon alfa-2a (PEG): 180 mcg/week
Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

Simeprevir in Treatment Experienced Genotype 1 HCV
ASPIRE Trial: Results

ASPIRE: SVR 24, by Treatment Regimen

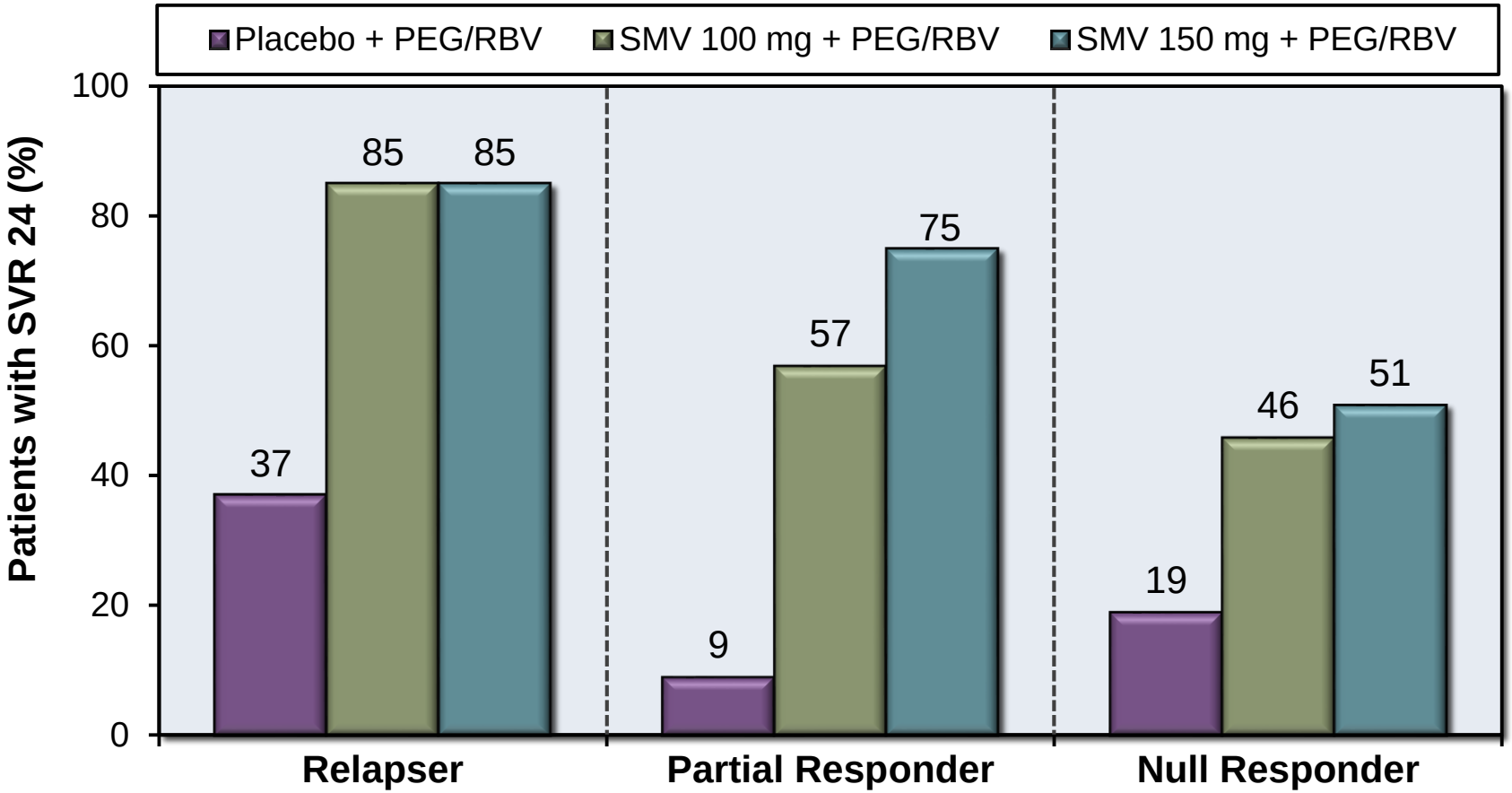


Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

Hepatitis web study

Simeprevir in Treatment Experienced Genotype 1 HCV
ASPIRE Trial: Results

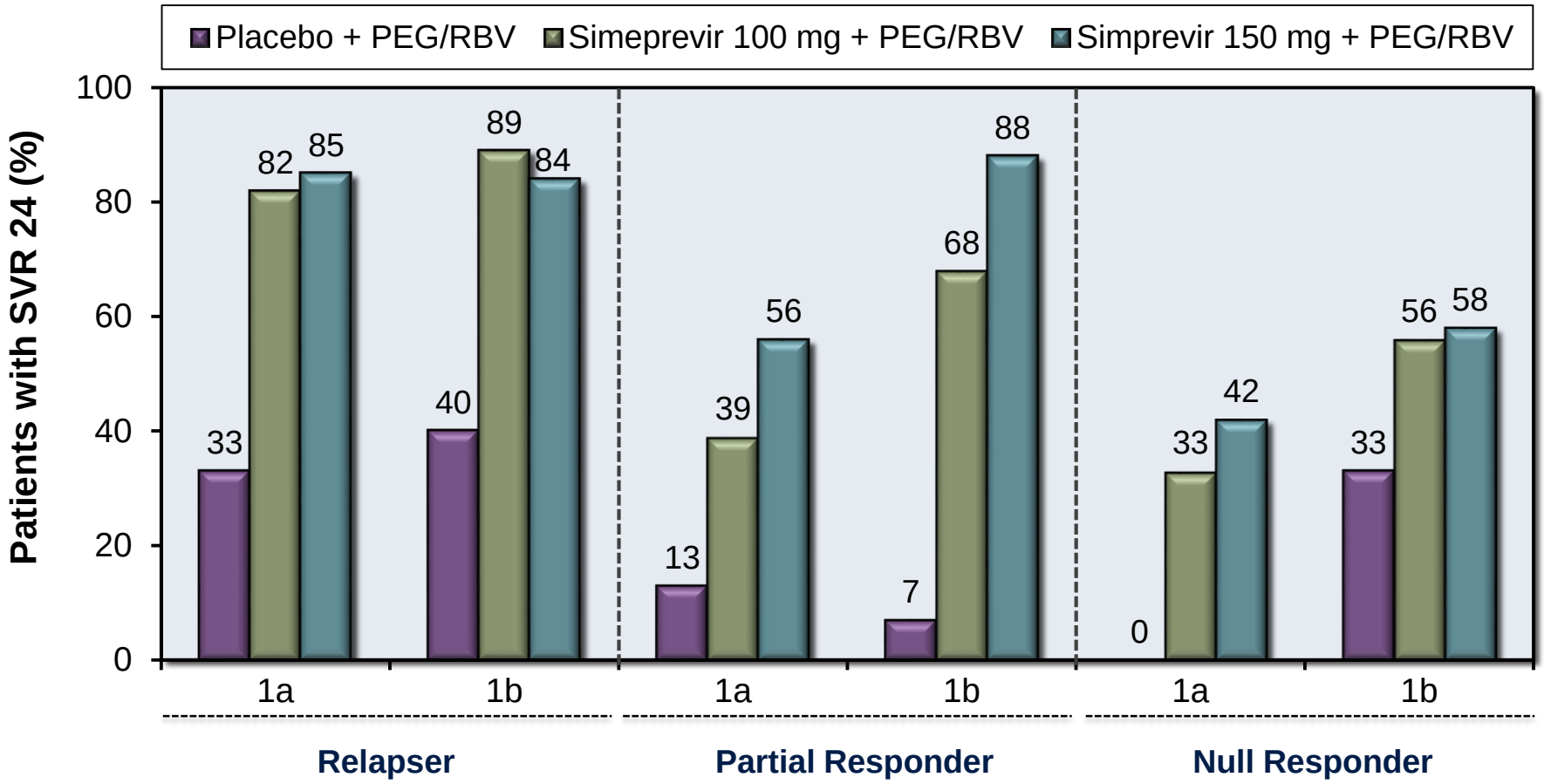
ASPIRE: SVR 24, by Prior Treatment Response



Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

Simeprevir in Treatment Experienced Genotype 1 HCV
ASPIRE Trial: Results

ASPIRE: SVR 24, by Prior Treatment Response and GT 1 Subtype



Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

Simeprevir in Treatment Experienced Genotype 1 HCV ASPIRE Trial: Conclusions

Conclusion: “In treatment-experienced patients, 12, 24, or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks peginterferon and ribavirin significantly increased rates of SVR at 24 weeks compared with patients given placebo, peginterferon, and ribavirin, and was generally well tolerated.”

Source: Zeuzem S, et al. Gastroenterol. 2014;146:430-41.

Simeprevir in Treatment-Naïve and Treatment-Experienced Patients

Hepatitis web study

Treatment Naïve and Treatment Experienced

Simeprevir with Peginterferon and Ribavirin in GT-4
RESTORE

Moreno C, et al. J Hepatol. 2015;62:1047-55.

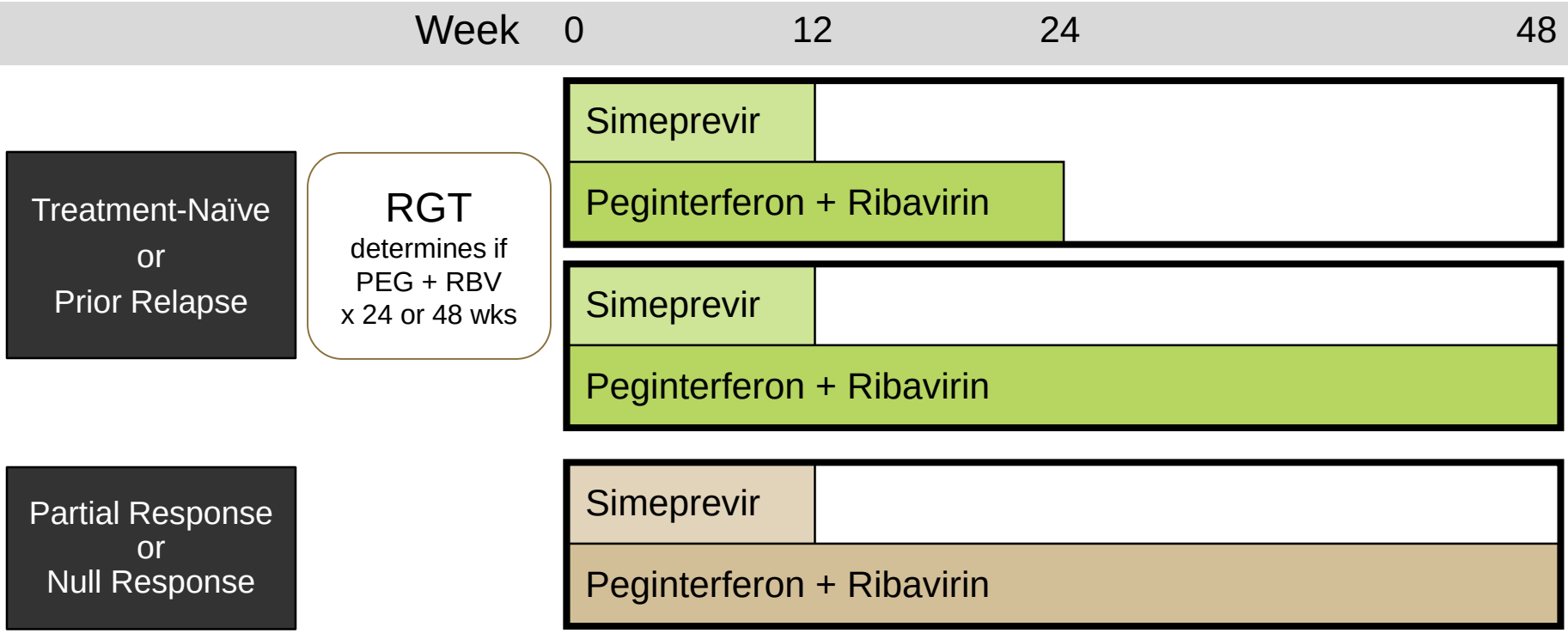
Simeprevir + Peginterferon + Ribavirin in Genotype 4
RESTORE: Study Features

RESTORE Trial: Features

- **Design**: Open-label, phase 3, study evaluating simeprevir plus peginterferon plus ribavirin for treatment naïve and experienced patients with genotype 4 chronic HCV
- **Setting**: Multicenter and International
- **Entry Criteria**
  - Chronic HCV genotype 4 (n = 107)
  - Treatment naïve (n = 35) or treatment experienced relapsers (n = 22)
  - Experienced (Nonresponder): partial (n = 10), null (n = 40)
- **Patient Characteristics**
  - Sex: male 79%
  - Race: white (72%); black (28%)
  - Median age: 49
  - IL genotype: 7.5% CC
  - METAVIR Fibrosis Stage: F4 = 29%; F3 = 14%
- **Primary End-Points**: Efficacy (SVR12)

Source: Moreno C, et al. J Hepatol. 2015;62:1047-55.

Simeprevir + Peginterferon + Ribavirin in Genotype 4
RESTORE: Study Design



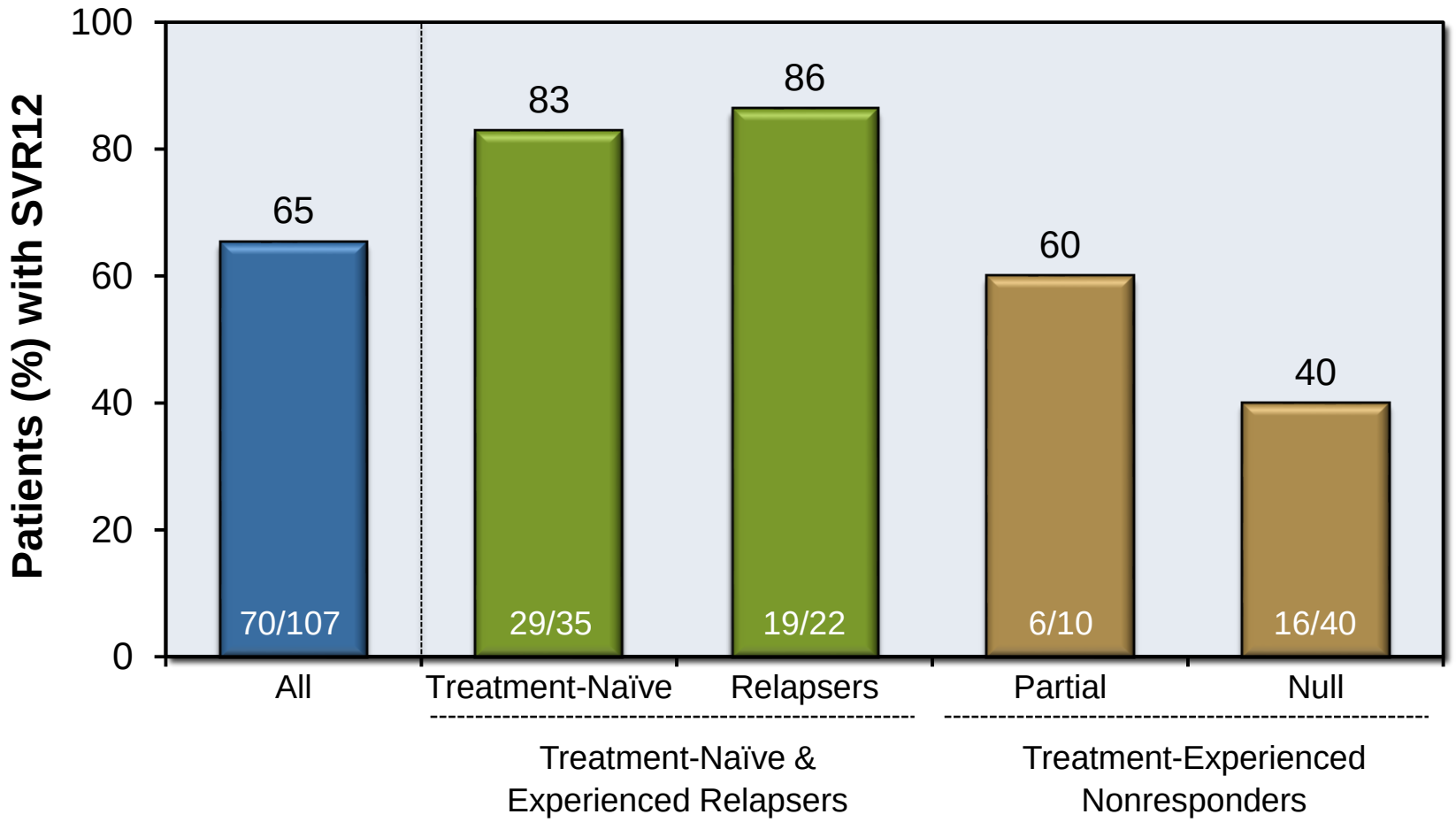
Response Guided Therapy (RGT) Criteria: Week 4 HCV RNA < 25 IU/mL (detectable or undetectable) and Week 12 HCV RNA < 25 IU/mL (undetectable)

Drug Dosing
Simeprevir: 150 mg once daily
Peginterferon alfa-2a (PEG): 180 mcg/week
Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

Source: Moreno C, et al. J Hepatol. 2015;62:1047-55.

Simeprevir + Peginterferon + Ribavirin in Genotype 4
RESTORE: Results

RESTORE: SVR12 by Prior Treatment Status



Source: Moreno C, et al. J Hepatol. 2015;62:1047-55.

Hepatitis web study

Simeprevir + Peginterferon + Ribavirin in Genotype 4
RESTORE: Conclusions

Conclusions: “Efficacy and safety of simeprevir 150 mg QD for 12 weeks with peginterferon and ribavirin in treatment-naïve or -experienced patients with chronic HCV GT4 infection were in line with previous reports for HCV GT1 infection.”

Source: Moreno C, et al. J Hepatol. 2015;62:1047-55.

Simeprevir + Sofosbuvir

Treatment Naïve and Treatment Experienced

Simeprevir + Sofosbuvir +/- Ribavirin in Genotype 1 COSMOS Trial

Lawitz E, et al. Lancet. 2014;384;1756-65.

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Study Features

COSMOS Trial: Features

- **Design**: Randomized, phase 2a, open-label, using sofosbuvir + simeprevir +/- ribavirin in treatment naive or experienced, chronic HCV GT 1
- **Setting**: 23 centers in United States
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - Age ≥18
  - HCV RNA greater than 10,000 IU/mL
  - Cohort 1: prior nonresponders; Metavir F0-F2
  - Cohort 2: treatment naïve & prior nonresponders; Metavir F3-F4
- **Patient Characteristics (range in different treatment arms)**
  - N = 167 (n = 80 in Cohort 1 and n = 87 in Cohort 2)
  - Baseline GT1a with Q80K: Cohort 1 = 50%; Cohort 2 = 40%
  - Non-CC IL28b Genotype: Cohort 1 = 94%; Cohort 2 = 79%
- **End-Points**: Primary = SVR12

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Baseline Characteristic

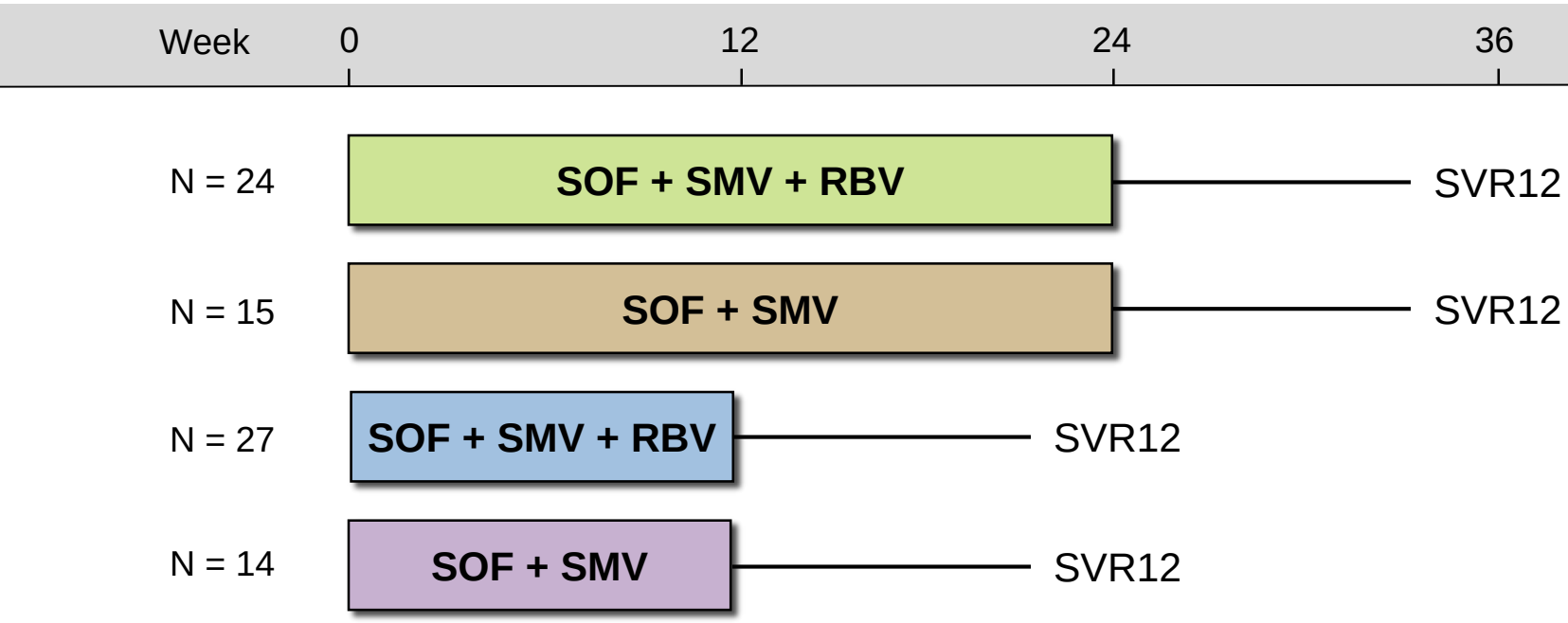
Baseline Characteristic (n = 167)	Cohorts 1 and 2
Median Age, years (range)	57 (27-70)
Male, %	64
White, %	81
Median Body Mass Index (BMI)	28
HCV genotype	1a= 78%; 1b = 22%
IL28B non-CC genotype, (%)	86%
Mean baseline HCV RNA, $\log_{10}$ IU/ml	6.6
Metavir Score	F01= 20%; F2=28%; F3 = 28%; F4=25%
Previous HCV treatment No response (%) Treatment-naïve (%)	 76% 24%

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Hepatitis web study

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Design for Cohort 1

Cohort 1: Prior Nonresponders; Metavir Scores F0-F2



Drug Dosing

SOF= Sofosbuvir: 400 mg once daily

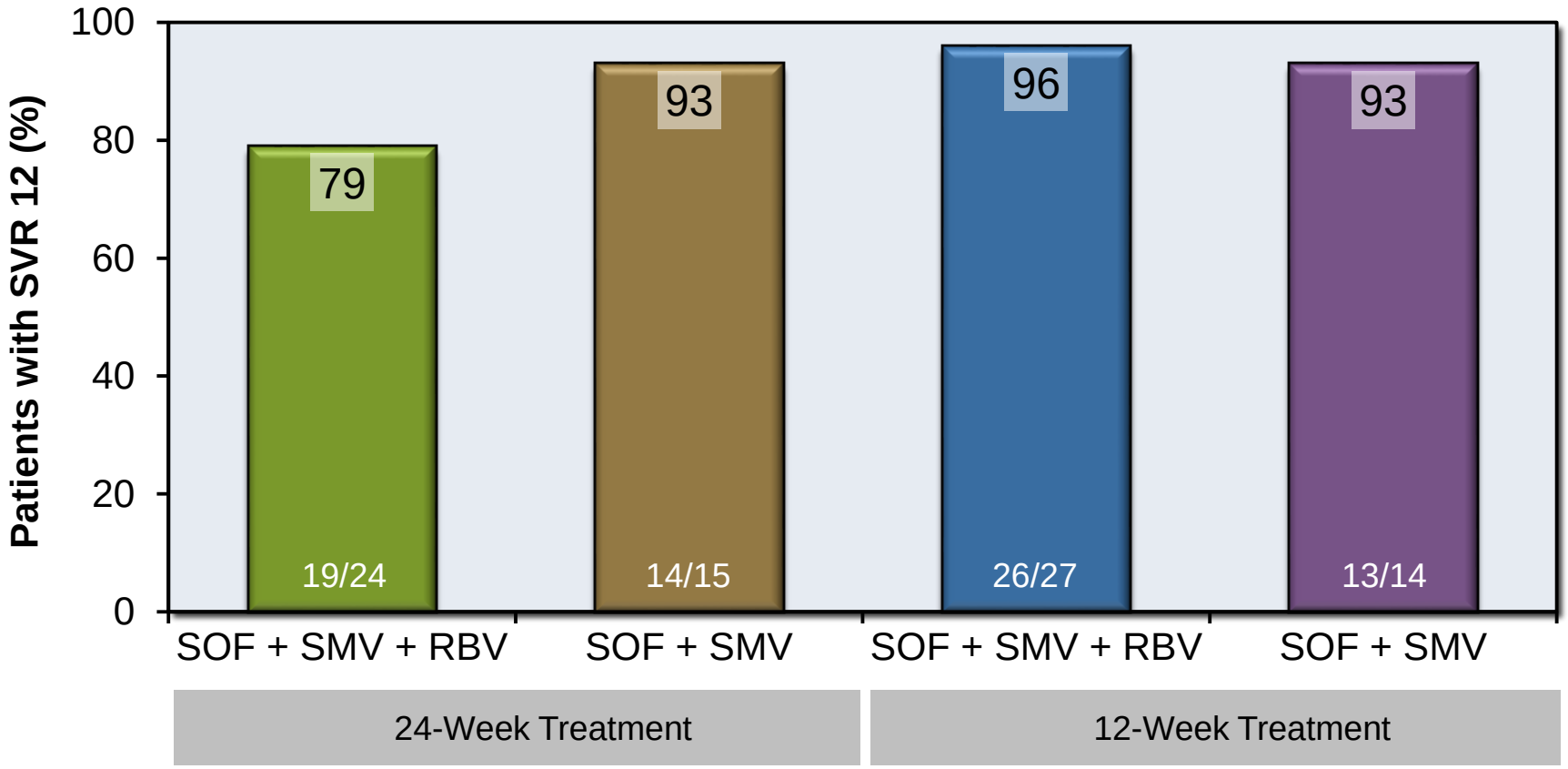
SMP =Simeprevir: 150 mg once daily

RBV = Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Results for Cohort 1

COSMOS (Cohort 1): SVR 12 by Regimen

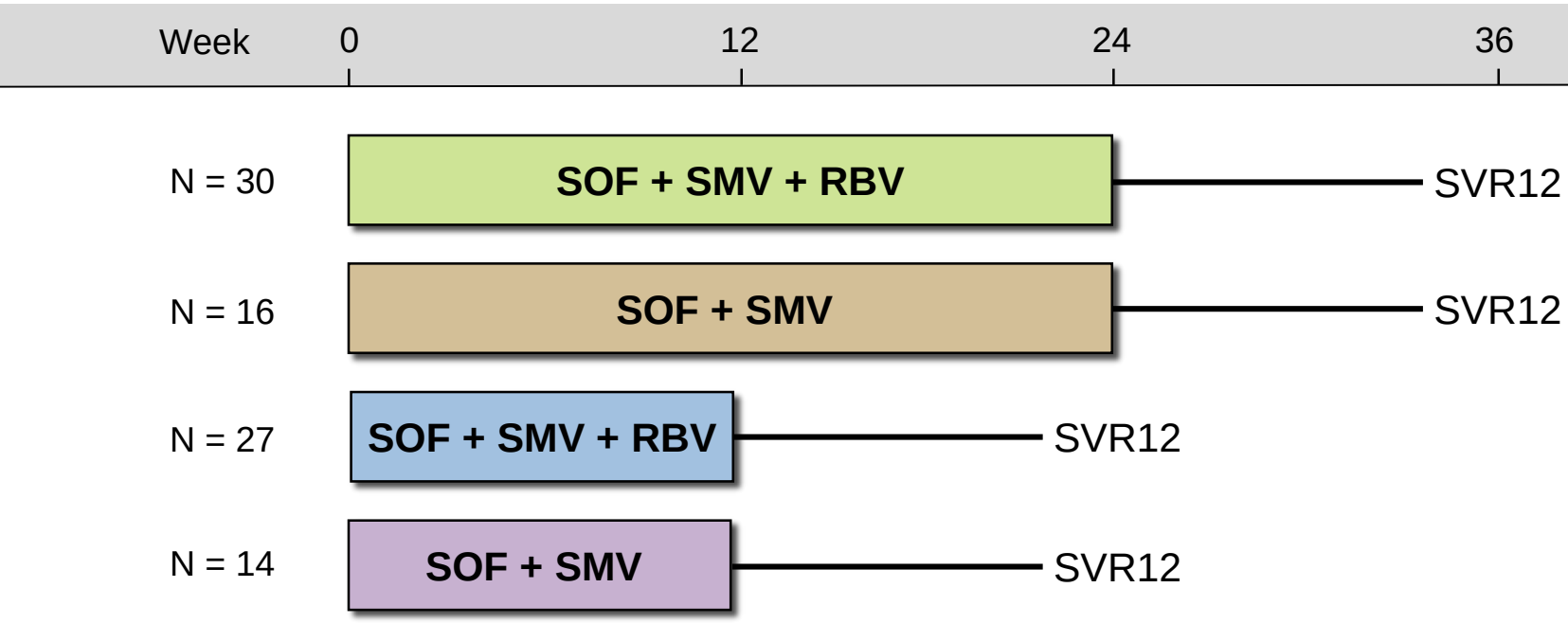


SOF = sofosbuvir; SMV = simeprevir; RBV = ribavirin

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Design for Cohort 2

Cohort 2: Treatment Naïve & Prior Nonresponders; Metavir Scores F3-F4



Drug Dosing

Sofosbuvir: 400 mg once daily

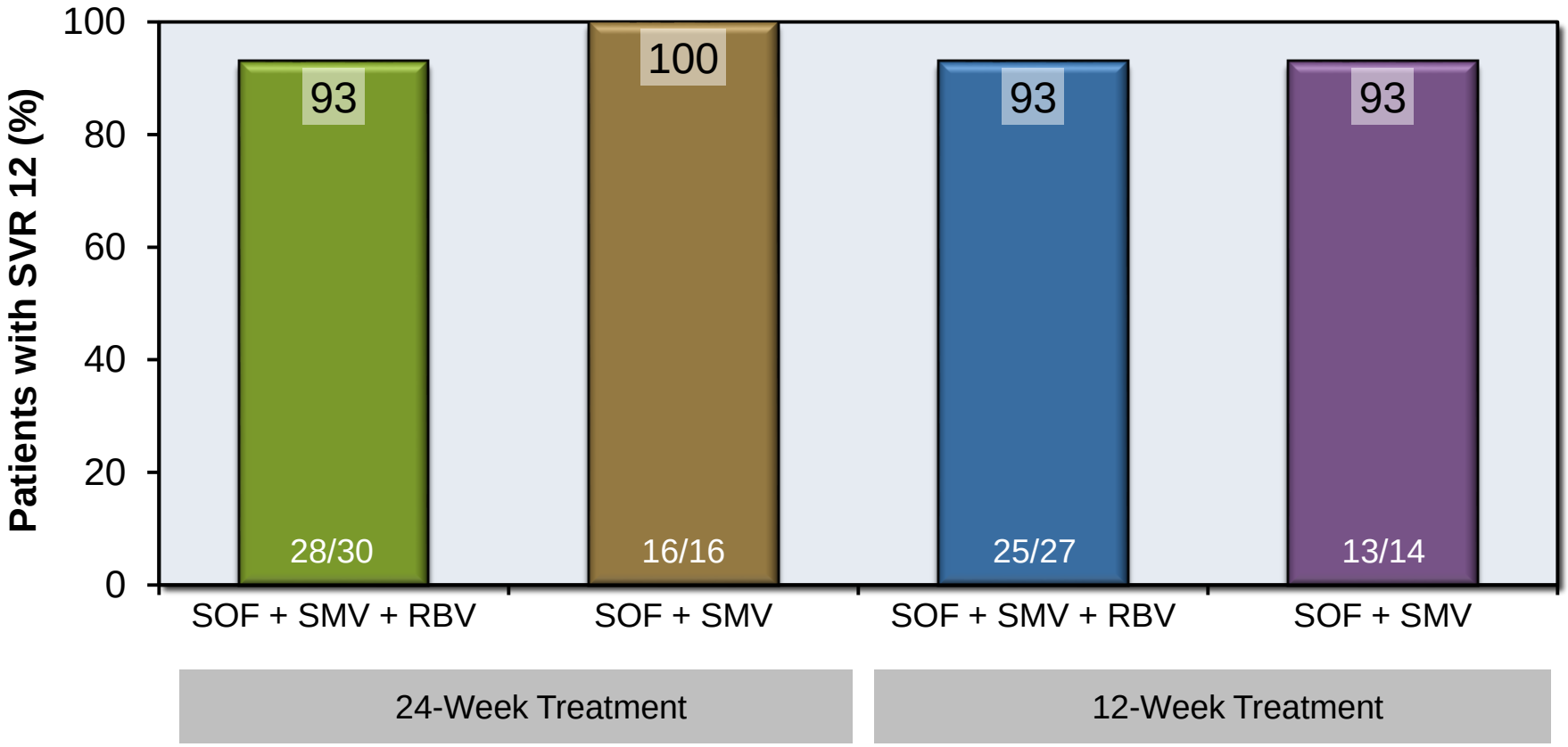
Simeprevir: 150 mg once daily

Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Results

COSMOS (Cohort 2 with F3-F4 Fibrosis): SVR12 by Regimen



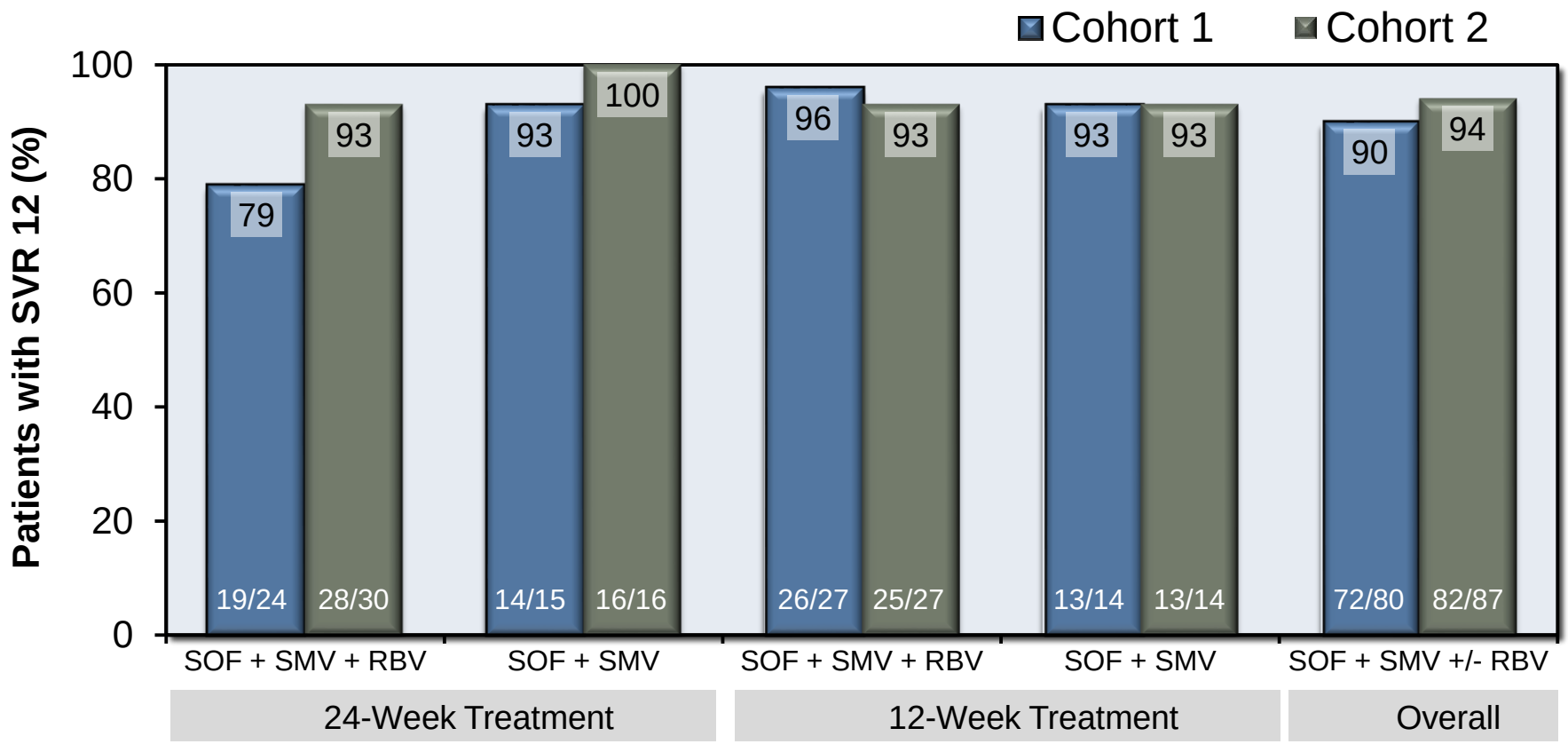
SOF = sofosbuvir; SMV = simeprevir; RBV = ribavirin

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Hepatitis web study

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Results for Cohort 1 & 2

Cohort 1 & 2: SVR12

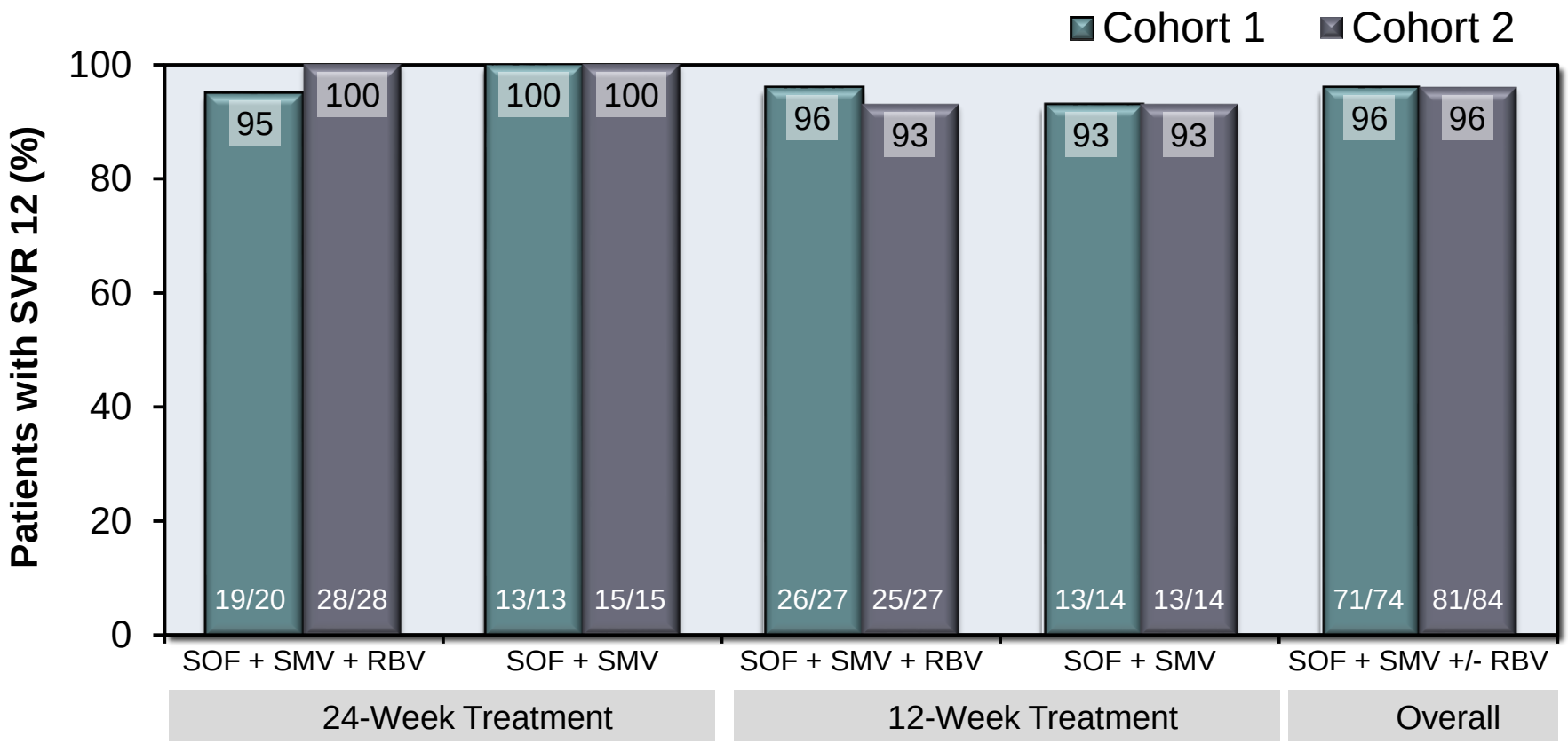


Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Hepatitis web study

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Results for Cohort 1 & 2

Cohort 1 & 2: SVR12 (Non-VR excluded analysis*)



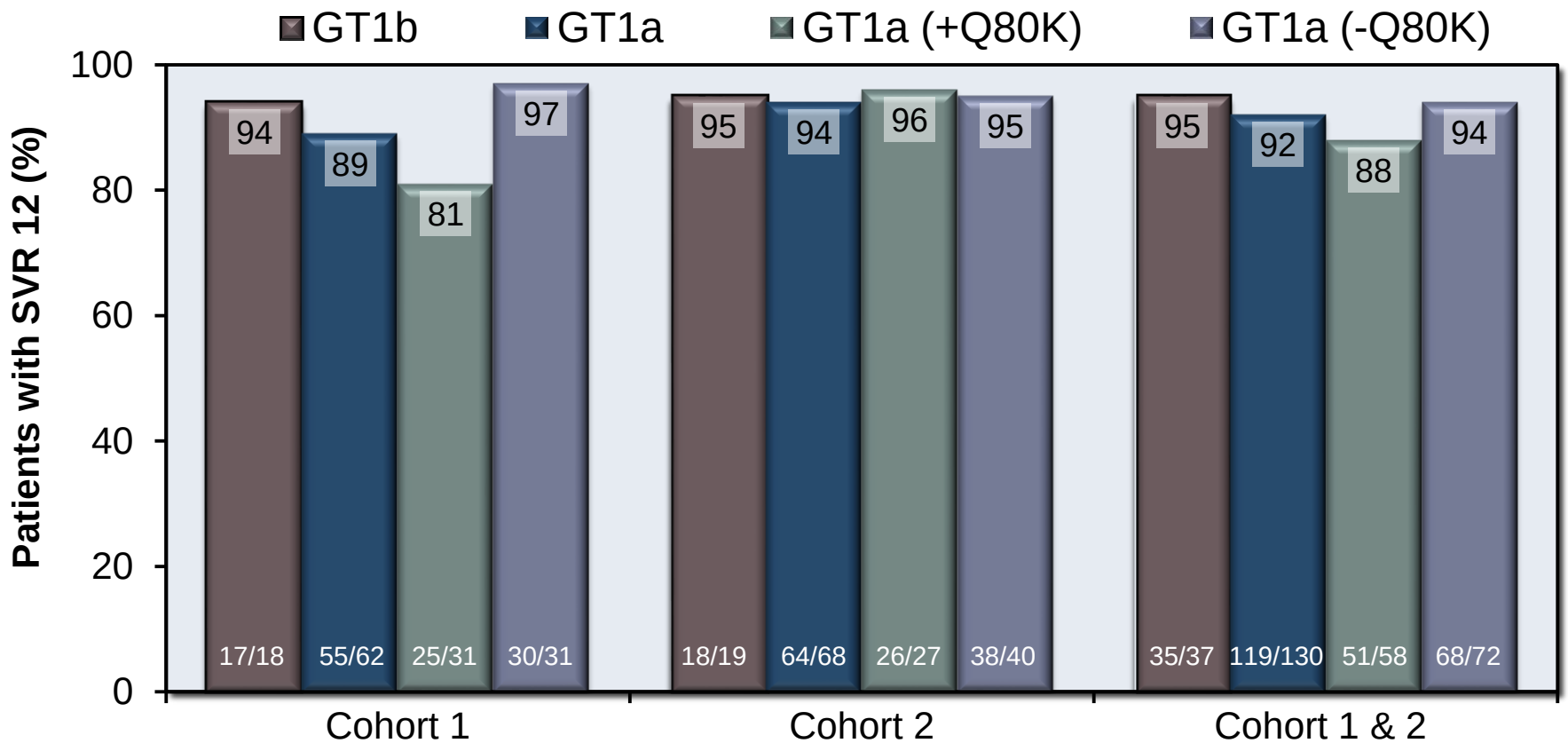
*Non-VR excluded analysis = SVR12 excludes early discontinuation due to non-virologic reasons or missing data at SVR12 time point

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Hepatitis web study

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Results for Cohort 1 & 2

Impact of Q80K on SVR in Patients with GT1



*Q80K = Gln80Lys

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Hepatitis web study

Simeprevir + Sofosbuvir +/- Ribavirin for HCV GT 1
COSMOS Trial: Interpretation

Interpretation: “Combined simeprevir and sofosbuvir was efficacious and well tolerated.”

Source: Lawitz E, et al. Lancet. 2014;384;1756-65.

Hepatitis web study

Treatment Naïve and Treatment Experienced

Simeprevir + Sofosbuvir in GT1 without Cirrhosis
OPTIMIST-1 Trial

Kwo P, et al. 50th EASL; 2015. Abstract LB14.

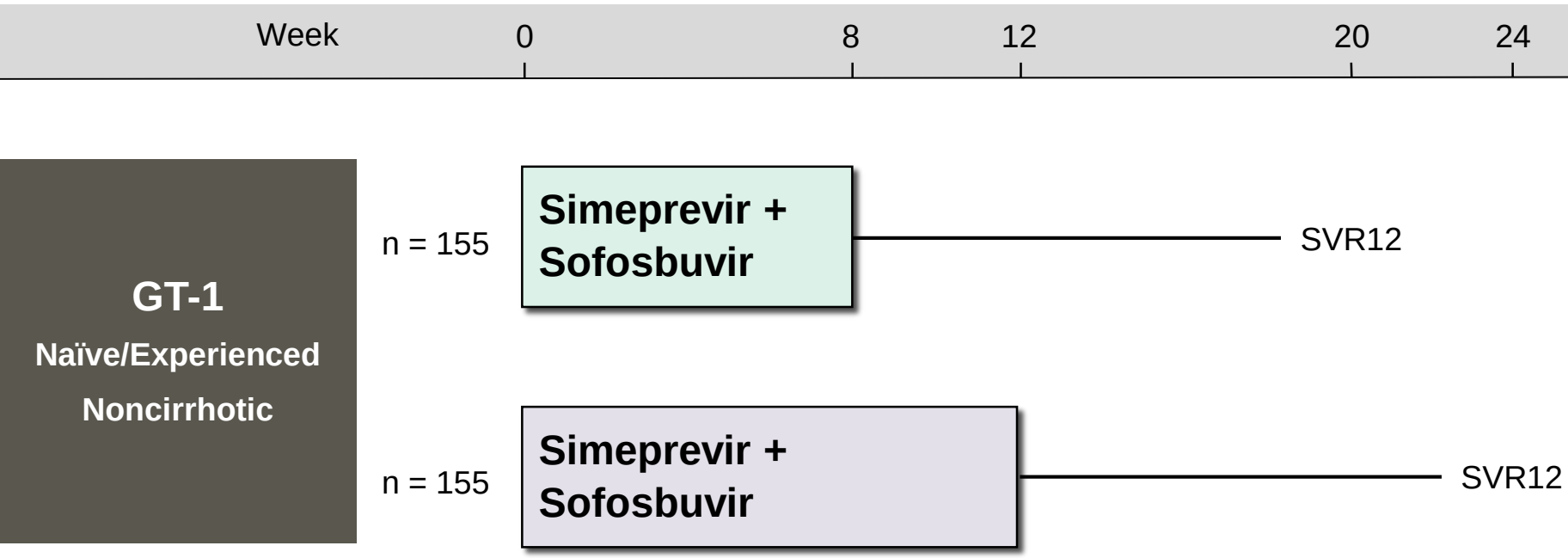
Simeprevir + Sofosbuvir for HCV GT 1 without Cirrhosis
OPTIMIST-1 Trial: Study Features

OPTIMIST 1 Trial: Features

- **Design**: Randomized, phase 3, open-label, using sofosbuvir plus simeprevir for 8 or 12 weeks in treatment naive or experienced patients with chronic HCV genotype 1 infection without cirrhosis
- **Setting**: multicenter in United States and Canada
- **Entry Criteria**
  - Chronic HCV Genotype 1a or 1b
  - Documented lack of cirrhosis
  - Age 18-70
  - HCV RNA greater than 10,000 IU/mL
  - Treatment experienced required to have ≥1 INF-based regimen +/- RBV
- **Exclusion**
  - Cirrhosis, hepatic decompensation, or non-HCV-related liver disease
  - Coinfection with HBV or HIV
- **End-Points**: Primary = SVR12 by intent-to-treat analysis

Source: Kwo P, et al. 50th EASL; 2015. Abstract LB14.

Simeprevir + Sofosbuvir for HCV GT 1 without Cirrhosis
OPTIMIST-1 Trial: Study Design



Drug Dosing

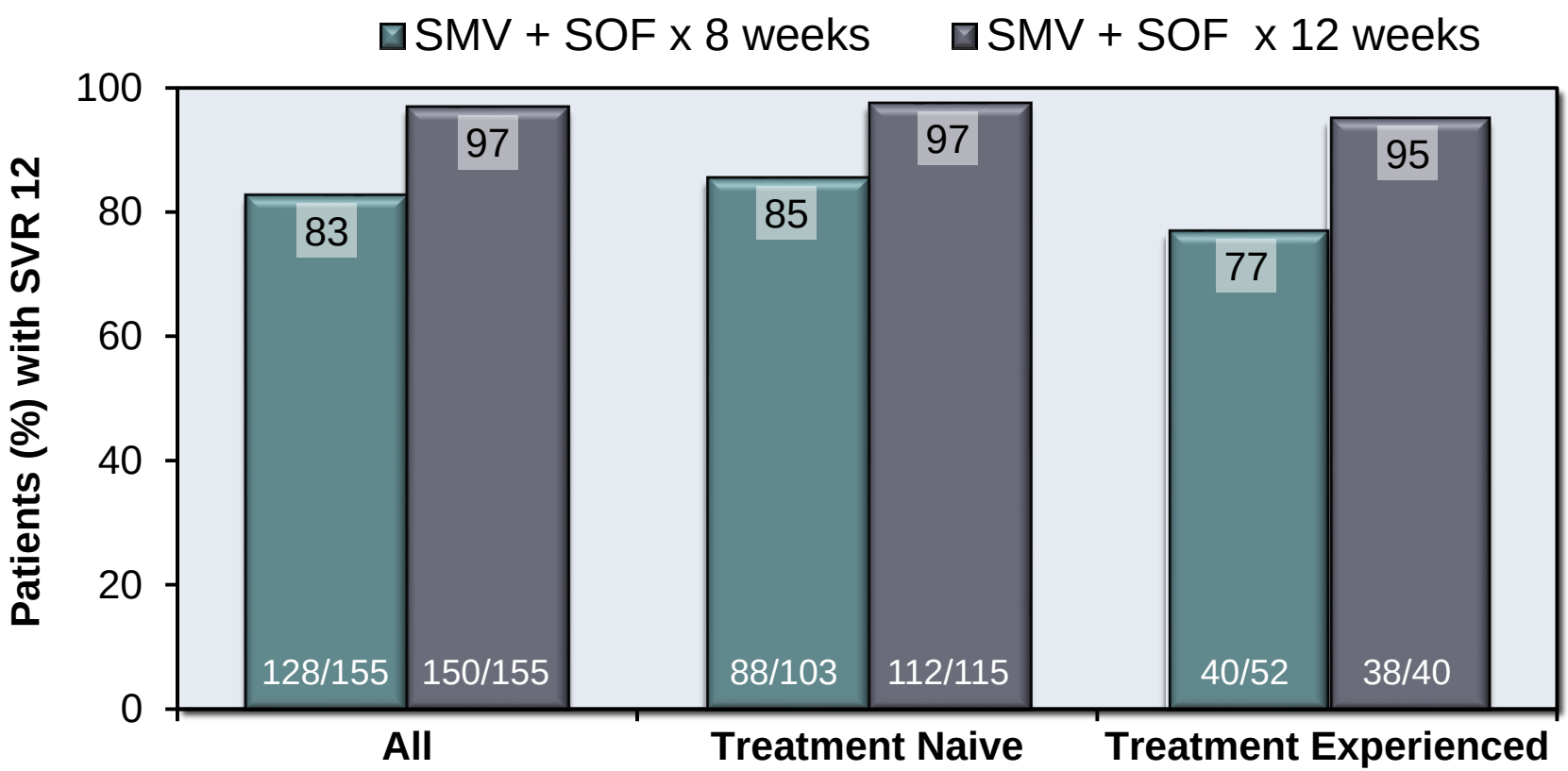
Simeprevir: 150 mg once daily

Sofosbuvir: 400 mg once daily

Source: Kwo P, et al. 50th EASL; 2015. Abstract LB14.

Simeprevir + Sofosbuvir for HCV GT 1 without Cirrhosis
OPTIMIST-1 Trial: Results

OPTIMIST 1: SVR12, by Treatment Experience

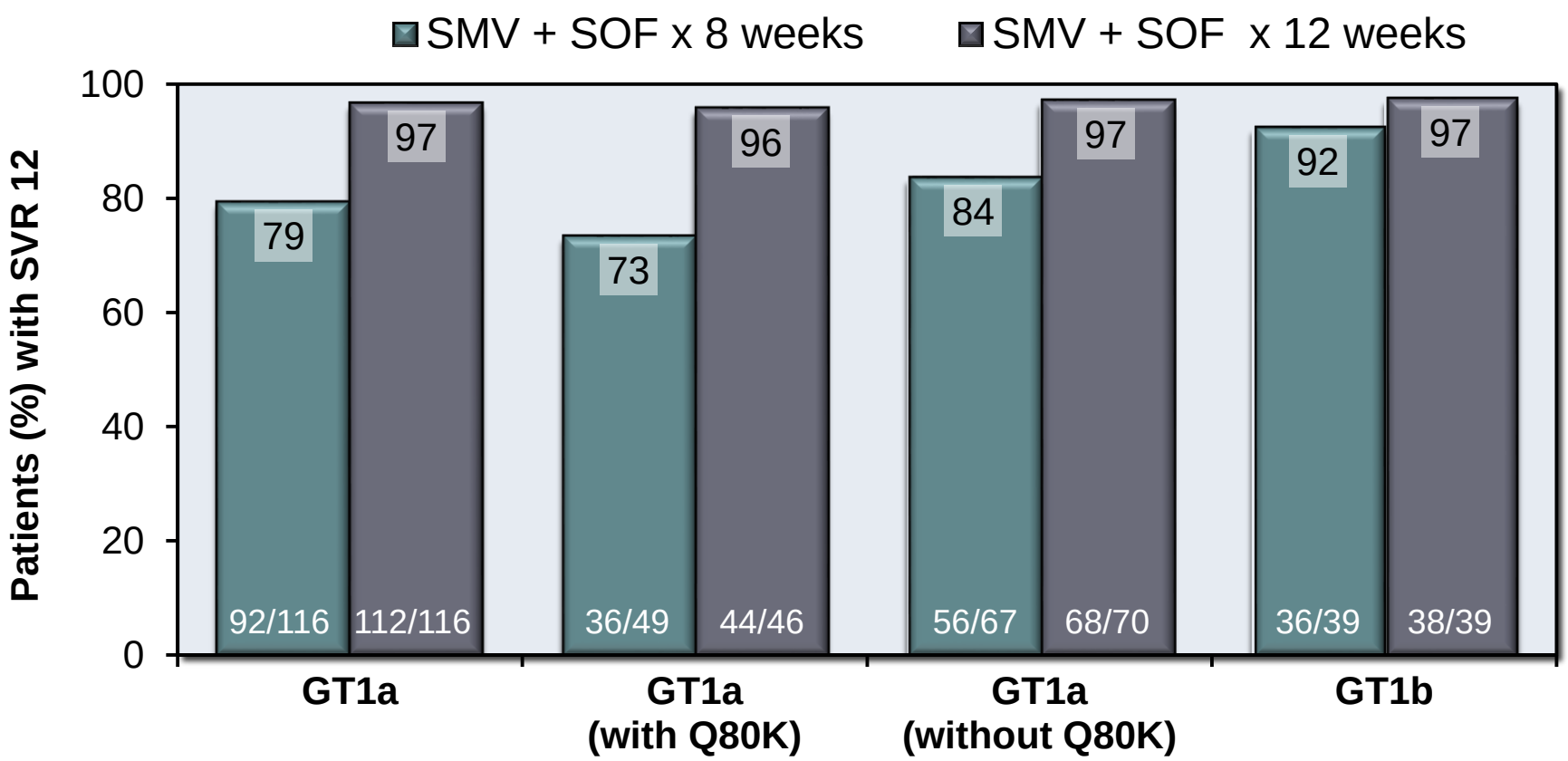


SVR12 = sustained virologic response at 12 weeks

Source: Kwo P, et al. 50th EASL; 2015. Abstract LB14.

Simeprevir + Sofosbuvir for HCV GT 1 without Cirrhosis
OPTIMIST-1 Trial: Results

OPTIMIST 1: SVR12, by Genotype 1 Subtype



SVR12 = sustained virologic response at 12 weeks

Source: Kwo P, et al. 50th EASL; 2015. Abstract LB14.

Treatment Naïve and Treatment Experienced

Simeprevir + Sofosbuvir in GT1 with Cirrhosis
OPTIMIST-2 Trial

Lawitz E, et al. 50th EASL; 2015. Abstract LP04.

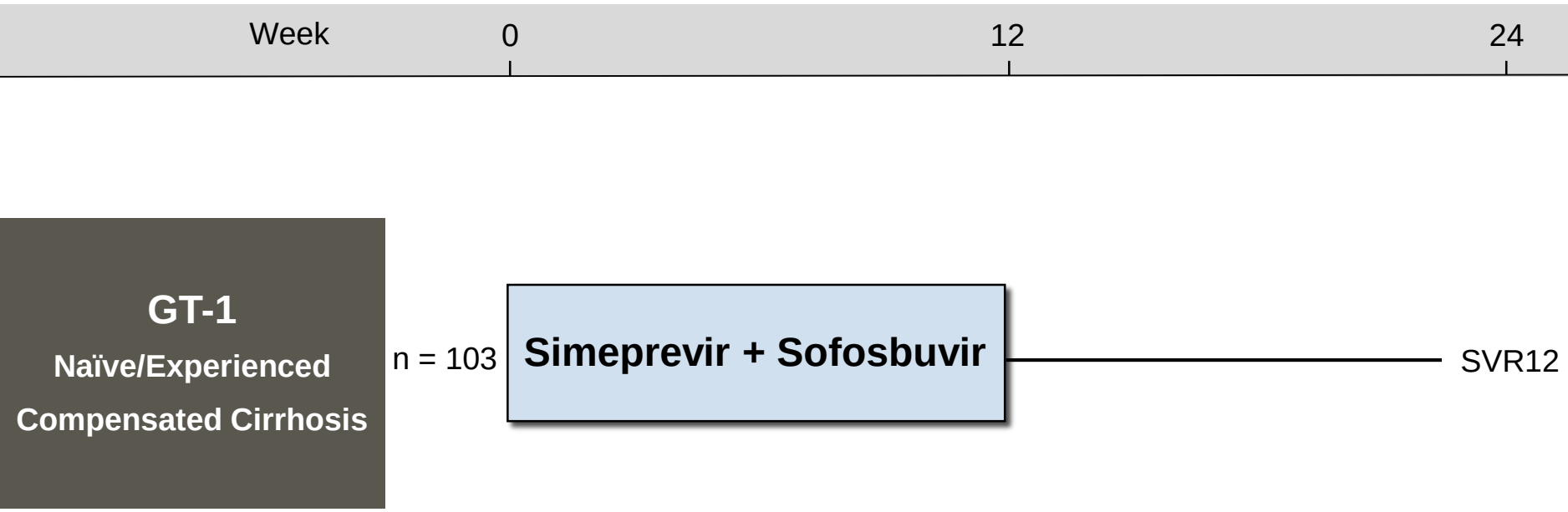
Simeprevir + Sofosbuvir for HCV GT 1 with Cirrhosis
OPTIMIST-2 Trial: Study Features

OPTIMIST 2 Trial: Features

- **Design**: Randomized, phase 3, open-label, single-arm trial using sofosbuvir plus simeprevir for 12 weeks in treatment naive or experienced patients with chronic HCV genotype 1 infection and compensated cirrhosis
- **Setting**: multicenter in United States and Canada
- **Entry Criteria**
  - Chronic HCV Genotype 1 infection
  - Studies indicating cirrhosis with compensation
  - Age 18-70
  - HCV RNA greater than 10,000 IU/mL
  - Any treatment history allowed
- **Exclusion**
  - Hepatic decompensation, or non-HCV-related liver disease
  - Coinfection with HBV or HIV
- **End-Points**: Primary = SVR12 by intent-to-treat analysis

Source: Lawitz E, et al. 50th EASL; 2015. Abstract LP04.

Simeprevir + Sofosbuvir for HCV GT 1 with Cirrhosis
OPTIMIST-2 Trial: Study Design



Drug Dosing

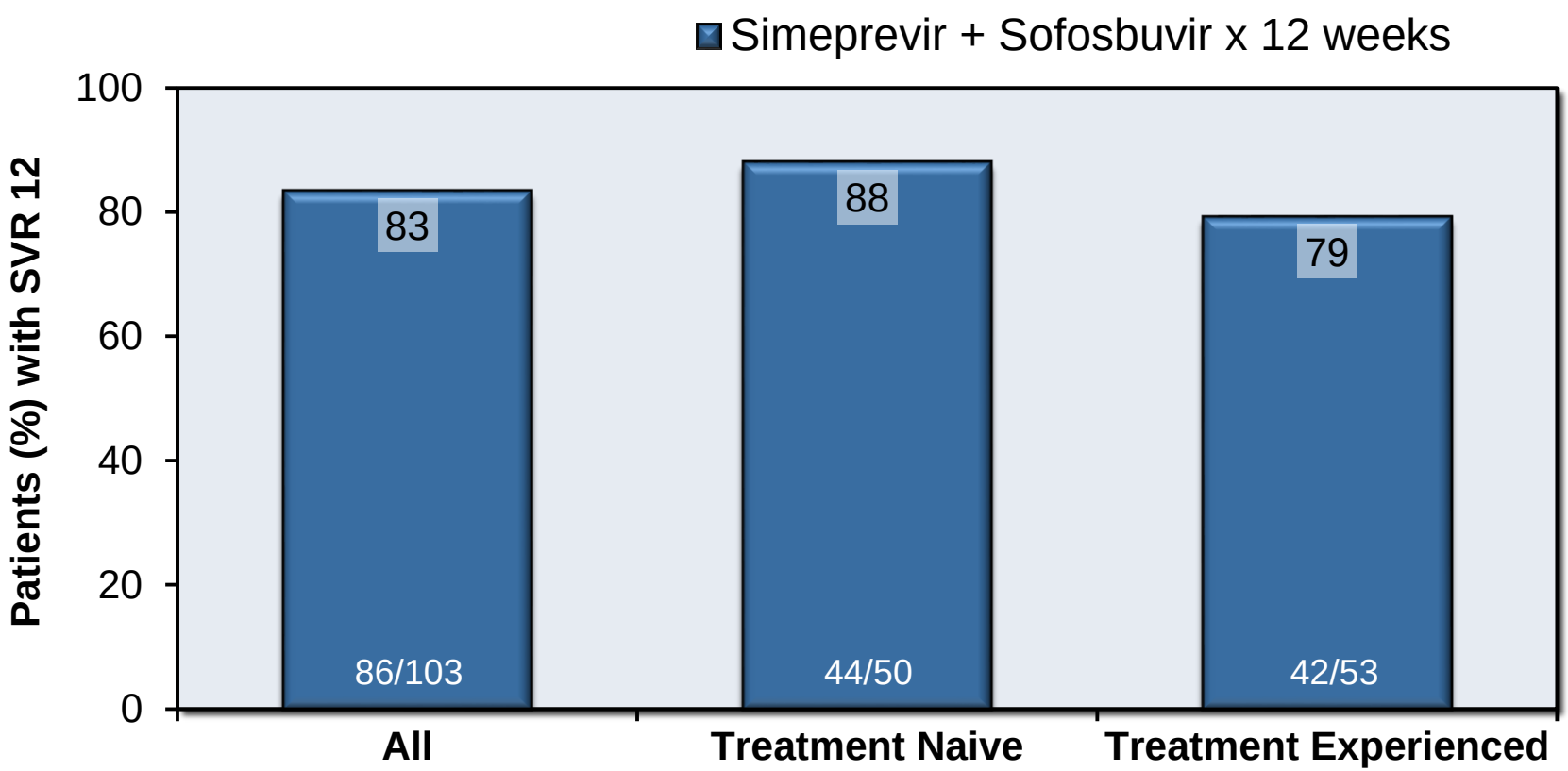
Simeprevir: 150 mg once daily

Sofosbuvir: 400 mg once daily

Source: Lawitz E, et al. 50th EASL; 2015. Abstract LP04.

Simeprevir + Sofosbuvir for HCV GT 1 with Cirrhosis
OPTIMIST-2 Trial: Results

OPTIMIST 2: SVR12, by Treatment Experience

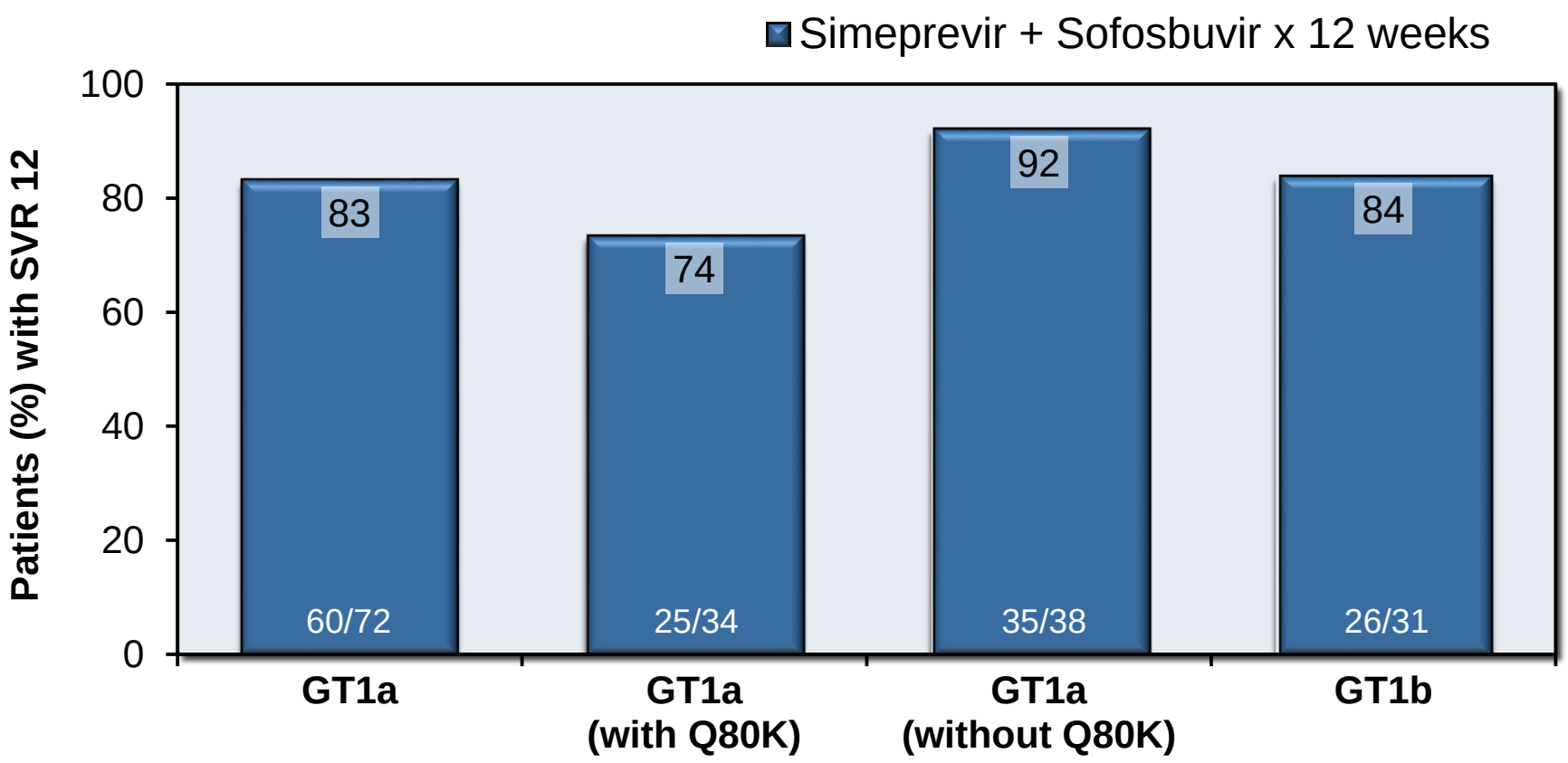


SVR12 = sustained virologic response at 12 weeks

Source: Lawitz E, et al. 50th EASL; 2015. Abstract LP04.

Simeprevir + Sofosbuvir for HCV GT 1 with Cirrhosis
OPTIMIST-2 Trial: Results

OPTIMIST 2: SVR12, by Genotype 1 Subtype



SVR12 = sustained virologic response at 12 weeks

Source: Lawitz E, et al. 50th EASL; 2015. Abstract LP04.

Simeprevir in Patients with HCV-HIV Coinfection

Hepatitis web study

Treatment Naïve and Treatment Experienced

HIV Coinfection

Simeprevir in HIV Coinfection, GT-1
C212 Trial

Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

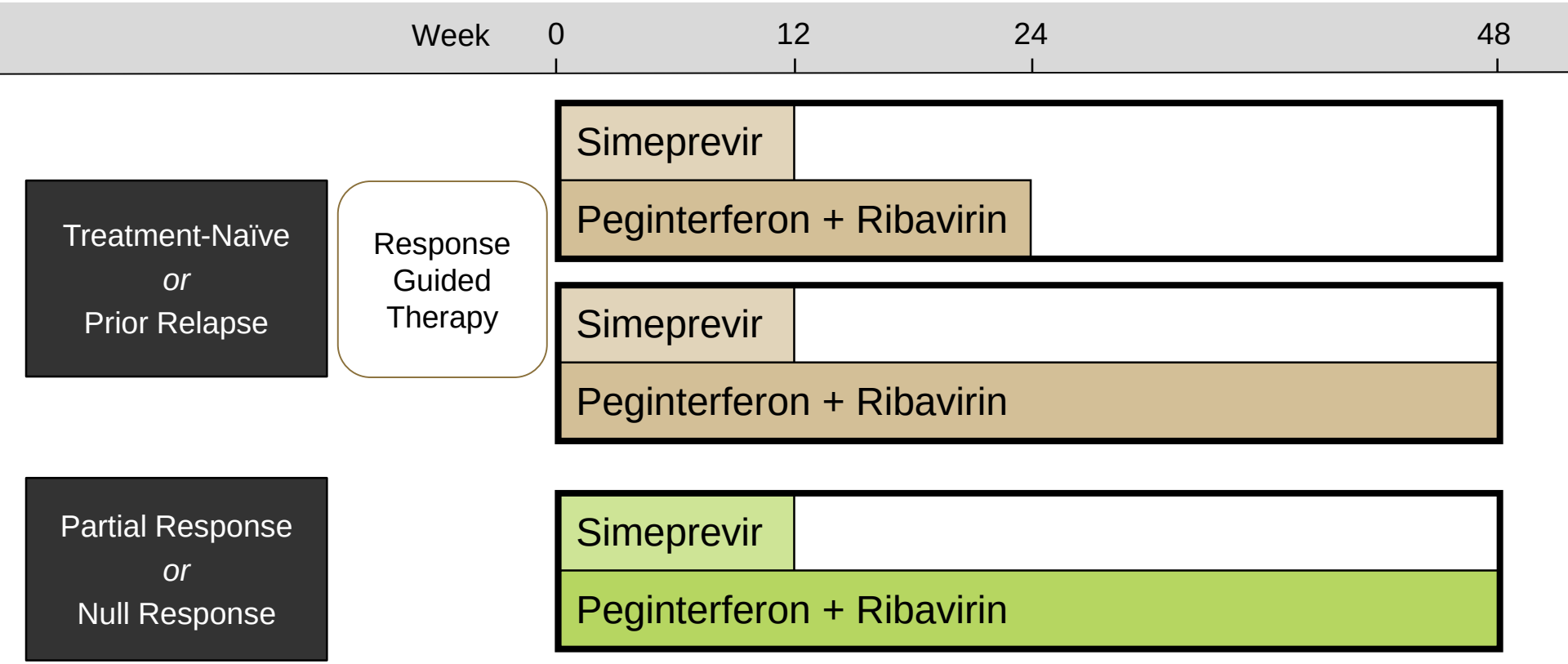
Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Study Features

C212 Trial: Features

- **Design**: Open-label, phase 3, trial evaluating simeprevir + PEG + RBV in HCV-HIV and GT 1 (treatment naïve and experienced)
- **Setting**: 39 sites in 7 countries
- **Entry Criteria**
  - HIV coinfection; HCV genotype 1
  - Treatment naïve or treatment experienced
  - Group 1: HCV treatment-naïve or prior relapse
  - Group 2: Prior partial or null response or cirrhosis
  - CD4 ≥ 200 if on stable ARV therapy; CD4 ≥ 500 if no ARV therapy
  - Stable antiretroviral therapy = HIV RNA < 50 copies/ml > 8 weeks
- **Patient Characteristics**
  - N = 106 HCV-HIV coinfected patients
  - Race: white (82%); black (14%)
  - Baseline Median CD4 (cells/mm^3): 629 cells/mm^3
- **Primary End-Points**: Efficacy (SVR12), safety, and impact on HIV

Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Design



Drug Dosing

Simeprevir: 150 mg once daily

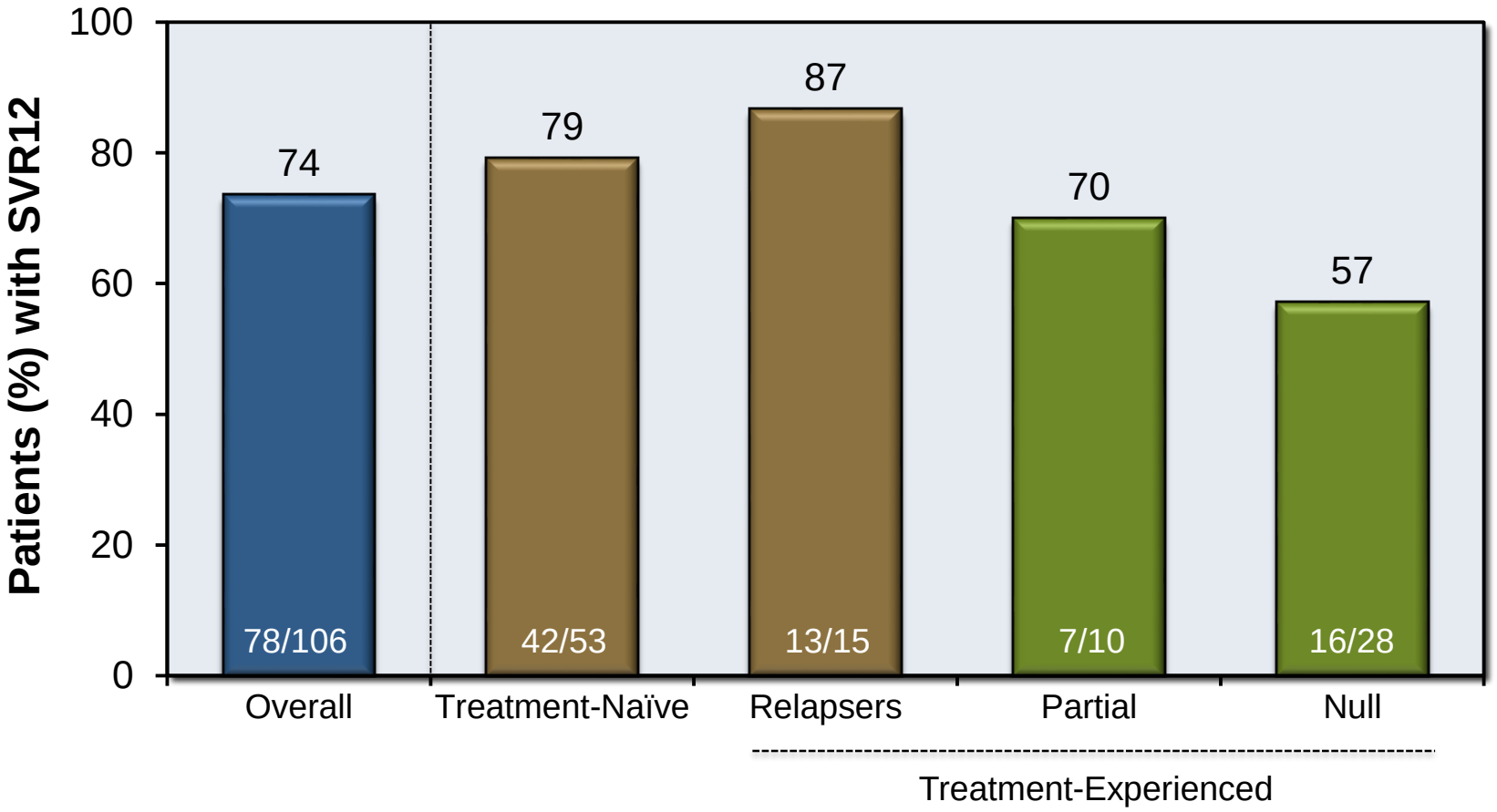
Peginterferon alfa-2a (PEG): 180 mcg/week

Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Results

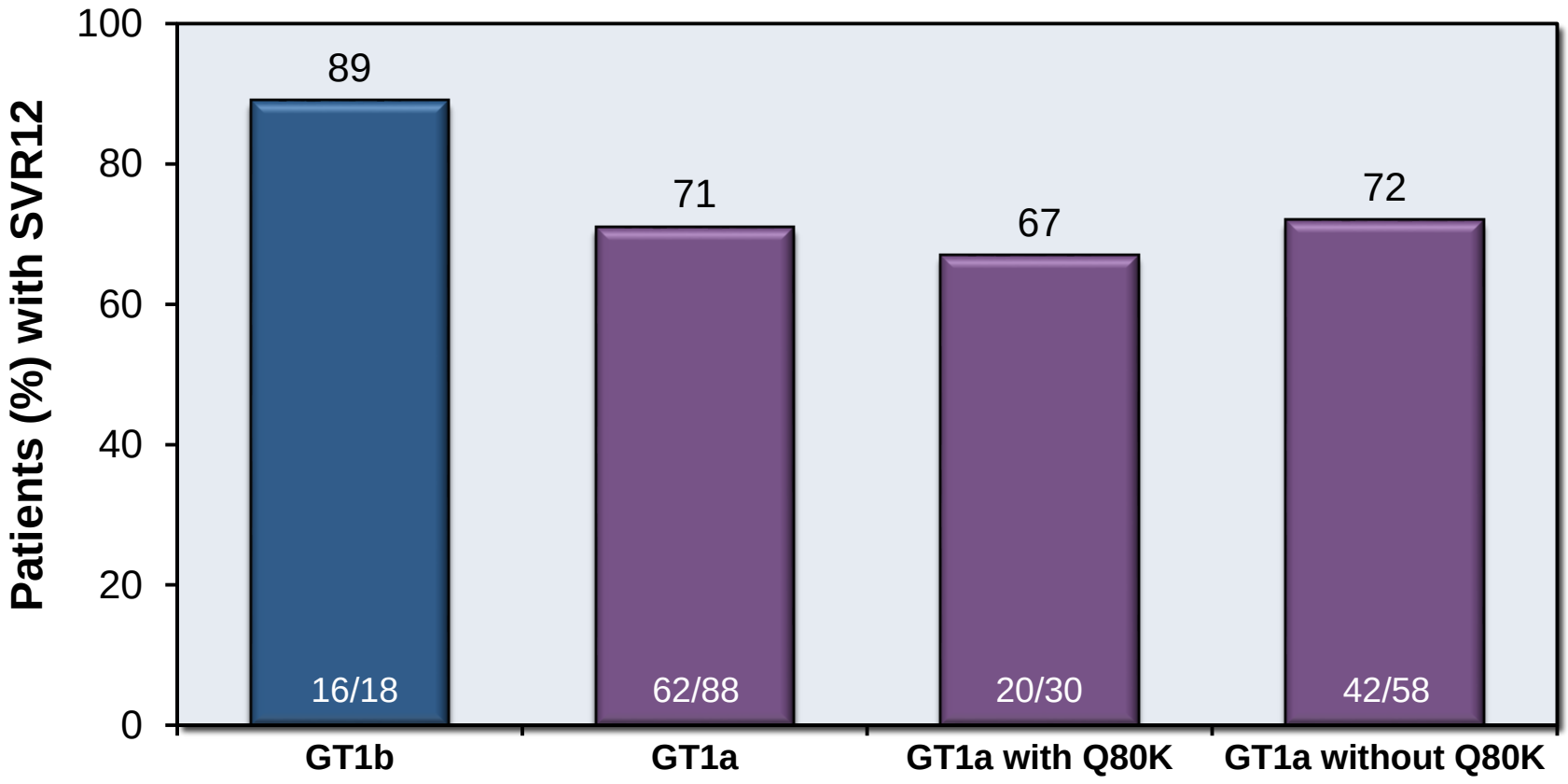
C212: SVR12 by Prior Treatment Status



Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Results

C212: SVR12 by GT1 Subtype and Baseline NS3 Q80K Polymorphism

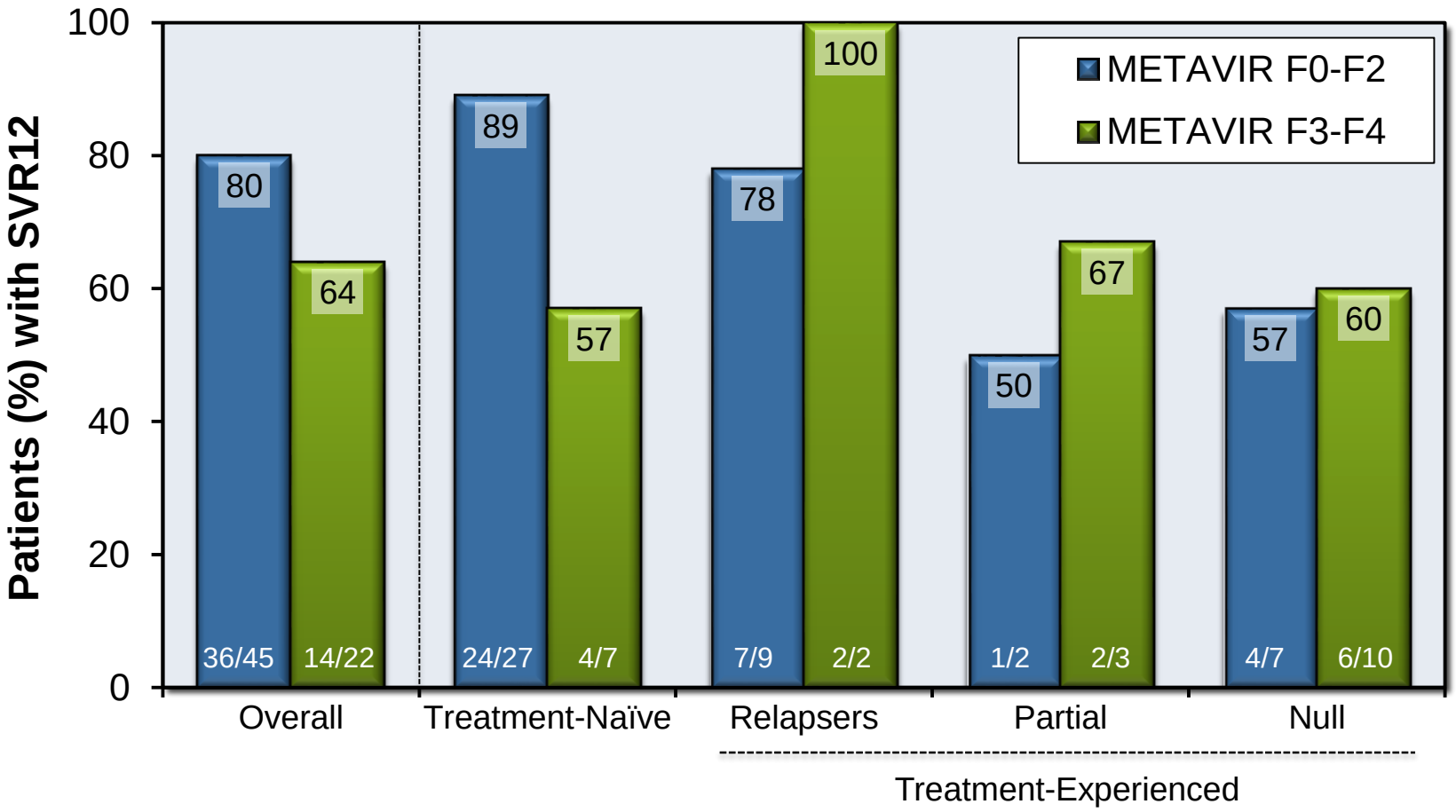


Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

Hepatitis web study

Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Results

C212: SVR12 by Fibrosis Stage and Prior History

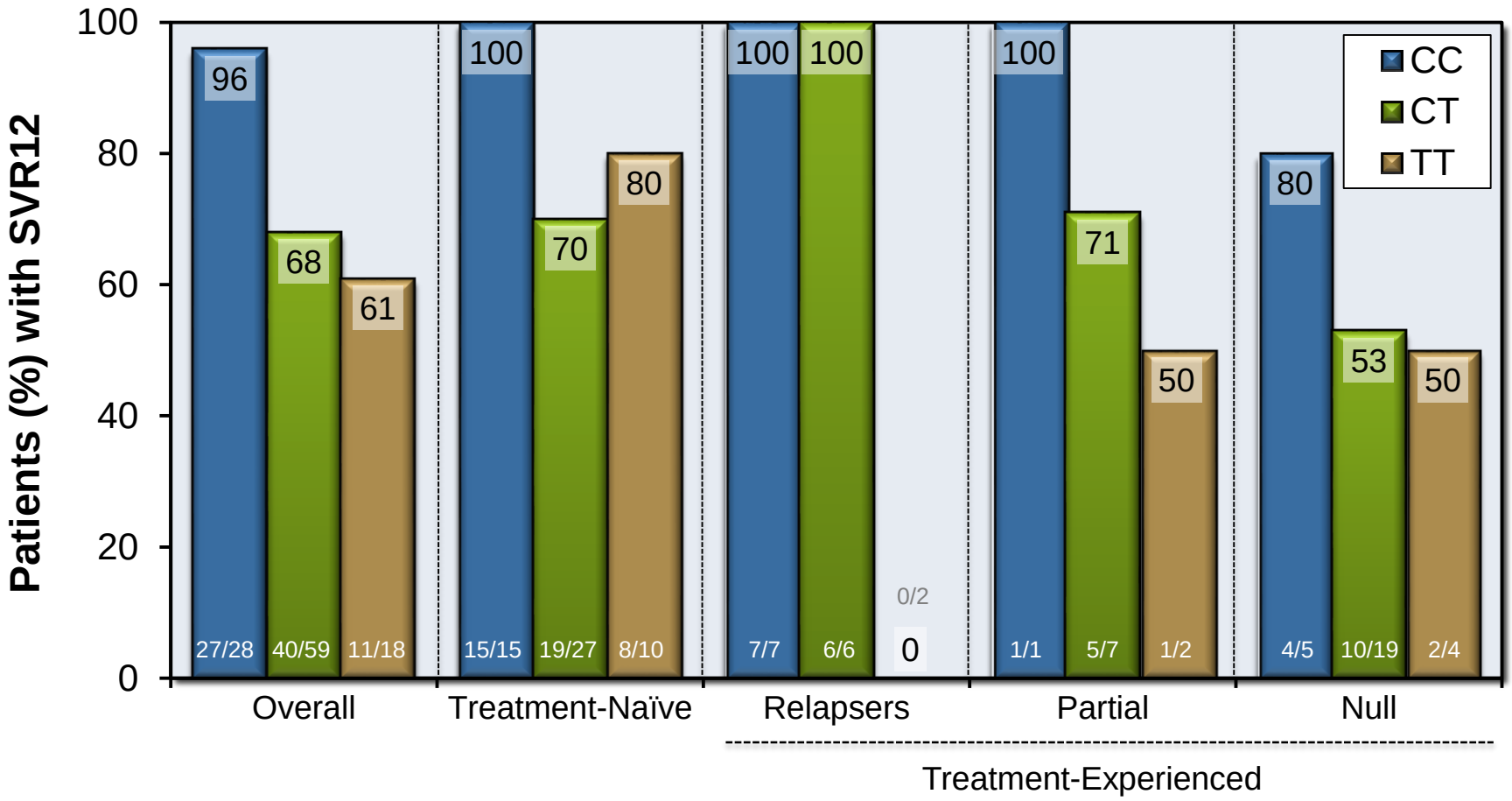


Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

Hepatitis web study

Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Results

C212: SVR12 by IL28B Genotype



Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

Simeprevir + PEG + Ribavirin for HCV-HIV Coinfection Study C212: Conclusions

Conclusions: “Simeprevir was generally well tolerated with safety similar to that observed in HCV-monoinfected patients and high SVR12 rates in HCV treatment-naive patients, prior relapsers, prior partial responders, and prior null responders with HIV-1 coinfection.”

Source: Dieterich D, et al. Clin Infect Dis. 2014;59:1579-87.

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

www.hepatitisc.uw.edu

Hepatitis Web Study

http://depts.washington.edu/hepstudy/

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Hepatitis web study