

# Sofosbuvir

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Antiviral Drugs Advisory Committee  
Meeting

October 25, 2013

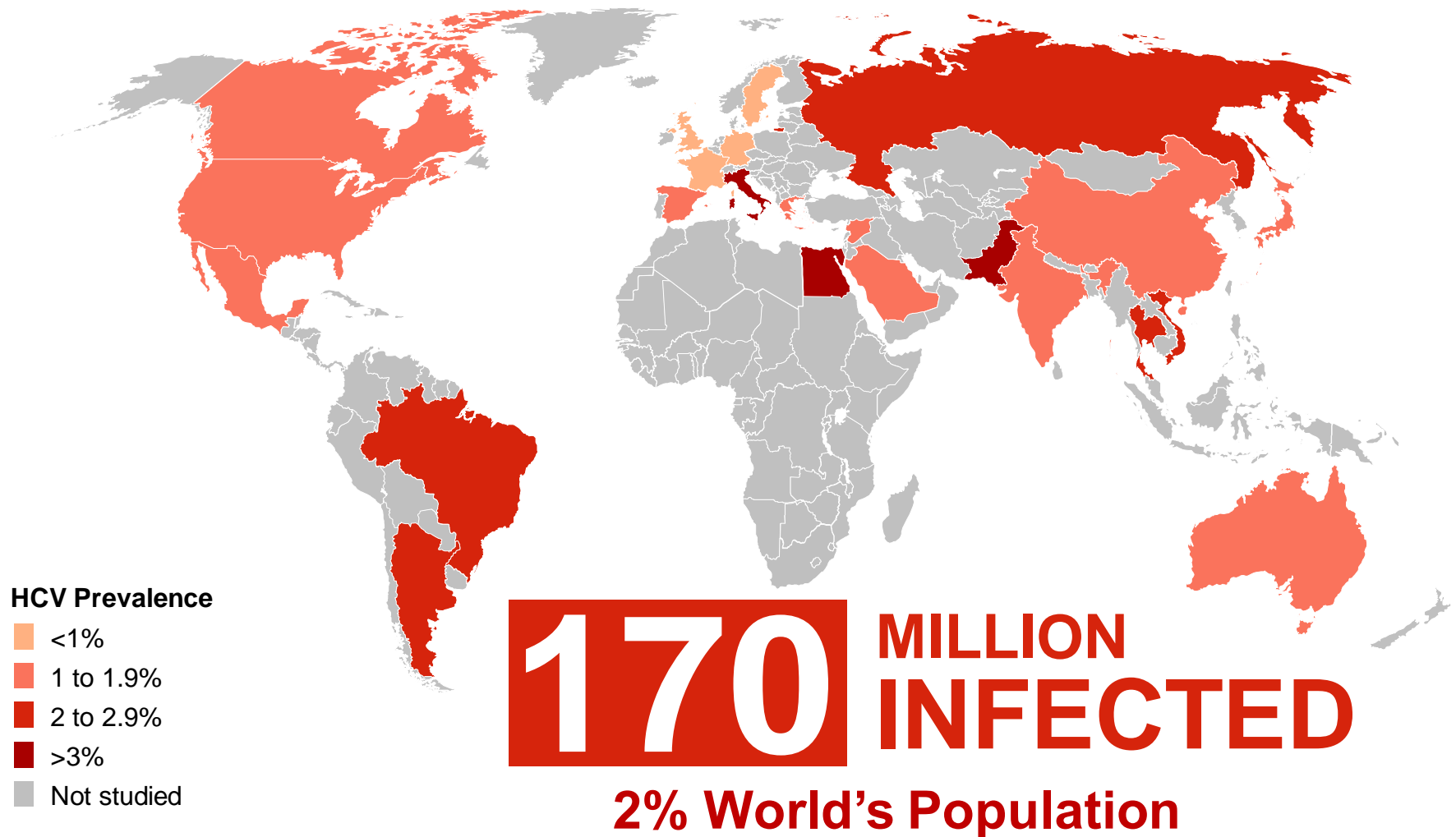
NDA 204671

# Introduction

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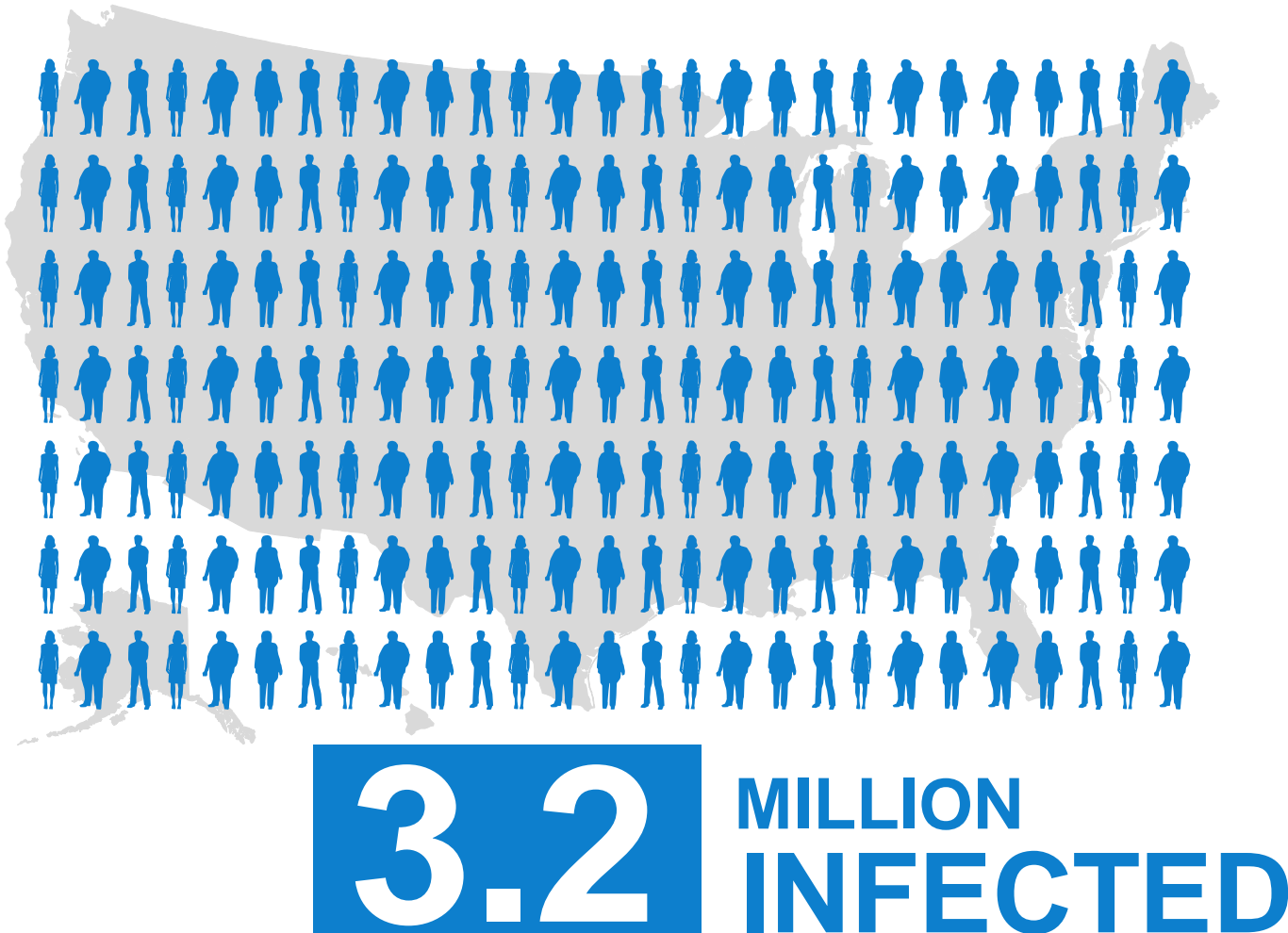
John McHutchison, MD  
Sr. Vice President, Liver Diseases  
Gilead Sciences

# The Global Burden of Disease Due to HCV



# The Burden of Disease Due to HCV: US

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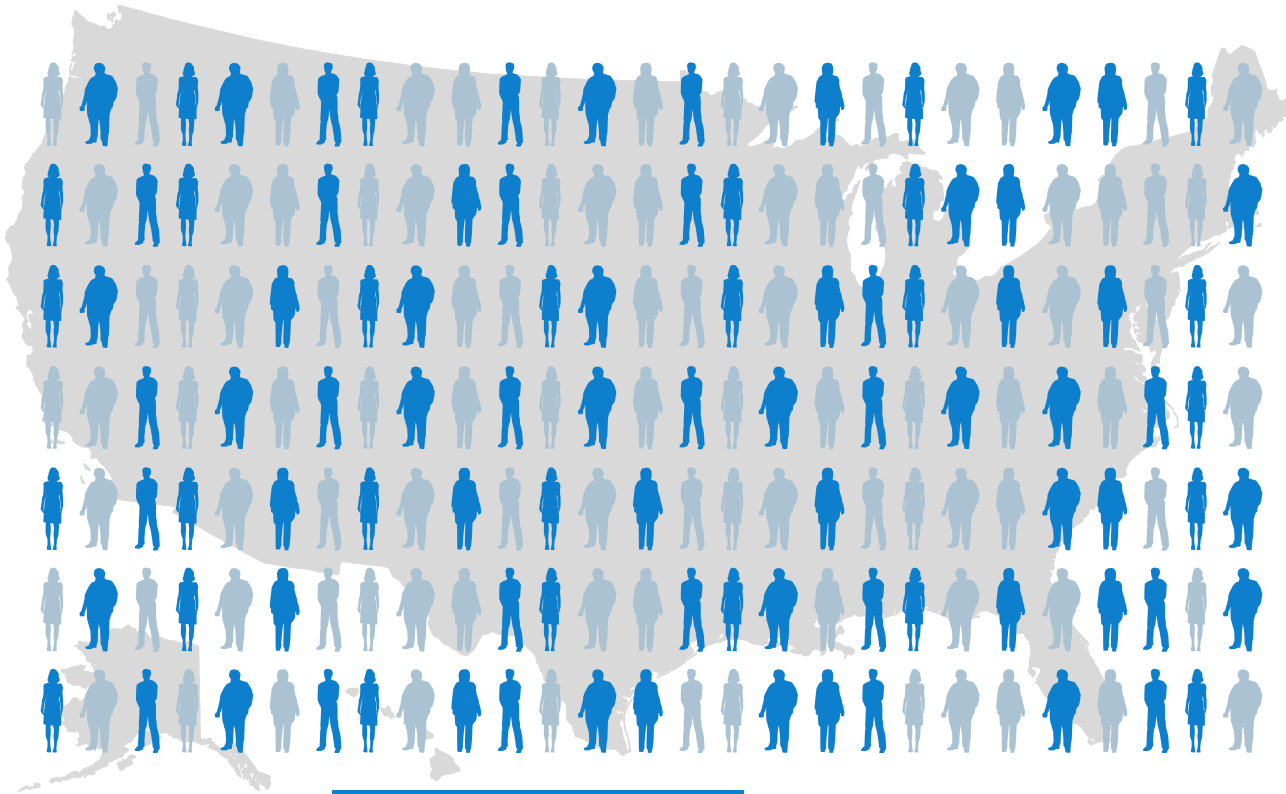
Amstrong GL, et al. *Ann Intern Med.* 2006;144:705-714;  
Holmberg SD, et al. *N Engl J Med.* 2013;368:1859-1861.

**CC-4**

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# Many Patients Have Not Been Diagnosed

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**50%** are **DIAGNOSED**

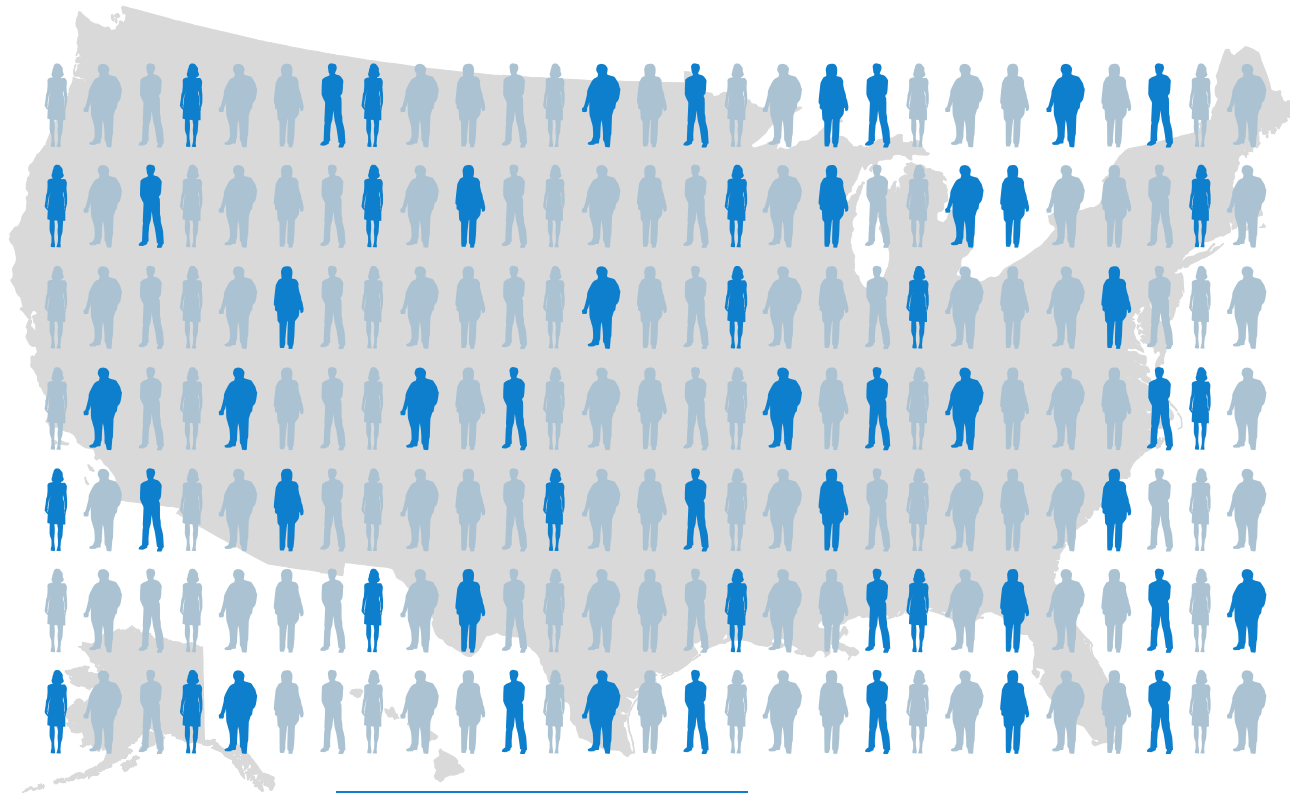
Holmberg SD, et al. *N Engl J Med*. 2013;368:1859-1861;  
Kershenobich C, et al. *Liver Int*. 2011;31(suppl 2):4-17.

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# One in Three Patients Cannot Currently Be Treated

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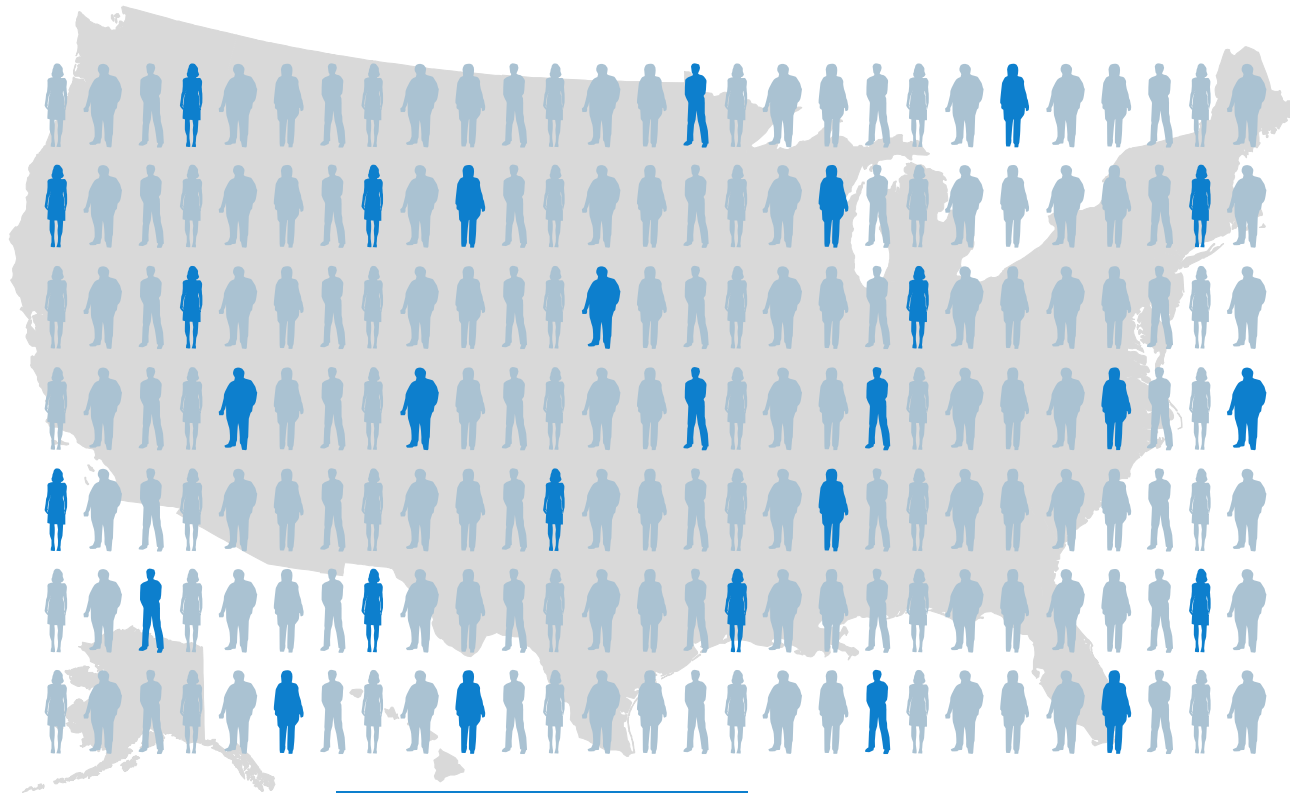
Of the diagnosed, **30%** are **INELIGIBLE** for current treatment

Muir AJ, Provenzale D. *J Clin Gastroenterol*. 2002;34:268-271;  
Falck-Ytter Y, et al. *Ann Intern Med*. 2002;136:288-292;  
Volk ML, et al. *Hepatology*. 2009;50:1750-5.

**CC-6**

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# Only a Minority of Patients Are Currently Treated

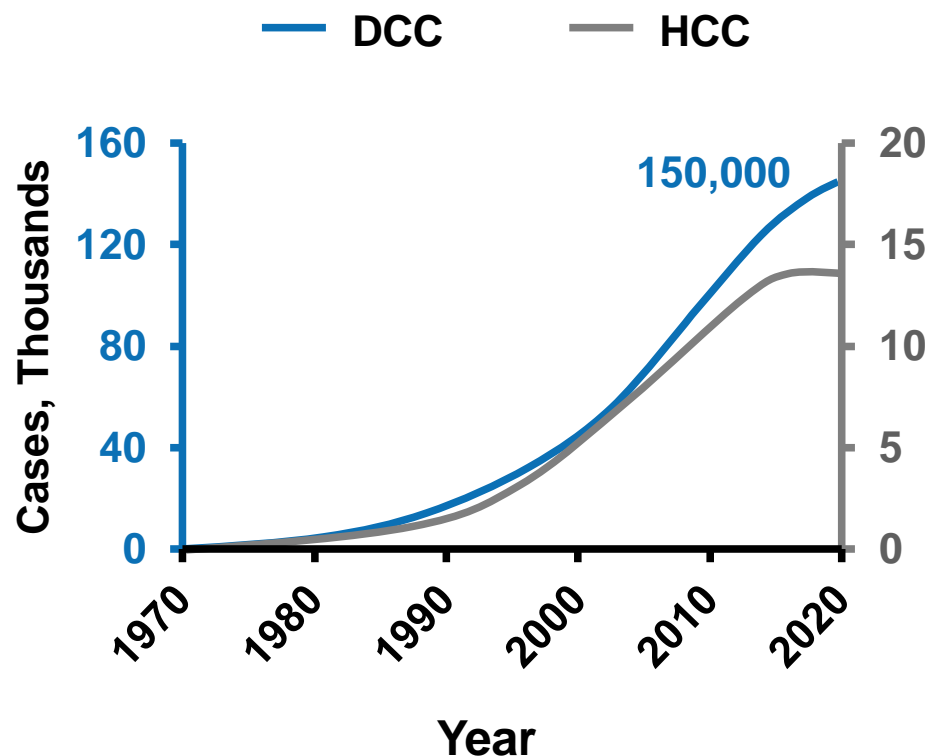
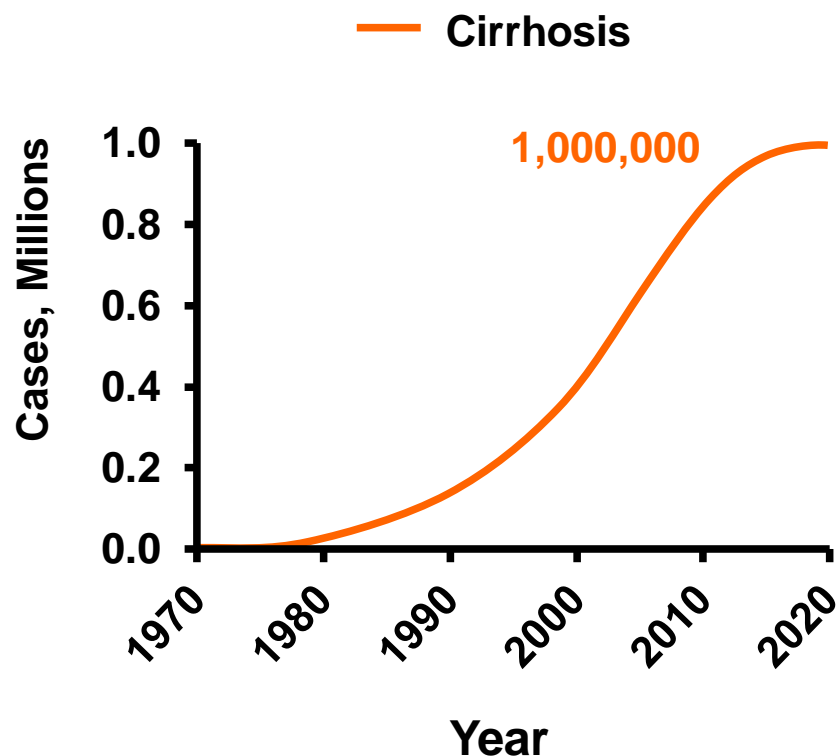


Less than

**15%** are  
**TREATED**

# The Burden of Disease Due to HCV

## Forecasted Prevalence of Liver Disease Complications in the US

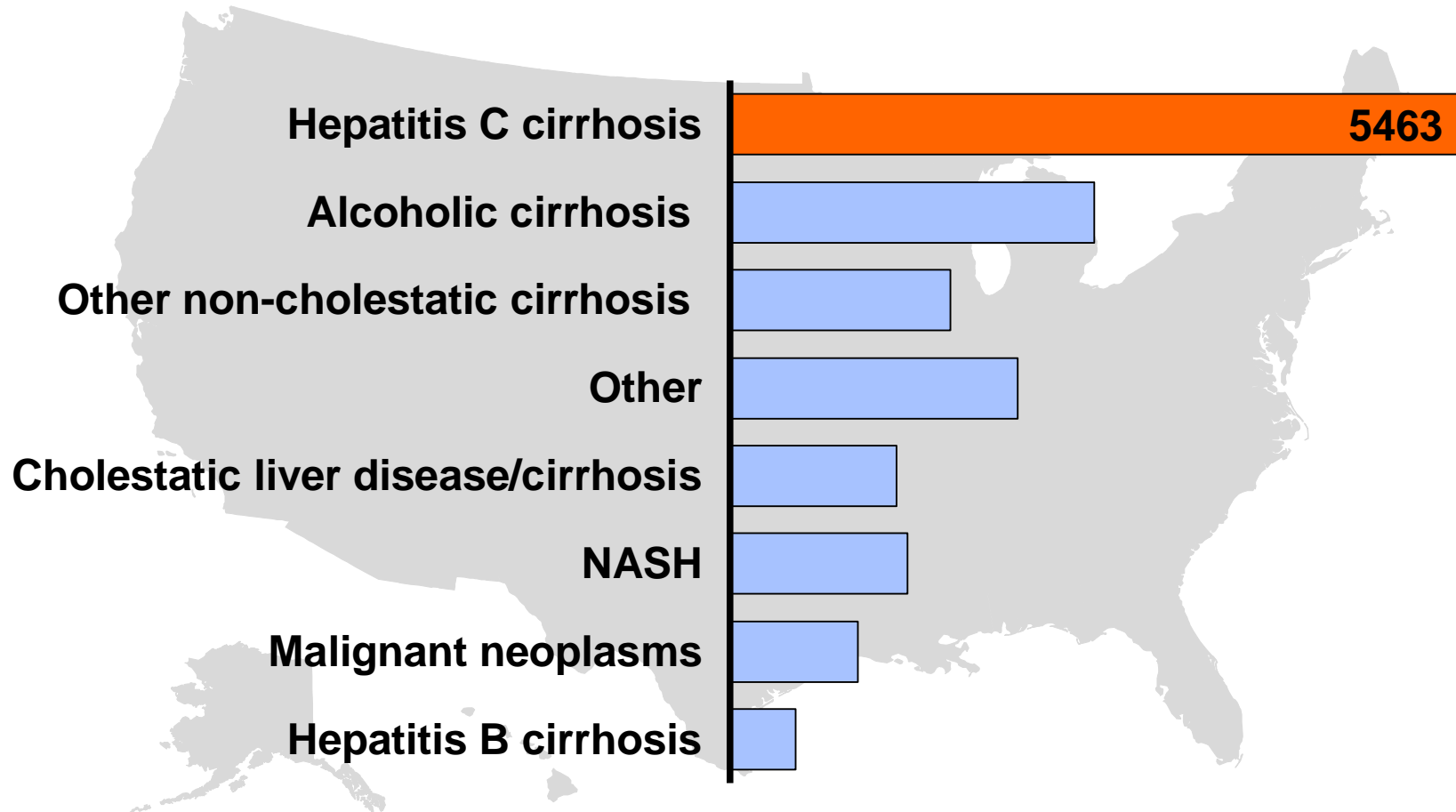


DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma.  
Davis GL, et al. *Gastroenterology*. 2010;138:513-521.



# HCV-Related Morbidity Is the Primary Indication for Liver Transplant in the US

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NASH=nonalcoholic steatohepatitis.

Numbers represent patients who are transplant candidates waiting at more than one center.

<http://optn.transplant.hrsa.gov/latestData/rptData.asp>; Accessed Aug. 23, 2013.

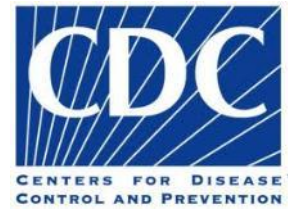
# Hepatitis C Public Health Initiatives



INSTITUTE OF MEDICINE  
OF THE NATIONAL ACADEMIES

**2010<sup>1</sup>**

- ◆ Underappreciated health concern
- ◆ 15,000 preventable deaths per year
- ◆ Improve awareness, diagnosis, and access to care



**2012<sup>2,3</sup>**



**2013<sup>4</sup>**

- ◆ One-time testing and linkage to care for infected persons born during 1945–1965

1. IOM (Institute of Medicine). Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C. 2010.
2. CDC VitalSigns. May 2013. Available at: [www.cdc.gov/vitalsigns/HepatitisC/](http://www.cdc.gov/vitalsigns/HepatitisC/).
3. Morgan, RL, et al. *Ann Int Med*. 2013;158:329-337.
4. US Preventive Services Task Force. Screening for hepatitis C virus infection in adults. 2013. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf/uspshcpc.htm>.

# Confirmed Link Between SVR and Short-Term Benefits

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## RNA Suppression

Swain MG, et al. *Gastroenterology*. 2010;139:1593-1601.  
Maylin S, et al. *Gastroenterology*. 2008;135:821-829.



## ALT Normalization

George SL, et al. *Hepatology*. 2009;49:729-738.



## Quality of Life Improvement

Spiegel BM, et al. *Hepatology*. 2005;41:790-800.



## Histological Benefit

Poynard T, et al. *Gastroenterology*. 2002;122:1303-1313.

# Confirmed Link Between SVR and Clinical Outcomes

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## Mortality

### All cause

Backus LI, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516.

### Liver related or liver transplantation

Alberti A. *Liver Int*. 2011;31:18-22.

van der Meer AJ, et al. *JAMA*. 2012; 308:2584-2593.

### HCC related

Morgan RL, et al. *Ann Intern Med*. 2013;158:329-337.



## Hepatocellular Cancer

Morgan RL, et al. *Ann Intern Med*. 2013;158:329-337.

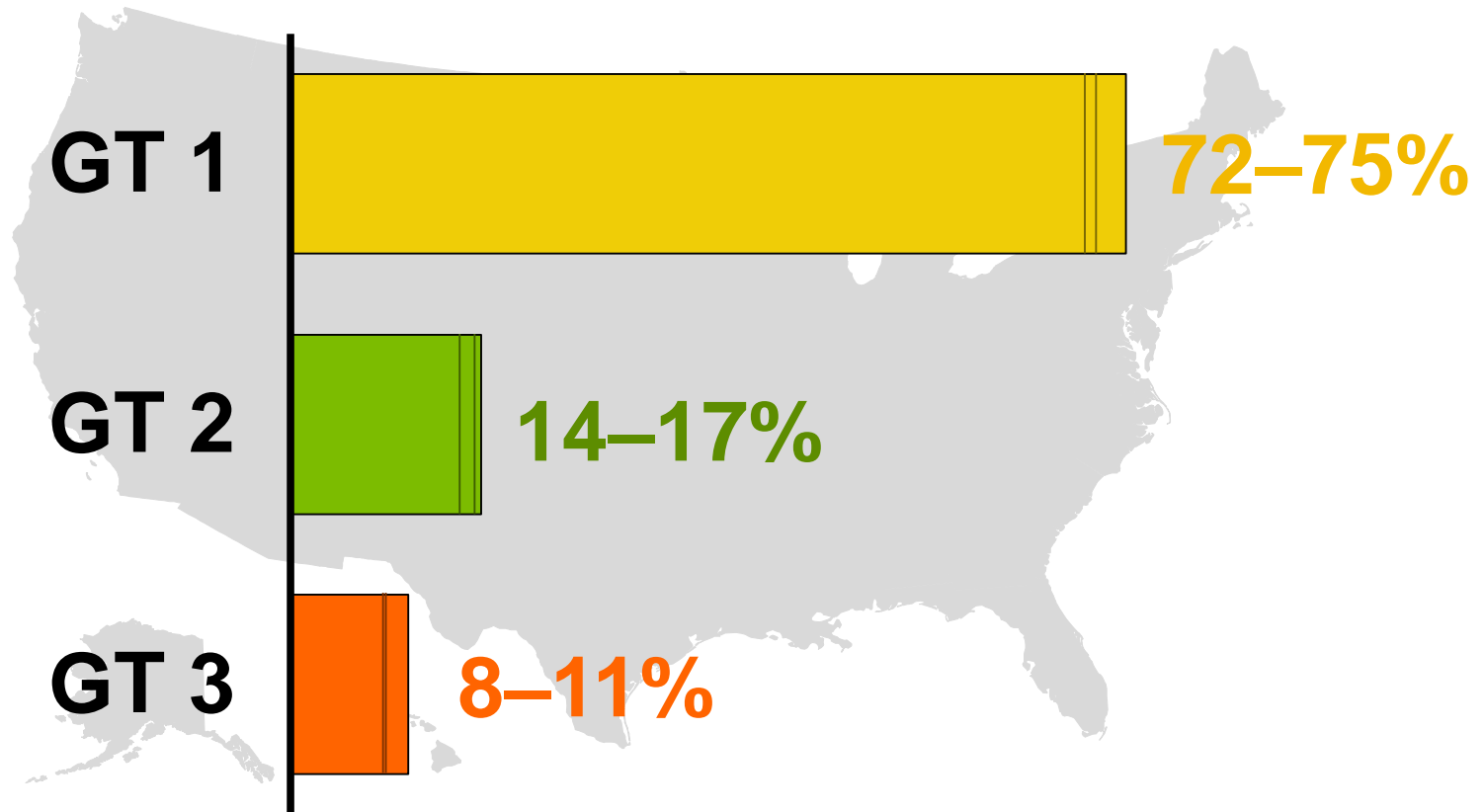


## Decompensation

Bruno S, et al. *Hepatology*. 2010;51:2069-2076.

# Prevalence of HCV Genotypes in the US

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1. Nainan OV, et al. *Gastroenterology*. 2006;131:478-484.
2. Blatt LM, et al. *J Viral Hepat*. 2000;7:196-202.
3. Backus LI, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516.

# Current Standard of Care for GT 2 or 3

## Practice Guidelines



**Genotype 2 or 3 HCV**  
**PEG/RBV**  
**24 weeks of treatment<sup>1-3</sup>**  
**GT 2 SVR: 71–75%**  
**GT 3 SVR: 61–66%**

### ◆ Limitations

- Long duration of treatment
- Requires weekly injection
- No effective regimen for patients who have failed prior therapy

1. Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.
2. Shiffman ML, et al. *N Engl J Med*. 2007;357:124-134.
3. Marcellin P, et al. *Hepatology*. 2012;56:2039-2050.

# Current Standard of Care for GT 1

## Practice Guidelines



**Genotype 1 HCV**  
**HCV PI + PEG/RBV<sup>a</sup>**  
**GT 1 SVR with response-guided treatment:<sup>1</sup>**  
**Telaprevir (24–48 wk): 79%**  
**Boceprevir (28–48 wk): 63–66%**

### ◆ Limitations

- Long, complex, response-guided treatment
- Significant side effects
- High discontinuation rates
- Viral resistance

PI=protease inhibitor; TID=three times daily.

a. HCV PI=telaprevir 750 mg TID, boceprevir 800 mg TID.

Prescribing information (US): Pegasys (180 µg) or PegIntron (1.5 µg/kg) + RBV (weight-based dosing).

1. Ghany MG, et al. *Hepatology*. 2011;54:1433-1444 (AASLD Guidelines).

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# Need for Improved Therapy

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Need for simple, short, effective, well-tolerated therapy,  
without risk of viral resistance

## Genotype 2 or 3 HCV

PEG/RBV

24 weeks of treatment<sup>1-4</sup>

GT 2 SVR: 71–75%

GT 3 SVR: 61–66%

## Genotype 1 HCV

HCV PI (telaprevir or boceprevir) + PEG/RBV<sup>1,4</sup>

24–48 weeks of treatment

GT 1 SVR: 63–79%

1. Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.
2. Shiffman ML, et al. *N Engl J Med*. 2007;357:124-134.
3. Marcellin P, et al. *Hepatology*. 2012;56:2039-2050.
4. Ghany MG, et al. *Hepatology*. 2011;54:1433-1444 (AASLD Guidelines).



# Sofosbuvir Program: Key Findings

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- ◆ Met primary efficacy endpoints in all studies
- ◆ High efficacy rates across HCV GT 1–6
- ◆ First interferon-free regimens (GT 2, GT 3)
- ◆ Shorter duration than current therapies
- ◆ Safe and well-tolerated regimens
- ◆ No evidence of resistance in combination regimens
- ◆ Inclusion of patients historically excluded, and those with advanced liver disease

# Proposed Indication

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- ◆ Sofosbuvir is indicated for the treatment of chronic hepatitis C infection, in combination with other agents in adult patients with genotypes 1 to 6 and/or adult patients awaiting liver transplantation.

# Agenda

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**Introduction**

John McHutchison, MD

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**Clinical Efficacy**

William Symonds, PharmD

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**Clinical Safety**

Diana Brainard, MD

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**Benefit / Risk**

John McHutchison, MD

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# Sofosbuvir Response Team

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**Clinical Efficacy**

Dr. William Symonds

**Clinical Safety**

Dr. Diana Brainard

**Biometrics**

Dr. Neby Bekele

**Clinical Pharmacology**

Dr. Brian Kearney

**Virology**

Dr. Evguenia Svarovskaia

**DMPK**

Dr. Adrian Ray

**Toxicology**

Dr. Chin Tay

# External Specialists

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## **Ira Jacobson, MD**

Chief, Division of Gastroenterology and Hepatology  
Vincent Astor Distinguished Professor of Medicine  
Weill Cornell Medical College  
Attending Physician, New York-Presbyterian Hospital Cornell Campus

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## **Zobair Younossi, MD, MPH**

Vice President Research, Inova Health System  
Chairman, Department of Medicine, Inova Fairfax Hospital  
Professor of Medicine  
Virginia Commonwealth University - Inova Campus

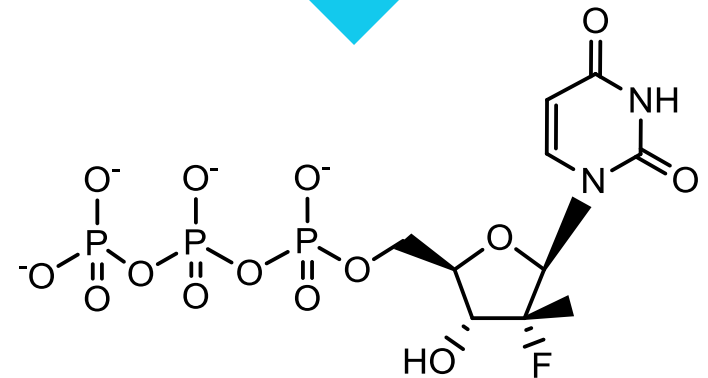
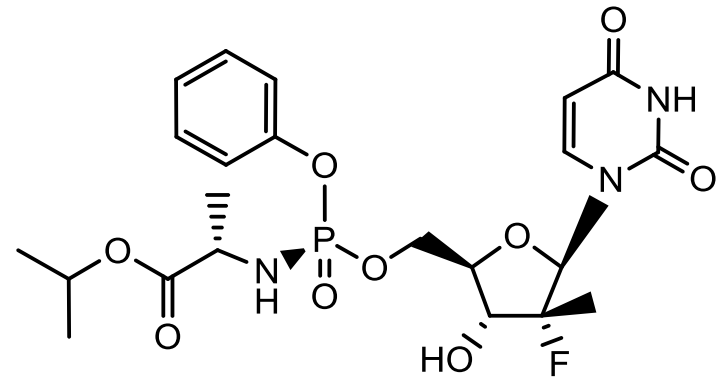
# Clinical Efficacy

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William Symonds, PharmD  
Vice President, Liver Diseases  
Gilead Sciences

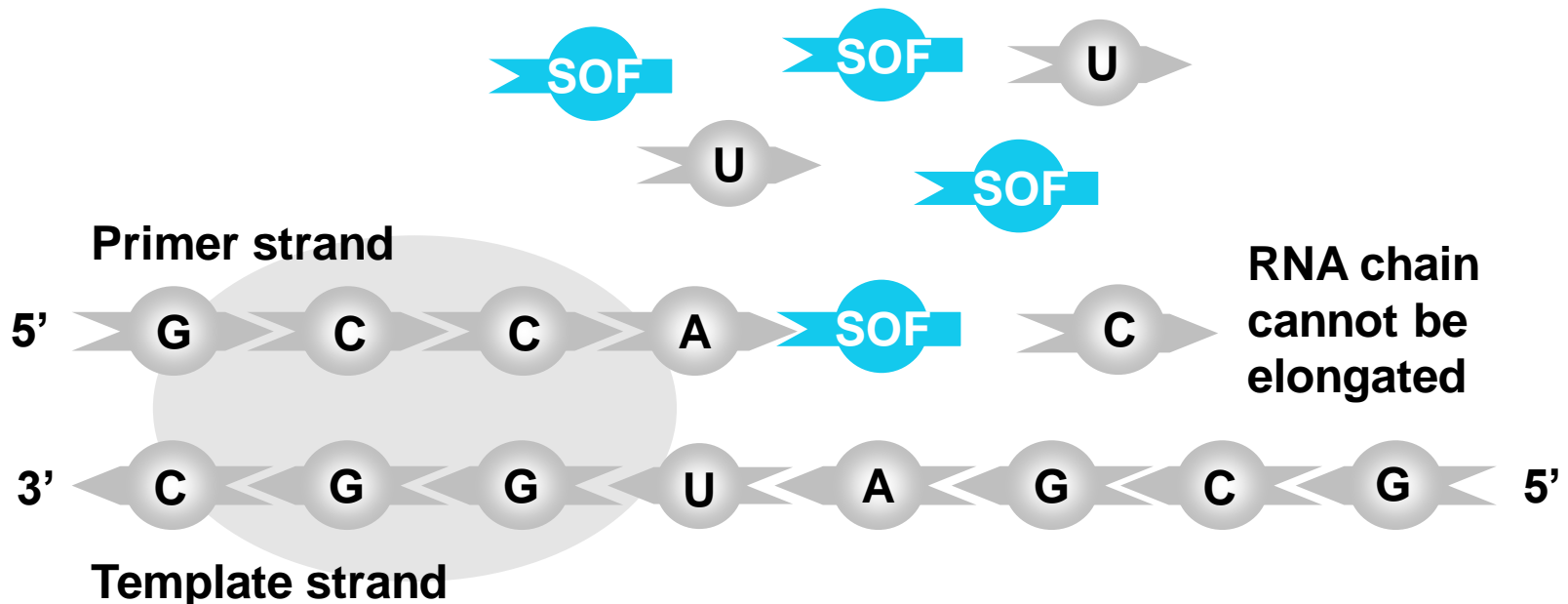
# Sofosbuvir

- ◆ Uridine nucleotide analog HCV NS5B polymerase inhibitor
- ◆ Prodrug, efficiently taken up by hepatocytes
- ◆ Undergoes intracellular activation to triphosphate form



# Sofosbuvir Mechanism of Action

- ◆ Competes with natural nucleotides
- ◆ Chain termination stops replication
- ◆ Mechanism applies to all HCV genotypes





# Benefits of Sofosbuvir Inhibition of NS5B

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- ◆ Active site of the NS5B enzyme is relatively well conserved across genotypes
- ◆ The S282T mutation causes reduced sensitivity to sofosbuvir in vitro
- ◆ The S282T mutation has not been detected in untreated patients
- ◆ S282T mutations in sofosbuvir-treated patients are rare

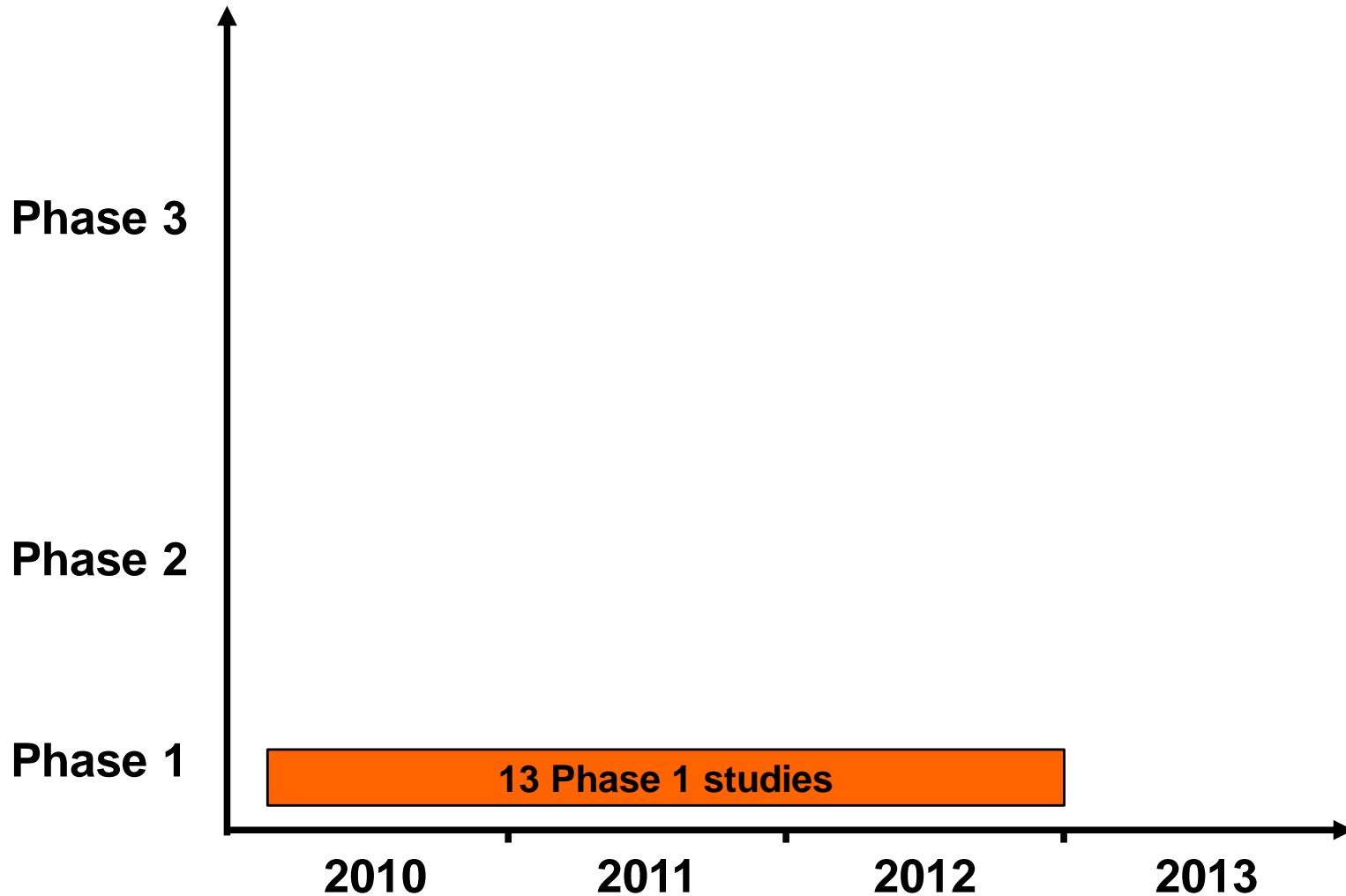
# Sofosbuvir Nonclinical Safety

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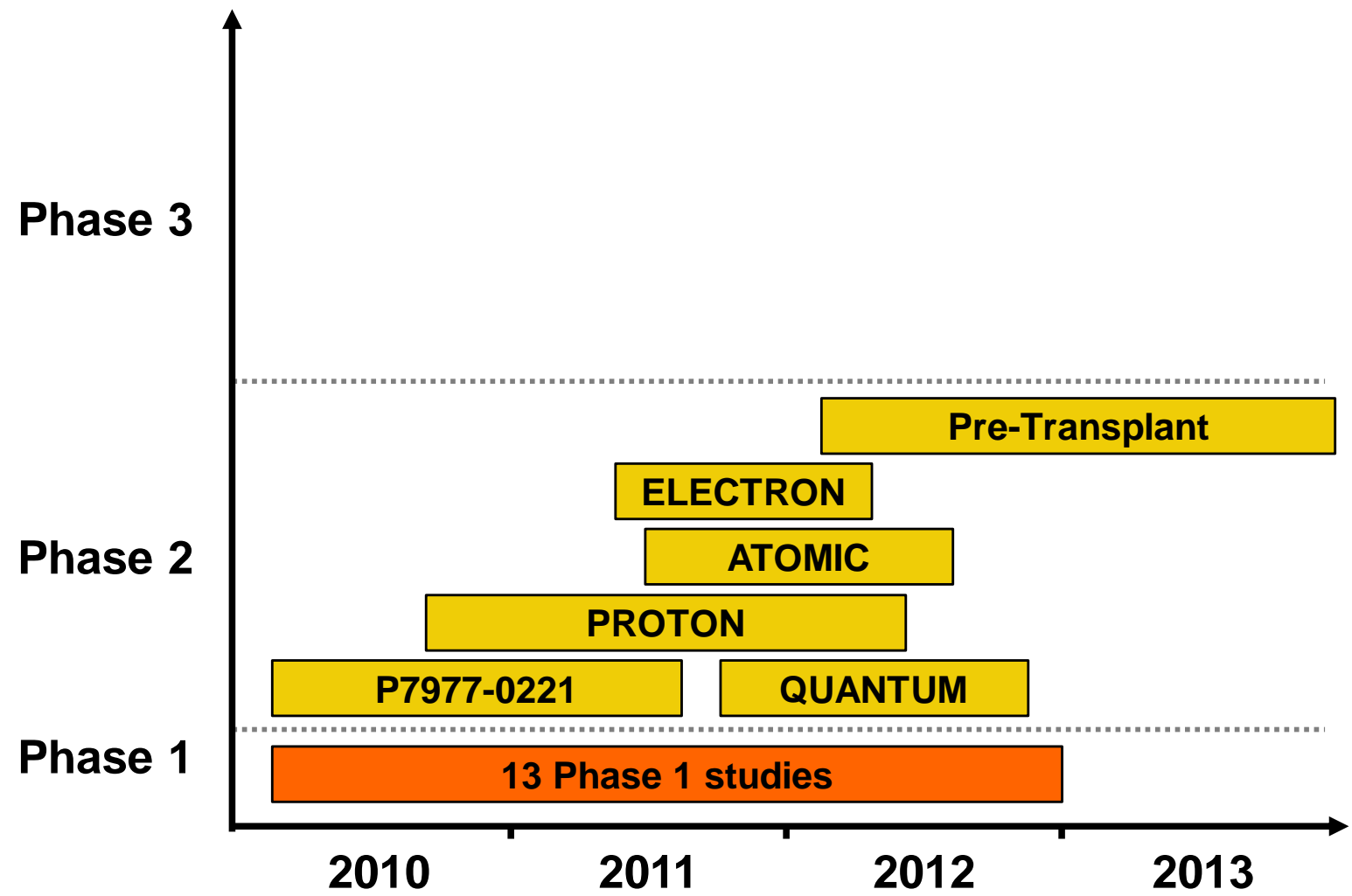
- ◆ The active triphosphate metabolite of sofosbuvir is not an inhibitor of host DNA or RNA polymerases, including mitochondrial polymerases
- ◆ Sofosbuvir was well tolerated in chronic toxicity studies
- ◆ Sofosbuvir is not genotoxic
- ◆ Sofosbuvir had no adverse effects on fertility or embryo-fetal development
  - Proposed pregnancy category B

# Sofosbuvir Development Program (GT 1–6)

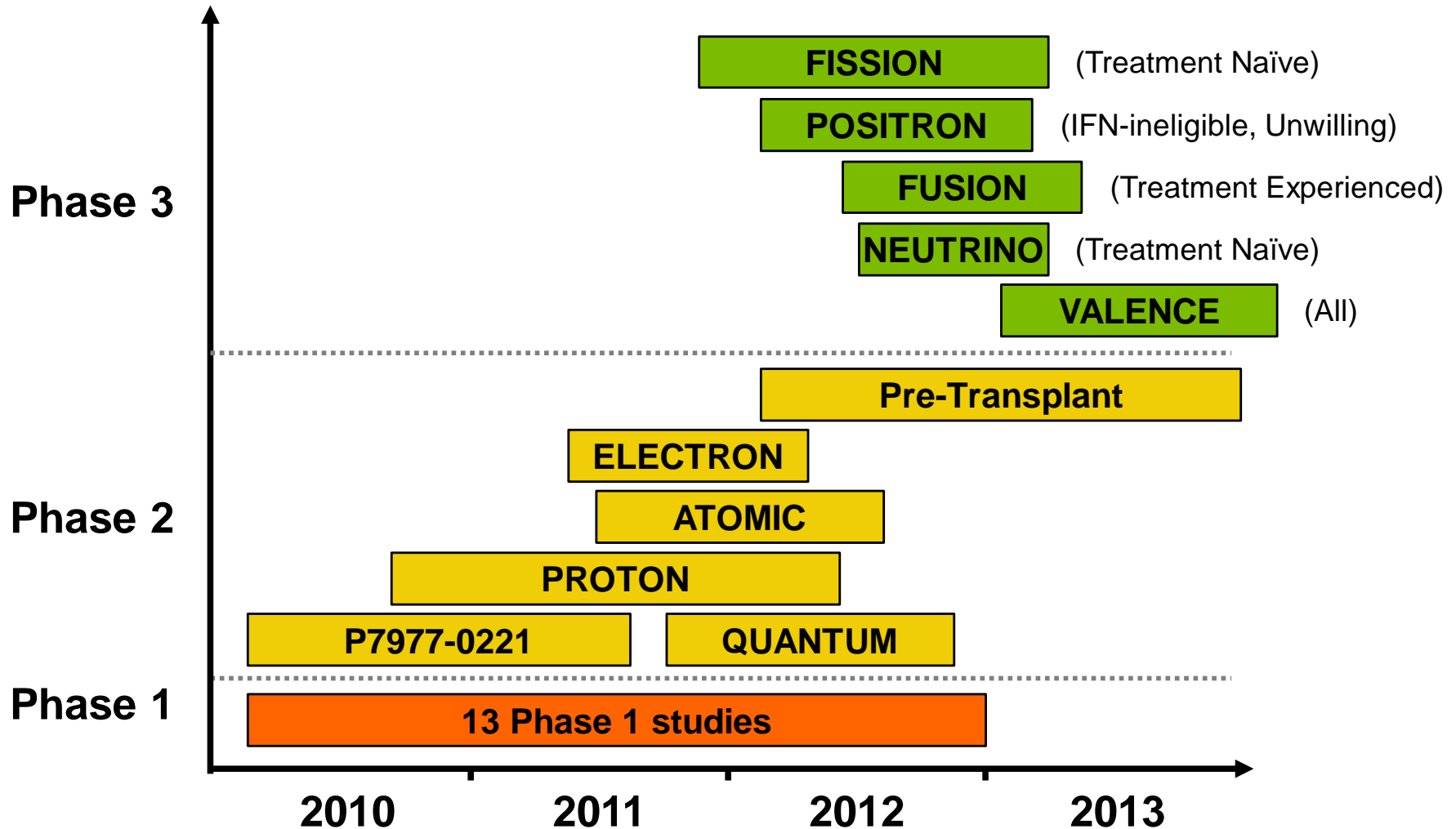
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# Sofosbuvir Development Program (GT 1–6)



# Sofosbuvir Development Program (GT 1–6)



IFN=interferon.

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# Sofosbuvir: Clinical Pharmacology Profile

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- ◆ Sofosbuvir is an orally bioavailable nucleotide prodrug
- ◆ Sofosbuvir is rapidly taken up by the liver
- ◆ Long half-life (~18 h) for active triphosphate
- ◆ Sofosbuvir (5%), GS-331007 (>90%) of systemic exposure
- ◆ Only sofosbuvir delivers active drug to hepatocytes

# Sofosbuvir:

## Clinical Pharmacology in Special Populations

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- ◆ No CYP450 hepatic metabolism
- ◆ No dose adjustment in hepatic impairment
- ◆ No dose adjustment if creatinine clearance >30 mL/min
- ◆ No impact of HCV patient characteristics on exposure
  - No impact of BMI, age, sex, race, or cirrhosis on pharmacokinetics

# Sofosbuvir: Drug Interactions Profile

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- ◆ No clinically significant interactions
  - Methadone
  - Cyclosporine, tacrolimus
  - Antiretrovirals (FTC, TDF, RPV, EFV, DRV/r, RAL)
- ◆ Potential interactions
  - Potent P-glycoprotein and/or BCRP inducers
    - Antimycobacterials, anticonvulsants, St. John's wort

BCRP=breast cancer resistance protein; DRV/r=darunavir boosted with ritonavir; EFV=efavirenz; FTC=emtricitabine; RAL=raltegravir; RPV=rilpivirine; TDF=tenofovir disoproxil fumarate.



# Sofosbuvir Phase 2 Development Program

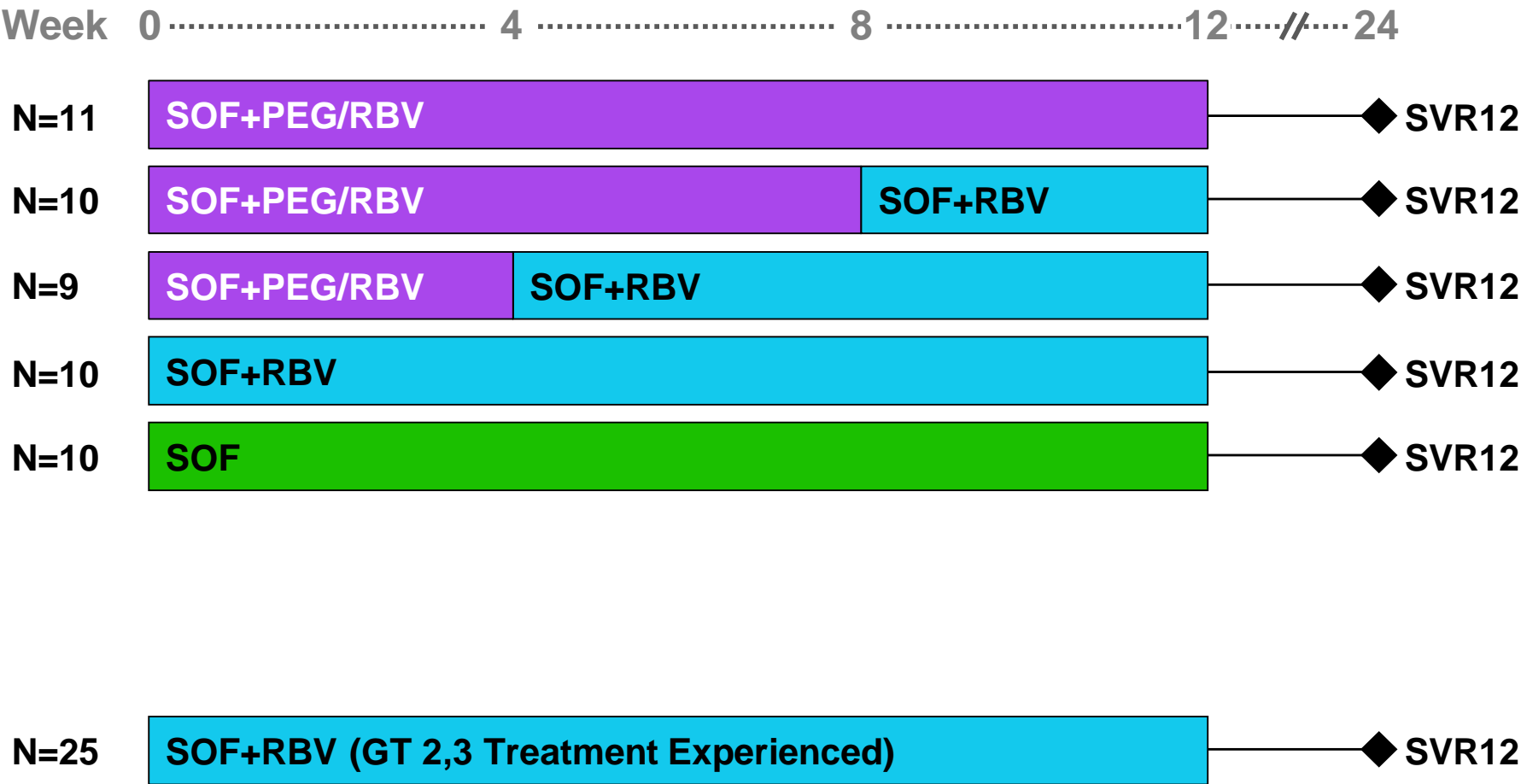
## Objectives

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- ◆ Define dose and duration
- ◆ Demonstrate antiviral activity in HCV GT 1–6
- ◆ Determine potential for interferon-free regimens
- ◆ Characterize resistance profile

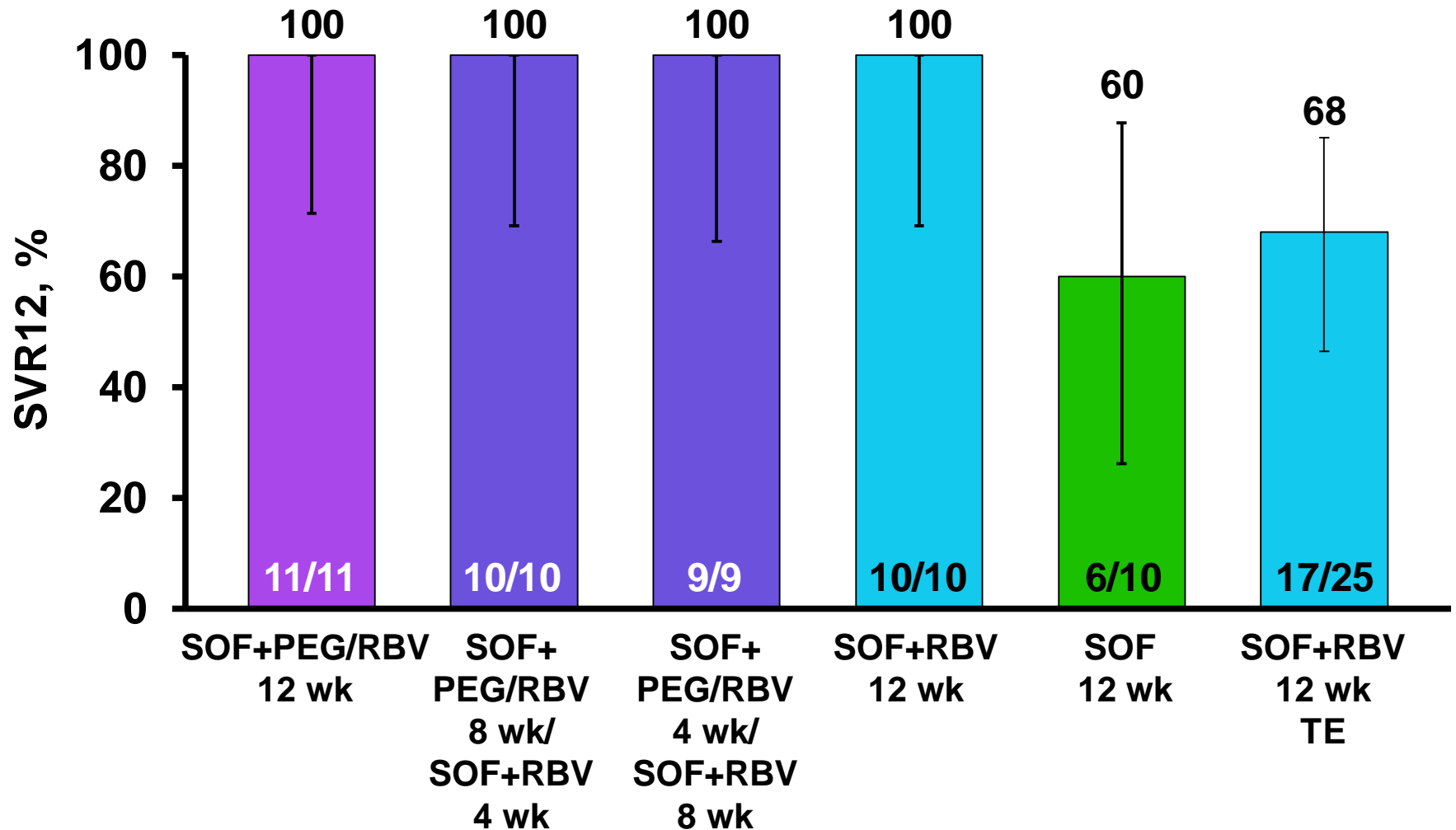
# Study Design

## GT 2,3 Treatment Naïve and Experienced (ELECTRON)



# Results: SVR12

## GT 2,3 Treatment Naïve and Experienced (ELECTRON)

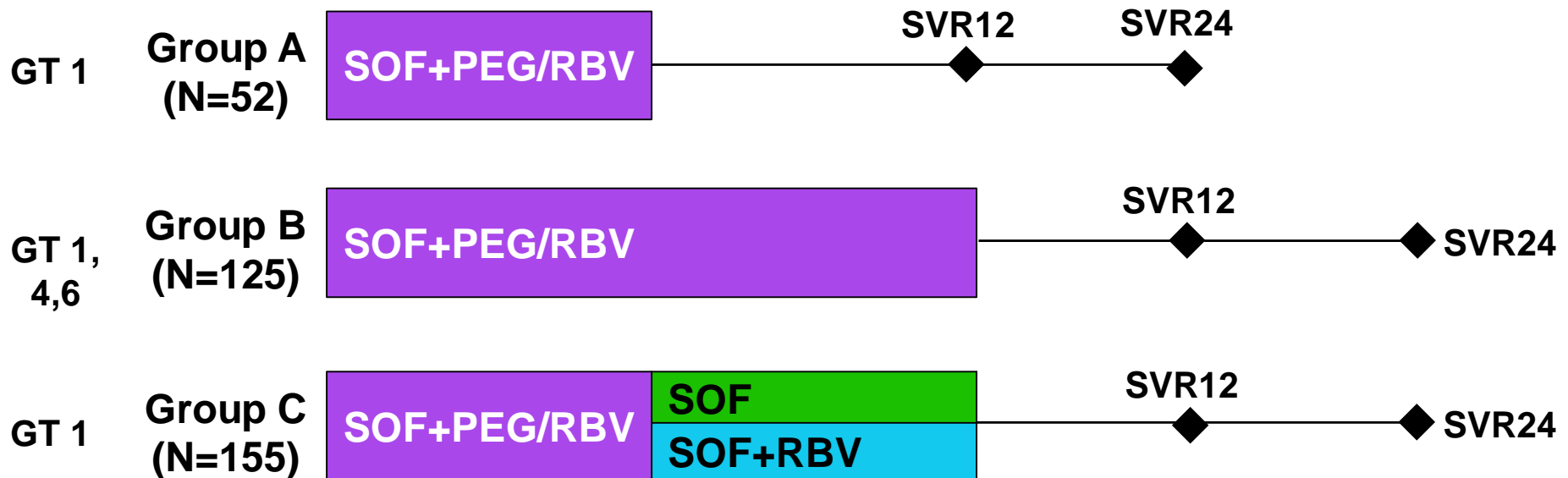


TE=treatment experienced.

# Study Design

## GT 1,4,6 Treatment Naïve (ATOMIC)

Week 0 ..... 12 ..... 24 ..... // ..... 36 ..... // ..... 48



SOF (400 mg) + PEG (180 µg) + RBV (1000-1200 mg).

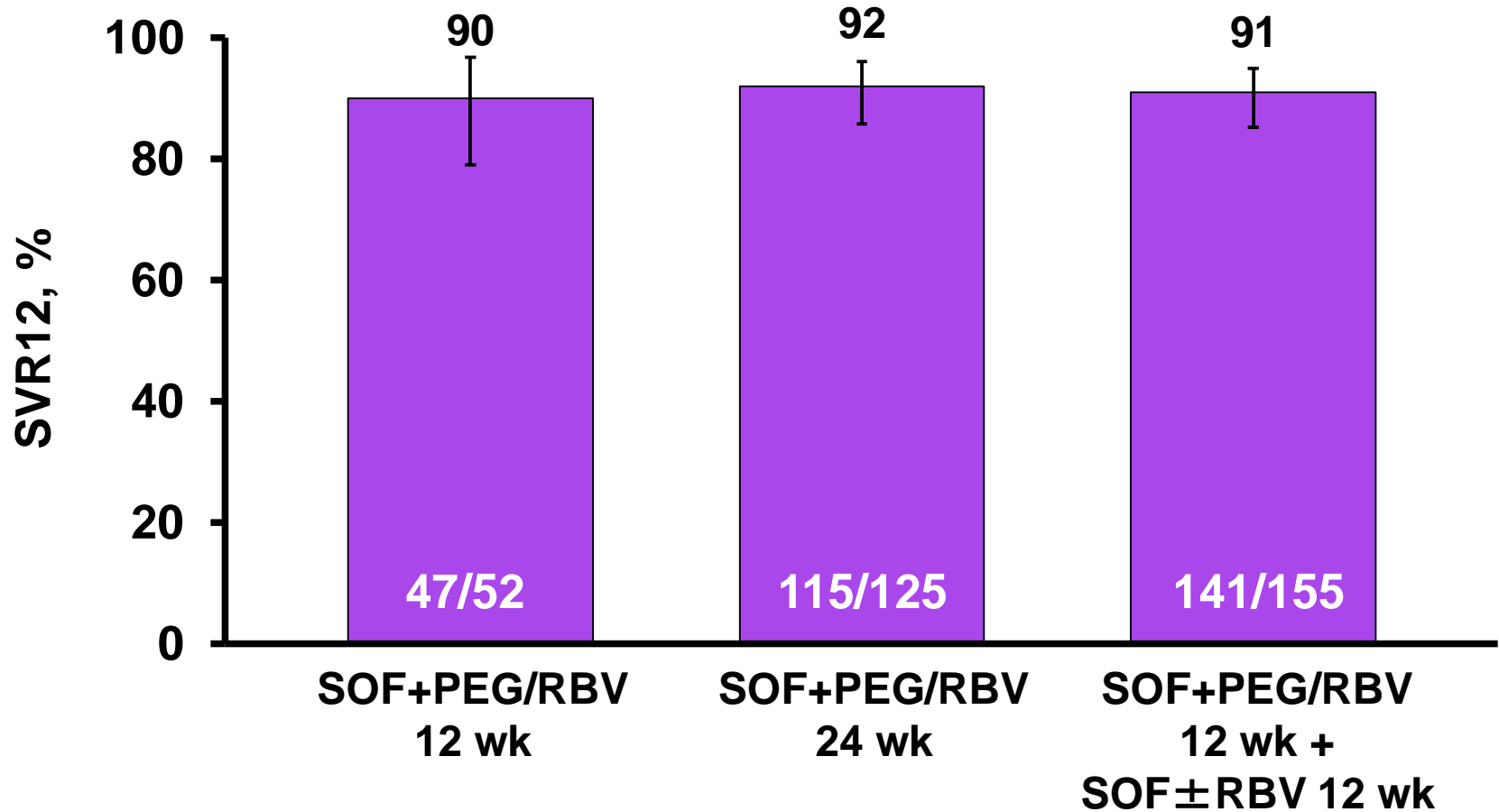
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# Results: SVR12

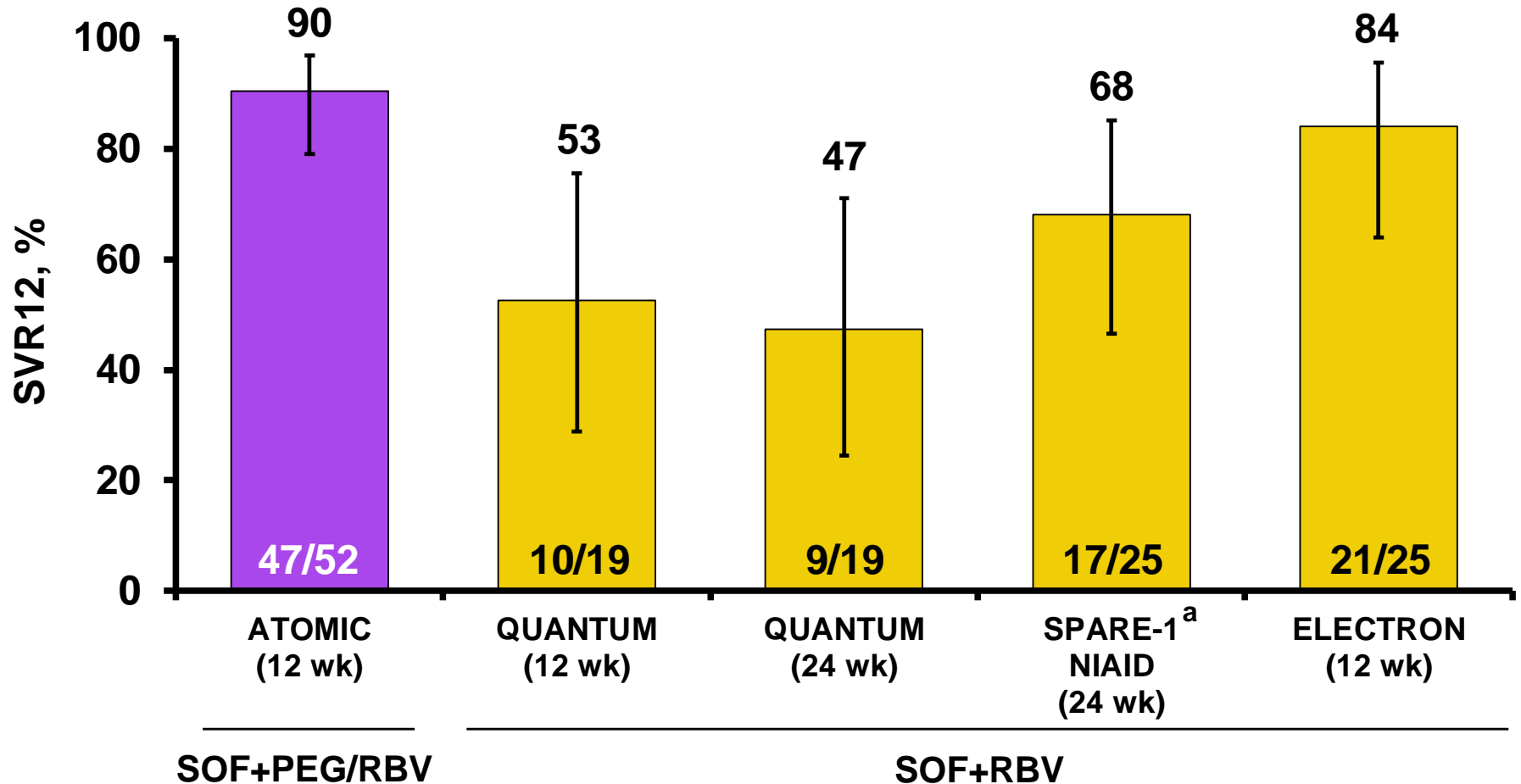
GT 1,4,6 Treatment Naïve (ATOMIC)

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# Results: SVR Rates Across Phase 2

## GT 1 Treatment-Naïve Patients, 12 or 24 Weeks



a. Osinusi A, et al. *JAMA*. 2013;310:804-811.

# Observations from Phase 2 Program

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- ◆ Define dose and duration
  - SOF 400 mg QD administered for 12 weeks
- ◆ Demonstrate antiviral activity across HCV genotypes
  - Antiviral activity demonstrated in GT 1,2,3,4, and 6
- ◆ Determine need for interferon in regimen
  - Interferon not required in GT 2,3
  - SOF+PEG/RBV in GT 1,4, and 6
- ◆ Characterize resistance profile
  - S282T mutation detected in single monotherapy patient

# Sofosbuvir Phase 3 Study Program

## Phase 3 Studies

### SOF+RBV Studies

#### GT 2,3 Treatment Naïve (FISSION)

PEG/RBV (N=243)

SOF+RBV (N=256)

#### GT 2,3 IFN-unable (POSITRON)

SOF+RBV (N=207)

PBO (N=71)

#### GT 2,3 Treatment Experienced (FUSION)

SOF+RBV (N=103) PBO

SOF+RBV (N=98)

#### GT 2,3 All<sup>a</sup> (VALENCE)

SOF+RBV (N=84)

SOF+RBV (N=250)

PBO (N=85)

### SOF+PEG/RBV Study

#### GT 1,4,5,6 Treatment Naïve (NEUTRINO)

SOF+PEG/RBV (N=327)

a. Includes treatment-naïve, IFN-unable, and treatment-experienced patients.



# Sofosbuvir Phase 3 Program

## Trial Designs with Concurrent Control Arms

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- ◆ FISSION: Treatment-naïve GT 2,3 patients who are interferon eligible, permitting a standard of care PEG/RBV comparator
- ◆ POSITRON: GT 2,3 patients who could not take interferon permitting a placebo comparator

# Sofosbuvir Phase 3 Program

## Trial Designs without Concurrent Control Regimens

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- ◆ FUSION: GT 2,3 patients who had failed prior interferon treatment and could not be re-treated necessitating a historical control arm
- ◆ NEUTRINO: SOF+PEG/RBV in untreated patients with GT 1,4,5, or 6 HCV infection compared to a historical control based on multiple factors including:
  - High SVR rate in Phase 2
  - Inclusion of GT 4,5,6
  - Complexity of treatment algorithms for PI-based therapy

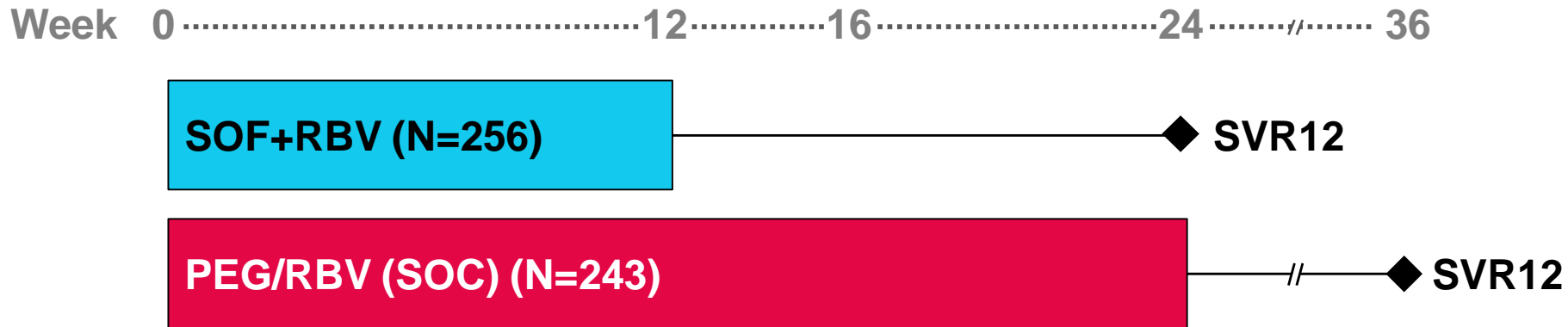
# Endpoints and Analyses

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- ◆ Sustained virologic response 12 weeks following treatment (SVR12)
  - HCV RNA analyzed by COBAS® TaqMan® HCV Test v2.0 HPS, with LLOQ of 25 IU/mL
- ◆ Phase 3 patient registries
  - SVR patients: monitor SVR patients for 3 years
  - Non-SVR patients: follow any sofosbuvir-resistant virus until reversion to wild-type
- ◆ HRQOL evaluations as exploratory endpoint

# Study Design

## GT 2,3 Treatment Naïve Interferon Eligible (FISSION)



- ◆ 499 patients randomized and treated
- ◆ Pre specified 3:1 ratio of GT 3 to 2
- ◆ Stratified by HCV genotype, HCV RNA, and cirrhosis
- ◆ Primary endpoint: noninferiority to PEG/RBV with a 15% margin

SOF (400 mg) + RBV (1000–1200 mg): PEG (180 µg) + RBV (800 mg).

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# Results: Demographics

## GT 2,3 Treatment Naïve Interferon Eligible (FISSION)

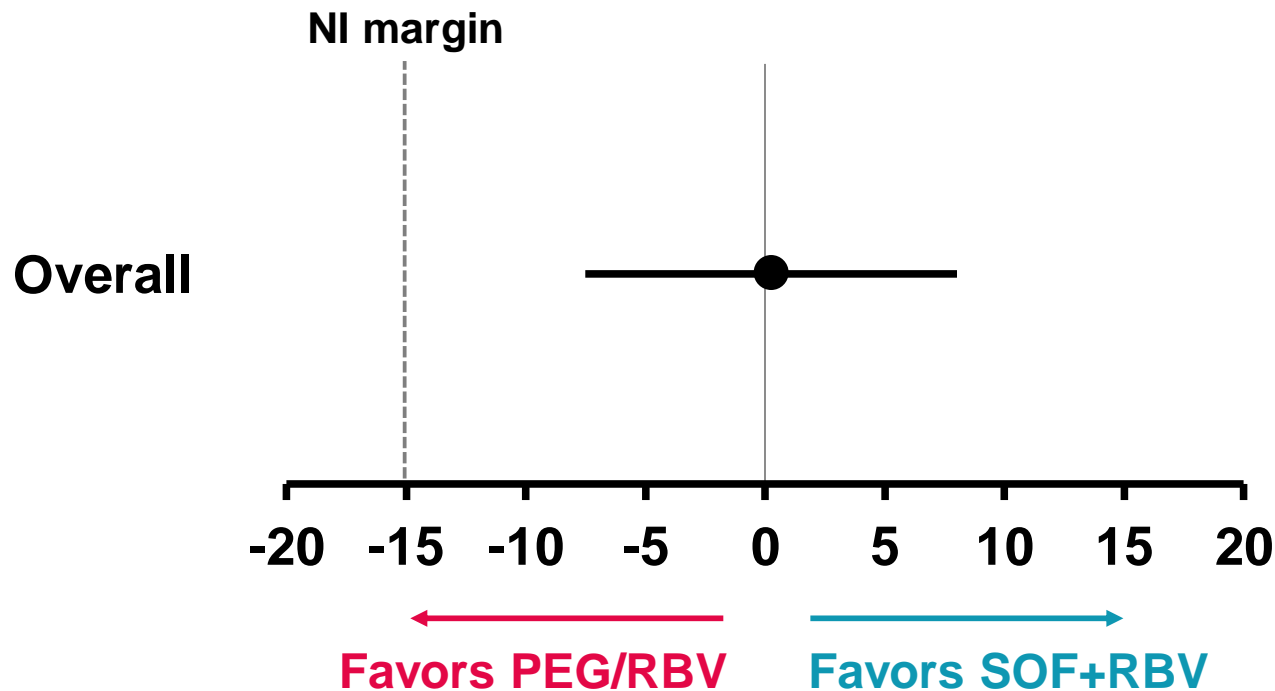
Parameter	SOF+RBV (N=256)	PEG/RBV (N=243)
Mean age (range), y	48 (20–72)	48 (19–77)
Male, n (%)	171 (67)	156 (64)
White, n (%)	223 (87)	212 (87)
Mean BMI (range), kg/m <sup>2</sup>	28 (17–51)	28 (19–52)
IL28B CC, n (%)	108 (42)	106 (44)
HCV GT 3, n (%)	183 (71)	176 (72)
Mean BL HCV RNA (range), log <sub>10</sub> IU/mL	6.0 (3.2–8.3)	6.0 (3.2–7.6)
Cirrhosis, n (%)	50 (20)	50 (21)

- ◆ Arms were balanced with respect to demographics and baseline characteristics

# Results: SVR12

## GT 2,3 Treatment Naïve Interferon Eligible (FISSION)

SVR12	SOF+RBV %	PEG/RBV %
Overall	67	67



NI=noninferiority.

Central horizontal line represents 95% confidence interval.

# Results: Virologic Outcomes

## GT 2,3 Treatment Naïve Interferon Eligible (FISSION)

Outcome	SOF+RBV (N=256) n (%)	PEG/RBV (N=243) n (%)
SVR12	171 (67)	162 (67)
No SVR12	85 (33)	81 (33)
On-treatment failure <sup>a</sup>	1 (<1) <sup>b</sup>	18 (7)
Relapse <sup>c</sup>	76 (30)	46 (21)
Other	8 (3)	17 (7)

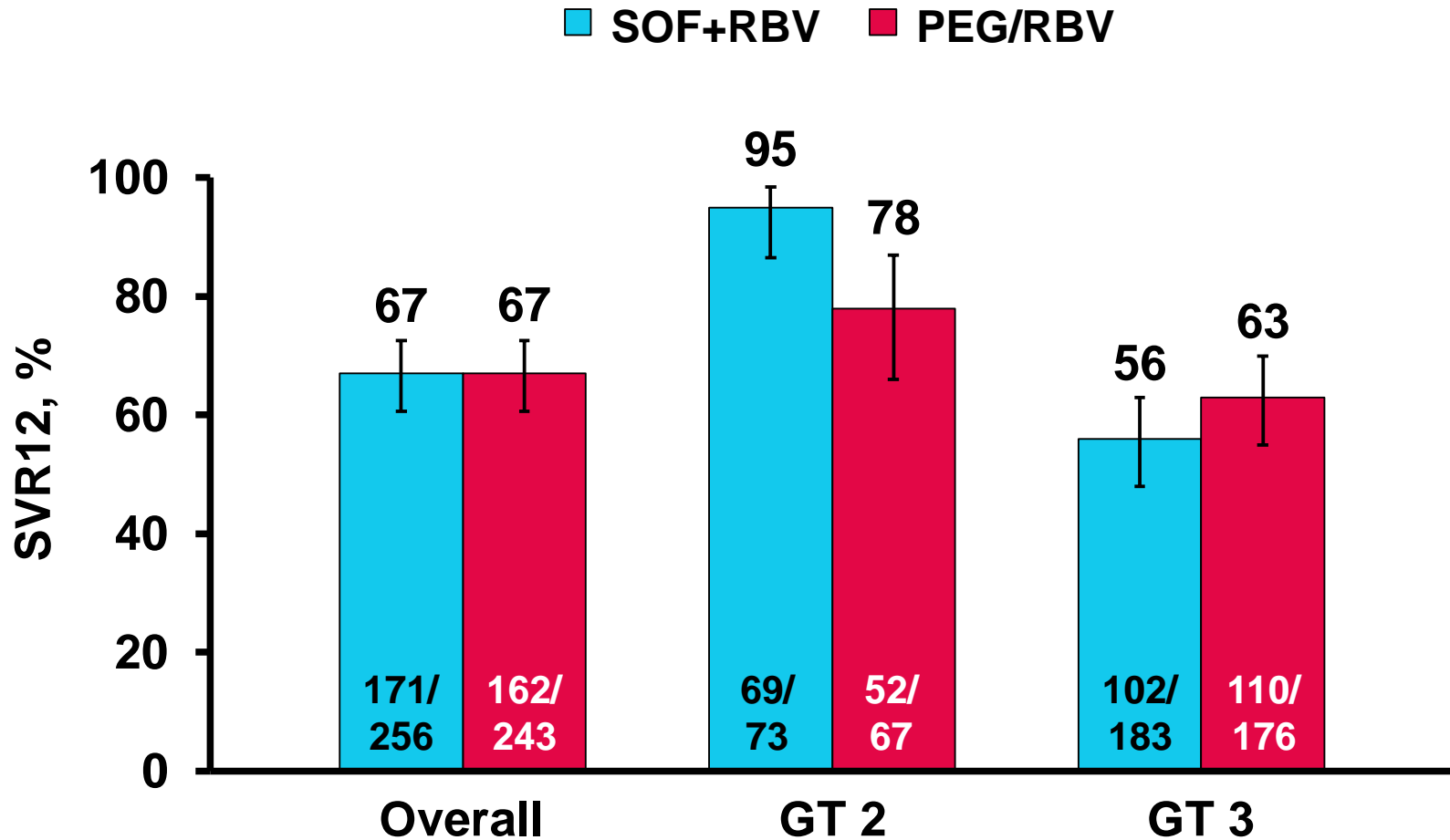
a. Breakthrough, rebound, or nonresponse (HCV RNA >LLOQ through Wk 12).

b. Patient with breakthrough had undetectable plasma drug levels after Wk 4.

c. Percent of relapse is based on patients who achieved HCV RNA <LLOQ at last on-treatment visit; N=252 for SOF+RBV and N=217 for PEG/RBV (N represents the number of patients who reached <LLOQ at end of therapy).

# Results: SVR12 by HCV Genotype

GT 2,3 Treatment Naïve Interferon Eligible (FISSION)



Error bars represent 95% confidence intervals.

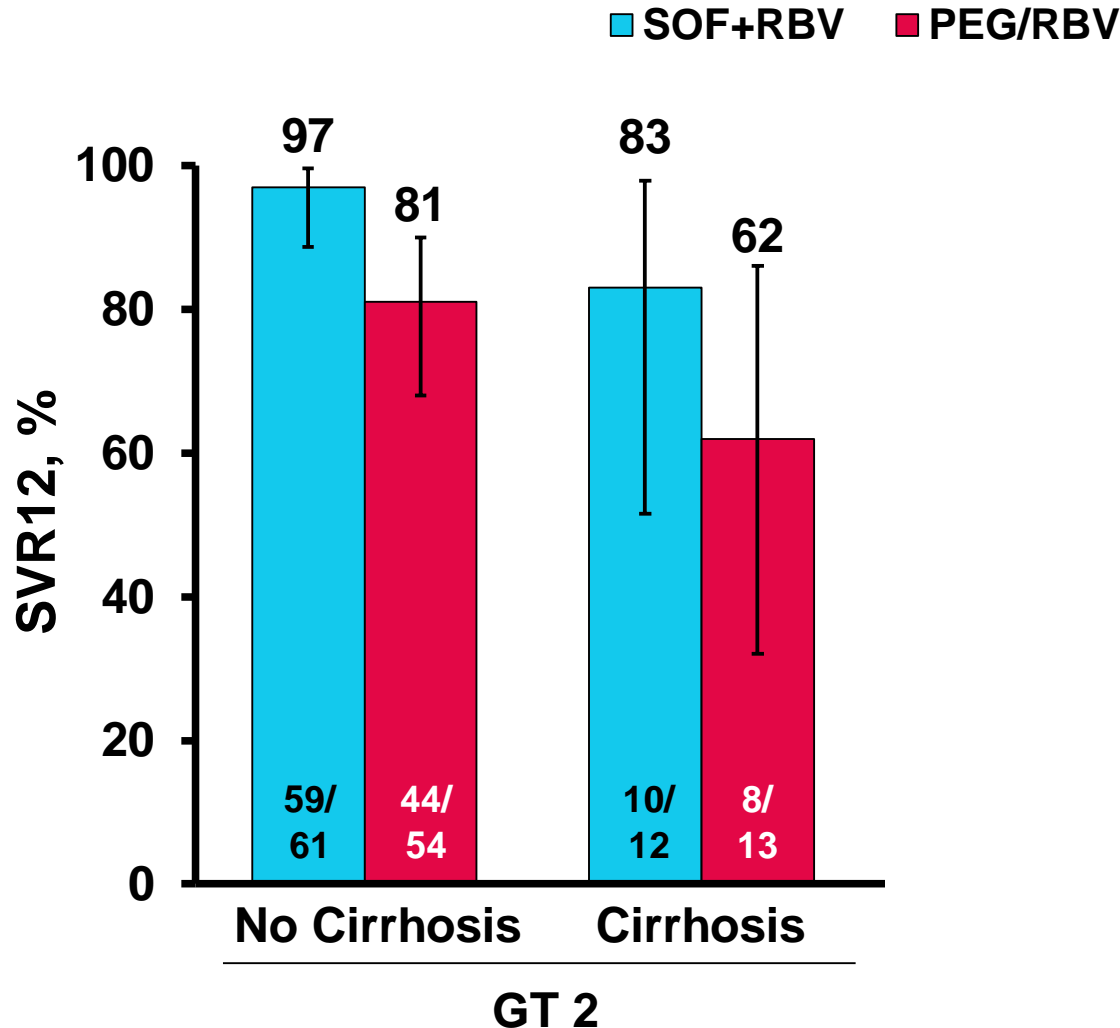
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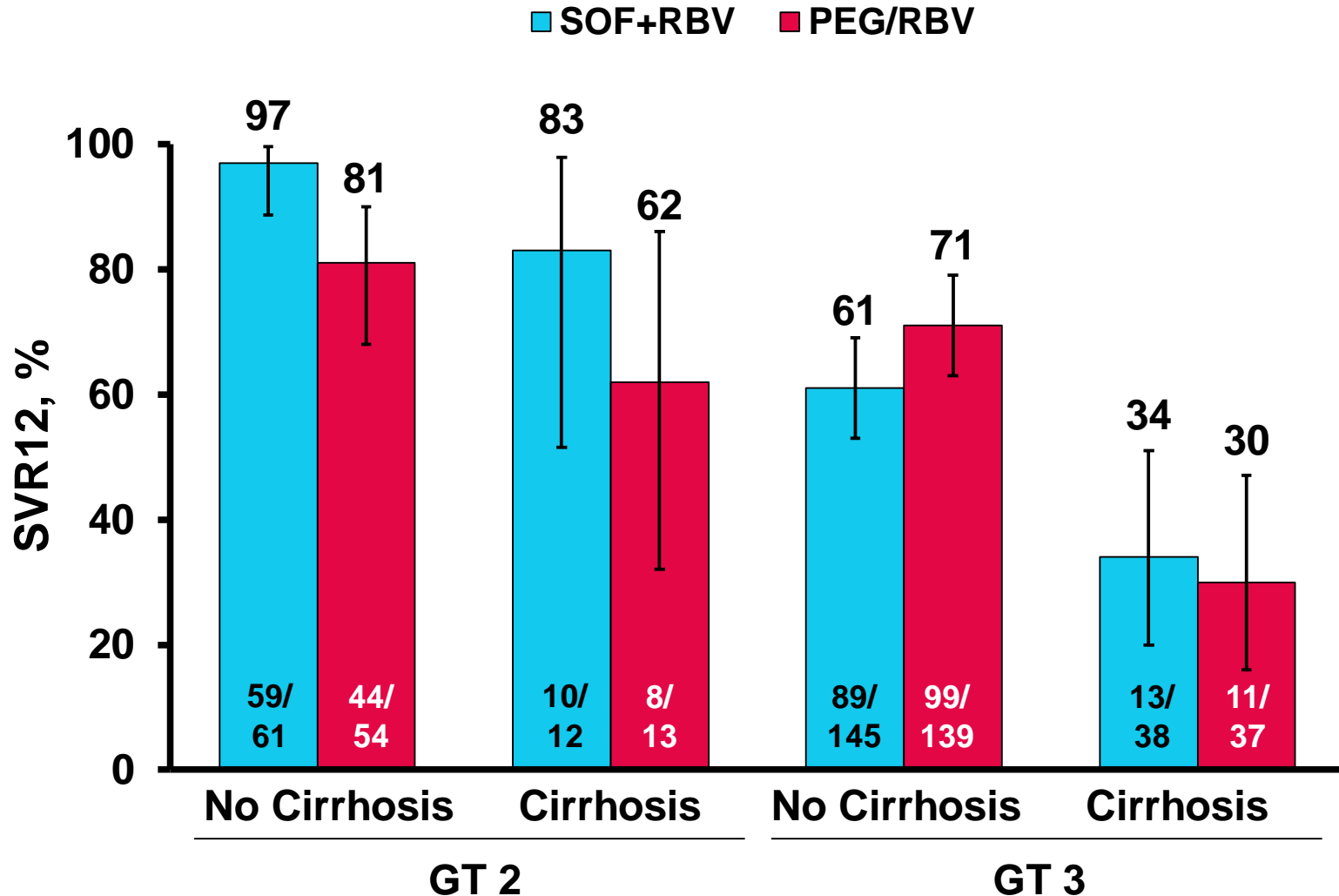
# Results: SVR12 by HCV Genotype and Cirrhosis

## GT 2,3 Treatment Naïve Interferon Eligible (FISSION)



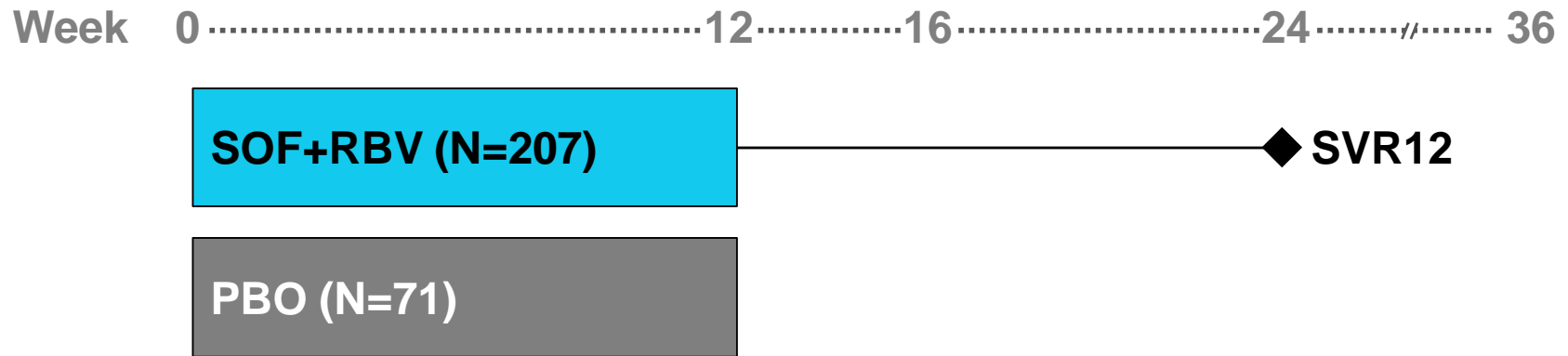
# Results: SVR12 by HCV Genotype and Cirrhosis

## GT 2,3 Treatment Naïve Interferon Eligible (FISSION)



# Study Design

## GT 2,3 IFN Ineligible, Intolerant, Unwilling (POSITRON)



- ◆ 278 patients randomized 3:1 to SOF+RBV or placebo
- ◆ No pre specified ratio of GT 3 to 2
- ◆ Stratified by cirrhosis
- ◆ Primary endpoint: superiority compared with placebo

# Results: Demographics

## GT 2,3 IFN Ineligible, Intolerant, Unwilling (POSITRON)

Parameter	SOF+RBV (N=207)	PBO (N=71)
Mean age (range), y	52 (21–75)	52 (28–67)
Male, n (%)	117 (57)	34 (48)
White, n (%)	188 (91)	66 (93)
Mean BMI (range), kg/m <sup>2</sup>	28 (18–53)	28 (20–43)
IL28B CC, n (%)	97 (47)	29 (41)
GT 2, n (%)	109 (53)	34 (48)
Mean BL HCV RNA (range), log <sub>10</sub> IU/mL	6.3 (3.2–7.5)	6.3 (3.7–7.6)
Cirrhosis, n (%)	31 (15)	13 (18)
Interferon unwilling, n (%)	102 (49)	30 (42)
Interferon ineligible, n (%)	88 (43)	33 (46)
Interferon intolerant, n (%)	17 (8)	8 (11)

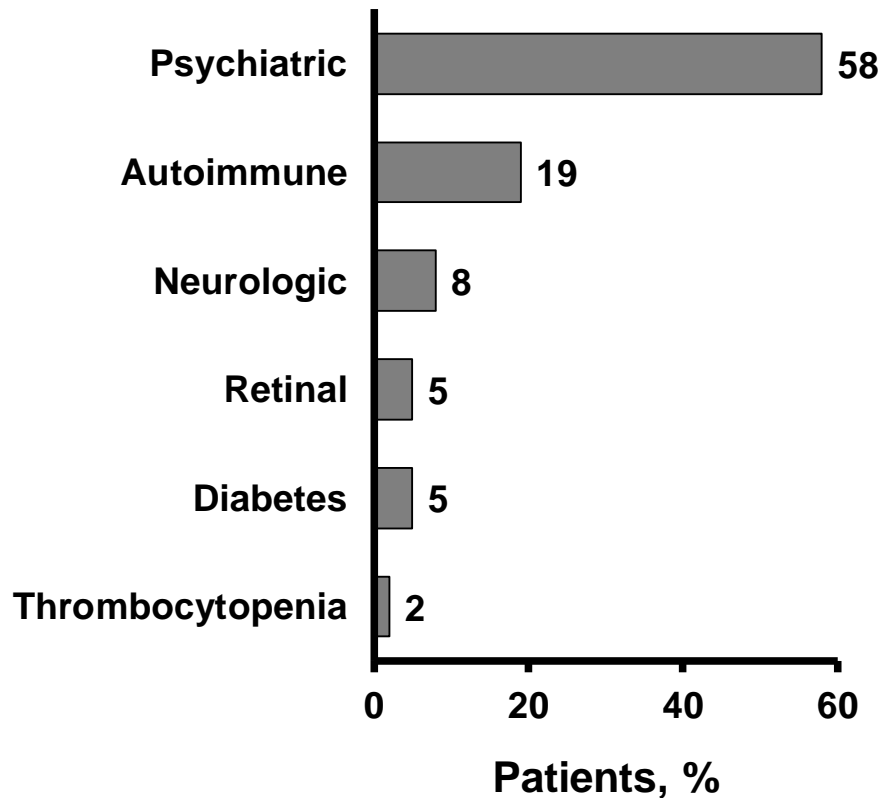
- ◆ Arms were balanced with respect to demographics and baseline characteristics

# Reasons for Interferon Ineligibility or Intolerance

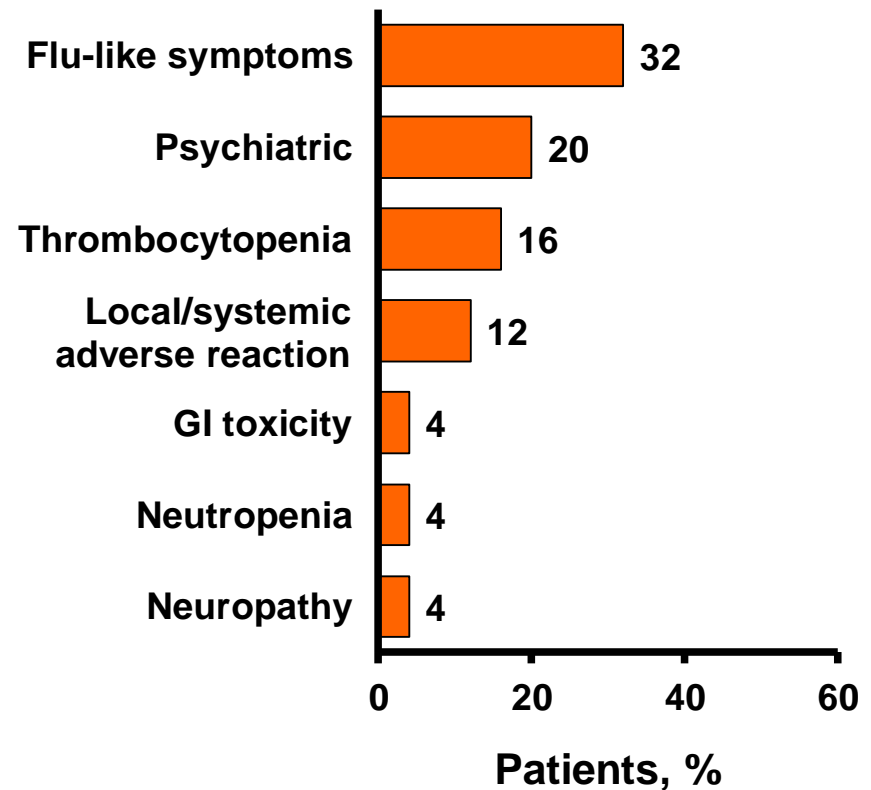
## GT 2,3 IFN Ineligible, Intolerant, Unwilling (POSITRON)

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IFN Ineligible (n=121)

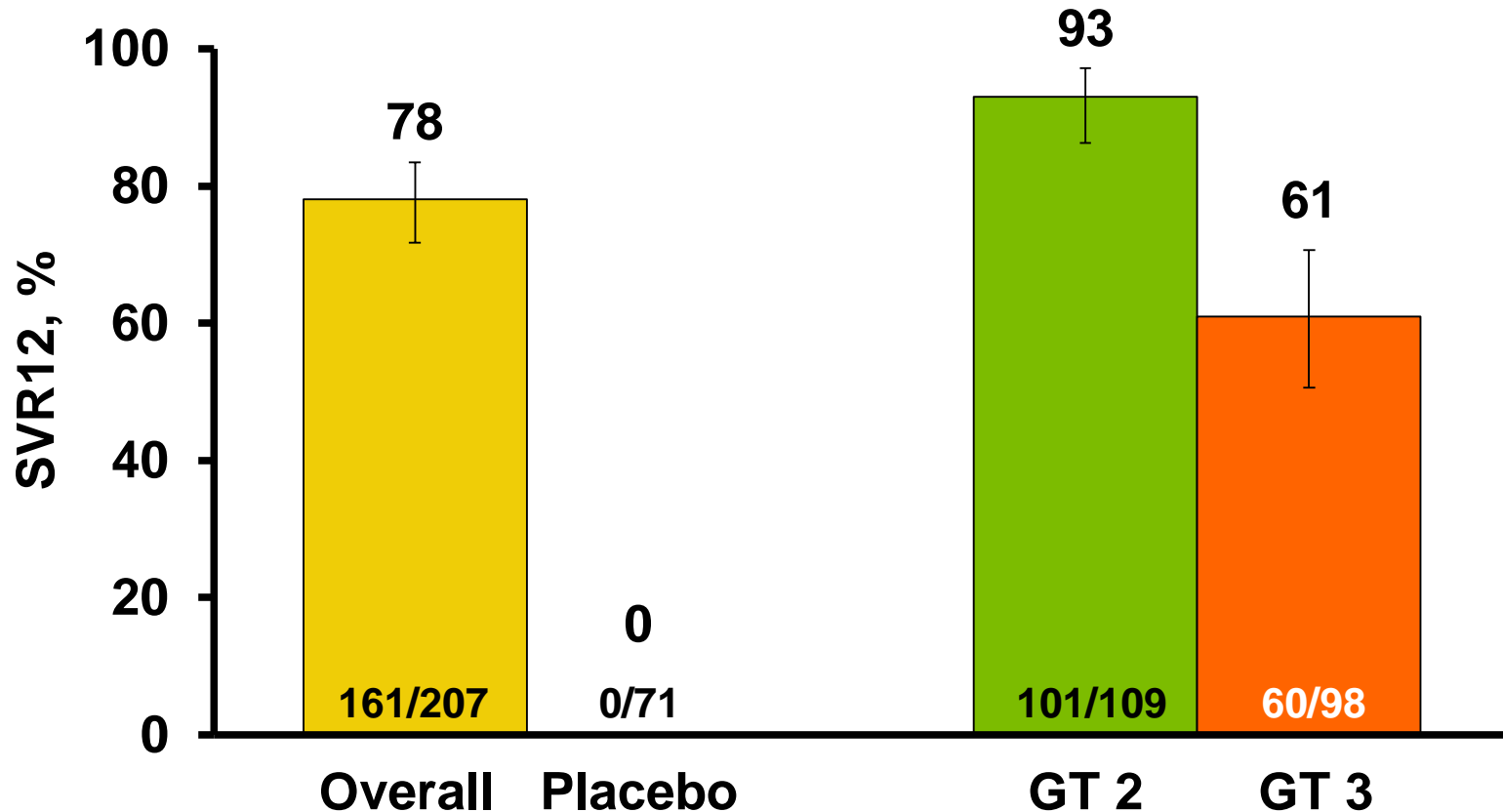


IFN Intolerant (n=25)



# Results: SVR12 by HCV Genotype

GT 2,3 IFN Ineligible, Intolerant, Unwilling (POSITRON)

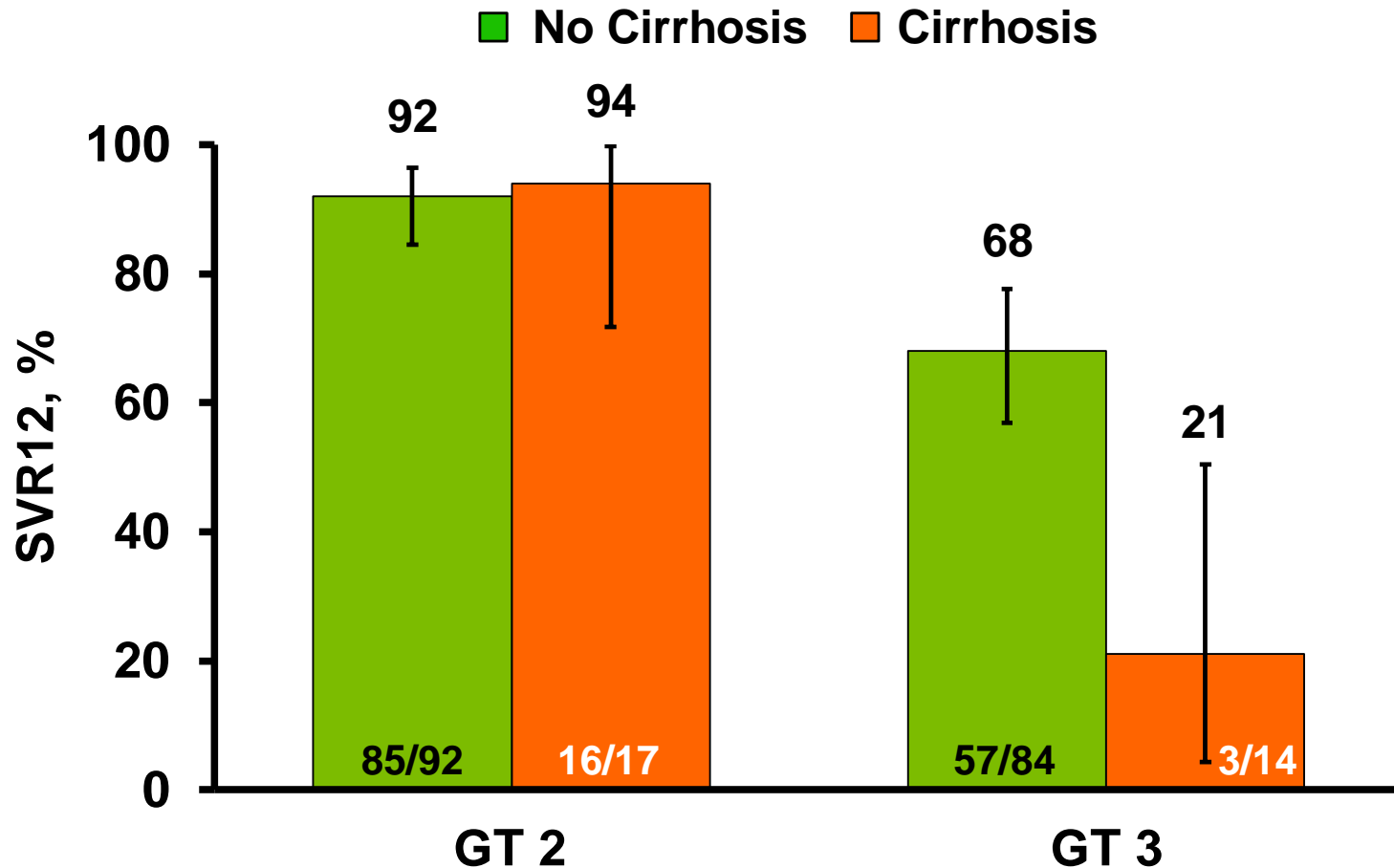


- ♦ Study met primary endpoint of superiority over placebo ( $p < 0.001$ )

# Results: SVR12 by HCV Genotype and Cirrhosis

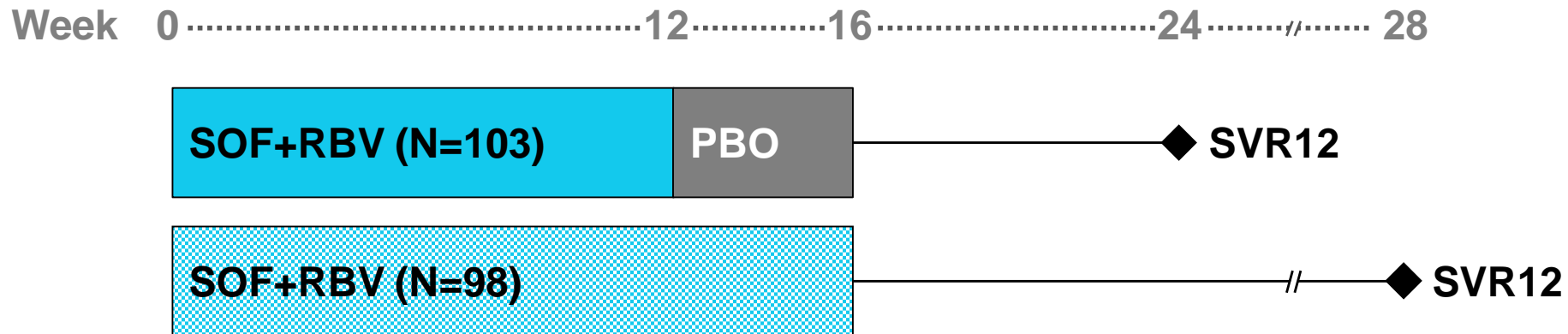
## GT 2,3 IFN Ineligible, Intolerant, Unwilling (POSITRON)

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# Study Design

## GT 2,3 Treatment Experienced (FUSION)



- ◆ 201 patients randomized and treated
- ◆ No pre specified ratio of GT 3 to 2
- ◆ Stratified by HCV genotype and cirrhosis
- ◆ Primary endpoint: superiority of each arm to historical control rate of 25%



# Results: Demographics

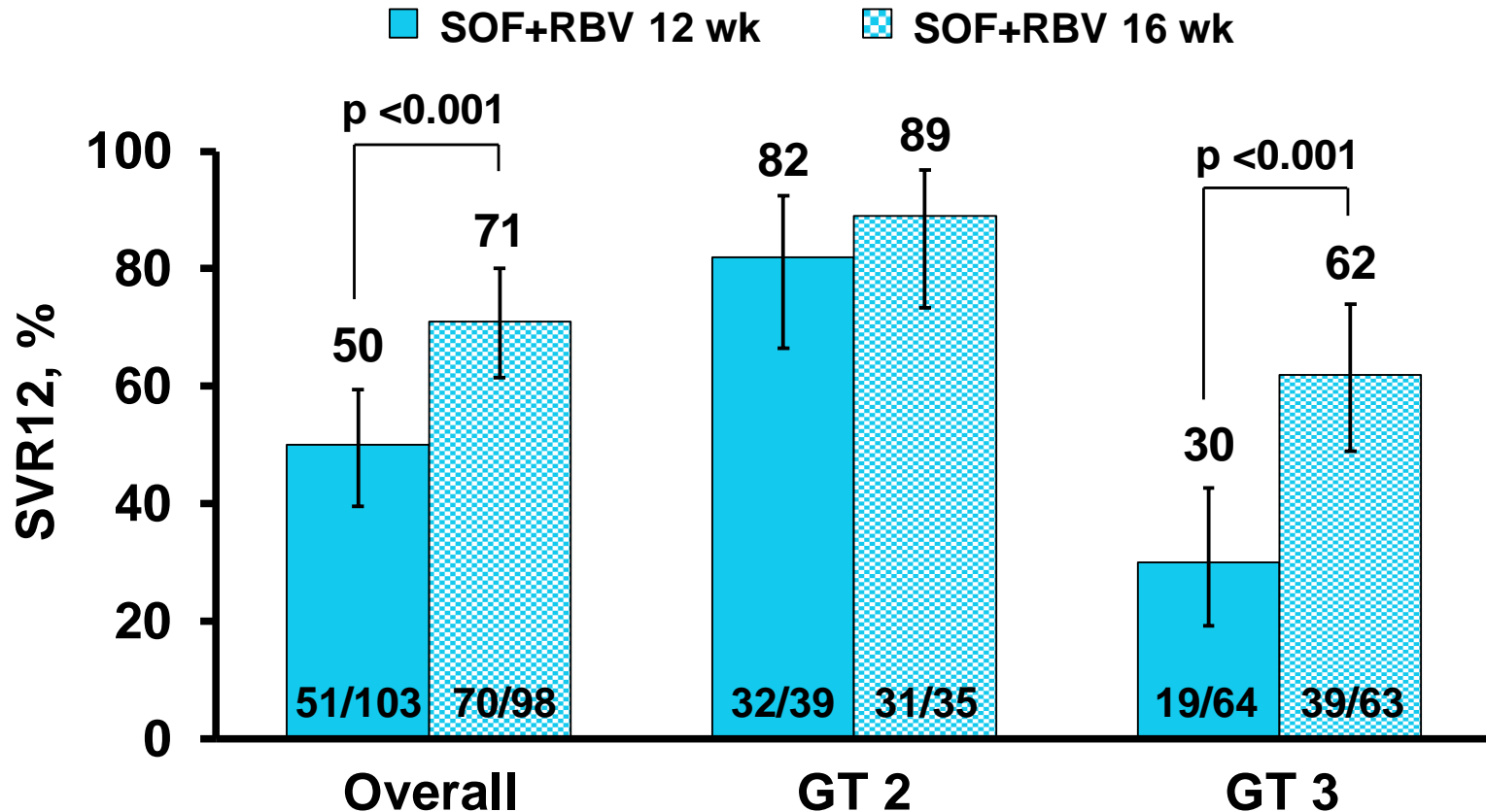
## GT 2,3 Treatment Experienced (FUSION)

Parameter	SOF+RBV 12 wk (N=103)	SOF+RBV 16 wk (N=98)
Mean age (range), y	54 (30–69)	54 (24–70)
Male, n (%)	73 (71)	67 (68)
White, n (%)	88 (85)	86 (88)
Mean BMI (range), kg/m <sup>2</sup>	28 (19–43)	29 (20–44)
IL28B CC, n (%)	31 (30)	30 (31)
HCV GT 3, n (%)	64 (62)	63 (64)
Mean BL HCV RNA (range), log <sub>10</sub> IU/mL	6.5 (4.7–7.6)	6.5 (5.1–7.6)
Cirrhosis, n (%)	36 (35)	32 (33)
Prior relapse, n (%)	78 (76)	73 (74)

- ◆ Arms were balanced with respect to demographics and baseline characteristics

# Results: SVR12 by HCV Genotype

## GT 2,3 Treatment Experienced (FUSION)



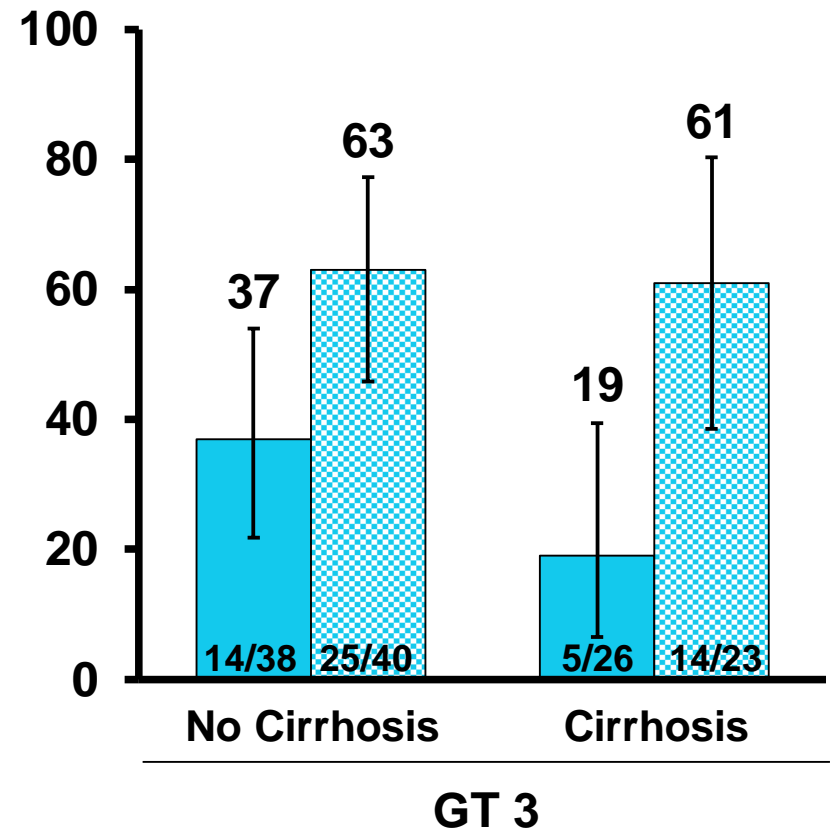
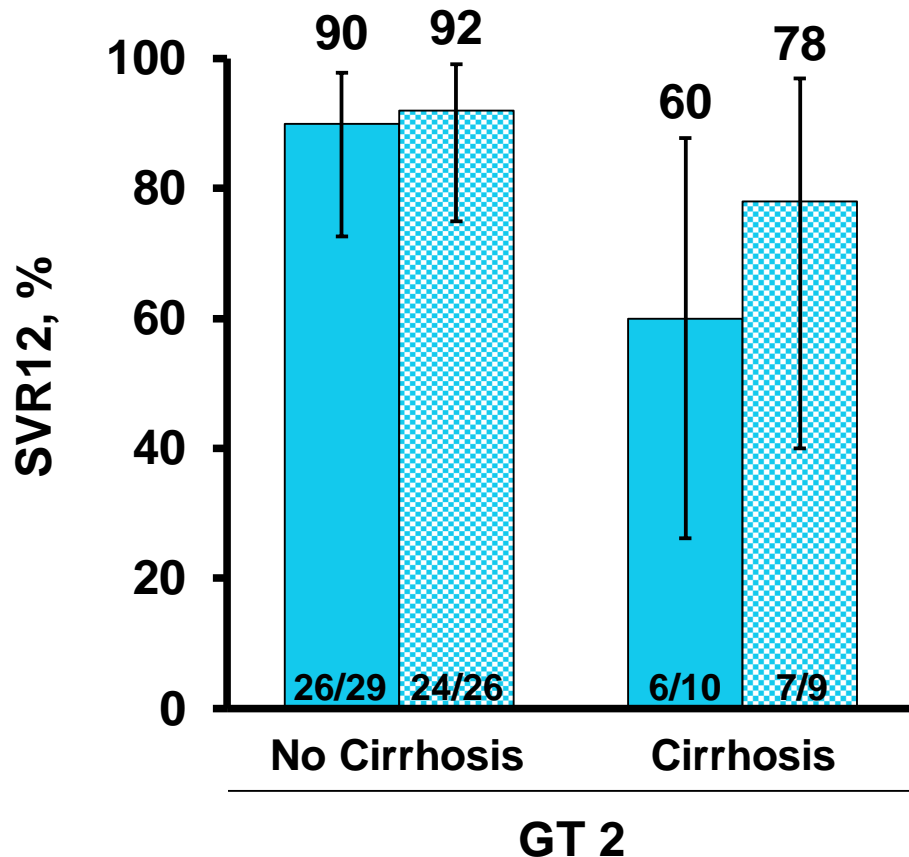
- ♦ Study met primary endpoint of superiority in each arm over historical control rate of 25% ( $p < 0.001$  for both)

# Results: SVR12 by HCV Genotype and Cirrhosis

## GT 2,3 Treatment Experienced (FUSION)

■ SOF+RBV 12 wk

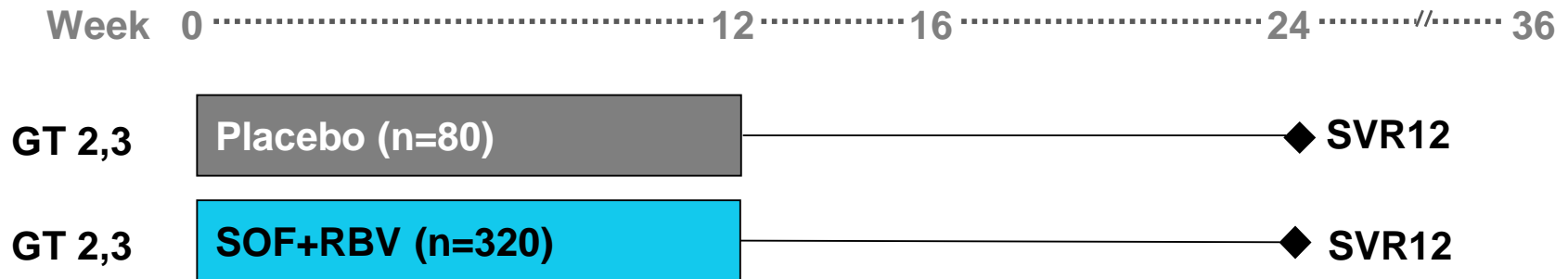
▤ SOF+RBV 16 wk



# Study Design: Original

## GT 2,3 Treatment Naïve/Experienced (VALENCE)

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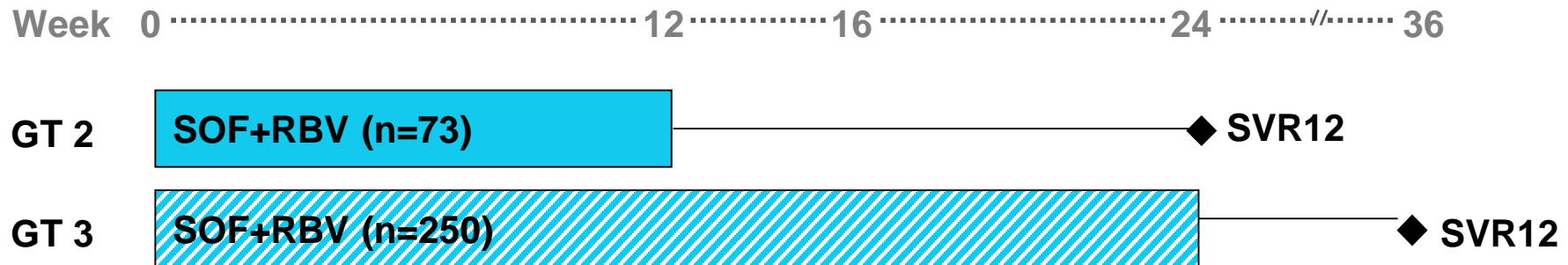
### ♦ Population:

- GT 2 or 3
- Interferon-naïve, interferon ineligible, or interferon failures
- Approximately 25% compensated cirrhosis

### ♦ Primary endpoint: SVR12

# Study Design

## GT 2,3 Treatment Naïve/Experienced (VALENCE)<sup>a</sup>



### ◆ Amendment to protocol

- Placebo stopped
- GT 3 extended to 24 wk, GT 2 unchanged

### ◆ Primary endpoint: SVR12

a. Post amendment study arms shown.

# Demographics and Baseline Characteristics

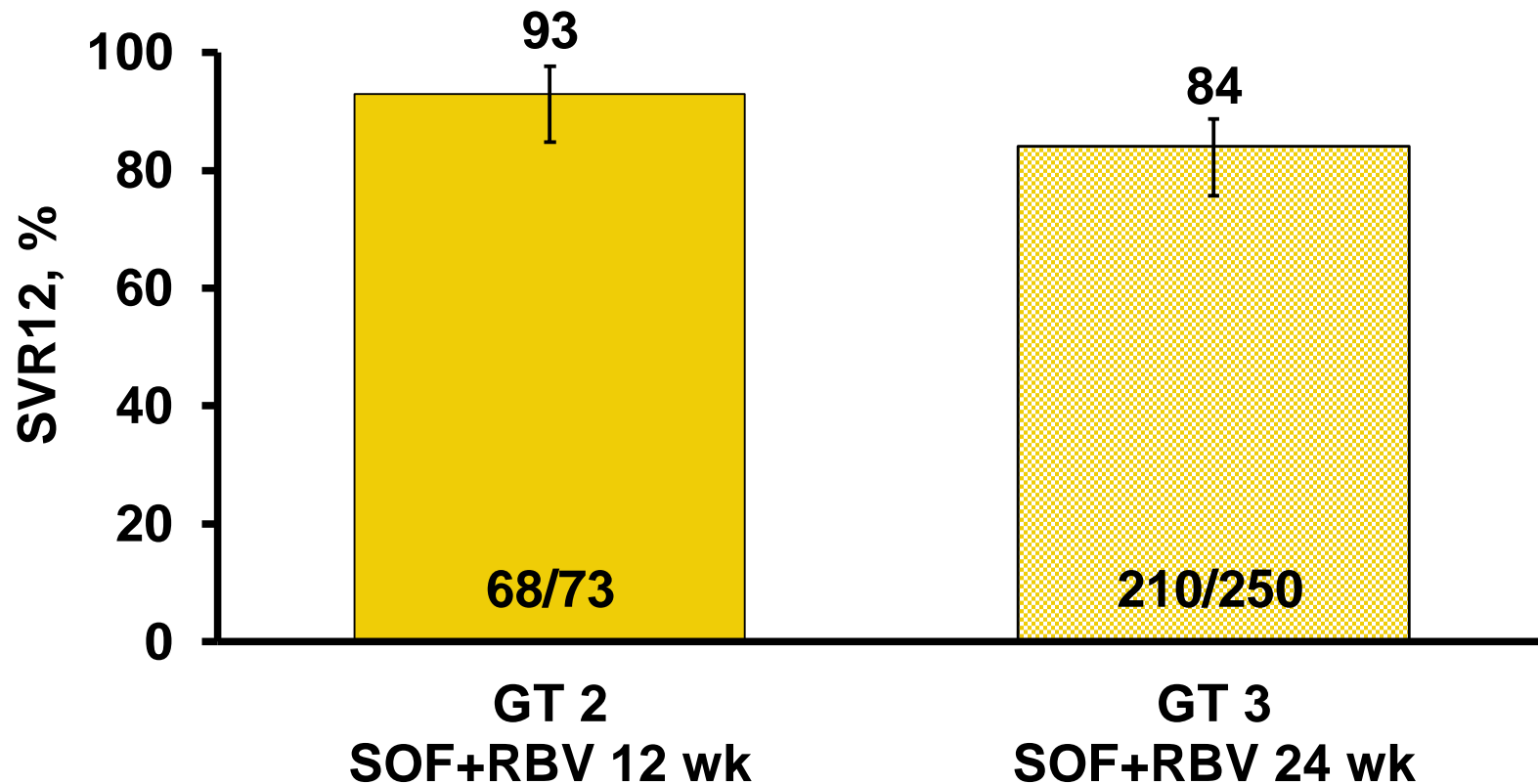
## GT 2,3 Treatment Naïve/Experienced (VALENCE)

Parameter	SOF+RBV 12 wk GT 2 (n=73)	SOF+RBV 24 wk GT 3 (n=250)
Mean age (range), y	58 (28–74)	48 (19–69)
Male, %	55	62
White, %	89	94
Mean BMI (range), kg/m <sup>2</sup>	26 (20–35)	25 (17–41)
IL28B CC, %	33	34
Cirrhosis, %	14	23
Treatment-naïve, %	44	42
Mean HCV RNA, log <sub>10</sub> IU/mL	6.5	6.3

# Efficacy Summary

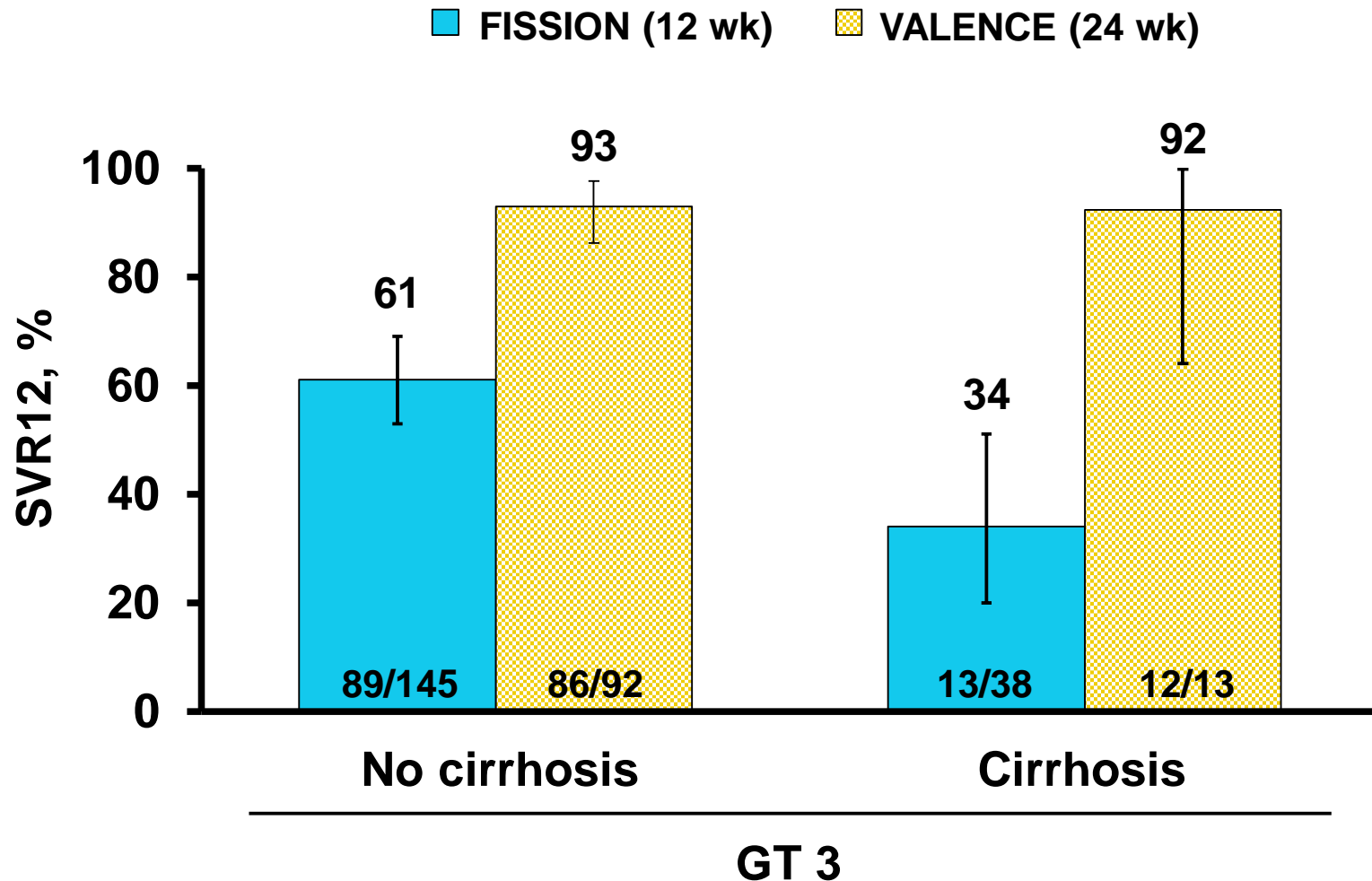
GT 2,3 Treatment Naïve/Experienced (VALENCE)

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# Results: SVR12 by Cirrhosis Status

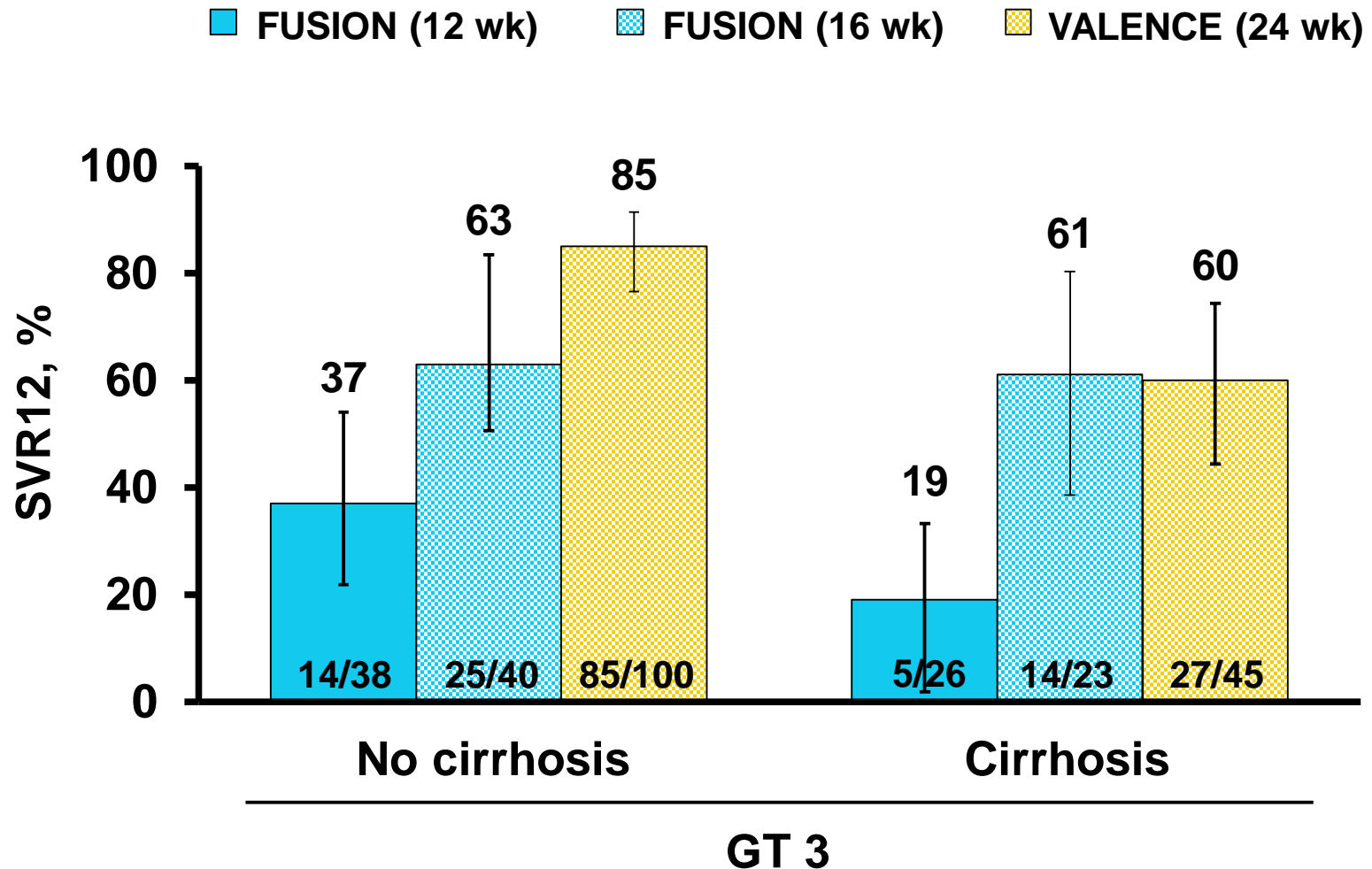
## GT 3 Treatment Naïve (FISSION and VALENCE)





# Results: SVR12 by Cirrhosis Status

GT 3 Treatment Experienced (FUSION and VALENCE)



# Summary of GT 2,3 Efficacy

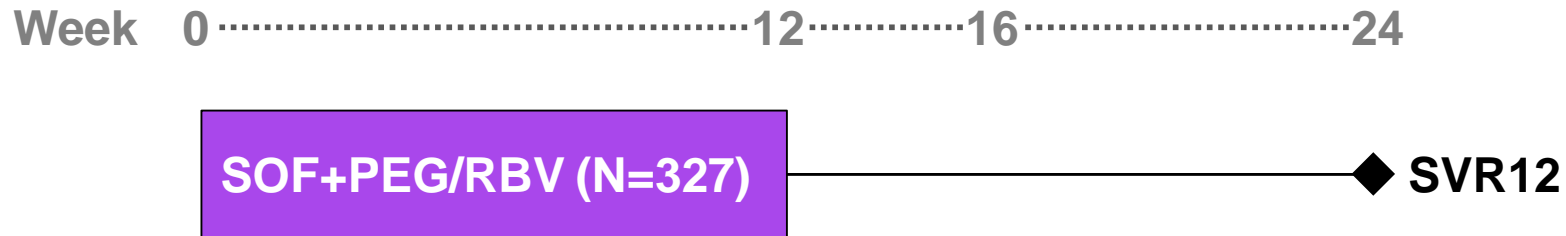
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- ◆ SOF+RBV met primary endpoint
- ◆ GT 2 patients achieved consistently high SVR rates across all studies
  - SOF+RBV for 12 weeks
- ◆ GT 3 patients achieved high SVR rates with longer therapy
  - SOF+RBV for 24 weeks

# Study Design

## GT 1,4,5,6 Treatment Naïve (NEUTRINO)

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- ◆ 327 patients enrolled and treated
  - 89% GT 1
  - 9% GT 4
  - <1% GT 5
  - 2% GT 6
- ◆ Primary endpoint: superiority to historical control rate of 60%

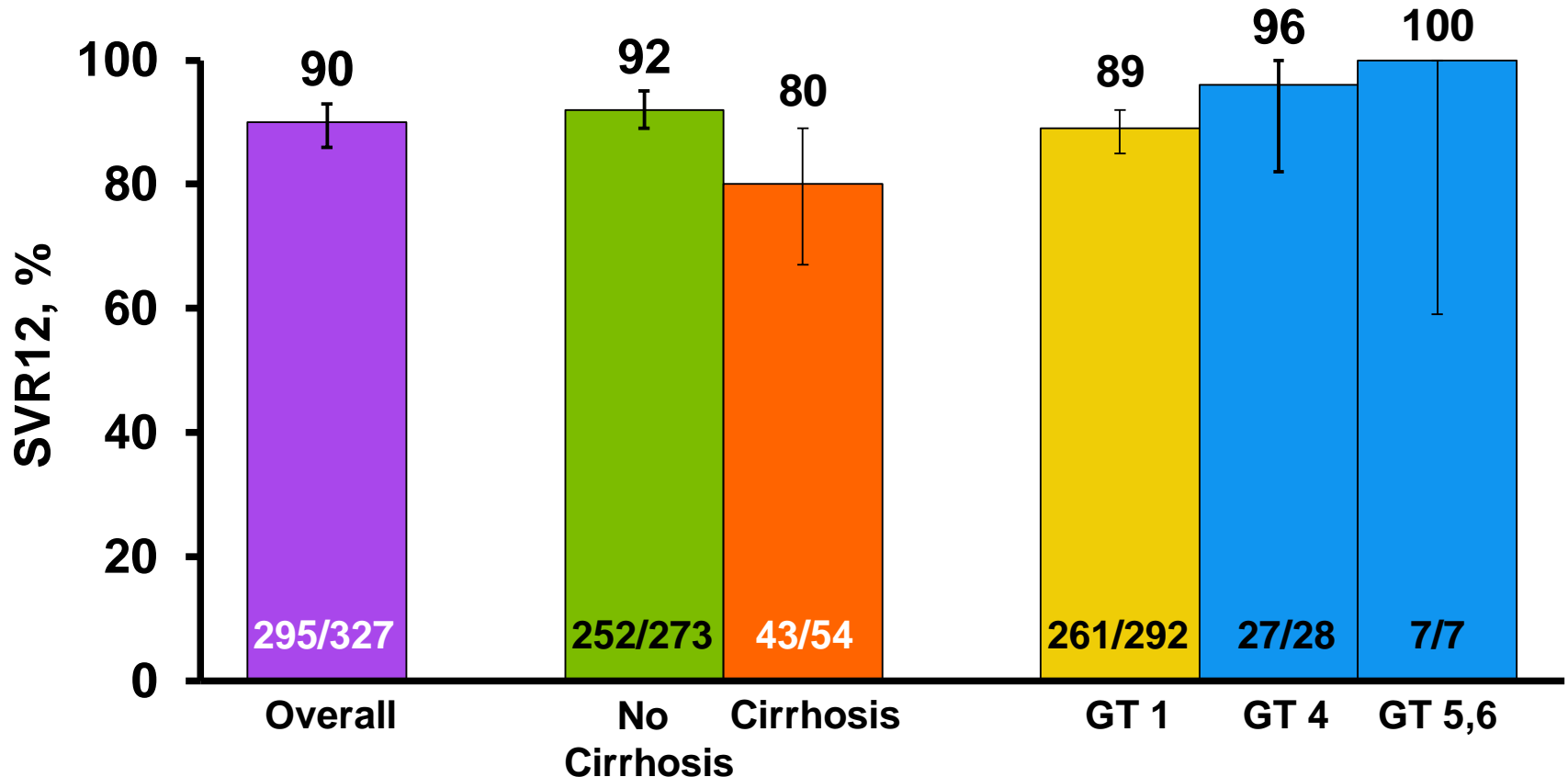
# Results: Demographics

## GT 1,4,5,6 Treatment Naïve (NEUTRINO)

Parameter	SOF+PEG/RBV (N=327)
Mean age (range), y	52 (19–70)
Male, n (%)	209 (64)
Black, n (%)	54 (17)
Hispanic, n (%)	46 (14)
Mean BMI (range), kg/m <sup>2</sup>	29 (18–56)
IL28B CC, n (%)	95 (29)
GT 1, n (%)	292 (89)
GT 4,5,6, n (%)	35 (11)
Mean baseline HCV RNA (range), log <sub>10</sub> IU/mL	6.4 (2.1–7.6)
Cirrhosis, n (%)	54 (17)

# Results: SVR12 Overall and by Subgroup

## GT 1,4,5,6 Treatment Naïve (NEUTRINO)



- ♦ Study met primary endpoint of superiority over historic control rate of 60% ( $p < 0.001$ )

# SOF+PEG/RBV 12 wk

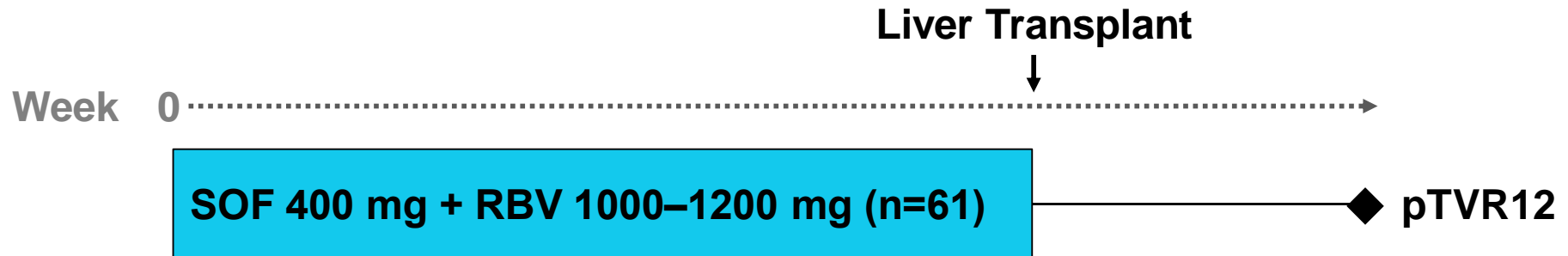
GT 1,4,5,6

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- ◆ Primary endpoint met in NEUTRINO
  - Results replicate Phase 2 results in GT 1 with same regimen
- ◆ GT 1 patients achieved high SVR rates overall and in major subpopulations
- ◆ GT 4 patients achieved a high SVR rate
  - Results consistent with Phase 2 results in GT 4 with 24-week regimen
- ◆ GT 5,6 patients: all achieved SVR
  - Small number reflects low prevalence in US

# Study Design: Pre-Liver Transplant

GT 1–6



- ◆ Objective: prevention of HCV recurrence following OLT
- ◆ Study entry criteria
  - Patients undergoing liver transplant for HCC due to HCV meeting Milan criteria
    - MELD score <22 and HCC-weighted MELD score ≥22
- ◆ Treatment duration: shorter of 24 weeks or until transplant
  - Re-treatment permitted if relapse after first treatment course
  - Recent amendment to allow up to 48 weeks

HCC=hepatocellular carcinoma; MELD=model for end-stage liver disease;  
OLT=orthotopic liver transplant; pTVR=post-transplant virologic response.

**CC-71**

Sofosbuvir Advisory Committee. October 25, 2013.

# Baseline Disease Characteristics: Pre-Liver Transplant

## GT 1–6

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	<b>SOF+RBV (N=61)</b>
<b>HCV RNA &gt;6 log<sub>10</sub> IU/mL, n (%)</b>	41 (67)
<b>Genotype, n (%)</b>	
1a	24 (39)
1b	21 (34)
2	8 (13)
3a	7 (12)
4	1 (2)
<b>IL-28B Non-CC allele, n (%)</b>	47/60 (78)
<b>Child-Turcotte-Pugh score, n (%)</b>	
5/6 (A)	44 (73)
7/8 (B)	17 (27)
<b>MELD score of 7 or 8, n (%)</b>	30 (49)
<b>Prior HCV treatment, n (%)</b>	46 (75)

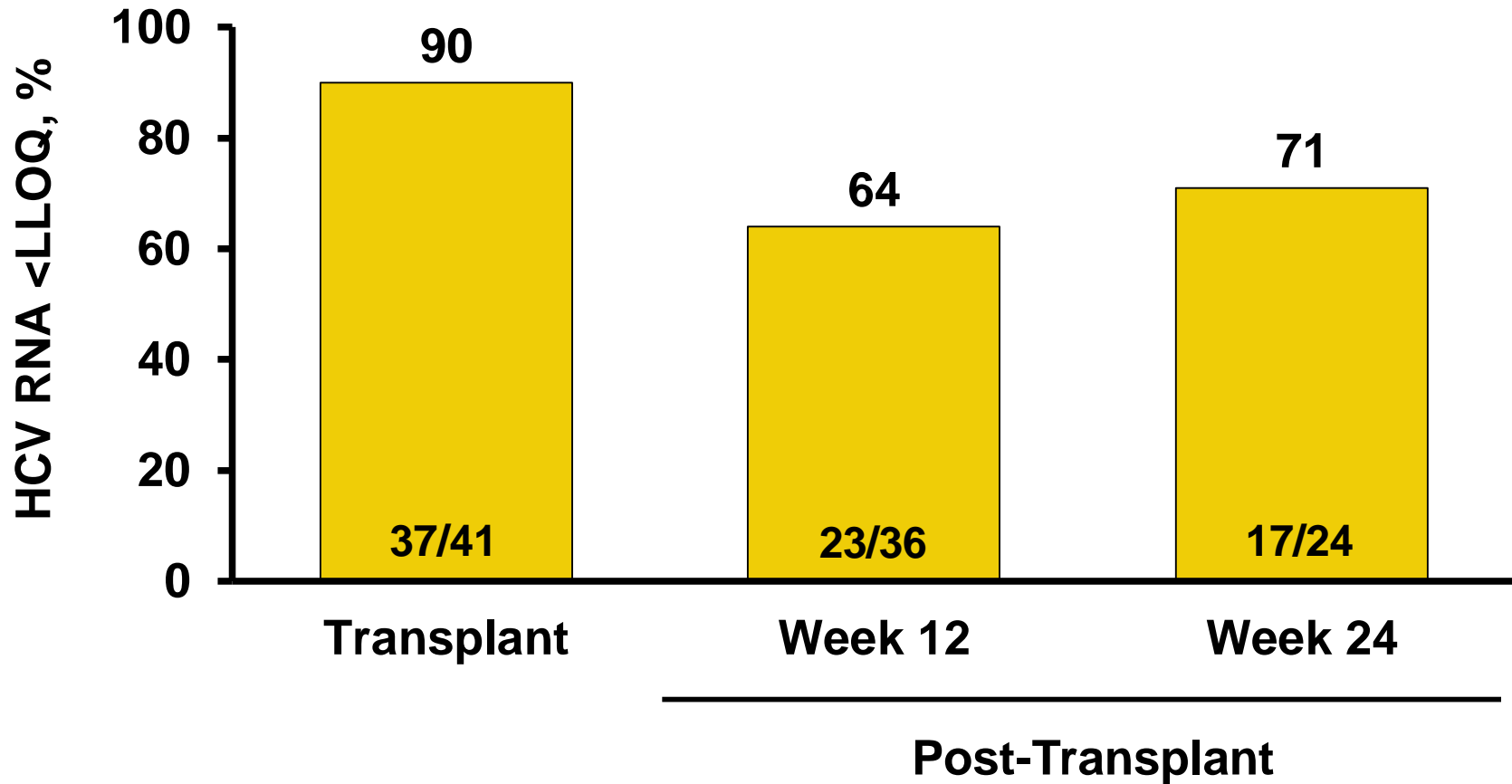
MELD=model for end-stage liver disease.



# Results: Post-Transplant Virologic Response

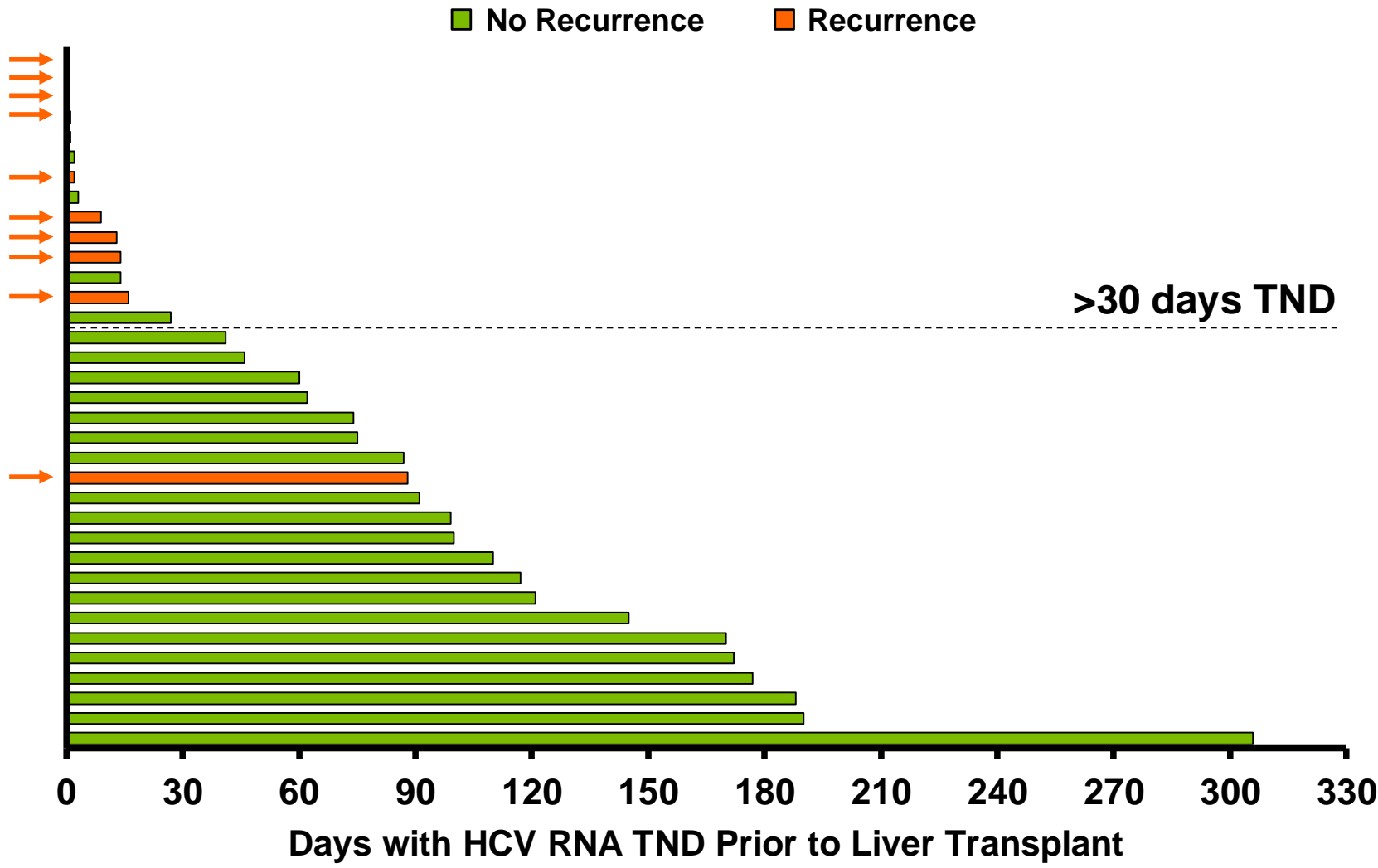
## GT 1–6

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# Time TND Pre-Transplant: pTVR vs Recurrence

## GT 1-4



# Resistance Surveillance in Phase 3 Studies

## GT 1–6

Study <sup>a</sup>	SOF+RBV %	SOF+PEG/RBV %
FISSION (n=74/256)	0	-
POSITRON (n=40/207)	0	-
FUSION (n=77/201)	0	-
NEUTRINO (n=29/327)	-	0

- ◆ S282T identified as primary mutation in all replicon genotypes (1–6)
- ◆ No genotypic or phenotypic resistance to sofosbuvir observed
- ◆ L159F identified in 3% of relapse patients; no phenotypic shift

n=number of patients analyzed for resistance.

# Summary of Phase 3 Studies

## GT 1–6

Study	Population	Total Patients	Cirrhosis, %	Lower Limit of Platelets
FISSION	GT 2,3 Treatment naïve	499	20	≥75,000/mm <sup>3</sup>
POSITRON	GT 2,3 IFN unable	278	16	No lower limit
FUSION	GT 2,3 Treatment experienced	201	34	≥50,000/mm <sup>3</sup>
NEUTRINO	GT 1,4,5,6 Treatment naïve	327	17	≥90,000/mm <sup>3</sup>
VALENCE	GT 2,3 All	419	21	>50,000/mm <sup>3</sup>
Total		1724	20	

- ◆ Expanded inclusion criteria
  - No upper limit for age or BMI
  - Opiate replacement therapy permitted

# Efficacy Conclusions

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- ◆ All Phase 3 studies achieved their primary efficacy endpoints
- ◆ High SVR rates in majority of HCV genotypes
- ◆ No on-treatment viral breakthrough
- ◆ No resistance in patients who do not achieve SVR
- ◆ Patients with cirrhosis can benefit from sofosbuvir based treatment regimens
- ◆ Treatment with SOF+RBV up to time of transplant may prevent reinfection in majority

# Proposed Sofosbuvir Dosage and Administration

## GT 1–6

<b>Patients</b>	<b>Duration</b>	<b>SOF Dose (Daily)</b>	<b>PEG Dose</b>	<b>RBV Dose (Daily)</b>
<b>Treatment naïve, GT 1, 4,5, or 6 CHC</b>	12 wk	400 mg	See PEG PI	See RBV PI
<b>GT 2 CHC</b>	12 wk	400 mg	--	<75 kg: 1000 mg ≥75 kg: 1200 mg
<b>GT 3 CHC</b>	24 wk	400 mg	--	<75 kg: 1000 mg ≥75 kg: 1200 mg
<b>Awaiting liver transplant</b>	Until transplant	400 mg	--	<75 kg: 1000 mg ≥75 kg: 1200 mg

CHC=chronic hepatitis C; PI=prescribing information.

**CC-78**

Sofosbuvir Advisory Committee. October 25, 2013.

# Clinical Safety

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Diana Brainard, MD  
Senior Director, Liver Diseases  
Gilead Sciences

# Sofosbuvir Safety Overview

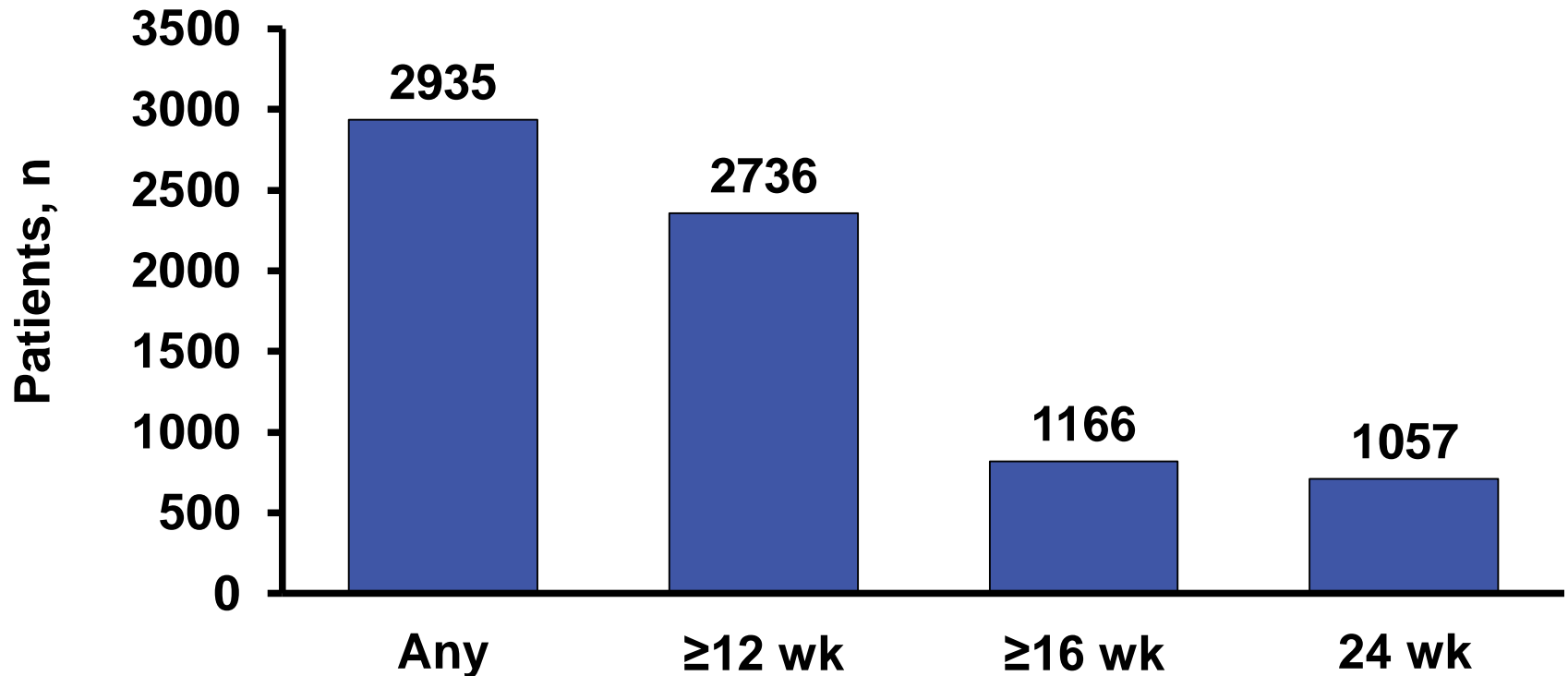
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- ◆ Sofosbuvir, in combination with other agents, is well tolerated
  - SOF+RBV studied in 1866 patients for up to 42 weeks
  - SOF+PEG/RBV studied in 891 patients for up to 24 weeks
- ◆ Safety profile defined by coadministered antivirals
- ◆ Safety profile similar across all subgroups including patients with cirrhosis (20% of Phase 3 population)
- ◆ Treatment discontinuation for AEs uncommon
- ◆ No additional toxicities associated with longer treatment duration



# Duration of Sofosbuvir Exposure

## Phase 2 and 3 Studies<sup>a</sup>



- ◆ In addition, 570 individuals received  $\geq 1$  dose of sofosbuvir in Phase 1 studies

a. Includes patients with safety data provided to the FDA after the original NDA submission.

# Safety Profile of IFN and RBV

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## IFN AEs<sup>1</sup>

- ◆ Constitutional
- ◆ Neuropsychiatric
- ◆ Hematologic
- ◆ Autoimmune
- ◆ Dermatologic
- ◆ Gastrointestinal

## RBV AEs<sup>2</sup>

- ◆ Hemolytic anemia
- ◆ Teratogenic
- ◆ Cough
- ◆ Pruritus
- ◆ Neuropsychiatric

IFN=interferon.

1. Pegasys and Pegintron prescribing information.

2. Brok J, et al. *Cochrane Database of Systematic Reviews*. 2009;4:1-64.

# Sofosbuvir Safety Analysis

## Phase 3 Studies and Pre-Transplant Study

### SOF+RBV Studies

#### GT 2,3 Treatment Naïve (FISSION)

PEG/RBV (N=243)

SOF+RBV (N=256)

#### GT 2,3 IFN-unable (POSITRON)

SOF+RBV (N=207)

PBO (N=71)

#### GT 2,3 Treatment Experienced (FUSION)

SOF+RBV (N=103) PBO

SOF+RBV (N=98)

#### GT 2,3 All<sup>a</sup> (VALENCE)

SOF+RBV (N=84)

SOF+RBV (N=250)

PBO (N=85)

#### Pre-Transplant Study

SOF+RBV until transplant (N=61)

### SOF+PEG/RBV Study

#### GT 1,4,5,6 Treatment Naïve (NEUTRINO)

SOF+PEG/RBV (N=327)

a. Includes treatment naïve, IFN-unable, and treatment experienced patients.

# Sofosbuvir Safety Analysis

## Pooled Analysis of Phase 3 SOF+RBV 12-Week Arms

### SOF+RBV Studies

#### GT 2,3 Treatment Naïve (FISSION)

PEG/RBV (N=243)

SOF+RBV (N=256)

#### GT 2,3 IFN-unable (POSITRON)

SOF+RBV (N=207)

PBO (N=71)

#### GT 2,3 Treatment Experienced (FUSION)

SOF+RBV (N=103) PBO

SOF+RBV (N=98)

### Pooled Analysis

**SOF+RBV  
12 wk  
(N=566)**

# GT 2,3 Phase 3 Studies: Patient Disposition

	Placebo (N=71)	SOF+RBV 12 wk (N=566)	SOF+RBV 16 wk (N=98)	PEG/RBV 24 wk (N=243)
Treatment Status	%	%	%	%
Completed	96	97	100	78
Discontinued	4	3	0	22
Reason for discontinuation				
AE	4	1	0	11
Virologic failure	0	<1	0	7
Lost to follow-up	0	<1	0	2
Other	0	<1	0	2
Withdrew consent	0	<1	0	<1
Death	0	<1	0	0

# GT 2,3 Treatment Naïve (FISSION): AE Summary

## SOF+RBV vs PEG/RBV

Patients	SOF+RBV <sup>a</sup> (N=256) %	PEG/RBV <sup>a</sup> (N=243) %
Any adverse event	86	96
Grade ≥3 AE	7	19
Serious AE	3	1
Treatment DC due to AE	1	11

a. RBV dose 1000–1200 mg/day for SOF+RBV and 800 mg/day for PEG/RBV.

# GT 2,3 Treatment Naïve (FISSION): Most Common AEs (≥15%) SOF+RBV vs PEG/RBV

Patients	SOF+RBV (N=256) %	PEG/RBV (N=243) %	p-value <sup>a</sup>
Fatigue	36	55	<0.001
Headache	25	44	<0.001
Nausea	18	29	0.006
Insomnia	12	29	<0.001
Rash	9	18	0.005
Diarrhea	9	17	0.007
Irritability	10	16	0.033
Decreased appetite	7	18	<0.001
Myalgia	8	16	0.006
Pruritus	7	17	<0.001
Flu-like symptoms	3	18	<0.001
Chills	3	18	<0.001

a. p-value from 2-sided Fisher's exact test.

# GT 2,3 Treatment Naïve (FISSION): Selected Laboratory Abnormalities SOF+RBV vs PEG/RBV

<b>Hematologic Abnormalities, Patients</b>	<b>SOF+RBV<sup>a</sup> (N=256) %</b>	<b>PEG/RBV<sup>a</sup> (N=243) %</b>
<b>Hemoglobin &lt;10.0 g/dL</b>	9	14
<b>Hemoglobin &lt;8.5 g/dL</b>	<1	2
<b>ANC &lt;750/mm<sup>3</sup></b>	0	15
<b>Platelets &lt;50,000/mm<sup>3</sup></b>	0	7
<b>Grade ≥3 Chemistry Abnormalities, Patients</b>		
<b>Bilirubin</b>	2	<1
<b>ALT</b>	0	4
<b>AST</b>	0	2
<b>CK</b>	2	<1
<b>Lipase</b>	<1	2

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase;  
CK=creatinine kinase.

a. RBV dose 1000–1200 mg/day for SOF+RBV and 800 mg/day for PEG/RBV.



# GT 2,3 IFN-Unable (POSITRON): AE Summary

## Placebo vs SOF+RBV

---

Patients	Placebo (N=71) %	SOF+RBV (N=207) %
Any adverse event	77	89
Grade ≥3 AE	1	8
Serious AE	3	5
Treatment DC due to AE	4	2

# GT 2,3 IFN-Unable (POSITRON): Most Common AEs (≥10%)

## Placebo vs SOF+RBV

Patients	Placebo (N=71) %	SOF+RBV (N=207) %	p-value <sup>a</sup>
Fatigue	24	44	0.003
Nausea	18	22	0.61
Headache	20	21	1.00
Insomnia	4	19	0.002
Pruritus	8	11	0.66
Anemia	0	13	<0.001

a. 2-sided p-value using Fisher’s exact test to assess difference between treatment arms.

# GT 2,3 IFN-Unable (POSITRON): Selected Laboratory Abnormalities Placebo vs SOF+RBV

<b>Hematologic Abnormalities, Patients</b>	<b>Placebo (N=71) %</b>	<b>SOF+RBV<sup>a</sup> (N=207) %</b>
<b>Hemoglobin &lt;10.0 g/dL</b>	0	7
<b>Hemoglobin &lt;8.5 g/dL</b>	0	<1
<b>ANC &lt;750/mm<sup>3</sup></b>	1	0
<b>Platelets &lt;50,000/mm<sup>3</sup></b>	3	0
<b>Grade ≥3 Chemistry Abnormalities, Patients</b>		
<b>Bilirubin</b>	0	2
<b>ALT</b>	8	<1
<b>AST</b>	14	0
<b>Lipase</b>	1	2

ALT=alanine aminotransferase; ANC=absolute neutrophil count;  
AST=aspartate aminotransferase.

a. RBV dose 1000–1200 mg/day for SOF+RBV.

**CC-91**

Sofosbuvir Advisory Committee. October 25, 2013.

# GT 2,3 Treatment Experienced (FUSION): AE Summary

## SOF+RBV 12 wk vs 16 wk

Patients	SOF+RBV 12 wk (N=103)	SOF+RBV 16 wk (N=98)
	%	%
Any adverse event	89	88
Grade ≥3 AE	8	4
Serious AE	5	3
Treatment DC due to AE <sup>a</sup>	<1	0

a. Occurred during placebo treatment period.

**GT 2,3 Treatment Experienced (FUSION):**  
**Most Common AEs (≥15%)**  
**SOF+RBV 12 wk vs 16 wk**

---

<b>Patients</b>	<b>SOF+RBV 12 wk (N=103) %</b>	<b>SOF+RBV 16 wk (N=98) %</b>
<b>Fatigue</b>	45	47
<b>Headache</b>	25	33
<b>Insomnia</b>	20	29
<b>Nausea</b>	21	20

# GT 2,3 Treatment Experienced (FUSION): Selected Laboratory Abnormalities SOF+RBV 12 wk vs 16 wk

<b>Hematologic Abnormalities, Patients</b>	<b>SOF+RBV 12 wk (N=103) %</b>	<b>SOF+RBV 16 wk (N=98) %</b>
<b>Hemoglobin &lt;10.0 g/dL</b>	11	5
<b>Hemoglobin &lt;8.5 g/dL</b>	2	0
<b>ANC &lt;750/mm<sup>3</sup></b>	<1	0
<b>Platelets &lt;50,000/mm<sup>3</sup></b>	2	0
<b>Grade ≥3 Chemistry Abnormalities, Patients</b>		
<b>Bilirubin</b>	2	2
<b>ALT</b>	0	2 <sup>a</sup>
<b>Lipase</b>	2	0

ALT=alanine aminotransferase; ANC=absolute neutrophil count.

a. Associated with virologic relapse.

**CC-94**

# GT 2,3 (VALENCE): AE Summary

## Placebo vs SOF+RBV for 12 or 24 Weeks

	Placebo 12 wk <sup>a</sup> (N=85) %	SOF+RBV 12 wk (N=84) %	SOF+RBV 24 wk (N=250) %
<b>Patients</b>			
<b>Any adverse event</b>	72	86	91
<b>Grade ≥3 AE</b>	5	4	7
<b>Serious AE</b>	2	0	4
<b>Treatment DC due to AE</b>	1	1	<1

a. Mean treatment duration in the placebo arm was 8 weeks prior to discontinuation of the study arm by Sponsor.

# GT 2,3 (VALENCE): Most Common AEs ( $\geq 15\%$ )

## Placebo vs SOF+RBV for 12 or 24 Weeks

<b>Patients</b>	<b>Placebo 12 wk<sup>a</sup> (N=85) %</b>	<b>SOF+RBV 12 wk (N=84) %</b>	<b>SOF+RBV 24 wk (N=250) %</b>
<b>Headache</b>	27	29	30
<b>Fatigue</b>	19	23	30
<b>Pruritus</b>	9	24	27
<b>Asthenia</b>	6	25	21
<b>Nausea</b>	11	31	13
<b>Insomnia</b>	2	11	16

- a. Mean treatment duration in the placebo arm was 8 weeks prior to discontinuation of the study arm by Sponsor.



# Pre-Liver Transplant Study: AE Summary

## SOF+RBV Until Liver Transplant

	<b>SOF+RBV (N=61) %</b>	<b>CPT A (N=44) %</b>	<b>CPT B (N=17) %</b>
<b>Patients</b>			
<b>Any adverse event</b>	90	86	100
<b>Grade <math>\geq 3</math> AE</b>	18	18	18
<b>Serious AE</b>	18	16	24
<b>Death (pneumonitis, SBP)</b>	3	2	6

- ◆ Median SOF+RBV treatment of 21 weeks (range 2–42)

# SOF+RBV: Safety Summary

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- ◆ SOF+RBV was well tolerated
  - Few discontinuations
  - Low rates of Grade  $\geq 3$  and serious AEs
- ◆ Improved safety profile as compared to current standard of care
- ◆ Adverse event profile consistent with RBV treatment
- ◆ Extending SOF+RBV treatment beyond 12 weeks does not impact the safety profile
- ◆ Safety profile similar in patients with more advanced liver disease

# Sofosbuvir Primary Safety Analysis

## SOF+RBV Studies

### GT 2,3 Treatment Naïve (FISSION)

PEG/RBV (N=243)

SOF+RBV (N=256)

### GT 2,3 IFN-unable (POSITRON)

SOF+RBV (N=207)

PBO (N=71)

### GT 2,3 Treatment Experienced (FUSION)

SOF+RBV (N=103) PBO

SOF+RBV (N=98)

### GT 2,3 All<sup>a</sup> (VALENCE)

SOF+RBV (N=84)

SOF+RBV (N=250)

PBO (N=85)

### Pre-Transplant Study

SOF+RBV until transplant (N=61)

## SOF+PEG/RBV Study

### GT 1,4,5,6 Treatment Naïve (NEUTRINO)

SOF+PEG/RBV (N=327)

a. Includes treatment naïve, IFN-unable, and treatment experienced patients.

# GT 1,4,5,6 Treatment Naïve (NEUTRINO): Patient Disposition

## SOF+PEG/RBV

---

Treatment Status	SOF+PEG/RBV (N=327) %
Completed	98
Discontinued	2
Reason for discontinuation	
Adverse event	2
Withdrew consent	<1
Protocol violation	<1

- ◆ Anemia was the only AE leading to treatment discontinuation in >1 patient (n=2)

# GT 1,4,5,6 Treatment Naïve (NEUTRINO): AE Summary

## SOF+PEG/RBV

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	<b>SOF+PEG/RBV (N=327) %</b>
<b>Patients</b>	
<b>Any adverse event</b>	95
<b>Grade <math>\geq 3</math> AE</b>	15
<b>Serious AE</b>	1
<b>Death</b>	0

- ◆ Grade  $\geq 3$  AEs occurring in  $>1\%$  of patients included neutropenia, anemia, fatigue, and headache

**GT 1,4,5,6 Treatment Naïve (NEUTRINO):**  
**Most Common AEs (≥15%)**  
**SOF+PEG/RBV**

---

<b>Patients</b>	<b>SOF+PEG/RBV (N=327) %</b>
<b>Fatigue</b>	59
<b>Headache</b>	36
<b>Nausea</b>	34
<b>Insomnia</b>	25
<b>Anemia</b>	21
<b>Rash</b>	18
<b>Decreased appetite</b>	18
<b>Pyrexia</b>	18
<b>Chills</b>	17
<b>Neutropenia</b>	17
<b>Pruritus</b>	17
<b>Flu-like symptoms</b>	16

**GT 1,4,5,6 Treatment Naïve (NEUTRINO):**  
**Most Common AEs (≥15%)**  
**SOF+PEG/RBV vs PEG/RBV (Through Week 12 of Treatment)**

	NEUTRINO SOF+PEG/RBV <sup>a</sup> (N=327)	FISSION PEG/RBV <sup>a</sup> (N=243)
Patients	%	%
Fatigue	58	51
Headache	36	43
Nausea	34	26
Insomnia	25	27
Anemia	21	7
Rash	17	12
Decreased appetite	17	17
Pyrexia	17	12
Chills	17	18
Neutropenia	17	10
Pruritus	16	13
Flu-like symptoms	16	17

a. RBV dose 1000–1200 mg/day for SOF+PEG/RBV and 800 mg/day for PEG/RBV.

# GT 1,4,5,6 Treatment Naïve (NEUTRINO): Selected Laboratory Abnormalities SOF+PEG/RBV

<b>Hematologic Abnormalities, Patients</b>	<b>SOF+PEG/RBV (N=327) %</b>
<b>Hemoglobin &lt;10.0 g/dL</b>	23
<b>Hemoglobin &lt;8.5 g/dL</b>	2
<b>ANC &lt;750/mm<sup>3</sup></b>	20
<b>Platelets &lt;50,000/mm<sup>3</sup></b>	<1
<b>Grade ≥3 Chemistry Abnormalities, Patients</b>	
<b>Bilirubin</b>	0
<b>ALT</b>	2
<b>AST</b>	3
<b>CK</b>	<1
<b>Lipase</b>	<1

ALT=alanine aminotransferase; ANC=absolute neutrophil count;  
AST=aspartate aminotransferase; CK=creatinine kinase.



# Anemia

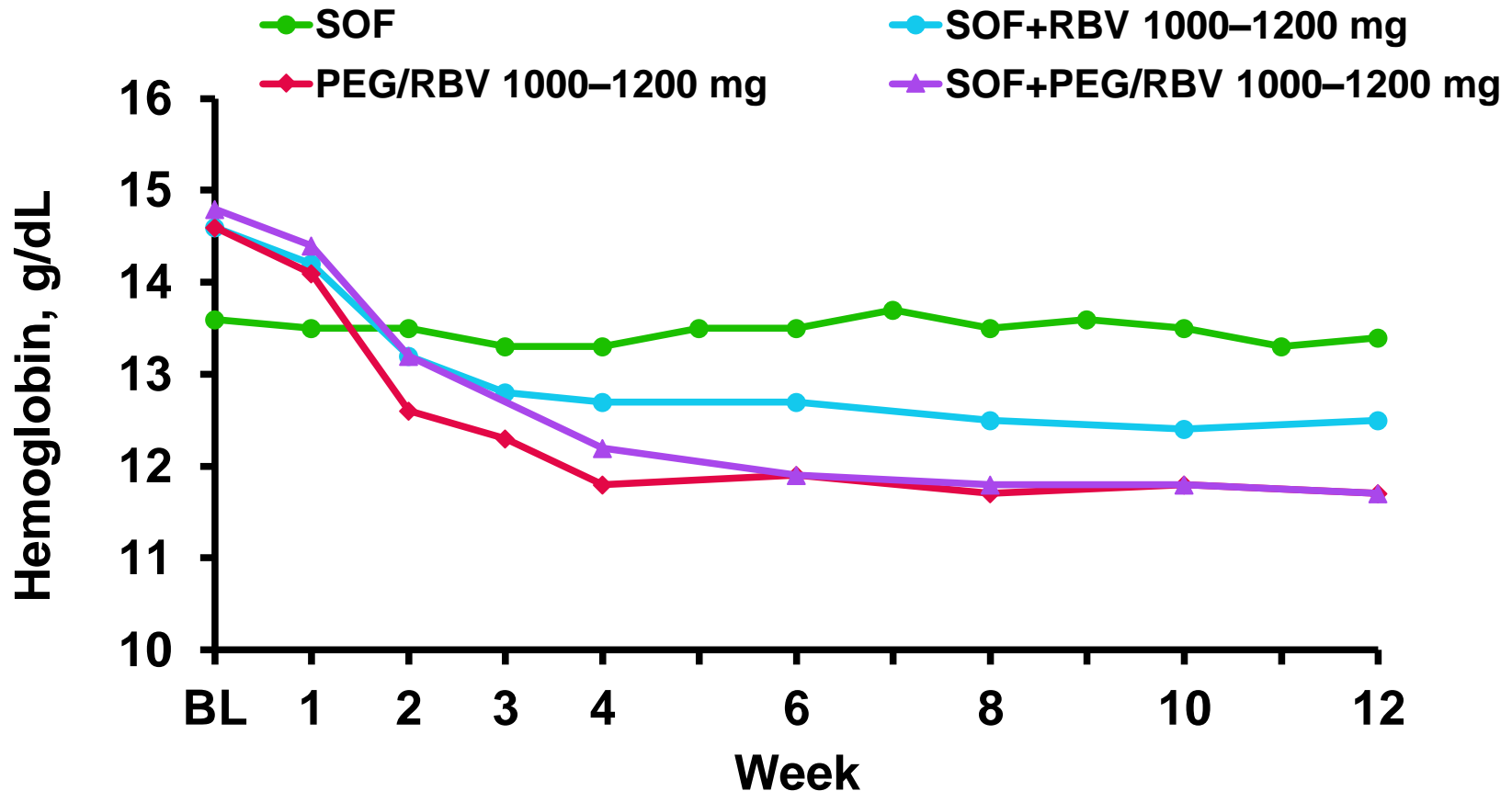
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- ◆ Anemia observed with SOF+RBV and SOF+PEG/RBV treatment
- ◆ Hemoglobin reductions with SOF+RBV similar to historical data with RBV monotherapy<sup>1,2</sup>
  - RBV monotherapy results in ~2 g/dL reduction
- ◆ Interferon contributes to anemia through bone marrow suppression
  - PEG/RBV results in ~3.5 g/dL reduction<sup>3</sup>
  - Less reticulocytosis

1. Dusheiko G, et al. *J Hepatology*. 1996;25:591-598.
2. DiBisceglie AM, et al. *Ann Intern Med*. 1995;123:897-903.
3. Pegasys/Copegus and Pegintron/Rebetol prescribing information.

# Mean Hemoglobin Level Over 12 Weeks

Sofosbuvir Monotherapy, SOF+RBV, PEG/RBV, SOF+PEG/RBV



- ◆ Sofosbuvir does not increase hemoglobin reductions seen with PEG/RBV 1000-1200 mg

SOF=monotherapy; SOF+RBV=pooled 12-week arms of Phase 3 studies;  
PEG/RBV=PROTON; SOF+PEG/RBV=NEUTRINO.

**CC-106**

Sofosbuvir Advisory Committee. October 25, 2013.

# Anemia Management

	Placebo (N=71) %	SOF+RBV <sup>a</sup> 12 wk (N=566) %	SOF+RBV <sup>a</sup> 16 wk (N=98) %	PEG/RBV <sup>b</sup> 24 wk (N=243) %	SOF+ PEG/RBV <sup>a</sup> (N=327) %
<b>AEs leading to RBV dose reduction</b>	<b>0</b>	<b>10</b>	<b>6</b>	<b>11</b>	<b>20</b>
Hb <10.0 g/dL	0	9	5	14	23
Hb <8.5 g/dL	0	<1	0	2	2

- ◆ Anemia managed through RBV dose reduction
  - Erythropoietin use not permitted
- ◆ Transfusion rate <1% in all treatment arms

a. RBV dose 1000–1200 mg/day for SOF+RBV and SOF+PEG/RBV.

b. RBV dose 800 mg/day for PEG/RBV.

# Sofosbuvir Safety Conclusions

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- ◆ Safety profile of sofosbuvir is defined by coadministered antivirals
  - RBV
  - PEG/RBV
- ◆ Sofosbuvir does not alter the expected AE profile of RBV or PEG/RBV
- ◆ Sofosbuvir-containing regimens are characterized by low rates of treatment discontinuations, Grade  $\geq 3$  AEs, and SAEs
- ◆ No treatment duration-related toxicities
- ◆ Safety profile similar across more vulnerable subgroups
  - Study population representative of US HCV-infected patients

# **Benefit / Risk**

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John McHutchison, MD  
Sr. Vice President, Liver Diseases  
Gilead Sciences

# Sofosbuvir: A Significant Advance for Patients



**GT 2**

**GT 3**

**SOF+RBV**  
All-oral therapy

**GT 1**

**GT 4**

**GT 5**

**GT 6**

**SOF+PEG/RBV**

- Short
- IFN limiting
- No response-guided treatment



**CC-110**

Sofosbuvir Advisory Committee. October 25, 2013.

# Sofosbuvir: Attributes

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- ◆ Once daily
- ◆ Oral
  - With or without food
- ◆ Few drug interactions
- ◆ No dose adjustments for special populations
- ◆ Unique MOA
  - Broad genotypic coverage
  - High barrier to resistance

# Demonstrated Benefits

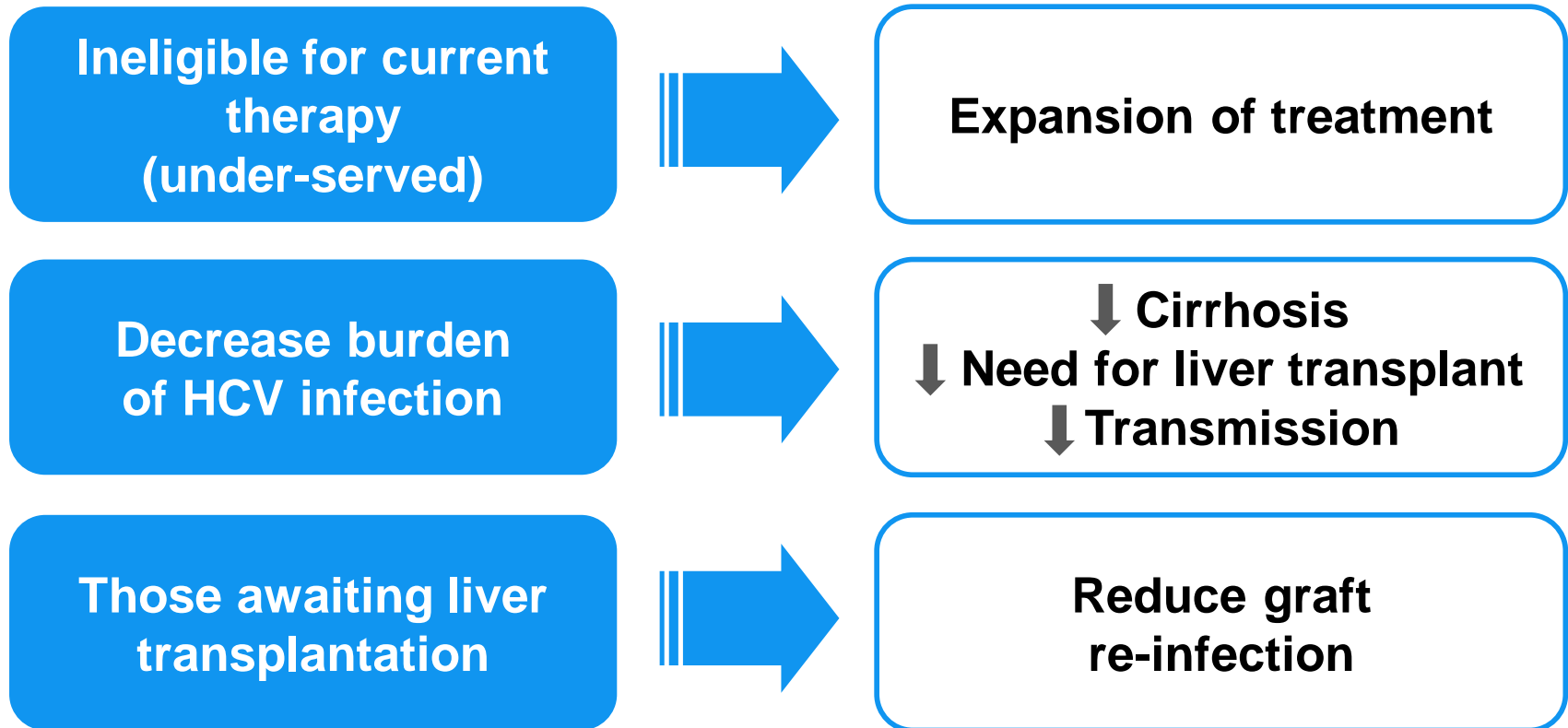
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- ◆ High SVR rates
- ◆ Shortened duration to 12–24 weeks
- ◆ Low risk of resistance
- ◆ Excellent safety and tolerability
- ◆ Efficacy and safety preserved in those patients with the greatest need
  - Pre-transplant
  - Compassionate use



# Potential Benefits

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# Demonstrated Risks

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- ◆ Ribavirin
  - Teratogenic effects
  - Hemolytic anemia
- ◆ Pegylated interferon
  - Neuropsychiatric, respiratory, autoimmune, and infectious events
  - Hematologic toxicity

# Potential Risks

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- ◆ Need further studies in
  - GT 1-infected patients, prior treatment failures
- ◆ Unknown risks in very advanced disease
  - Critically ill
  - Severe kidney and liver dysfunction

# Planned and Ongoing Studies

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- ◆ GT 1 infected patients
  - Phase 3 ongoing with fixed-dose combination of sofosbuvir plus an NS5A inhibitor (ledipasvir)
- ◆ GT 3 RCT
  - 16-wk SOF+RBV
  - 24-wk SOF+RBV
  - 12-wk: addition of PEG to SOF+RBV
- ◆ Special populations
  - Advanced liver disease
  - HIV/HCV coinfection
  - Severe renal impairment
- ◆ Pediatrics

# Benefit / Risk Conclusions

---

- ◆ Favorable benefit / risk for the treatment of all HCV GTs
- ◆ High SVRs across GT 1–6
- ◆ No resistance detected
- ◆ No additive safety burden
- ◆ First treatment option for many patients who currently have none
- ◆ Enables treatment of those in greatest clinical need

# Proposed Indication

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- ◆ Sofosbuvir is indicated for the treatment of chronic hepatitis C infection, in combination with other agents in adult patients with genotypes 1 to 6 and/or adult patients awaiting liver transplantation.

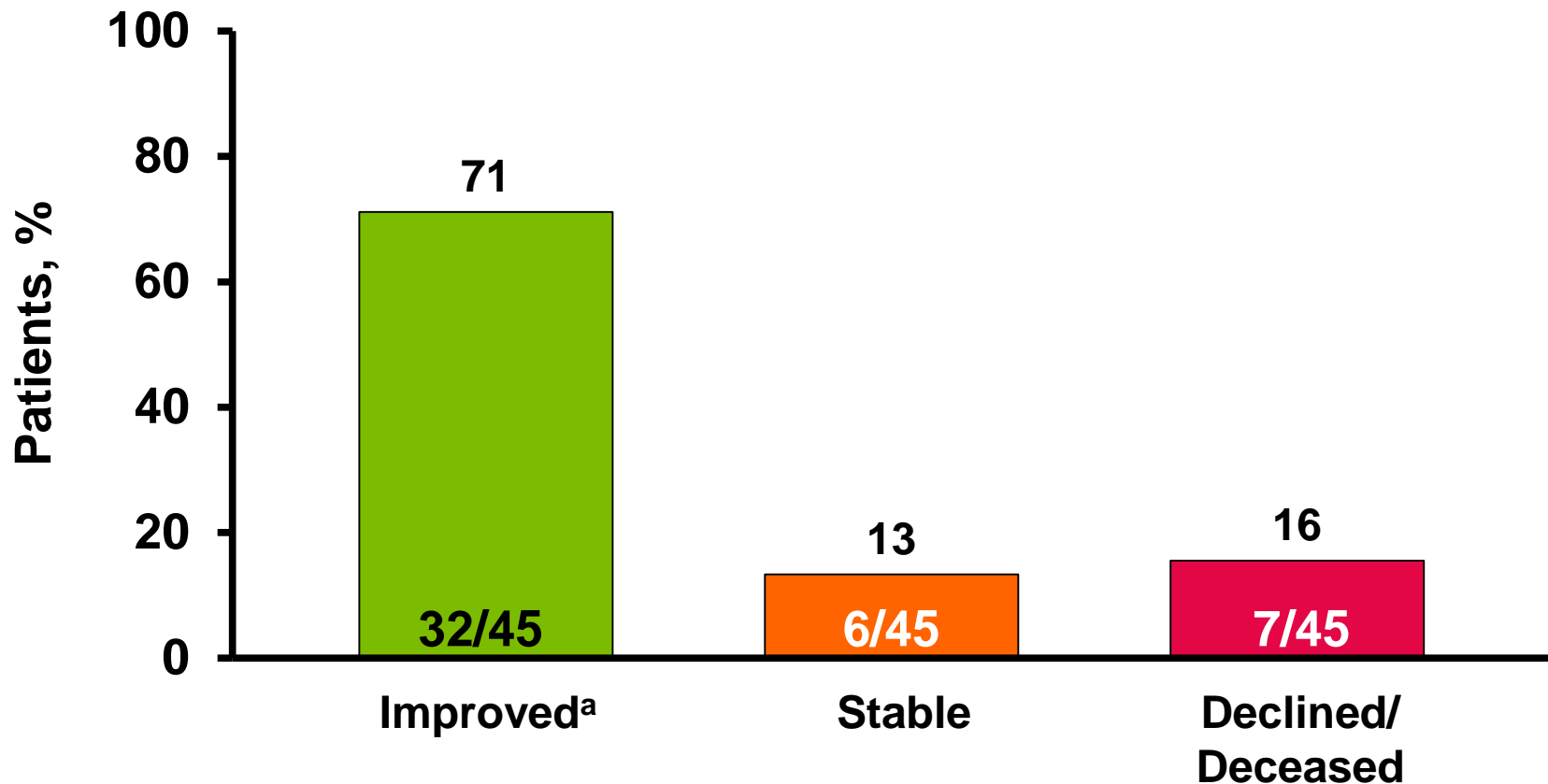
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# Backup Slides Shown

# Results: Clinical Outcomes

## GT 1–6 (Compassionate Use Study)

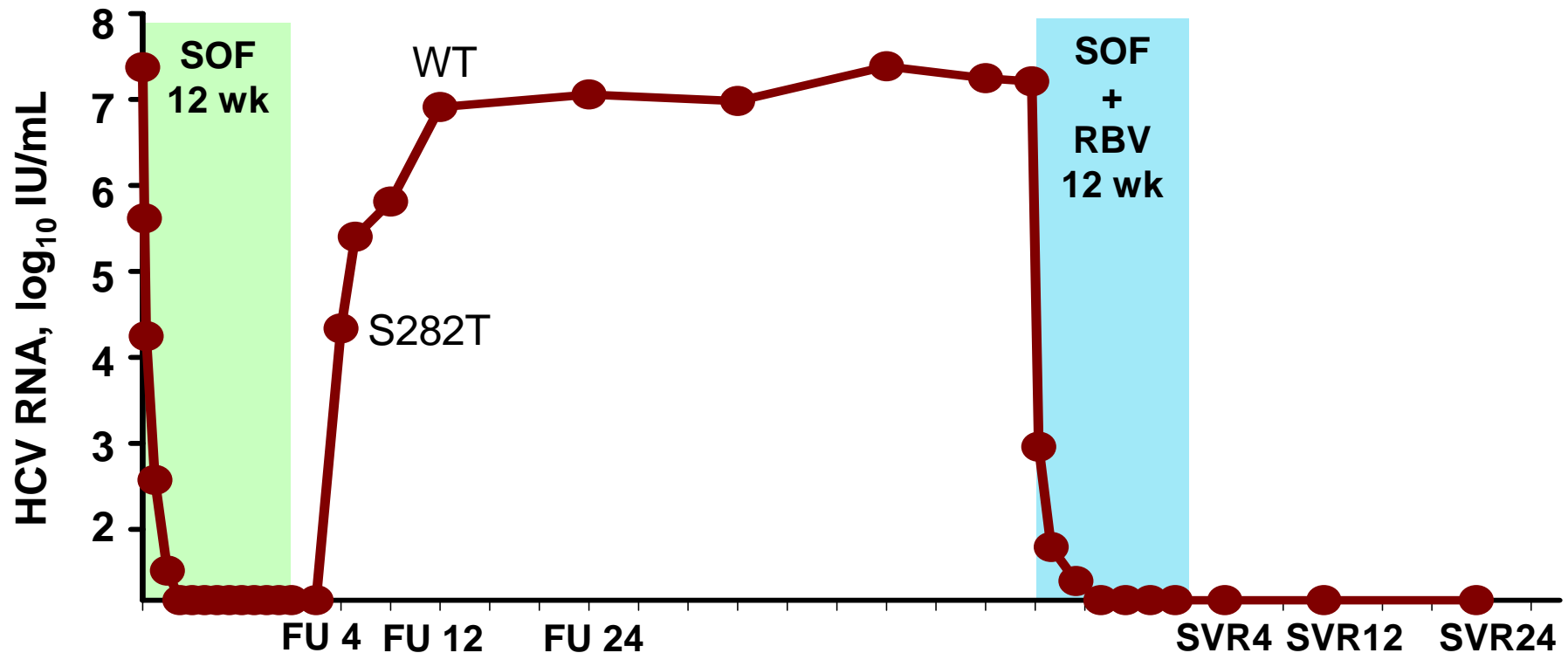
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- a. Improvement was defined as improvement of decompensation events; less hepatic encephalopathy, less ascites, improvement in liver related laboratory values.



# SOF+RBV Retreatment of Single GT 2b Patient with S282T Detected Following Sofosbuvir Monotherapy



**EF-319**

# Factors for Lack of Resistance to Sofosbuvir

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- ◆ Sofosbuvir binds to a highly conserved active site of NS5B
- ◆ S282T is the only known mutation conferring phenotypic resistance to sofosbuvir
  - Not associated with high level resistance (<20 fold)
- ◆ S282T results in a severe reduction of replication capacity in vitro and in vivo
- ◆ No S282T was detected in patients at baseline by population (n=1992) and deep sequencing (n=576)

# FISSION:

## SVR24 in SOF+RBV vs SVR12 in PEG/RBV

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	SOF+RBV n/N (%)	PEG/RBV n/N (%)
SVR12	170/253 (67.2)	162/243 (66.7)
SVR24	166/253 (65.6)	156/243 (64.2)

# SVR12 in Patients with HCV RNA $\geq$ LLOQ at Week 4

---

## ◆ GT 1: NEUTRINO

- 4 patients had quantifiable HCV RNA at Week 4
- 1/4 (25%) achieved SVR12

## ◆ GT 2,3: VALENCE excluded

- 7 patients had quantifiable HCV RNA at Week 4
- 1/7 (14%) achieved SVR12 (POSITRON)

## ◆ GT 3: VALENCE

- 3 patients had quantifiable HCV RNA at Week 4
- 1/3 (33%) achieved SVR12 (TN patient)
- 2/3 (67%) did not achieve SVR12 (TE patients)

# Effect of RBV Dose Reductions and Interruptions on SVR

## GT 2,3

	<b>FISSION<sup>a</sup></b>	<b>POSITRON<sup>a</sup></b>	<b>FUSION</b>	
	<b>SOF+RBV</b>	<b>SOF+RBV</b>	<b>SOF+RBV</b>	<b>SOF+RBV</b>
	<b>12 wk</b>	<b>12 wk</b>	<b>12 wk</b>	<b>16 wk</b>
	<b>(n=245)</b>	<b>(n=207)</b>	<b>(n=97)</b>	<b>(n=95)</b>
<b>Patients with RBV Dose Reductions/Interruptions</b>				
<b>SVR12, n/N (%)</b>	26/30 (87)	27/32 (84)	5/7 (71)	7/8 (88)
<b>95% CI</b>	69–96	67–95	29–96	47–100
<b>Patients without RBV Dose Reductions/Interruptions</b>				
<b>SVR12, n/N (%)</b>	143/210 (68)	133/168 (79)	45/90 (50)	62/87 (71)
<b>95% CI</b>	61–74	72–85	39–61	61–81

a. Imputed SVR12 failures due to missing data were excluded.

# Dose Reductions in PEG or RBV on SVR12

## GT 1 Treatment Naïve (NEUTRINO)

	Patients %	SVR12 Rate %
Overall		90
No dose reductions/interruptions	63	92
PEG dose reductions/interruptions	21	93
RBV dose reductions/interruptions	24	92
PEG and RBV dose reductions/interruptions	8	92

Study treatment completers only.

# Black Patients

## Summary

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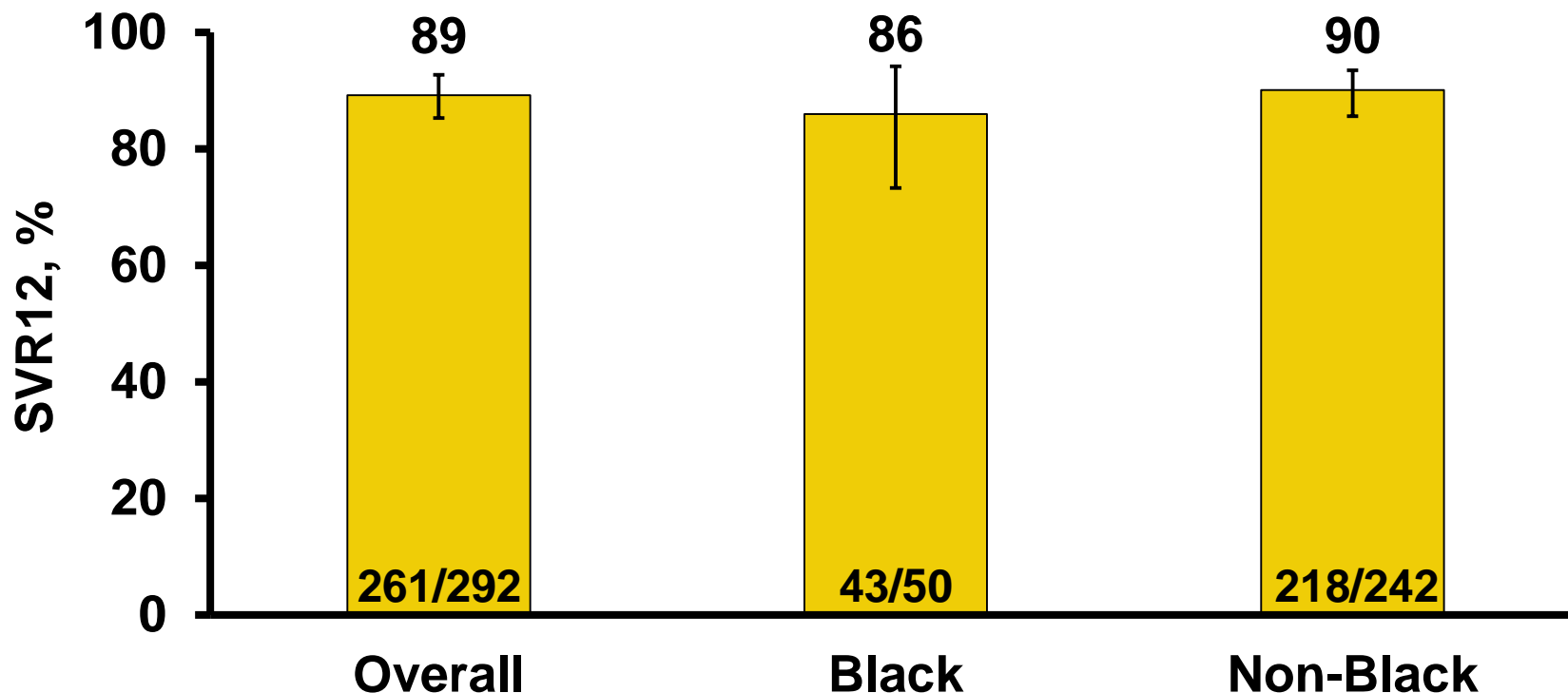
- ◆ 186 patients treated<sup>a</sup>
  - 100 with SOF+PEG/RBV
  - 86 with SOF+RBV<sup>a</sup>
- ◆ 143/186 (77%) achieved SVR12<sup>a</sup>
- ◆ 81 patients included in the Phase 3 studies

a. Includes 50 patients from SPARE.

# Influence of Race on SVR12 Results

GT 1 Treatment Naïve (NEUTRINO)

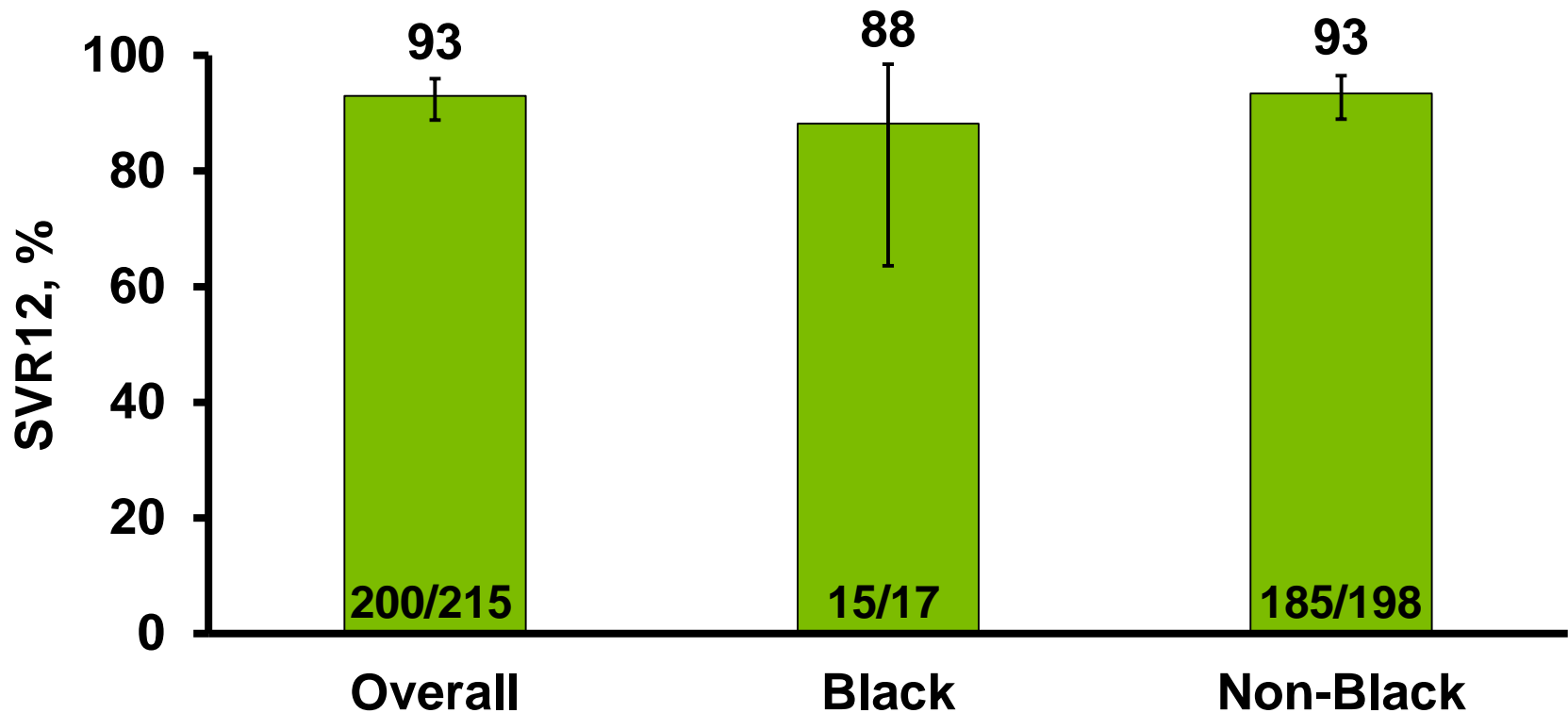
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# Influence of Race on SVR12 Results

GT 2 Phase 3 SOF+RBV 12-wk<sup>a</sup> Patients



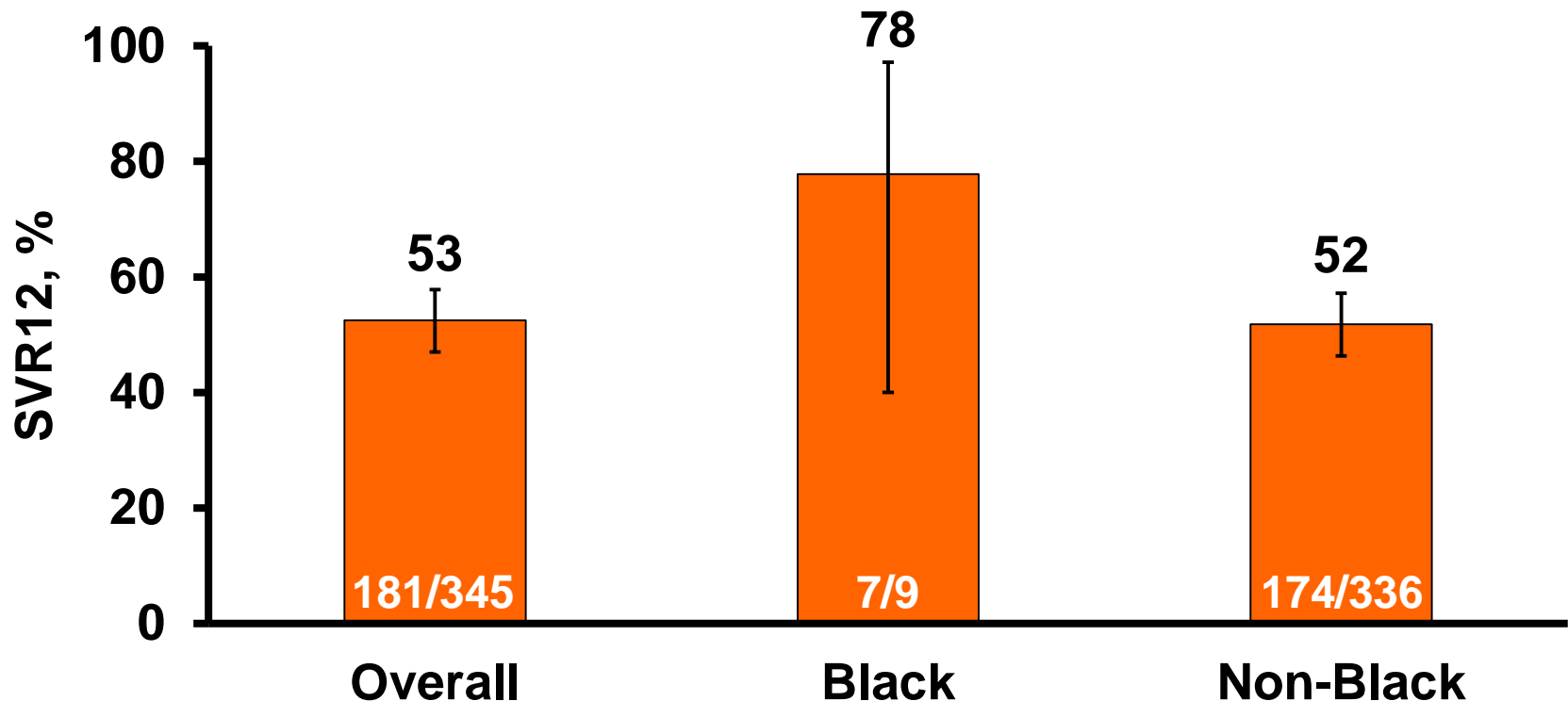
a. Pooled from 12-week SOF+RBV arms of FISSION, POSITRON, and FUSION.

**EF-112**

Sofosbuvir Advisory Committee. October 25, 2013.

# Influence of Race on SVR12 Results

GT 3 Phase 3 SOF+RBV 12-wk<sup>a</sup> Patients



a. Pooled from 12-week SOF+RBV arms of FISSION, POSITRON, and FUSION.

**EF-113**

Sofosbuvir Advisory Committee. October 25, 2013.

# Hispanic/Latino Patients

## Summary

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- ◆ 209 patients treated
  - 128 with SOF+PEG/RBV
  - 81 with SOF+RBV
- ◆ 170/209 (81%) achieved SVR12
- ◆ 123 patients included in the Phase 3 studies

# Concomitant Medication In Population PK Analyses

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- ◆ Anticoagulants
- ◆ Selective serotonin reuptake inhibitors
- ◆ Statins
- ◆ Calcium channel blockers
- ◆ Acid Reducing Agents (H2 receptor antagonists, and proton pump inhibitors)
- ◆ Diuretics
- ◆ Methadone

# Management of Potential Drug-Drug Interactions

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Concomitant Drug Class: Drug Name	Effect on Concentration
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<b>Anticonvulsants:</b>	
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Carbamazepine	
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Phenytoin	
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Phenobarbital	
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Oxcarbazepine	
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↓ SOF

<b>Antimycobacterials:</b>	
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Rifabutin	
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Rifapentine	
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Rifampin	
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↓ SOF

<b>Antiretrovirals:</b>	
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Tipranavir/ritonavir	
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↓ SOF

<b>Herbal supplements:</b>	
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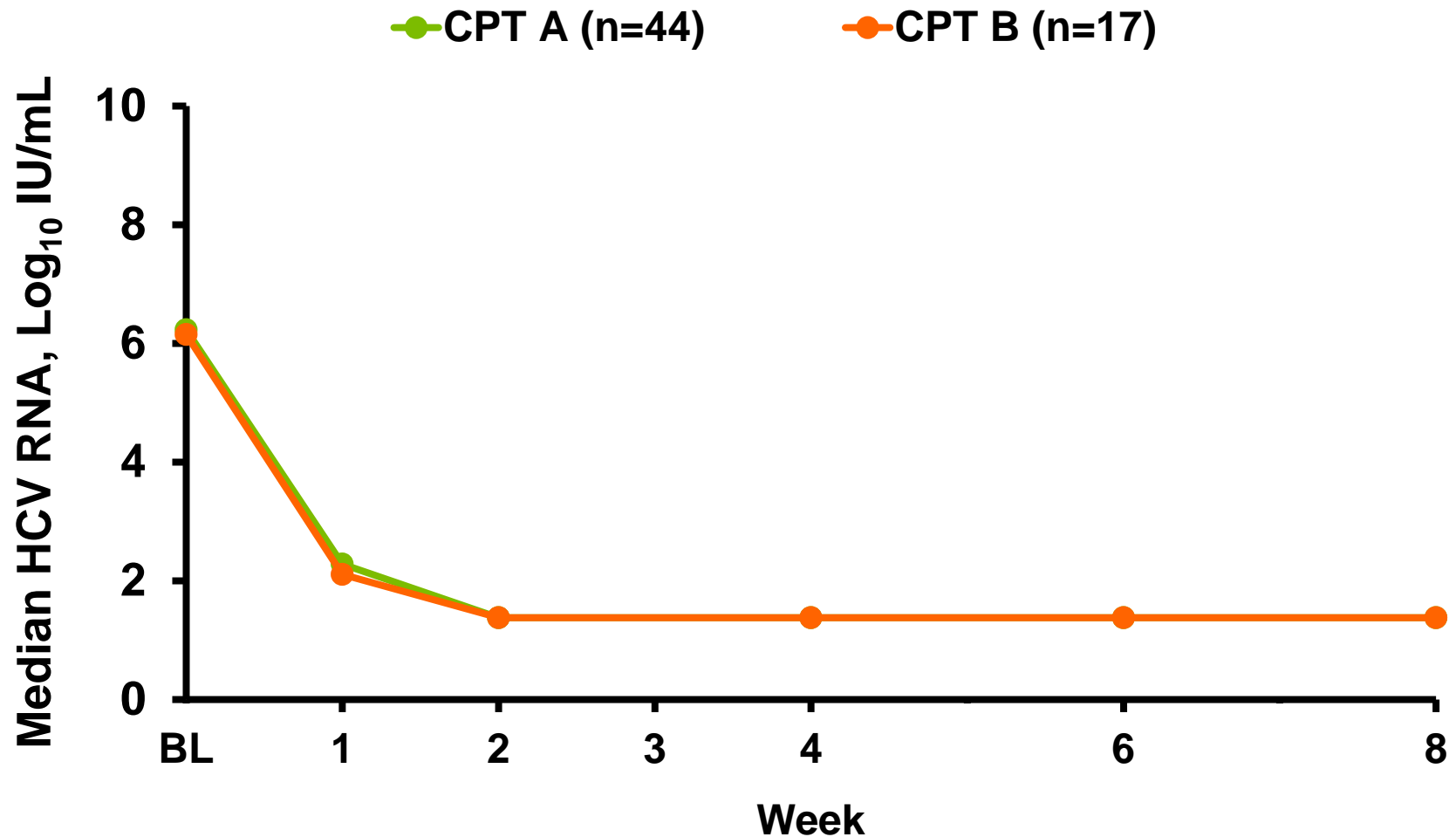
St John's Wort	
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↓ SOF

# Pre-Transplant: HCV RNA Reduction

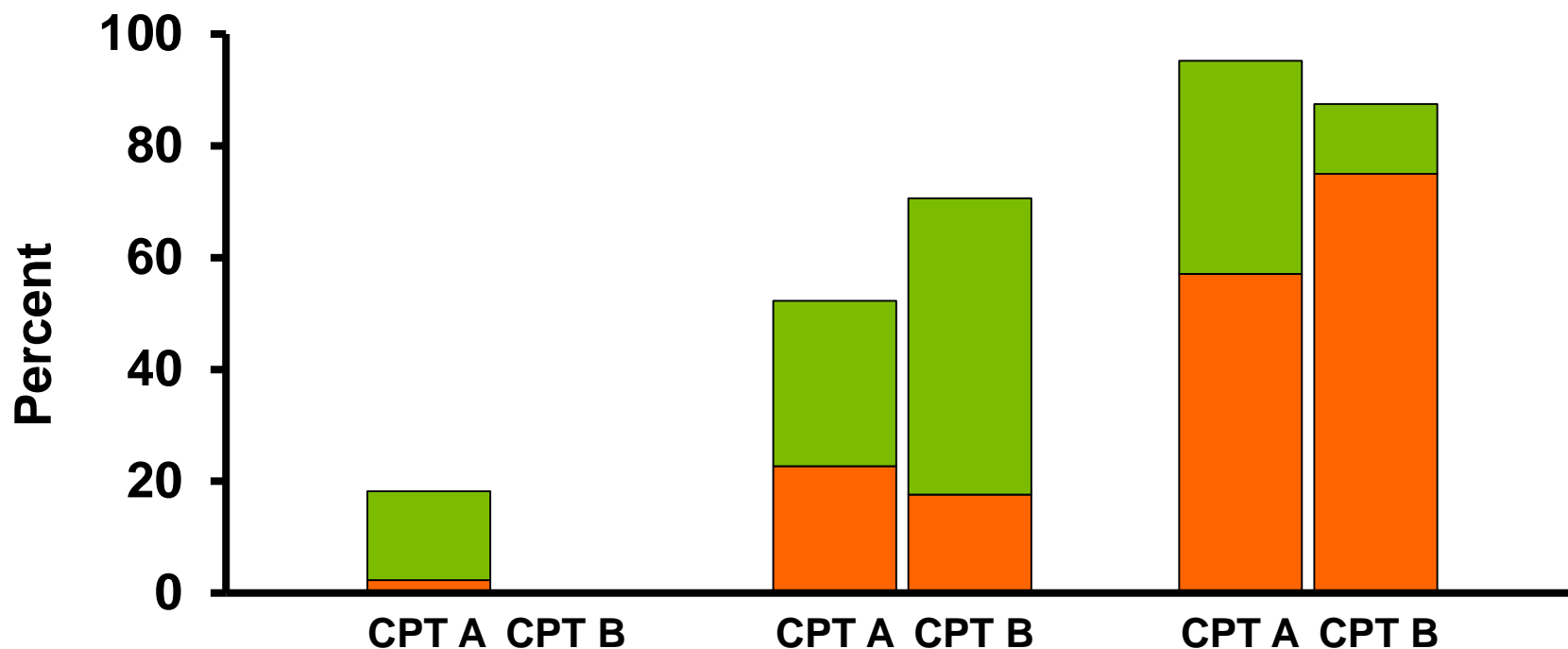
## CPT A vs CPT B



# Pre-Transplant: Early Viral Response (HCV RNA <LLOQ and <LLOQ, TND)

CPT A vs CPT B

■ <LLOQ, TND    ■ < LLOQ but ≥LOD

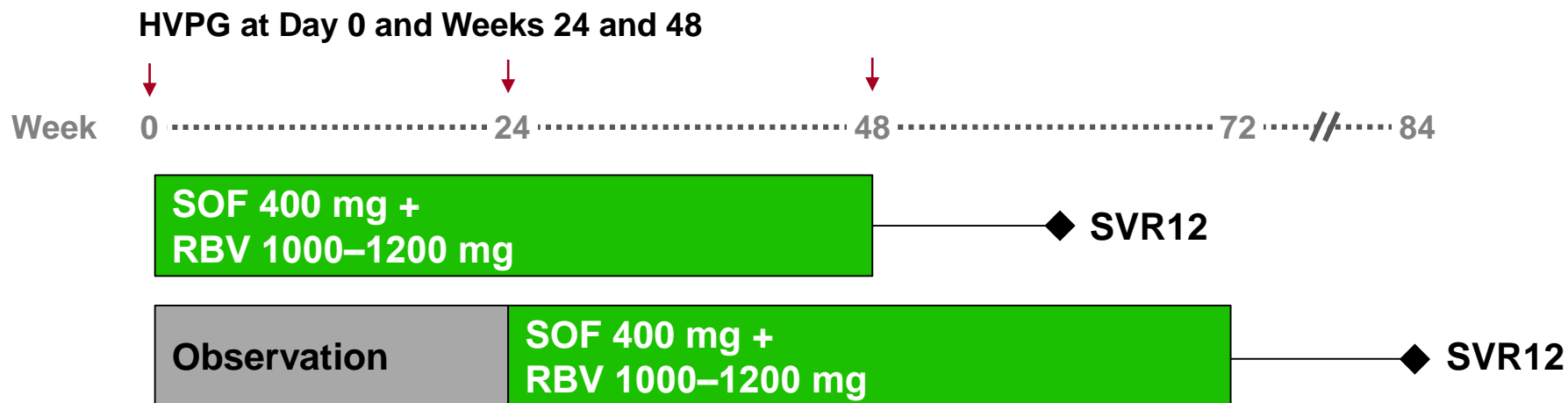


	Week 1		Week 2		Week 4	
LLOQ n/N=	8/44	0/17	23/44	12/17	40/42	14/16
LOD n/N=	1/44	0/17	10/44	3/17	24/42	12/16

**EF-205**

# Study Design

## GT 1–6 Decompensated Liver Disease



- ♦ Patients with decompensated disease
  - CTP 5–10 (60% CTP 7–10) with evidence of varices on endoscopy
  - HVPG >6 mmHg
- ♦ Primary endpoint: SVR12 status
  - Secondary endpoint: effects of SOF+RBV for 24 weeks on hepatic portal pressure and hepatic function
- ♦ Enrollment complete, study ongoing



# Creatine Kinase Elevations

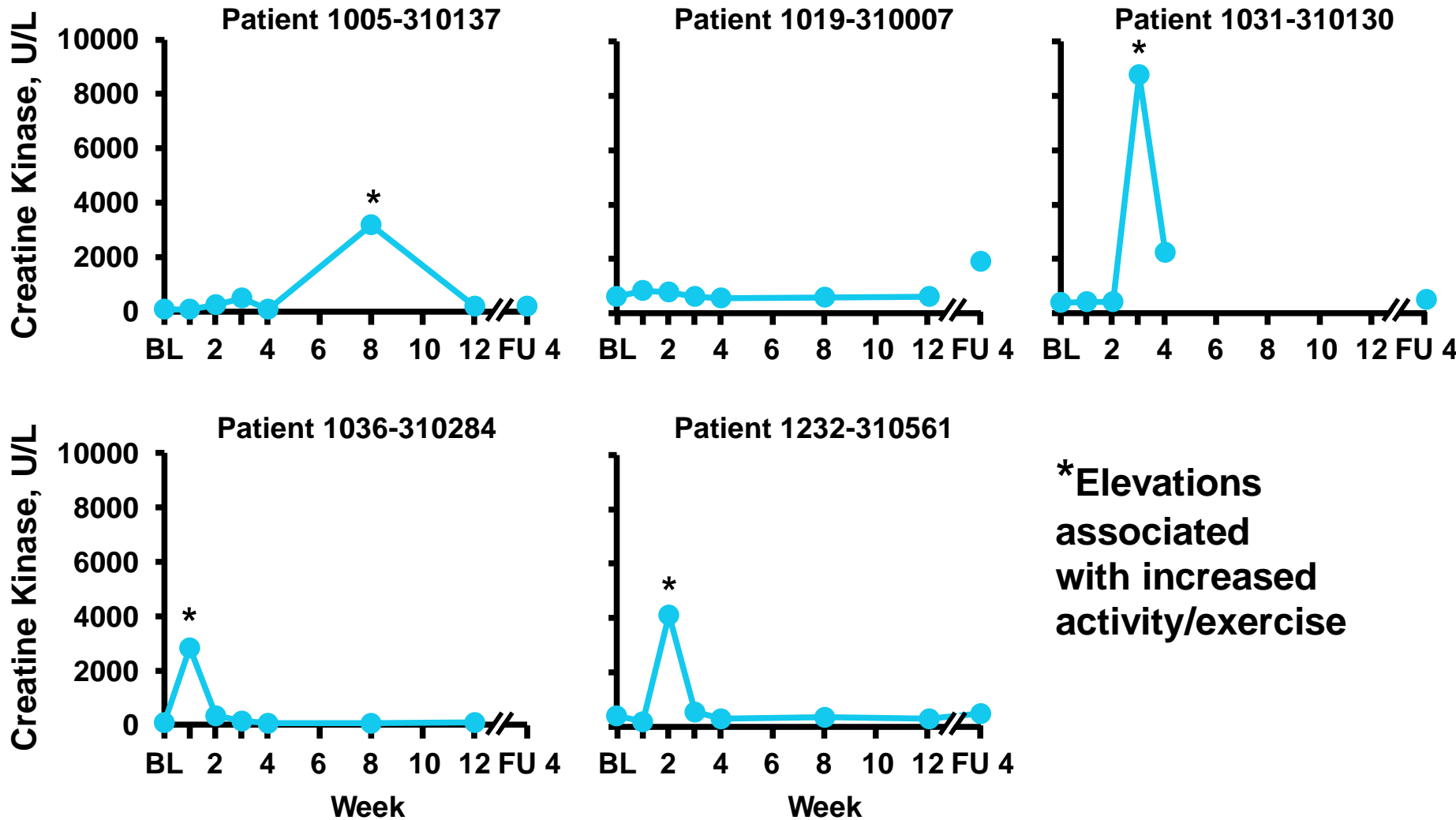
## Phase 3 Studies

Parameter	SOF+RBV (N=254) %	PEG/RBV (N=242) %	SOF+PEG/RBV (N=327) %
Total	7	4	3
Grade 1, 3 to <6 x ULN	4	2	2
Grade 2, 6 to <10 x ULN	<1	1	<1
Grade 3, 10 to <20 x ULN	1	0	<1
Grade 4, ≥20 x ULN	<1	<1	0

UPN=upper limit of normal.

# Patients with Grade 3–4 Elevation in Creatine Kinase

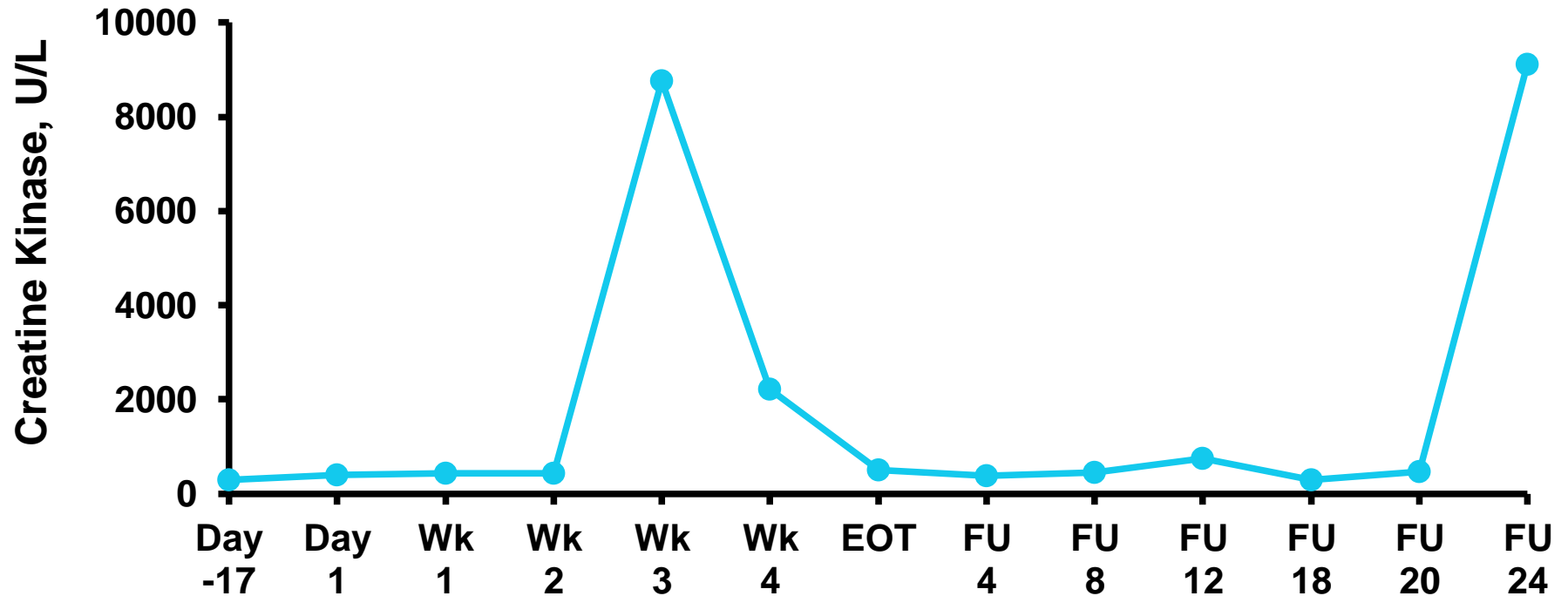
## SOF+RBV



FU 4=4-wk follow-up.

# Creatine Kinase Profile of Patient 310130

SOF+RBV



- ◆ 42-year-old male with cirrhosis
- ◆ Concomitant medications: methadone, diazepam
- ◆ Intensive manual labor on the day prior to the Week 3 visit

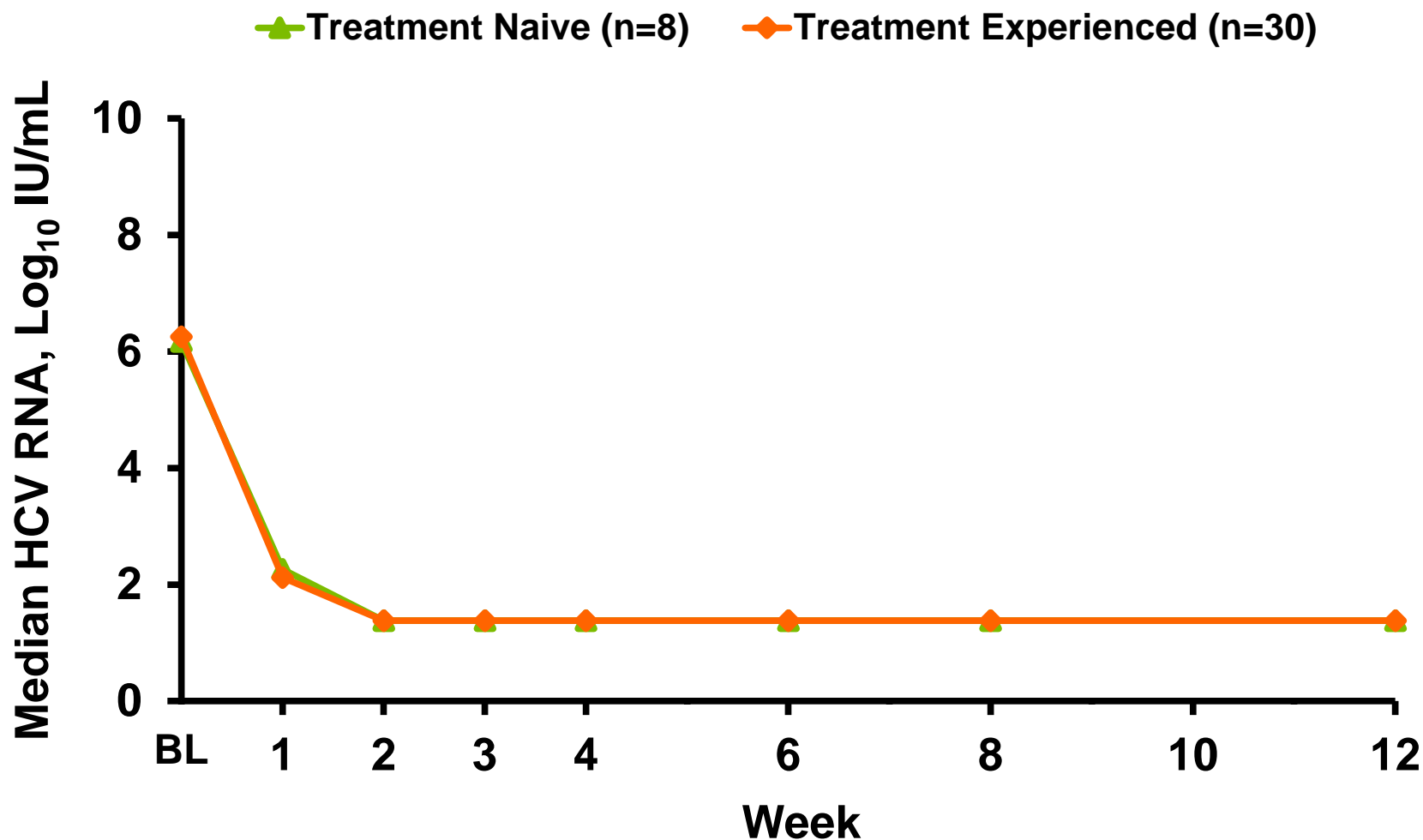
EOT=end of treatment; FU=follow-up week.

**SA-244**

Sofosbuvir Advisory Committee. October 25, 2013.

# HCV RNA Reduction By Any Prior Treatment

## GT 1-4 (Pre-Transplant Study)



**EF-198**

Sofosbuvir Advisory Committee. October 25, 2013.

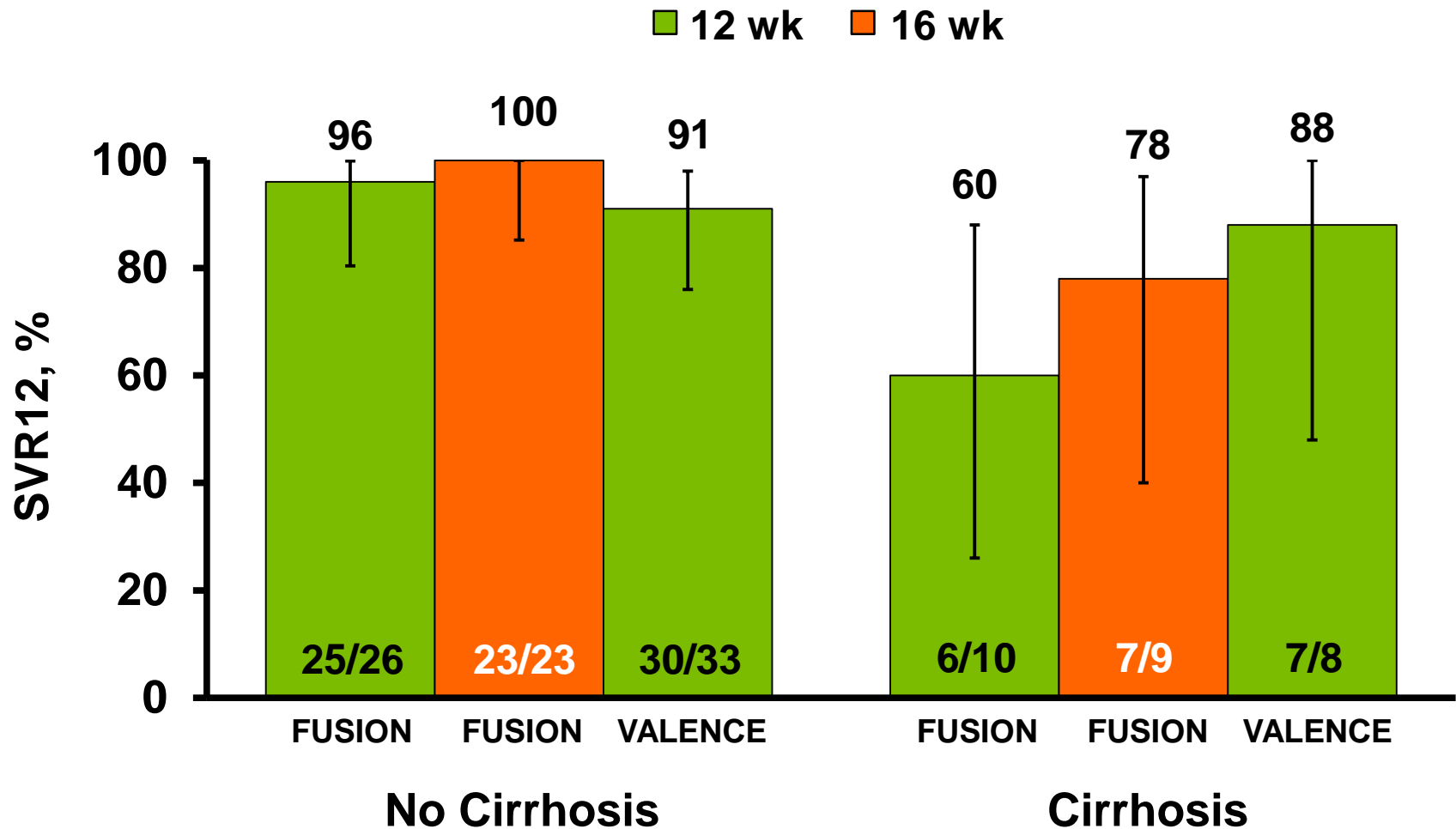
# Baseline Characteristics for Recurrence and No Recurrence

## GT 1–4 (Pre-Transplant Study)

Parameter	Recurrence (N=10)	No Recurrence (N=28)
Median age, y	59	58
Male, %	70	71
IL28B CC, %	0	36
GT, n (%)		
1a	2 (20)	11 (39)
1b	7 (70)	8 (29)
2a	0 (0)	1 (4)
2b	0 (0)	4 (14)
3a	1 (10)	3 (11)
4a	0 (0)	1 (4)
Child-Pugh		
CPT A (5–6), n (%)	8 (80)	20 (71)
CPT B (7–9)	2 (20)	8 (29)
BL platelet count, median	106	97
Treatment naïve, n/N (%)	1/10 (10)	7/28 (25)

# SVR12 in Phase 3

## GT 2 Treatment-Experienced Patients



**EF-282**

# Post-Transplant Outcome in Treatment-Experienced Patients

## Pre-Transplant Study

---

	PEG/RBV (N=38)	PEG (N=5)	PI+PEG/RBV (N=3)
No recurrence	17	2	2
Recurrence	9 <sup>a</sup>	3 <sup>b</sup>	0
No transplant	9	0	1
Death post-transplant	3	0	0

a. 2 HCV RNA >LLOQ at transplant.  
b. 1 HCV RNA >LLOQ at transplant.

# Sofosbuvir Compassionate Use/Expanded Access **Treated** Patients by Region

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**Overall: 285**

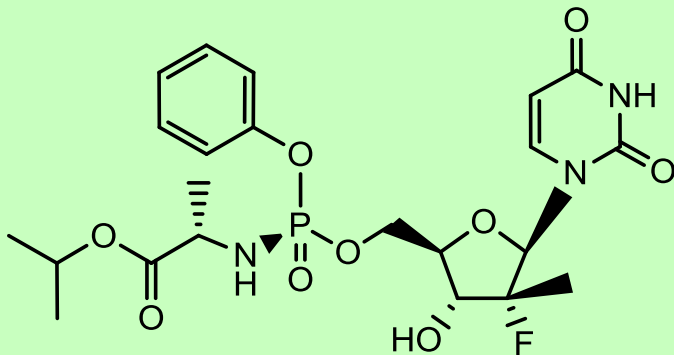
**RR-11**



# Structural Comparison

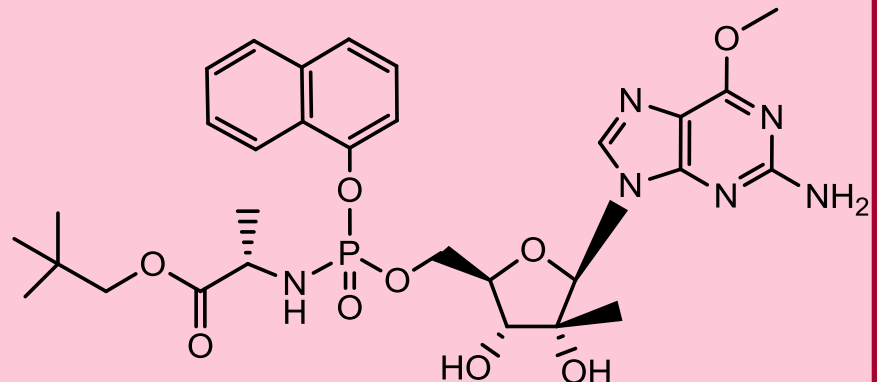
## Sofosbuvir and BMS-094

### Sofosbuvir



- Uridine nucleotide prodrug
- 2'F,2'CMe Substitutions

### BMS-094



- Guanosine nucleotide prodrug
- 2'CMe Substitution

# In Vitro Cytotoxicity

## Cell Lines

	Cell Lines CC <sub>50</sub> , µM				
	Liver		Prostate	Fibroblast	T-Cell
	Huh7	HepG2	PC3	MRC-5	MT-4
SOF	66	>89	>89	>89	>100
BMS-094	0.47	1.9	0.45	1.1	1.1

No meaningful toxicity was observed with sofosbuvir;  
however, BMS-094 showed cytotoxicity in vitro

CC<sub>50</sub>=50% cytotoxic concentration.

# In Vitro Cytotoxicity

## Primary Cells

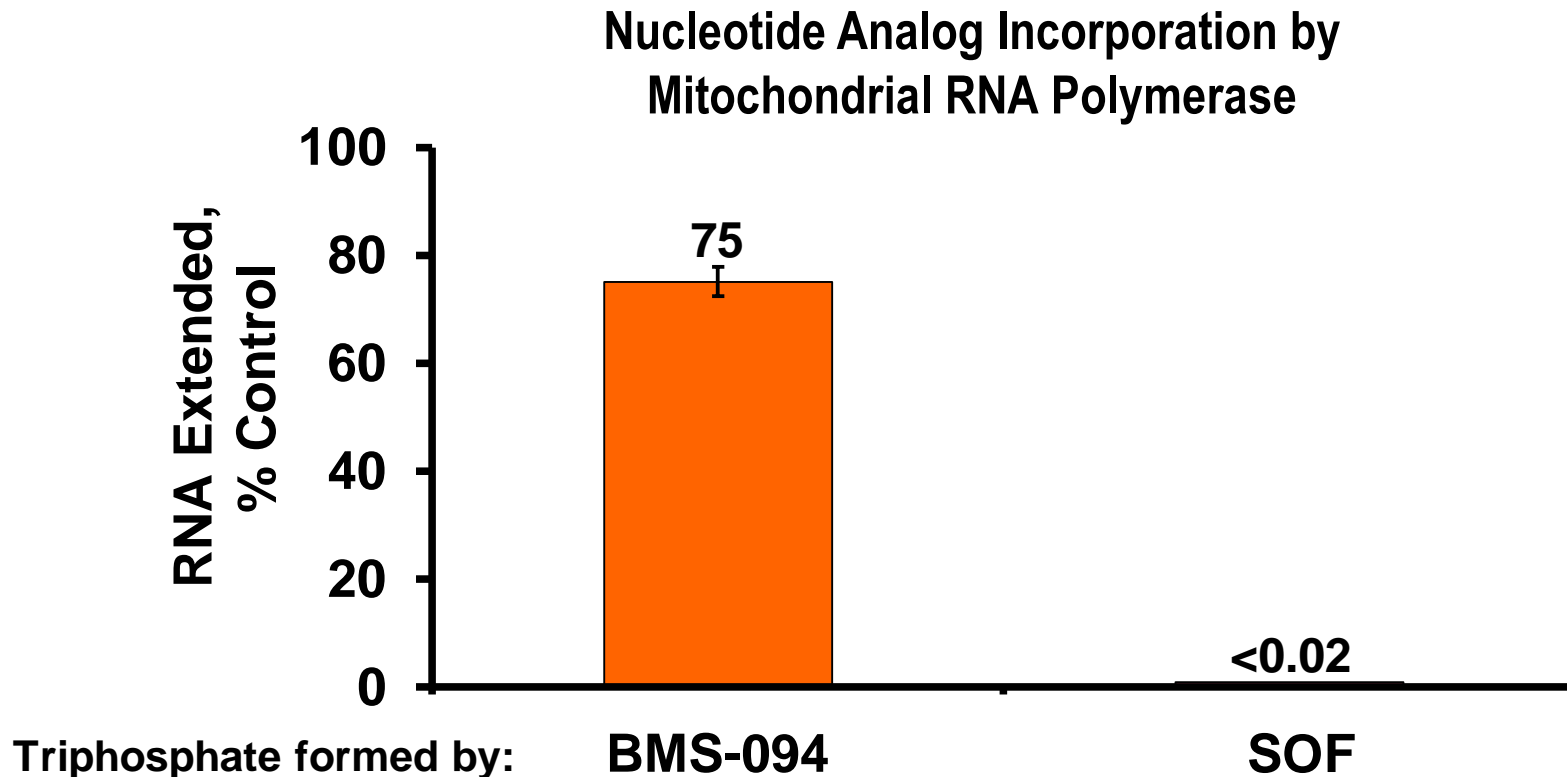
	Primary Cells CC <sub>50</sub> , µM				
	Liver	PBMC		Bone Marrow	
	Hepatocyte	Quiescent	Stimulated	Erythroid	Myeloid
<b>SOF</b>	>100	>100	>100	>50	>50
<b>BMS-094</b>	6.7	11	7.8	4.5	2.6

**No meaningful toxicity was observed with sofosbuvir; however, BMS-094 showed potent cytotoxicity in vitro**

# Incorporation by Mitochondrial RNA Polymerase

## Sofosbuvir and BMS-094

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**The triphosphate of sofosbuvir is not a substrate for mitochondrial RNA polymerase**

# Sofosbuvir: Mitochondrial Toxicity Potential

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- ◆ No evidence of cardiac and muscle tissue toxicity in repeat dose rat and dog studies at exposures 9- and 27-fold above clinical exposure
- ◆ No evidence of cardiac and skeletal muscle tissue toxicity in 2 year mouse and rat carcinogenicity study at exposures up to 30- and 15-fold above clinical exposure

# Cardiac Adverse Events

## VALENCE

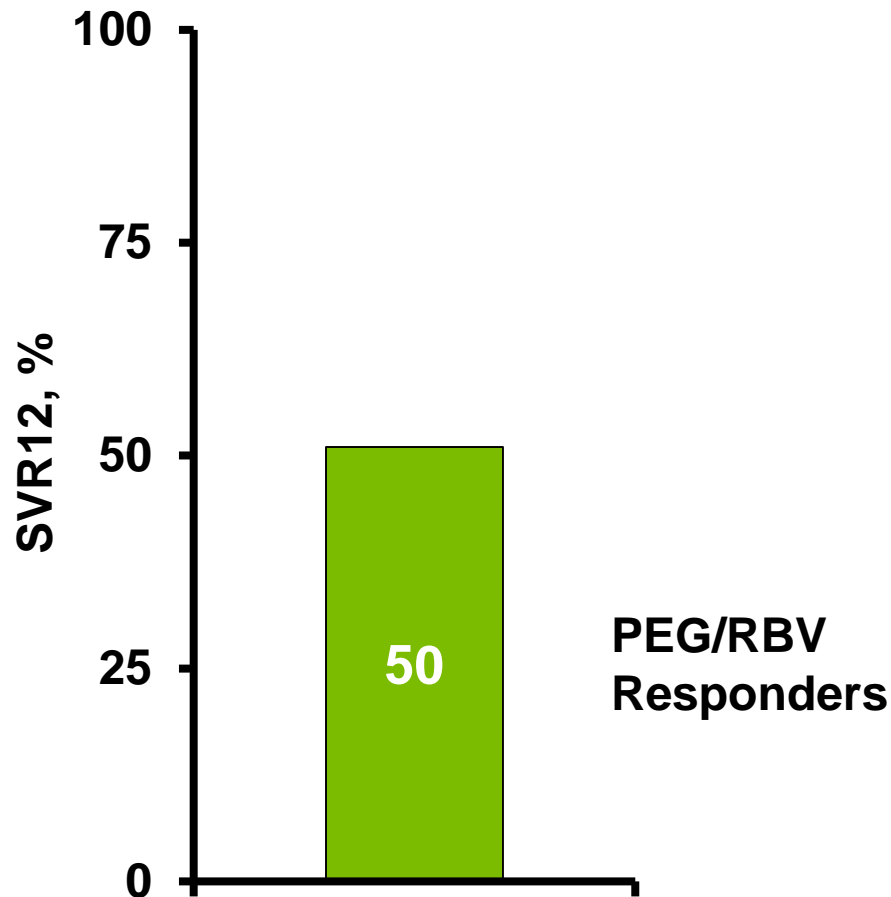
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Cardiac Disorder	Placebo (N=85) n (%)	SOF+RBV 12 wk (N=84) n (%)	SOF+RBV 24 wk (N=250) n (%)
Palpitations	1 (1)	1 (1)	5 (2)
Tachycardia	0	1 (1)	4 (2)
Arrhythmia	0	0	1 (<1)

# Projected SVR12 Rates with SOF+PEG/RBV

## GT 1 Treatment-Experienced Patients

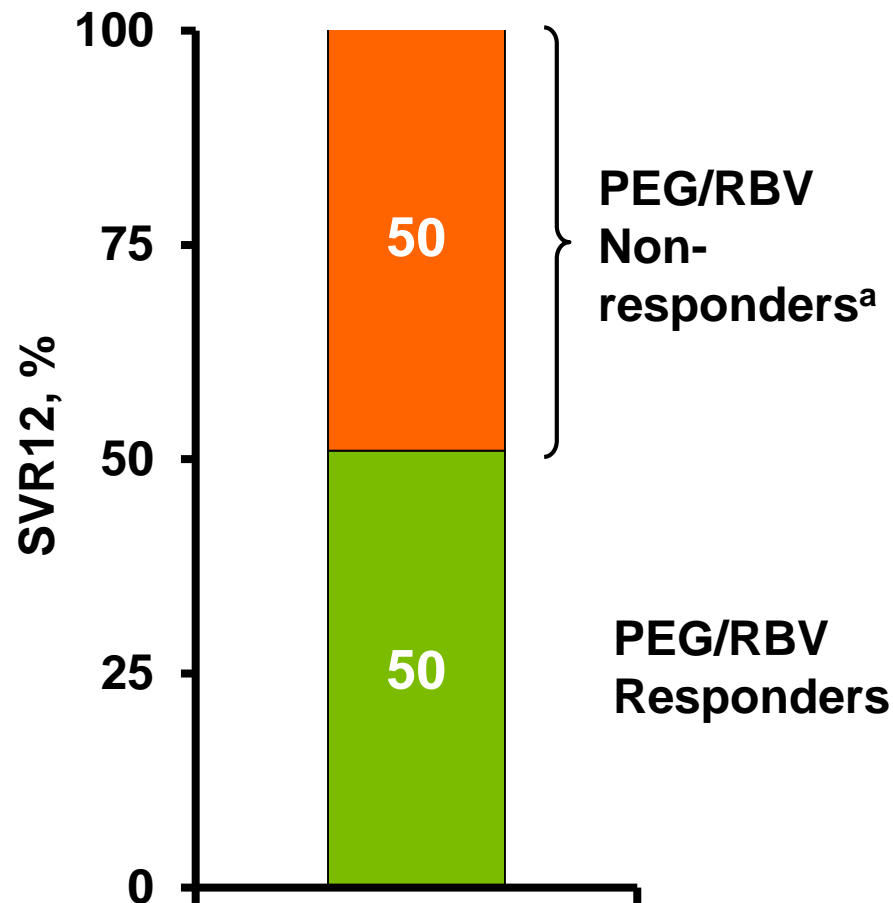
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# Projected SVR12 Rates with SOF+PEG/RBV

## GT 1 Treatment-Experienced Patients

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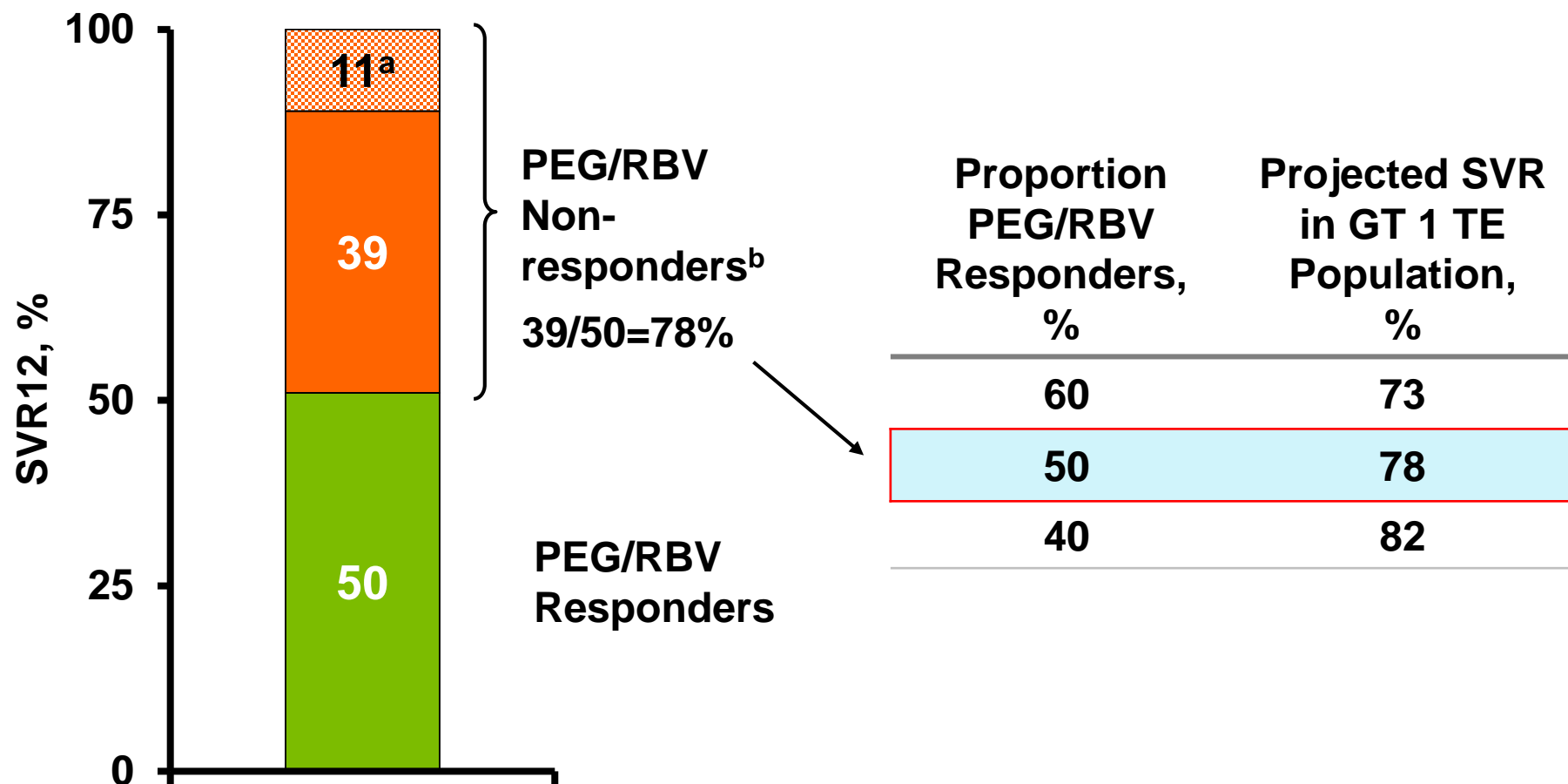
a. Relapsers, partial responders, null responders, discontinuations.

**EF-478**

Sofosbuvir Advisory Committee. October 25, 2013.



# Predicted SVR12 Rates in GT 1 Treatment-Experienced Patients

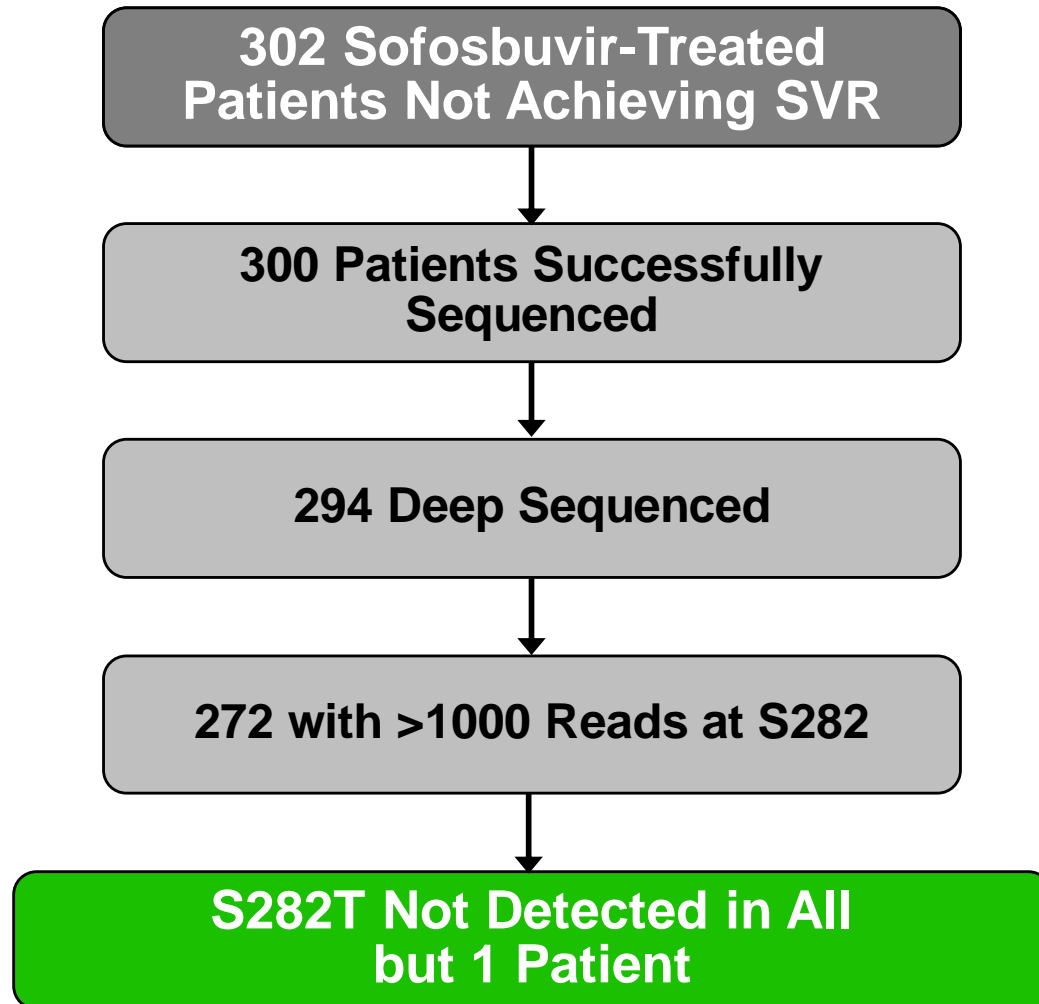


- a. 11% of patients who failed to achieve SVR12 in NEUTRINO.  
 b. Relapsers, partial responders, null responders, discontinuations.

**EF-479**

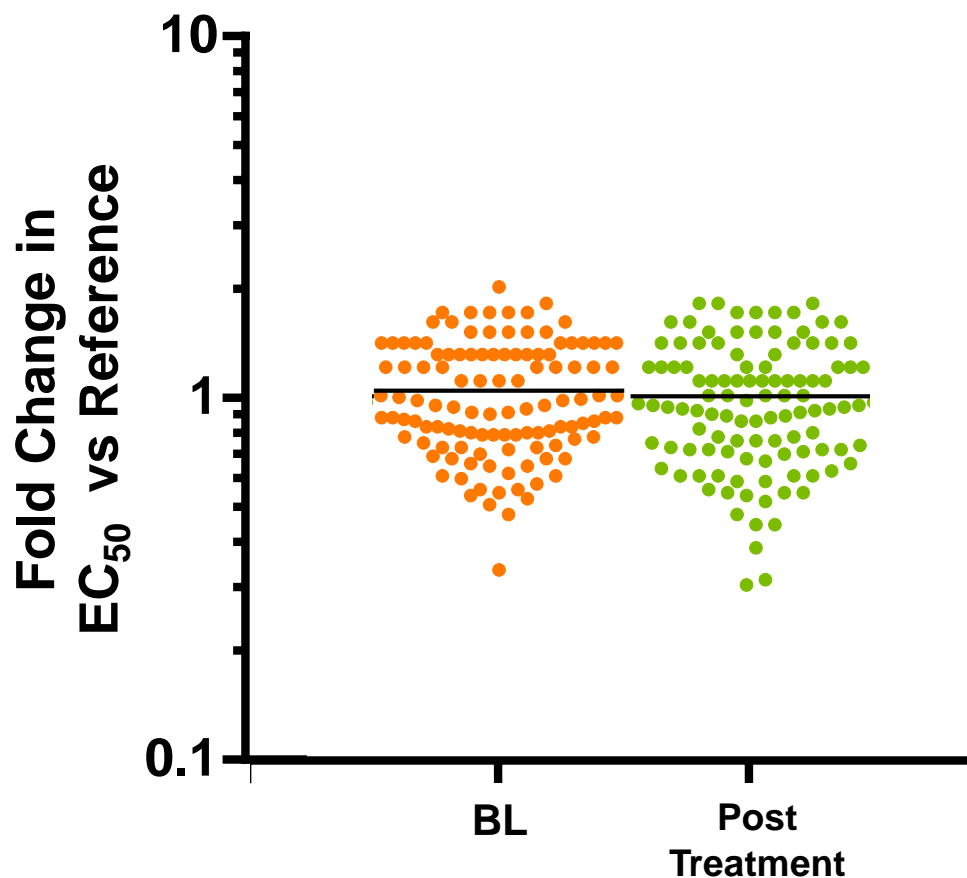
# Number of Patients Sequenced at Virologic Failure Across Phase 2/3 Studies

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# Sofosbuvir Susceptibility of Baseline and Post-Treatment HCV Patient Samples in Phase 3 Studies

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# Other NS5B Substitutions Observed in Phase 3 Studies

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- ◆ 63 NS5B substitutions observed in >2 patients at the population level
- ◆ No SOF+RBV phenotypic change for any of the 63 NS5B substitutions
- ◆ All are in polymorphic sites (at least in one genotype)
- ◆ None are in the active site

# NS5B V321A Variants Detected in Sofosbuvir Phase 3 Studies

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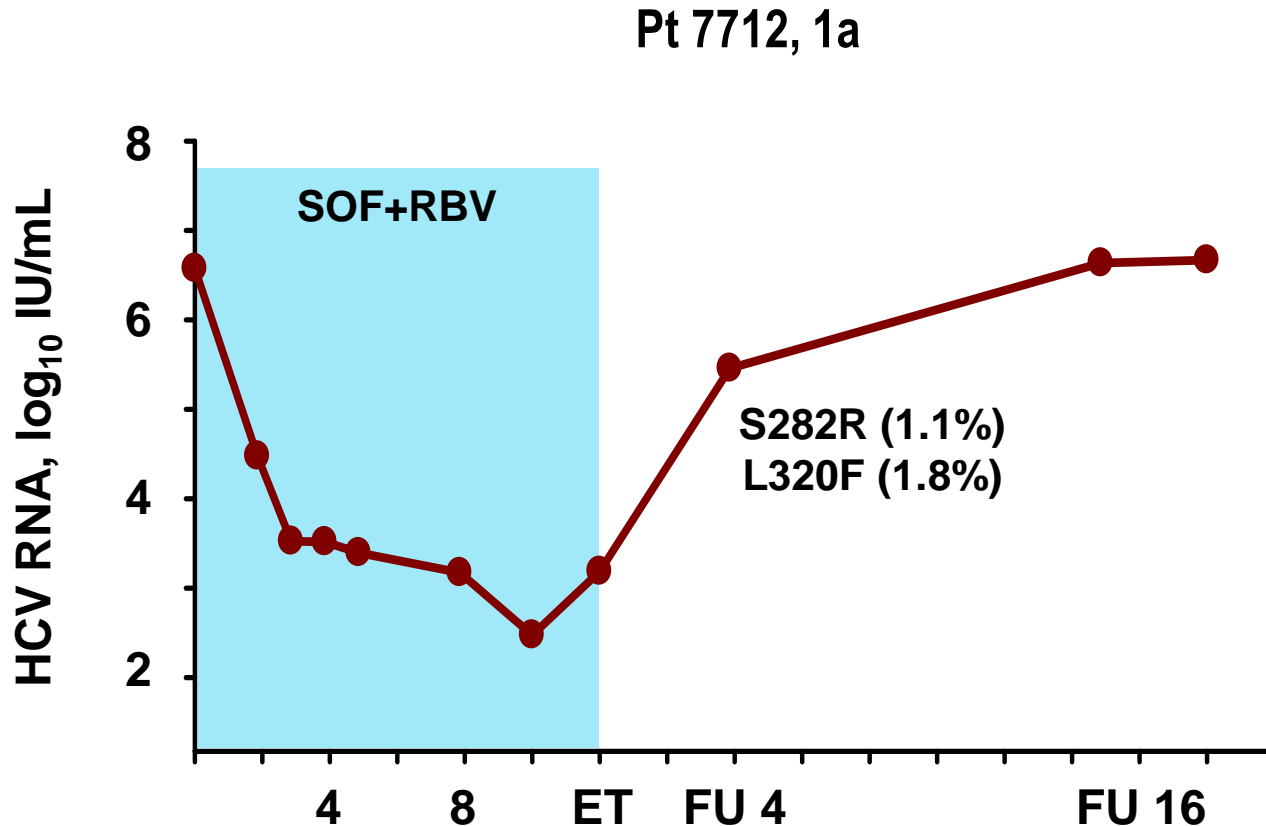
- ◆ Not detected at baseline
- ◆ 4 GT 3a patients at relapse
- ◆ Not selected in vitro
- ◆ No sofosbuvir or RBV phenotypic change

GT	Mutation	Replication Capacity, % of Wild-Type	Fold Change in EC <sub>50</sub> vs Wild-Type	
			SOF	RBV
3a	V321A	49	1.2	0.5
3a				
Patient Isolate FISSION 310286	V321A/V	90 <sup>a</sup>	0.8 <sup>a</sup>	1.0 <sup>a</sup>

<sup>a</sup>Relative to BL

# Patient with S282R and L320F Emerged

## Patients from P7977-2025



ET=end of treatment; FU=follow-up; Pt=patient; PTX=post-transplant.

**VR-46**

Sofosbuvir Advisory Committee. October 25, 2013.

# NS5B L159F Variants Detected in Sofosbuvir Phase 3 Studies

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- ◆ 4 GT 1b patients in Phase 3 at baseline
- ◆ 6 GT 3a patients at relapse
- ◆ Not selected in vitro
- ◆ No sofosbuvir or RBV phenotypic change

# NS5B L159F Variants: Phenotype

GT	Mutation	Replication Capacity, % of Wild-Type	Fold Change in EC <sub>50</sub> vs Wild-Type	
			SOF	RBV
1a	L159F	8.9	1.2	0.7
1b	L159F	24.1	1.3	1.0
3a	L159F	10.2	1.3	1.3
3a Patient Isolate FISSION 310257	L159F	2.3 <sup>a</sup>	0.8 <sup>a</sup>	1.5 <sup>a</sup>

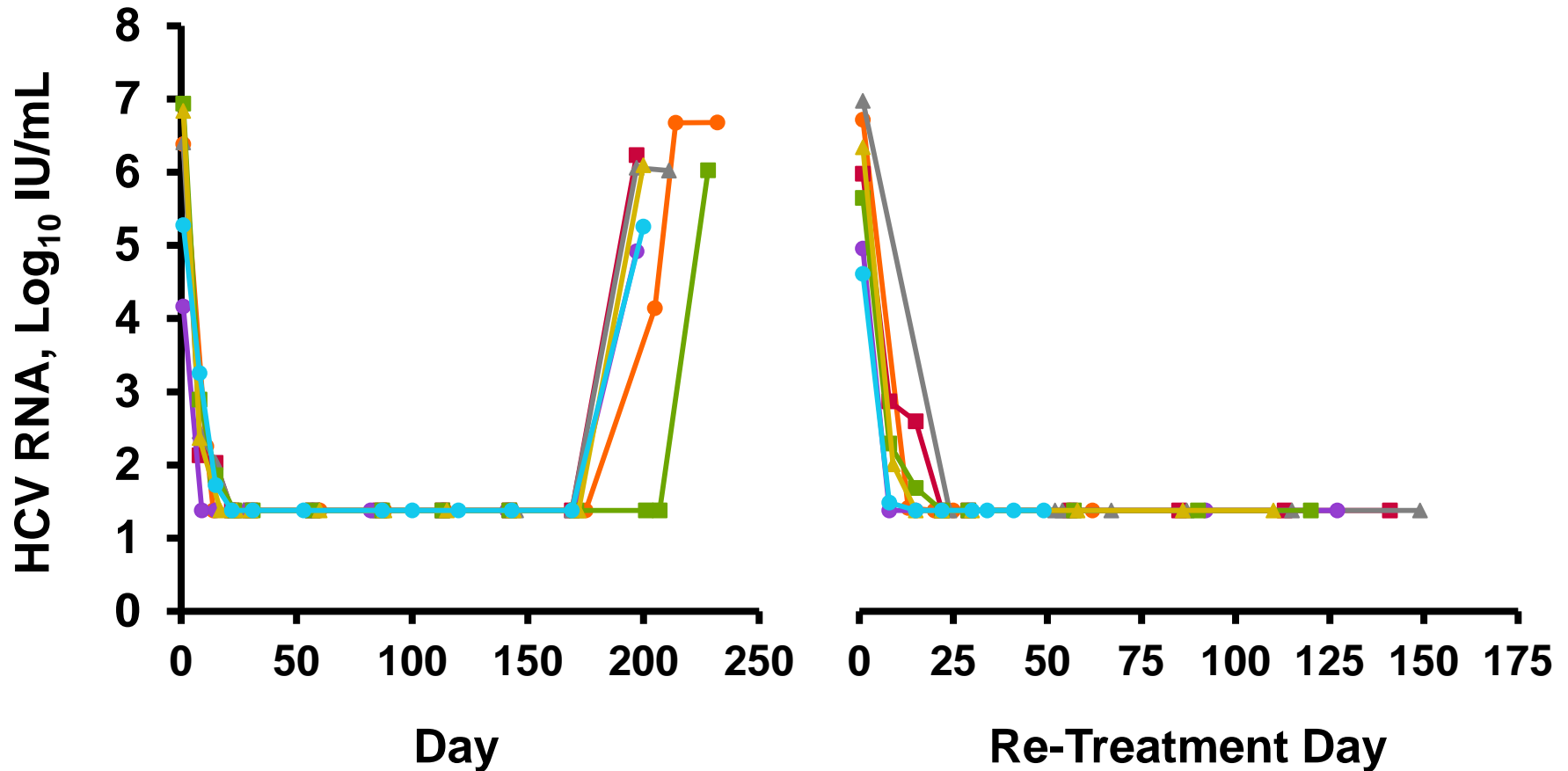
a. Relative to baseline.



# HCV RNA in Patients Retreated with Sofosbuvir

## Pre-Transplant Study

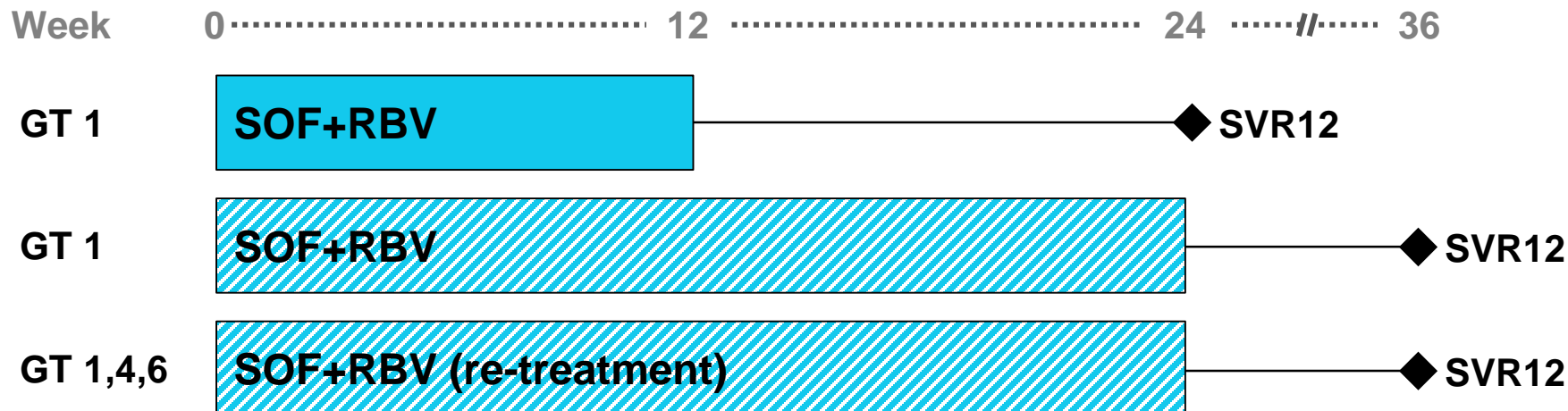
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# Design

## GT 1 Treatment Naïve (QUANTUM)

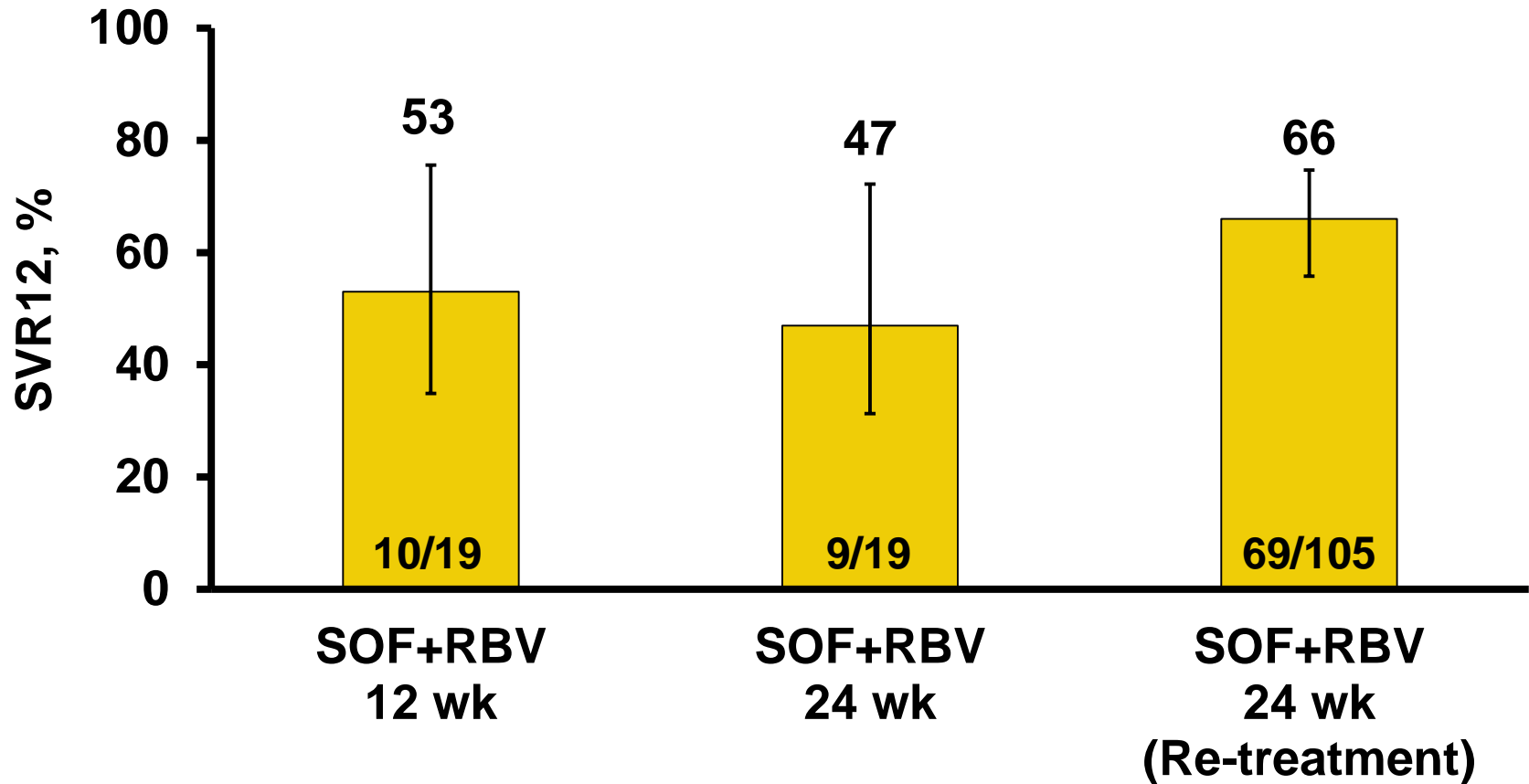
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# Results SVR12

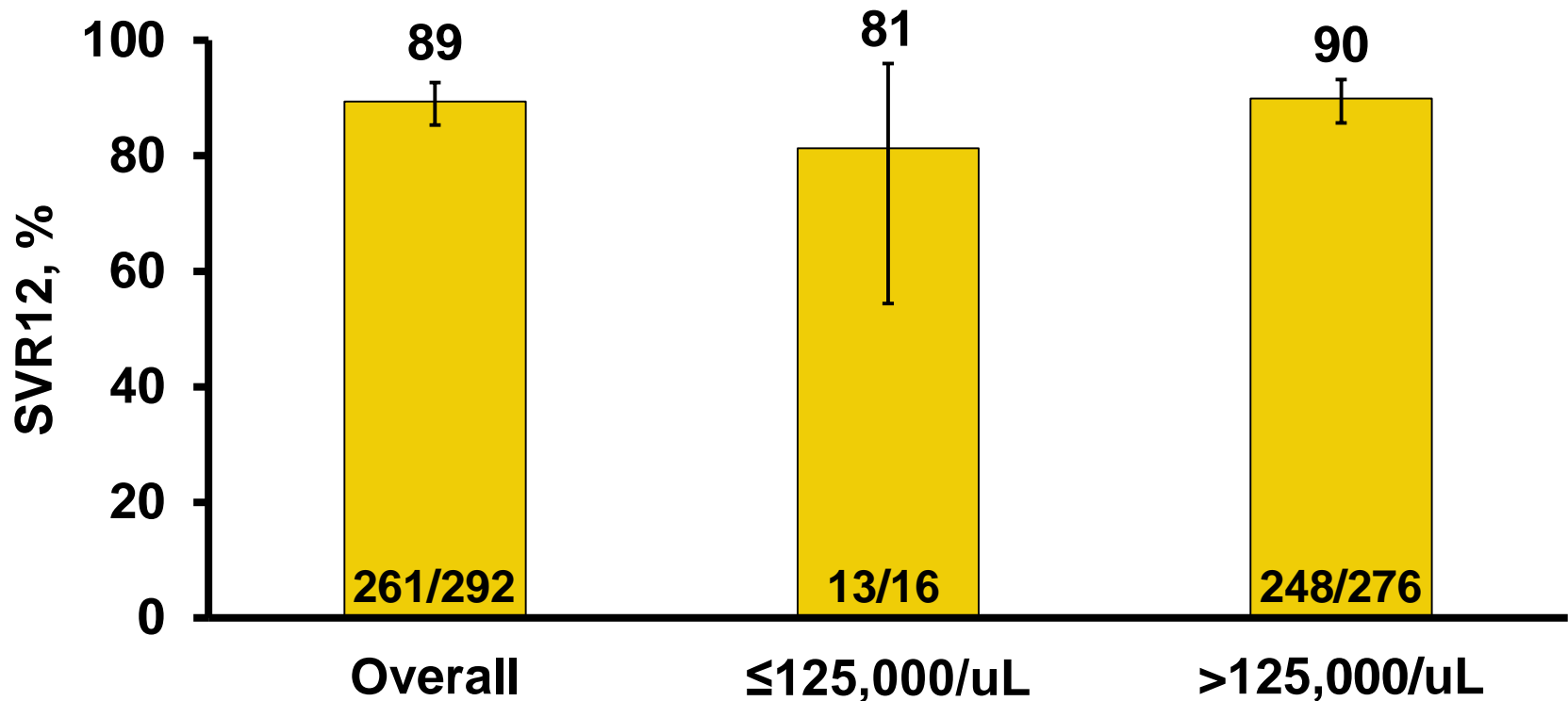
Treatment Naïve GT 1 (QUANTUM)

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# Influence of Platelet Count on SVR12

GT 1 All Phase 3 SOF+PEG/RBV 12-wk Patients

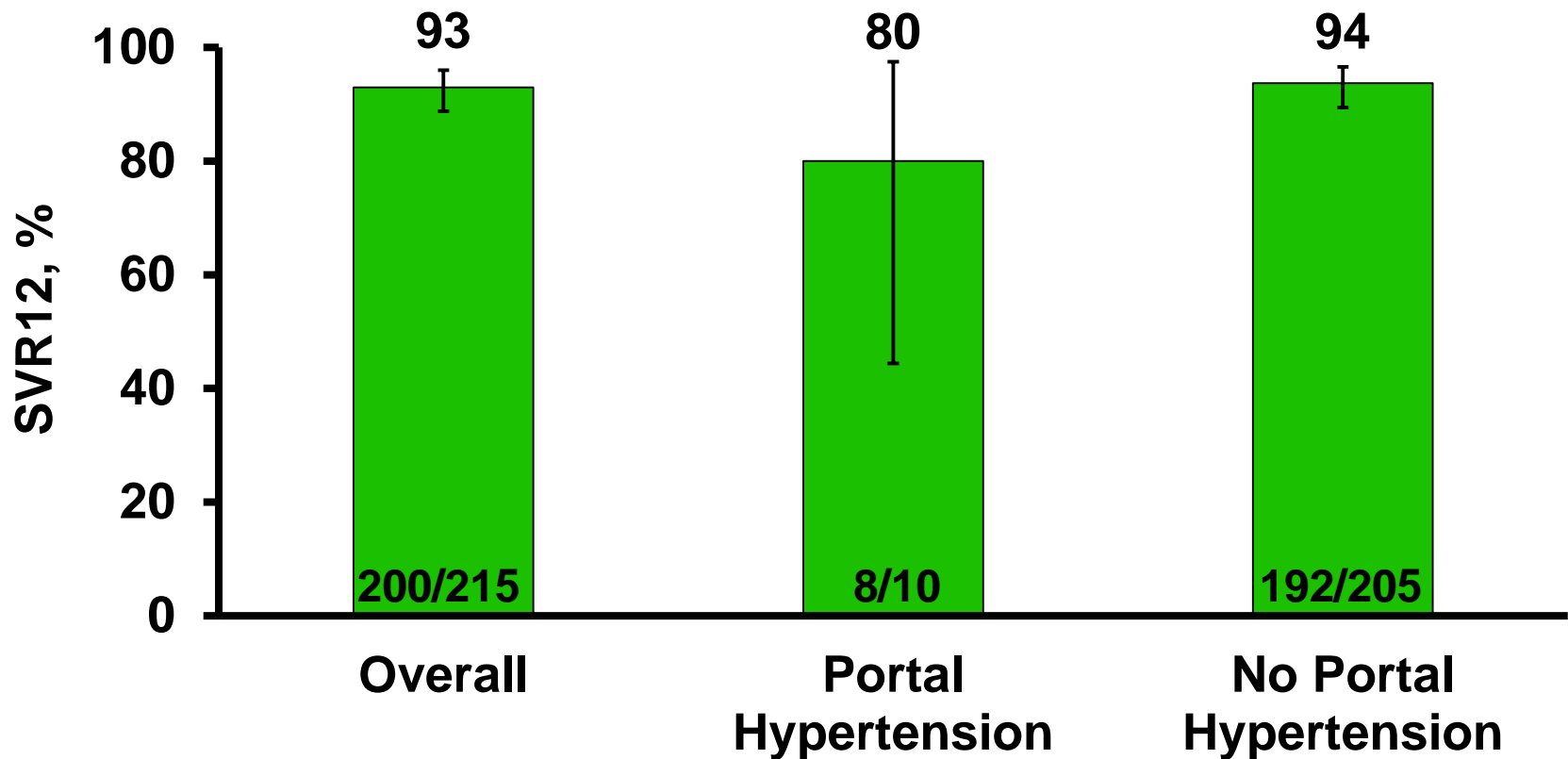


**EF-339**

Sofosbuvir Advisory Committee. October 25, 2013.

# Influence of Portal Hypertension on SVR12

GT 2 Phase 3 SOF+RBV 12-wk<sup>a</sup> Patients



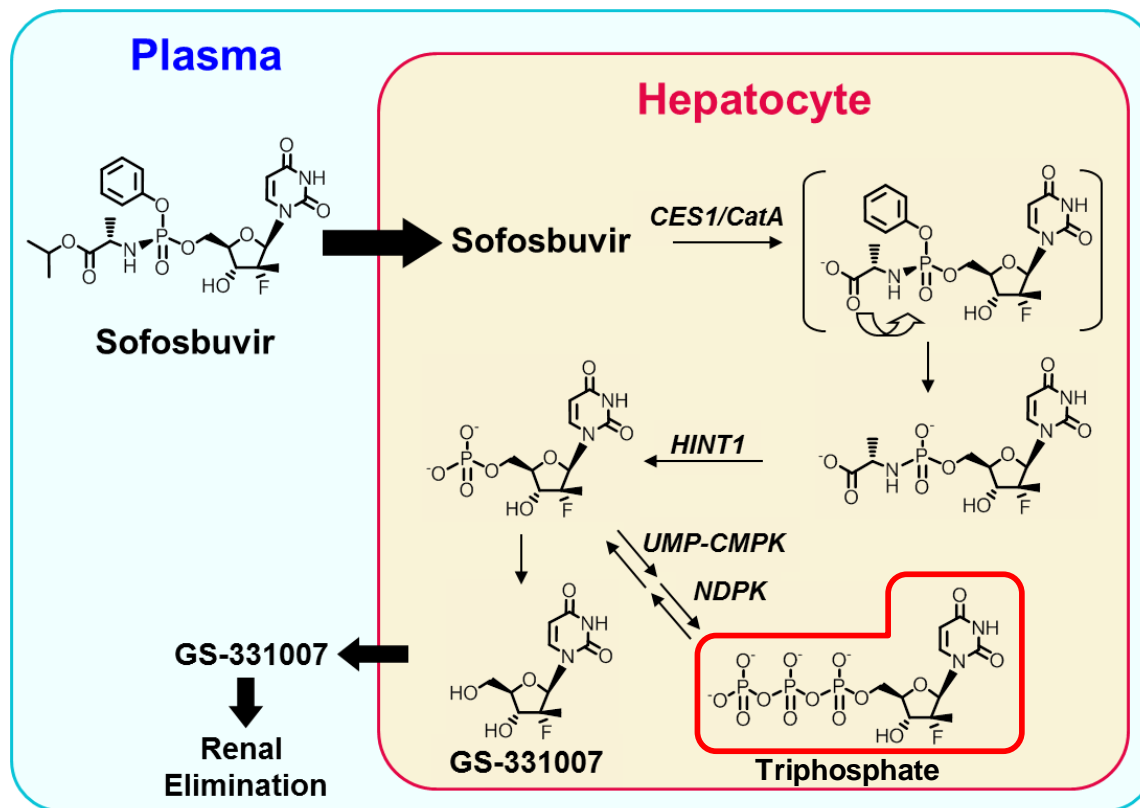
a. Pooled from 12-week SOF+RBV arms of FISSION, POSITRON, and FUSION.

**EF-342**

Sofosbuvir Advisory Committee, October 25, 2013.

# Potential Interference of Activation of Sofosbuvir

Sofosbuvir Is Activated by a Low Affinity and High Capacity Pathway Including Hydrolases and Nucleotide Kinases



**No drugs have been identified that are expected to cause a clinically meaningful decrease in sofosbuvir activation in hepatocytes**

CatA=cathepsin A; CES1=carboxylesterase 1; HINT1=histidine triad nucleotide binding protein; UMP-CMPK=UMP-CMP kinase; NDPK=nucleoside diphosphate kinase.

Adapted from Murakami E, et al. *J Biol Chem.* 2010;285:34337-34347.

**AD-80**

Sofosbuvir Advisory Committee. October 25, 2013.

# Replication Capacity and Susceptibility of NS5B S282T Mutants in Replicons

NS5B Substitution	Genotype	Replication Capacity, % of Wild-Type <sup>a</sup>	Fold Change in SOF EC <sub>50</sub> <sup>a</sup>
S282T	1a	1.3	8.4
	1b	8.4	8.8
	2a	11.2	2.4
	2b	11.3	16.2
	3a	11.3	3.5
	4a	5.3	6.1
	5a	3.2	18.1
	6a	4.7	8.8
Patient 5068			
S79N, V/I147I, S282T, T/I309T, T/I/A/V312T	2b	2.0	13.5

- ◆ S282T shows 2.4–18.1 fold reduced susceptibility to sofosbuvir
- ◆ S282T replication capacity ranged from 1.3–11.3% of wild-type

a. Compared with corresponding wild-type.

# Time <LLOQ TND Pre-Transplant vs Recurrence

## GT 1-4

■ Days at TND (pTVR)      ▨ Days on Drug (pTVR)      ▨ Days at TND –Post Treatment (pTVR)  
■ Days at TND (Recurrence)      ▨ Days on Drug (Recurrence)

