Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks Compared to Sofosbuvir with Ribavirin for 24 Weeks in Genotype 3 HCV-Infected Patients: The Randomized Controlled Phase 3 ASTRAL-3 Study

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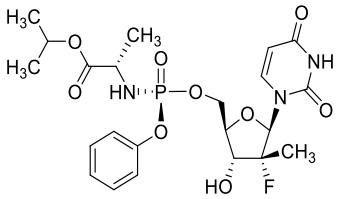
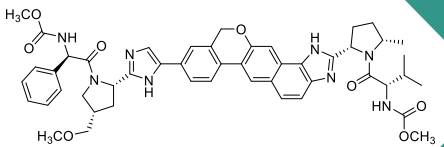
- Advisory: AbbVie, BMS, Gilead, Janssen, Merck

Background

SOF
Nucleotide polymerase inhibitor



- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL
NS5A inhibitor

- **Velpatasvir (VEL; GS-5816)[3-5]**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

SOF + **VEL**

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

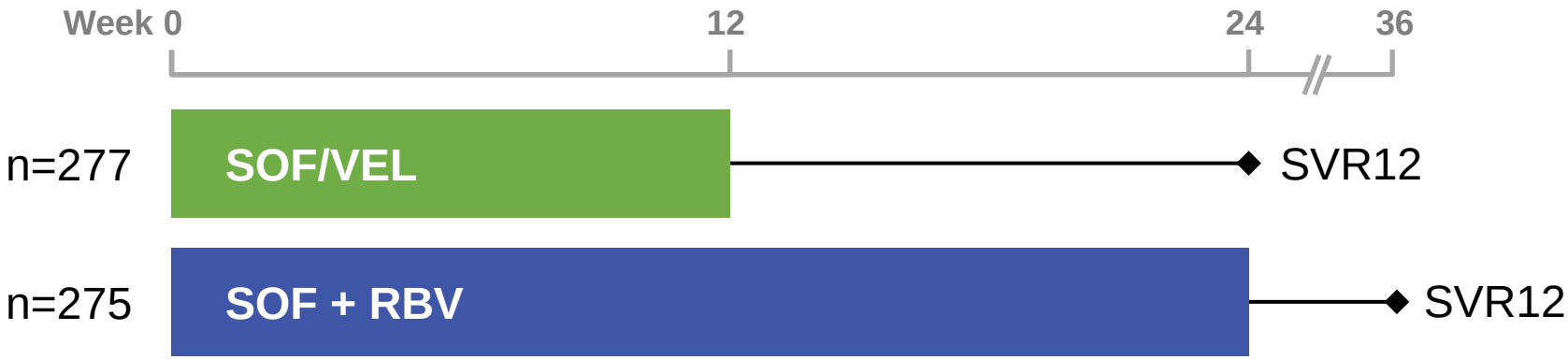
1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87;
3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. J Vir Hep 2015;22:1011-19.

Background and Aim
ASTRAL-3

- Phase 2 studies demonstrated that SOF + VEL administered as single agents resulted in high SVR12 rates in treatment-naïve and treatment-experienced patients with HCV GT 3 infection[1,2]
- SOF and VEL have been coformulated as an FDC
- This Phase 3 study evaluated SOF/VEL for 12 weeks compared to SOF + RBV for 24 weeks in HCV GT 3 infected patients

1. Everson G, et al. Ann Intern Med Nov 2015 2. Pianko S, et al. Ann Intern Med Nov 2015.

Study Design
ASTRAL-3



- Open-label, active-comparator trial
- Broad inclusion criteria
- 1:1 randomization to SOF/VEL or SOF + RBV
  - Stratified by prior treatment (TN/TE) and cirrhosis (presence/absence)
- Conducted at 76 sites in US, Canada, UK, Germany, France, Italy, Australia, and New Zealand

Study Methods
ASTRAL-3

- HCV genotyping
  - Versant HCV genotype LiPA 2.0
  - TruGene
- HCV RNA
  - COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 with LLOQ of 15 IU/mL
- HCV deep sequencing
  - Illumina MiSeq Platform (1% cut-off)
- Cirrhosis
  - Liver biopsy Metavir stage 4 or Ishak stage 5 or 6, or
  - Fibrotest >0.75 and APRI >2, or
  - Fibroscan >12.5 kPa

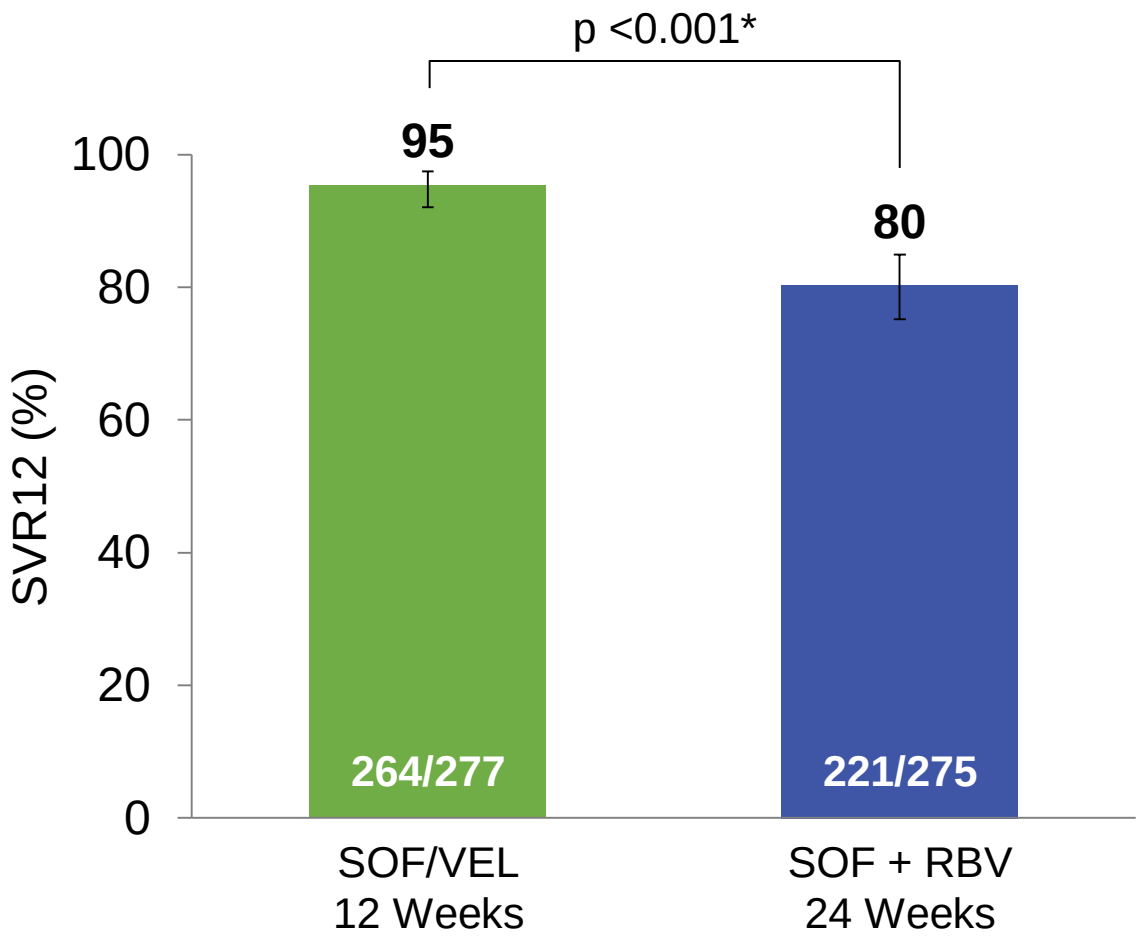
Results: Demographics
ASTRAL-3

	SOF/VEL 12 Weeks n=277	SOF + RBV 24 Weeks n=275
Mean age, y (range)	49 (21–76)	50 (19–74)
Male, n (%)	170 (61)	174 (63)
White, n (%)	250 (90)	239 (87)
Mean BMI, kg/m^2 (range)	26 (17–48)	27 (17–56)
Cirrhosis, n (%)	80 (29)	83 (30)
Treatment experienced, n (%)	71 (26)	71 (26)
IL28B CC, n (%)	105 (38)	111 (40)
HCV RNA, log_{10} IU/mL (range)	6.2 (3.7–7.5)	6.3 (3.6–7.5)

Results: Disposition
ASTRAL-3

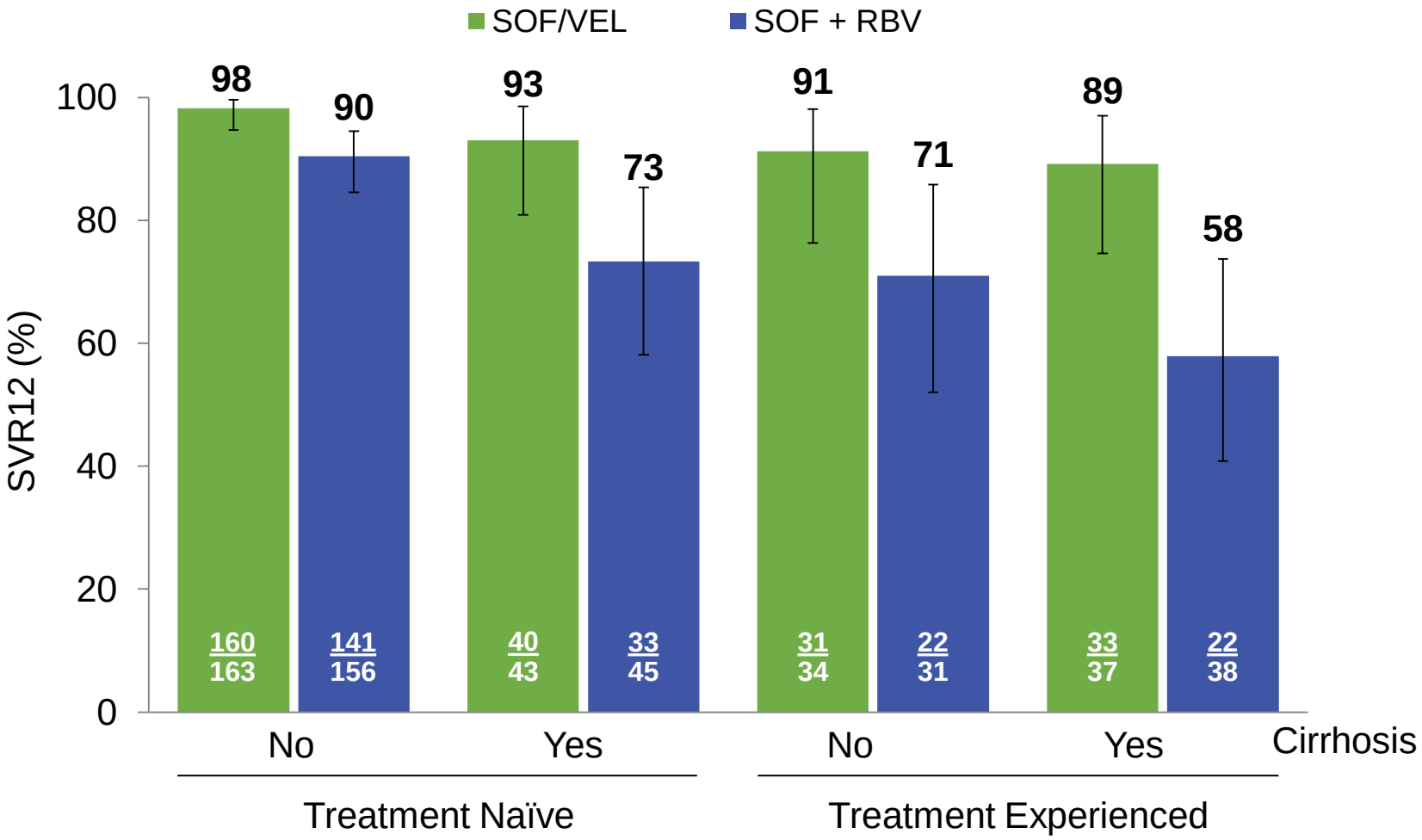
Patients, n (%)	SOF/VEL 12 Weeks n=277	SOF + RBV 24 Weeks n=275
Completed drug	275 (99)	254 (92)
Discontinued	2 (<1)	21 (8)
AE	0	9 (3)
Lost to follow-up	0	4 (1)
Noncompliance	1 (<1)	2 (<1)
Withdrew consent	0	3 (1)
Death	0	2 (<1)
Lack of efficacy	1 (<1)	1 (<1)

Results: SVR12
ASTRAL-3



*p-value for superiority of SOF/VEL compared with SOF+ RBV.
Error bars represent 95% confidence intervals.

Results: SVR12 by Cirrhosis and Treatment History
ASTRAL-3



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Results: SVR12 by Cirrhosis and Treatment History
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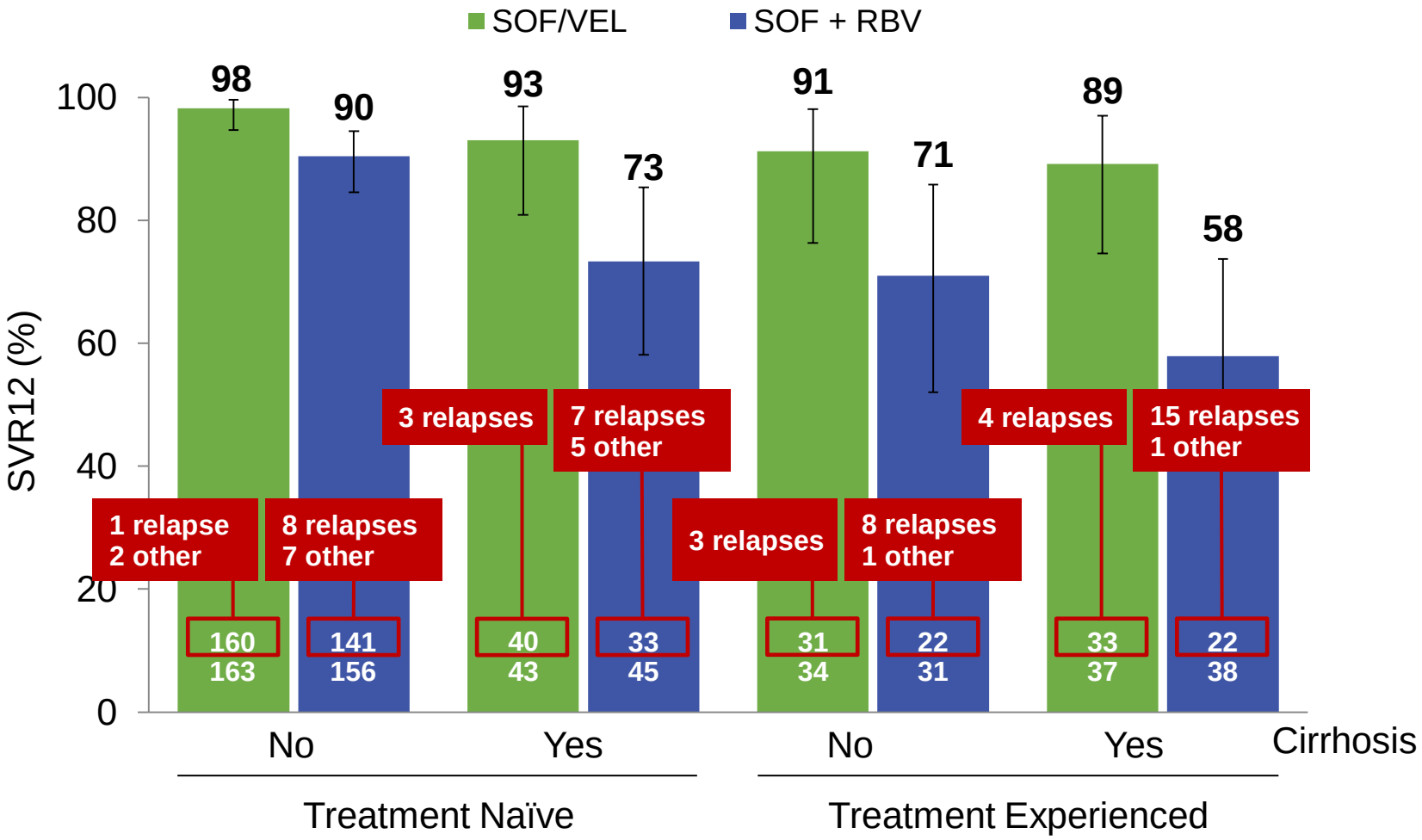

Error bars represent 95% confidence intervals.

Results: Safety
ASTRAL-3

	Patients, n (%)	SOF/VEL 12 Weeks n=277	SOF + RBV 24 Weeks n=275
Adverse Events	AE	245 (88)	260 (95)
	Grade 3–4 AE	12 (4)	23 (8)
	Serious AE	6 (2)	15 (5)
	D/C due to AE	0	9 (3)
	Death	0	3 (1)
Laboratory Abnormalities	Grade 3−4	20 (7)	47 (17)
	Hb <10 g/dL	0	10 (4)
	Hb <8.5 g/dL	0	0

- Deaths
  - Gunshot wounds, 52-year-old white male (Treatment Day 74)
  - Unknown causes, 58-year-old white female (Treatment Day 141)
  - Unknown causes, 66-year-old white male (118 days after completing treatment)
- Each assessed by investigator as unrelated to study drug

Results: AEs in >10% of Patients
ASTRAL-3

Adverse Event, n (%)	SOF/VEL 12 Weeks n=277	SOF + RBV 24 Weeks n=275
Headache	90 (32)	89 (32)
Fatigue	71 (26)	105 (38)
Insomnia	31 (11)	74 (27)
Nausea	46 (17)	58 (21)
Nasopharyngitis	34 (12)	33 (12)
Irritability	23 (8)	40 (15)
Cough	14 (5)	35 (13)
Pruritus	8 (3)	35 (13)
Dyspepsia	9 (3)	30 (11)

Conclusions
ASTRAL-3

- SOF/VEL for 12 weeks resulted in a 95% SVR12 rate in patients with HCV GT 3 infection
  - Statistically superior to SOF + RBV for 24 weeks ($p < 0.001$)
  - 91% SVR12 rate in patients with cirrhosis
- SOF/VEL was well tolerated and, compared with SOF + RBV, lacked toxicities commonly associated with RBV
- SOF/VEL for 12 weeks provides a simple, safe, highly effective, RBV-free treatment for patients with HCV GT 3 infection

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Back Up

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

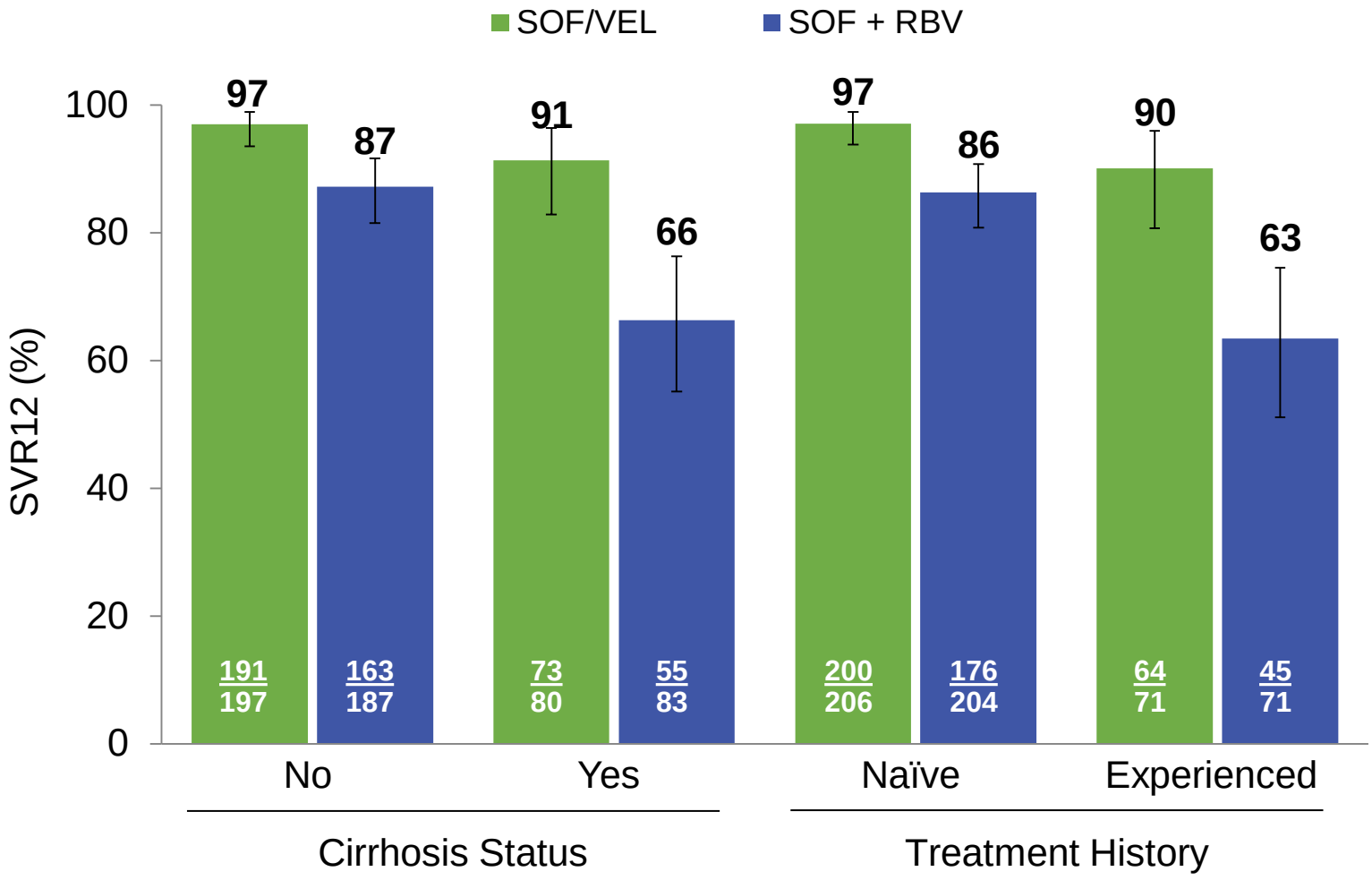
Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection

G.R. Foster, N. Afdhal, S.K. Roberts, N. Bräu, E.J. Gane, S. Pianko, E. Lawitz, A. Thompson, M.L. Shiffman, C. Cooper, W.J. Towner, B. Conway, P. Ruane, M. Bourlière, T. Asselah, T. Berg, S. Zeuzem, W. Rosenberg, K. Agarwal, C.A.M. Stedman, H. Mo, H. Dvory-Sobol, L. Han, J. Wang, J. McNally, A. Osinusi, D.M. Brainard, J.G. McHutchison, F. Mazzotta, T.T. Tran, S.C. Gordon, K. Patel, N. Reau, A. Mangia, and M. Sulkowski, for the ASTRAL-2 and ASTRAL-3 Investigators*

Study Endpoints
ASTRAL-3

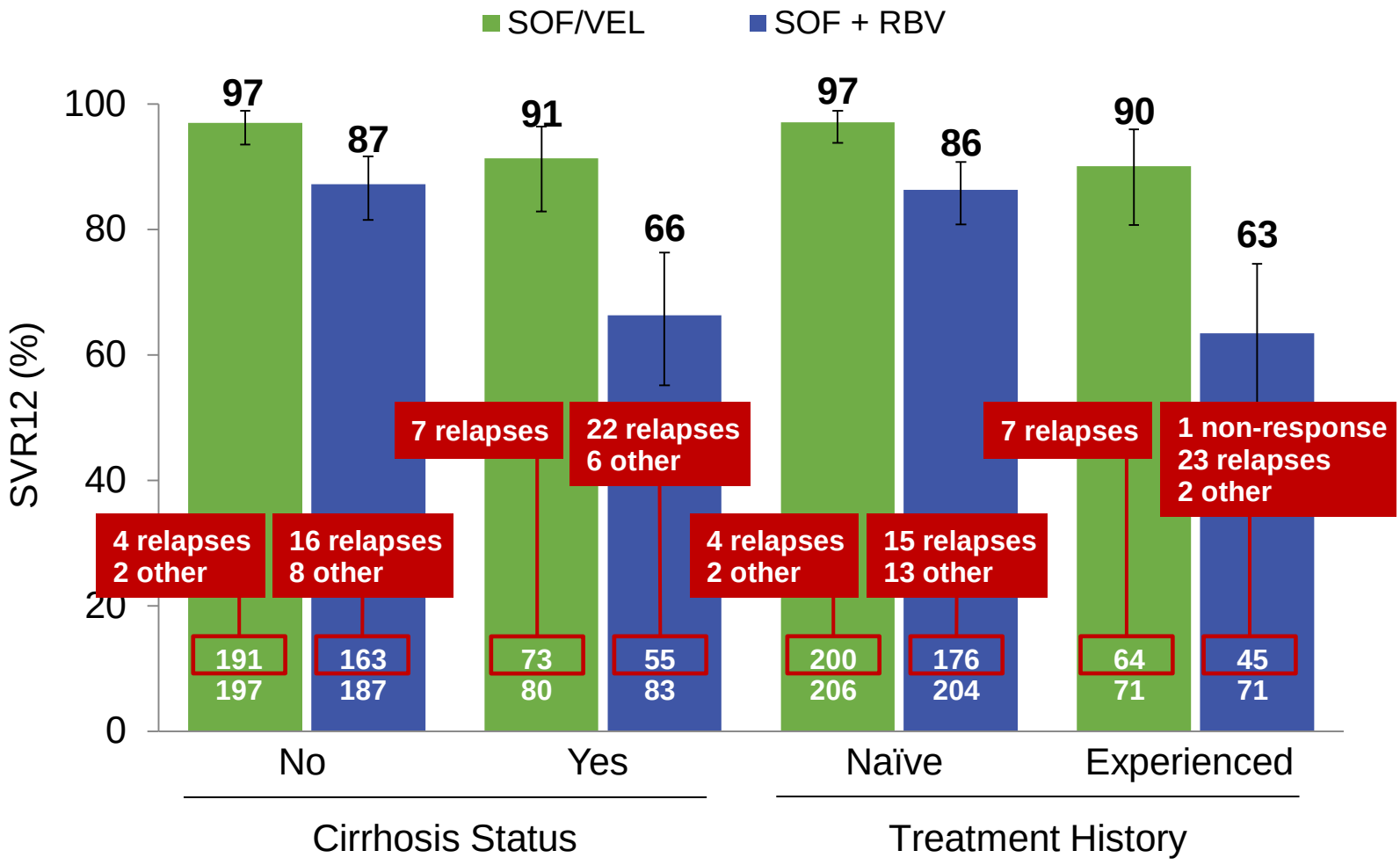
- Primary endpoint: SVR12
  - HCV RNA <LLOQ at post-treatment Week 12
- Efficacy analysis
  - Non-inferiority of SOF/VEL to SOF + RBV with 10% margin
    - Lower bound of 95% CI for difference in SVR12 rates must be greater than –10%
  - If non-inferiority established, then superiority evaluated at significance level of 0.05
- Safety
  - AEs and discontinuations
  - Laboratory abnormalities

Results: SVR12 by Cirrhosis or Treatment History ASTRAL-3



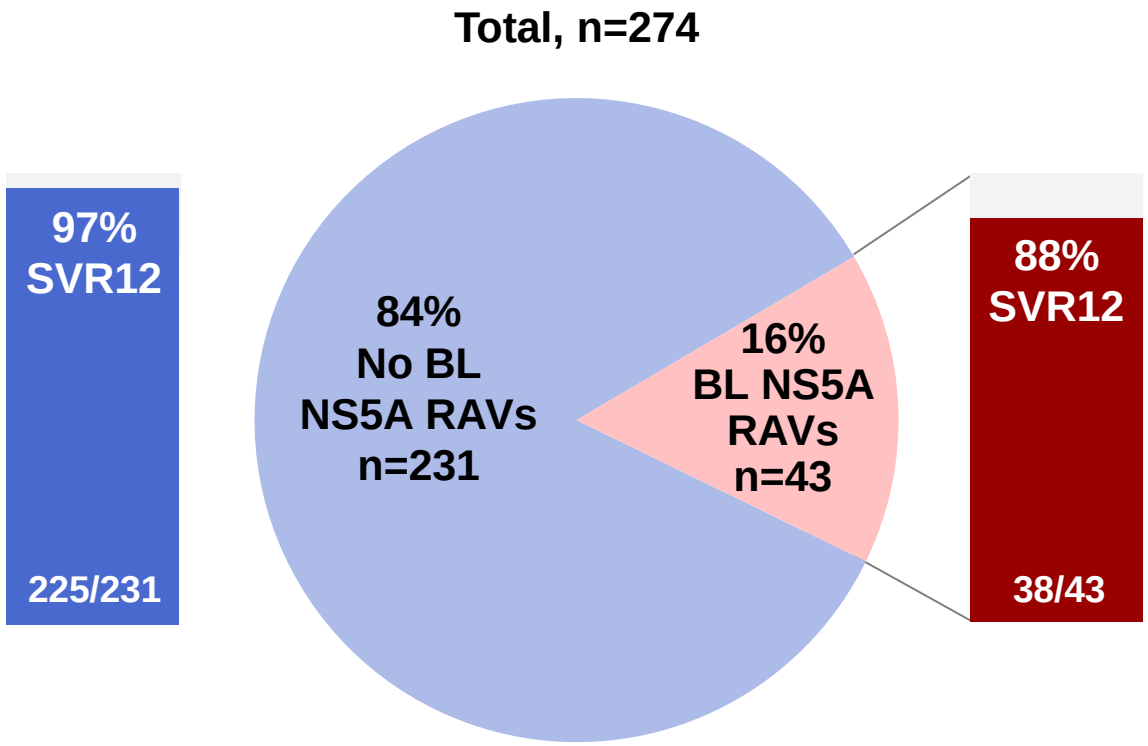
Error bars represent 95% confidence intervals.

Results: SVR12 by Cirrhosis or Treatment History
ASTRAL-3



Error bars represent 95% confidence intervals.

Results: Resistance Analysis
ASTRAL-3: SOF/VEL Group



- SVR12 was 84% (21/25) in patients with Y93H