HEPATITIS C ONLINE

Sofosbuvir-Velpatasvir (*Epclusa*)

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Sofosbuvir-Velpatasvir (*Epclusa*)

Background and Dosing

Sofosbuvir-Velpatasvir (*Epclusa*)

- **Approval Status**
  - Approval by United States FDA on June 28, 2016
- **Indications and Usage**
  - Indicated for the treatment of chronic HCV genotypes 1-6 in adults:
    - without cirrhosis or with compensated cirrhosis (Child-Pugh A)
    - with decompensated cirrhosis (Child-Pugh B and C) combined with ribavirin
- **Class and Mechanism**
  - Sofosbuvir: HCV NS5B polymerase inhibitor
  - Velpatasvir: HCV NS5A inhibitor
- **Preparation:** Sofosbuvir-Velpatasvir (fixed dose 400 mg/100 mg)
- **Dosing**: One tablet orally once daily, with or without food
- **Adverse Effects (AE)**: Headache and fatigue

Source: *Epclusa* Prescribing Information, Gilead Sciences.

Sofosbuvir-Velpatasvir (*Epclusa*) Indications and Usage

Sofosbuvir-Velpatasvir* for HCV Treatment in Patients with Genotype 1-6

Patient Population	Treatment	Duration
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	Sofosbuvir-Velpatasvir	12 weeks
Patients with decompensated cirrhosis (Child-Pugh B and C)	Sofosbuvir-Velpatasvir + Ribavirin^	12 weeks

A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease.

^The recommended dosage of ribavirin is based on weight (administered with food): 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily. The starting dosage and on-treatment dosage of ribavirin can be decreased based on hemoglobin and creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

Source: *Epclusa* Prescribing Information, Gilead Sciences.

Sofosbuvir-Velpatasvir (SOF-VEL): Summary of Key Studies

- **Phase 3 Trials**
  - **ASTRAL-1**: SOF-VEL x 12 weeks in TN and TE, GT 1-6
  - **ASTRAL-2**: SOF-VEL x 12 weeks in TN and TE, GT 2
  - **ASTRAL-3**: SOF-VEL x 12 weeks vs. SOF + RBV x 24 weeks, TN and TE, GT3
  - **ASTRAL-4**: SOF-VEL x 12 weeks in TN and TE, decompensated cirrhosis
  - **ASTRAL-5**: SOF-VEL x 12 weeks in TN and TE, HIV coinfection, GT 1-4
  - **POLARIS-2**: SOF-VEL x 12 weeks vs. SOF-VEL-VOX x 8 weeks, GT 1-4
  - **POLARIS-3**: SOF-VEL x 12 weeks vs. SOF-VEL-VOX x 8 weeks, GT3, cirrhosis
  - **Cirrhosis (Japan)**: SOF-VEL +/- RBV x 12 weeks in GT 1-6, decompensated cirrhosis
- **Phase 2 Trials**
  - **Cirrhosis (Spain)**: SOF-VEL +/- RBV x 12 weeks in GT 3 and compensated cirrhosis
  - **ESRD**: SOF-VEL x 12 weeks in GT 1-6, ESRD on dialysis
- **Phase 4 Trial**
  - **ACTG A5360 (MINMON)**: SOF-VEL x 12 weeks with minimal monitoring

Abbreviations: SOF-VEL = sofosbuvir-velpatasvir; TN = treatment-naïve; TE = treatment experienced; SOF = sofosbuvir; RBV = ribavirin; ESRD = end-stage renal disease

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1

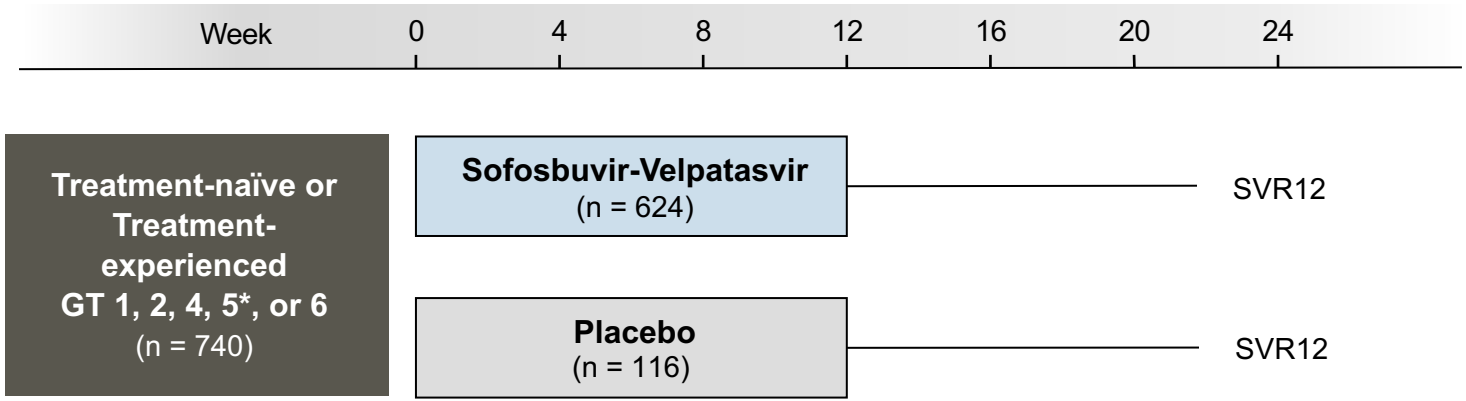
Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Study Features

- **Design**: Randomized, placebo-controlled, phase 3 trial using a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks in treatment-naïve and treatment-experienced patients with GT 1, 2, 4, 5, or 6 chronic HCV
- **Setting**: 81 sites in United States, Europe, and Hong Kong
- **Entry Criteria**
  - Chronic HCV GT 1, 2, 4, 5, or 6
  - HCV RNA ≥10,000 IU/mL at screening
  - Prior treatment failure with interferon allowed (but no prior NS5A or NS5B)
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Study Design



Randomized 5:1 ratio for treatment to placebo. Stratified by cirrhosis and HCV genotype.
*Genotype 5 patients (n = 6) were assigned to active arm (and not randomized)
Placebo recipients were eligible for deferred treatment with sofosbuvir-velpatasvir

Drug Dosing
Sofosbuvir-Velpatasvir (400/100 mg): fixed dose combination; one pill once daily

Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Baseline Characteristics

Baseline Characteristic	Sofosbuvir-Velpatasvir (n = 624)	Placebo (n = 116)
Age, mean (range)	54 (18-82)	53 (25-74)
Male, n (%)	374 (60)	68 (59)
Race, n (%) White Black Asian	 493 (79) 52 (8) 62 (10)	 90 (78) 11 (9) 11 (9)
HCV genotype, % 1a 1b 2 4 5 6	 210 (34) 118 (19) 104 (17) 116 (19) 35 (6) 41 (7)	 46 (40) 19 (16) 21 (18) 22 (19) 0 8 (7)
Body mass index, mean (range)	27 (17-57)	26 (18-40)
HCV RNA ≥800,000 IU/mL, n (%)	461 (74)	87 (75)
IL28B non-CC, n (%)	433 (69)	79 (68)

Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

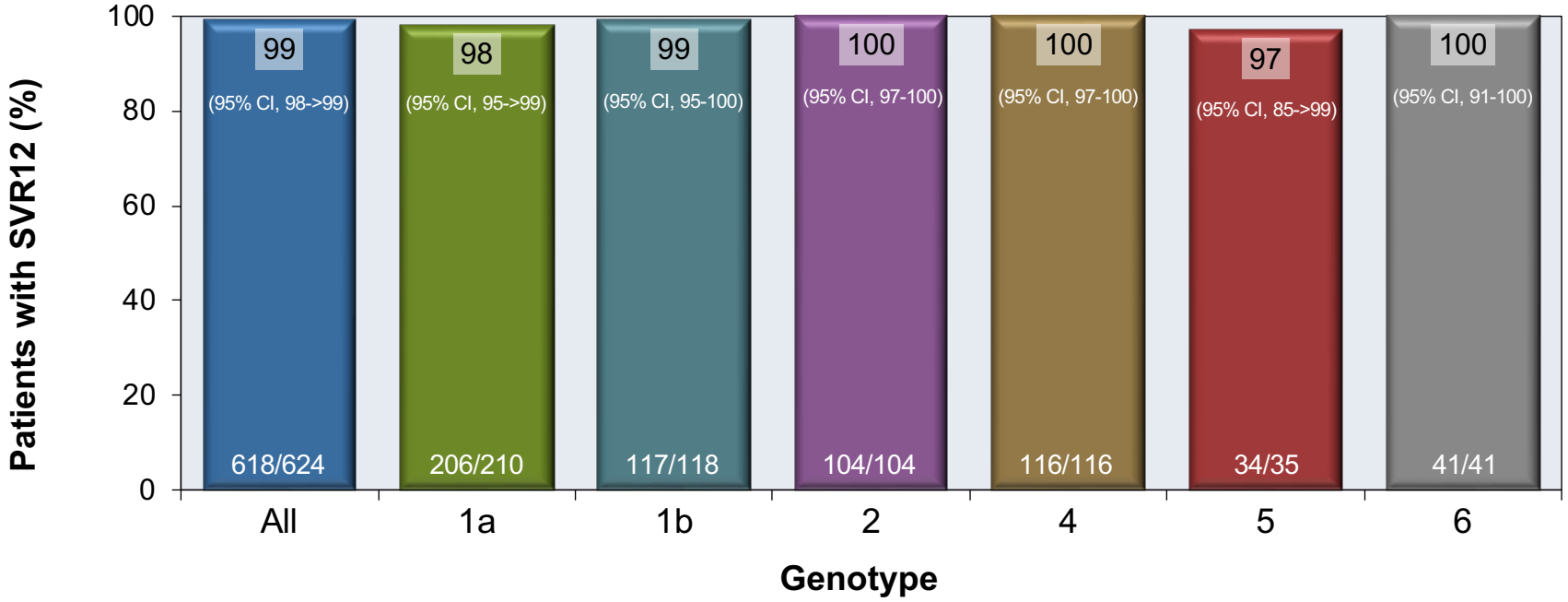
Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Baseline Characteristics

Baseline Characteristics	Sofosbuvir-Velpatasvir (n = 624)	Placebo (n = 116)
Cirrhosis, n (%)	121 (19)	21 (18)
Treatment experienced, n (%)	201 (32)	33 (28)
Prior therapy, n (%)		
Peginterferon + Ribavirin	122 (61)	24 (73)
Peginterferon + Ribavirin + Protease Inhibitor	56 (28)	6 (18)
Standard Interferon +/- Ribavirin	23 (11)	3 (9)

Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Results

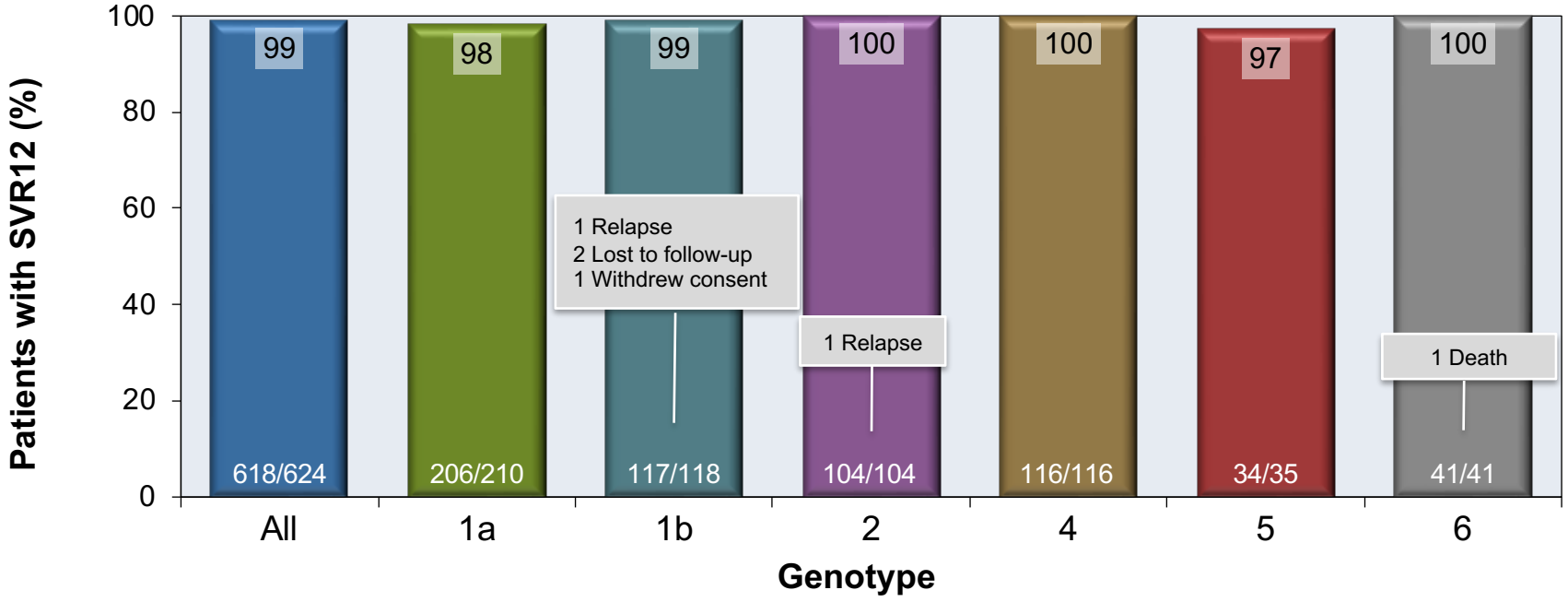
ASTRAL-1: SVR12 Results by Genotype



Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Results

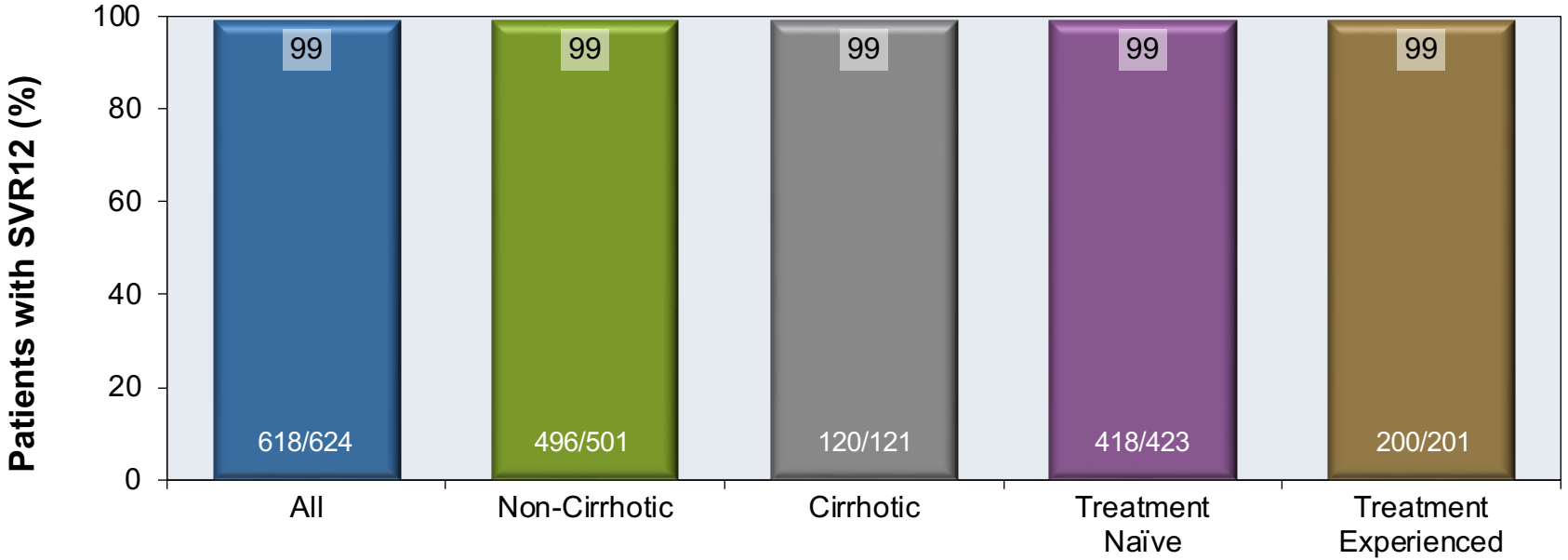
ASTRAL-1: SVR12 Results by HCV Genotype



Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Results

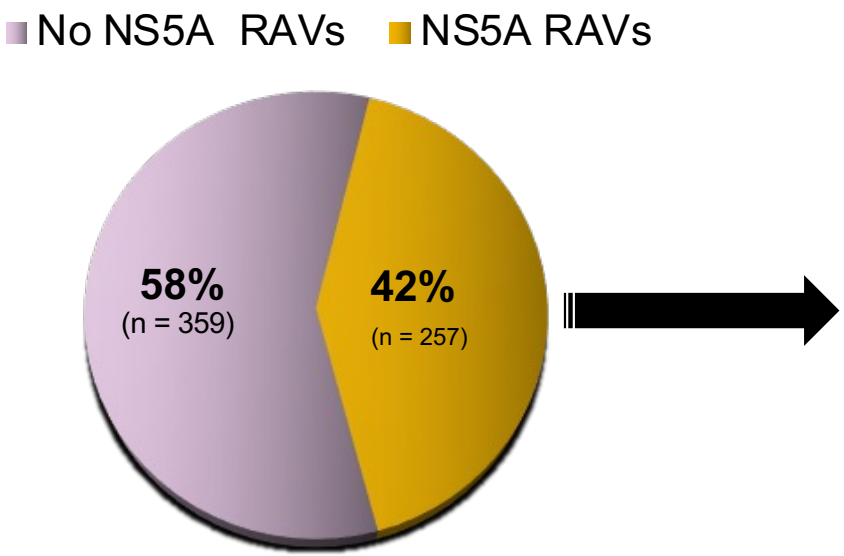
ASTRAL-1: SVR12 Results by Cirrhosis Status and Treatment Experience



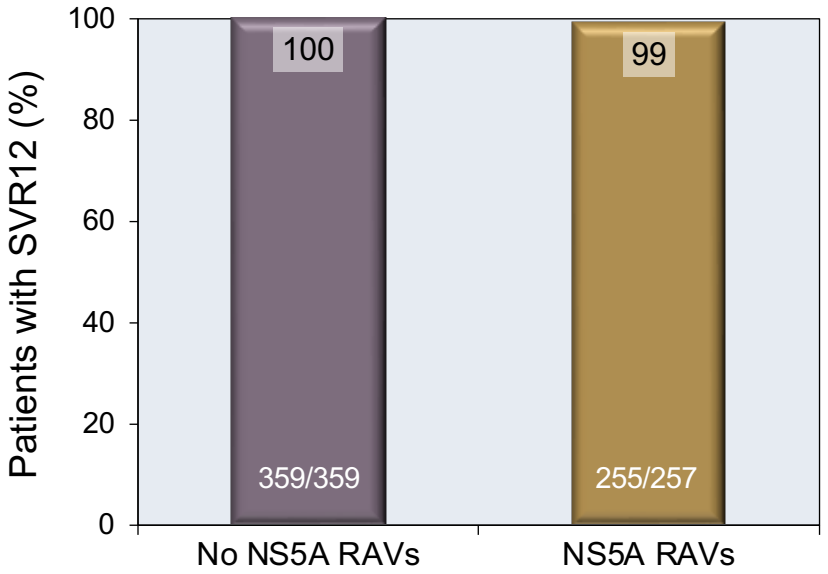
Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Resistance

Baseline Resistance-Associated Variants (RAVs)



Response to Treatment (SVR12)



Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Adverse Events

Adverse Event (AE), n (%)	Sofosbuvir-Velpatasvir (n = 624)	Placebo (n = 116)
Discontinuation due to AE	1 (<1)	2 (2)
Serious AEs	15 (2)	0
Deaths	1[§] (<1)	0
Any AE in ≥10% of patients		
Headache	182 (29)	33 (28)
Fatigue	126 (20)	23 (20)
Nasopharyngitis	79 (13)	12 (10)
Nausea	75 (12)	13 (11)
Laboratory AEs		
Hemoglobin <10 g/dL	2 (<1)	0
Lymphocyte count 350 to <500/mm^3	3 (<1)	0
Neutrophil count 500 to <750/mm^3	4 (1)	0
Platelet count 25K to <50K/mm^3	1 (<1)	0

[§]This death was not considered to be study-related.

Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Conclusion

Conclusions: “Once-daily sofosbuvir–velpatasvir for 12 weeks provided high rates of sustained virologic response among both previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5, or 6, including those with compensated cirrhosis.”

Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in Genotype 2
ASTRAL-2*

*Published in tandem with ASTRAL-3 Trial

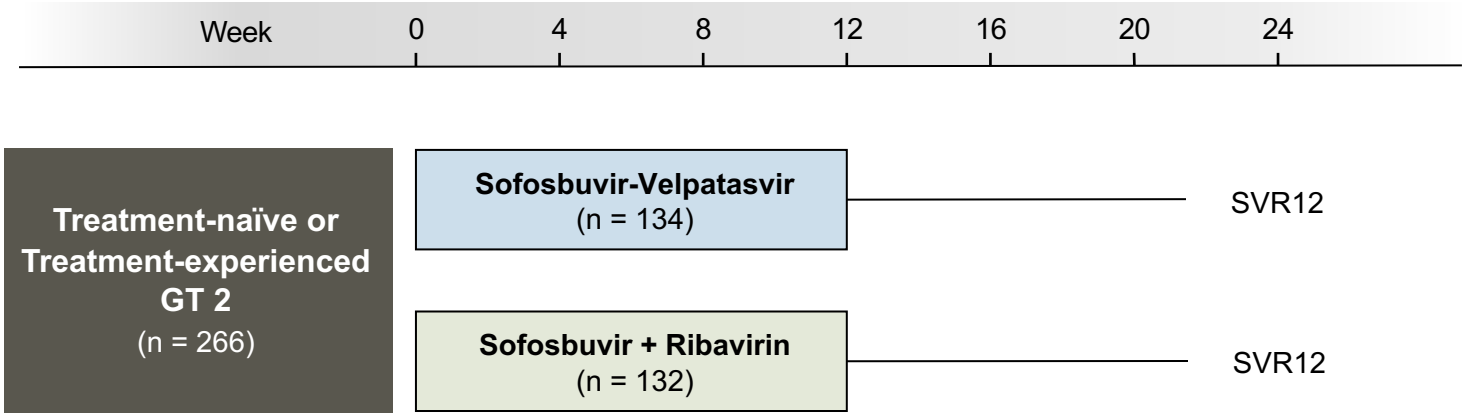
Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Study Features

- **Design**: Randomized, placebo-controlled, open-label, phase 3 trial using a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks compared with sofosbuvir plus ribavirin in treatment-naïve and treatment-experienced patients with GT 2 chronic HCV
- **Setting**: 51 sites in United States
- **Entry Criteria**
  - Chronic HCV GT 2
  - HCV RNA ≥10,000 IU/mL at screening
  - Prior treatment failure with interferon allowed (but no prior NS5A or NS5B)
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Study Design



*Randomization stratified by treatment experience and cirrhosis status.

Drug Dosing
Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily
Sofosbuvir: 400 mg once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg

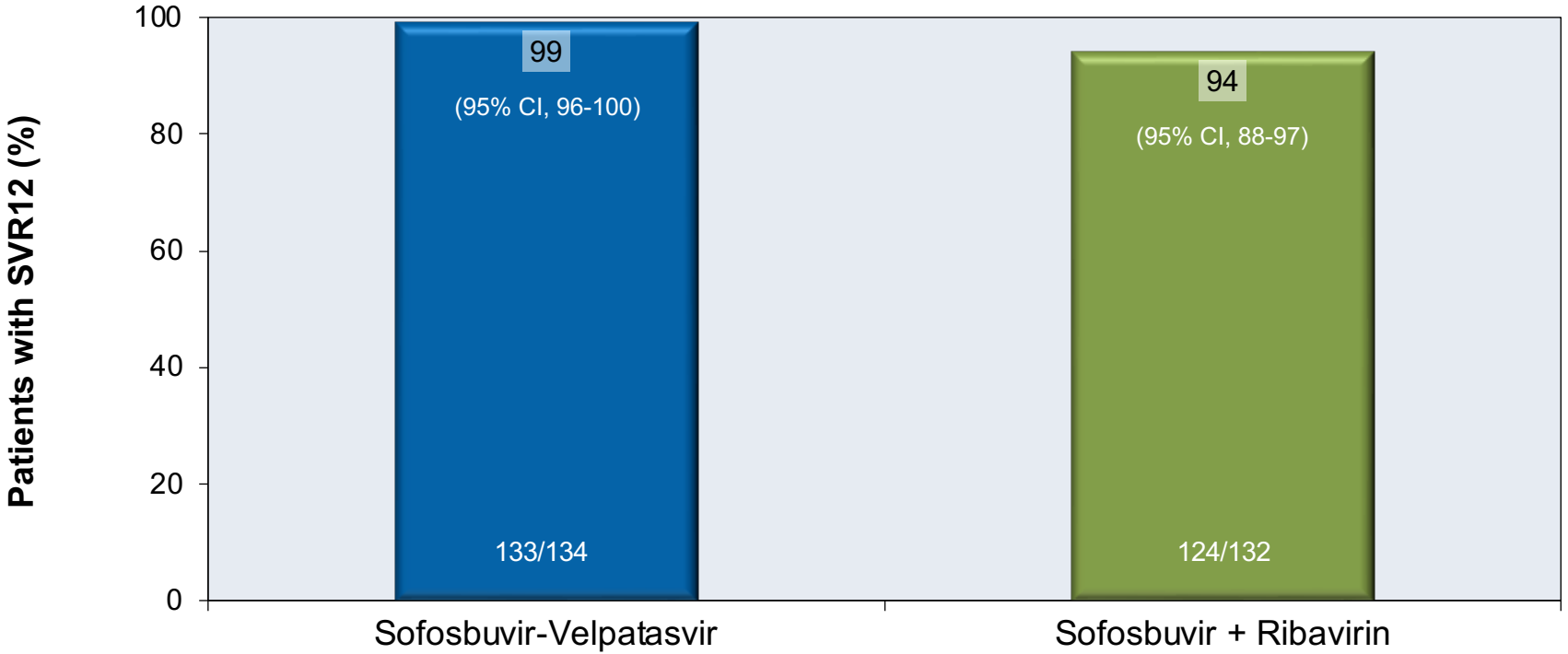
Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Baseline Characteristics

Baseline Characteristics	Sofosbuvir-Velpatasvir (n = 134)	Sofosbuvir + Ribavirin (n = 132)
Age, mean (range)	57 (26-81)	57 (23-76)
Male, n (%)	86 (64)	72 (55)
Race, n (%) White Black Asian	 124 (93) 6 (4) 1 (1)	 111 (84) 12 (9) 5 (4)
Body mass index, mean (range)	28 (17-45)	29 (19-61)
HCV RNA ≥800,000 IU/mL, n (%)	111 (83)	101 (77)
IL28B non-CC, n (%)	79 (59)	86 (65)
Cirrhosis, n (%)	19 (14)	19 (14)
Treatment-experienced, n (%)	19 (14)	20 (15)
Prior response, n/total (%) Non-response Relapse or breakthrough	 3/19 (16) 16/19 (84)	 3/20 (15) 17/20 (85)

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Results



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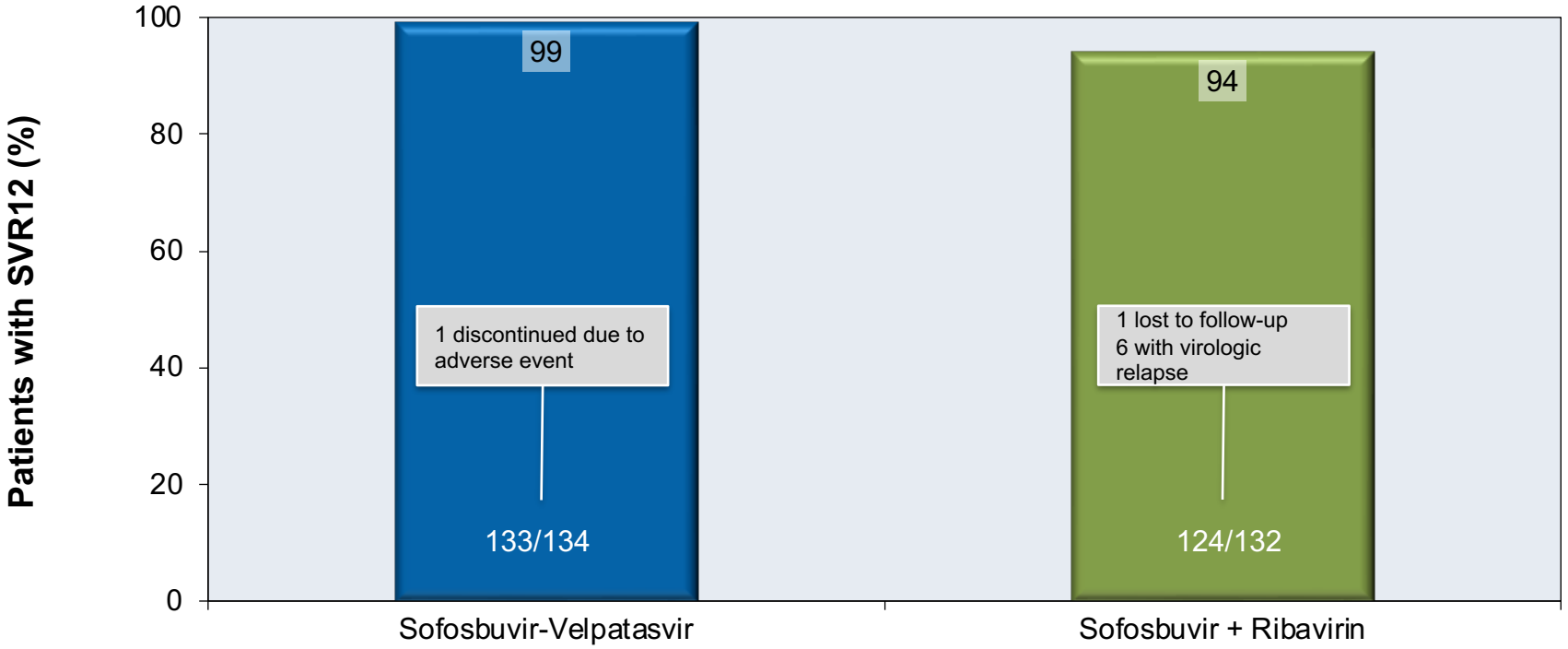
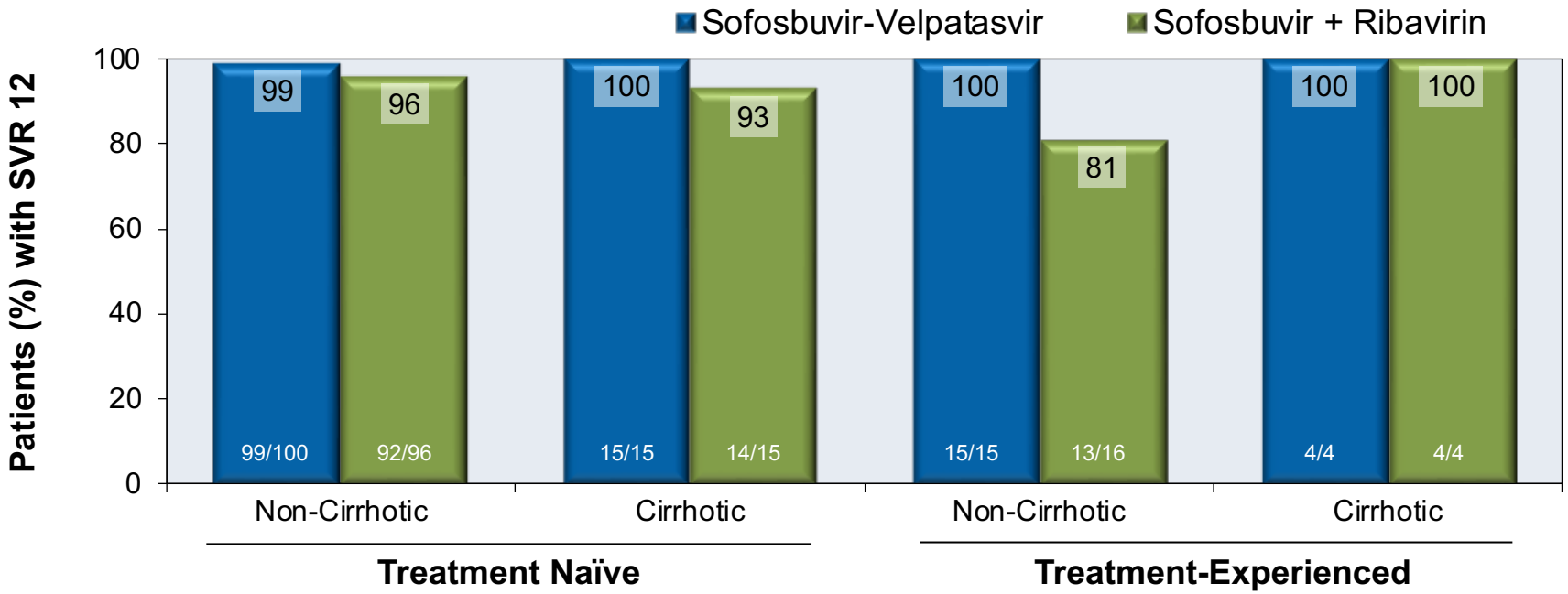
Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Results



Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Results

SVR12 Results by Treatment Experience and Cirrhosis Status



Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Adverse Events

Adverse Event (AE), n (%)	Sofosbuvir-Velpatasvir (n = 134)	Sofosbuvir + Ribavirin (n = 132)
Discontinuation due to AE	1 (1)	0
Serious AEs	2 (1)	2 (2)
Deaths	2§ (1)	0
Any AE in ≥10% of patients		
Fatigue	20 (15)	47 (36)
Headache	24 (18)	29 (22)
Nausea	14 (10)	19 (14)
Insomnia	6 (4)	18 (14)
Laboratory AEs		
Hemoglobin <10 g/dl	0	6 (5)
Total bilirubin >2.5 to 3 mg/dL	0	3 (2)
Platelet count 25K to <50K/mm^3	0	0

§ Deaths were not considered to be study-related.

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 2
ASTRAL-2: Conclusions

Conclusions: “Among patients with HCV genotype 2 [or 3] with or without previous treatment, including those with compensated cirrhosis, 12 weeks of treatment with sofosbuvir-velpatasvir resulted in rates of sustained virologic response that were superior to those with standard treatment with sofosbuvir-ribavirin.”

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in Genotype 3
ASTRAL-3*

*Published in tandem with ASTRAL-2 Trial

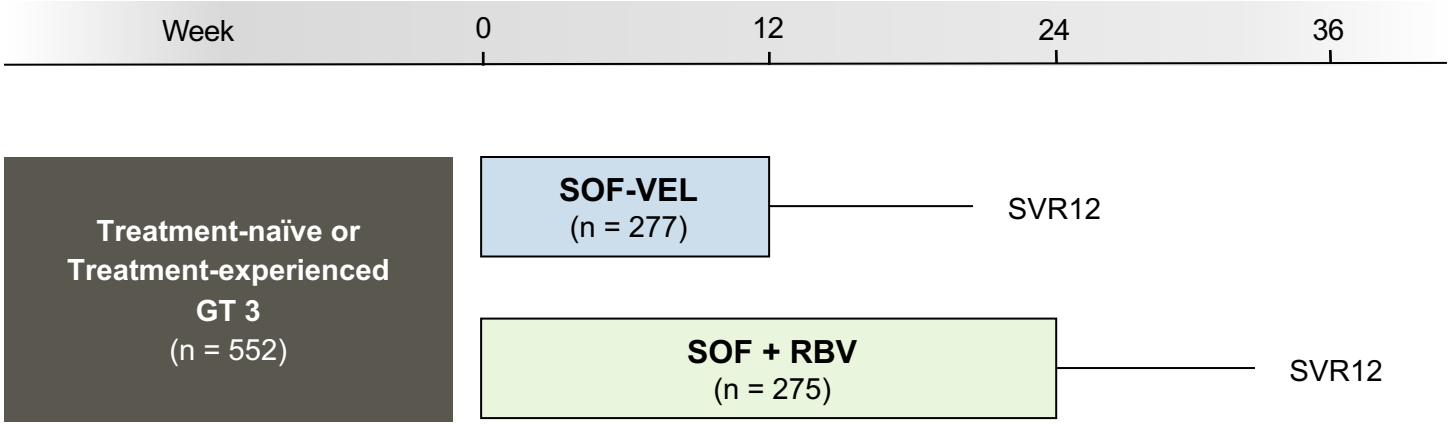
Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Study Features

- **Design**: Randomized, placebo-controlled, open-label, phase 3 trial using a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks (compared with sofosbuvir + ribavirin) in treatment-naïve and treatment-experienced patients with GT 3 chronic HCV
- **Setting**: 76 sites in US, Canada, Europe, Australia, and New Zealand
- **Entry Criteria**
  - Chronic HCV GT 3
  - HCV RNA ≥10,000 IU/mL at screening
  - Prior treatment failure with interferon allowed (but no prior NS5A or NS5B)
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Study Design



*Randomization stratified by treatment experience and cirrhosis status.

Abbreviations: SOF-VEL = sofosbuvir-velpatasvir; RBV = ribavirin

Drug Dosing
Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily
Sofosbuvir: 400 mg once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg

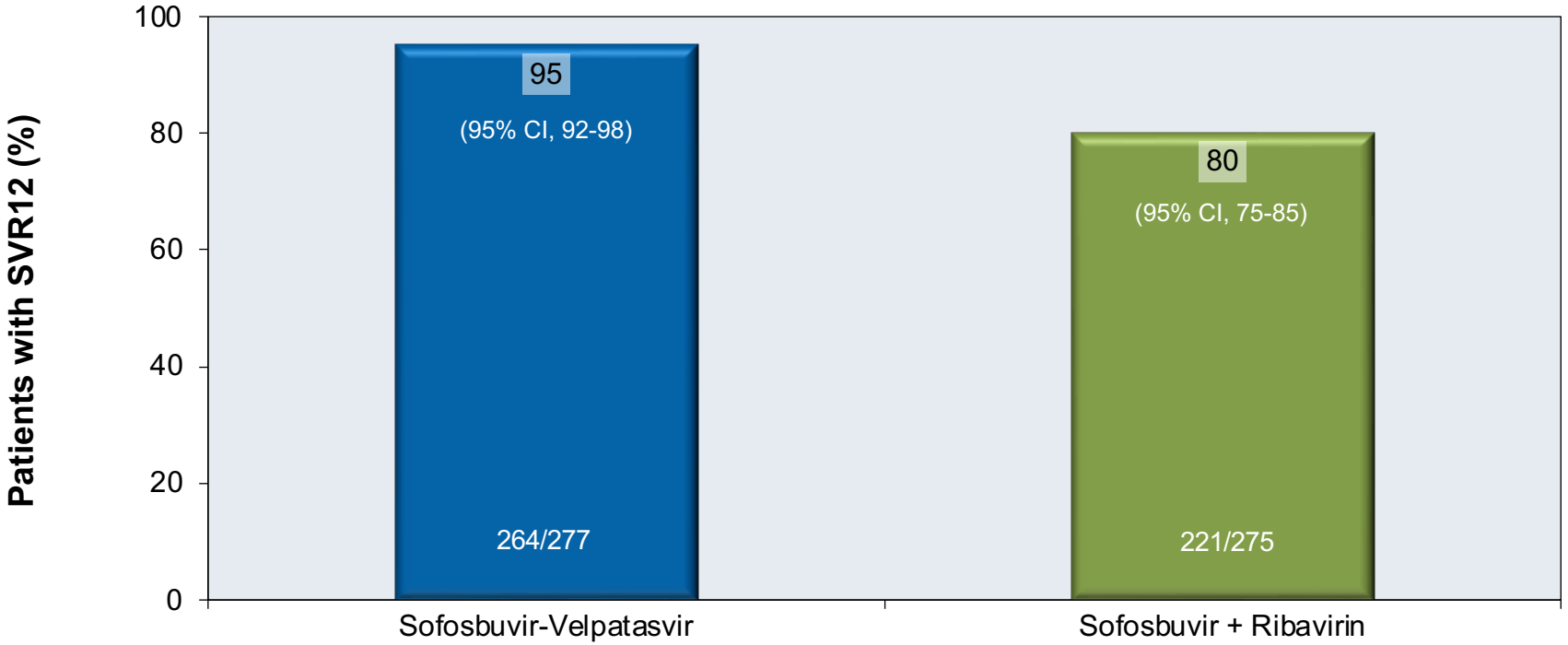
Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Baseline Characteristics

Baseline Characteristics	Sofosbuvir-Velpatasvir (n = 277)	Sofosbuvir + Ribavirin (n = 275)
Age, mean (range)	49 (21-76)	50 (19-74)
Male, n (%)	170 (61)	174 (63)
Race, n (%) White Black Asian	 250 (90) 3 (1) 23 (8)	 239 (87) 1 (<1) 29 (11)
Body mass index, mean (range)	26 (17-48)	27 (17-56)
HCV RNA ≥800,000 IU/mL, n (%)	191 (69)	194 (71)
IL28B non-CC, n (%)	172 (62)	164 (60)
Cirrhosis, n (%)	80 (29)	83 (30)
Treatment-experienced, n (%)	71 (26)	71 (26)
Prior response, no./total (%) Non-response Relapse or breakthrough	 20/71 (28) 51/71 (72)	 24/71 (34) 47/71 (66)

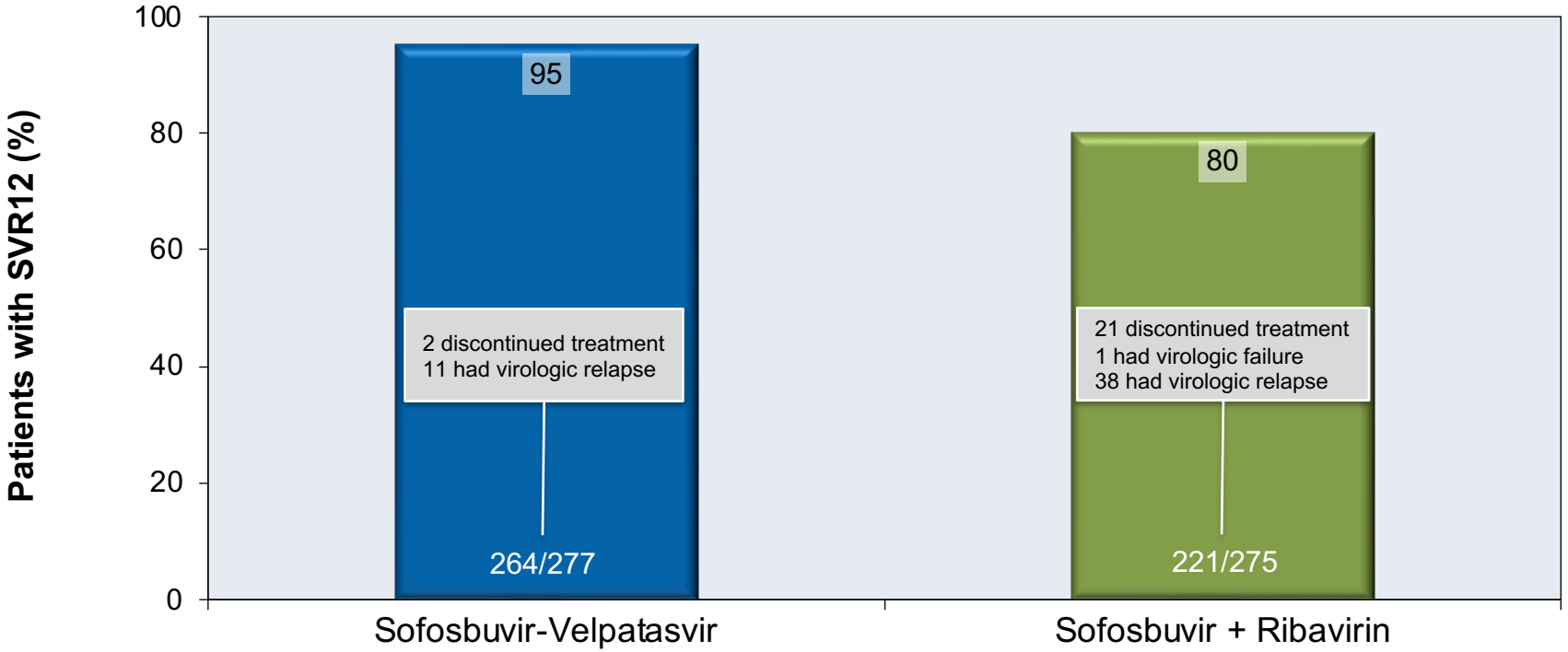
Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Results



Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

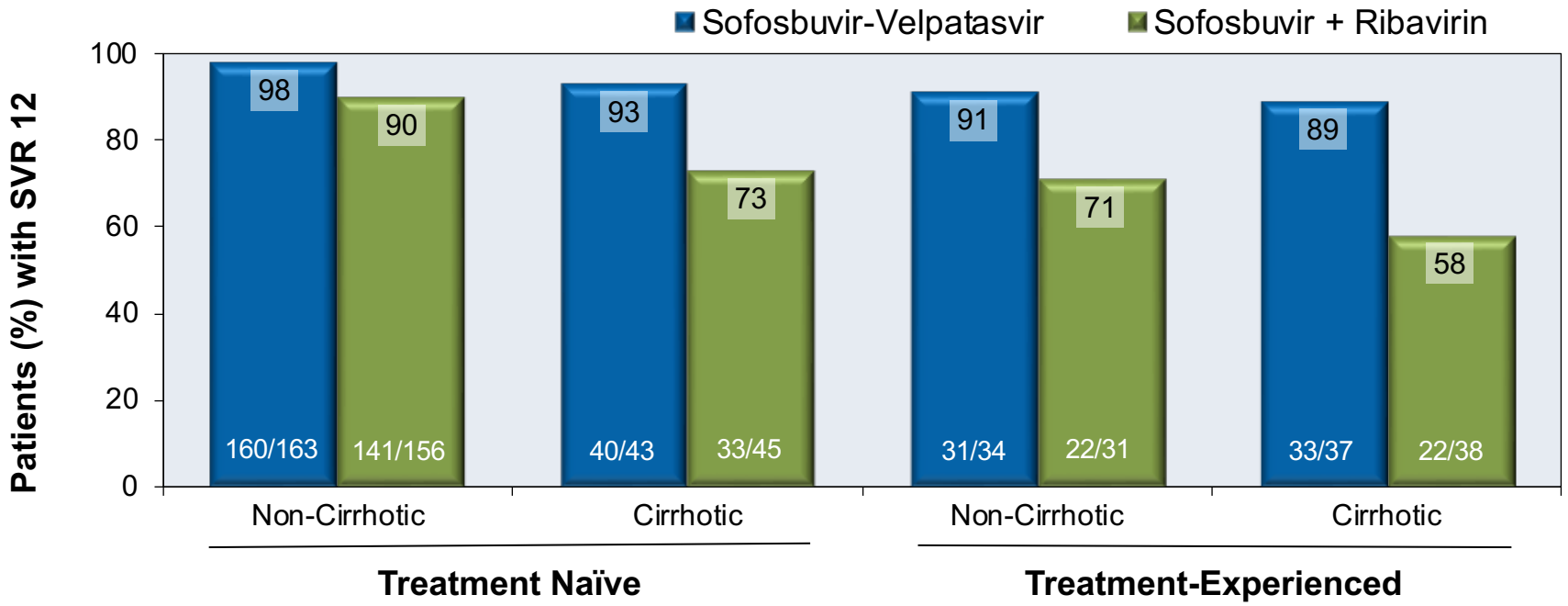
Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Results



Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Results

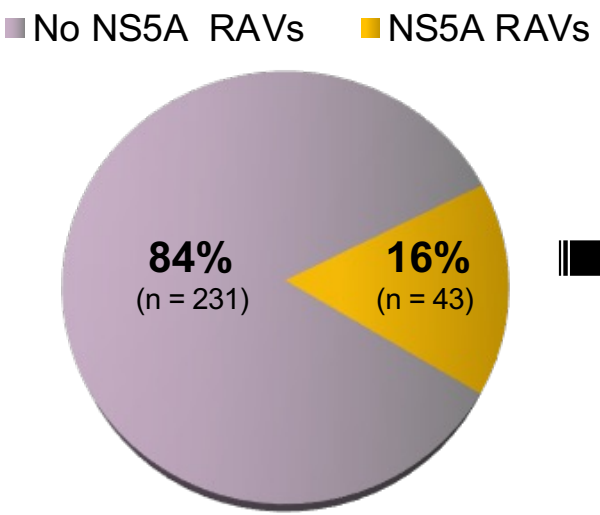
SVR12 Results by Treatment Experience and Cirrhosis Status



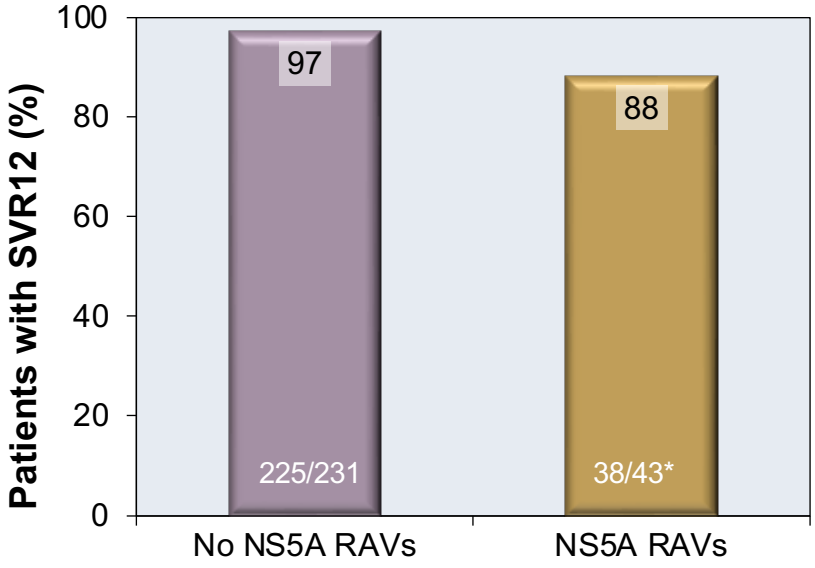
Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Resistance

Baseline Resistance-Associated Variants (RAVs)



Response to Treatment (SVR12)



* SVR12 in 84% (21/25) of patients with Y93H

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Adverse Events

Adverse Event (AE), n (%)	Sofosbuvir-Velpatasvir (n = 277)	Sofosbuvir + Ribavirin (n = 275)
Discontinuation due to AE	0	9 (3)
Serious AEs	6 (2)	15 (5)
Deaths	0	3 (1)
Any AE in ≥10% of patients		
Fatigue	71 (26)	105 (38)
Headache	90 (32)	89 (32)
Nausea	46 (17)	58 (21)
Insomnia	31 (11)	74 (27)
Laboratory AEs		
Hemoglobin <10 g/dL	0	10 (4)
Total bilirubin >2.5 to 3 mg/dL	0	2 (1)
Platelet count 25K to <50K/mm^3	1 (<1)	1 (<1)

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Conclusions

Conclusions: “Among patients with HCV genotype [2 or] 3 with or without previous treatment, including those with compensated cirrhosis, 12 weeks of treatment with sofosbuvir-velpatasvir resulted in rates of sustained virologic response that were superior to those with standard treatment with sofosbuvir-ribavirin.”

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4

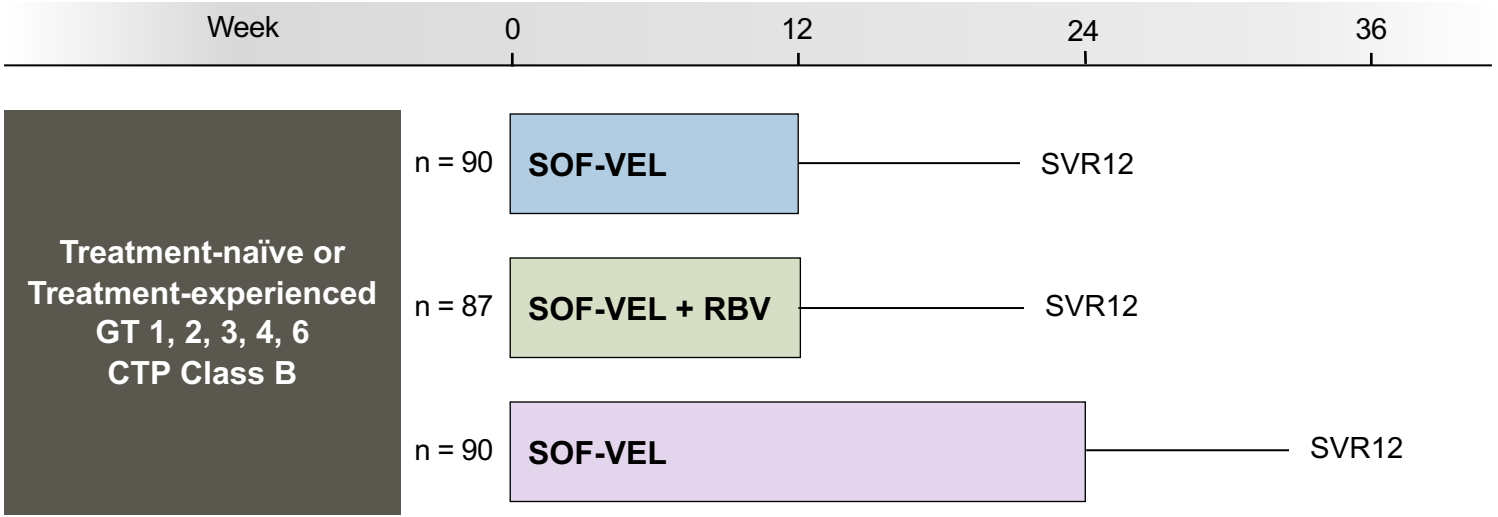
Source: Curry MP, et al. N Engl J Med. 2015;373:2618-28.

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Study Features

- **Design**: Randomized, open label, phase 3 trial to examine the safety and efficacy of a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks +/- ribavirin or for 24 weeks in patients with GT 1, 2, 3, 4, or 6 chronic HCV with decompensated cirrhosis
- **Setting**: 47 sites in United States
- **Entry Criteria**
  - Chronic HCV GT 1, 2, 3, 4, or 6
  - Child-Turcotte-Pugh class B
  - Prior treatment failure (except for prior NS5A or NS5B) allowed
- **Exclusion Criteria**
  - Prior or impending (within 12 weeks of study entry) liver transplantation
  - Platelet count <30,000/mm^3 or CrCl <50 mL/min
- **Primary End Point**: SVR12

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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Study Design



Abbreviations: SOF-VEL = sofosbuvir-velpatasvir; RBV = ribavirin; CTP =Child-Turcotte-Pugh

Drug Dosing
Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily
Sofosbuvir: 400 mg once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg

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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Participants

Baseline Characteristics	SOF-VEL 12 weeks (n = 90)	SOF-VEL + RBV 12 weeks (n = 87)	SOF-VEL 24 weeks (n = 90)
Mean age, years (range)	58 (42-73)	58 (40-71)	58 (46-72)
Male sex, %	63	76	70
Race, %			
White	88	91	90
Black	7	6	7
Asian	3	0	2
HCV Genotype, %			
1a	56	62	61
1b	20	16	18
2	4	5	4
3	16	15	13
4	4	2	2
6	0	0	1
HCV RNA ≥800,000 IU/mL, %	66	52	50
IL28B genotype, non-CC, %	78	75	78
Mean eGFR, mL/min (range)	89 (15-169)	90 (50-167)	90 (43-198)

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

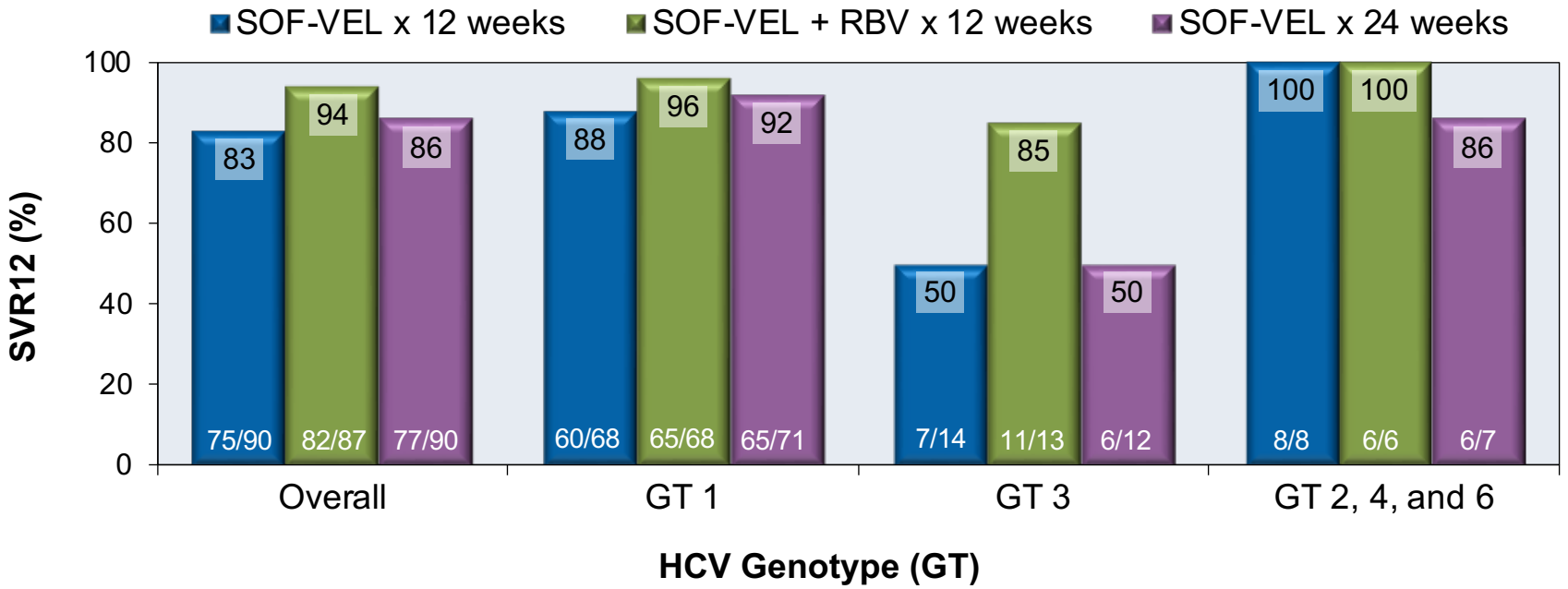
Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Participants

Baseline Characteristic	SOF-VEL 12 weeks (n = 90)	SOF-VEL + RBV 12 weeks (n = 87)	SOF-VEL 24 weeks (n = 90)
CPT score, %			
≤6	3	7	8
7	40	26	23
8	34	47	38
9	21	15	24
10	1	5	7
MELD score, %			
<10	40	33	29
10-15	56	62	66
≥16	4	5	6
Ascites, %			
None	18	25	17
Mild or moderate	80	70	82
Severe	2	5	1
Prior HCV treatment, %			
No	36	46	53
Yes	64	54	47
Protease inhibitor regimen	16	26	17
Peginterferon + ribavirin	83	74	83

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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Results

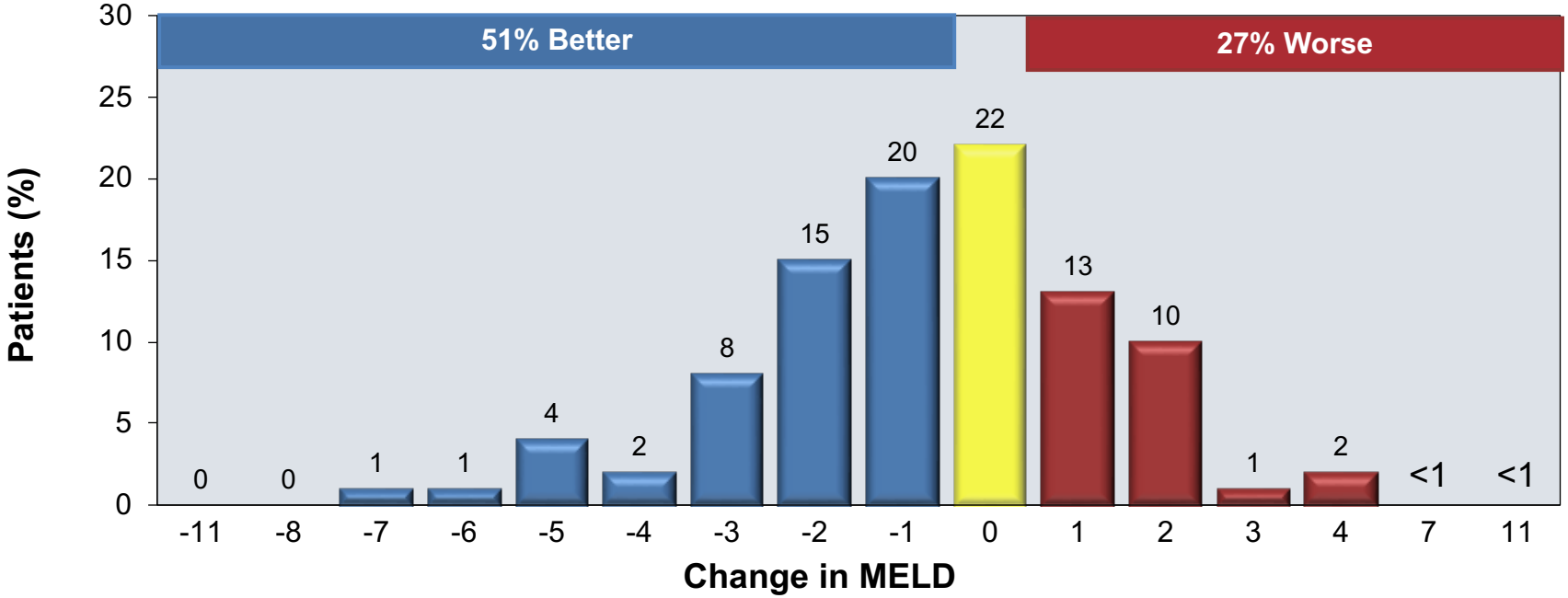
SVR12 Results by Genotype



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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Change in MELD Scores on Treatment

Change in MELD in Patients with Baseline MELD <15

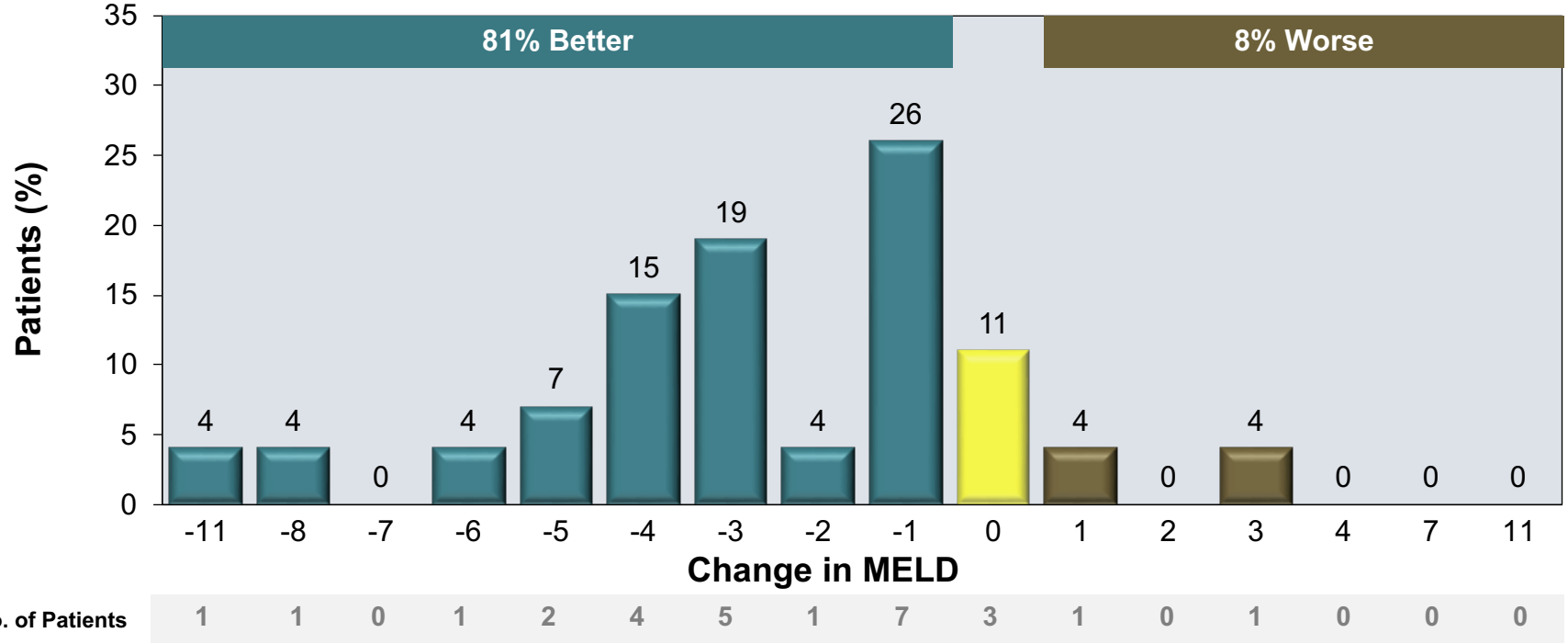


No. of Patients	0	0	3	2	9	4	18	34	44	49	30	22	2	4	1	1

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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Change in MELD Scores on Treatment

Change in MELD in Patients with Baseline MELD ≥15



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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Adverse Events

Adverse Event (AE), %	SOF-VEL 12 weeks (n = 90)	SOF-VEL + RBV 12 weeks (n = 87)	SOF-VEL 24 weeks (n = 90)
Discontinuation due to AE	1	5	4
Serious AEs	19	16	18
Deaths	3	3	3
Any AE in ≥10% of patients			
Fatigue	26	39	23
Nausea	24	25	20
Headache	26	21	19
Anemia	4	31	3
Diarrhea	7	21	8
Insomnia	10	14	10
Pruritus	11	5	4
Muscle spasm	3	11	2
Dyspnea	4	10	0
Hemoglobin <10 g/dL	8	23	9

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

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis
ASTRAL-4: Conclusions

Conclusions: “Treatment with sofosbuvir–velpatasvir with or without ribavirin for 12 weeks and with sofosbuvir–velpatasvir for 24 weeks resulted in high rates of sustained virologic response in patients with HCV infection and decompensated cirrhosis.”

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

Sofosbuvir-Velpatasvir in HCV-HIV Coinfection

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5

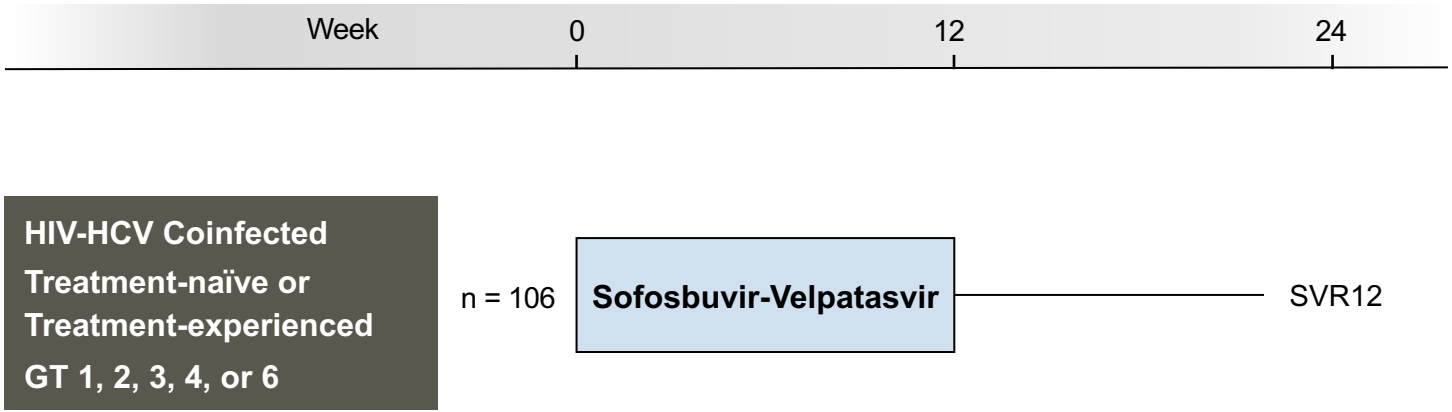
Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Study Features

- **Design**: Single-arm, open-label, multicenter, phase 3 trial of sofosbuvir-velpatasvir in HIV-HCV coinfected treatment-naïve and treatment-experienced patients with genotypes 1-6 HCV
- **Setting**: Multiple sites in US
- **Entry Criteria**
  - Chronic HCV GT 1-6
  - Age ≥18 years
  - HIV coinfection
  - CD4 count ≥100 cells/mm^3 and HIV RNA ≤50 copies/mL
  - On stable ART for ≥8 weeks
  - Prior treatment failure allowed (but no prior NS5A or NS5B)
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Study Design



Drug Dosing: Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Participants

Baseline Characteristic	Sofosbuvir-Velpatasvir (n = 106)
Age, mean, years (range)	54 (25-72)
Male, n (%)	91 (86)
Black race, n (%)	48 (45)
HCV genotype, n (%)	
1a	66 (62)
1b	12 (11)
2	11 (10)
3	12 (11)
4	5 (5)
IL28B non-CC, n (%)	82 (77)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.3 (5.0-7.4)
Cirrhosis, n (%)	19 (18)
Treatment experienced, n (%)	31 (29)

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Participants

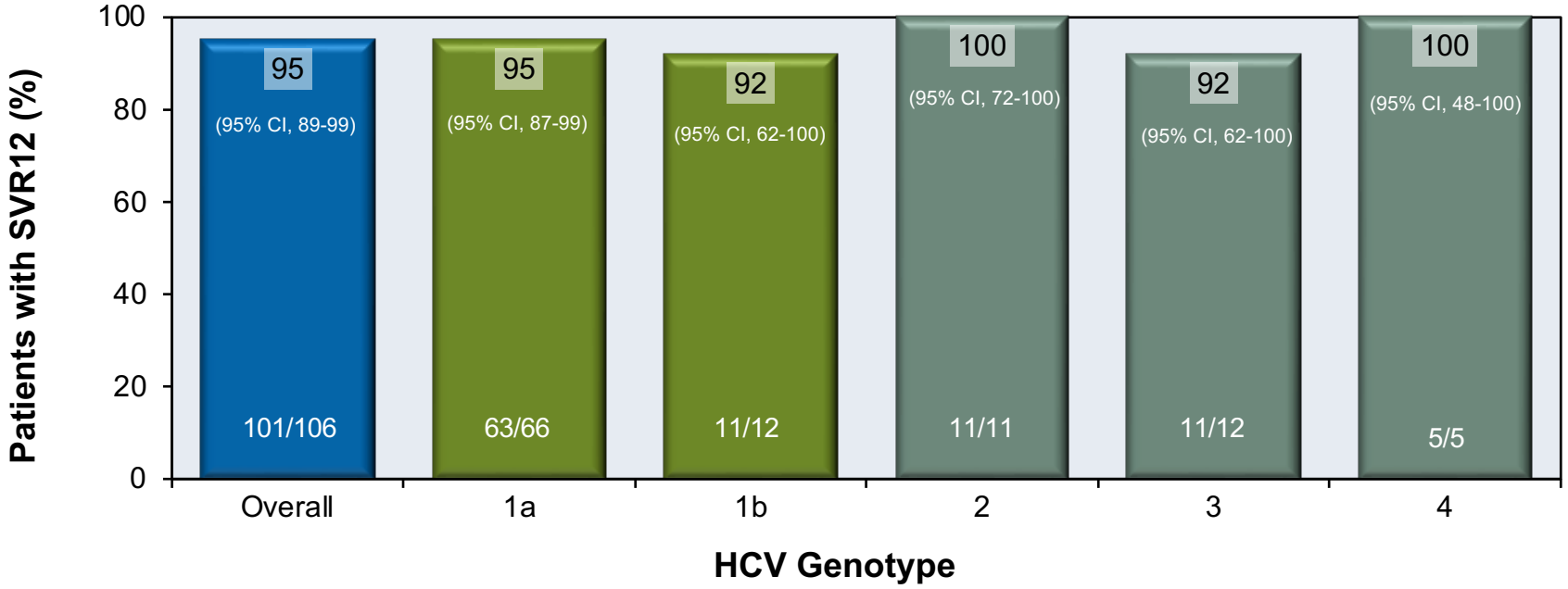
HIV Baseline Characteristics	Sofosbuvir-Velpatasvir (n = 106)
Mean CD4 cell count, (range)	598 (183-1513)
Nucleos(t)ide pair	
TDF with boosted agent (Ritonavir or Cobicistat)	56 (53)
TDF without boosted agent	35 (33)
Abacavir-lamivudine	15 (14)
Other antiretroviral agent(s)	
Protease Inhibitor (DRV, LPV, or ATV)	50 (47)
NNRTI (RPV)	13 (12)
Integrase inhibitor (RAL or EVG)	36 (34)
Other (>1 of above classes)	7 (7)

Abbreviations: TDF, Tenofovir disoproxil fumarate; RTV, ritonavir; DRV, darunavir; LPV, lopinavir; ATV, atazanavir; RPV, rilpivirine; RAL, raltegravir; EVG, elvitegravir

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Results

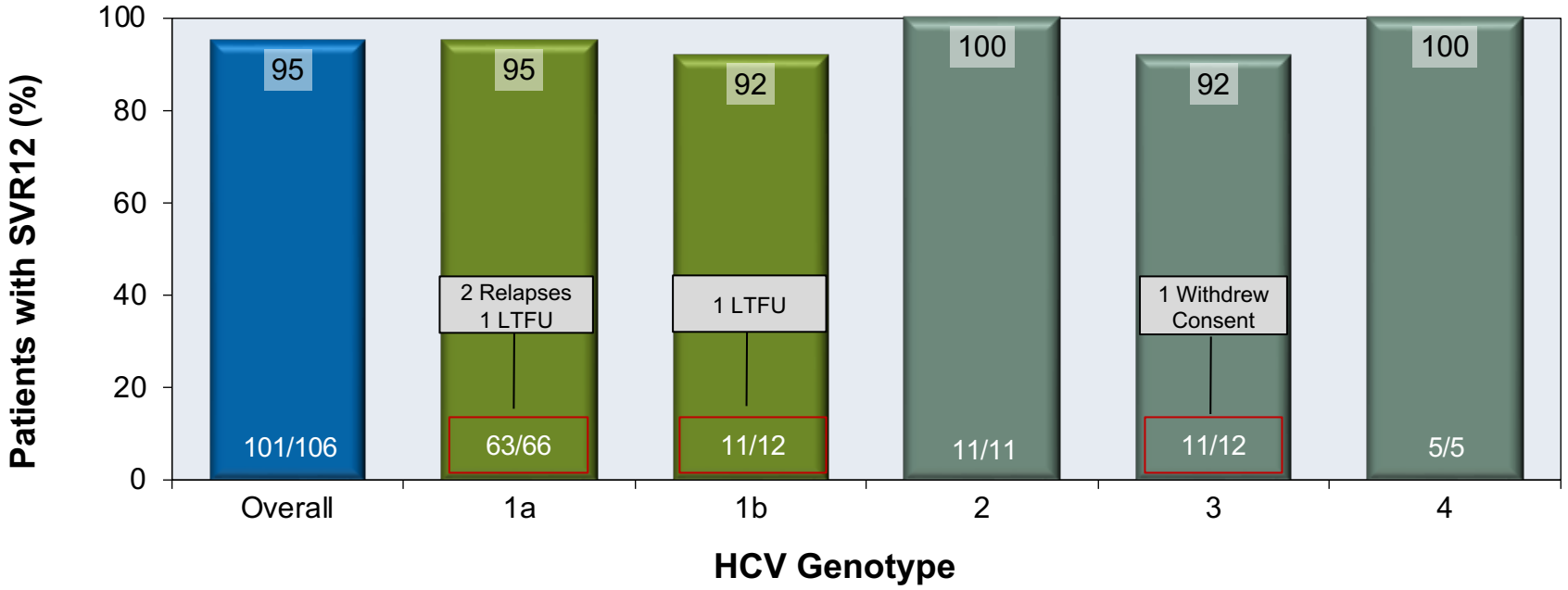
SVR12 Results by Genotype



Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Results

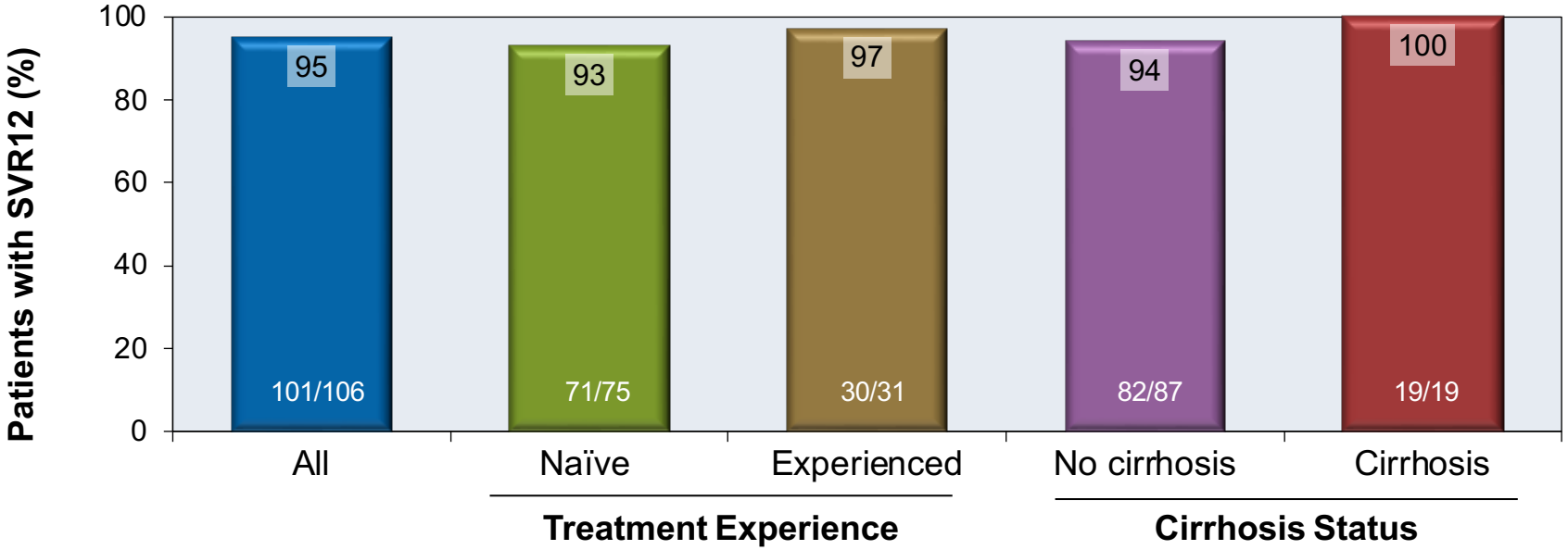
SVR12 Results by Genotype



Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Results

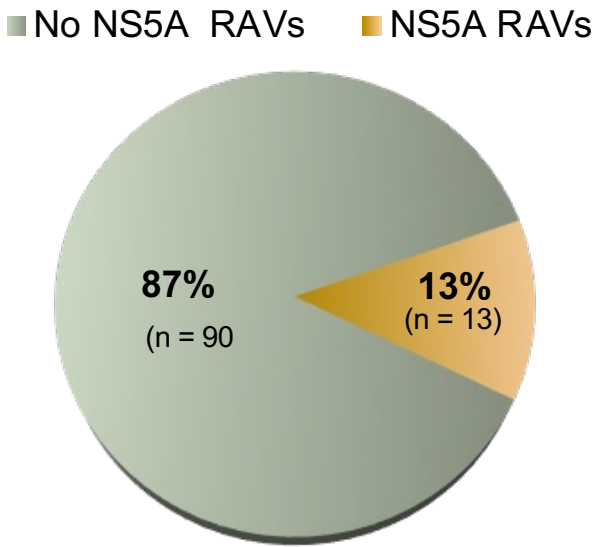
SVR12 Results by Treatment Experience and Cirrhosis Status



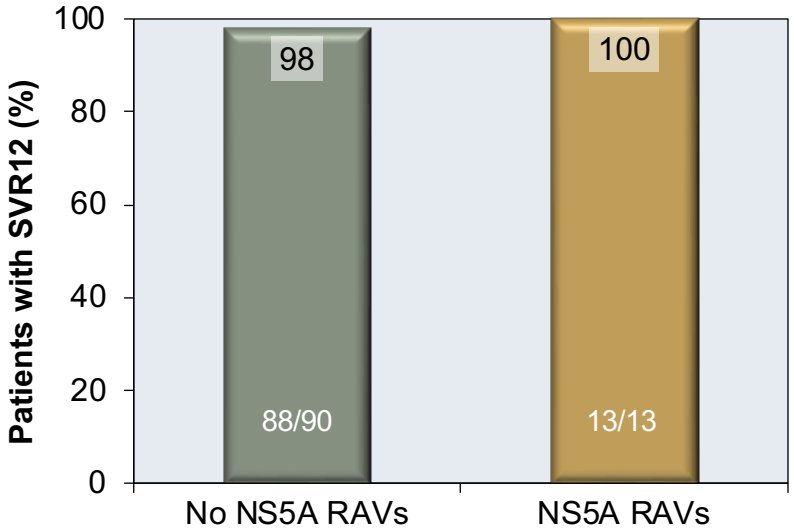
Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Resistance

Baseline Resistance-Associated Variants (RAVs)



Response to Treatment (SVR12)



Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Tenofovir Pharmacokinetics

Mean (%CV) PK Parameters of Tenofovir by Boosted or Unboosted ART Regimen		
Tenofovir PK Parameter	**Sofosbuvir-Velpatasvir + Unboosted Tenofovir DF-Containing Regimens** (n = 35)	**Sofosbuvir-Velpatasvir + Boosted Tenofovir DF-Containing Regimens** (n = 56)
AUC_{tau} (h•ng/mL)	3590 (23.2)	3740 (26.3)
C_{max} (ng/mL)	319 (26.4)	351 (30.8)
C_{tau} (ng/mL)	91.2 (37.9)	92.9 (41.4)

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Adverse Events

Adverse Event (AE), n (%)	Sofosbuvir-Velpatasvir (n = 106)
Discontinuation due to AE	2 (2)
Serious AEs	2 (2)
Deaths	0
Any AE in >5% of patients	
Fatigue	26 (25)
Headache	14 (13)
Arthralgia	9 (8)
Upper respiratory tract infection	9 (8)
Diarrhea	9 (8)
Insomnia	7 (7)
Nausea	7 (7)

The majority of AEs were mild in severity (grade 1 or 2)
No patient with confirmed on-treatment HIV virologic breakthrough

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients
ASTRAL-5: Conclusions

Conclusions: “Sofosbuvir-velpatasvir for 12 weeks was safe and provided high rates of SVR12 in patients coinfected with HCV and HIV-1.”

Source: Wyles D, et al. Clin Infect Dis. 2017;65:6-12.

Sofosbuvir-Velpatasvir versus Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve GT 1-6

POLARIS-2

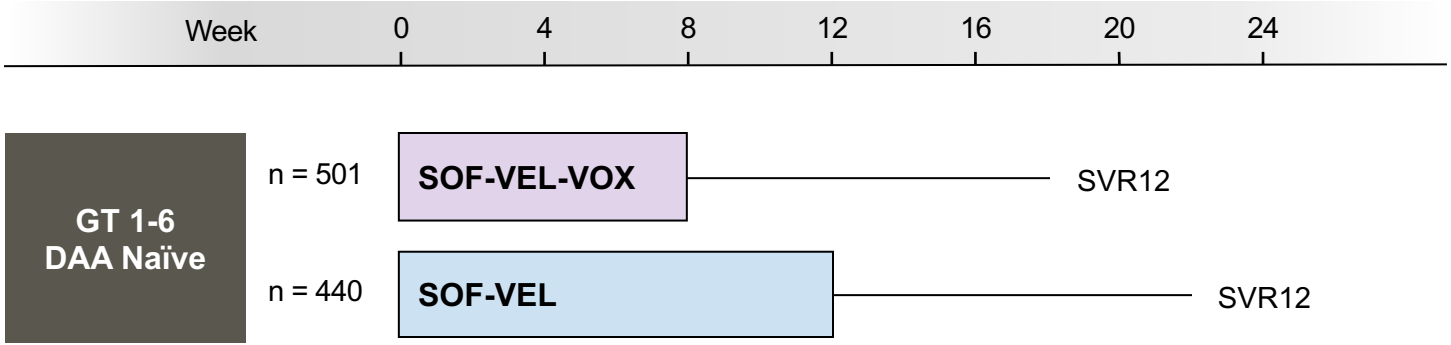
Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Study Features

- **Design**: Randomized, open-label, phase 3 trial to compare efficacy of sofosbuvir-velpatasvir-voxilaprevir (SOF-VEL-VOX) for 8 weeks versus sofosbuvir-velpatasvir (SOF-VEL) for 12 weeks in DAA-naïve patients with GT 1-6 chronic HCV infection.
- **Setting**: 117 sites in United States, Canada, New Zealand, Australia, France, Germany, and United Kingdom
- **Entry Criteria**
  - Age ≥18 years
  - Chronic HCV GT 1-6 (all GT 5, 6 assigned to SOF-VEL-VOX)
  - HCV RNA ≥10,000 IU/mL at screening
  - No prior treatment with DAA; prior peginterferon + ribavirin allowed
  - Patients with compensated cirrhosis allowed except if GT3
- **Primary End Point**: SVR12

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Study Design



GT 3 patients with cirrhosis were enrolled in separate study (POLARIS-3)
GT 1-4 randomized 1:1; all GT 5, 6 assigned to SOF-VEL-VOX
Stratified by GT, cirrhosis, and prior treatment experience

Abbreviations: SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir

Drug Dosing
SOF-VEL-VOX (400/100/100 mg): fixed dose combination; one pill once daily
SOF-VEL (400/100 mg): fixed dose combination; one pill once daily

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Baseline Characteristics

Baseline Characteristic	SOF-VEL-VOX x 8 weeks (n = 501)	SOF-VEL x 12 weeks (n = 440)
Age, mean (range)	53 (18-78)	55 (19-82)
Male, n (%)	255 (51)	237 (54)
White, n (%)	391 (78)	365 (83)
HCV genotype—no. (%) 1a 1b 2 3 4 5 6	 169 (34) 63 (13) 63 (13) 92 (18) 63 (13) 18 (4) 30 (6)	 172 (39) 59 (13) 53 (12) 89 (20) 57 (13) 0 9 (2)*
Body mass index, mean kg/m^2 (range)	26.9 (16.9-57.3)	27.1 (17.9-54.0)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.1 (0.75)	6.2 (0.66)
IL28B CC, n (%)	166 (33)	136 (31)
Cirrhosis, n (%)	90 (18)	84 (19)

Abbreviations: SD, standard deviation
* 9 patients with GT6 were assigned to SOF-VEL and initially misclassified as GT1

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

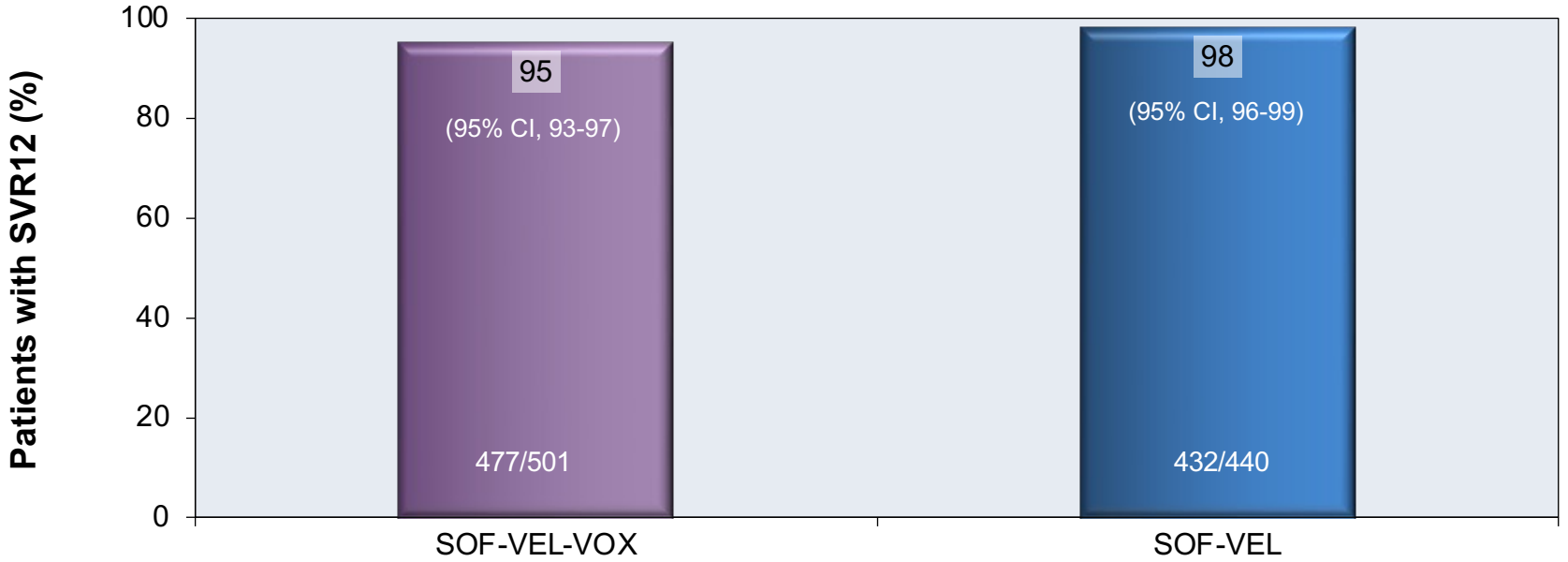
SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Baseline Characteristics

Information on Prior Treatment	**SOF-VEL-VOX** x 8 weeks (n = 501)	**SOF-VEL** x 12 weeks (n = 440)
Treatment-Naïve	383 (76)	340 (77)
Treatment-Experienced	118 (24)	100 (23)
Peginterferon + Ribavirin	93 (79)	81 (81)
Other	25 (21)	19 (19)
Most Recent Treatment Response		
Nonresponder	50 (42)	47 (47)
Relapse	55 (47)	44 (44)
Other	13 (11)	9 (9)

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

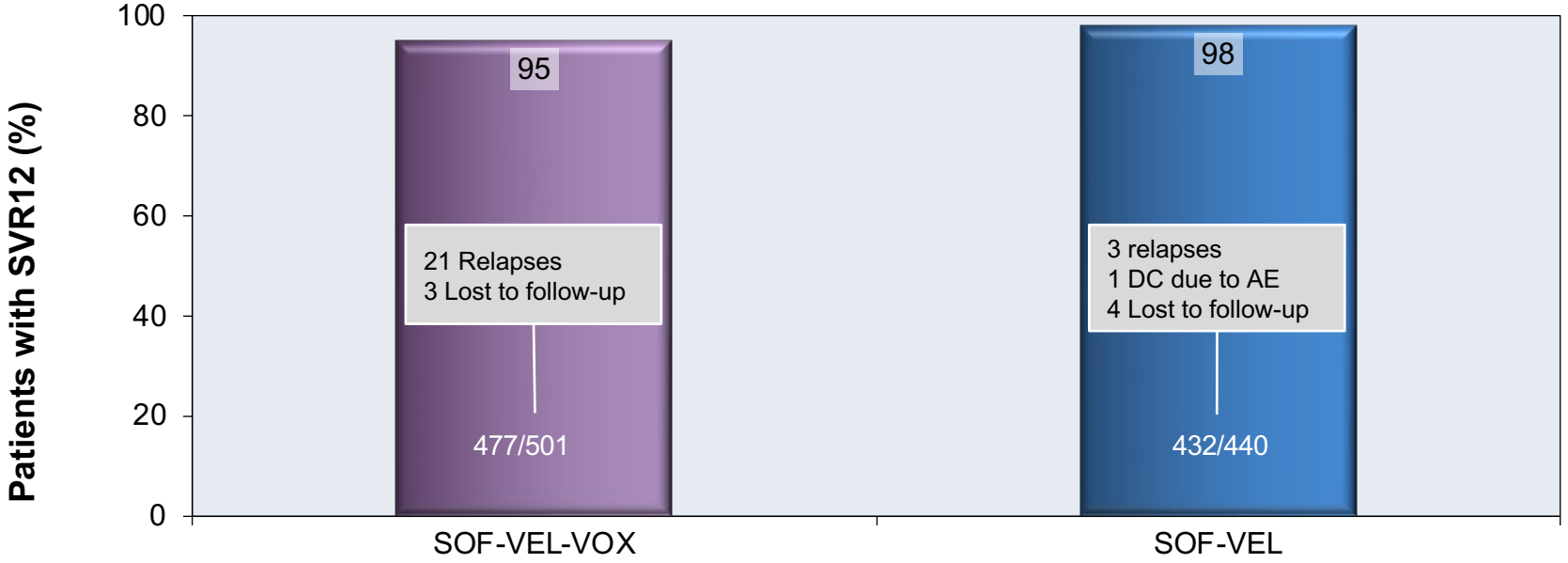
POLARIS-2: Overall SVR12 by Treatment Arm



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

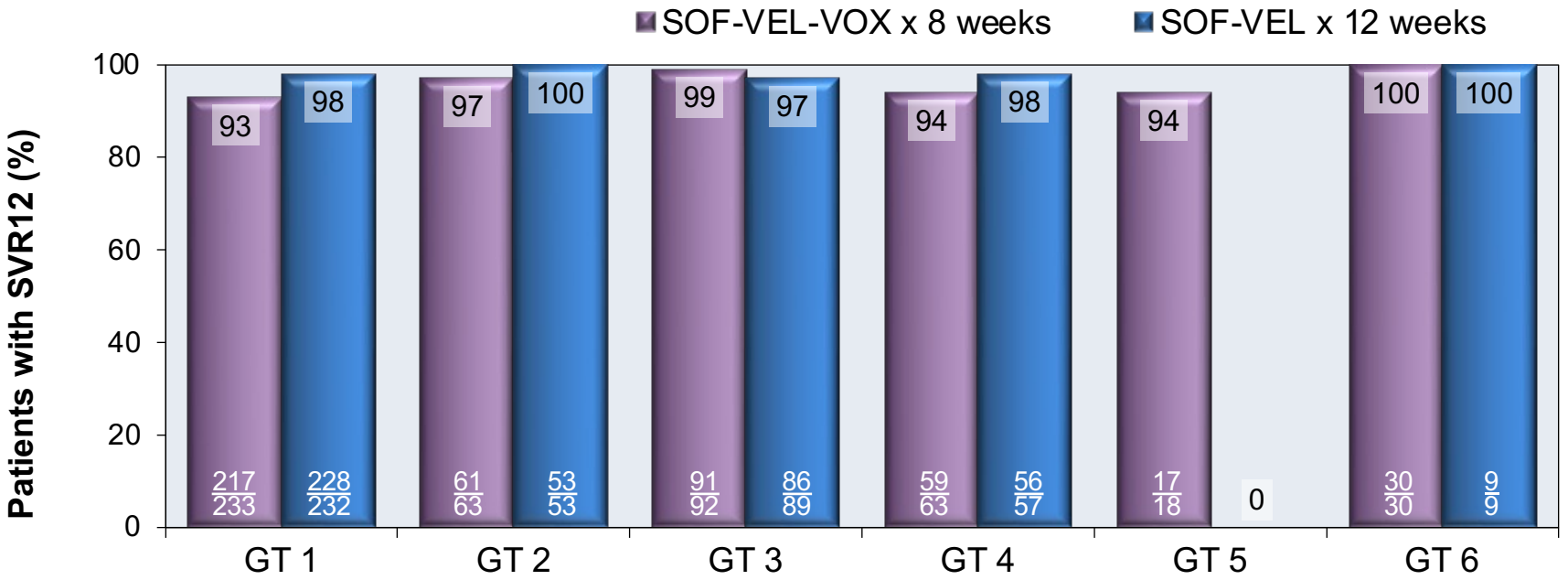
POLARIS-2: Overall SVR12 by Treatment Arm



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

POLARIS-2: SVR by Treatment Arm and Genotype

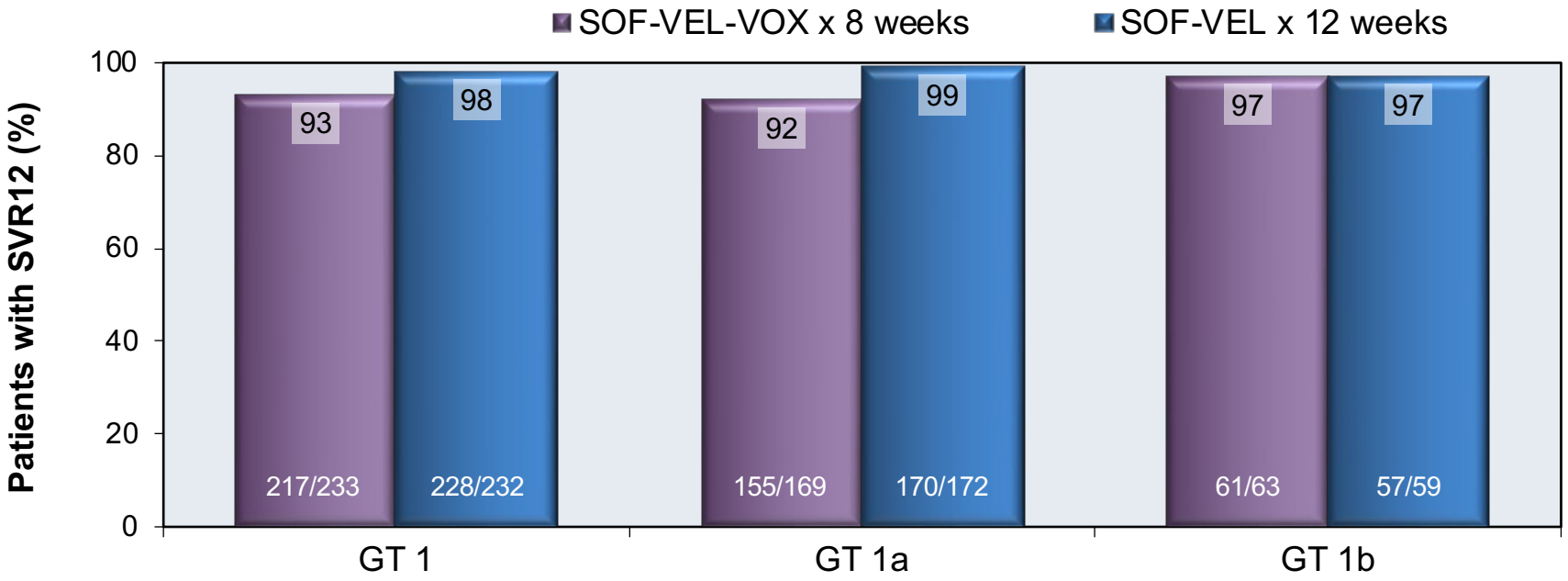


Abbreviations: DCAE, Discontinuation due to AE; LTFU, Lost to follow-up.
Two patients had unknown genotype were assigned to SOF-VEL-VOX and went on to achieve SVR12

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6 POLARIS-2: Results

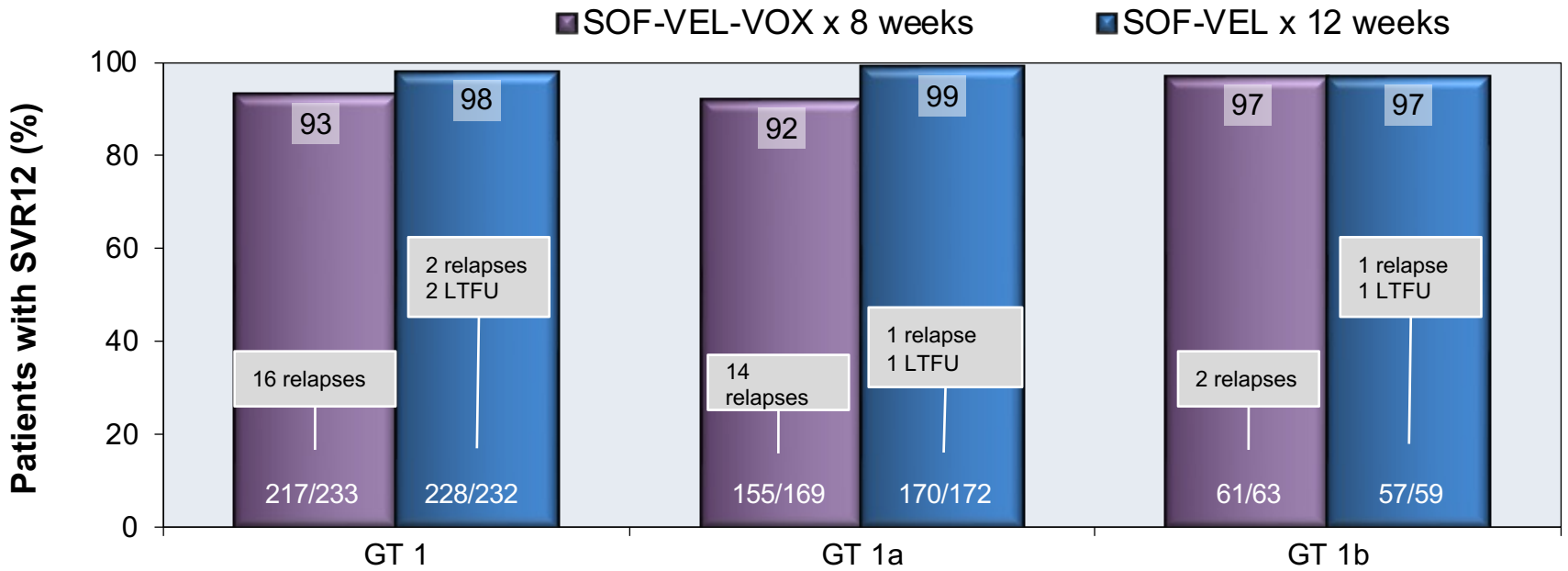
POLARIS-2: SVR by Treatment Arm and Genotype 1 Subtype



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

POLARIS-2: SVR by Treatment Arm & Genotype 1 Subtype

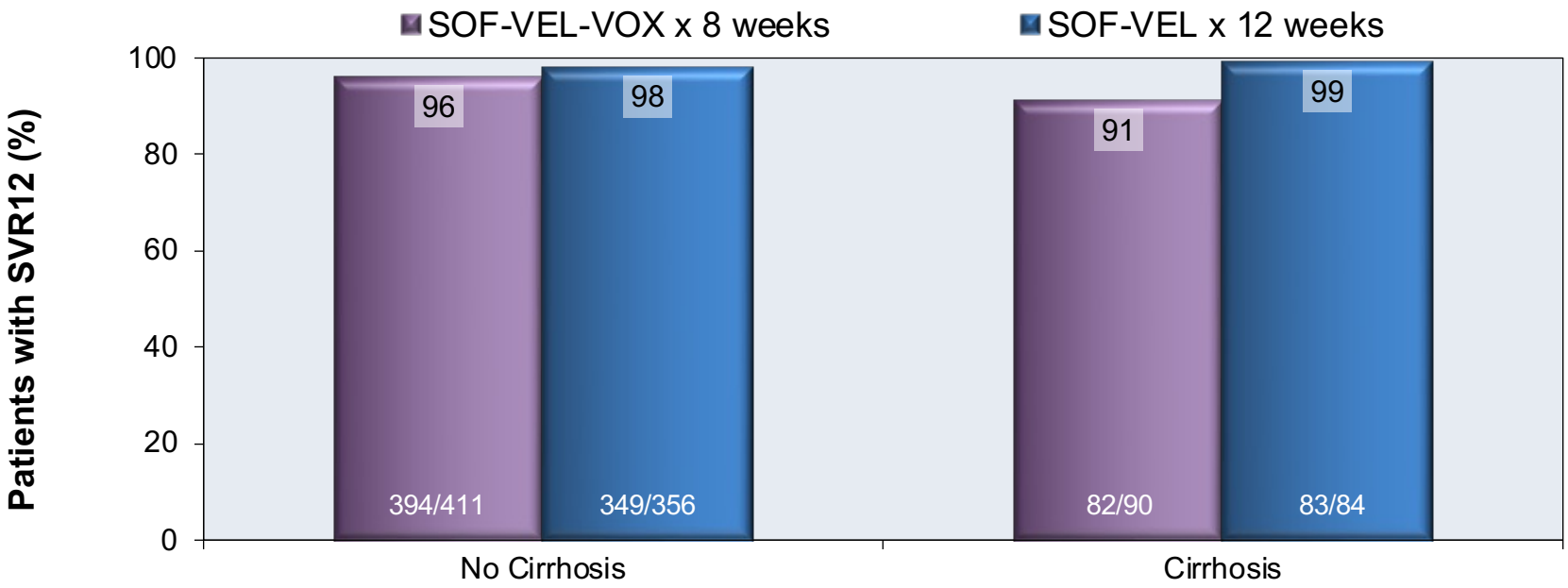


Abbreviations: LTFU, Lost to follow-up

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6 POLARIS-2: Results

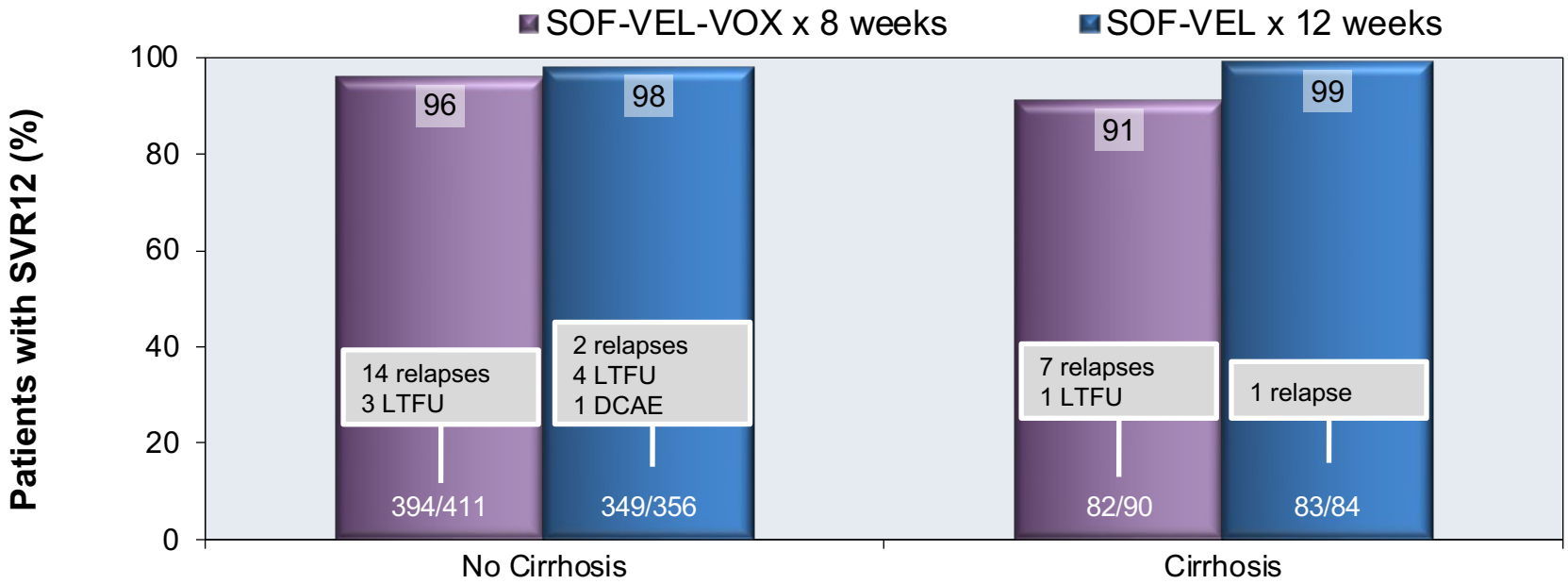
POLARIS-2: SVR12 by Cirrhosis Status



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6 POLARIS-2: Results

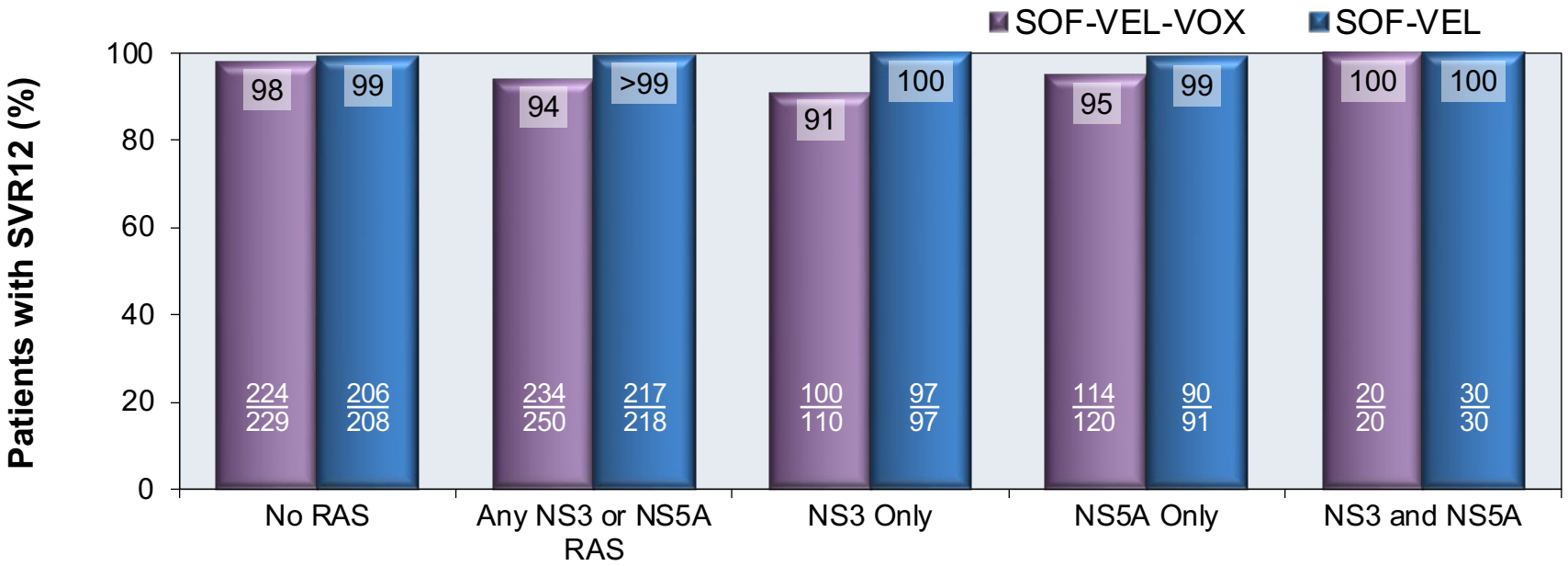
POLARIS-2: SVR12 by Cirrhosis Status



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

POLARIS-2: SVR12 by Baseline RASs*



* Using a 15% reporting threshold

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Adverse Events

Adverse Event (AE), n (%)	**SOF-VEL-VOX** x 8 weeks (n = 501)	**SOF-VEL** x 12 weeks (n = 440)
Discontinuation due to AE	0	2 (<1) [§]
Serious AE	15 (3)	7 (2)
Serious Related AE	0	0
Deaths	0	0
Any AE in >10% of patients		
Headache	134 (27)	99 (23)
Fatigue	106 (21)	90 (20)
Diarrhea	88 (18)	32 (7)
Nausea	80 (16)	40 (9)
Laboratory AEs (Grade 3-4)	24 (5)	16 (4)

[§] One patient discontinued due to upper respiratory infection; 1 patient due to C. difficile infection. Neither were considered related to study medication by investigator.

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in DAA-Naïve HCV GT 1-6
POLARIS-2: Conclusions

Conclusions: “In phase 3 trials of patients with HCV infection, we did not establish that sofosbuvir-velpatasvir-voxilaprevir for 8 weeks was noninferior to sofosbuvir-velpatasvir for 12 weeks, but the 2 regimens had similar rates of SVR in patients with HCV genotype 3 and cirrhosis. Mild gastrointestinal adverse events were associated with treatment regimens that included voxilaprevir.”

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

Sofosbuvir-Velpatasvir in Persons with Compensated Cirrhosis

Sofosbuvir-Velpatasvir versus Sofosbuvir-Velpatasvir-Voxilaprevir in GT 3 and Cirrhosis

POLARIS-3

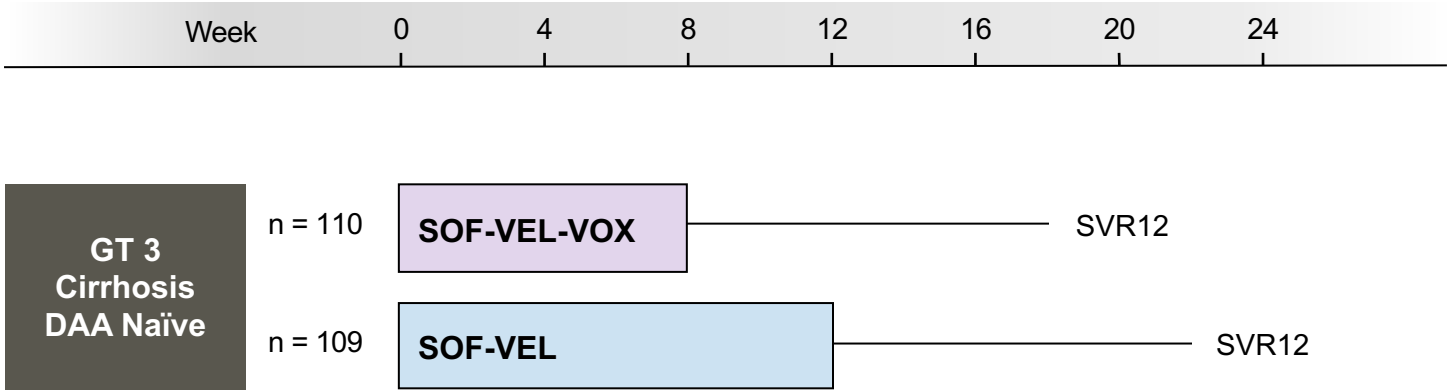
Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Study Features

- **Design**: Open-label, randomized, phase 3 trial to compare efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir (SOF-VEL-VOX) for 8 weeks versus sofosbuvir-velpatasvir (SOF-VEL) for 12 weeks in patients with HCV genotype 3 and cirrhosis who were DAA-naïve
- **Setting**: 84 sites in United States, Canada, New Zealand, Australia, France, Germany, and United Kingdom
- **Entry Criteria**
  - Age ≥18 years
  - Chronic HCV GT 3 with compensated cirrhosis
  - HCV RNA ≥10,000 IU/mL at screening
  - No prior treatment with DAA; prior peginterferon plus ribavirin allowed
- **Primary End Point**: SVR12

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Study Design



Abbreviations: SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir

Drug Dosing
SOF-VEL-VOX (400/100/100 mg): fixed dose combination; one pill once daily
SOF-VEL (400/100 mg): fixed dose combination; one pill once daily

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Baseline Characteristics

Baseline Characteristic	**SOF-VEL-VOX** x 8 weeks (n = 110)	**SOF-VEL x** 12 weeks (n = 109)
Age, mean (range)	54 (25-75)	55 (31-69)
Male, n (%)	74 (67)	100 (92)
White, n (%)	100 (91)	97 (89)
Cirrhosis Features		
Platelets <100 x 10^3/μL, n (%)	30 (29)	21 (19)
Mean FibroScan (range), kPa	23 (13-75)	22 (13-75)
Body mass index, mean, kg/m^2 (range)	28 (20-50)	27 (18-46)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.0 (1.6-7.6)	6.3 (4.1-7.5)
IL28B CC, n (%)	41 (37)	52 (48)

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

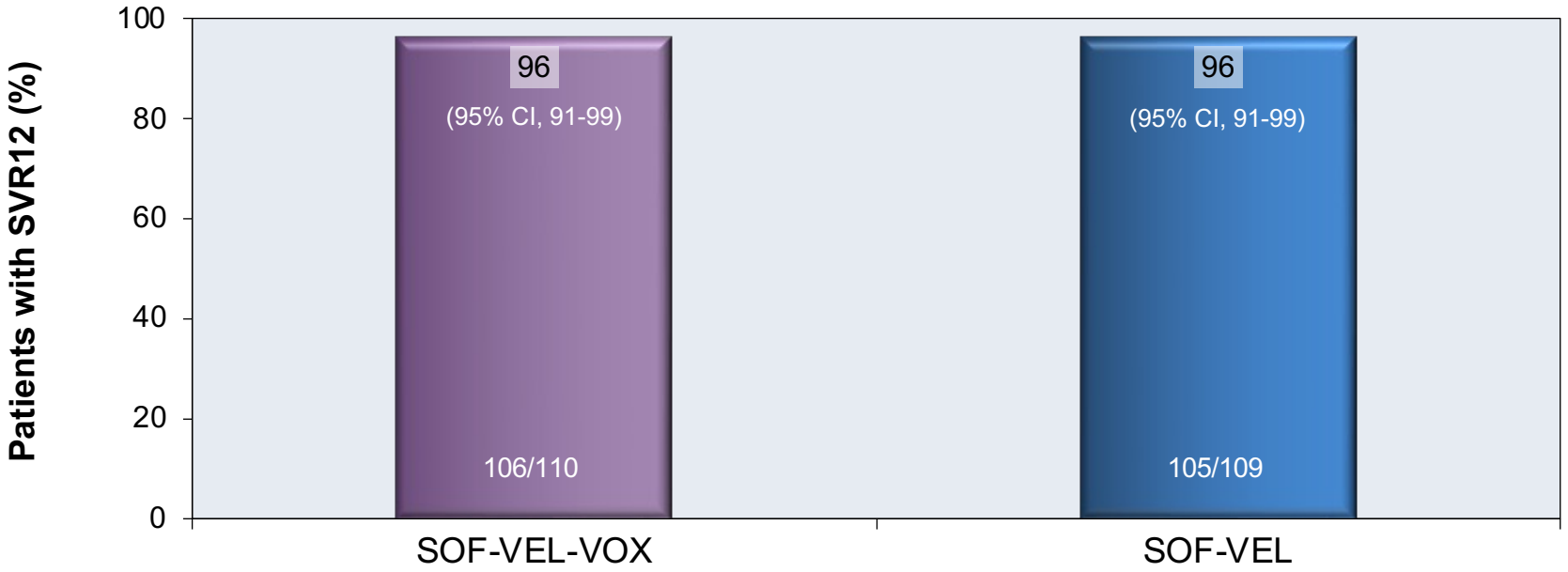
SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Baseline Characteristics

Information on Prior Treatment	**SOF-VEL-VOX** x 8 weeks (n = 110)	**SOF-VEL** x 12 weeks (n = 109)
Treatment-Naïve	75 (68)	77 (71)
Treatment-Experienced	35 (32)	32 (29)
Peginterferon + Ribavirin	31 (89)	30 (94)
Other	4 (11)	2 (6)
Most Recent Treatment Response		
Nonresponder	16 (46)	8 (25)
Relapse	16 (46)	20 (63)
Other	3 (9)	4 (13)

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Results

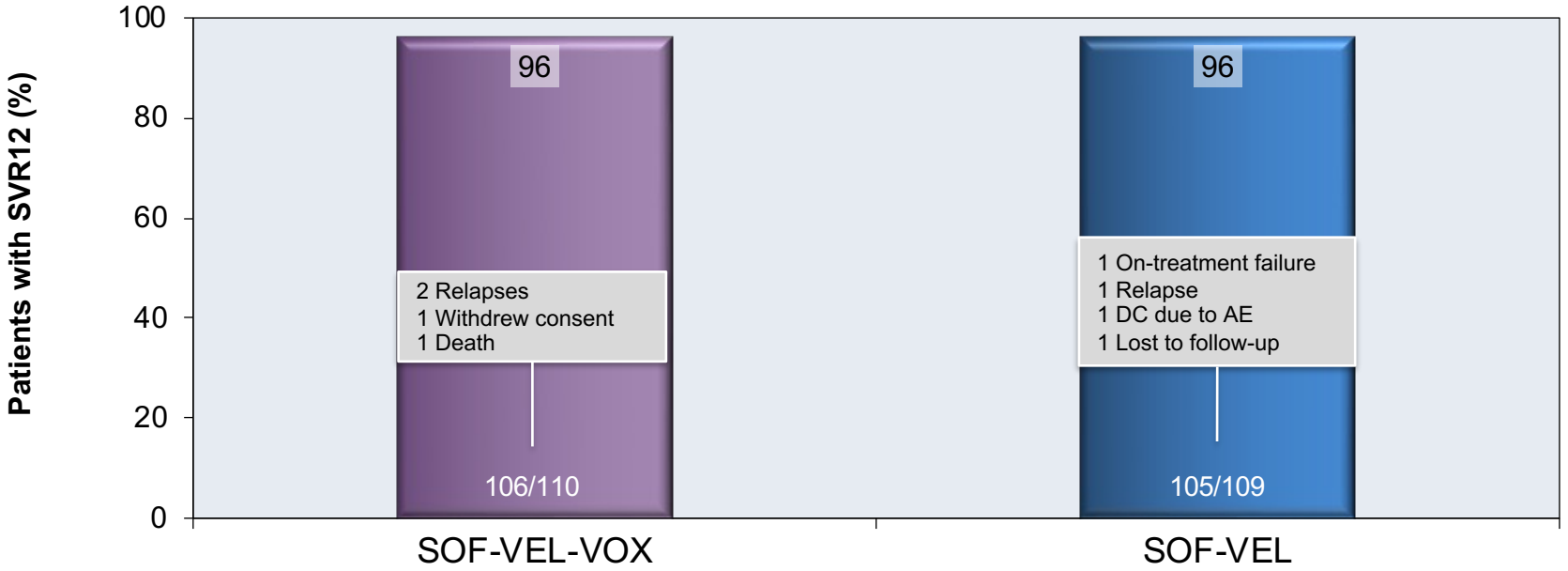
POLARIS-3: Overall SVR12 by Treatment Arm



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Results

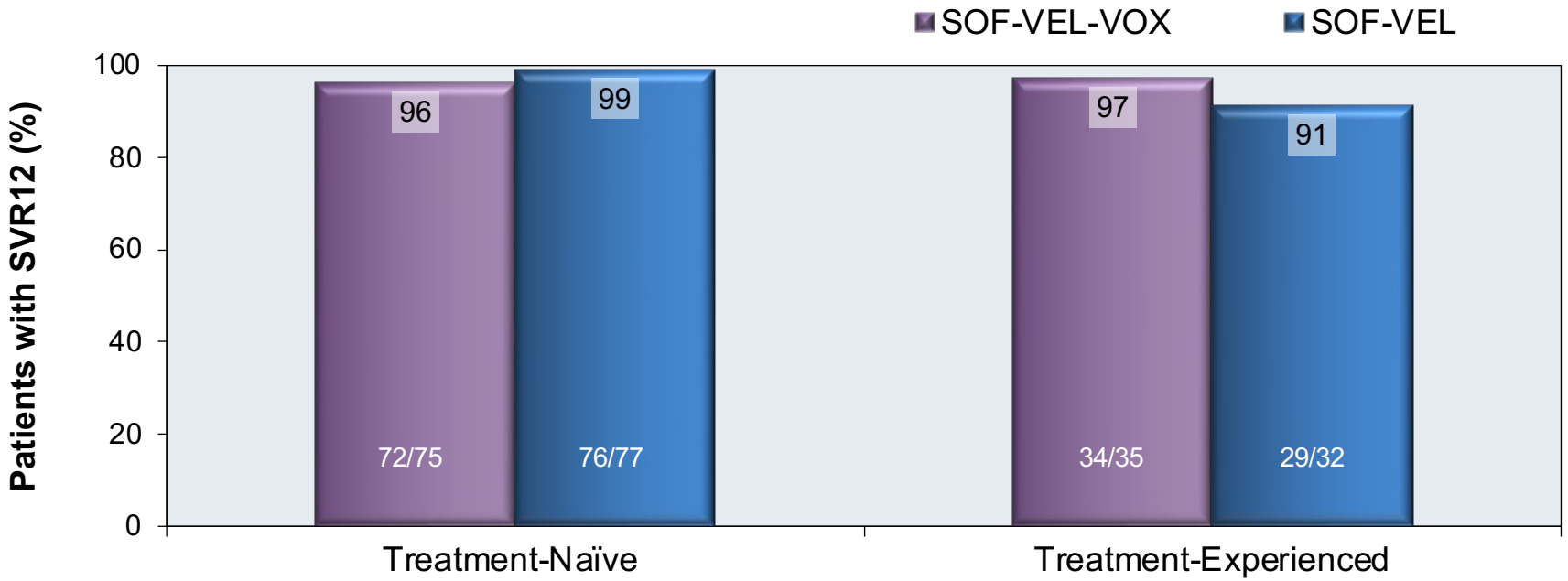
POLARIS-3: Overall SVR12 by Treatment Arm



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Results

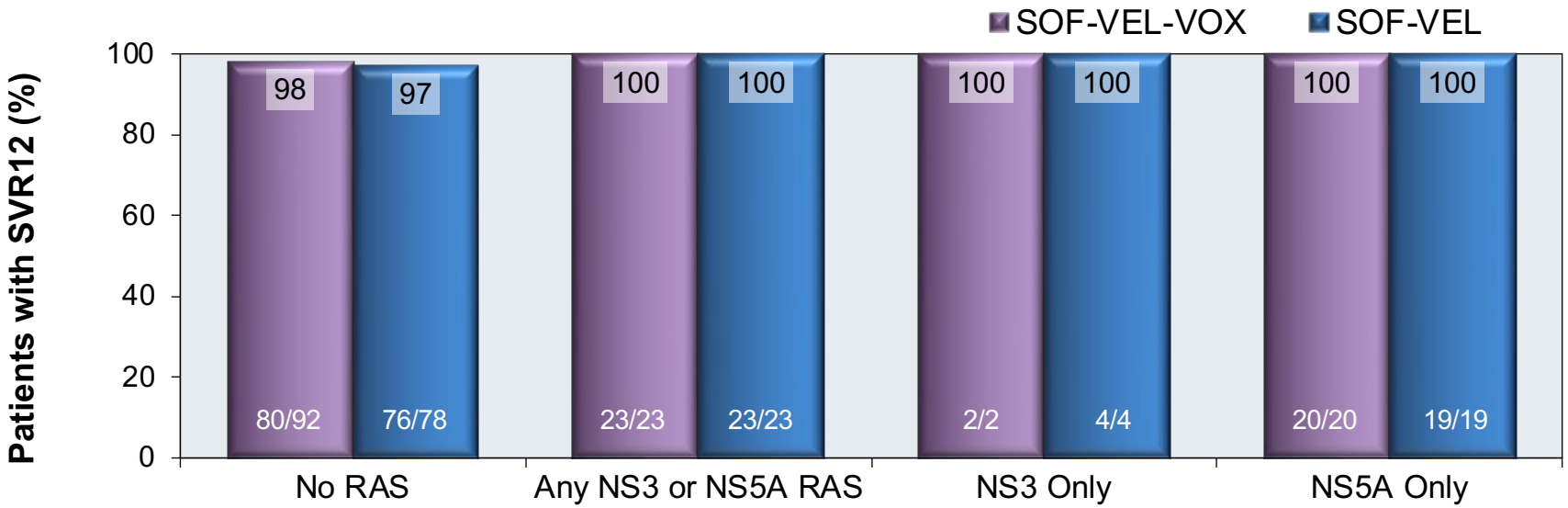
POLARIS-3: SVR12 by Treatment Experience



Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Results

POLARIS-3: SVR12 by Baseline RAS



Y93H: 6 patients in SOF-VEL-VOX group and 4 in SOF-VEL group; all achieved SVR.
No treatment-emergent RASs in SOF-VEL-VOX group. Both virologic failures in SOF-VEL group had Y93H.

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Adverse Events

Adverse Event (AE), n (%)	**SOF-VEL-VOX** x 8 weeks (n = 110)	**SOF-VEL** x 12 weeks (n = 109)
Discontinuation due to AE	0	1 (1)
Serious AE	2 (2)	3 (3)
Serious Related AE	0	0
Deaths	1 (1) §	0
Common AE		
Headache	27 (25)	32 (29)
Fatigue	28 (25)	31 (28)
Nausea	23 (21)	10 (9)
Diarrhea	17 (15)	5 (5)
Laboratory AEs (Grade 3-4)	14 (13)	9 (8)

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

SOF-VEL-VOX versus SOF-VEL in GT 3 and Cirrhosis
POLARIS-3: Conclusions

Conclusions: “In phase 3 trials of patients with HCV infection, we did not establish that sofosbuvir-velpatasvir-voxilaprevir for 8 weeks was noninferior to sofosbuvir-velpatasvir for 12 weeks, but the 2 regimens had similar rates of SVR in patients with HCV genotype 3 and cirrhosis. Mild gastrointestinal adverse events were associated with treatment regimens that included voxilaprevir.”

Source: Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

Sofosbuvir-Velpatasvir +/- Ribavirin in HCV GT 3 and Cirrhosis

HCV GT 3 Cirrhosis Study (Spain)

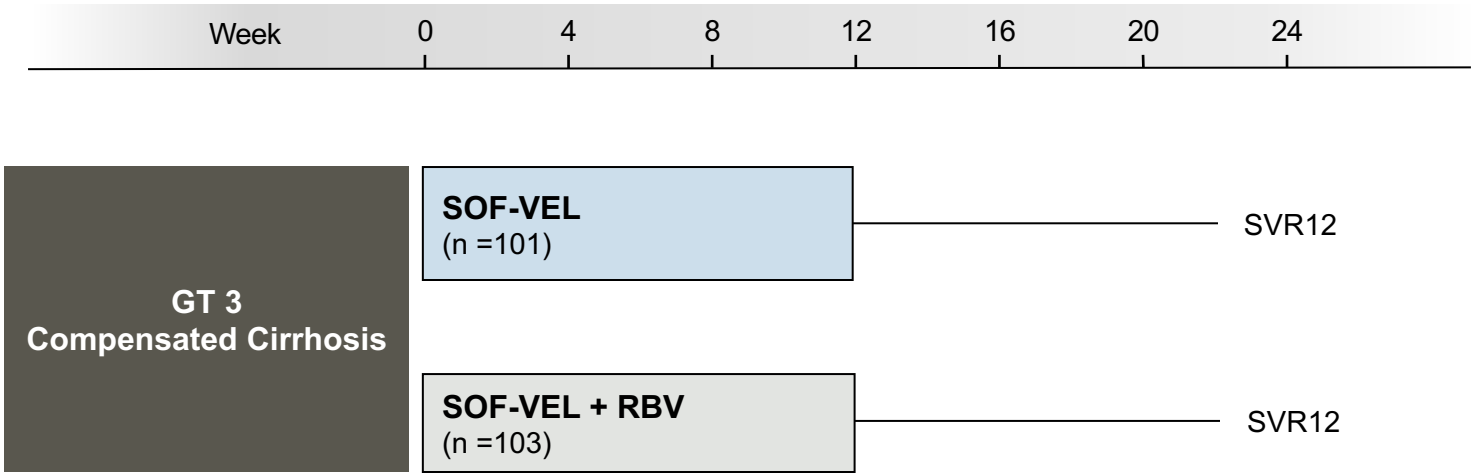
Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis
Study Features

- **Design**: Randomized, open-labeled, phase 2 trial to evaluate the safety and efficacy of the fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks with or without ribavirin in treatment-naïve or treatment-experienced adults with GT 3 chronic HCV infection and compensated cirrhosis
- **Setting**: 29 sites in Spain
- **Key Eligibility Criteria**
  - Chronic HCV GT3
  - Age ≥18 years
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - Compensated cirrhosis
  - HIV coinfection allowed
- **Primary End Point**: SVR12

Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis Study Design



Abbreviations: SOF-VEL, Sofosbuvir-velpatasvir, RBV, Ribavirin

Drug Dosing: Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

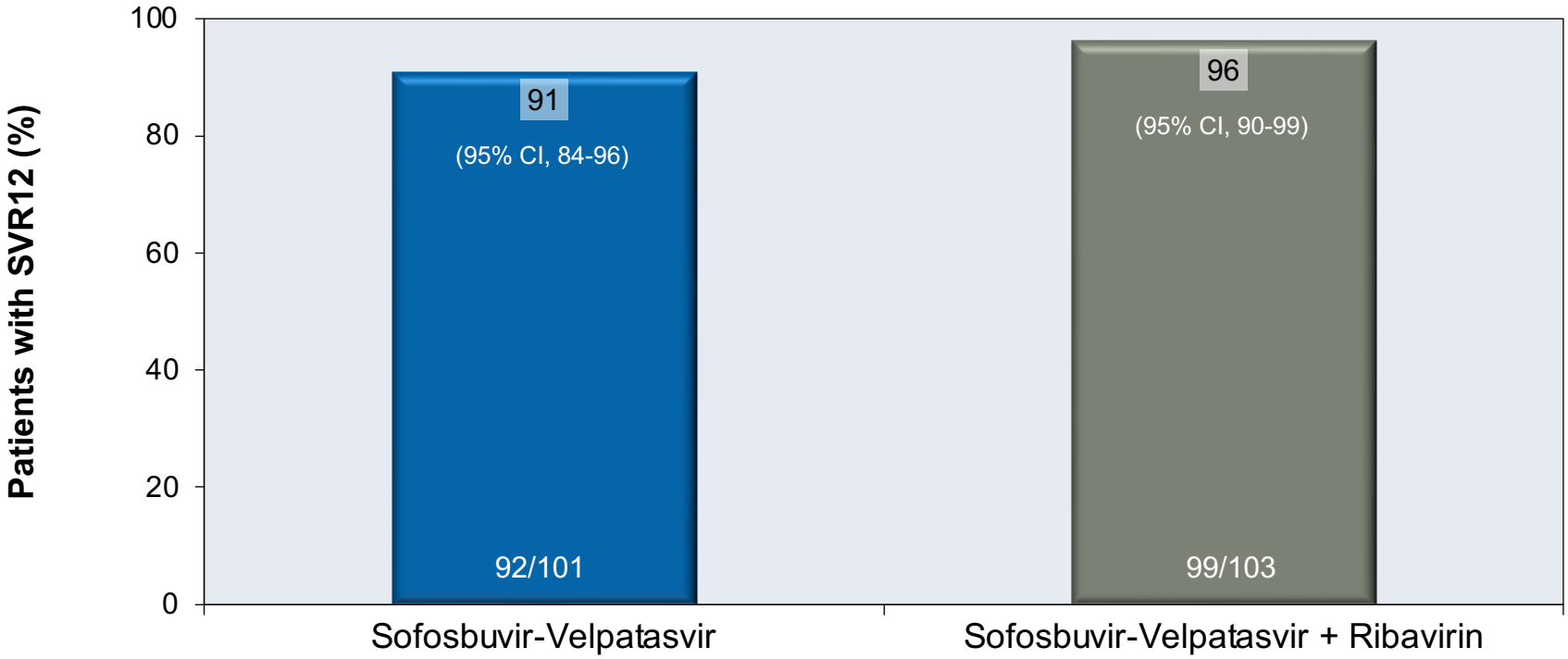
Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis
Baseline Characteristics

Baseline Characteristics	SOF-VEL (n = 101)	SOF-VEL + RBV (n = 103)
Age, mean years (standard deviation, SD)	51 (7.3)	51 (7.6)
Male, n (%)	75 (74)	87 (85)
Race, n (%) White Asian	 84 (83) 17 (17)	 95 (92) 9 (8)
Body mass index, mean kg/m^2 (SD)	27 (5.1)	27 (4.9)
HCV RNA, mean $\log_{10}$ IU/mL (SD)	6.2 (0.64)	6.3 (0.56)
Non-CC IL28B genotype, n (%)	36 (36)	50 (49)
Prior Treatment, n (%) DAA +/- Peg-IFN +/- RBV Peg-IFN + RBV Other (IFN +/- RBV or Peg-IFN alone)	 1 (1) 14 (14) 12 (12)	 2 (2) 18 (17) 8 (8)
Platelets (x 10^3/μL), mean (SD)	150 (62)	148 (69)
HIV coinfection n (%)	16 (16)	14 (14)

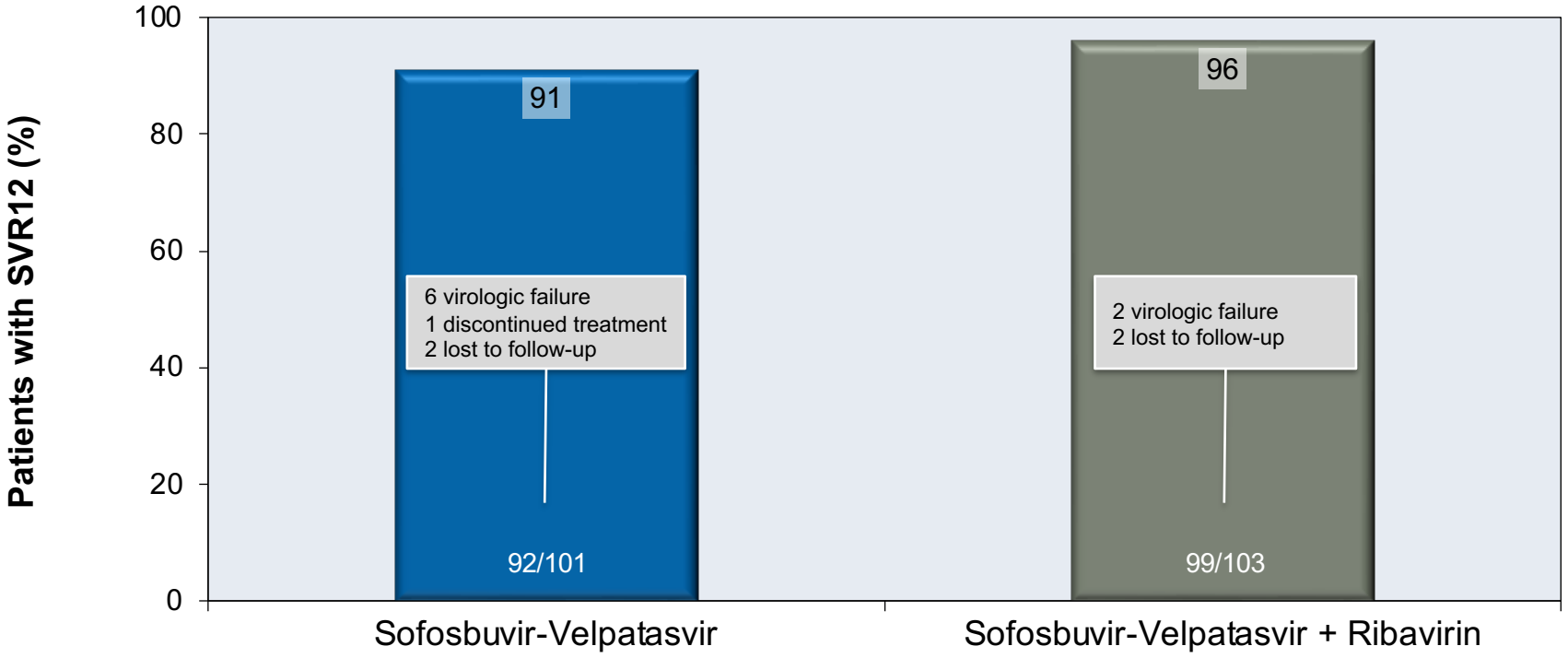
Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis
Results: ITT Analysis by Treatment Arm



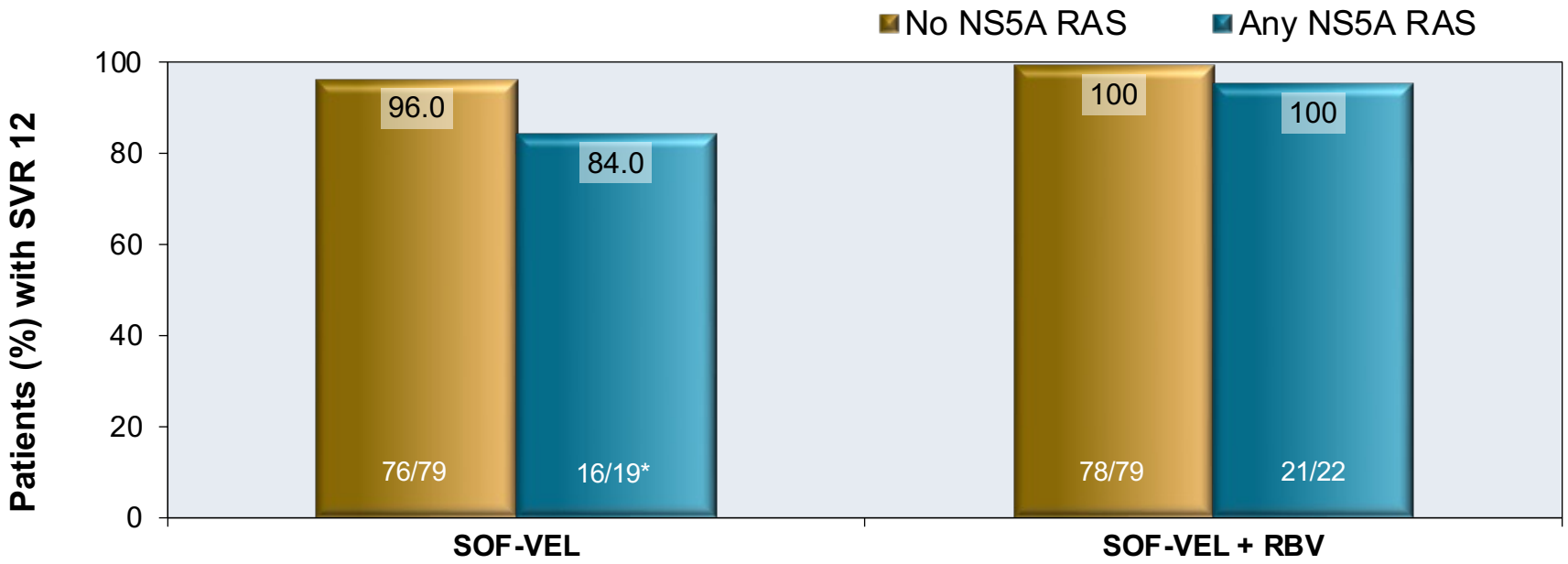
Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis
Results: ITT Analysis by Treatment Arm



Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis Results: ITT Analysis by Treatment Arm and NS5A RAS



Abbreviations: RAS, resistance-associated variant; SOF-VEL, sofosbuvir-velpatasvir; RBV, ribavirin.
* All patients with baseline RAS who did not achieve SVR had viral relapse; one had on-treatment failure.

Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis Results: Adverse Events

Adverse Events (AE), n (%)	SOF-VEL (n = 101)	SOF-VEL + RBV (n = 103)
Any AE	48 (48)	77 (75)
Serious AE*	4 (4)	2 (2)
AE leading to SOF-VEL discontinuation	1 (1)	1 (1)
AEs present in ≥10%		
Asthenia	12 (12)	28 (27)
Headache	8 (8)	25 (24)
Insomnia	1 (1)	12 (12)
Deaths	0	0

Abbreviations: SOF-VEL = sofosbuvir-velpatasvir

* SAEs reported in this study were an accident at work, hepatic cancer, hepatocellular carcinoma, limb injury, non-small cell lung cancer, pharyngotonsillitis, and urinary tract infection; all were assessed as unrelated to study drug.

Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis Results: Laboratory Abnormalities

Selected Lab Abnormalities, n (%)	SOF-VEL (n = 101)	SOF-VEL + RBV (n = 103)
Hemoglobin		
< 8.5 g/dL	0	0
<10 g/dL	1 (1)	5 (5)
Lymphocyte		
350 to <500/mm^3	1 (1)	0
<350/mm^3	0	0
Platelets		
25,000 to <50,000/mm^3	1 (1)	1 (1)
<25,000/mm^3	0	0
Total bilirubin		
>2.5-5x ULN	0	2 (2)
>5x ULN	0	0

Abbreviations: ULN, upper limit of normal

Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir +/- Ribavirin for HCV GT 3 and Cirrhosis Conclusions

Conclusions: “Consistent with findings from previous studies, a high rate of patients (91% and 96%) with genotype 3 HCV infection and compensated cirrhosis achieved an SVR12 with sofosbuvir and velpatasvir, with or without ribavirin. Of patients treated with sofosbuvir and velpatasvir without ribavirin, fewer patients with baseline NS5A RASs achieved an SVR12 compared with patients without baseline NS5A.”

Source: Esteban R, et al. Gastroenterol. 2018;155:1120-27.e4.

Sofosbuvir-Velpatasvir in Persons with Decompensated Cirrhosis

Sofosbuvir-Velpatasvir with or without Ribavirin in Decompensated Cirrhosis (Japan)

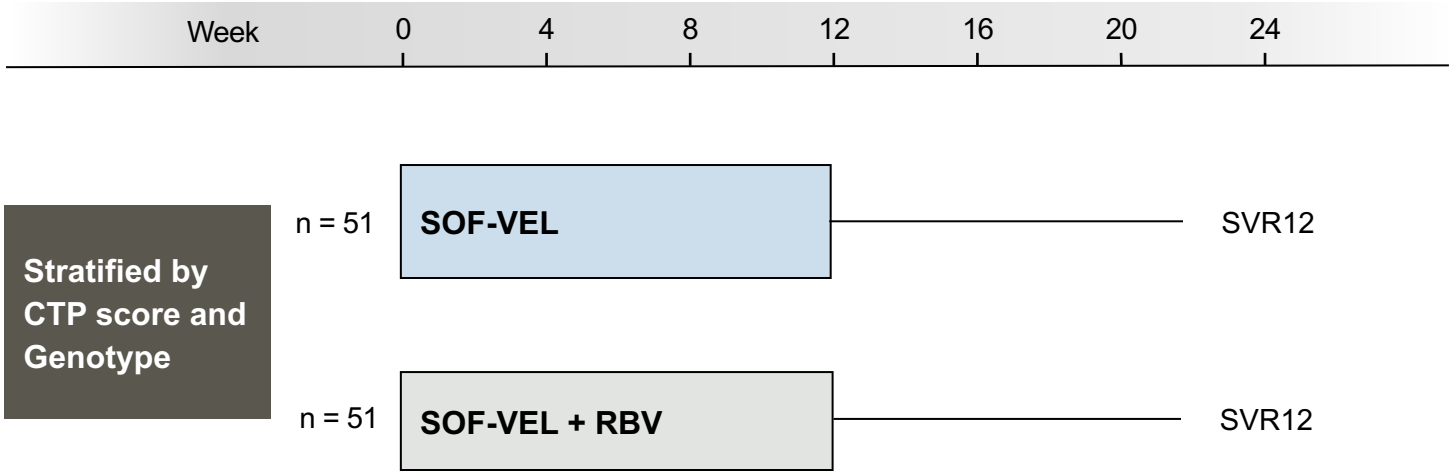
Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Study Features

- **Design**: Randomized, open-labeled, phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks with or without ribavirin in treatment-naïve or treatment-experienced adults with chronic HCV infection and decompensated cirrhosis
- **Setting**: 13 sites in Japan
- **Key Eligibility Criteria**
  - Chronic HCV GT 1, 2, 3, 4, 5, or 6
  - Age ≥20 years
  - Decompensated cirrhosis (Child-Turcotte-Pugh score 7-12)
  - Hepatocellular carcinoma excluded in imaging within 4 months of baseline
  - Naïve or treated with peginterferon +/- ribavirin (PR) or PR +/- sofosbuvir
  - HIV, chronic hepatitis B coinfections excluded
- **Primary End Point**: SVR12

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Study Design



Abbreviations: CTP, Child-Turcotte-Pugh; SOF-VEL, Sofosbuvir-velpatasvir; RBV, Ribavirin

Drug Dosing: Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Participants

Baseline Characteristics	SOF-VEL (n = 51)	SOF-VEL + RBV (n = 51)
Age, mean years (range)	66 (43-82)	66 (41-83)
Female, n (%)	33 (65)	29 (57)
Body mass index, mean kg/m^2 (range)	26.5 (20.4-43.0)	25.8 (18.3-58.6)
HCV RNA, mean $\log_{10}$ IU/mL (range)	5.7 (3.7-7.1)	
IL28B CC genotype, n (%)	33 (65)	37 (73)
HCV genotype, n (%) 1 1a / 1b 2 3b	 41 (80) 1 (2) / 40 (78) 9 (18) 1 (2)	 39 (76) 0 / 39 (76) 11 (22) 0
Treatment-naïve, n (%)	27 (53)	31 (61)

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

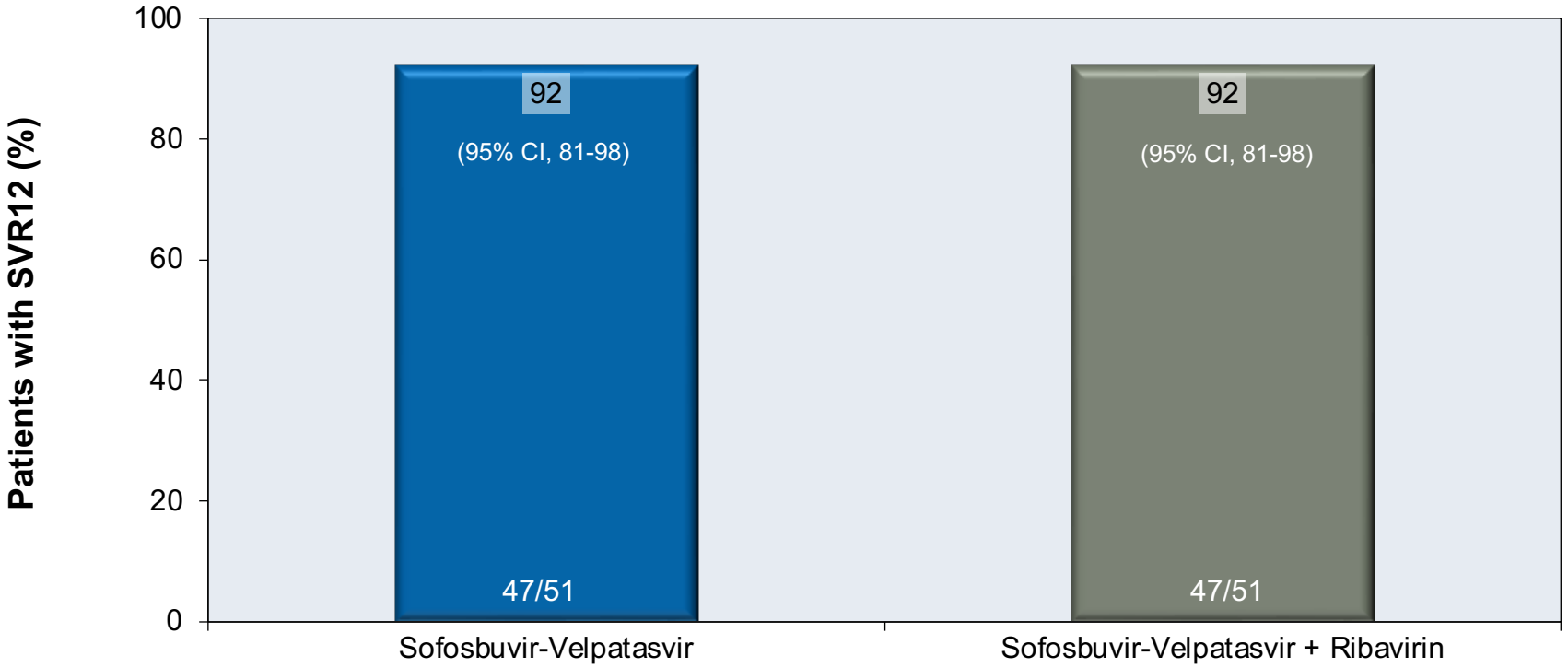
Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Participants

Baseline Characteristics	SOF-VEL (n = 51)	SOF-VEL + RBV (n = 51)
Child-Turcotte-Pugh (class B) score 7-9 n (%)	40 (78)	39 (73)
MELD score ≥15	46 (90)	48 (76)
Ascites		
None	19 (37)	16 (31)
Mild/moderate	32 (63)	33 (65)
Severe	0	2 (4)
Encephalopathy		
None	23 (45)	22 (43)
Medication-controlled	28 (55)	29 (57)
Mean estimated GFR, mL/min (range)	93 (40-183)	89 (42-299)

Abbreviations: MELD, Model for End-Stage Liver Disease; GFR, glomerular filtration rate

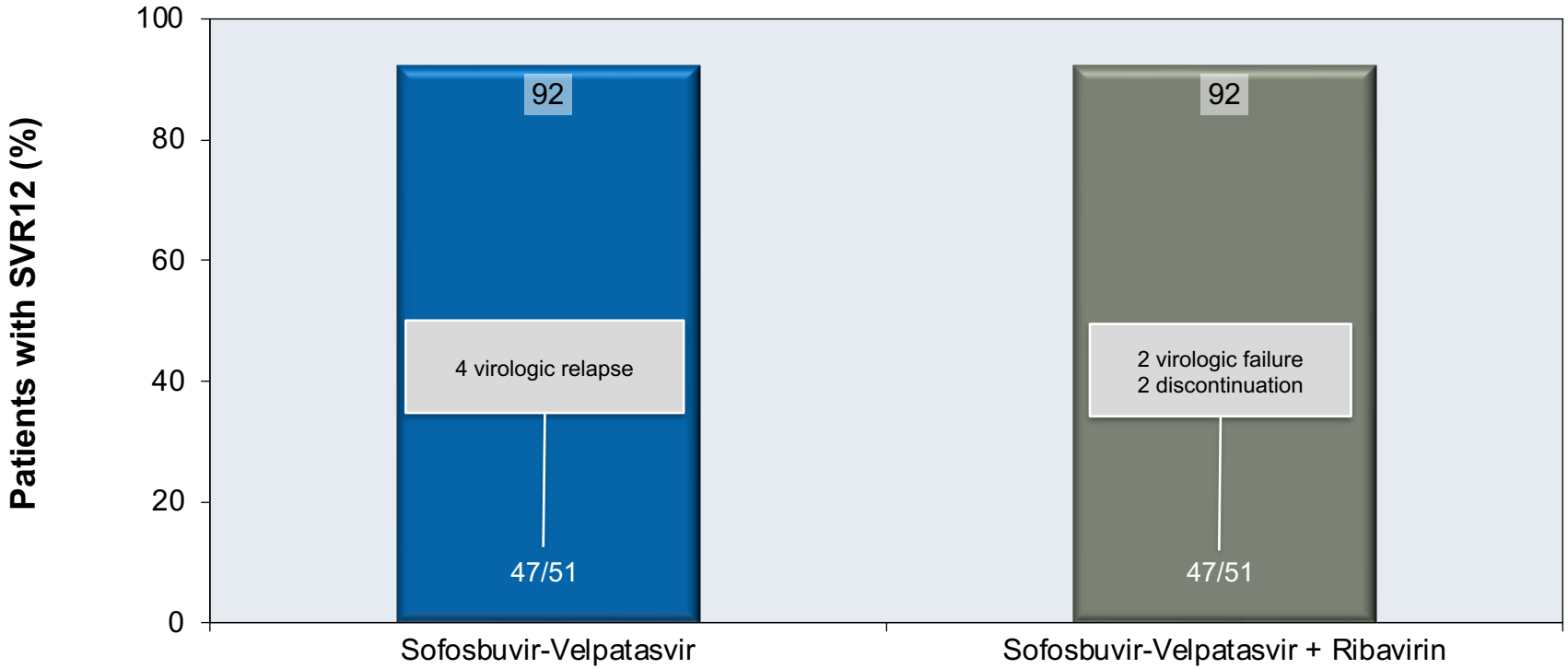
Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Results



Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

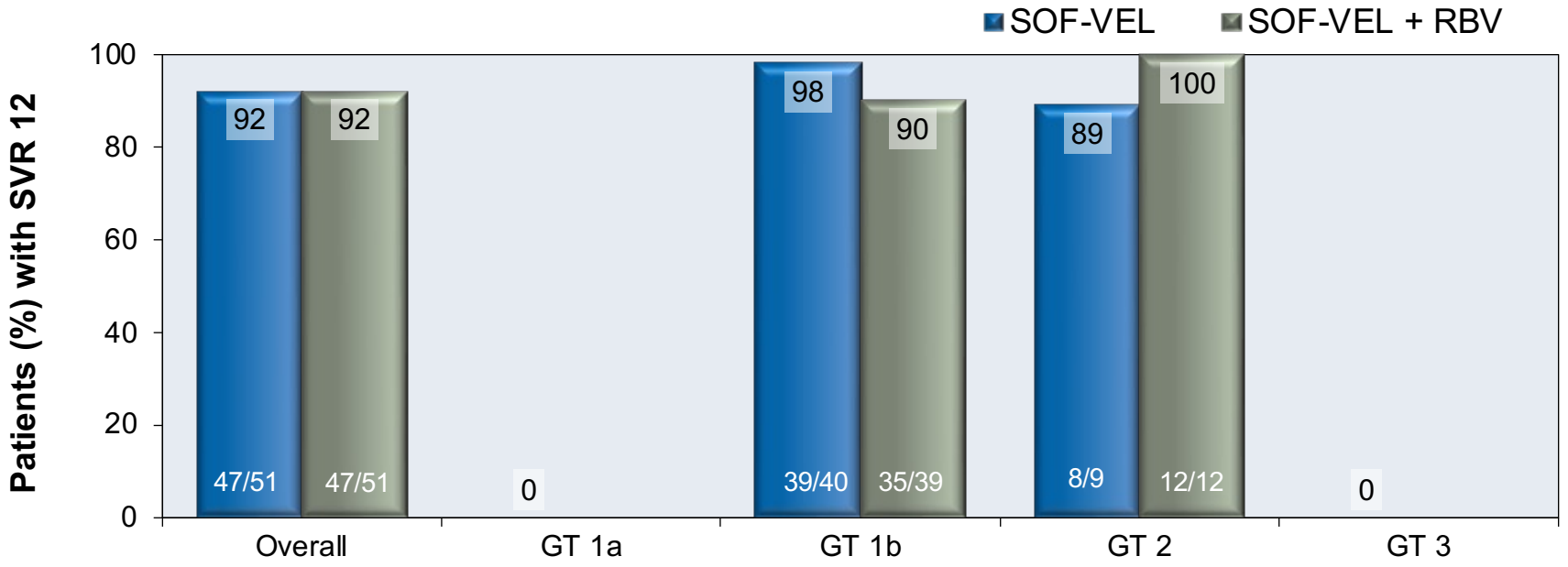
Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Results



Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Results

SVR12, Overall and by Genotype

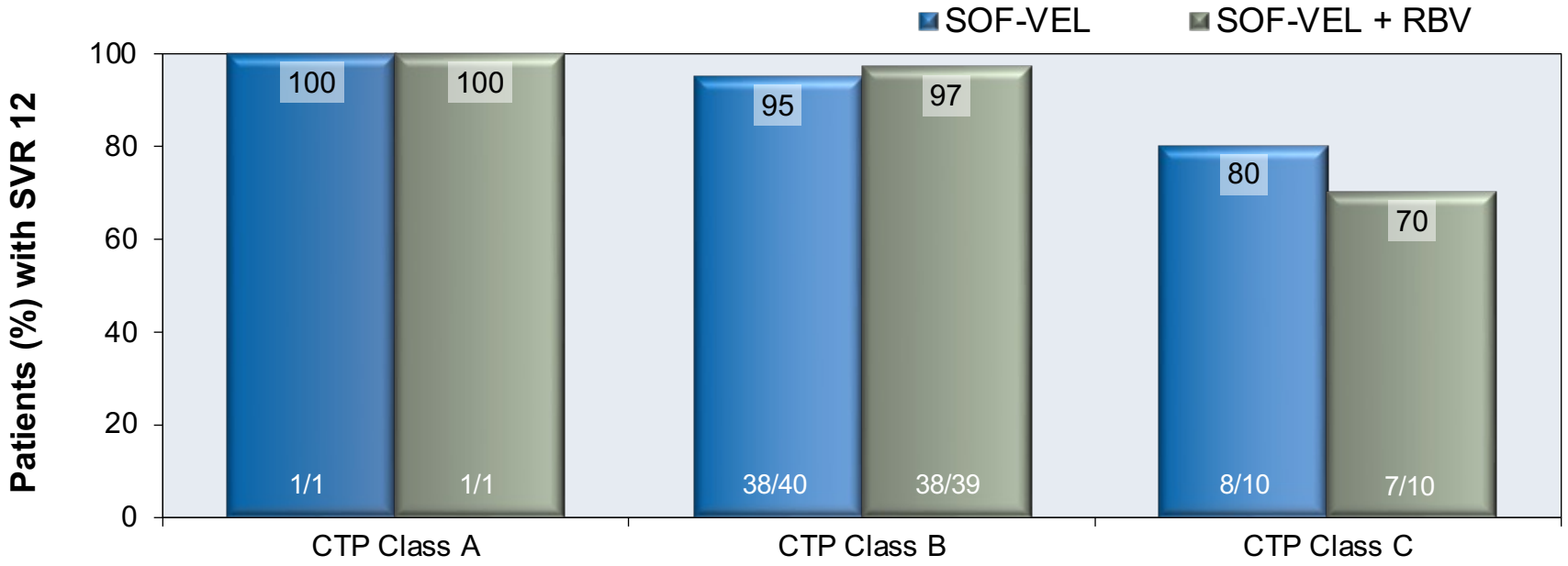


Abbreviations: SOF-VEL, sofosbuvir-velpatasvir; RBV, ribavirin

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Results

SVR12 by Child-Turcotte-Pugh (CTP) Class



Abbreviations: SOF-VEL, sofosbuvir-velpatasvir; RBV, ribavirin

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Adverse Events

Adverse events (AEs), n (%)	SOF-VEL (n = 51)	SOF-VEL + RBV (n = 51)
Any AE	35 (69)	44 (86)
Grade ≥3 AE	2 (4)	5 (10)
Serious AE	4 (8)	7 (14)
AE leading to		
Discontinuation of SOF-VEL	0	2 (4)
Discontinuation of RBV	n/a	9 (18)
Interruption of RBV	n/a	18 (35)
Deaths	0	3 (6)
Common AE in ≥10% in either group		
Anemia	0	20 (39)
Nasopharyngitis	7 (14)	3 (6)
Diarrhea	0	7 (14)

Abbreviations: SOF-VEL, sofosbuvir-velpatasvir; RBV, ribavirin

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Laboratory Abnormalities

Lab abnormalities*, n (%)	SOF-VEL (n = 51)	SOF-VEL + RBV (n = 51)
Hemoglobin <10 g/dl	2 (4)	7 (14)
Lymphocytes <500 cells/mm^3	0	5 (10)
Platelets 25,000 to 50,000 cells/mm^3	1 (2)	6 (12)
Hyperglycemia >250-500 mg/dL	5 (10)	9 (18)
Total bilirubin >2.5 x ULN	6 (12)	12 (24)

*Occurring ≥10% in either group. ULN, upper limit of normal

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir +/- Ribavirin for Decompensated Cirrhosis Conclusion

Conclusion: “Sofosbuvir-velpatasvir for 12 weeks provides a highly effective and well-tolerated therapy for Japanese patients with HCV and decompensated cirrhosis. Ribavirin did not improve efficacy but increased toxicity.”

Source: Takehara T, et al. J Gastroenterol. 2019;54:87-95.

Sofosbuvir-Velpatasvir in Persons with Renal Disease

Sofosbuvir-Velpatasvir in End-Stage Renal Disease on Dialysis

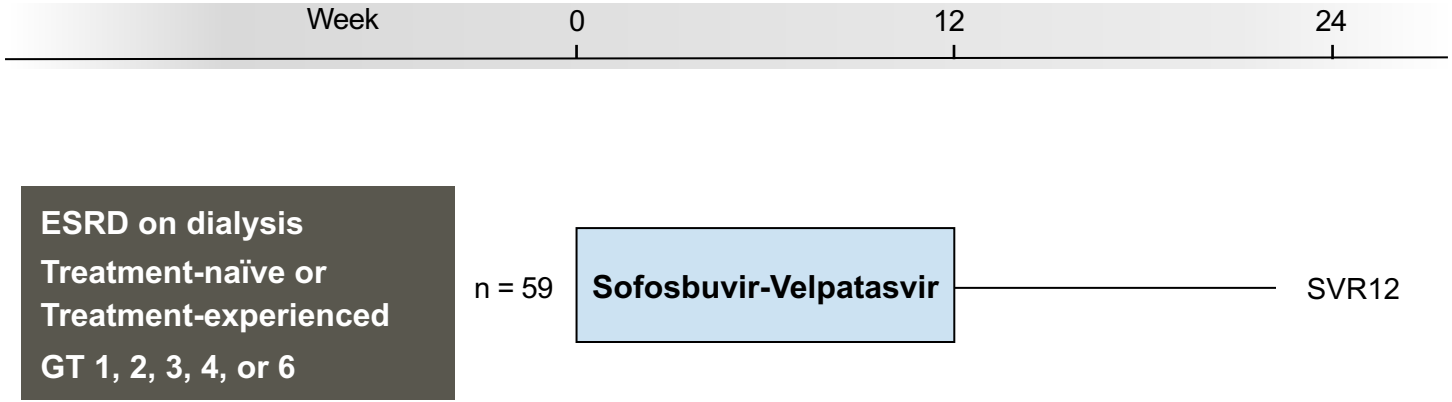
Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis
Study Features

- **Design**: Single-arm, open-label, multicenter, phase 2 trial of sofosbuvir-velpatasvir for 12 weeks in end-stage renal disease patients on dialysis
- **Setting**: 22 sites in Canada, United Kingdom, Spain, Israel, New Zealand, and Australia
- **Entry Criteria**
  - Chronic HCV GT 1-6
  - Age ≥18 years
  - End-stage renal disease on peritoneal or hemodialysis
  - HIV coinfection allowed if stable on antiretroviral therapy x ≥8 weeks
  - Prior treatment failure allowed (but no prior NS5A or NS5B)
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis Study Design



Abbreviations: ESRD, end-stage renal disease

Drug Dosing: Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily

Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis
Study Participants

Baseline Characteristic	Sofosbuvir-Velpatasvir (n = 59)
Age, mean, years (range)	60 (33-91)
Male, n (%)	35 (59)
Black race, n (%)	6 (10)
HCV genotype, n (%) 1a / 1b / other 2 3 4 6	 15 (25) / 11 (19) / 1 (2) 7 (12) 19 (32) 4 (7) 2 (3)
Body mass index, mean kg/m^2 (SD)	26 (17-39)
Mean HCV RNA, log_{10} IU/mL (range)	5.8 (3.1-7.7)
Cirrhosis, n (%)	17 (29)
Treatment experienced, n (%)	13 (22)

Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

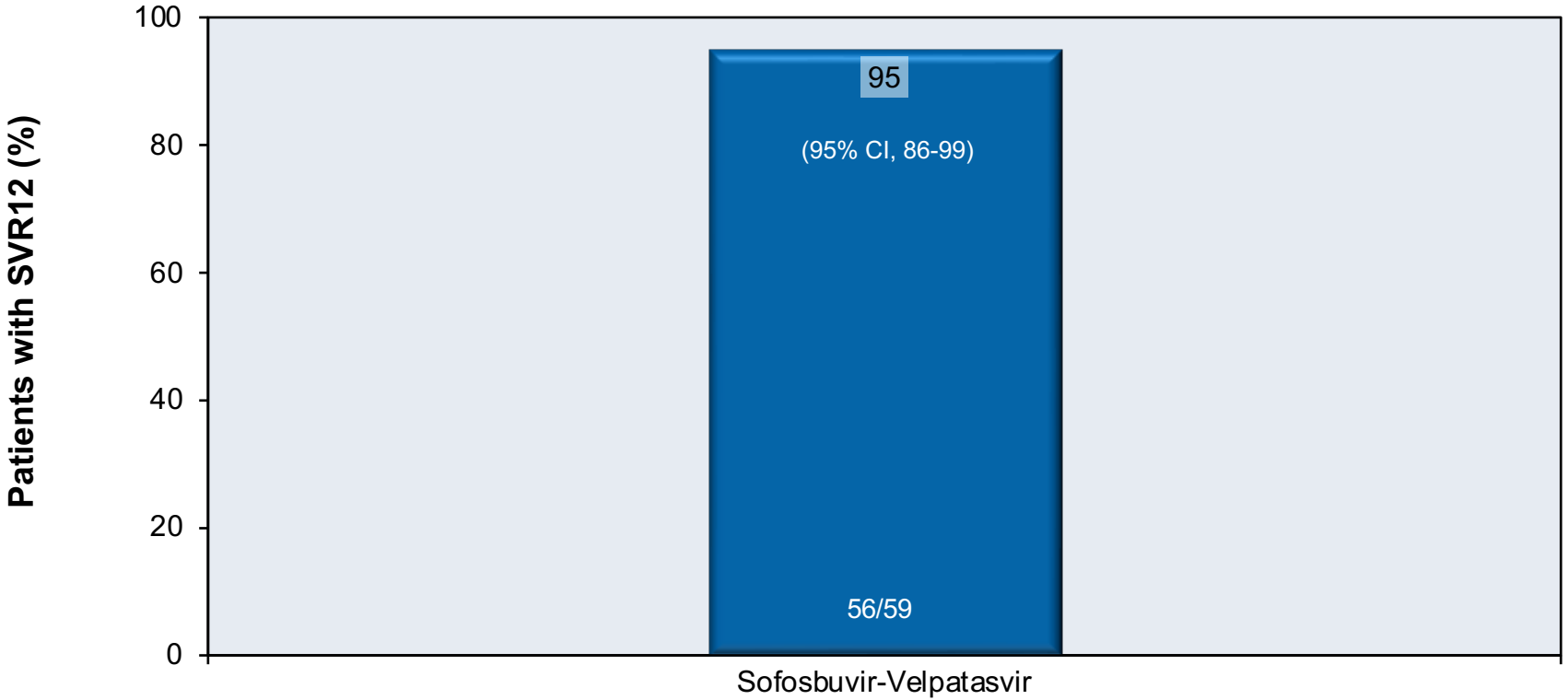
Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis
Study Participants

Other Characteristics	Sofosbuvir-Velpatasvir (n = 59)
Prior HCV treatment experience, n/N (%)	
Peg-IFN + ribavirin	6/13 (46)
Other	7 (13) (54)
Type of dialysis, n (%)	
Hemodialysis	54 (92)
Peritoneal dialysis	5 (9)
Mean duration of dialysis, years (range)	7 (0-40)
Prior renal transplant, n (%)	19 (32)

Abbreviations: Peg-IFN, pegylated interferon

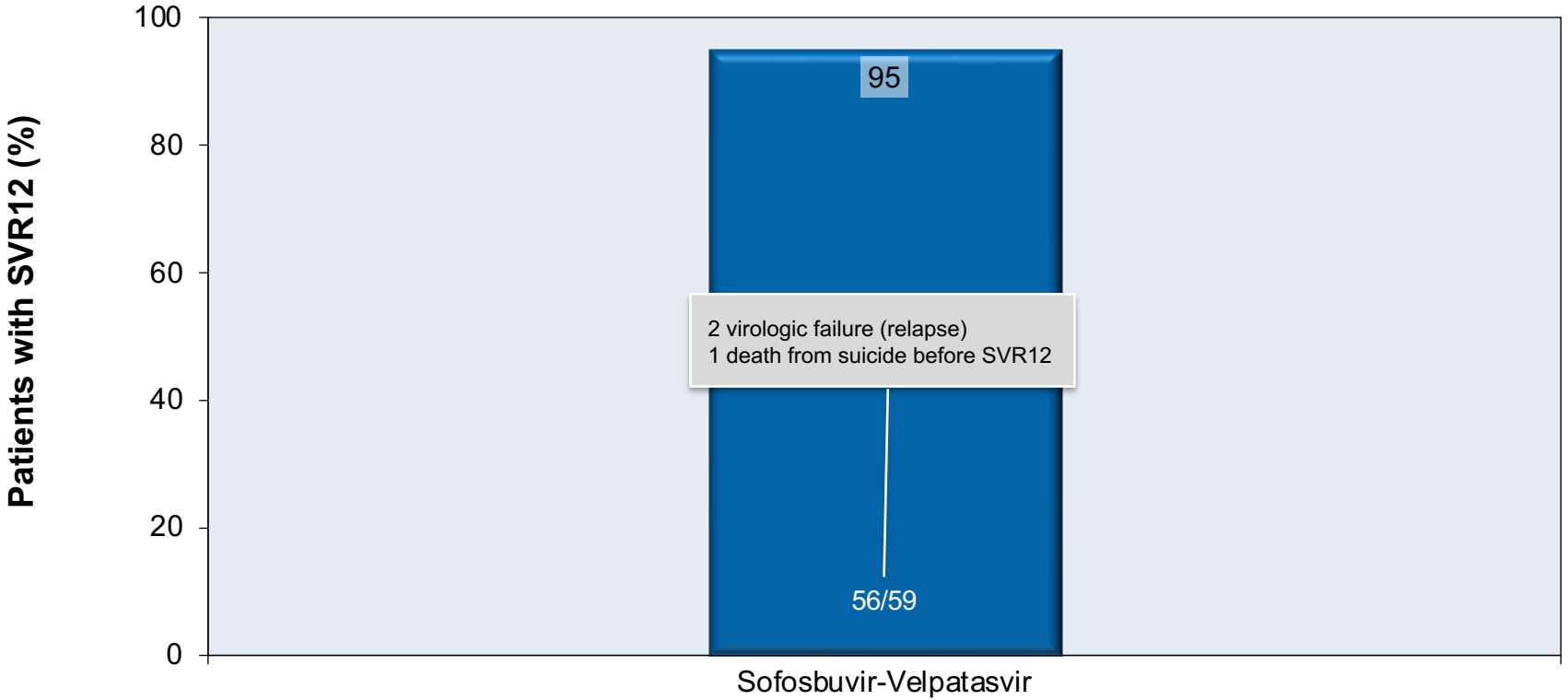
Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis Results: ITT Analysis



Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis Results: ITT Analysis



Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis Results: Adverse Events

Adverse Events (AEs), n (%)	Sofosbuvir-Velpatasvir (n = 59)
Any adverse event	47 (80)
Grade 3 AEs	7 (12)
Serious AEs	11 (19)
AE leading to SOF-VEL discontinuation	0
Deaths	2 (3)
AEs occurring in ≥10% patients	
Headache	10 (17)
Fatigue	8 (14)
Nausea	8 (14)
Vomiting	8 (14)
Insomnia	6 (10)

Abbreviations: SOF-VEL, sofosbuvir-velpatasvir

Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis Results: Laboratory Abnormalities

Grade 3-4 Lab Abnormalities, n (%)	Sofosbuvir-Velpatasvir (n = 59)
Creatinine	
Grade 3	1 (2)
Grade 4	14 (24)
Hyperglycemia	
Grade 3	5 (9)
Hemoglobin	
Grade 3	4 (7)
Hyperkalemia	
Grade 3	2 (3)
Grade 4	1 (2)

Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis Conclusions

Conclusions: “Treatment with sofosbuvir/velpatasvir for 12 weeks was safe and effective in patients with ESRD undergoing dialysis.”

Source: Borgia SM, et al. J Hepatol. 2019;71:660-5.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HCV/HIV Coinfection
ACTG A5360 (MINMON)

Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

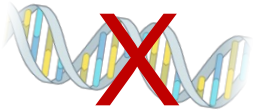
Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Study Overview

- **Design**: Phase 4 open-label single-arm trial to examine the safety and efficacy of a minimal monitoring approach to HCV care delivery using 12 weeks of sofosbuvir-velpatasvir in treatment-naïve patients
- **Setting**: Multiple sites in Brazil, South Africa, Thailand, Uganda & United States
- **Entry criteria**:
  - Chronic HCV infection as determined by HCV RNA >1000 IU/ml
  - Treatment-naïve
  - Age 18 or older
  - HIV coinfection permitted
  - Compensated cirrhosis permitted (FIB-4 ≥3.25, capped at ≤20% participants)
  - Absence of coinfection with HBV
- **Primary End-point**: SVR ≥22 weeks post-treatment initiation

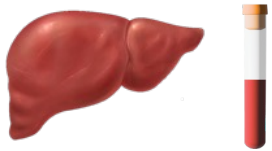
Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON):

No Genotype



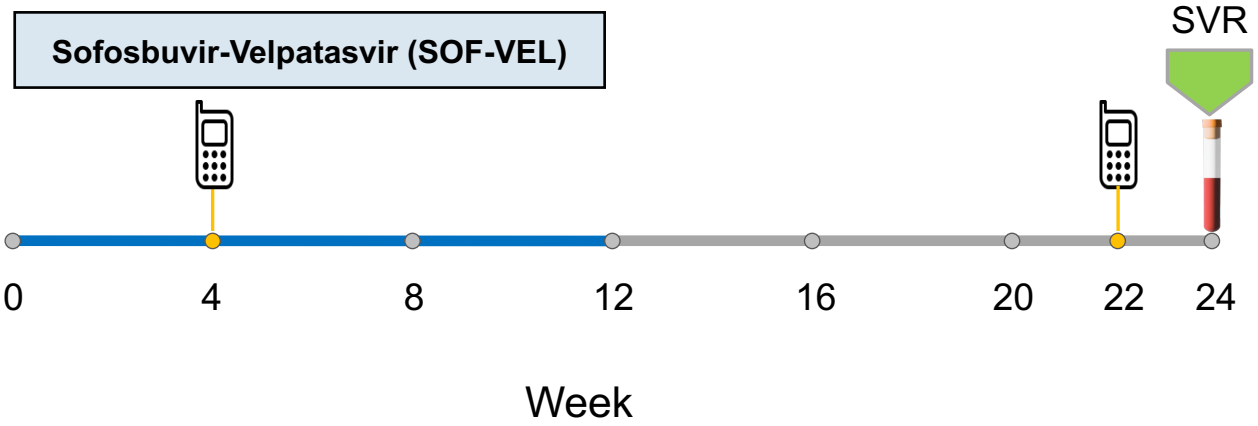
Cirrhosis Status by Fib-4



All pills provided at Entry

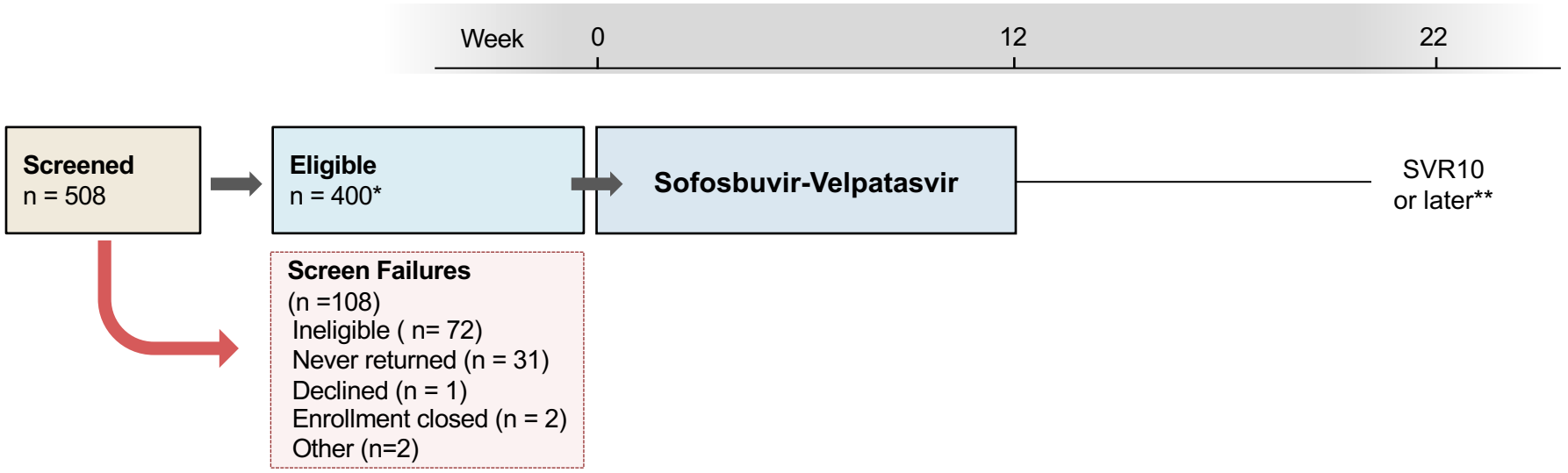
Sofosbuvir-Velpatasvir

- No pre-treatment genotyping
- Cirrhosis determination based on Fib-4
- All treatment medication provided at entry
- No scheduled on treatment visits/labs
- Remote contact at weeks 4 and 22



Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Trial Design



Drug Dosing
Sofosbuvir-velpatasvir: 400/100 mg once daily
*Final analytic set was n = 399 since one study participant never started SOF-VEL
**SVR ascertainment permitted out to week 76 of study

Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

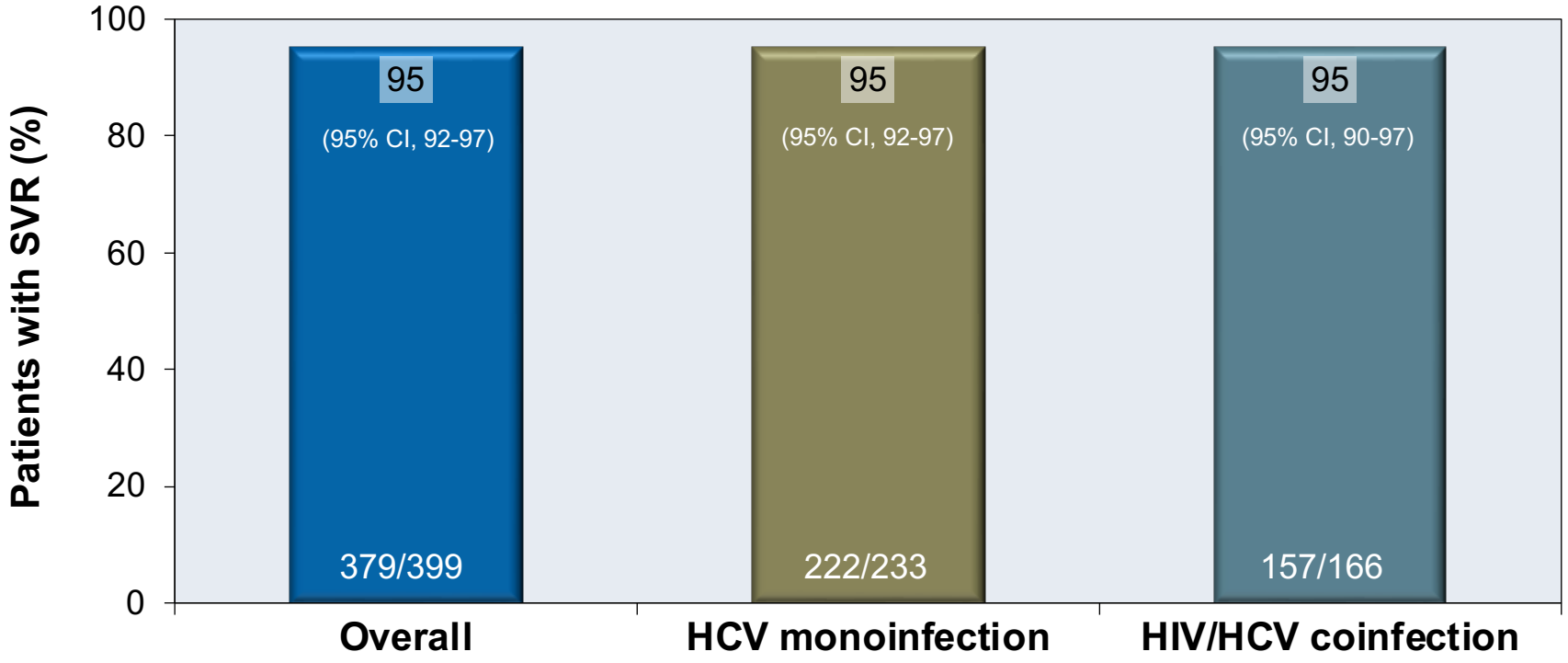
Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Study Population

Baseline Characteristic	Sofosbuvir-Velpatasvir (n = 399)
Age, median (range)	47 (20-82)
Female sex at birth, n (%)	139 (35)
Identity across transgender spectrum, n (%)	22 (6)
Race, n (%) White Black Asian	 166 (42) 72 (18) 113 (28)
HCV RNA $\log_{10}$ IU/mL, median (IQR)	6.1 (5.6 – 6.6)
Current injection drug use, n (%)	12 (3)
Current alcohol use, n (%)	161 (40%)
Cirrhosis (by FIB-4 ≥3.25), n (%)	34 (9)
HIV coinfection, n (%) Suppressed on antiretroviral therapy, n (% of HIV/HCV)	166 (42) 164 (99)

IQR, interquartile range; FIB-4, Fibrosis-4 index

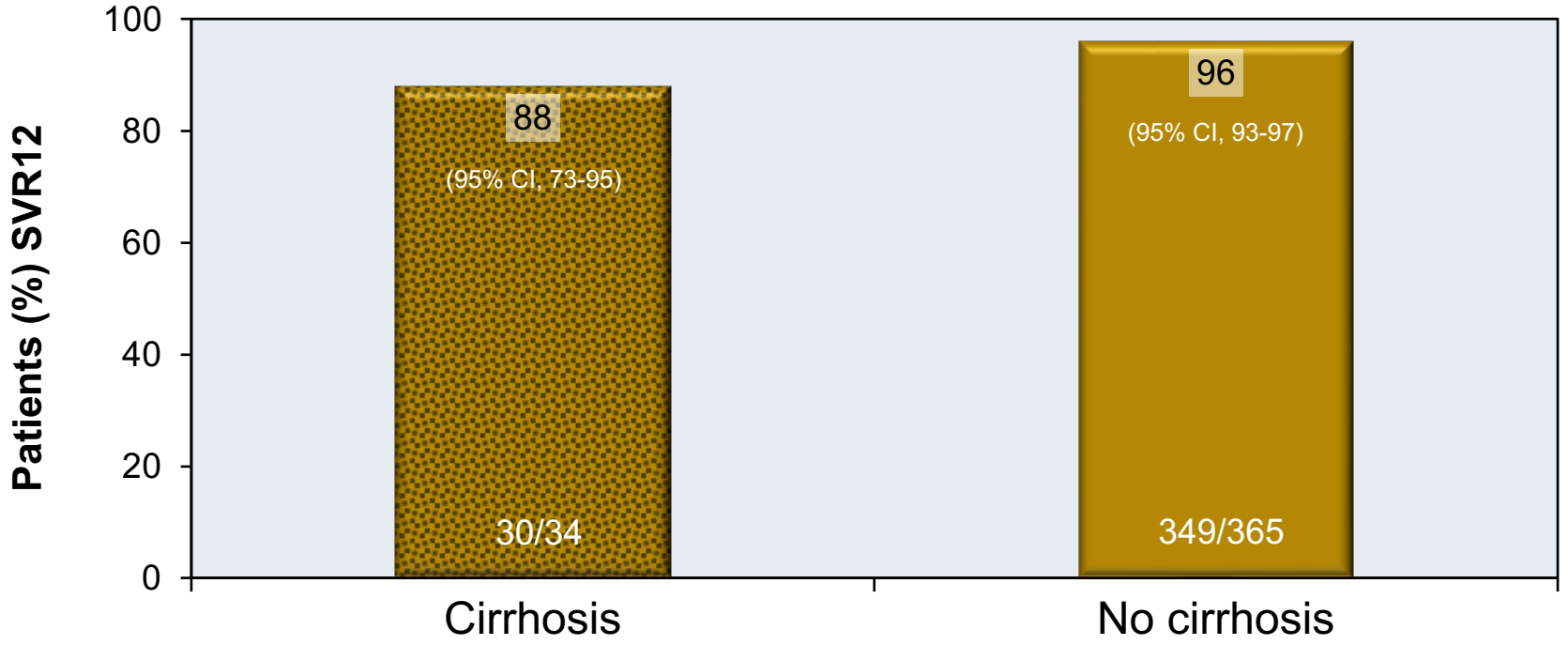
Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Results, Overall and by HIV Status



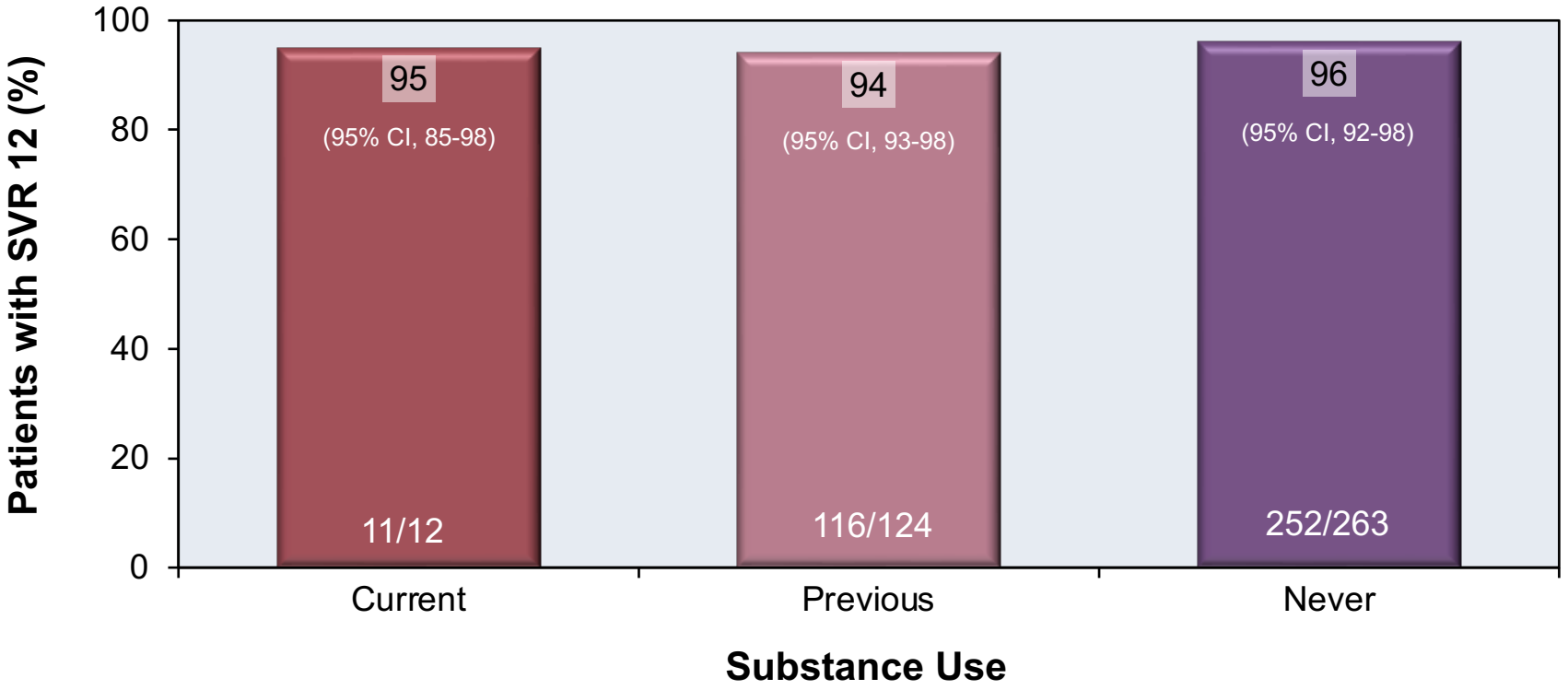
Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Results by Cirrhosis Status



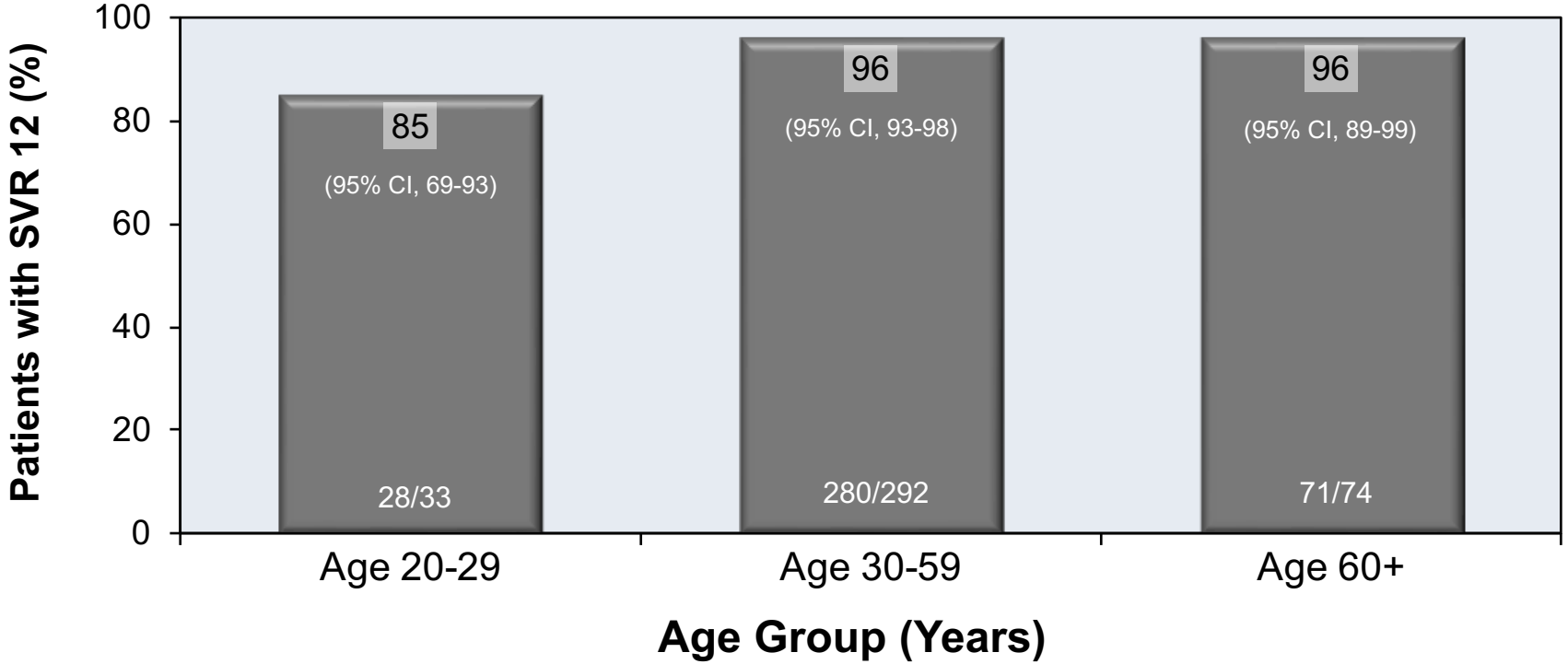
Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Results by Injection Drug Use Status



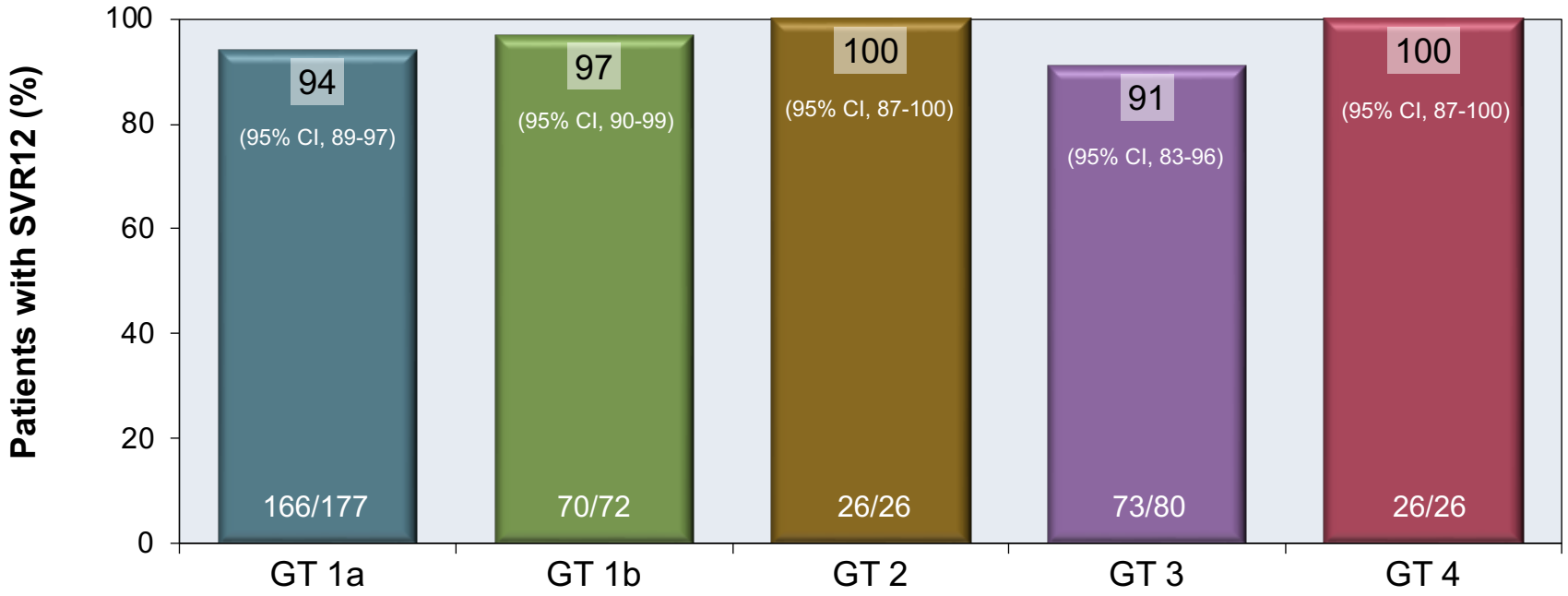
Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Results by Age



Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

MINMON Study: Sofosbuvir-velpatasvir with minimal monitoring Results by HCV Genotype



Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

MINMON Study: Sofosbuvir-velpatasvir with minimal monitoring Study events

- 15 (3.8%) participants with following events:
  - n=3 adverse events (AE)
  - n=8 abnormal lab values at baseline
  - n=6 non-AE clinical events
- 3 participants reported losing medications
  - 1 after 14 days on study
  - 2 received replacement (interruption: 4 and 7 days)
- 2 participants reported premature discontinuation
  - One loss of medications, one due to AE

Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Sofosbuvir-Velpatasvir with Minimal Monitoring +/- HIV Coinfection ACTG A5360 (MINMON): Conclusions

Interpretation: “In this diverse global population of people with HCV, the MINMON approach with sofosbuvir–velpatasvir treatment was safe and achieved SVR comparable to standard monitoring observed in real-world data. Coupled with innovative case finding strategies, this strategy could be crucial to the global HCV elimination agenda.”

Source: Solomon SS, et al. Lancet Gastroenterol Hepatol. 2022;7:307-17.

Acknowledgments

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HEPATITIS B ONLINE

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