All-Oral 12-Week Combination Treatment With Daclatasvir and Sofosbuvir in Patients Infected With HCV Genotype 3: ALLY-3 Phase 3 Study

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Background

- HCV genotype (GT) 3 is common worldwide and remains a significant disease burden[1]
- GT 3 infection is associated with increased risk of fibrosis progression, steatosis, and hepatocellular carcinoma in patients with cirrhosis[2-4]
- Current therapies for patients with GT 3 infection include:
  - US and Europe
    - 24-week sofosbuvir (SOF) + ribavirin (RBV)[5]
    - 12-week SOF + peginterferon/RBV[5]
  - Europe
    - 24-week daclatasvir (DCV) + SOF ± RBV[6]

[1] Pol S, *et al*. *Liver Int* 2014;34(suppl 1):18-23.
[2] Nkontchou G, *et al*. *J Viral Hepat* 2011;18:e516-522.
[3] Larsen C, *et al*. *J Med Virol* 2010;82:1647-1654.
[4] Bochud PY, *et al*. *J Hepatol* 2009;51:655-666.
[5] SOVALDI (sofosbuvir) prescribing information. 2014.
[6] DAKLINZA (daclatasvir) summary of product characteristics. 2014.

Daclatasvir and Sofosbuvir

- **Daclatasvir (DCV)**
  - Potent, pangenotypic[a] NS5A inhibitor
  - Once daily with low potential for drug–drug interactions
  - Safe and well tolerated in > 6000 subjects
  - DCV in combination is approved in Japan and Europe; currently under regulatory review in the US

- **Sofosbuvir (SOF)**
  - Pangenotypic nucleotide NS5B inhibitor
  - Once daily with low potential for drug–drug interactions
  - Safe and well tolerated
  - Approved in combination with other HCV agents in the US, Europe, and Canada

[a] Pangenotypic: GT 1–6 *in vitro* and GT 1–4 in clinical trials.

ALLY Phase 3 Program

All-Oral DCV + SOF in Patients With High Unmet Medical Need

ALLY-1
N = 113

- Patients with cirrhosis or post-liver transplant
- GT 1 to 6
- DCV + SOF + RBV, 12 weeks

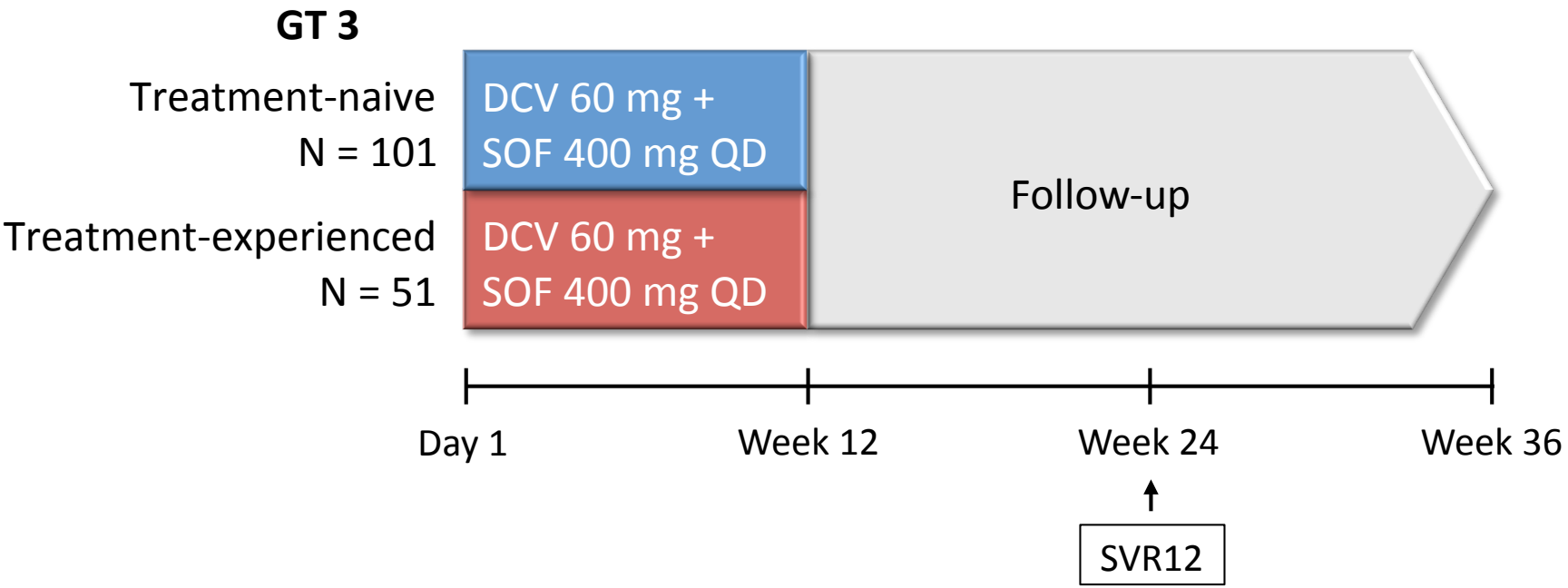
ALLY-2
N = 203

- Patients with HIV coinfection
- GT 1 to 6
- DCV + SOF, 8 or 12 weeks

ALLY-3
N = 152

- Patients with GT 3 infection
- Treatment-naive or treatment-experienced
- DCV + SOF, 12 weeks

ALLY-3: Study Design



- Primary endpoint: SVR12
  - HCV RNA < lower limit of assay quantitation (LLOQ) at posttreatment Week 12[a]
- Eligible patients
  - Age ≥ 18 years with chronic GT 3 infection and HCV RNA ≥ 10,000 IU/mL
  - Treatment-naive or -experienced (prior treatment failures), including patients with cirrhosis
  - Those who received prior treatment with NS5A inhibitors were excluded

[a] Assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).

Demographic and Baseline Disease Characteristics

Parameter	Treatment-Naive N = 101	Treatment-Experienced[a] N = 51
Age, median years (range)	53 (24-67)	58 (40-73)
Male, n (%)	58 (57)	32 (63)
Race, n (%)		
White	92 (91)	45 (88)
Black	4 (4)	2 (4)
Asian	5 (5)	2 (4)
Other	0	2 (4)[b]
HCV RNA, n (%)		
< 800,000 IU/mL	31 (31)	13 (25)
≥ 800,000 IU/mL	70 (69)	38 (75)
Cirrhosis, n (%)[c]	19 (19)	13 (25)
IL28B genotype, n (%)		
CC	40 (40)	20 (39)
Non-CC	61 (60)	31 (61)
Prior treatment failure, n (%)		
Relapse	–	31 (61)
Null response	–	7 (14)
Partial response	–	2 (4)
Other (intolerant, VBT)	–	11 (22)

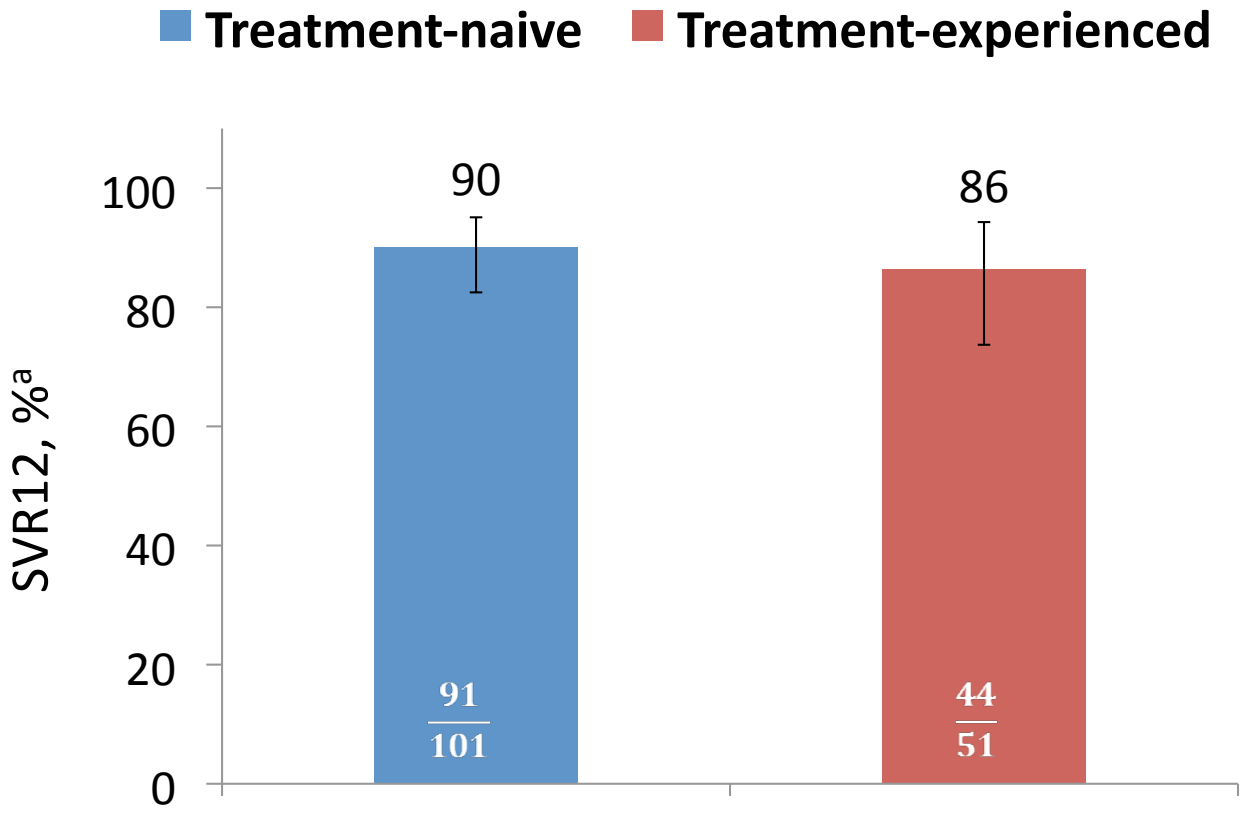
[a] Patients who previously failed treatment with sofosbuvir (n = 7) or alisporivir (n = 2) were included.

[b] American Indian/Alaska native.

[c] Cirrhosis determined by liver biopsy (METAVIR F4; n = 14), FibroScan (> 14.6 kPa, n = 11), or FibroTest score ≥ 0.75 and APRI (aspartate aminotransferase to platelet ratio index) > 2 (n = 7).

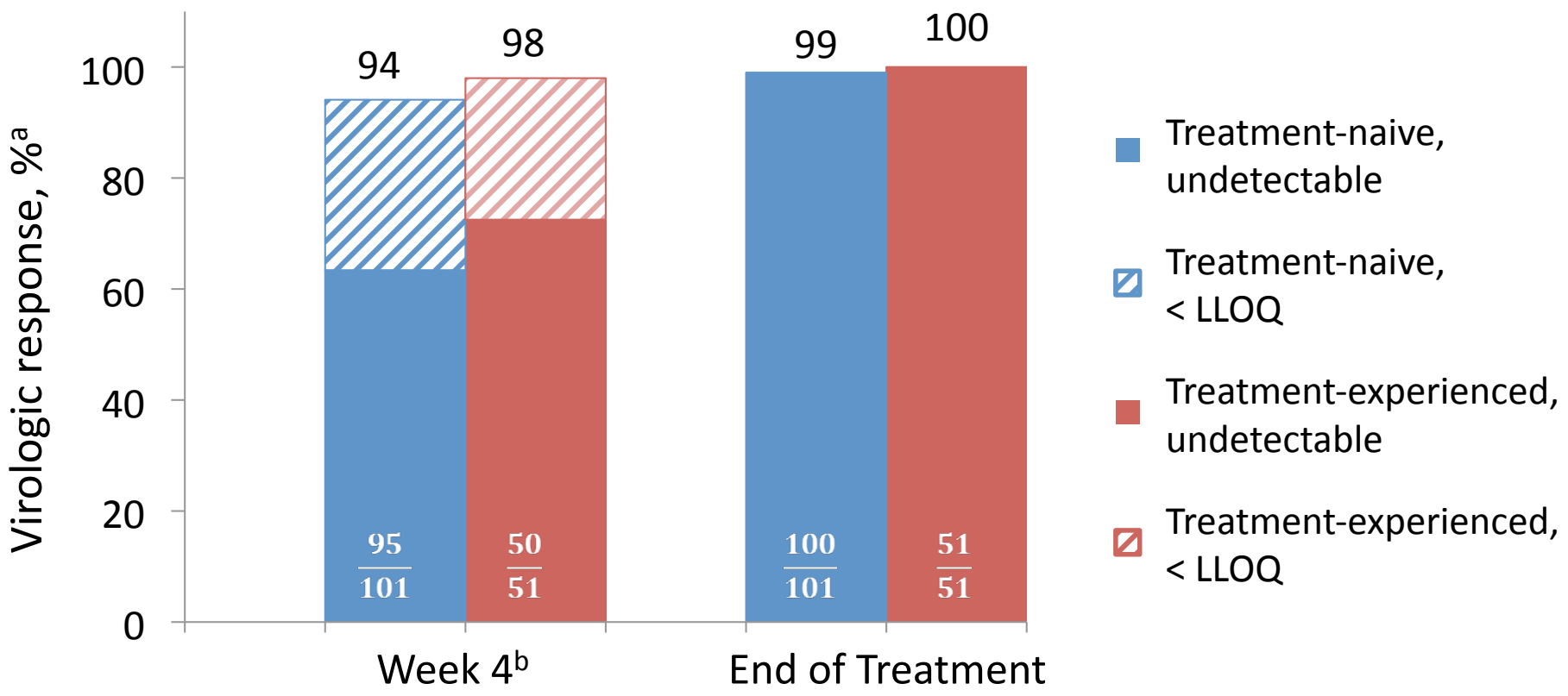
VBT, virologic breakthrough.

SVR12: Primary Endpoint



[a] HCV RNA < LLOQ (25 IU/mL); error bars reflect 95% confidence intervals.

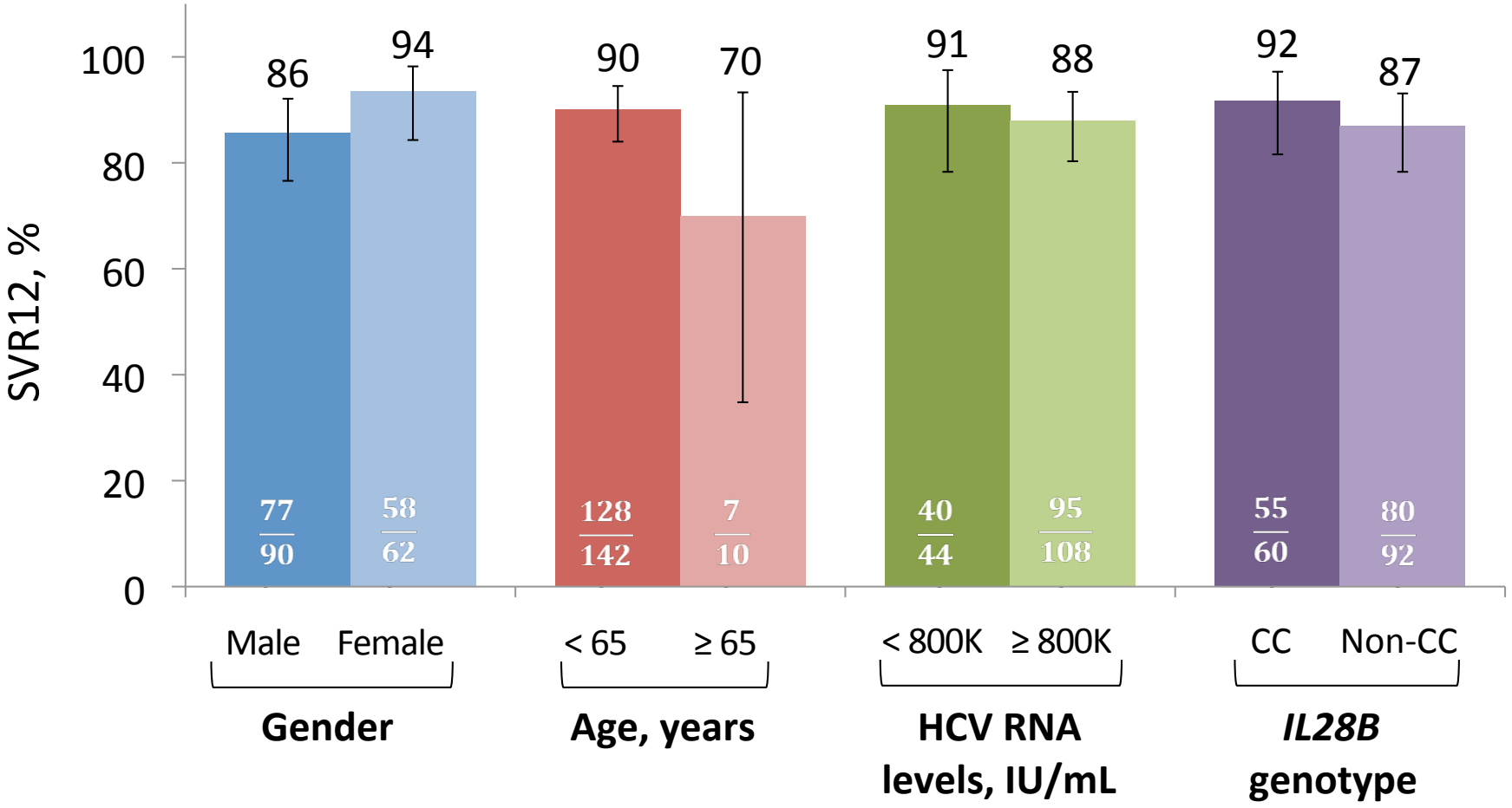
On-Treatment Virologic Response



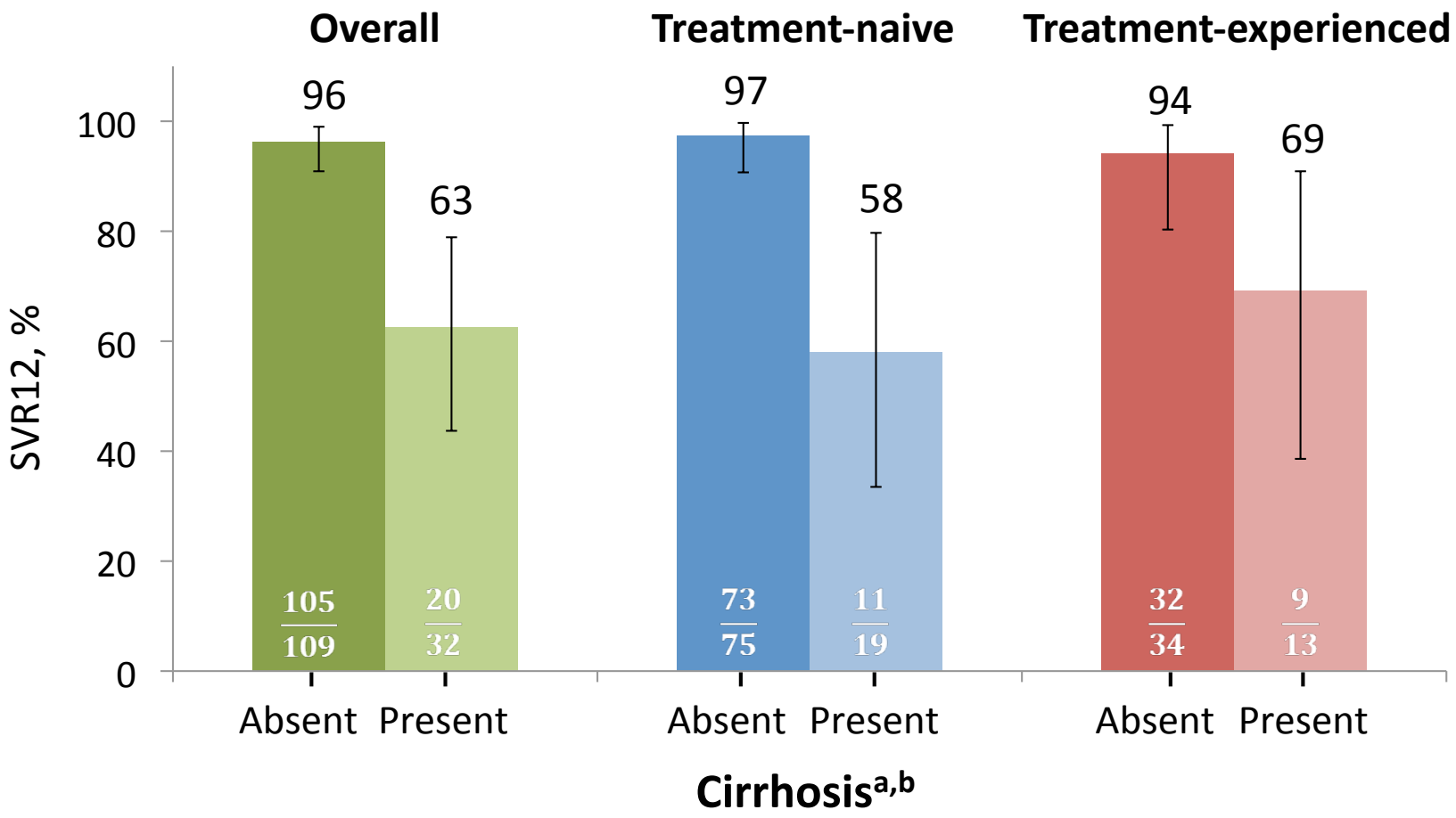
[a] Undetectable HCV RNA or HCV RNA < LLOQ (25 IU/mL).

[b] SVR12 rates based on Week 4 HCV RNA levels: < LLOQ, target detected, 86%; < LLOQ, target not detected, 91%.

SVR12 by Baseline Factors



SVR12 in Patients With Cirrhosis

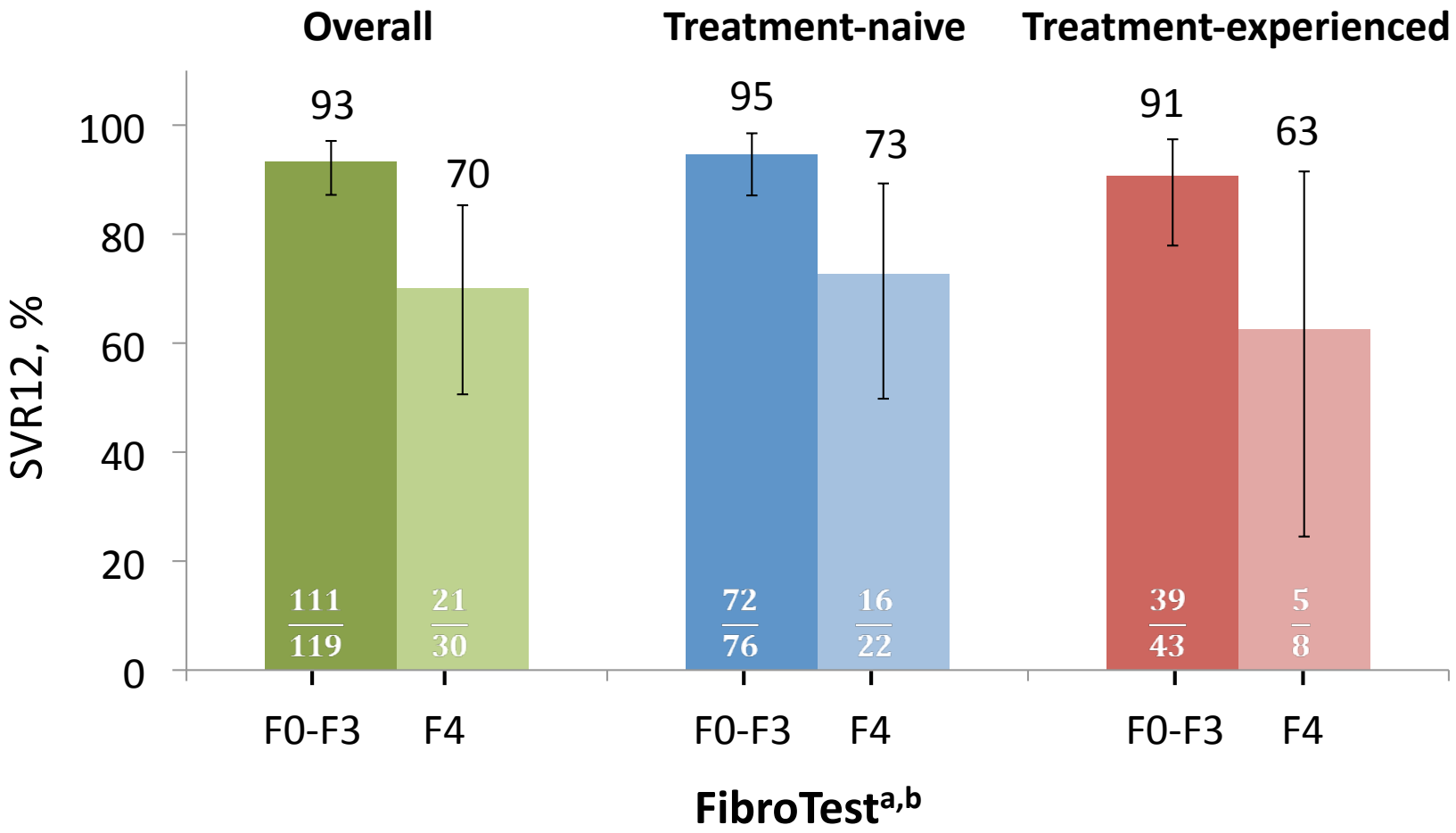


- Among patients with cirrhosis, 34% (11/32) had baseline platelet counts < 100,000/mm^3

[a] Cirrhosis status determined in 141 patients by liver biopsy (METAVIR F4), FibroScan (> 14.6 kPa), or FibroTest score ≥ 0.75 and APRI (aspartate aminotransferase to platelet ratio index) > 2.

[b] Cirrhosis status for 11 patients was inconclusive (FibroTest score > 0.48 to < 0.75 or APRI > 1 to ≤ 2).

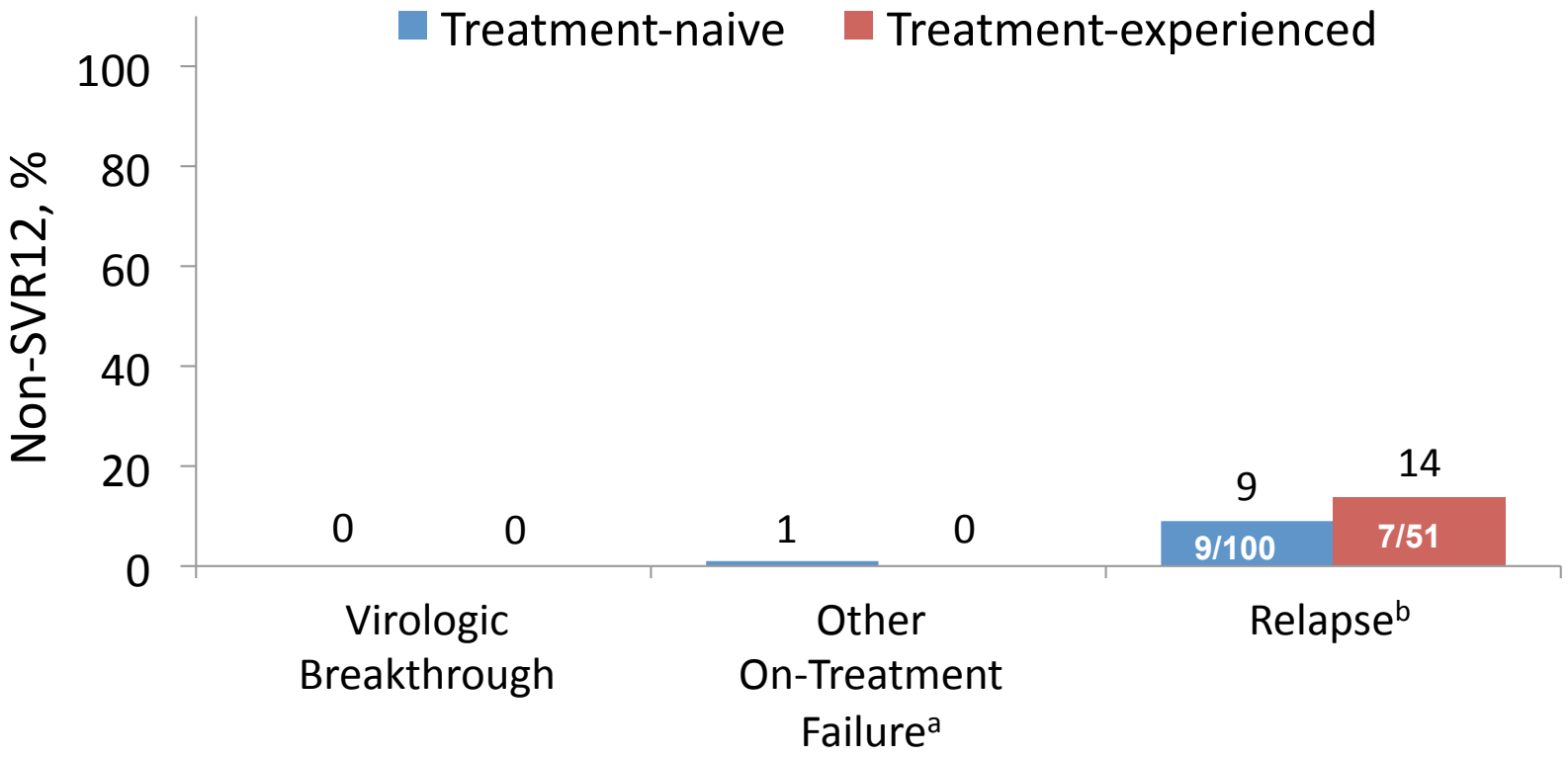
SVR12 in Patients by FibroTest Score



[a] Per protocol, FibroTest assessments (scores determined by BioPredictive) were performed during screening; data not available for 3 patients.

[b] FibroTest F4 defined as ≥ 0.75; F0-F3 defined as < 0.75.

Virologic Failure



- Of the 16 patients with relapse, 11 had cirrhosis
- 1 / 16 relapses occurred between post-treatment weeks 4 and 12
- Resistance-associated variants (RAVs) that emerged at relapse
  - NS5A-Y93H emerged in 9 / 16 patients

[a] One treatment-naive patient with cirrhosis who had detectable HCV RNA at the end of treatment.

[b] Percentages based on the number of patients with undetectable HCV RNA at the end of treatment.

On-Treatment Safety and Tolerability

Parameter, n (%)[a]	All patients N = 152
Death	0
Serious adverse events	1 (1)[b]
Adverse events leading to discontinuation	0
Grade 3 adverse events	3 (2)[c]
Grade 4 adverse events	0
Adverse events in ≥ 10% of patients (all grades)	
Headache	30 (20)
Fatigue	29 (19)
Nausea	18 (12)
Grade 3/4 laboratory abnormalities	
Hemoglobin < 9.0 g/dL	0
Absolute neutrophils < 0.75×10^9 /L	0
Absolute lymphocytes < 0.5×10^9 /L	1 (1)
Platelets < 50×10^9 /L	2 (1)
International normalized ratio > 2 × ULN	2 (1)
Lipase > 3 × ULN	3 (2)

[a] On-treatment events for death and adverse events; treatment-emergent events for Grade 3/4 laboratory abnormalities.

[b] One event of gastrointestinal hemorrhage at Week 2, considered not related to study treatment.

[c] Arthralgia in 1 patient; food poisoning, nausea, and vomiting in 1 patient; and serious adverse event of gastrointestinal hemorrhage in 1 patient.

Summary

- DCV + SOF for a shorter 12-week duration achieved high SVR12 rates in patients with GT 3 infection (treatment-naive, 90%; treatment-experienced, 86%)
  - High SVR rates of 96% were achieved in patients without cirrhosis
  - No virologic breakthroughs
- DCV + SOF in combination was safe and well tolerated
- Further options for optimizing treatment outcome with DCV + SOF in GT 3-infected patients with cirrhosis are currently being evaluated

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