

HEPATITIS WEB STUDY  HEPATITIS C ONLINE

# Treatment of Chronic HCV Genotype 2

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# Treatment of Chronic HCV Genotype 2

- Background and Definitions
- Initial Treatment
- Retreatment of Patients with Prior Treatment Failure
- Disappearance of Issues and Controversies
- Is There a Need for Future Therapies?
- Summary

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2

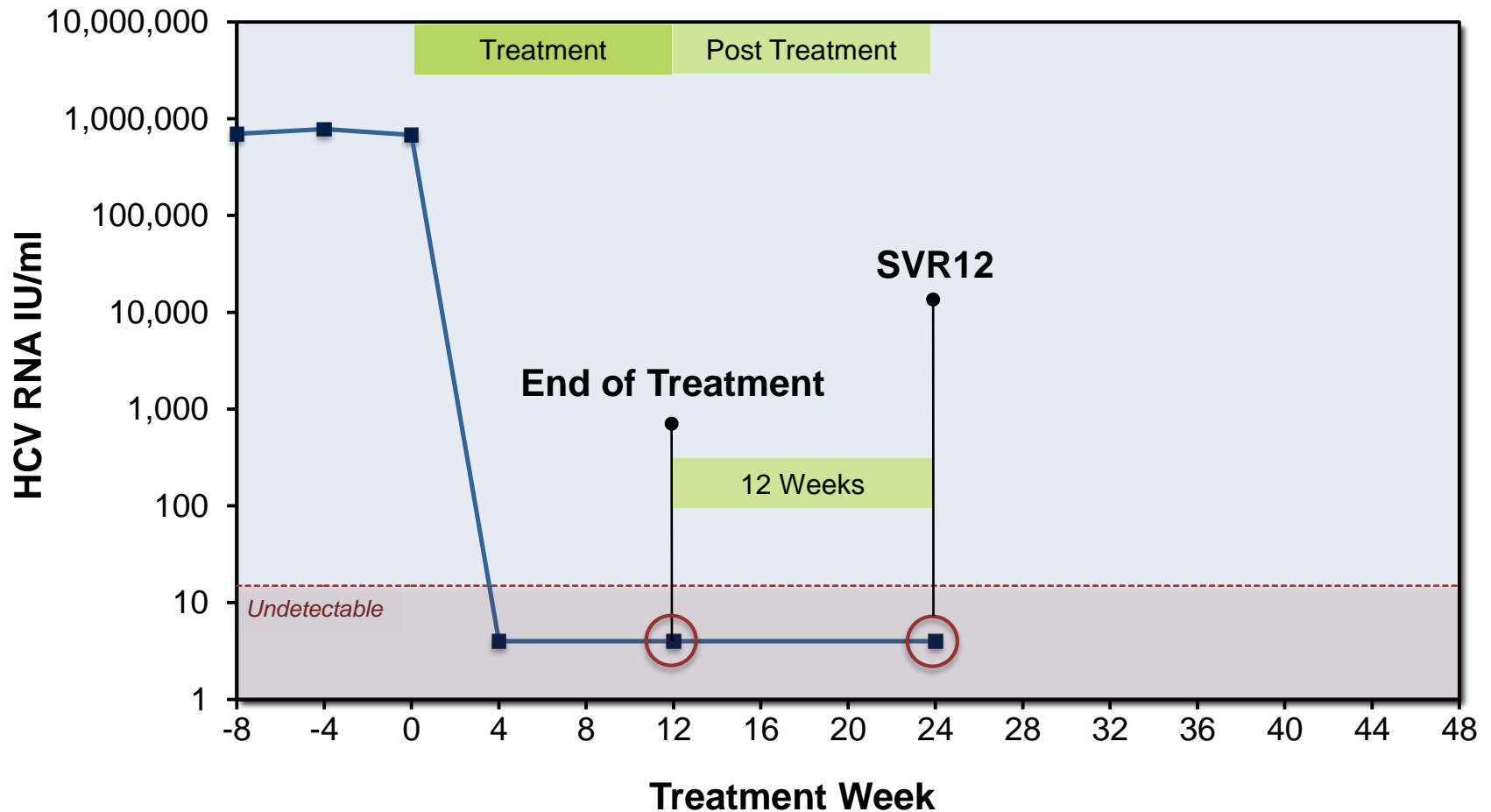
# Background and Definitions

# Treatment of Chronic HCV Genotype 2 Background

- Genotype 2 is second most common HCV genotype in US
- Up to 85% of patients have contraindications for interferon therapy
- Small proportion of untreated patients are genotype 2 today due to historically high treatment and cure rates

# Virologic Responses with HCV Therapy

## Sustained Virologic Response at 12 Weeks Post Therapy (SVR12)



Sustained Virologic Response (SVR12) = Undetectable HCV RNA 12 Weeks Post Treatment

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2

# Initial Treatment

# AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

## Initial Treatment of Patients with Genotype 2 Chronic HCV

### **Genotype 2 HCV: Initial Treatment**

#### **Recommended Regimen, Patients without Cirrhosis**

Sofosbuvir + Ribavirin x 12 weeks

#### **Recommended Regimen, Patients with Cirrhosis**

Sofosbuvir + Ribavirin x 16 weeks

#### **Recommended Regimen, Patients Not Able to Tolerate Ribavirin**

Daclatasvir + Sofosbuvir x 12 weeks (consider 24 weeks with cirrhosis)

# Treatment-Naïve with Genotype 2 Chronic HCV

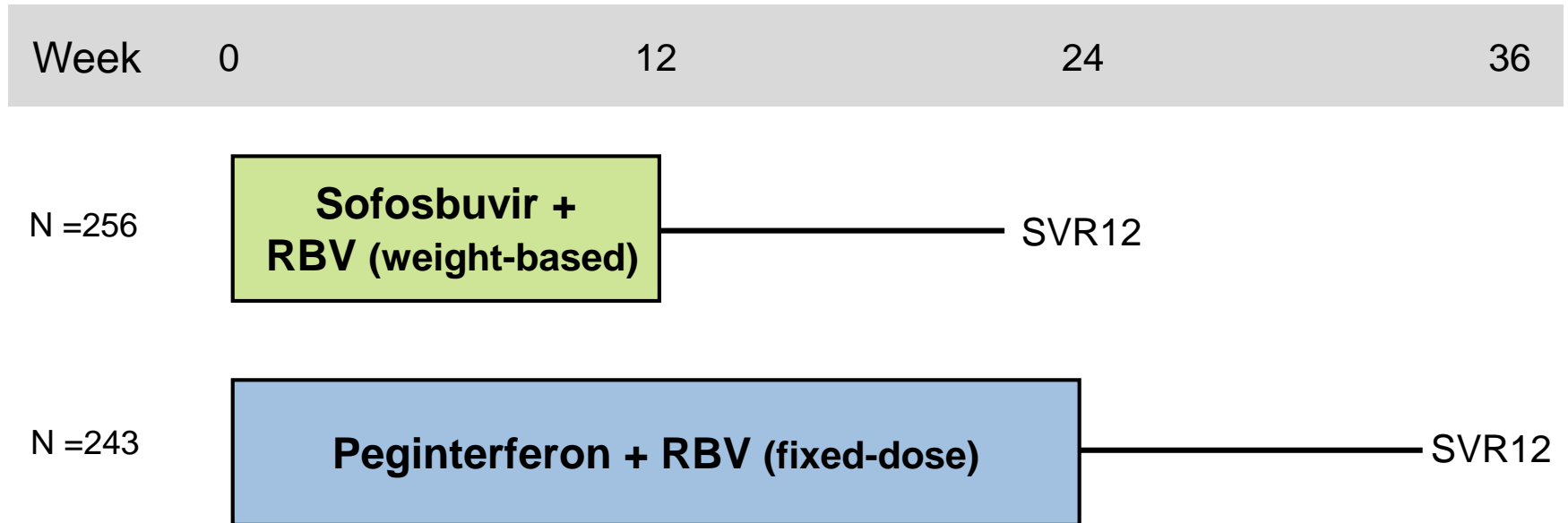
## Key Studies

- **Sofosbuvir + Ribavirin**
  - FISSION
  - POSITRON
  - VALENCE
- **Daclatasvir + Sofosbuvir**
  - A144040
  - ALLY-2



Initial Therapy: Genotype 2  
Sofosbuvir plus Ribavirin

# Sofosbuvir + Ribavirin for Treatment-Naïve HCV GT 2 or 3 FISSION Trial: Design



## Drug Dosing

Sofosbuvir: 400 mg once daily

Peginterferon alfa-2a: 180 µg once weekly

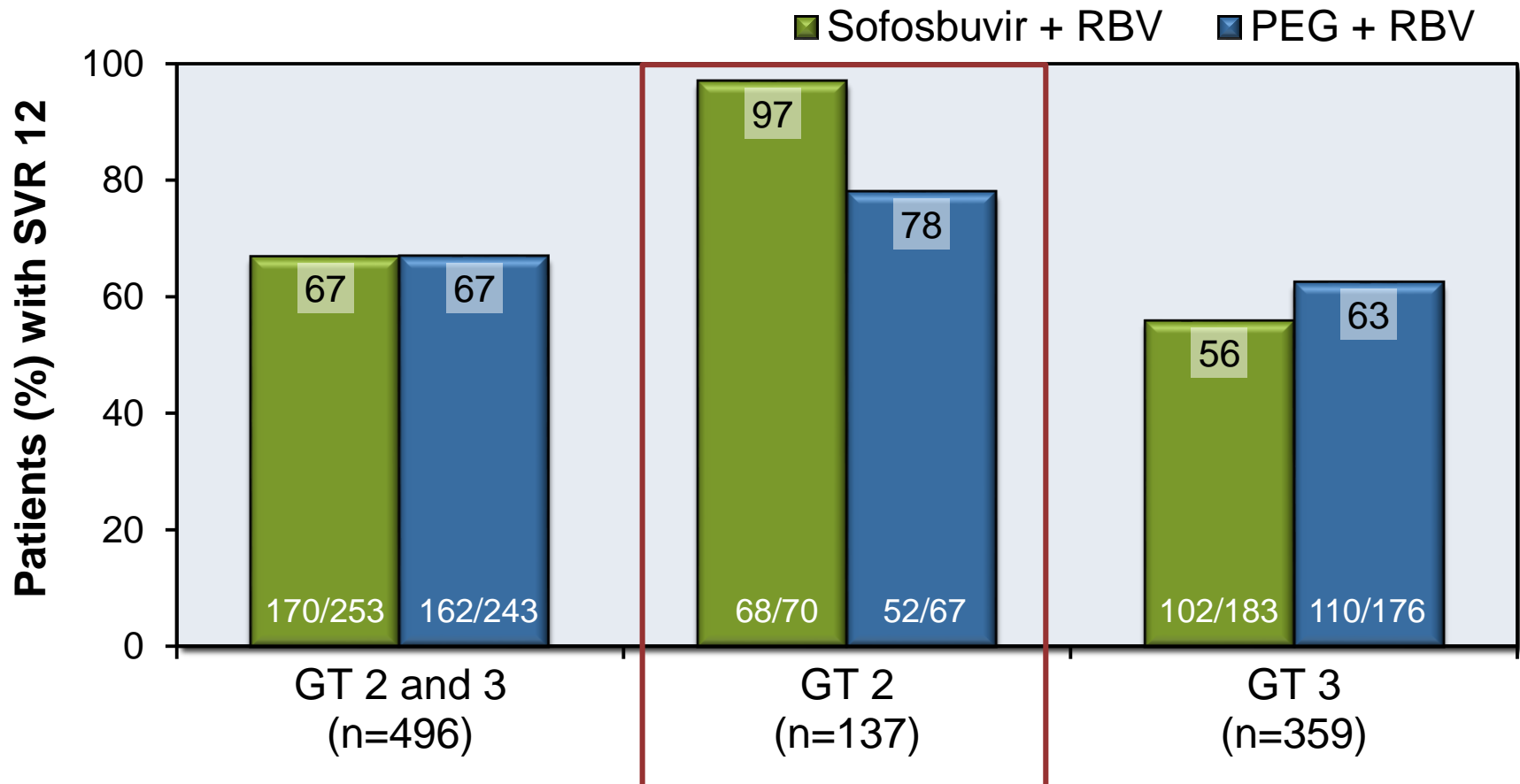
Weight-based Ribavirin (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Fixed-dose Ribavirin (in 2 divided doses): 800 mg/day

# Sofosbuvir + Ribavirin for Treatment-Naïve HCV GT 2 or 3

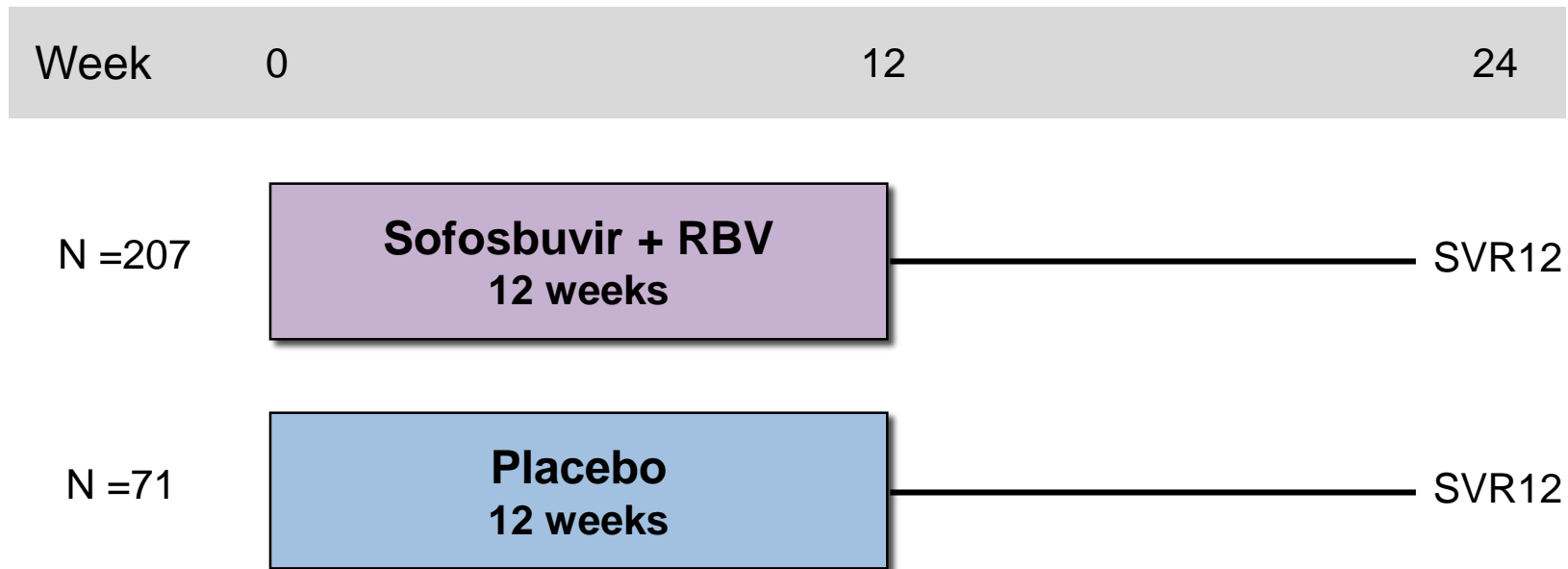
## FISSION Trial: Results

### SVR12 by Genotype



RBV = Ribavirin; PEG = Peginterferon

# Sofosbuvir + Ribavirin for HCV GT 2 or 3 (PEG-IFN not an option) POSITRON Trial: Design



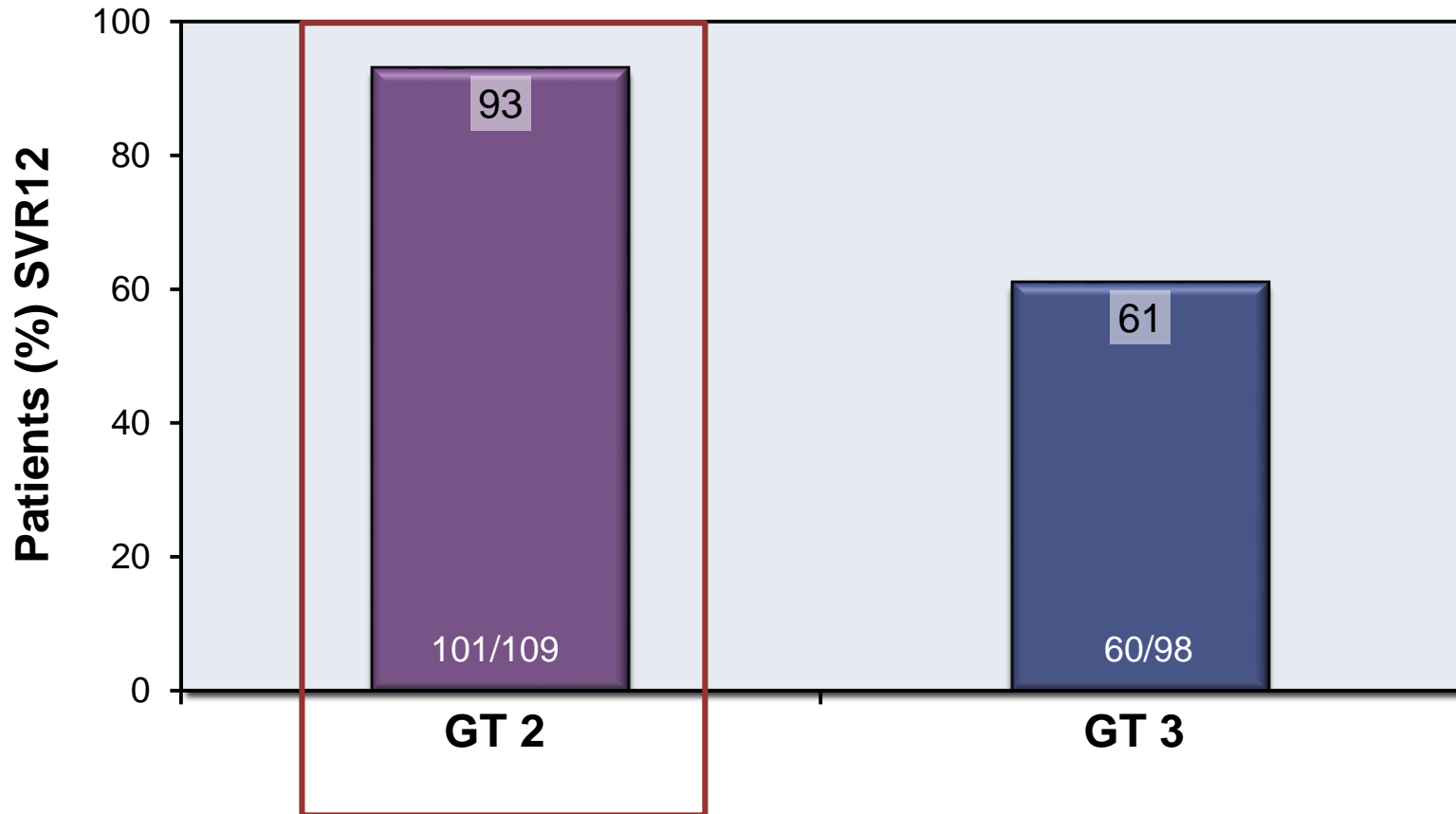
## Drug Dosing

Sofosbuvir: 400 mg once daily

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

# Sofosbuvir + Ribavirin for HCV GT 2,3 (PEG not an option) POSITRON: Results with Sofosbuvir + Ribavirin

## SVR12 by HCV Genotype



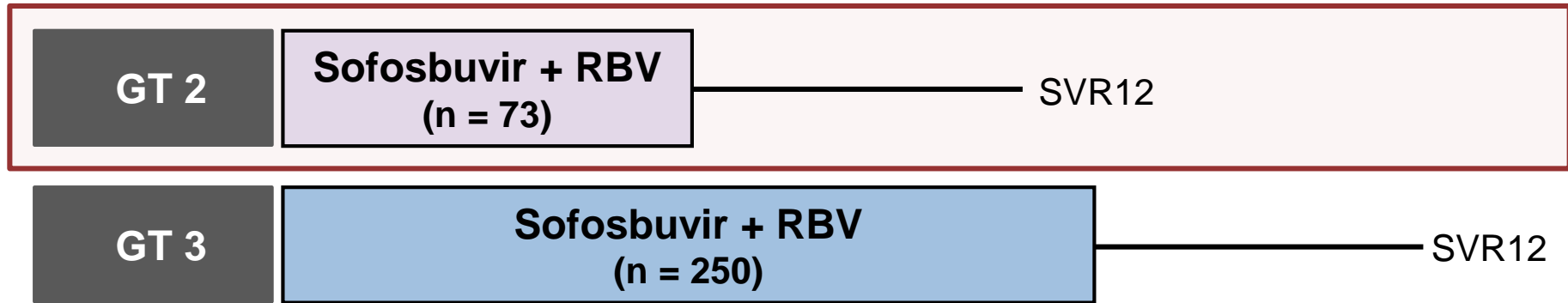
Placebo arm = 0% SVR12

Source: Jacobson I, et al. N Engl J Med. 2013;368:1867-77.

# Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

## VALENCE: Treatment Arms

Week 0 12 24 36



Note: 85 patients enrolled in placebo arm

**Original Study Protocol:** Placebo versus 12 weeks treatment for GT 2 and 3.

**Amended Protocol:** GT3 treatment extended from 12 to 24 weeks; Placebo arm offered alternative treatment

### Drug Dosing

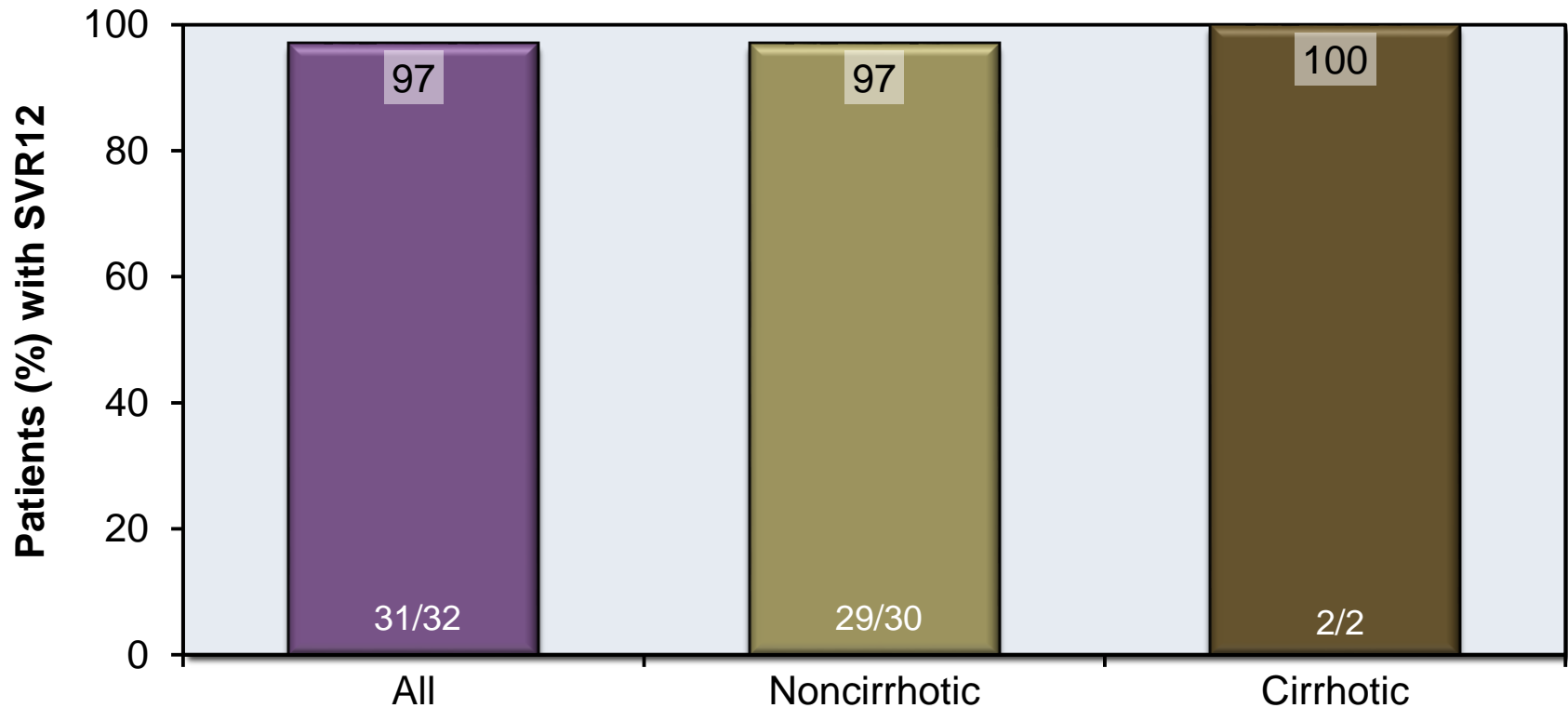
Sofosbuvir 400 mg once daily

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

# Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

## VALENCE: Results for Treatment-Naïve GT 2

### SVR12 for Treatment-Naïve GT 2



Initial Therapy: Genotype 2  
**Daclatasvir plus Sofosbuvir**



# Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 A1444040 Design: Treatment-Naïve 24 Week Rx (Part 1)

Week 0 12 24 36

Rx Naïve  
GT 2 or 3

n = 44

n = 16

SOF × 7 days, then DCV + SOF

SVR12

n = 14

DCV + SOF

SVR12

n = 14

DCV + SOF + RBV

SVR12

Rx Naïve  
GT 1a/1b

n = 44

n = 15

SOF × 7 days, then DCV + SOF

SVR12

n = 14

DCV + SOF

SVR12

n = 15

DCV + SOF + RBV

SVR12

## Drug Dosing

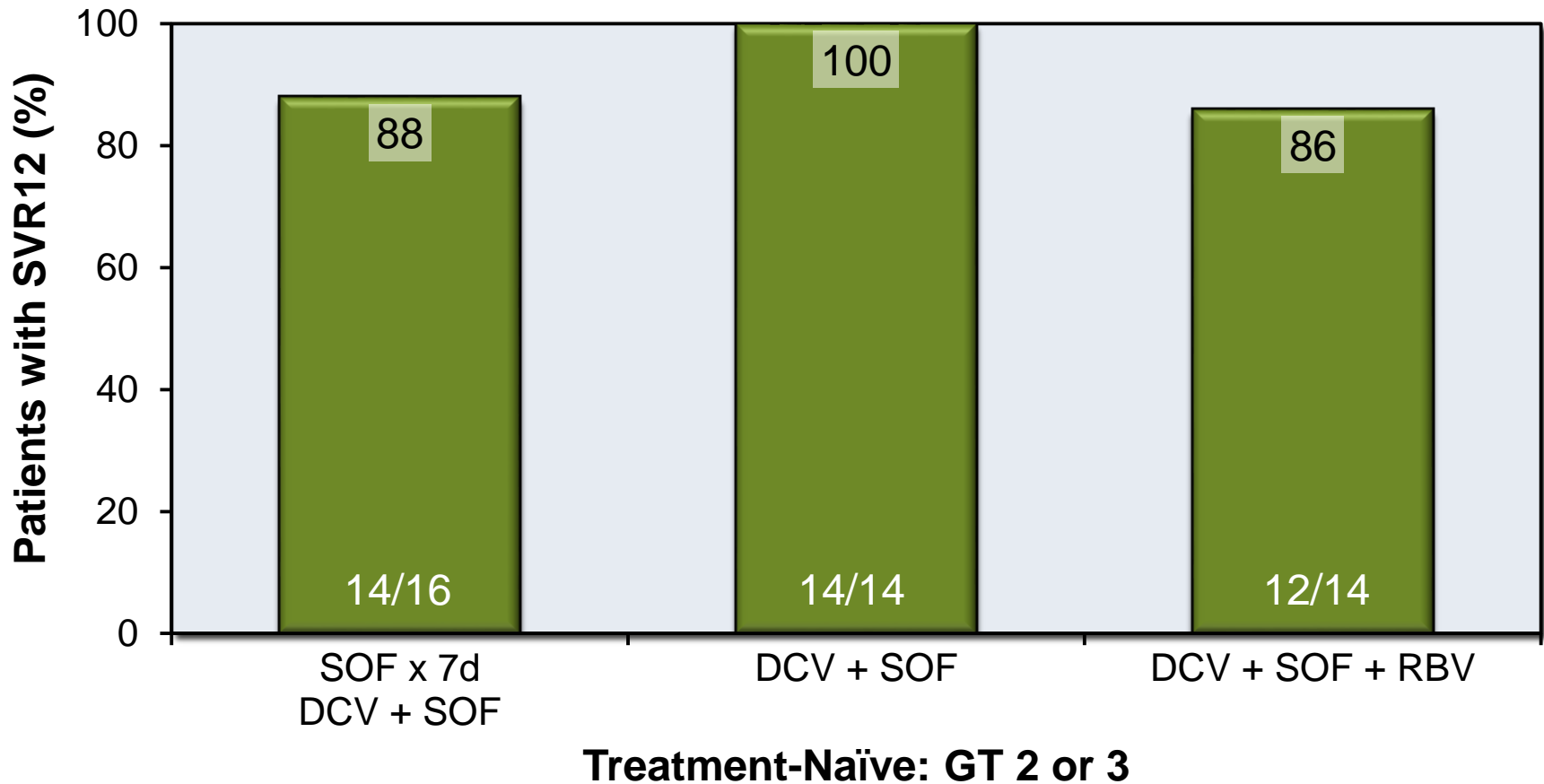
Daclatasvir (DCV): 60 mg once daily

Sofosbuvir (SOF): 400 mg once daily

Ribavirin (RBV): GT1, given weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Ribavirin (RBV): GT 2,3 (800 mg/day)

# Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 Treatment-Naïve 24 Week Rx: Results (Part 1)



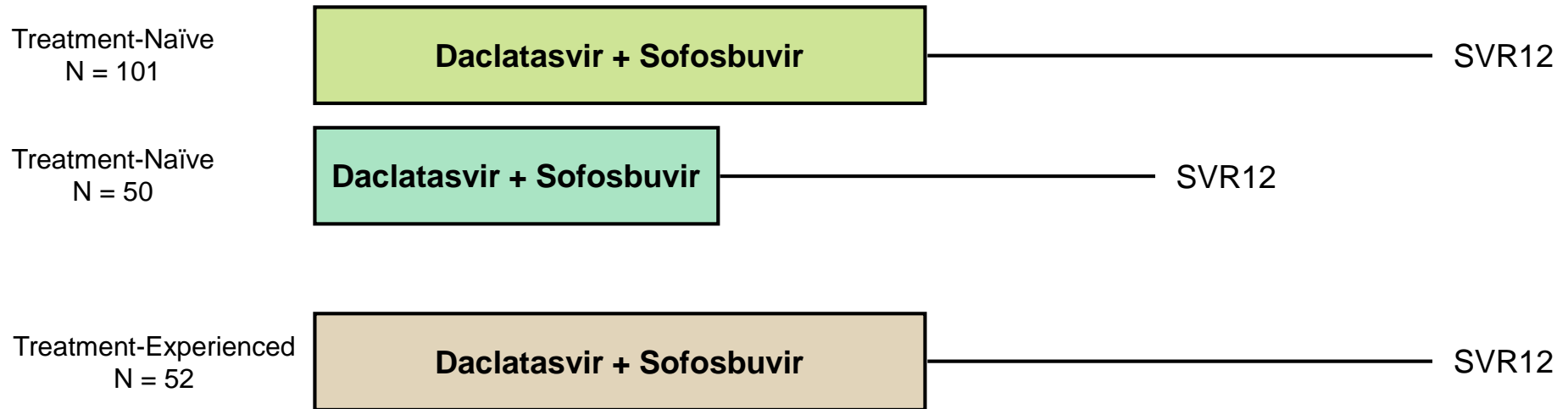
DCV = daclatasvir; SOF = sofosbuvir; RBV = ribavirin

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

# Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection

## ALLY-2 Trial: Design

Week 0 8 12 20 24



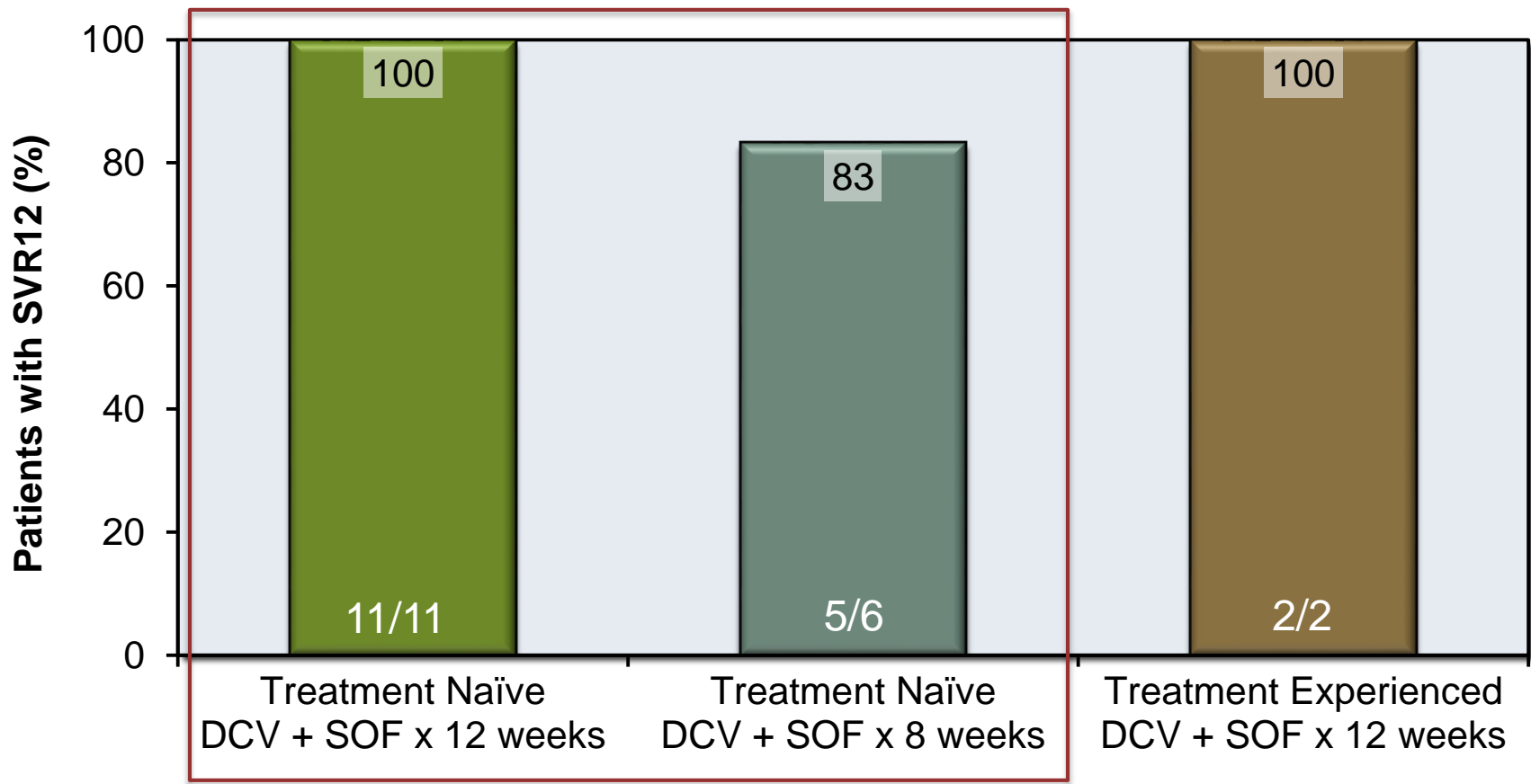
### Drug Dosing

Daclatasvir: 60 mg once daily; with efavirenz and nevirapine the dose was increased to 90 mg once daily and with ritonavir-boosted protease inhibitors the dose was decreased to 30 mg once daily

Sofosbuvir: 400 mg once daily

# Daclatasvir + Sofosbuvir for HCV GT 1-4 and HIV Coinfection ALLY-2 Trial: Results for Genotype 2

## SVR12, Genotype 2



Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Source: Wyles DL, et al. N Engl J Med. 2015;373:714-25.

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2  
Retreatment of Persons in Whom Prior Therapy Failed

# AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

## GT2 HCV: Retreatment of Prior Failure with PR

### Genotype 2 HCV: Retreatment, Prior Failure with Peginterferon + Ribavirin

#### Recommended Regimen

Sofosbuvir + Ribavirin x 16 or 24 weeks\*

#### Alternative Regimen

Sofosbuvir + Ribavirin + Peginterferon x 12 weeks (if patient interferon eligible)

\*The decision to use 16 or 24 weeks should be made on an individual patient basis

AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations  
GT 2 HCV: Retreatment of Prior Failure with SOF + RBV

**Genotype 2 HCV: Retreatment, Prior Failure with Sofosbuvir + Ribavirin**

**Recommended Regimen for Patients NOT Eligible to Receive Interferon**

Daclatasvir + Sofosbuvir +/- Ribavirin x 24 weeks

**Recommended Regimen for Patients Eligible to Receive Interferon**

Sofosbuvir + Ribavirin + Peginterferon x 12 weeks

# AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

## Criteria for Interferon Ineligible

### NOT Eligible to Receive Interferon Defined as one or more of the following:

- Intolerance to interferon
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to peginterferon or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/ $\mu$ L, a baseline platelet count below 90,000/ $\mu$ L or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

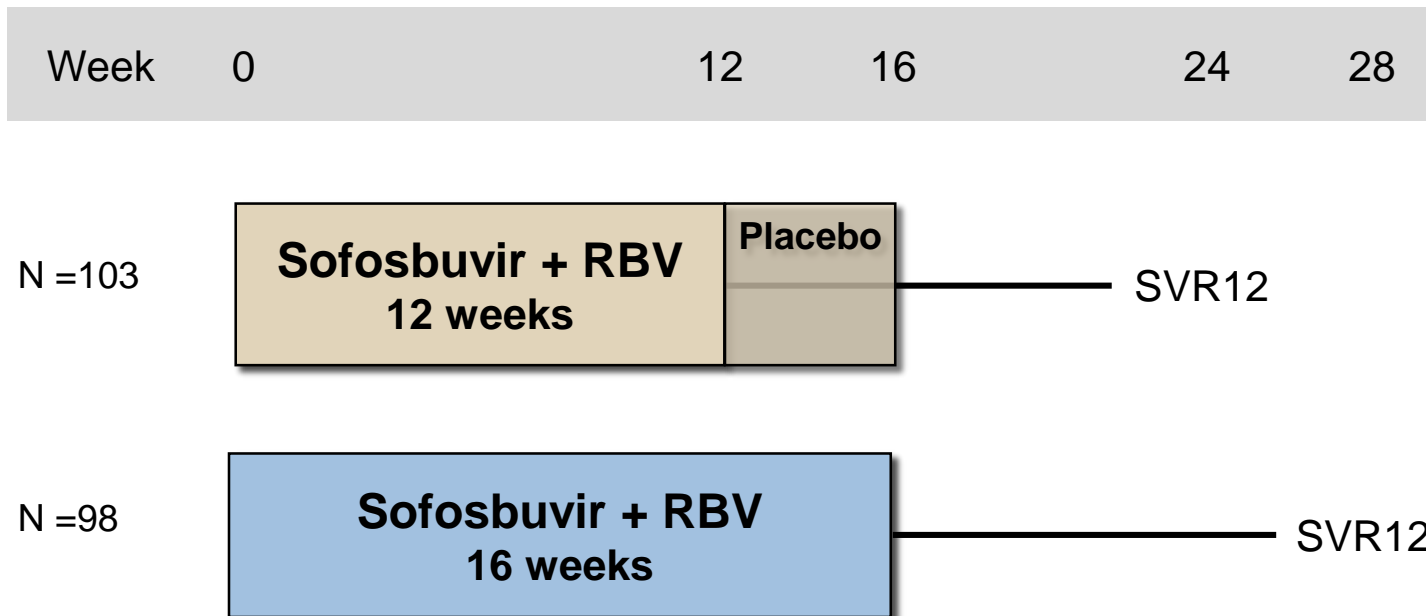


# Retreatment of Genotype 2 Chronic HCV

## Key Studies

- **Prior Failure with Peginterferon + Ribavirin**
  - FUSION
  - VALENCE
  - LONESTAR-2
  - BOSON
- **Prior Failure with Sofosbuvir + Ribavirin**
  - Retreatment of prior Sofosbuvir Failure

# Sofosbuvir + RBV in Treatment-Experienced HCV GT 2 or 3 FUSION Trial: Design



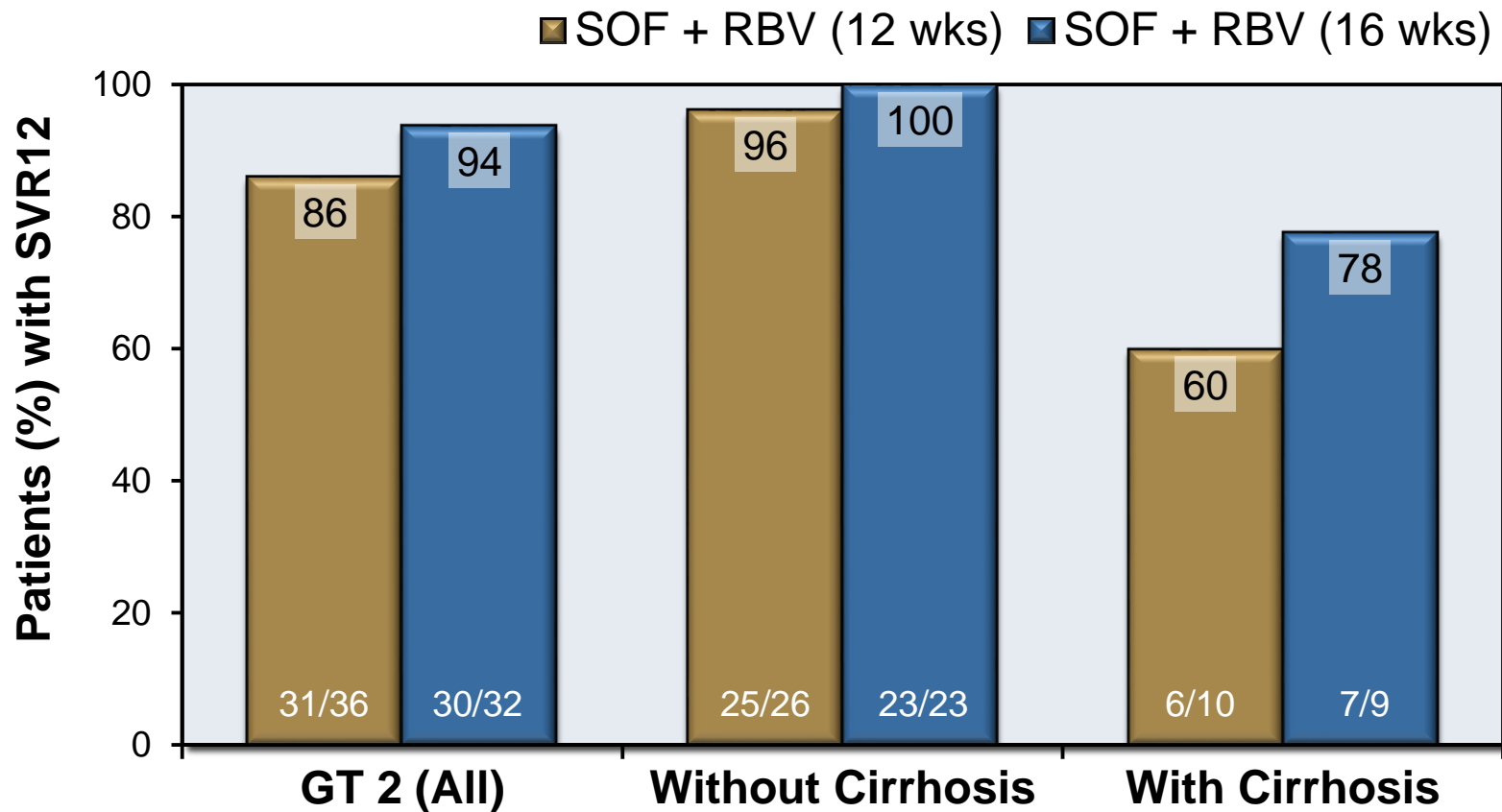
## Drug Dosing

Sofosbuvir: 400 mg once daily

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

# Sofosbuvir + RBV in Treatment-Experienced HCV GT 2 or 3 FUSION Trial: Results for GT2

## SVR12 for Treatment-Experienced GT2



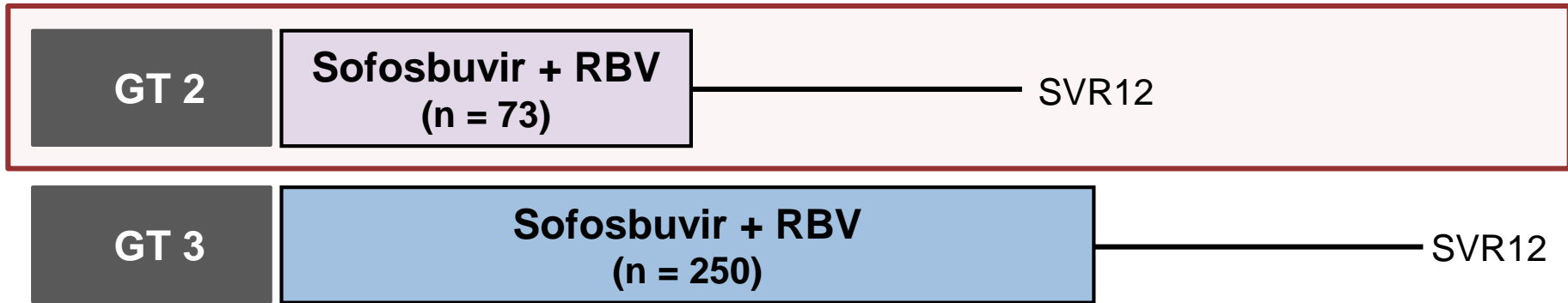
SOF = Sofosbuvir; RBV = Ribavirin

Source: Jacobson I, et al. *N Engl J Med.* 2013;368:1867-77.

# Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

## VALENCE: Treatment Arms

Week 0 12 24 36



Note: 85 patients enrolled in placebo arm

**Original Study Protocol:** Placebo versus 12 weeks treatment for GT 2 and 3.

**Amended Protocol:** GT3 treatment extended from 12 to 24 weeks; Placebo arm offered alternative treatment

### Drug Dosing

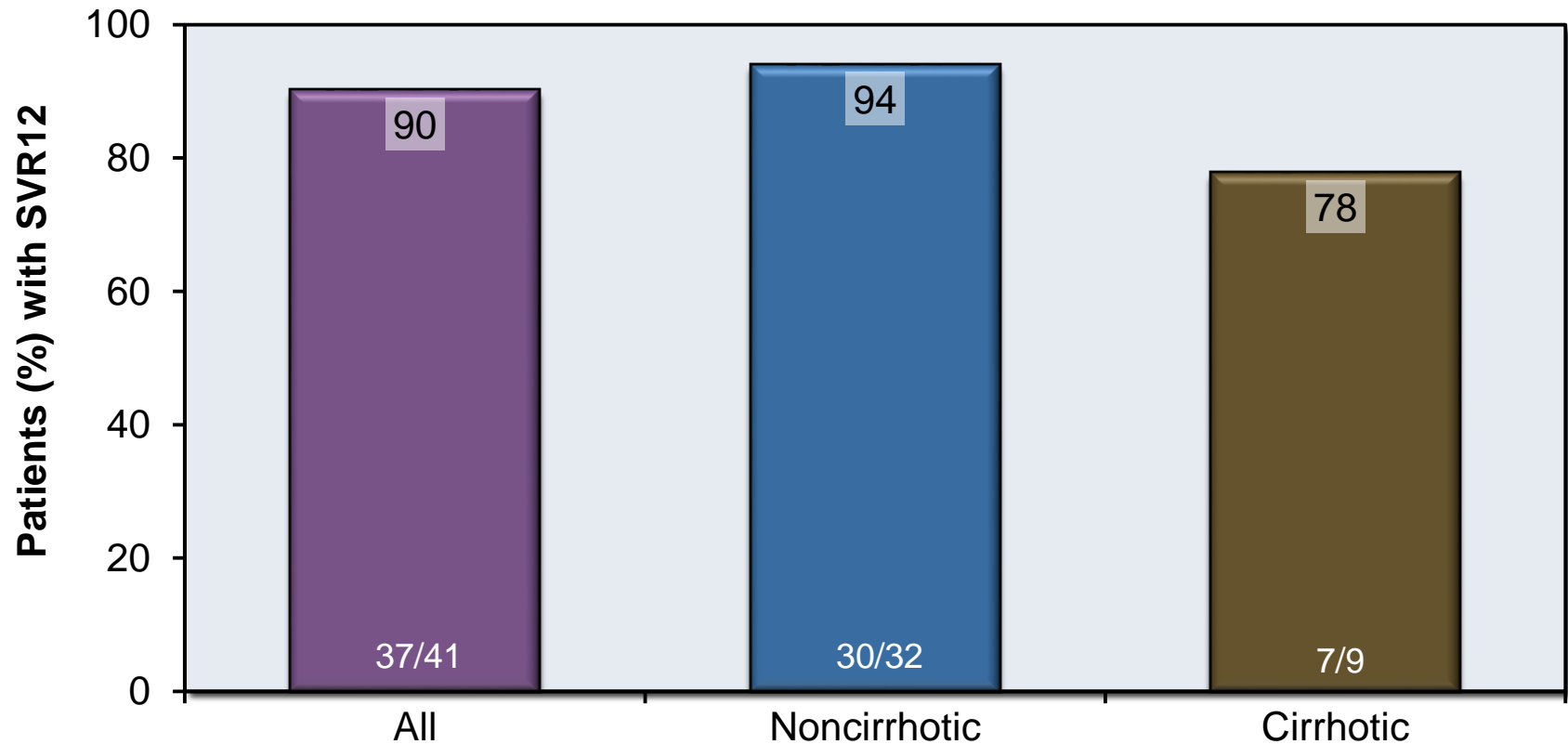
Sofosbuvir 400 mg once daily

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

# Sofosbuvir + Ribavirin for Treatment Naïve & Experienced HCV GT 2 or 3

## Treatment Experienced GT2 : 12 weeks of treatment

### SVR12 for Treatment-Experienced GT 2



# Sofosbuvir + PEG + RBV in Treatment-Experienced HCV GT 2 or 3 LONESTAR-2 Trial: Design

Week

0

12

24

**GT 2 or 3**

N = 47

**Sofosbuvir +  
Peginterferon + Ribavirin**

SVR12

## Drug Dosing

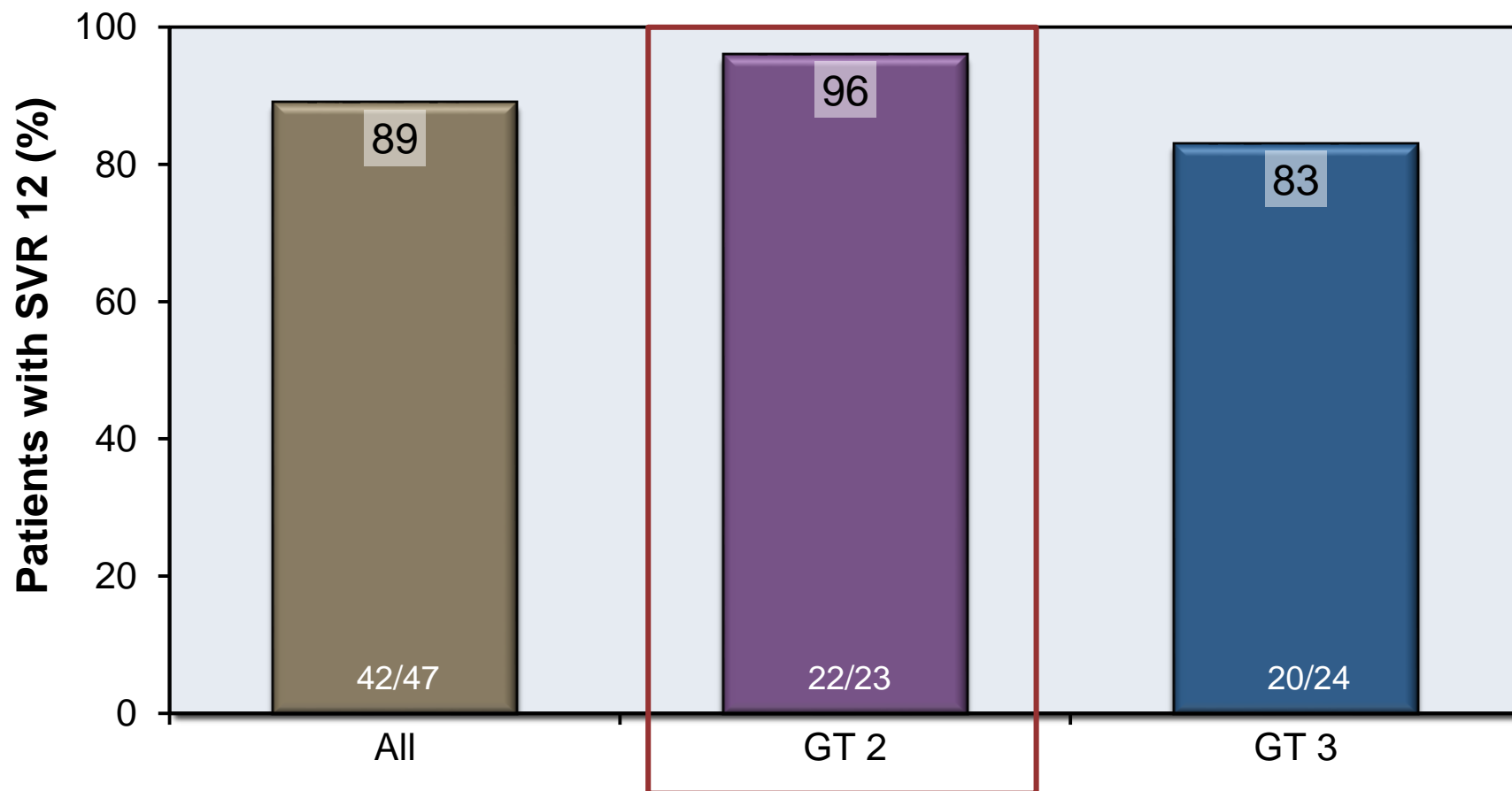
Sofosbuvir: 400 mg once daily

Peginterferon alfa-2a: 180 µg once weekly

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

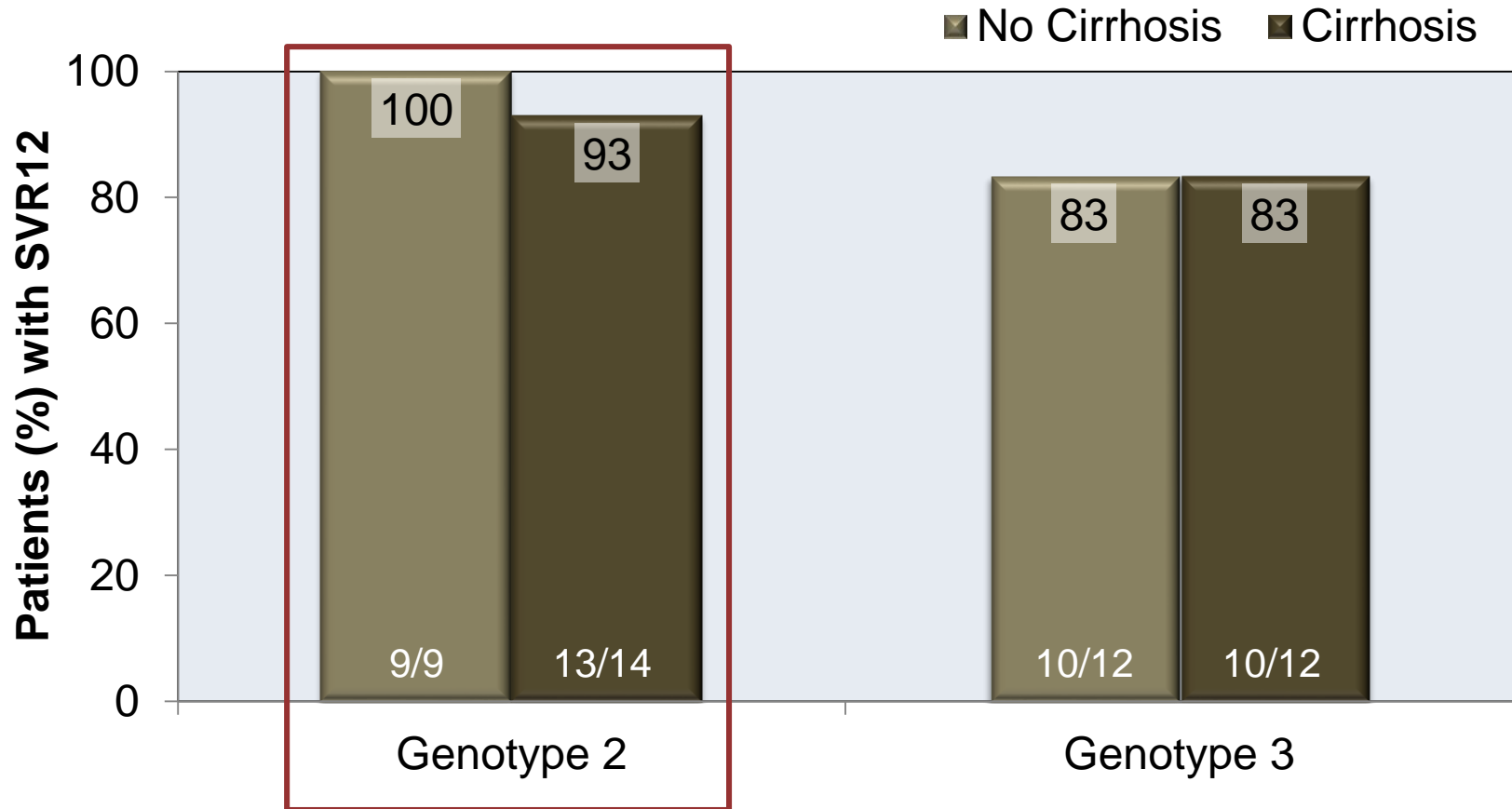
# Sofosbuvir + PEG + RBV for 12 weeks in Treatment-Experienced HCV GT 2 or 3 LONESTAR-2 Trial: Results

## SVR12 in Treatment-Experienced by HCV Genotype



# Sofosbuvir + PEG + RBV for 12 weeks in Treatment-Experienced HCV GT 2 or 3 LONESTAR-2 Trial: Results

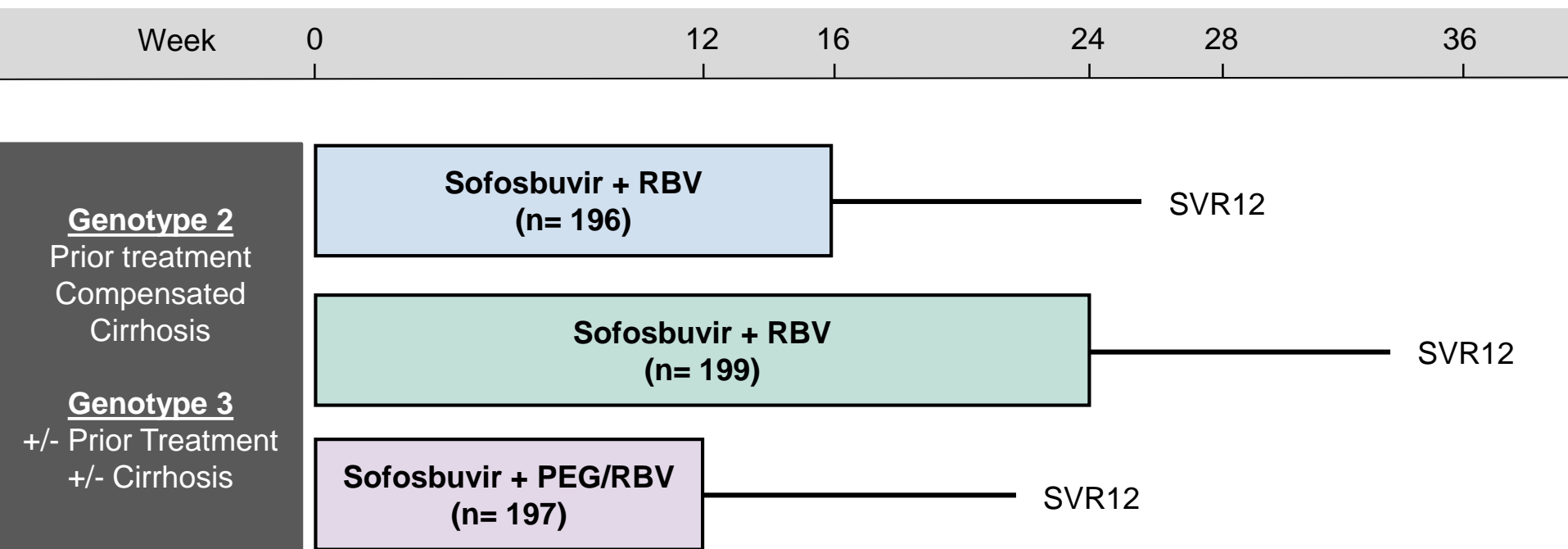
## LONESTAR-2 Trial: SVR12 by Cirrhosis Status





# Sofosbuvir + Ribavirin +/- Peginterferon for HCV GT 2 or 3

## BOSON: Treatment Arms



### Drug Dosing

Sofosbuvir 400 mg once daily

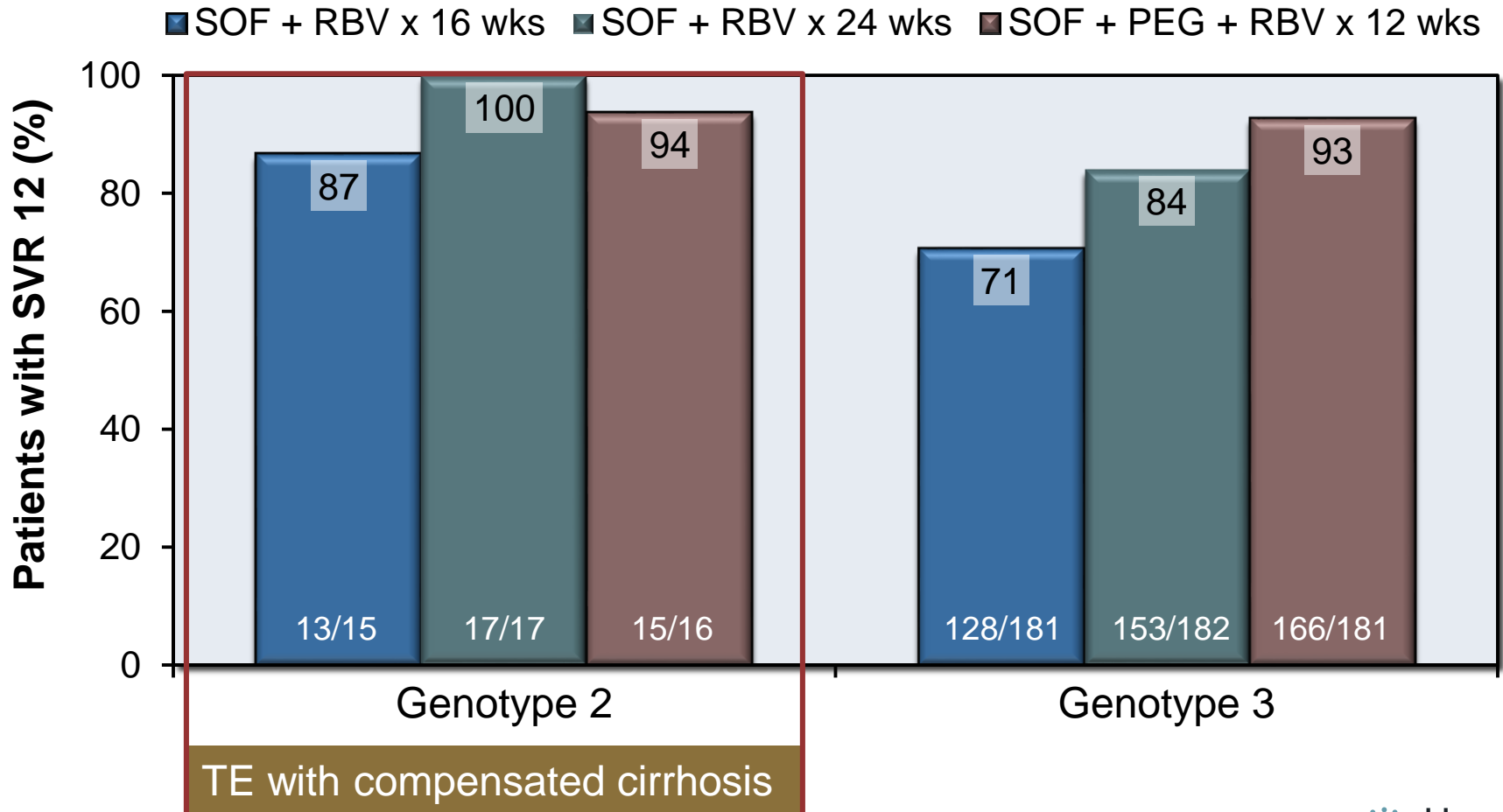
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Peginterferon alfa-2a: 180 ug/week

# Sofosbuvir + Ribavirin +/- Peginterferon for HCV GT 2 or 3

## BOSON: Results

### SVR12 by Regimen and Genotype



# Retreatment of SOF + RBV Failure with SOF-Containing Regimens in GT 2 or 3 Study Design

Week 0 12 24 36

**GT2  
or  
GT3**

N = 34

**Sofosbuvir +  
PEG + RBV**

SVR12

N = 73

**Sofosbuvir + RBV**

SVR12

## Drug Dosing

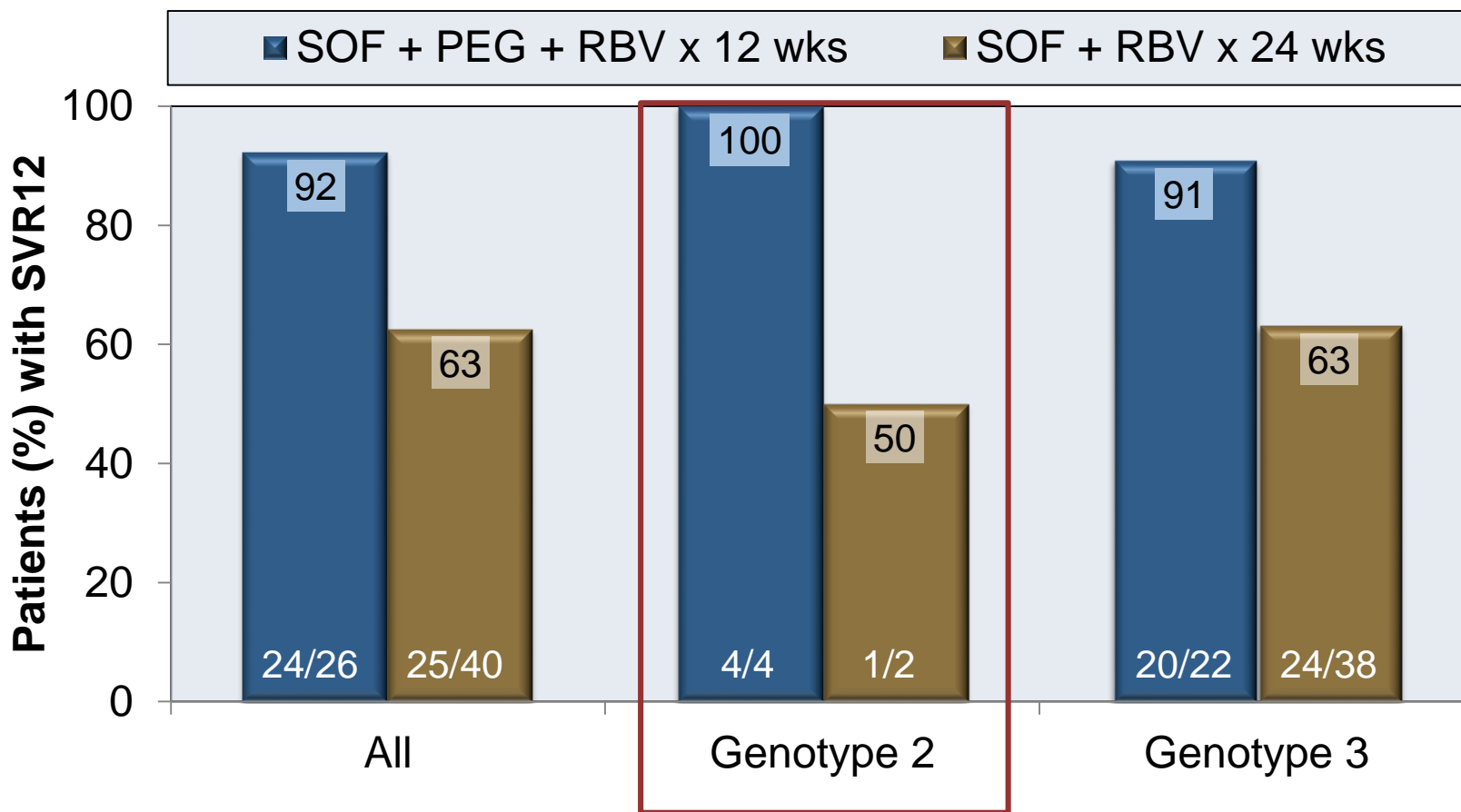
Sofosbuvir: 400 mg once daily

Peginterferon alfa-2a: 180 µg once weekly

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

# Retreatment of SOF + RBV Failure with SOF-Containing Regimens in GT 2 or 3 Preliminary Results, by Genotype

## SVR12 by Regimen and HCV Genotype



TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 2

# Issues and Controversies

# Hepatitis C Genotype 2

## Estimated Medication Costs for Treatment-Naïve & Prior Relapsers

### Patients with GT 2 HCV: Initial Treatment

Recommended Regimen and Duration	AWAC Regimen Cost
Sofosbuvir + Ribavirin x 12 weeks	\$85,000
Sofosbuvir + Ribavirin x 16 weeks	\$113,000
Daclatasvir + Sofosbuvir x 12 weeks	\$147,000
Daclatasvir + Sofosbuvir x 24 weeks	\$295,000

AWAC = Average Wholesale Acquisition Cost

Note: health care systems may receive substantial discounts

# Hepatitis C Genotype 2

## Estimated Medication Costs for Treatment-Naïve & Prior Relapsers

### Patients with GT 2 HCV: Retreatment of Patients with Prior Failure

Recommended Regimen and Duration	AWAC Regimen Cost
Sofosbuvir + Ribavirin x 16 weeks	\$113,000
Sofosbuvir + Ribavirin x 24 weeks	\$170,000
Sofosbuvir + Ribavirin + Peginterferon x 12 weeks	\$97,000
Daclatasvir + Sofosbuvir +/- Ribavirin x 24 weeks	\$295,000

AWAC = Average Wholesale Acquisition Cost

Note: health care systems may receive substantial discounts

# Treatment of Genotype 2 Chronic HCV

## Issues and Controversies

- Cost of Therapy: what is actual discounted cost and is there a need to wait for price competition?
- With cure rates as high as 96%, are we over-treating most patients by treating patients for 12-24 weeks?
  - ❖ Can we shorten therapy to 4 or 6 weeks to save treatment costs?
  - ❖ Can we revitalize response guided therapy or find pretreatment predictors of SVR with short therapy?
- When to Defer or Decline Therapy:
  - ❖ Decisions on when to warehouse?
  - ❖ Based on mild histology or lack of evidence of systemic disease
  - ❖ Short lifespan
  - ❖ Noncompliance
- (Non) Role of IL-28b Testing, now obviated
- For treatment purposes, liver fibrosis staging primarily used to meet insurance requirements and determine HCC surveillance strategy



# HCV Therapy for Genotype 2 Chronic HCV Cost Analysis Based on Cost per SVR

Patient Characteristics	Regimen Options	SVR	Cost per SVR
Naïve, no cirrhosis	SOF + RBV x 12 wks	92-98%	\$95,263
Naïve, cirrhosis	SOF + RBV x 16 wks	91-94%	~\$154,658
Treatment experienced, no cirrhosis	SOF + RBV x 12 wks	91-96%	\$96,276
Treatment experienced, cirrhosis	SOF + RBV x 16 wks	78%	\$154,658
	SOF + PEG + RBV x 12 wks	93%	\$113,269

Source for Figure: Camilla Graham, MD, MPH. Beth Israel Deaconess Medical Center

Data Sources: (1) Lawitz E, et al. NEJM 2013; 368:1878-87.

(2) Jacobson I, et al. NEJM 2013; 368:1867-77.

(3) Antiviral Drugs Advisory Committee Meeting, FDA and Gilead reviews, 10/25/2013.

(4) Package Insert, Gilead.com 12/7/2013.

# How is cost of therapy impacting treatment decisions?

HEPATITIS C: GENOTYPE 2

# Treatment Regimens Under Study

# Possible Future Regimens for GT-2

- **Unlikely**
  - ❖ Ledipasvir-Sofosbuvir
  - ❖ Ombitasvir-Paritaprevir-Ritonavir
  
- **Likely**
  - ❖ ABT-493 plus ABT-450
  - ❖ Regimens with 5816

**Treat now or defer therapy?**

# Factors Favoring Urgent GT2 Treatment

- Advanced Fibrosis (F3-F4)
  - Platelet count  $< 150,000/\mu\text{L}$
  - Large spleen and/or portal vein
  - Esophageal varices
- Synthetic dysfunction, decompensated disease
- Systemic disease
  - Cryoglobulinemia ([+] Rheumatoid Factor)

# Summary Points for Treatment of Chronic HCV GT-2

- Genotype 2 highly responsive to 12 weeks of all-oral therapy
- Relatively little retreatment data since high SVR rates with therapy in naïve patients
- Few GT2 studies moving forward with new therapies
- Will be difficult to enroll large studies required for licensing trials
- New pangenotypic drugs will be used for genotype 2 off-label (prediction)

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](http://www.hepatitisc.uw.edu)

Hepatitis Web Study

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

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