HEPATITIS C ONLINE

Sofosbuvir-Velpatasvir-Voxilaprevir (*Vosevi*)

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Sofosbuvir-Velpatasvir-Voxilaprevir (*Vosevi*)

Background and Dosing

Sofosbuvir-Velpatasvi-Voxilaprevir (*Vosevi*)

- **Approval Status**: Approved by United States FDA on July 18, 2017
- **Indications and Usage:** Adult patients with chronic HCV without cirrhosis or with compensated cirrhosis (Child-Pugh class A) with:
  - HCV genotypes 1-6 in previously treated with an NS5A inhibitor-containing regimen (treatment duration = 12 weeks)
  - HCV genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor (treatment duration = 12 weeks)
- **Class and Mechanism**
  - Sofosbuvir: HCV NS5B polymerase inhibitor
  - Velpatasvir: HCV NS5A inhibitor
  - Voxilaprevir: HCV NS3/4A protease inhibitor
- **Preparation:** Sofosbuvir-Velpatasvir-Voxilaprevir (fixed dose 400/100/100 mg)
- **Dosing**: One tablet orally once daily, with food
- **Adverse Effects (AE)**: Headache, fatigue, diarrhea, and nausea

Source: *Vosevi* Prescribing Information, Gilead Sciences.

Sofosbuvir-Velpatasvir-Voxilaprevir (*Vosevi*) Indications and Usage

Sofosbuvir-Velpatasvir-Voxilaprevir for Adults with Chronic HCV without Cirrhosis or with Compensated Cirrhosis (Child-Pugh A)		
HCV Genotype	**Patient Previously Treated With an HCV Regimen Containing:**	**Treatment Duration**
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[a]	12 weeks
1a or 3	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

[A] In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
[B] In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

Source: *Vosevi* Prescribing Information, Gilead Sciences.

Sofosbuvir-Velpatasvir-Velpatasvir (SOF-VEL-VOX): Summary of Phase 3 Studies

- **POLARIS-1**: SOF-VEL-VOX x 12 weeks in TE, GT 1-6
- **POLARIS-2**: SOF-VEL-VOX x 8 weeks vs. SOF-VEL x 12 weeks in DAA Naive, GT 1-6
- **POLARIS-3**: SOF-VEL-VOX x 8 weeks vs. SOF-VEL x 12 weeks in DAA Naive, GT 3 and Cirrhosis
- **POLARIS-4**: SOF-VEL-VOX vs. SOF-VEL x 12 weeks in DAA Experienced, GT 1-4

Abbreviations: SOF-VEL-VOX = sofosbuvir-velpatasvir;-voxilaprevir; SOF-VEL = sofosbuvir-velpatasvir; GT = genotype; TE = treatment experienced; DAA = direct-acting antiviral

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6
POLARIS-1

Note: POLARIS-1 published in tandem with POLARIS-4

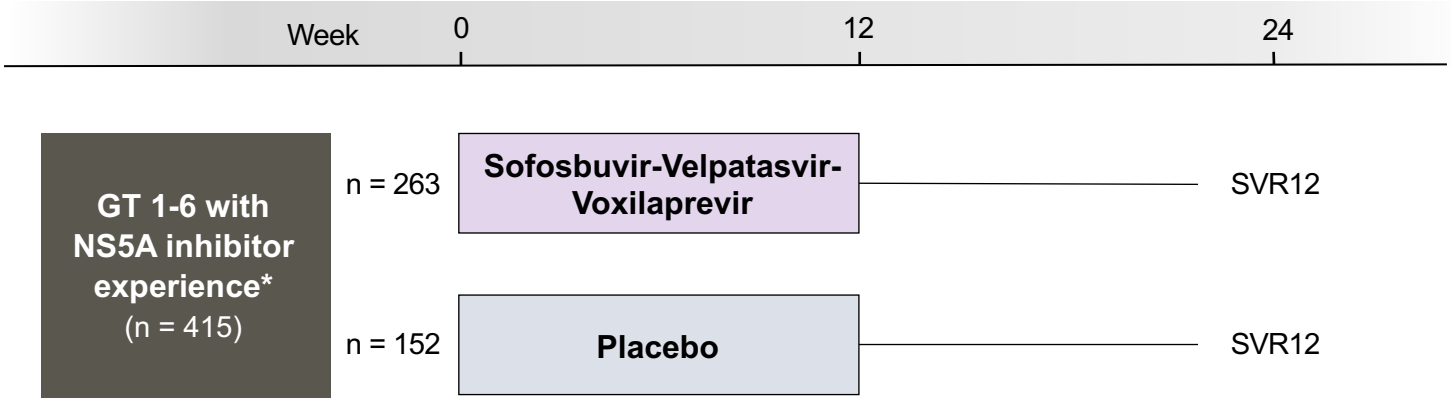
Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Study Features

- **Design**: Randomized, placebo-controlled, phase 3 trial to evaluate the efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks in NS5A-inhibitor-experienced patients with GT 1-6 chronic HCV infection
- **Setting**: 108 sites in United States, Canada, New Zealand, Australia, France, Germany, and United Kingdom
- **Entry Criteria**
  - Age ≥18 years
  - Chronic HCV (any genotype)
  - HCV RNA ≥10,000 IU/mL at screening
  - Prior treatment failure with DAA that contained NS5A inhibitor
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Study Design



- GT 1 patients randomized 2:1 ratio (active:placebo). Stratified by presence of cirrhosis (target ≥30%)
- Genotypes 2-6 were assigned to active arm (and not randomized)
- Placebo recipients were eligible for deferred treatment with sofosbuvir-velpatasvir-voxilaprevir

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

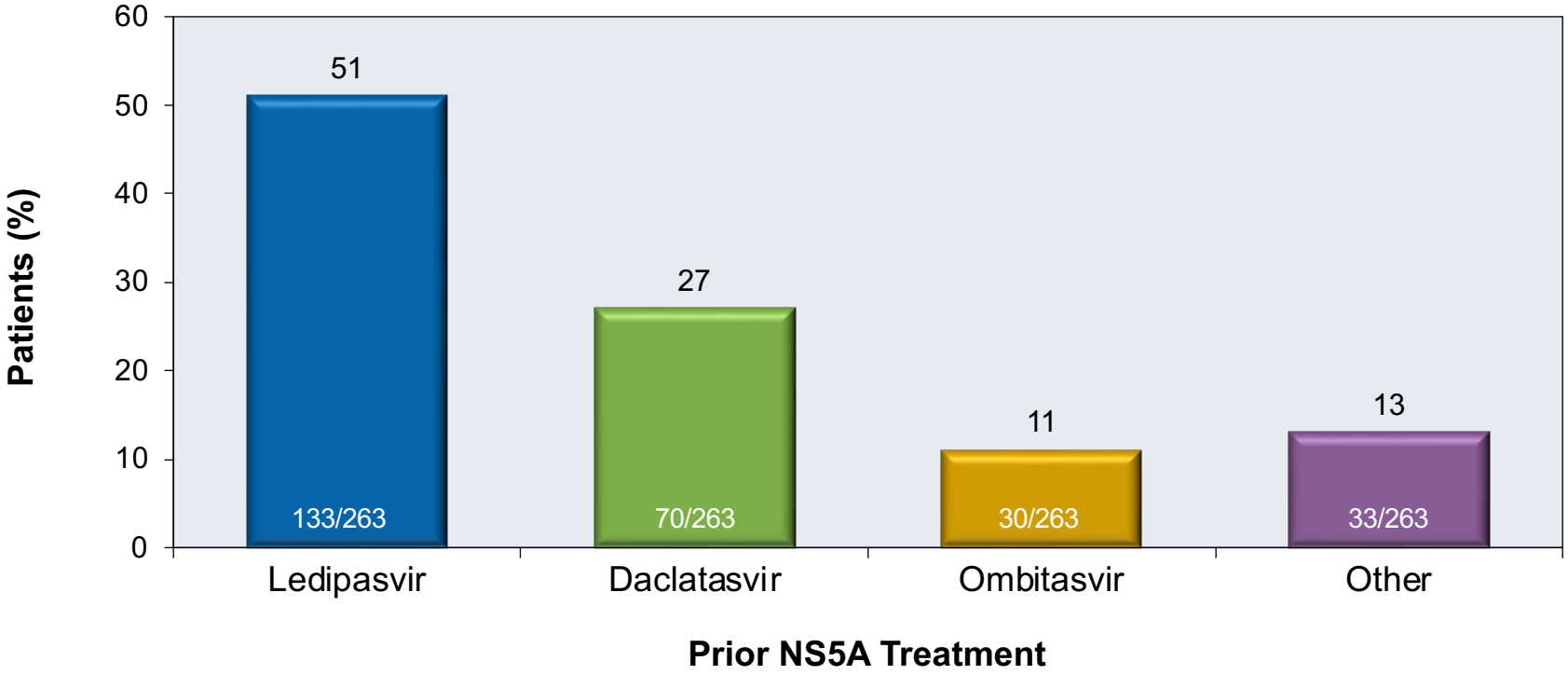
Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Baseline Characteristics

Baseline Characteristics	SOF-VEL-VOX (n = 263)	Placebo (n = 152)
Age, mean (range)	58 (27-84)	59 (29-80)
Male, n (%)	200 (76)	121 (80)
White, n (%)	211 (80)	124 (82)
HCV genotype—no. (%)		
1	150 (57)	150 (99)
1a	101 (38)	117 (77)
1b	45 (17)	31 (20)
1 (other)	4 (2)	2 (1)
2	5 (2)	0
3	78 (30)	0
4	22 (8)	0
5	1 (<1)	0
6	6 (2)	2 (1)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.3 ± 0.7	6.3 ± 0.6
IL28B CC, n (%)	47 (18)	27 (18)
Cirrhosis, n (%)	121 (46)	51 (34)

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

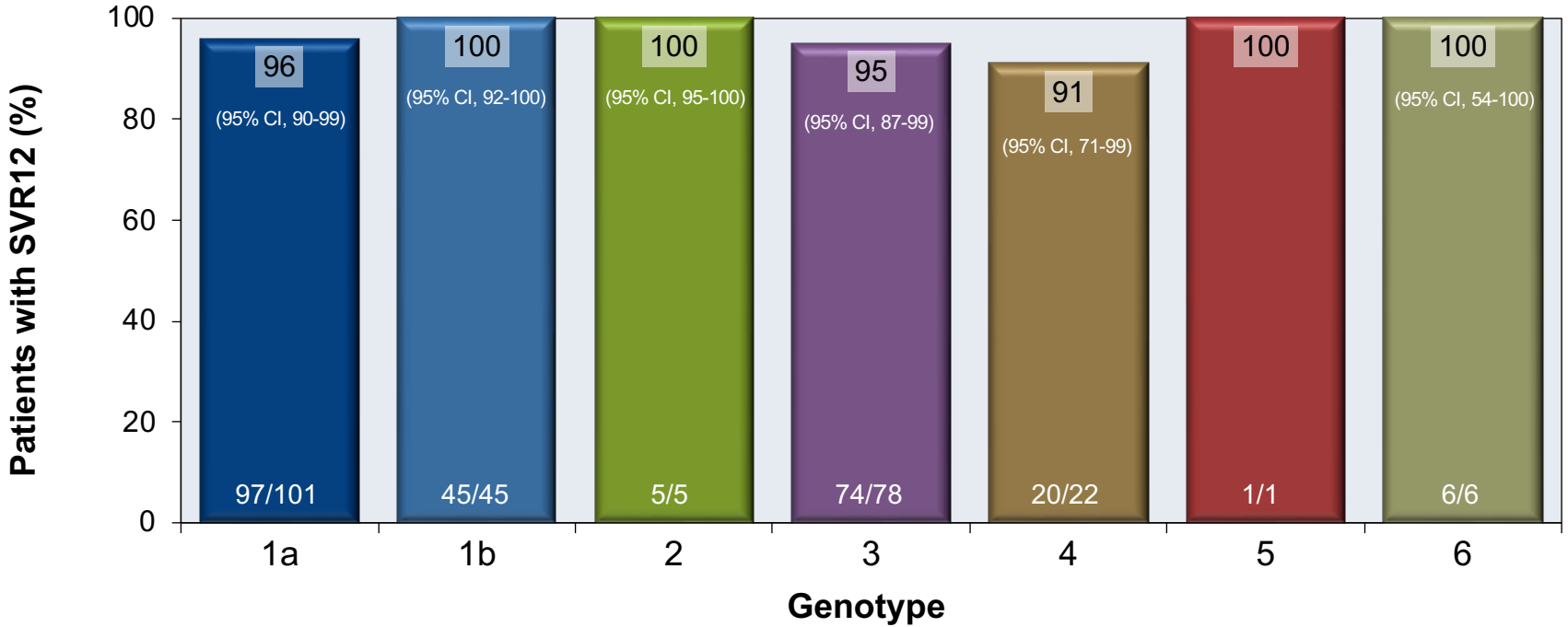
Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6
POLARIS-1: Prior NS5A Treatment



Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Results

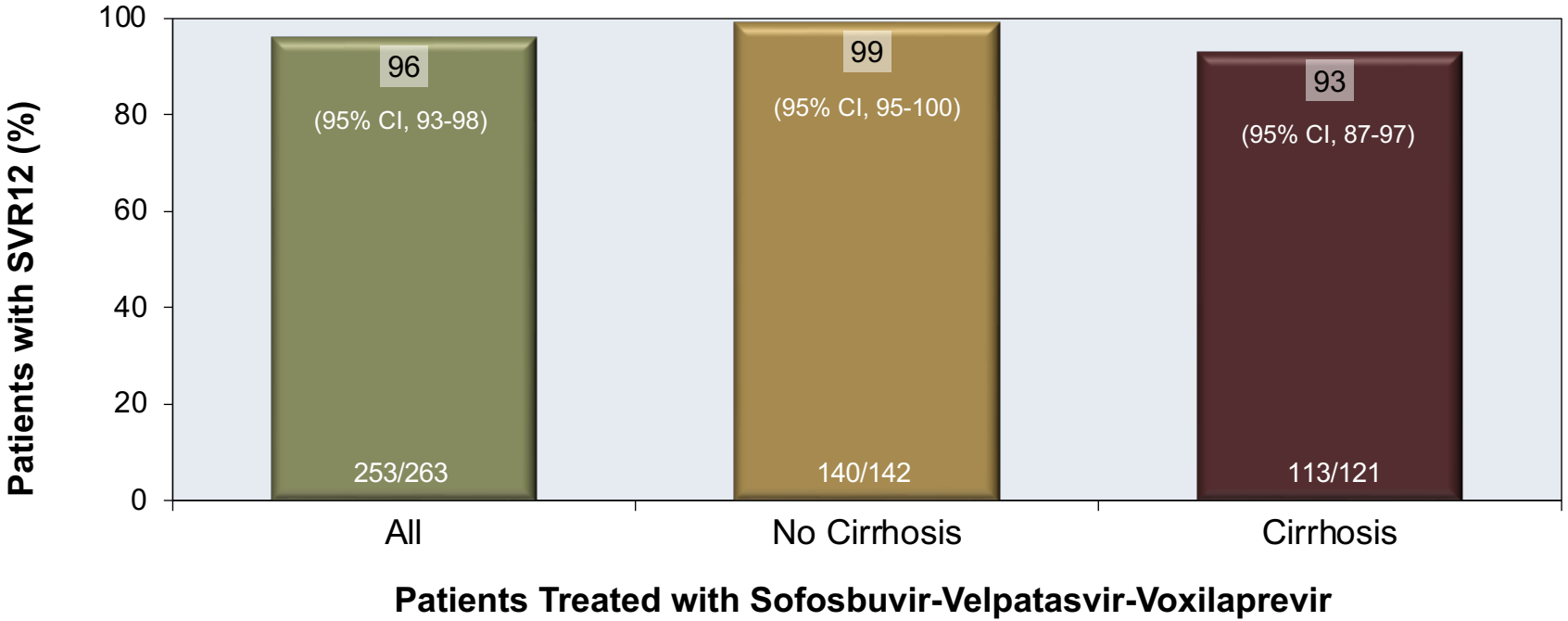
POLARIS-1: SVR12 Results by Genotype



Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Results

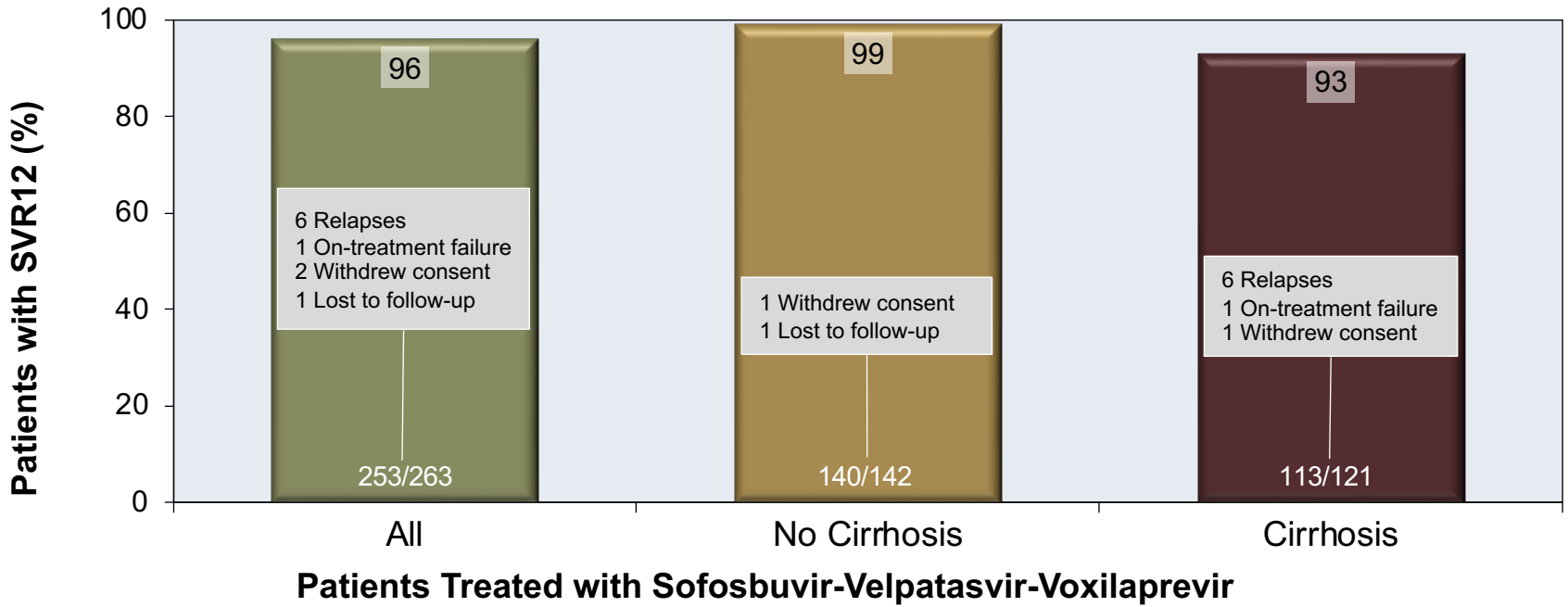
POLARIS-1: SVR 12 by Cirrhosis Status



Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Results

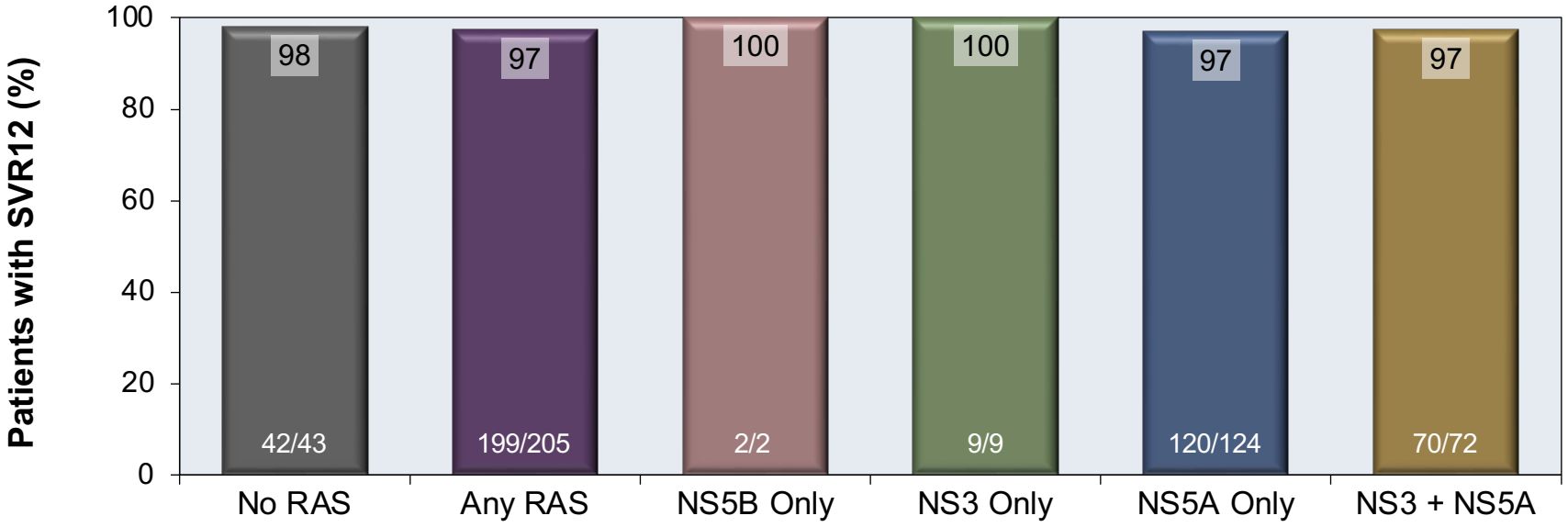
POLARIS-1: SVR 12 by Cirrhosis Status



Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Results

POLARIS-1: SVR12 by Baseline Resistance-Associated Substitutions (RAS)



83% of patients had baseline resistance-associated substitutions (RASs); 79% had NS5A RASs.
None who relapsed had treatment-emergent RASs.

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in NS5A-Experienced GT 1-6 POLARIS-1: Adverse Events

Adverse Event (AE)	SOF-VEL-VOX (n = 263)	Placebo (n = 152)
Discontinuation due to AE—no. (%)	1 (<1)[§]	3 (2)
Serious AEs—no. (%)	5 (2)	7 (5)
Deaths—no.	0	0
Any AE in ≥5% of patients—no. (%)		
Headache	66 (25)	26 (17)
Fatigue	56 (21)	30 (20)
Diarrhea	47 (18)	19 (12)
Nausea	37 (14)	12 (8)
Laboratory AEs Grade 3 or Above—no. (%)	18 (6.9%)	22 (14.5%)

[§]One participant in active arm discontinued due to angioedema attributed to ramipril.

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-1 and POLARIS-4: Conclusions

Conclusions: “Sofosbuvir-velpatasvir-voxilaprevir taken for 12 weeks provided high rates of sustained virologic response among patients across HCV genotypes in whom treatment with a DAA regimen had previously failed.”

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve GT 1-6
POLARIS-2

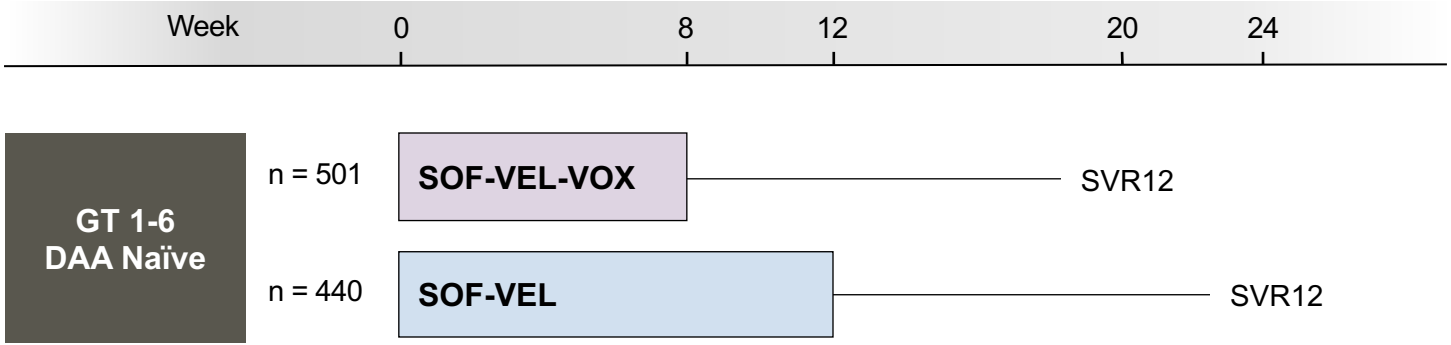
Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Study Features

- **Design**: Randomized, open-label, 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 DAA-naïve participants 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.

Sofosbuvir-Velpatasvir-Voxilaprevir 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.

Sofosbuvir-Velpatasvir-Voxilaprevir 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	169 (34)	172 (39)
1b	63 (13)	59 (13)
2	63 (13)	53 (12)
3	92 (18)	89 (20)
4	63 (13)	57 (13)
5	18 (4)	0
6	30 (6)	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.

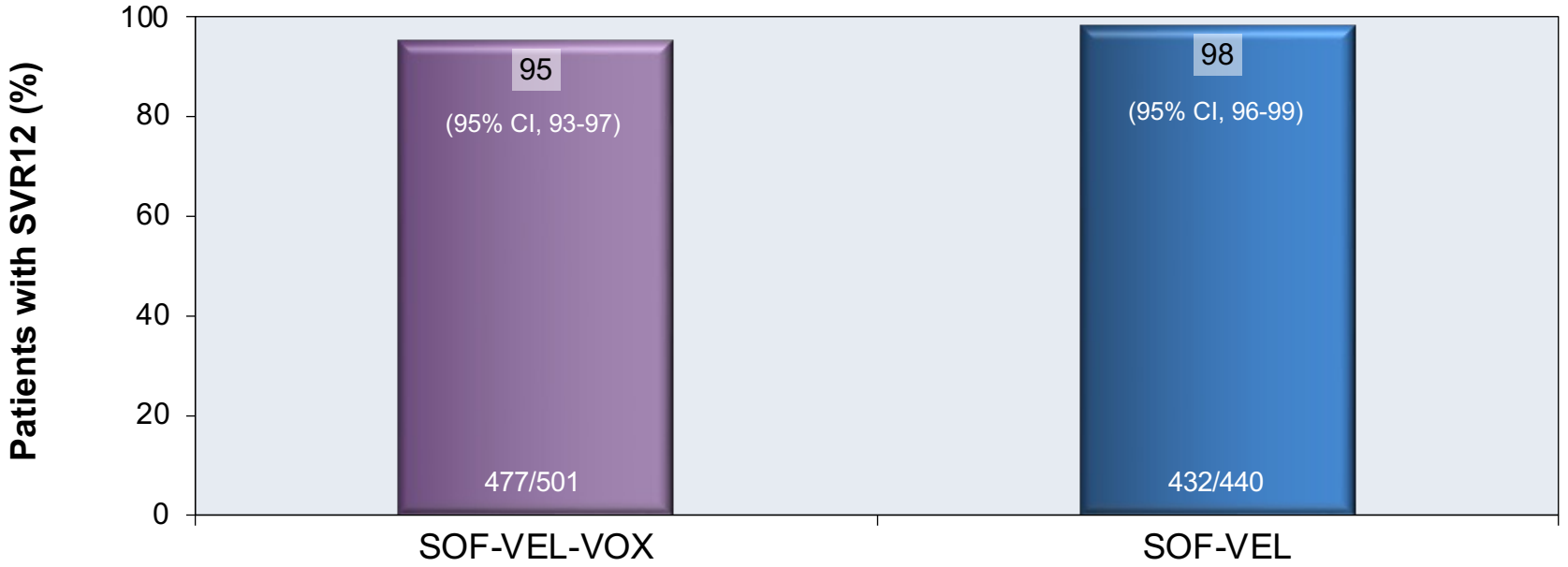
Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Baseline Characteristics

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.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

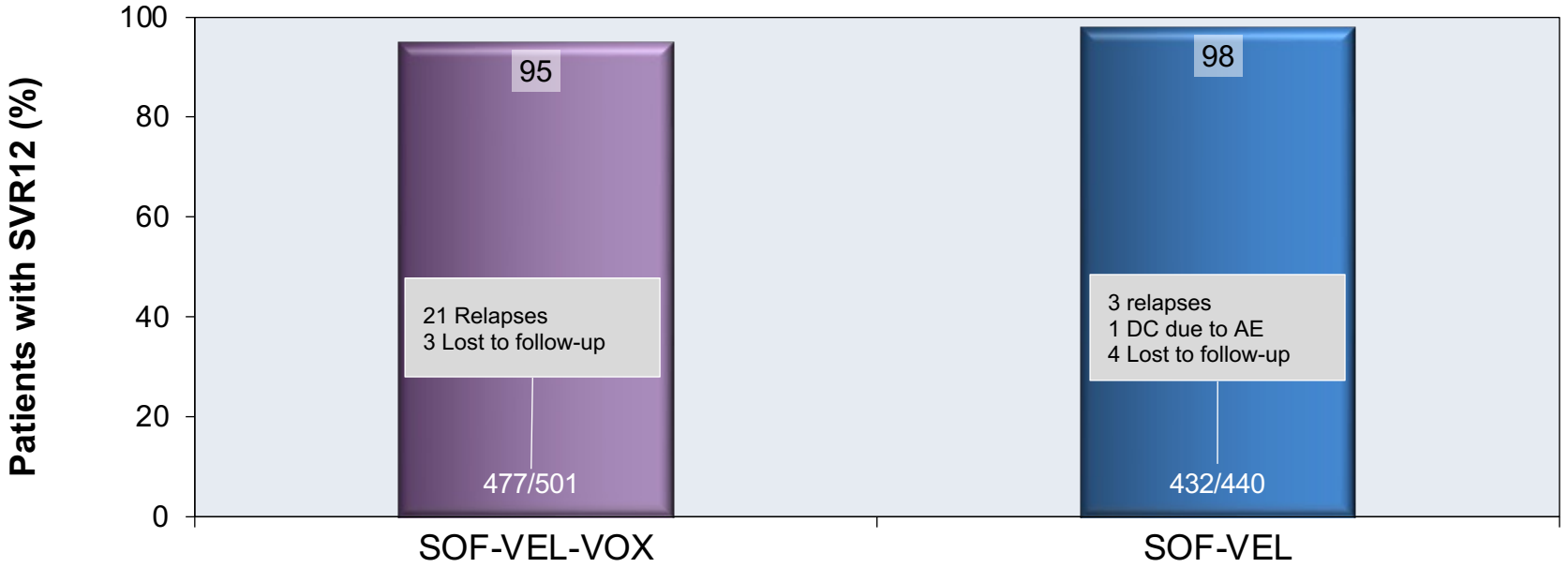
POLARIS-2: Overall SVR12 by Treatment Arm



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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT1-6
POLARIS-2: Results

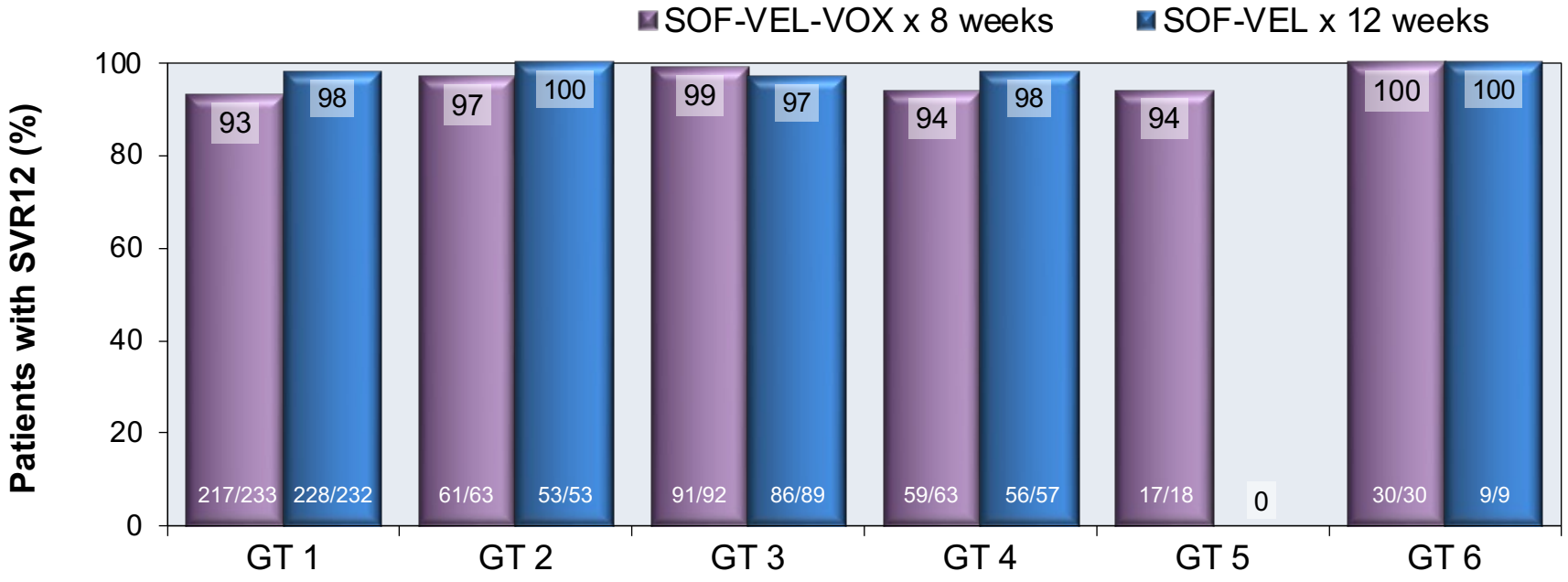
POLARIS-2: Overall SVR12 by Treatment Arm



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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

POLARIS-2: SVR by Treatment Arm and Genotype

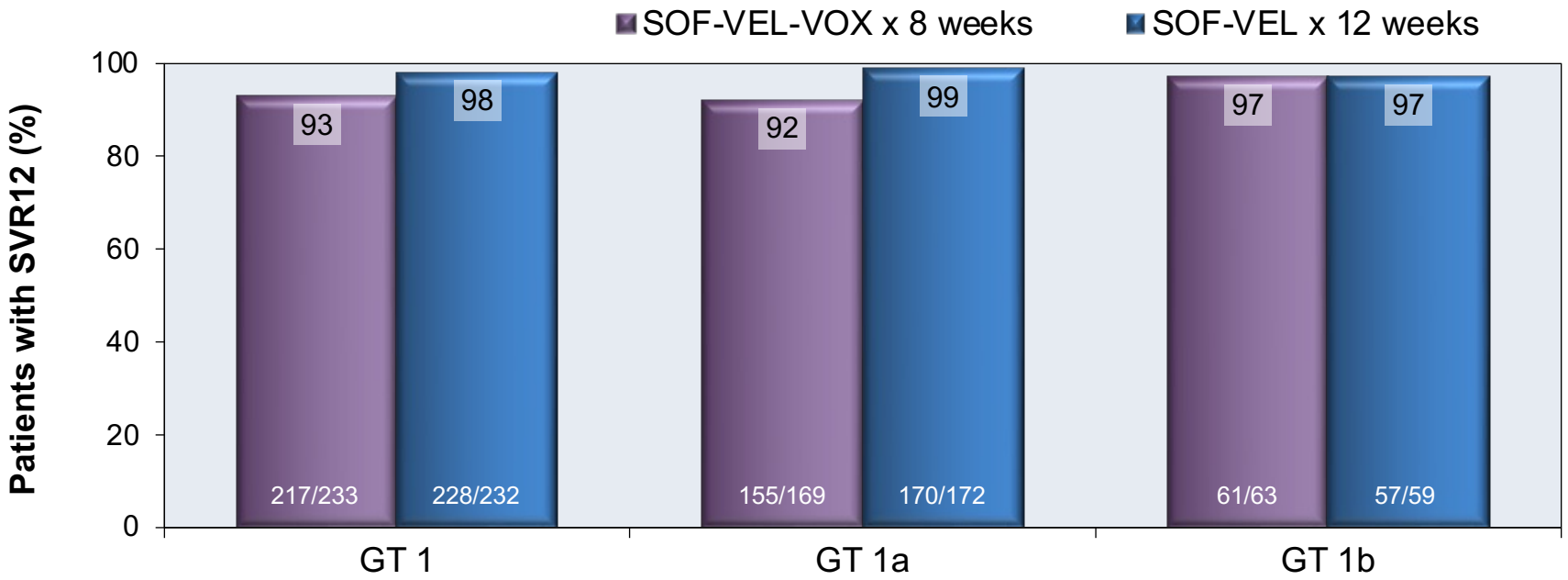


Abbreviations: DCAE, Discontinuation due to AE, LTFU, Lost to follow-up.
Two patients had unknown genotype were assigned to SOF-VEL-VOX and went on to achieve SVR12

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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

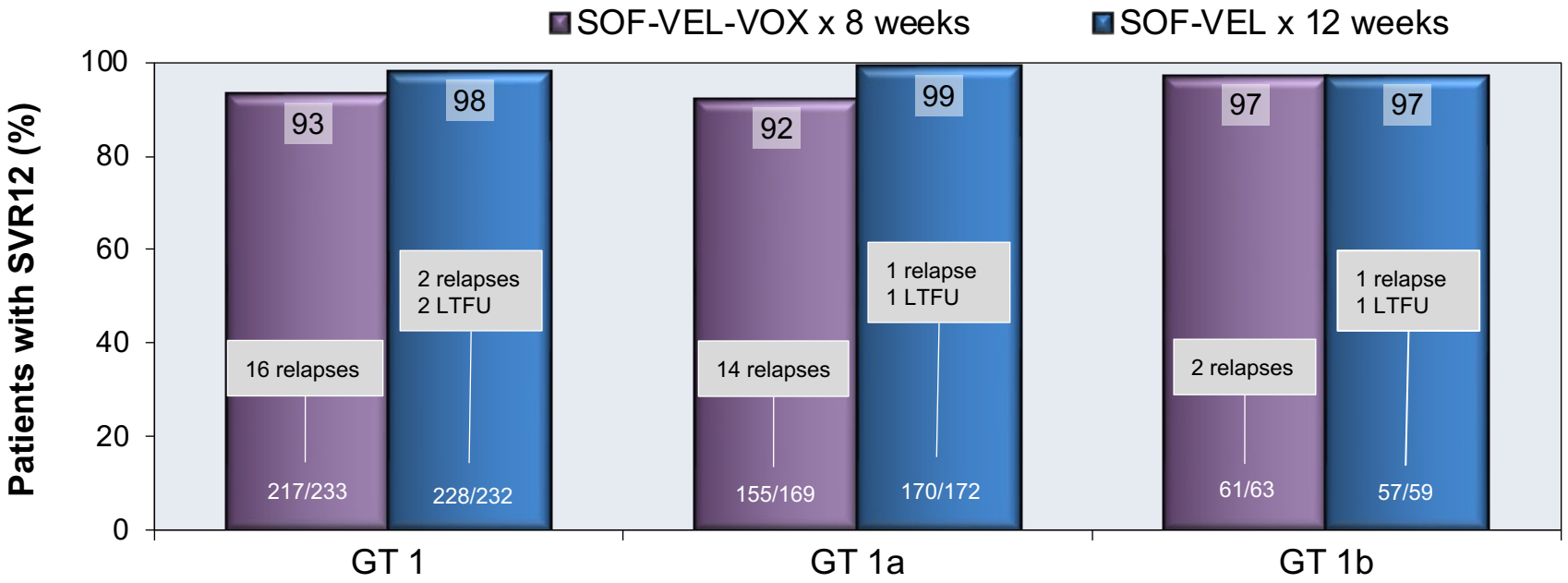
POLARIS-2: SVR by Treatment Arm and Genotype 1 Subtype



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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

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

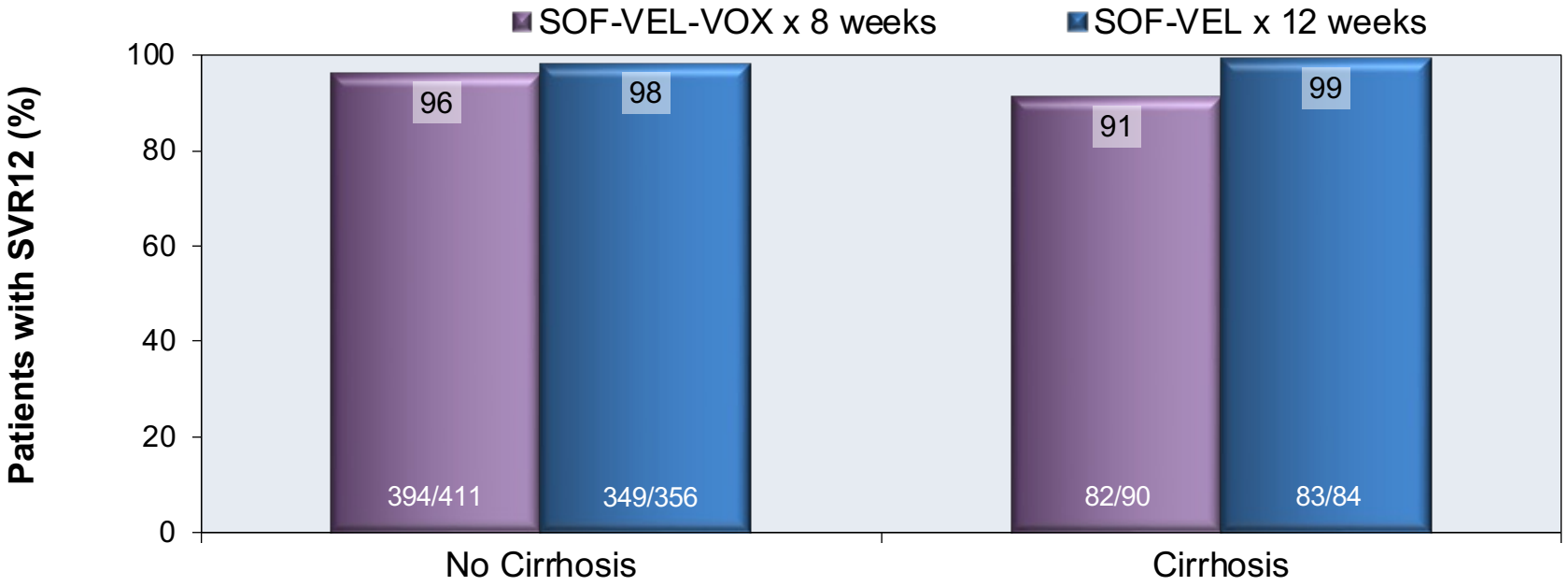


Abbreviations: LTFU = Lost to follow-up

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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

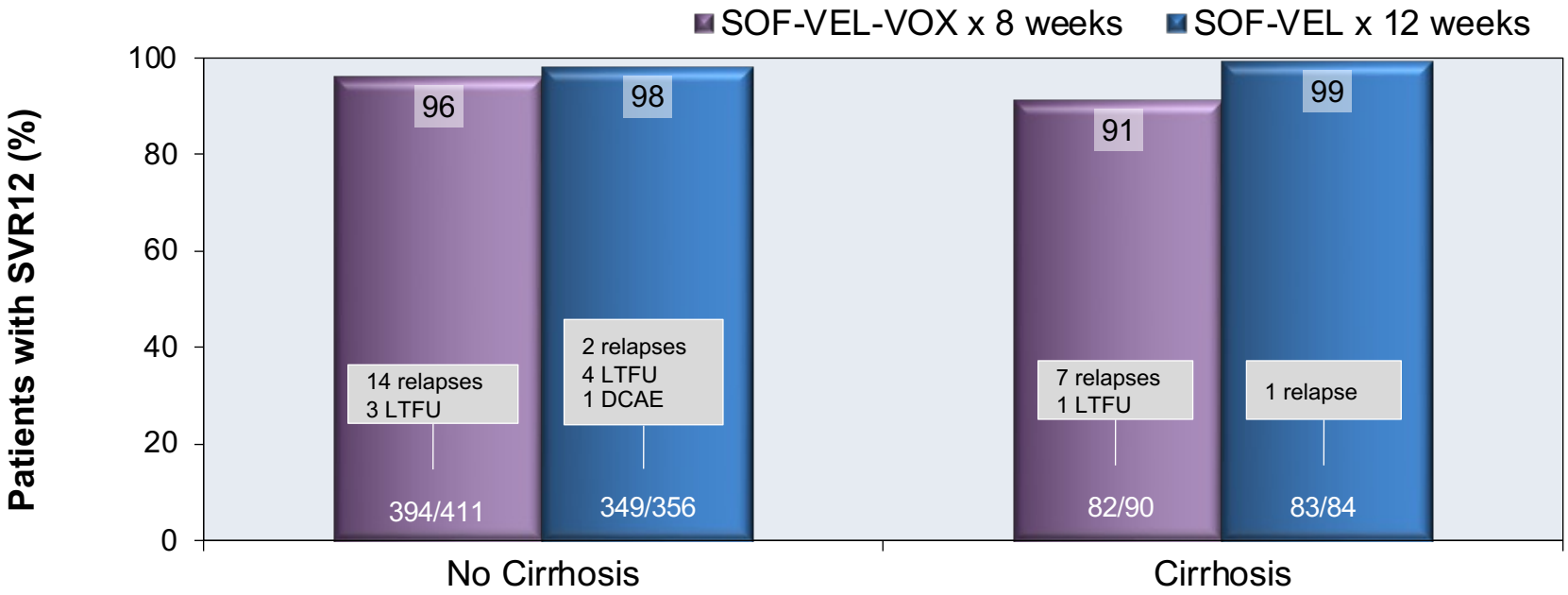
POLARIS-2: SVR12 by Cirrhosis Status



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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT 1-6
POLARIS-2: Results

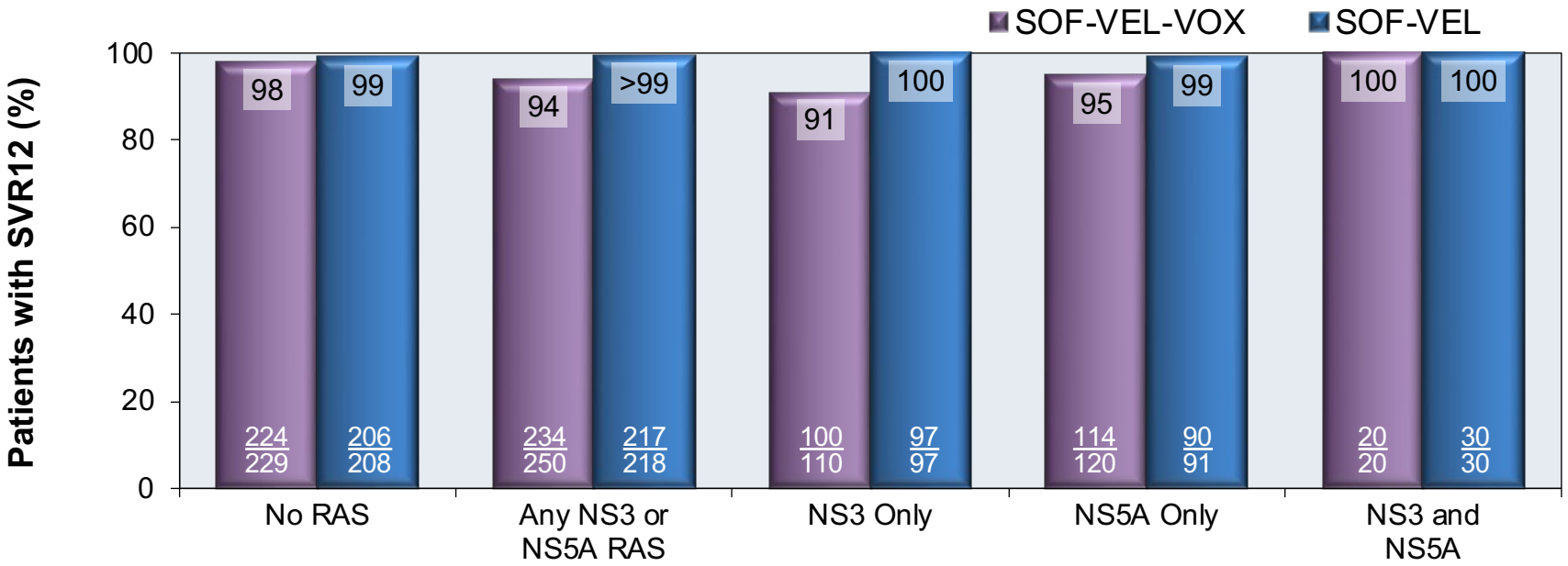
POLARIS-2: SVR12 by Cirrhosis Status



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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT1-6 POLARIS-2: Results

POLARIS-2: SVR12 by Baseline RASs*



*Using a 15% reporting threshold

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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT1-6
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 URI; 1 patient due to *C. difficile* infection. Neither considered related to study medication by investigator.

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

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Naïve HCV GT1-6
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-Voxilaprevir in GT 3 and Cirrhosis
POLARIS-3

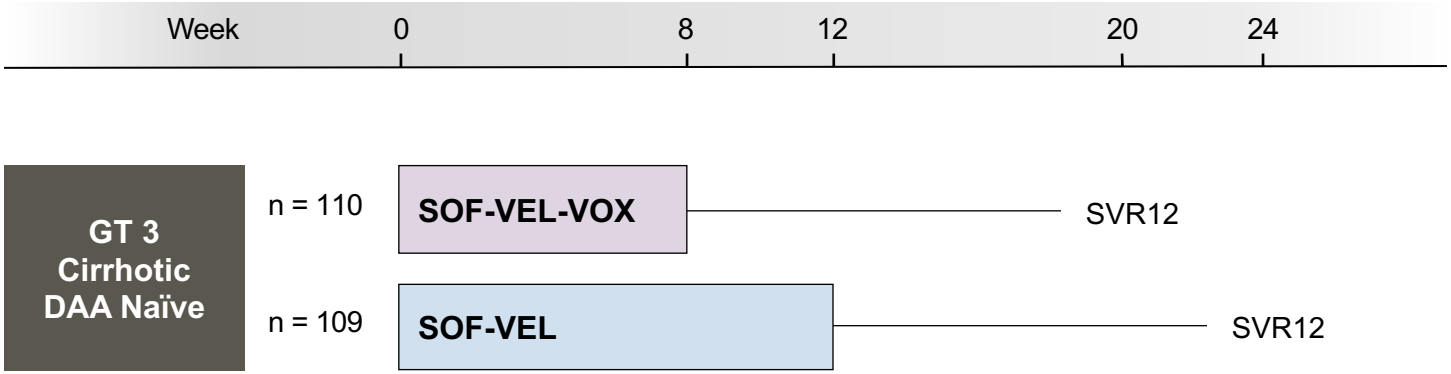
Jacobson IM, et al. Gastroenterology. 2017;153:113-22.

Sofosbuvir-Velpatasvir-Voxilaprevir 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.

Sofosbuvir-Velpatasvir-Voxilaprevir 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.

Sofosbuvir-Velpatasvir-Voxilaprevir 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.

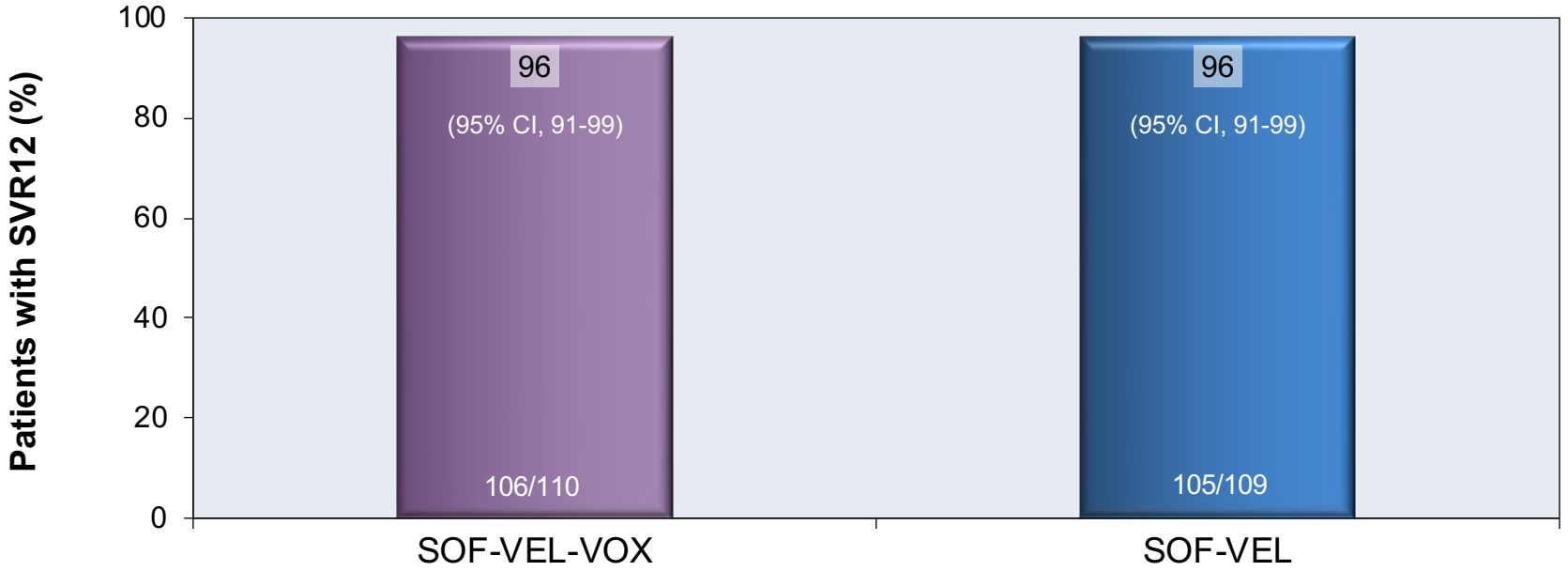
Sofosbuvir-Velpatasvir-Voxilaprevir in GT 3 and Cirrhosis
POLARIS-3: Baseline Characteristics

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.

Sofosbuvir-Velpatasvir-Voxilaprevir in GT 3 and Cirrhosis
POLARIS-3: Results

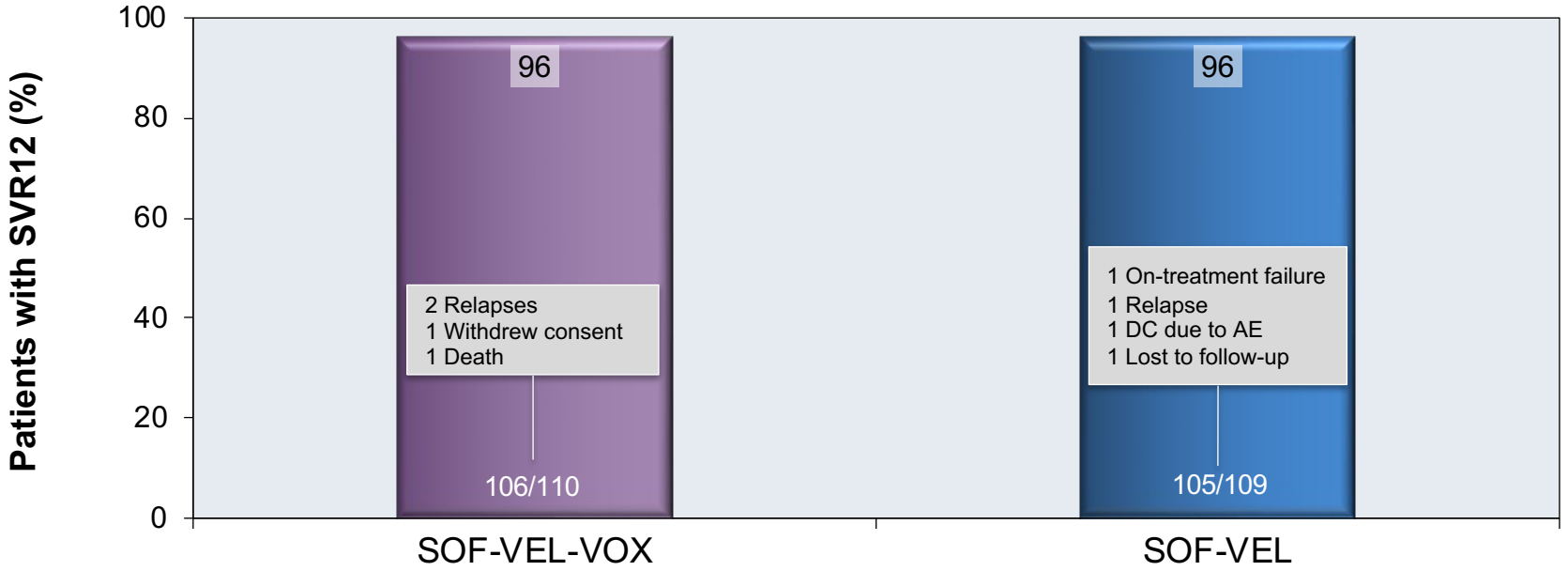
POLARIS-3: Overall SVR12 by Treatment Arm



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

Sofosbuvir-Velpatasvir-Voxilaprevir in GT 3 and Cirrhosis
POLARIS-3: Results

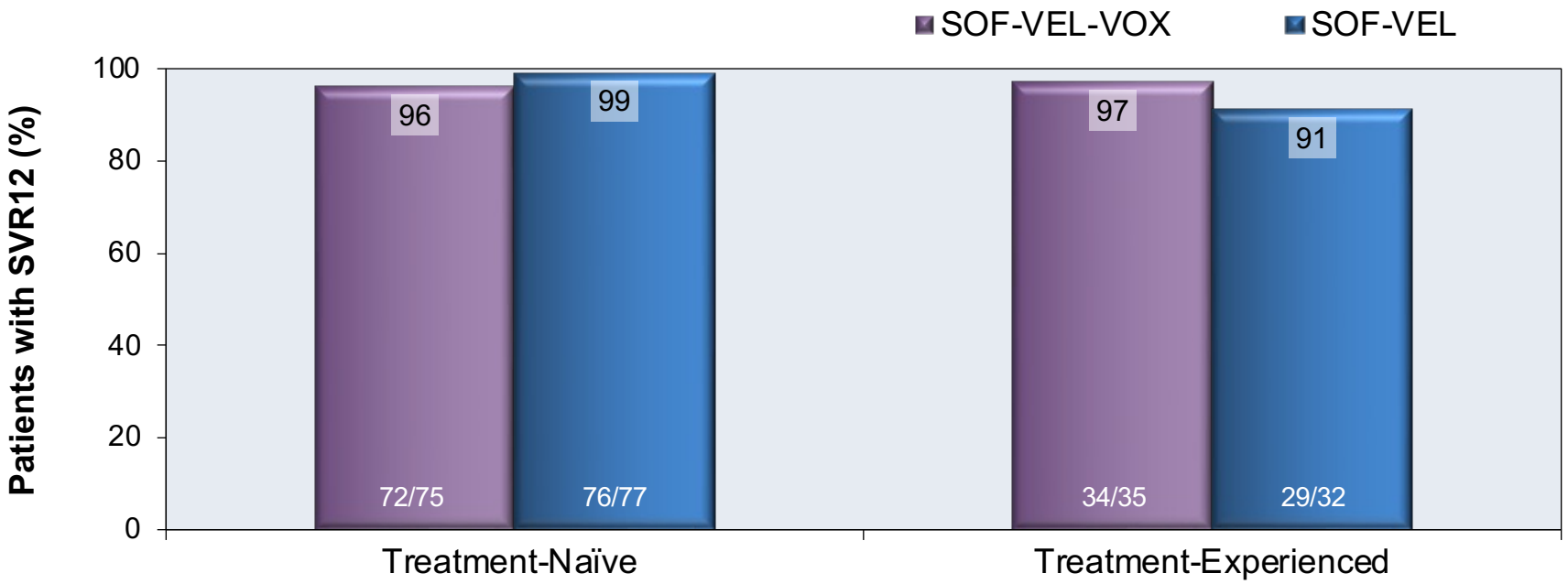
POLARIS-3: Overall SVR12 by Treatment Arm



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

Sofosbuvir-Velpatasvir-Voxilaprevir in GT 3 and Cirrhosis
POLARIS-3: Results

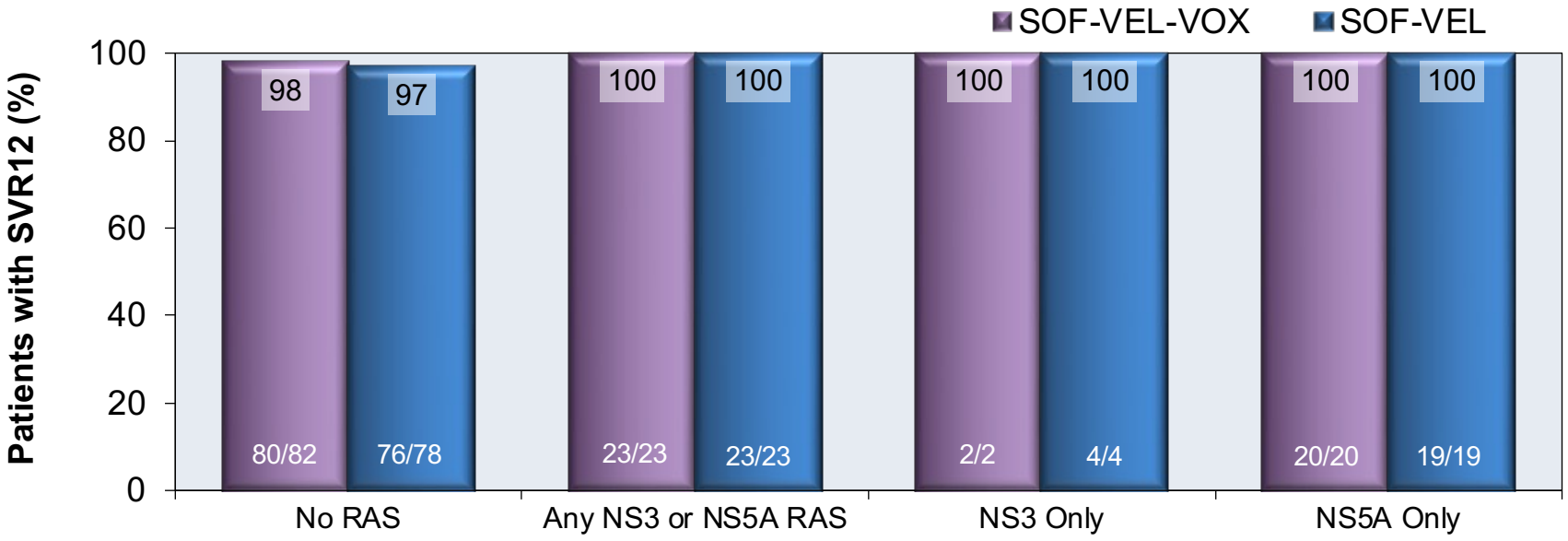
POLARIS-3: SVR12 by Treatment Experience



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

Sofosbuvir-Velpatasvir-Voxilaprevir 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.

Sofosbuvir-Velpatasvir-Voxilaprevir 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.

Sofosbuvir-Velpatasvir-Voxilaprevir 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-Voxilaprevir in DAA-Experienced GT 1-4
POLARIS-4

Note: POLARIS-4 published in tandem with POLARIS-1

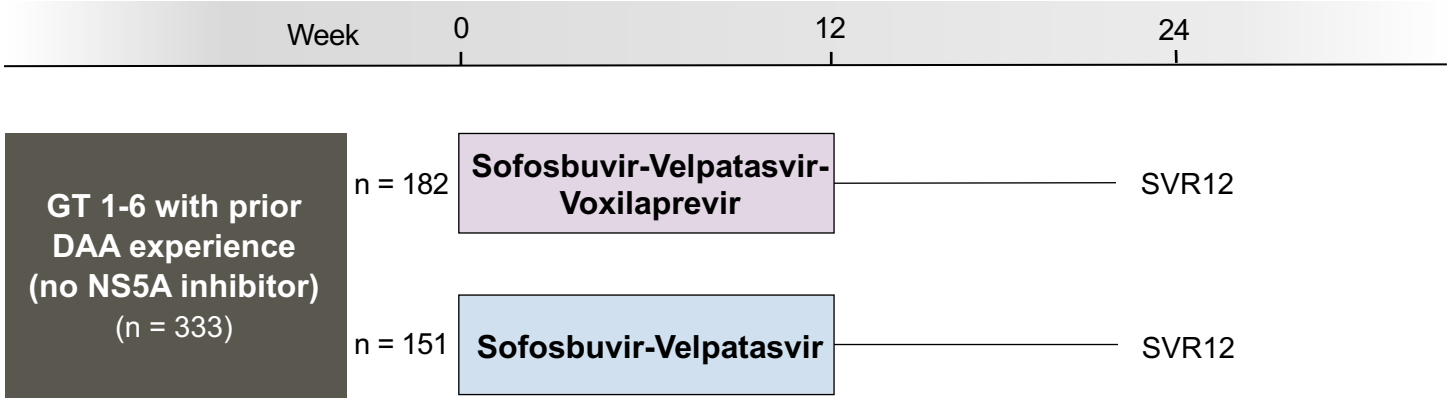
Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-4 POLARIS-4: Study Features

- **Design**: Open-label, randomized, active-comparator, phase 3 trial to compare efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir versus sofosbuvir-velpatasvir for 12 weeks in DAA-experienced patients who had not received prior NS5A inhibitor.
- **Setting**: 102 sites in United States, Canada, Europe, Australia, and New Zealand
- **Entry Criteria**
  - Age ≥18 years
  - Chronic HCV GT 1-6 (enrolled only GT 1-4)
  - HCV RNA ≥10,000 IU/mL at screening
  - DAA experienced (excluding prior NS5A use)
  - Patients with compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Study Design



GT 1, 2, 3 participants randomized 1:1. Stratified by presence of cirrhosis.
GT4 participants were assigned to active arm (and not randomized).
No GT 5, 6 participants were enrolled.

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

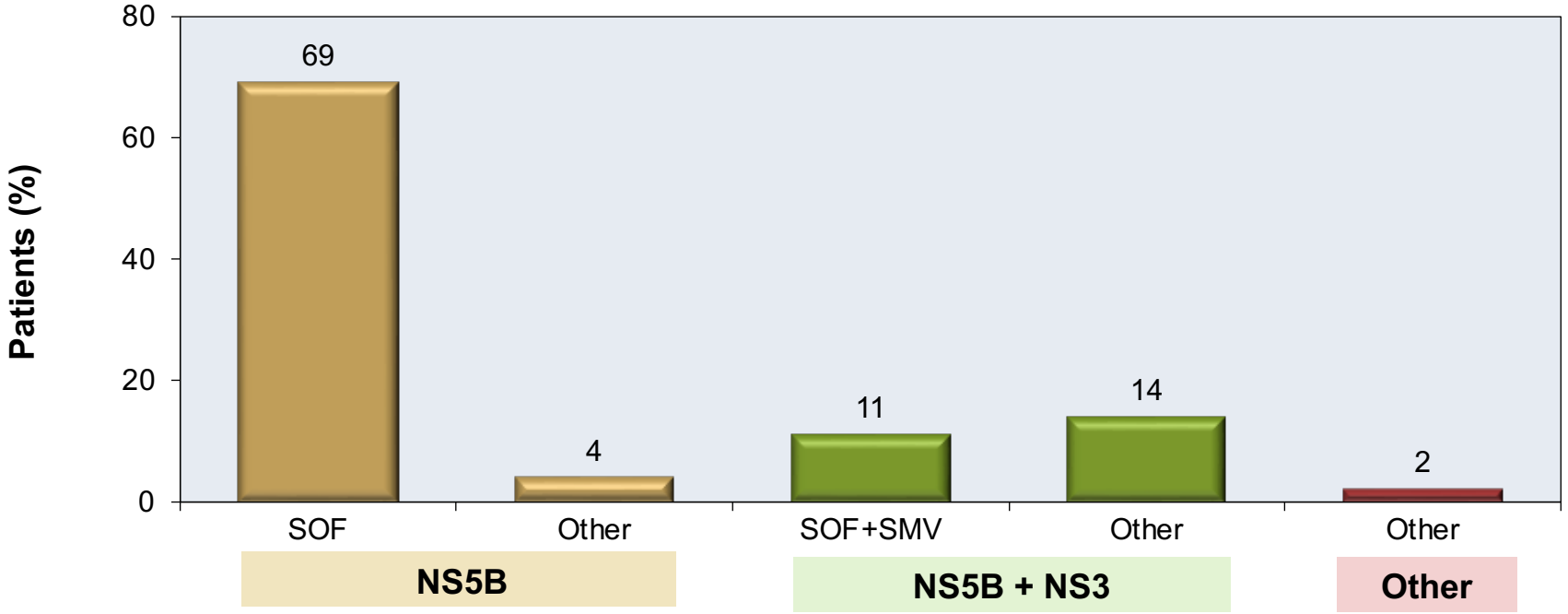
Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-3 POLARIS-4: Baseline Characteristics

Baseline Characteristics	SOF-VEL-VOX x 12 weeks (n = 182)	SOF-VEL x 12 weeks (n = 151)
Age, mean (range)	57 (25-85)	57 (24-80)
Male, n (%)	143 (79)	114 (75)
White, n (%)	160 (88)	131 (87)
Genotype, % 1 1a 1b 2 3 4	 78 (43) 54 (30) 24 (13) 31 (17) 54 (30) 19 (10)	 66 (44) 44 (29) 22 (15) 33 (22) 52 (34) 0
Body mass index, mean, kg/m^2 (range)	29 (18-45)	29 (18-53)
Mean HCV RNA, log_{10} IU/mL (range)	6.3 ± 0.6	6.3 ± 0.7
IL28B CC, n (%)	33 (18)	29 (19)
Cirrhosis, n (%)	84 (46)	69 (46)

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-3 POLARIS-4: Prior HCV Treatment

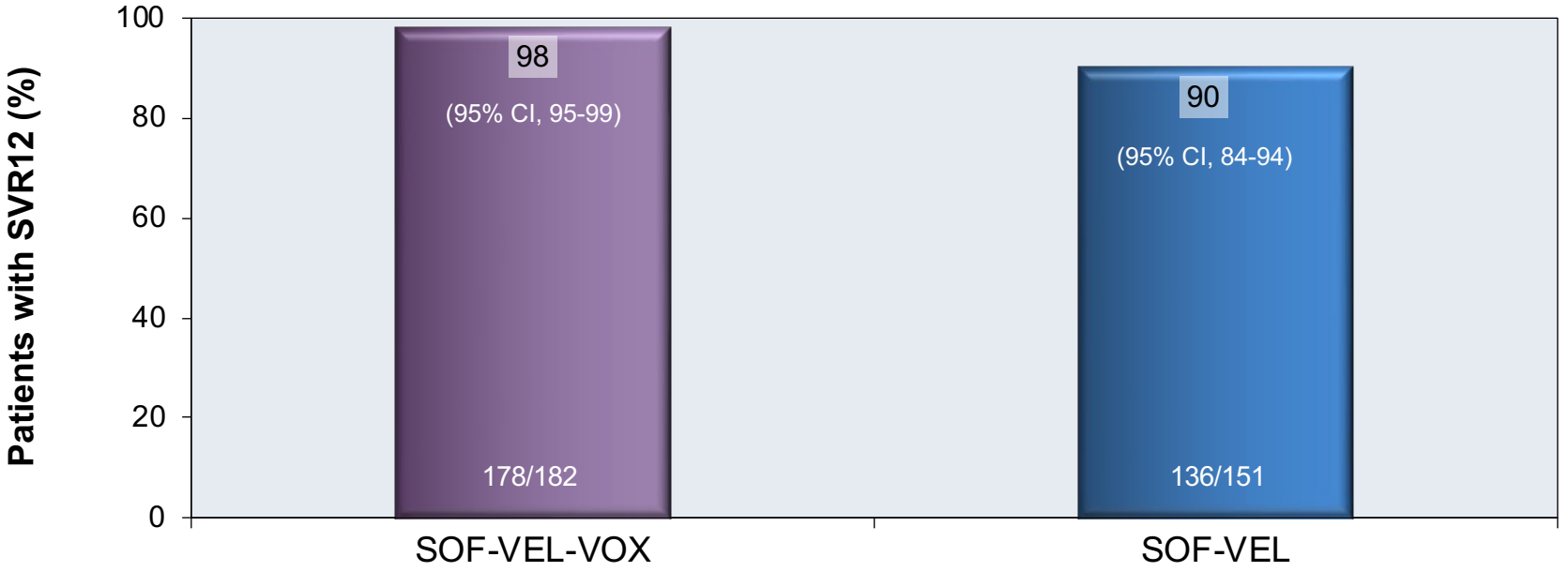


Other NS5B included mericitabine (n = 7); other NS5B plus NS3 included deleobuvir plus faldaprevir (n = 14), mericitabine plus danoprevir (n = 8), and sofosbuvir plus telaprevir (n = 6); one patient without prior DAA exposure is excluded.

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Results

POLARIS-4: Overall SVR12 by Treatment Arm

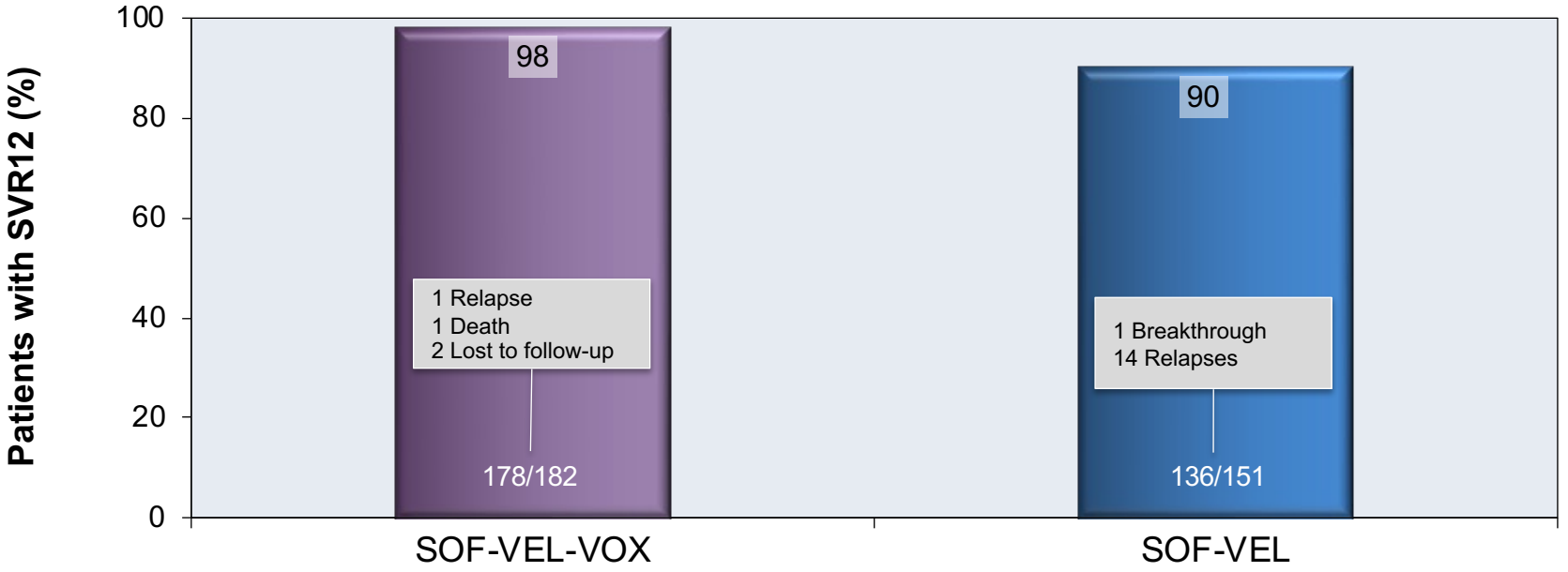


Abbreviations: SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir
P<0.001 for superiority compared with prespecified 85% performance goal for SOF-VEL-VOX

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Results

POLARIS-4: Overall SVR12 by Treatment Arm

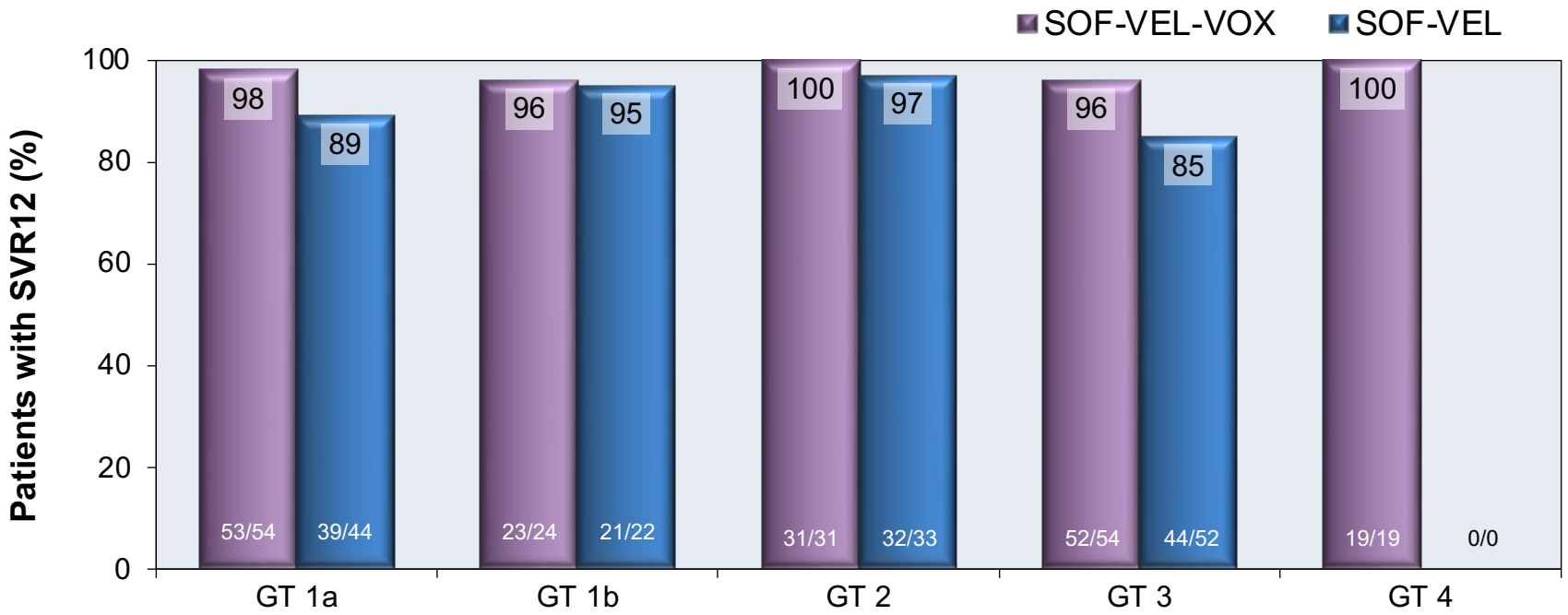


Abbreviations: SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir
P<0.001 for superiority compared with prespecified 85% performance goal for SOF-VEL-VOX

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Results

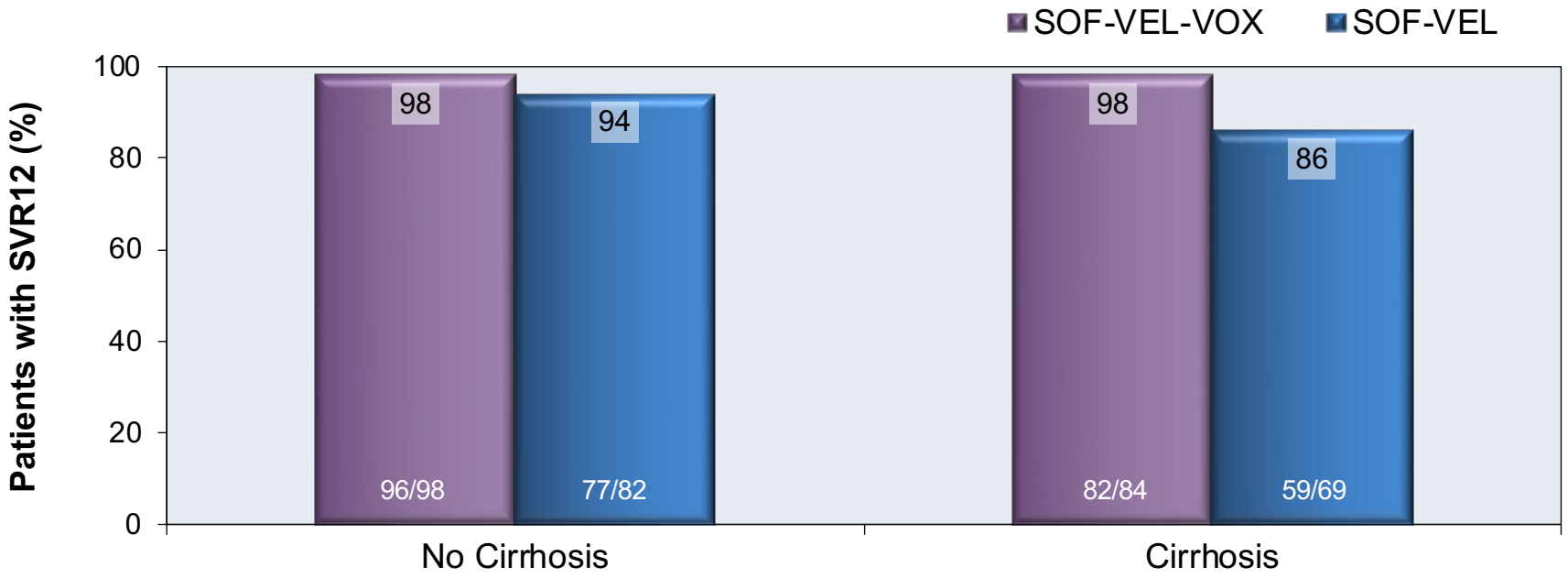
POLARIS-4: SVR12 by Genotype



Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Results

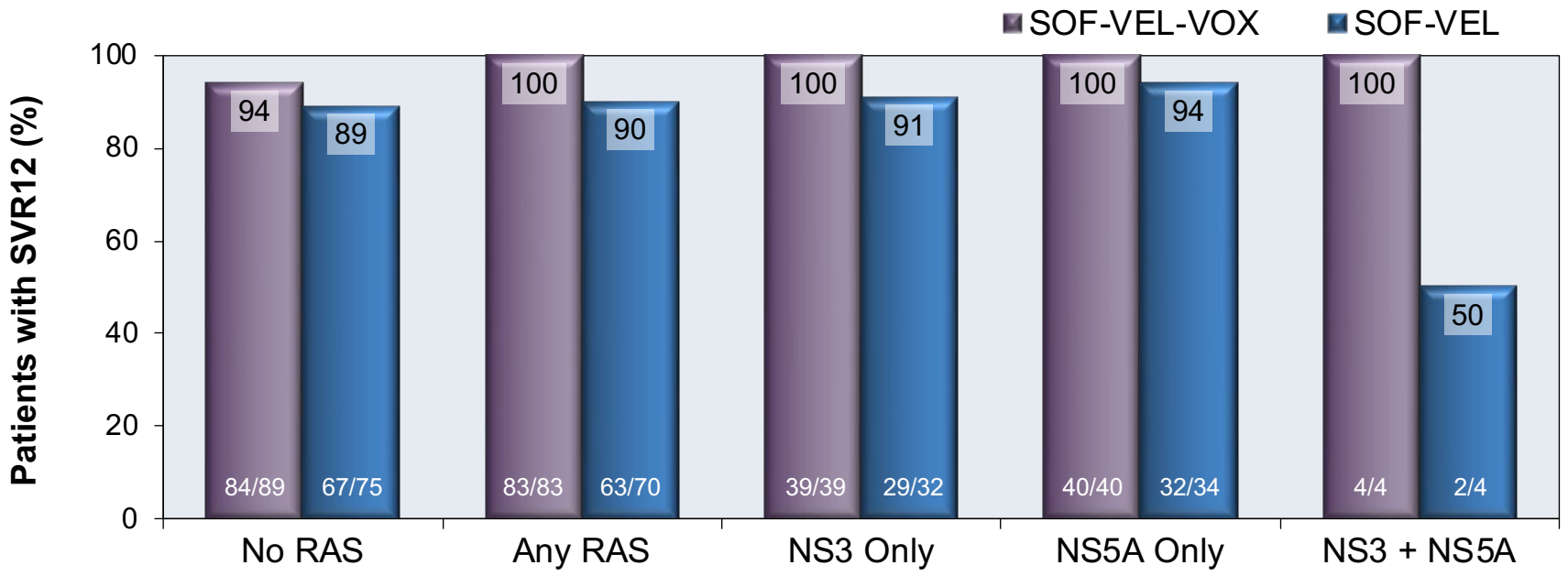
POLARIS-4: SVR12 by Cirrhosis Status



Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Results

POLARIS-4: Overall SVR by Baseline RAS



n = 22 patients had NS5B RASs – all went on to achieve SVR12.
No treatment-emergent RASs noted in the viral relapser on SOF-VEL-VOX. In SOF-VEL group, 10/15 developed Y93H or Y93C.

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-3 POLARIS-4: Adverse Events

Adverse Event (AE), n (%)	**SOF-VEL-VOX** x 12 weeks (n = 182)	**SOF-VEL** x 12 weeks (n = 151)
Discontinuation due to AE	0	1 (<1)
Serious AE	4 (2)	4 (3)
Deaths	1 (1)	0
AE in ≥5% of patients Headache Fatigue Diarrhea Nausea	 50 (27) 43 (24) 36 (20) 22 (12)	 43 (28) 43 (28) 7 (5) 12 (8)
Laboratory AEs (Grade 3-4)	11 (6)	10 (7)

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

§ One death in SOF-VEL-VOX group due to illicit drug overdose.

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-3 POLARIS-1 and POLARIS-4: Conclusions

Conclusions: “Sofosbuvir-velpatasvir-voxilaprevir taken for 12 weeks provided high rates of sustained virologic response among patients across HCV genotypes in whom treatment with a DAA regimen had previously failed.”

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1
RESOLVE

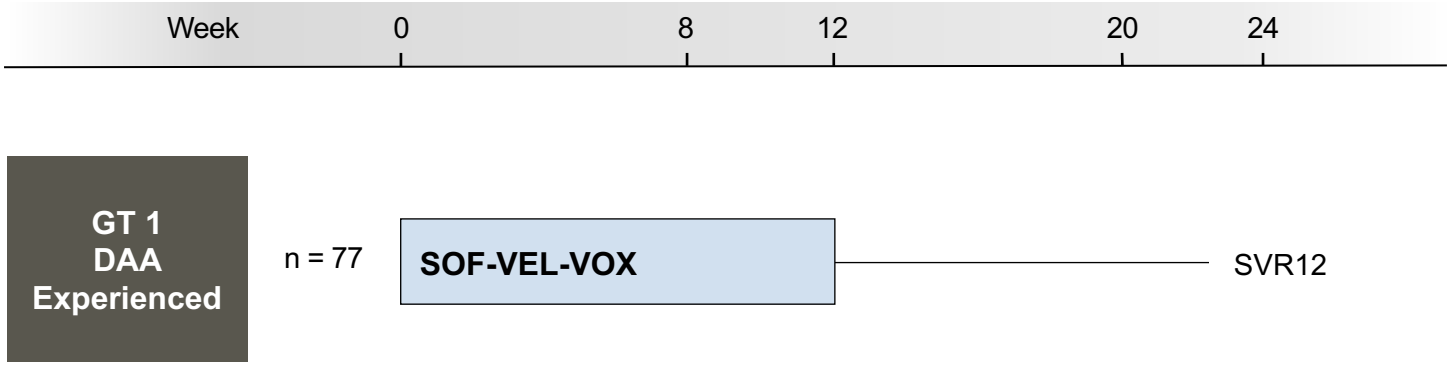
Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1 RESOLVE: Study Features

- **Design**: Open-label, phase 2b trial to evaluate the efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks in adults with chronic HCV GT 1 infection and a history of virologic rebound following DAA therapy
- **Setting**: 3 sites in United States
- **Entry Criteria**
  - Age >18 years
  - Chronic HCV genotype 1
  - HCV RNA ≥1,000 IU/mL at screening
  - Prior treatment failure with DAA treatment of 8 or more weeks duration
  - Participants with HIV and/or compensated cirrhosis allowed
- **Primary End Point**: SVR12

Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1 RESOLVE: 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

Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1
RESOLVE: Baseline Characteristics

Baseline Characteristic	**SOF-VEL-VOX** x 12 weeks (n = 77)
Age, mean (± SD)	60 (± 8)
Male, n (%)	64 (83)
Black, n (%)	66 (86)
Hispanic, n (%)	0
HCV subtype, n (%) 1a 1b	 58 (75) 19 (25)
Fibrosis stage, n (%) F0-F2 F3 F4	 28 (36) 18 (23) 31 (40)
Coinfections, n (%) HIV HIV/HBV	 17 (22) 2 (3)
History of injection drug use	39 (51)

Abbreviations: SD, standard deviation, HBV, chronic hepatitis B

Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

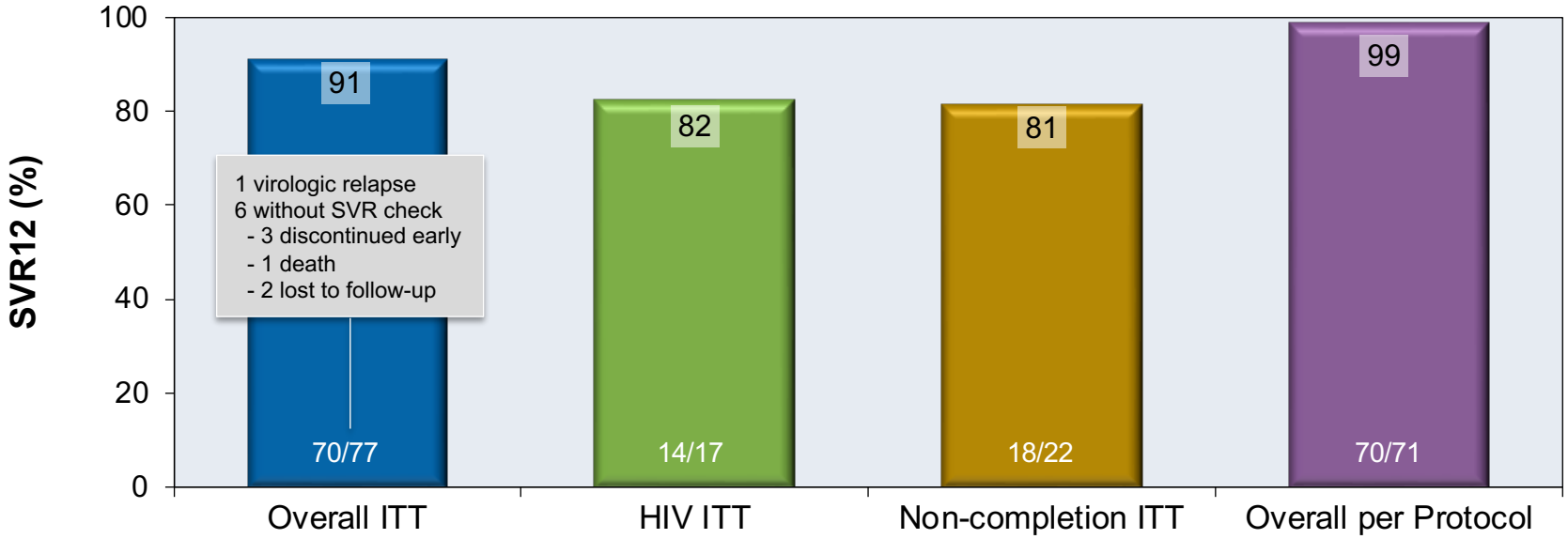
Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1 RESOLVE: Baseline Characteristics

Baseline Characteristic	**SOF-VEL-VOX** x 12 weeks (n = 77)
Previous DAA regimen*, n (%)	
Ledipasvir-Sofosbuvir	69 (89)
Paritaprevir-Ombitasvir-ritonavir-Dasabuvir	3 (4)
Daclatasvir-Asunaprevir	3 (4)
Elbasvir-Grazoprevir	2 (3)
Simeprevir + Sofosbuvir	2 (3)
Daclatasvir + Sofosbuvir	1 (1)
Sofosbuvir-Velpatasvir	1 (1)
Prior interferon therapy, n (%)	13 (17)
Previous non-completion, n (%)	22 (29)
Poor adherence	14 (18)
Interruption	4 (5)
Lost or stolen medication	2 (3)
Adverse event	1 (1)

*Total number of regimens exceeds that of individual participants because some underwent >1 prior DAA regimens

Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1 RESOLVE: Results



Abbreviations: ITT, intent-to-treat analysis.

Non-completion = Among those who had a history of prior non-completion. Per protocol, counting only those who completed 12 weeks of therapy

Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1 RESOLVE: Conclusions

Conclusion: “In Retreatment with 12 weeks of sofosbuvir-velpatasvir-voxilaprevir was safe and effective in patients with relapsed HCV following initial combination DAA-based treatment. Treatment response was not affected by HIV coinfection or previous treatment course.”

Source: Wilson E, et al. J Hepatol. 2019;71:498-504.

Sofosbuvir-Velpatasvir-Voxilaprevir in G/P Failure

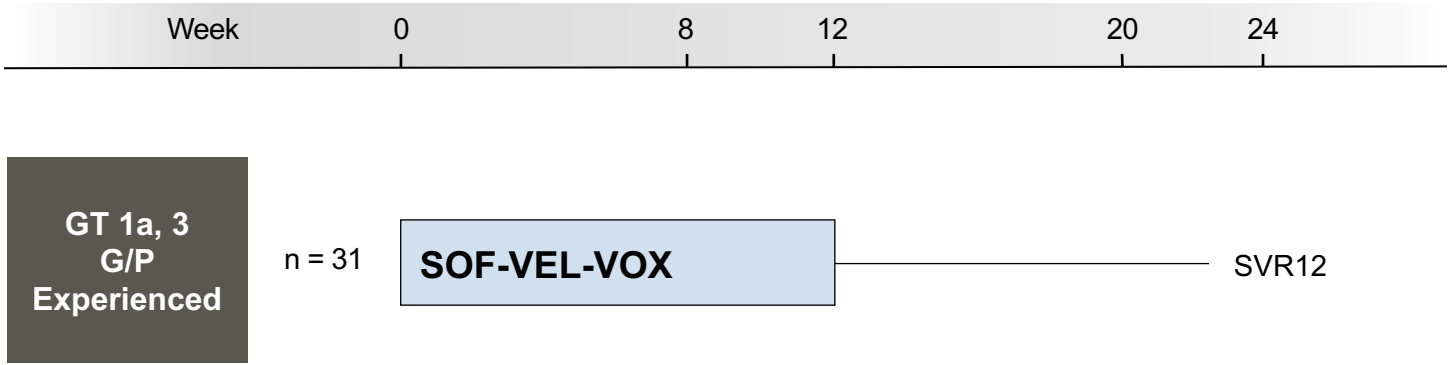
Source: Pearlman B, et al. Am J Gastroenterol. 2019;114:1550-2.

Sofosbuvir-Velpatasvir-Voxilaprevir in G/P-experienced GT 1a and 3 Study Features

- **Design**: Open-label, single-arm, prospective study to evaluate the efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks in adults with chronic HCV infection and a history of treatment failure with glecaprevir-pibrentasvir
- **Setting**: 3 medical centers in United States
- **Entry Criteria**
  - Age >18 years
  - Chronic HCV infection
  - Documented virologic failure following glecaprevir-pibrentasvir
  - Chart confirmed to have good adherence to above
- **Primary End Point**: SVR12

Source: Pearlman B, et al. Am J Gastroenterol. 2019;114:1550-52.

Sofosbuvir-Velpatasvir-Voxilaprevir in G/P-experienced GT 1a and 3 Study Design



Abbreviations: G/P, glecaprevir-pibrentasvir; SOF, sofosbuvir; VEL, velpatasvir; VOX = voxilaprevir

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

Source: Pearlman B, et al. Am J Gastroenterol. 2019;114:1550-2.

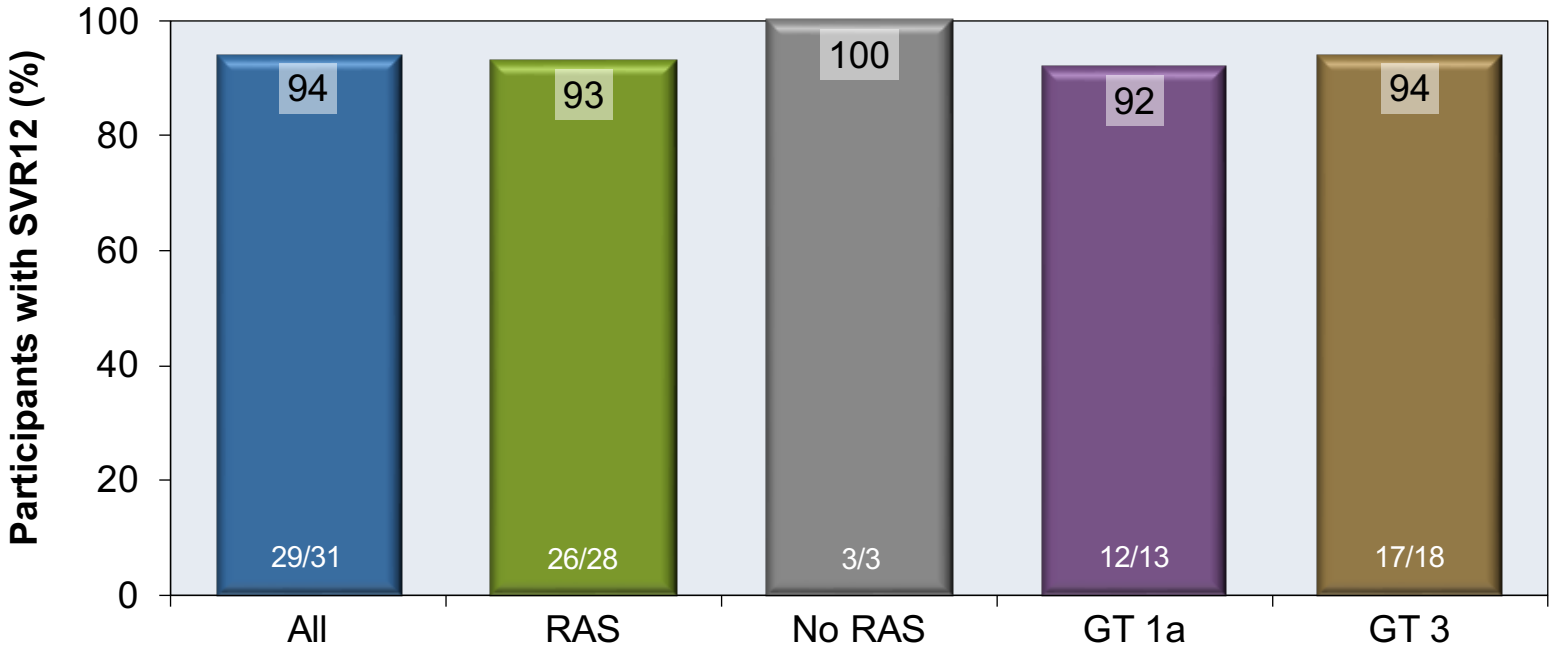
Sofosbuvir-Velpatasvir-Voxilaprevir in in G/P-experienced GT 1a and 3 Baseline Characteristics

Baseline Characteristic	SOF-VEL-VOX x 12 weeks (n = 31)
Male, n (%)	22 (77)
No prior treatment before G/P, n (%)	28 (90)
Black, n (%)	16 (52)
Cirrhosis, n (%)	18 (58)
Genotype 1a, n (%) Cirrhosis Prior relapse	13 (42) 6/13 13/13
Genotype 3a, n (%) Cirrhosis Prior relapse Prior breakthrough	18 (58) 12/18 15/18 3/18
Baseline RAS, n (%) None NS5a only NS3 only NS5a and NS3	28 (90) 3 (10) 14 (50) 3 (10) 11 (40)

Abbreviations: G/P, glecaprevir-pibrentasvir; RAS, resistance-associated substitution; NS, non-structural

Source: Pearlman B, et al. Am J Gastroenterol. 2019;114:1550-2.

Sofosbuvir-Velpatasvir-Voxilaprevir in in G/P-experienced GT 1a and 3 Results



Abbreviations: RAS, baseline resistance-associated substitution; GT, genotype

Source: Pearlman B, et al. Am J Gastroenterol. 2019;114:1550-2.

Sofosbuvir-Velpatasvir-Voxilaprevir in in G/P-experienced GT 1a and 3 Conclusions

Conclusion: “In conclusion, SOF/VEL/VOX once daily for 12 weeks is safe and effective for GT 1- and 3-chronically infected HCV patients who have failed G/P therapy.”

Source: Pearlman B, et al. Am J Gastroenterol. 2019;114:1550-2.

Acknowledgments

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HEPATITIS B ONLINE

HEPATITIS C ONLINE

IDEA INFECTIOUS DISEASES EDUCATION & ASSESSMENT