Sofosbuvir/Velpatasvir Fixed-Dose Combination for the Treatment of HCV in Patients With Decompensated Liver Disease: the Phase 3 ASTRAL-4 Study

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Disclosures

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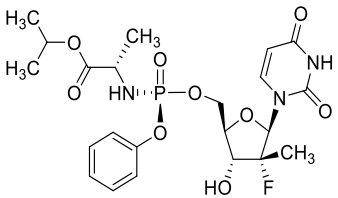
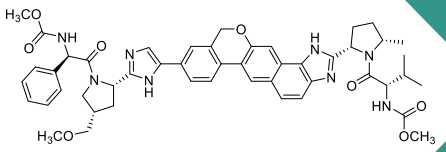
Introduction

SOF
Nucleotide polymerase inhibitor





VEL
NS5A inhibitor

SOF

VEL

- Sofosbuvir (SOF)[1,2]
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet
- Velpatasvir (VEL; GS-5816)[3-5]
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile
- SOF/VEL FDC
  - Once daily, oral, FDC (400/100 mg)

- Patients with chronic HCV infection and decompensated liver disease have significant morbidity and mortality rates[1,2]
- HCV treatment options remain limited in this population

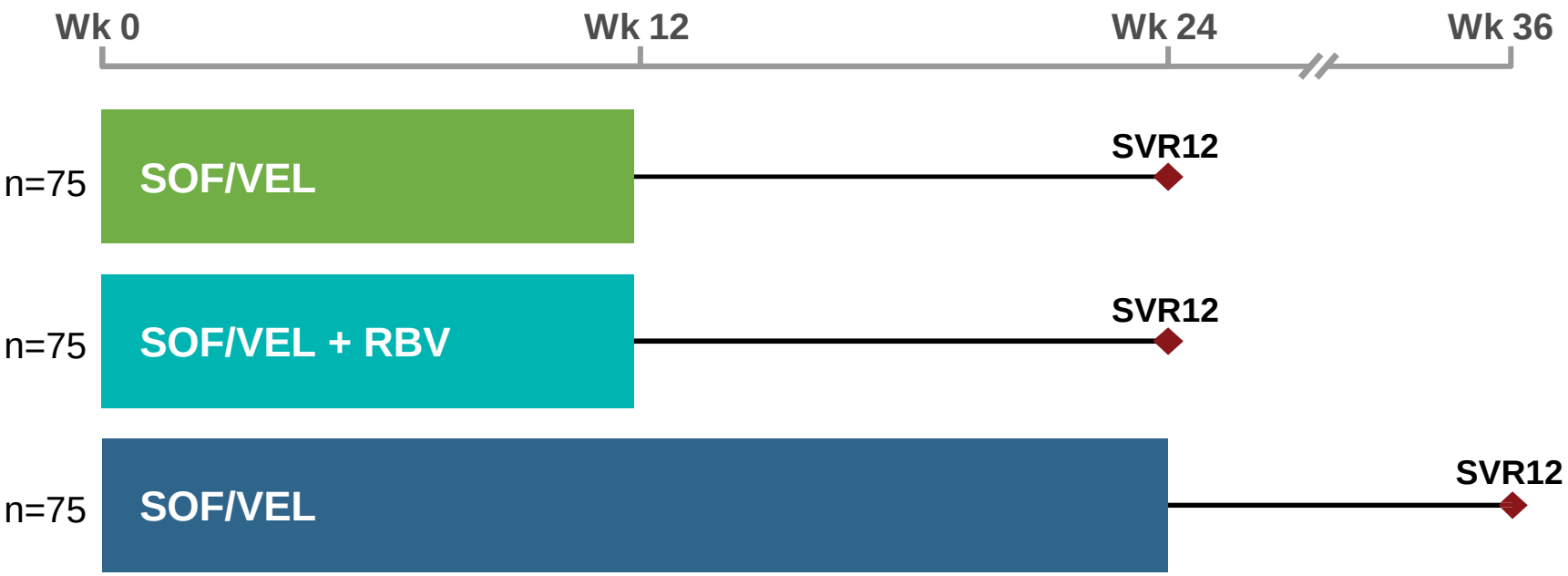
FDC, fixed-dose combination; GT, genotype; HCV, hepatitis C virus.

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. J Vir Hep 2015;22:1011-19.

Objectives

- To evaluate the safety and efficacy of SOF/VEL ± ribavirin (RBV) for 12 weeks and SOF/VEL for 24 weeks in patients with HCV GT 1–6 infection and decompensated liver disease

Study Design



SVR12, sustained virologic response 12 weeks after treatment end.

- Open-label, randomized (1:1:1) US study (NCT02201901)
- HCV GT 1–6 treatment-naïve or -experienced patients with Child-Pugh-Turcotte (CPT) B cirrhosis
- Key eligibility criteria: creatinine clearance (CL_{cr}) >50 mL/min, platelets >30,000/mm^3; no hepatocellular carcinoma or liver transplant

Methods

- Weight-based RBV dosing (1000 or 1200 mg/d)
- Primary endpoint: SVR12
  - HCV RNA < lower limit of quantitation (LLOQ) at follow-up Week 12
  - COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 (Roche Molecular Diagnostics, Pleasanton, CA; LLOQ 15 IU/mL)
- Secondary endpoints
  - Changes in Model for End-Stage Liver Disease (MELD) and CPT scores
- Safety
  - Adverse events (AEs) and discontinuations
  - Laboratory abnormalities

Baseline Host and Viral Demographics

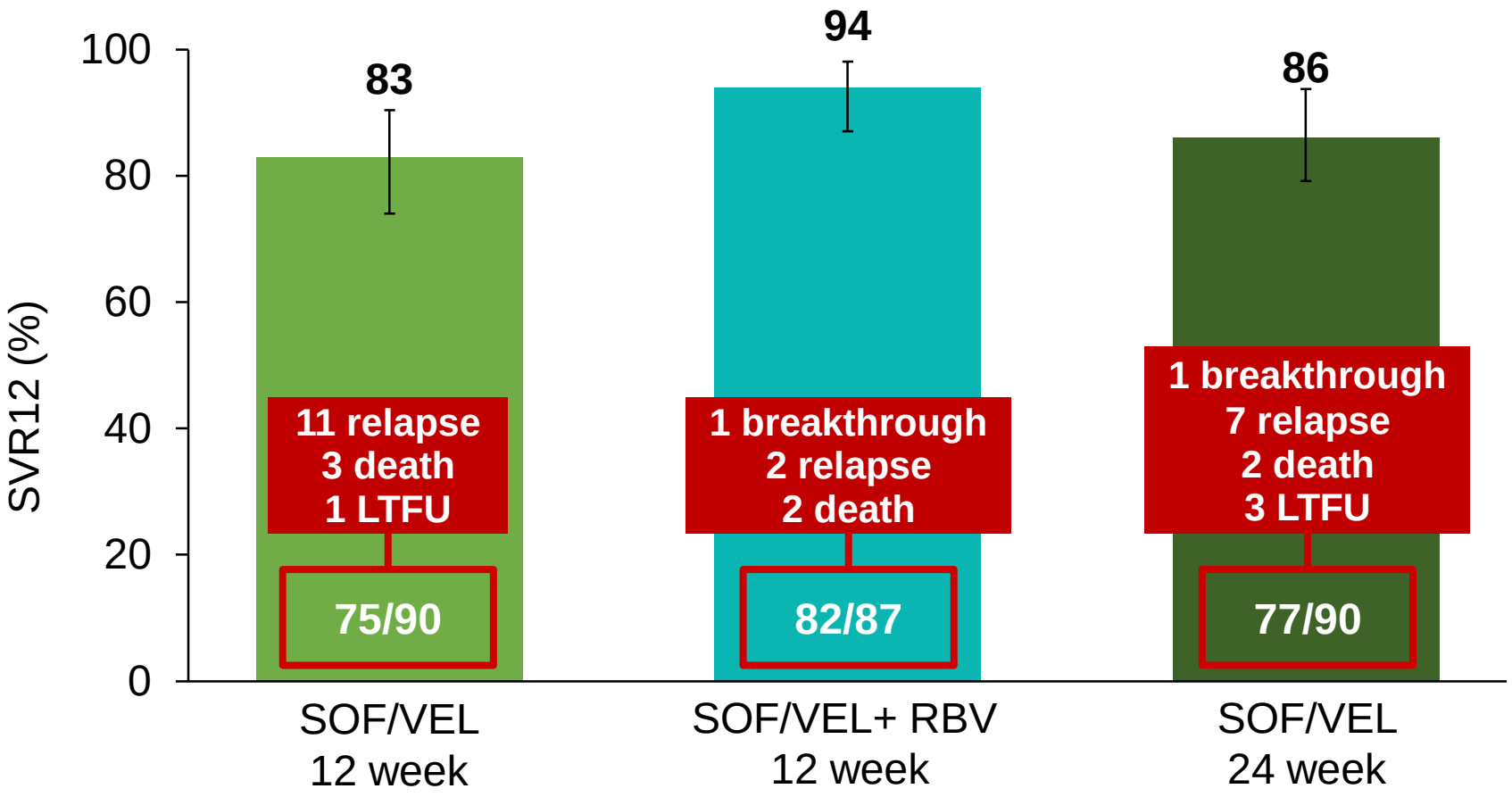
Patients	SOF/VEL 12 wk n=90	SOF/VEL+RBV 12 wk n=87	SOF/VEL 24 wk n=90
Mean age, y (range)	58 (42–73)	58 (40–71)	58 (46–72)
Male, n (%)	57 (63)	66 (76)	63 (70)
White, n (%)	79 (88)	79 (91)	81 (90)
BMI ≥30 kg/m^2, n (%)	42 (47)	33 (38)	38 (42)
Prior HCV treatment, n (%)	58 (64)	47 (54)	42 (47)
IL28B non-CC, n (%)	70 (78)	65 (75)	68 (76)
HCV RNA, $\log_{10}$ IU/mL (SD)	6.0 (0.5)	5.9 (0.6)	5.9 (0.6)
HCV GT, n (%)			
1	68 (76)	68 (78)	71 (79)
3	14 (16)	13 (15)	12 (13)
2, 4, 6	8 (9)	6 (7)	7 (8)

BMI, body mass index; IL28B, interleukin-28B; SD, standard deviation.

Baseline Liver Disease Characteristics

Patients	SOF/VEL 12 wk n=90	SOF/VEL+RBV 12 wk n=87	SOF/VEL 24 wk n=90
Median MELD (range)	10 (6–24)	10 (6–18)	11 (6–19)
MELD <15, n (%)	86 (96)	83 (95)	85 (84)
CPT B, n (%)	86 (96)	77 (89)	77 (86)
Ascites, n (%)	74 (82)	65 (75)	75 (83)
Encephalopathy, n (%)	52 (58)	54 (62)	59 (66)

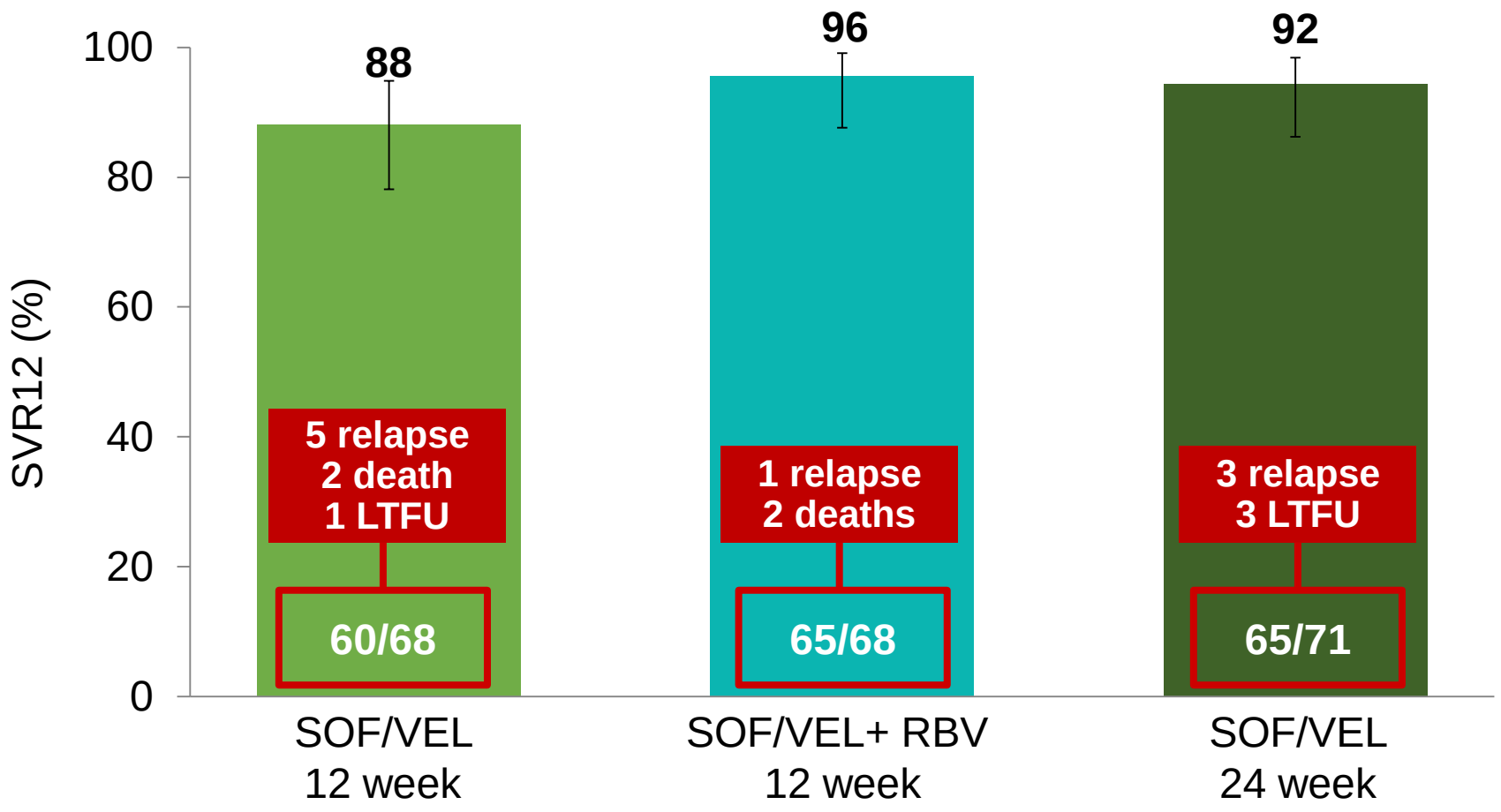
Overall SVR12



Patient with nondetectable drug levels at time of virologic failure..

Error bars represent 95% confidence intervals.

SVR12 in GT 1 Patients



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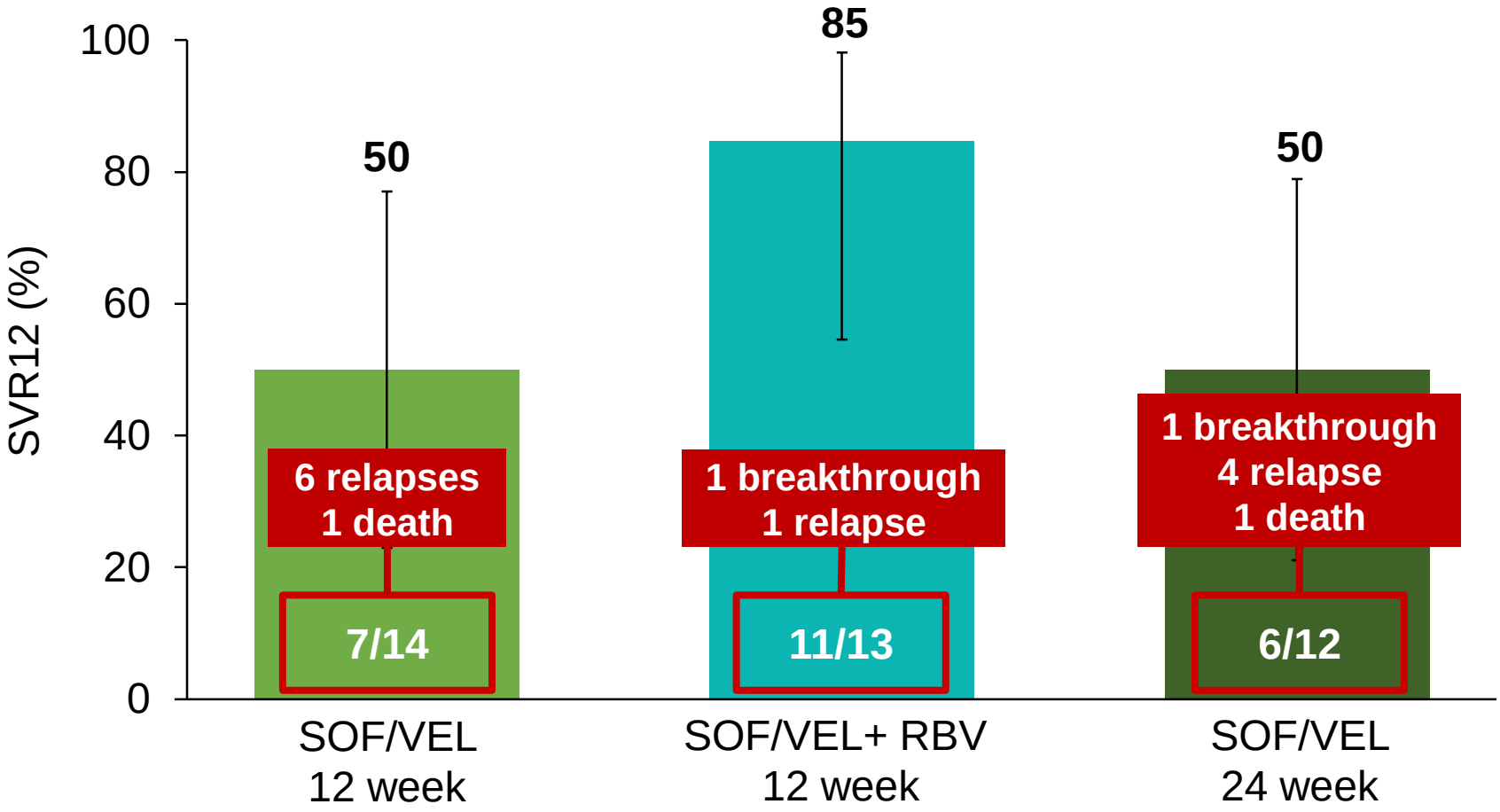
SVR12 in GT 3 Patients



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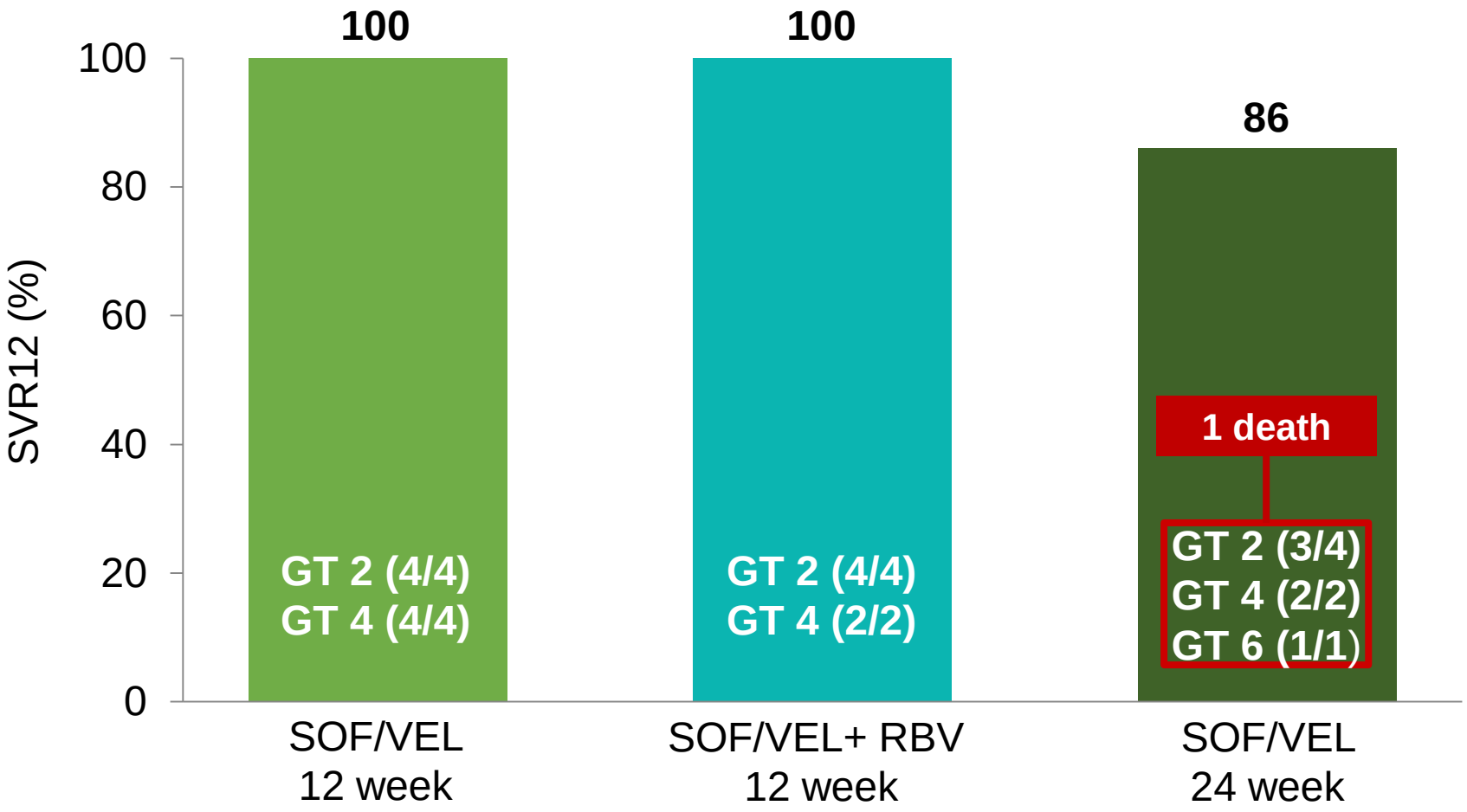
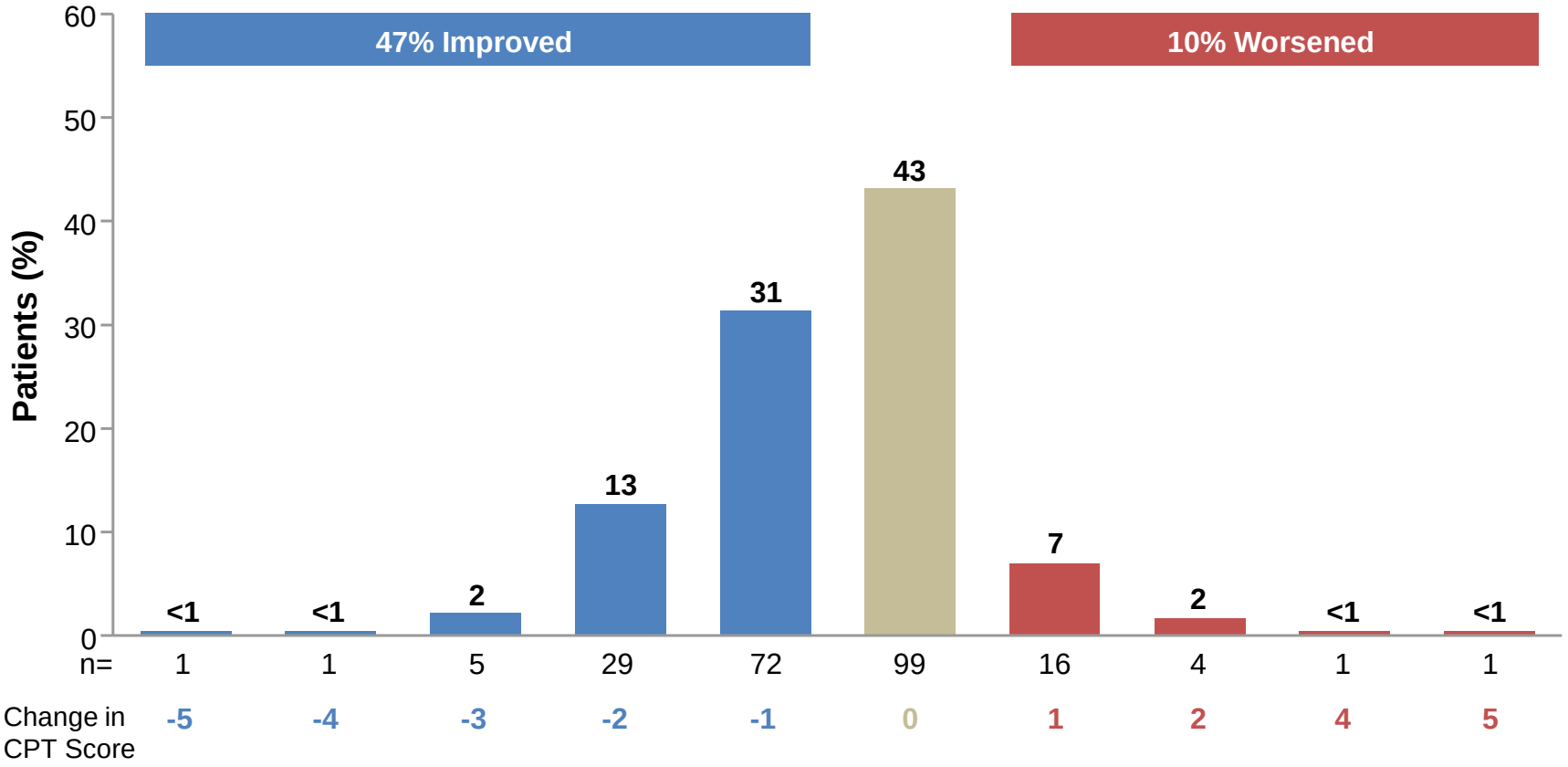
SVR12 in GT 2, 4, 6 Patients



Error bars represent 95% confidence intervals.

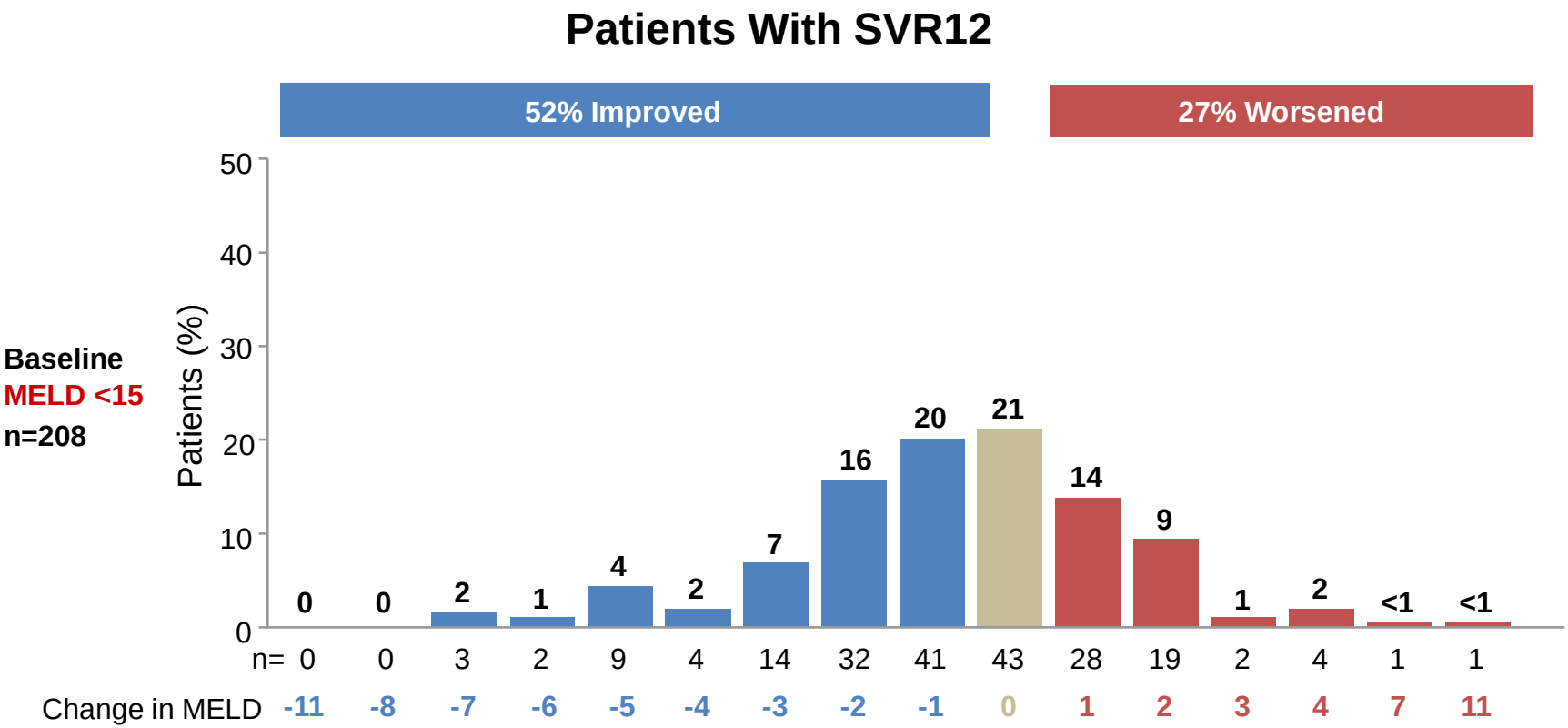
Results: CPT Score Change From Baseline Patients With SVR12



n=234; 5 patients had no follow-up Week 12 assessment.

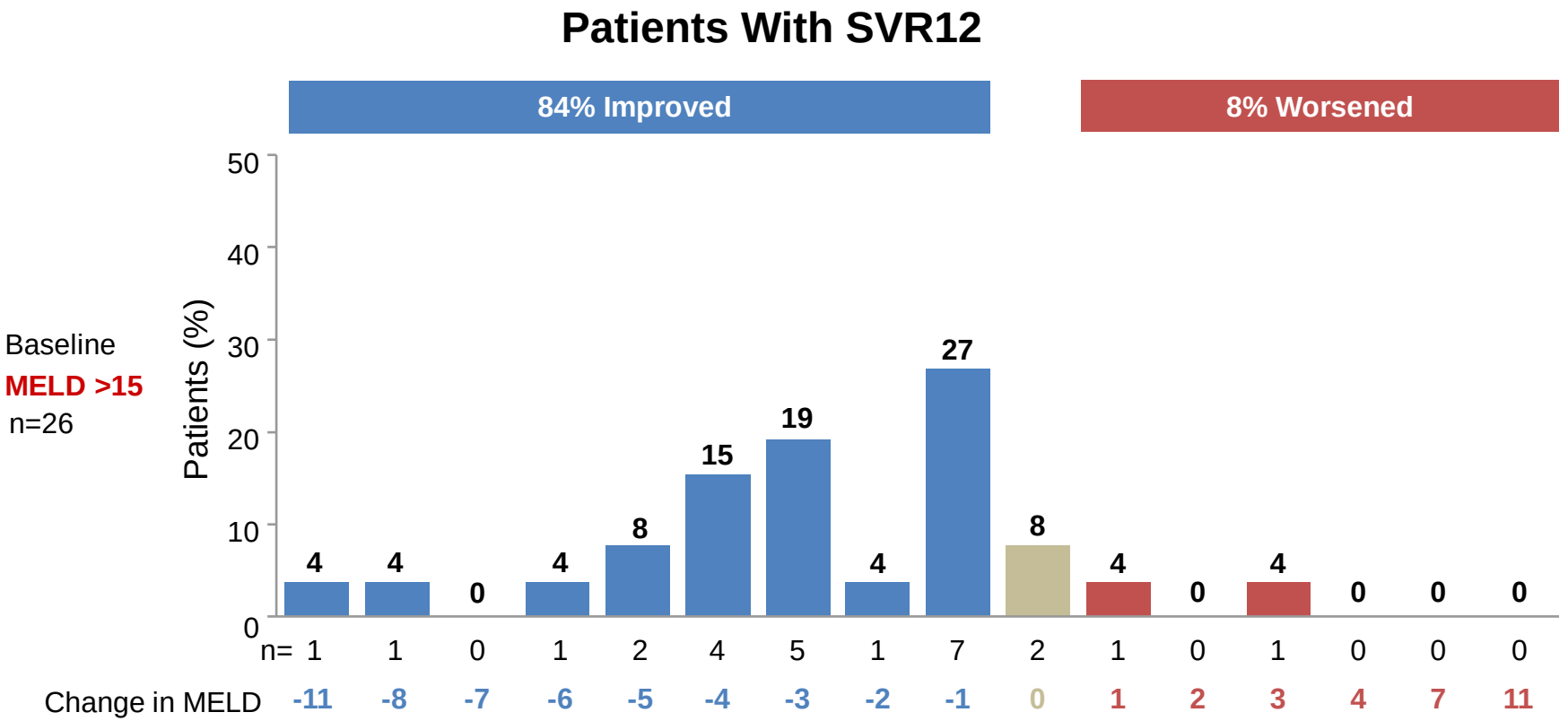
- Improvements in CPT score were driven largely by improvements in albumin and bilirubin

MELD Change: Baseline to Follow-up Week 12
Patients With SVR12



No follow-up Week 12 assessment for 5 patients

MELD Change: Baseline to Follow-up Week 12 Patients With SVR12



No follow-up Week 12 assessment for 5 patients.

- Improvements in MELD score were driven largely by improvements in total bilirubin

Overall Safety Summary

Patients, n (%)	SOF/VEL 12 wk n=90	SOF/VEL+RBV 12 wk n=87	SOF/VEL 24 wk n=90
Any AE	73 (81)	79 (91)	73 (81)
Grade 3 or 4 AE	16 (18)	11 (13)	17 (19)
Serious AE	17 (19)	14 (16)	16 (18)
Treatment related	0	1 (1)	1 (1)
AE leading to discontinuation	1 (1)	4 (5)	4 (4)
Transplant	0	0	1 (1)
Death	3 (3)	3 (3)	3 (3)

- Serious treatment-related AEs: dyspnea related to RBV; hepatorenal syndrome peritonitis, sepsis, and hypotension related to SOF/VEL
- Deaths: sepsis/septic shock/multiple organ failure (n=4); liver failure (n=2); cardiopulmonary arrest (n=1); respiratory failure (n=1); myocardial infarction (n=1)
  - None considered treatment related

Ribavirin Tolerance

Patients, n (%)	SOF/VEL+RBV 12 wk n=87
Hemoglobin <10 g/dL, n (%)	20 (23)
<8.5 g/dL, n (%)	6 (7)
Maximum median change, mg/dL (range)	-1.5 (-5.1–1.6)
RBV dosing	
Median average dose/d, mg (range)	1124 (486–1200)
Median days on RBV (range)	84 (4–89)
Discontinued, n (%)	15 (17)
Dose interruption ≥3 days, n (%)	4 (5)
Dose reduction, n (%)	32 (37)
Concomitant blood products or epoetin, n (%)	
Erythropoietin	1 (1)
Blood transfusion	0

Conclusions

- Treatment with SOF/VEL for 12 or 24 weeks or SOF/VEL + RBV for 12 weeks resulted in high SVR12 rates in HCV patients with decompensated liver disease[1]
- SOF/VEL + RBV for 12 weeks resulted in the highest overall SVR12 rates, with the lowest rates of virologic failure in HCV GT 1 and 3 patients
- Among patients who achieved SVR12, virologic response was associated with improved MELD and CPT scores in the majority of patients.
- SOF/VEL for 12 or 24 weeks or SOF/VEL + RBV for 12 weeks was safe and well tolerated, with AEs consistent with clinical sequelae of advanced liver disease and RBV toxicity

1. Curry M, et al. N Engl J Med 2015; 373: 2618-28

Acknowledgments

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