Fármacos en desarrollo para el VHC.

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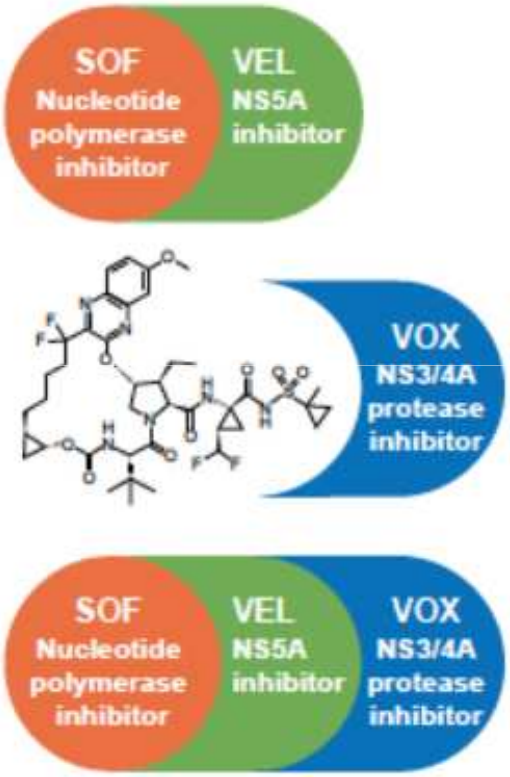
SOF/VEL/VOX



Sofosbuvir (SOF)/Velpatasvir (VEL)

- **SOF**: Nucleoside polymerase inhibitor with activity against HCV GT 1–6
- **VEL**: Potent pangenotypic NS5A inhibitor

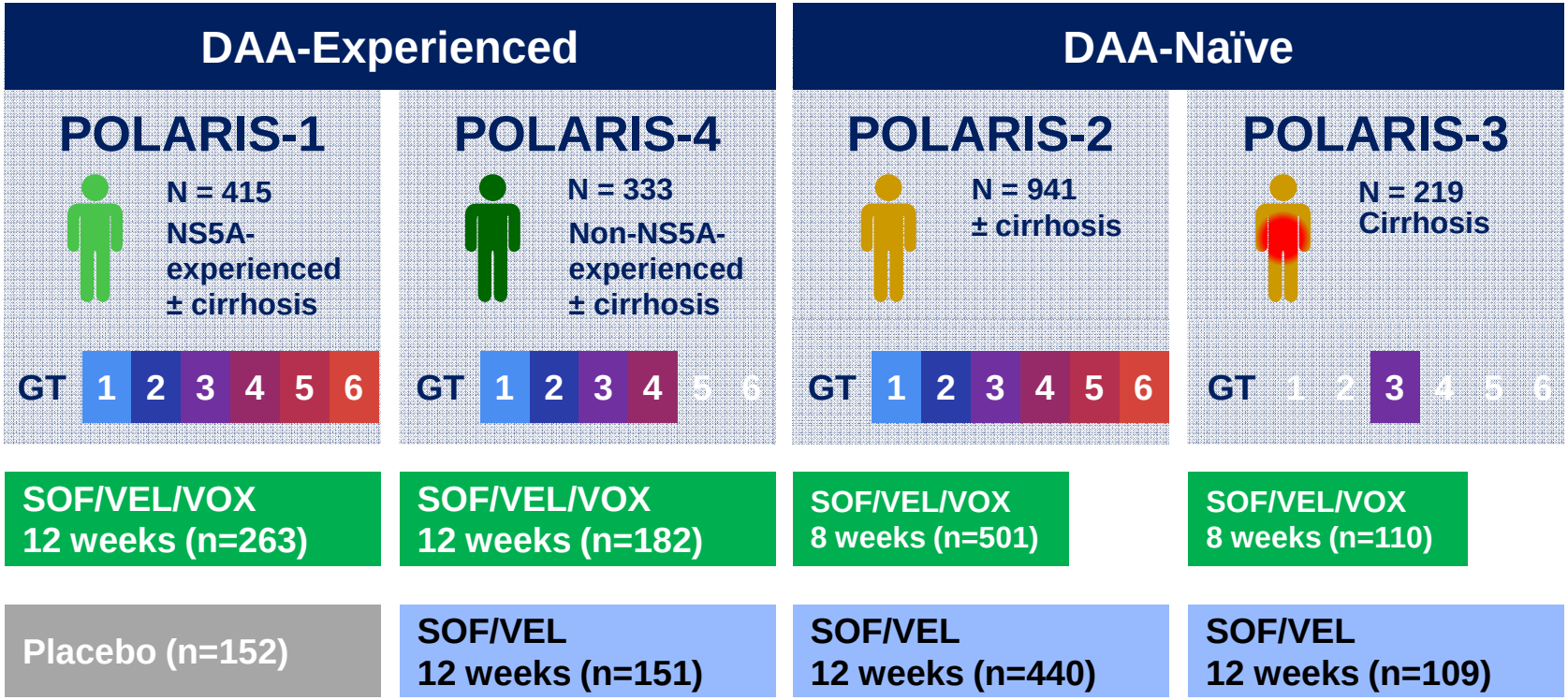
Voxilaprevir (VOX)

- HCV NS3/4A PI with potent antiviral activity against GT 1–6, including most RASs

SOF/VEL/VOX

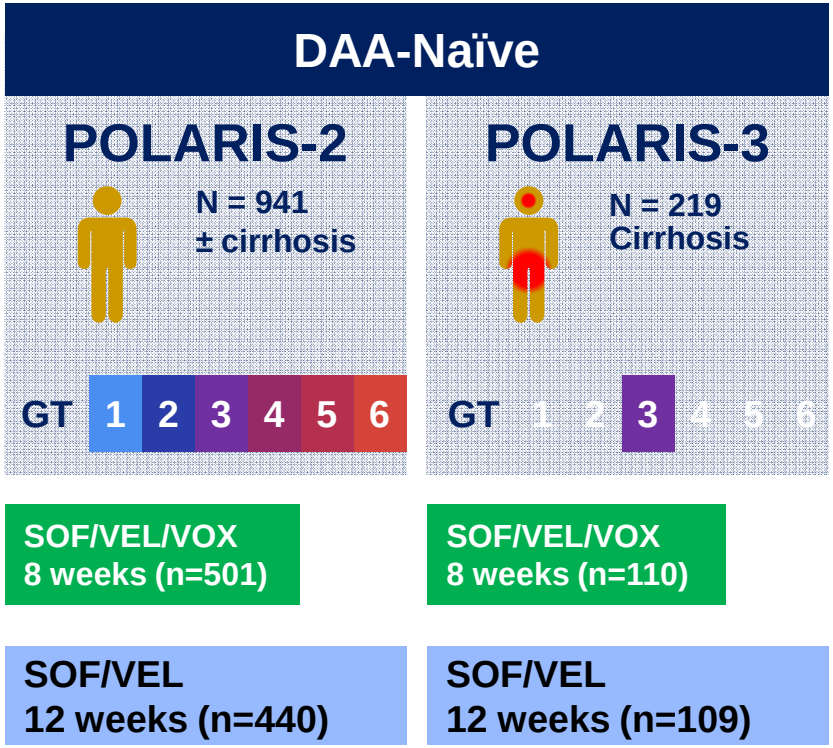
- Once daily, oral, fixed-dose combination (400/100/100 mg) for GT 1–6

POLARIS Phase 3 Program



Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

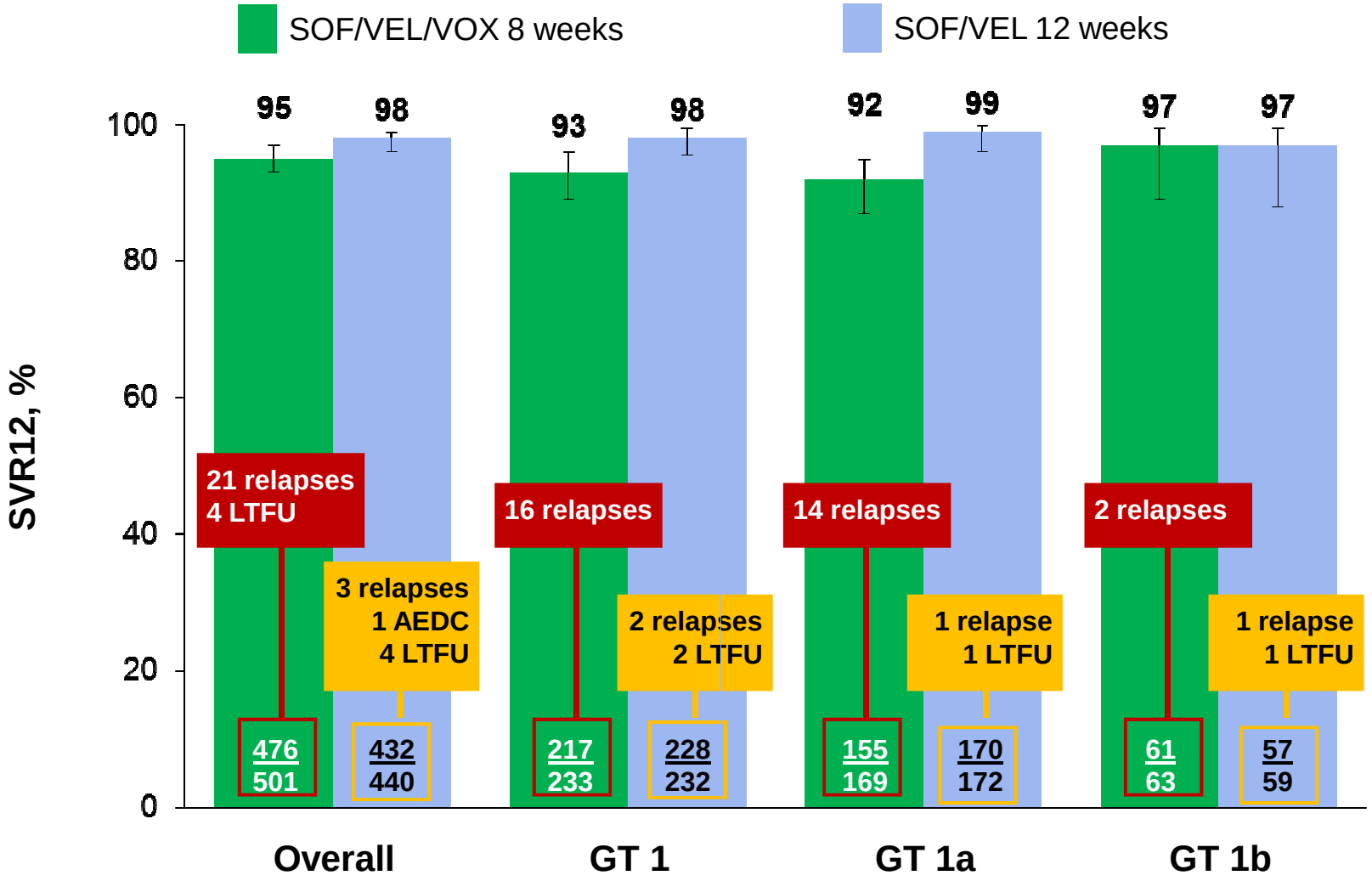
POLARIS Phase 3 Program



Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

POLARIS-2: SOF/VEL/VOX for 8 Weeks or SOF/VEL for 12 Weeks in DAA-Naïve HCV GT 1–6 (Except GT 3 Cirrhotics)

SVR12 by Genotype (GT 1)

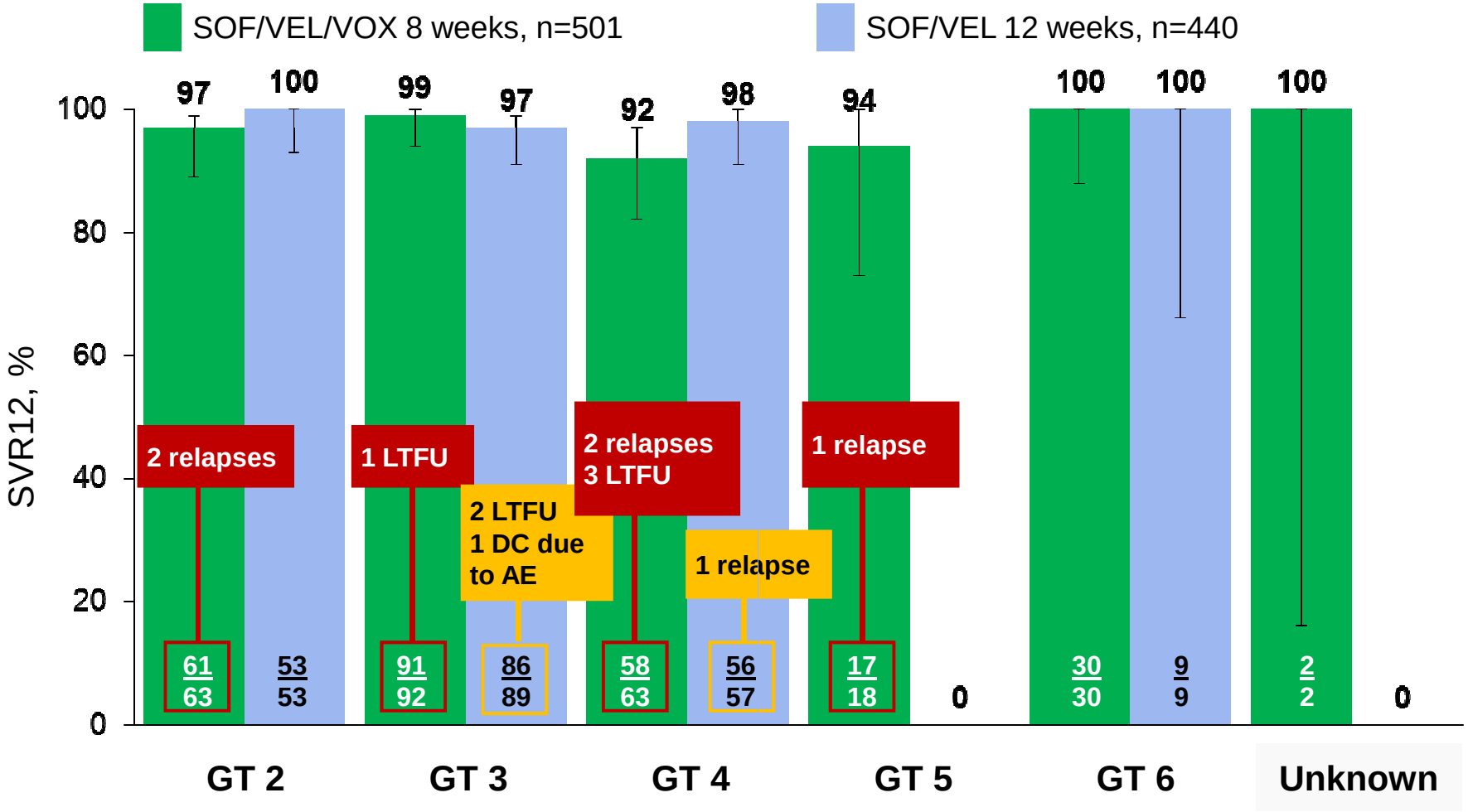


2 of 2 patients (100%) with GT 1 Other achieved SVR12 (1 each in SOV/VEL/VOX and SOF/VEL arm). AEDC, Discontinuation due to AE.

Jacobson IM, AASLD 2016, Oral LB-12

POLARIS-2: SOF/VEL/VOX for 8 Weeks or SOF/VEL for 12 Weeks in DAA-Naïve HCV GT 1–6 (Except GT 3 Cirrhotics)

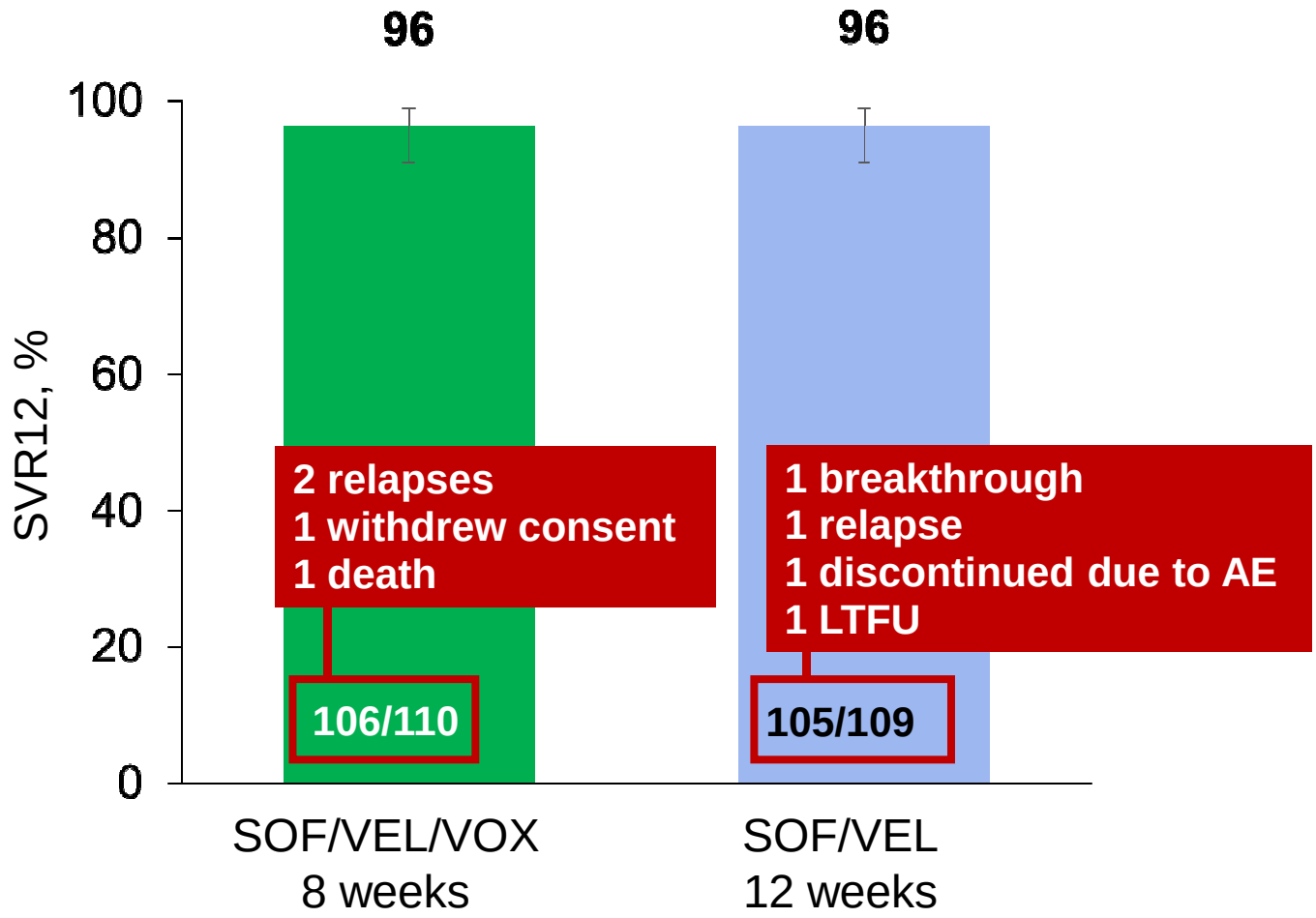
SVR12 by Genotype (GT 2-6)



Jacobson IM, AASLD 2016, Oral LB-12

POLARIS-3: SOF/VEL/VOX for 8 Weeks or SOF/VEL for 12 Weeks in DAA-Naïve HCV GT 3 Cirrhotics

Overall SVR12

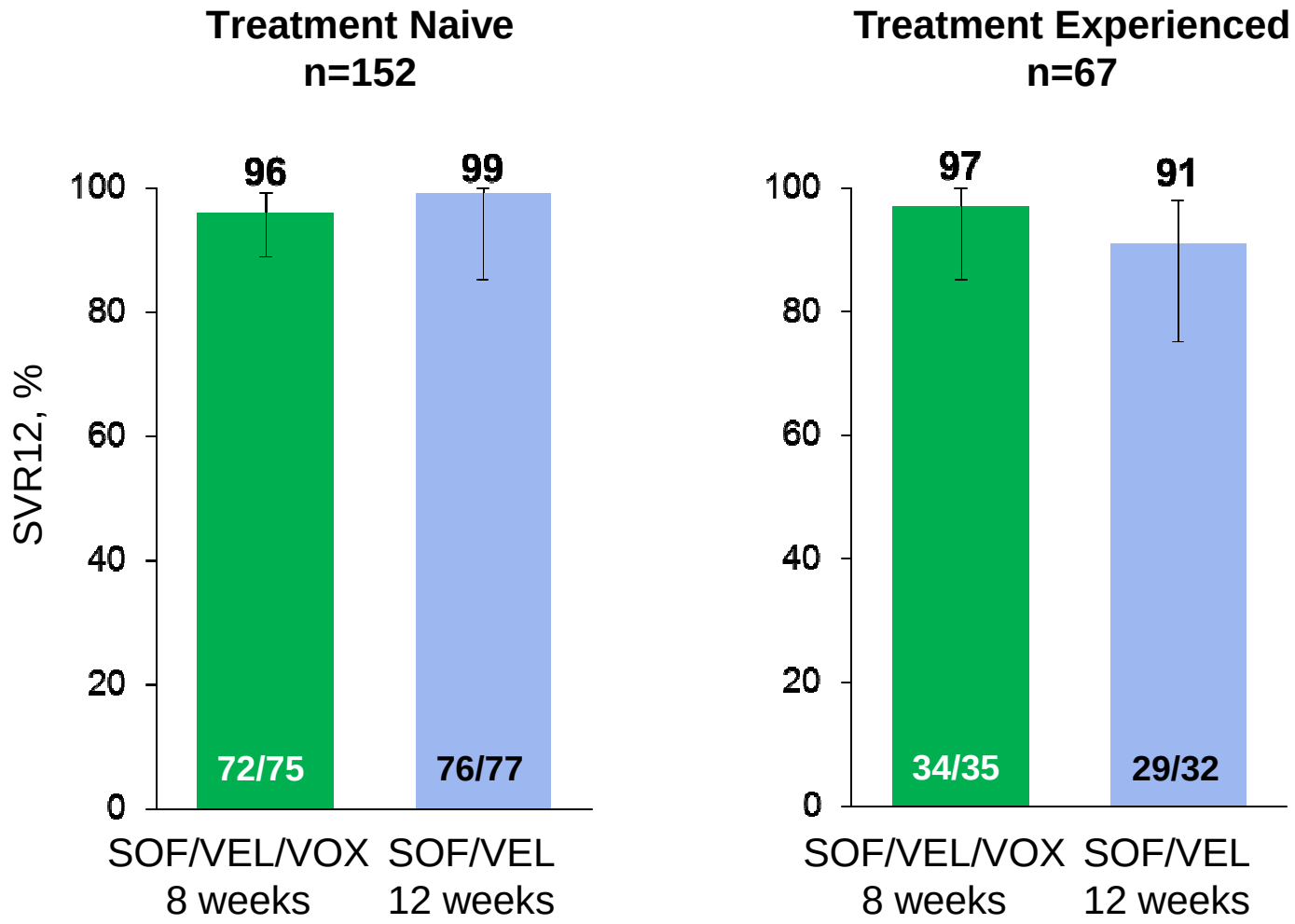


p <0.001 for superiority compared with prespecified 83% performance goal

Foster GR, AASLD 2016, Oral 258

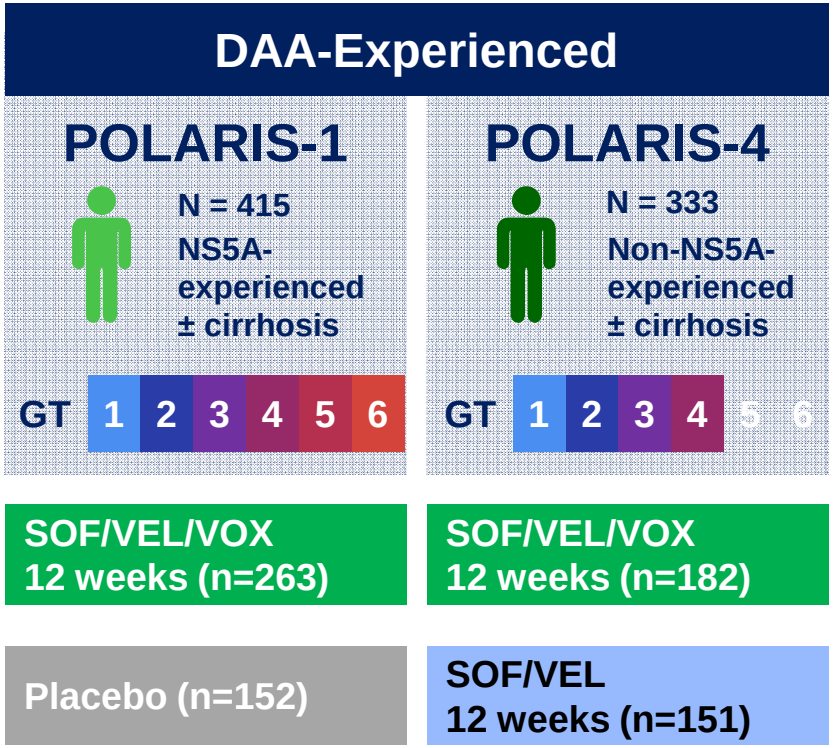
POLARIS-3: SOF/VEL/VOX for 8 Weeks or SOF/VEL for 12 Weeks in DAA-Naïve HCV GT 3 Cirrhotics

SVR12 by Prior Treatment Experience



Foster GR, AASLD 2016, Oral 258

POLARIS Phase 3 Program

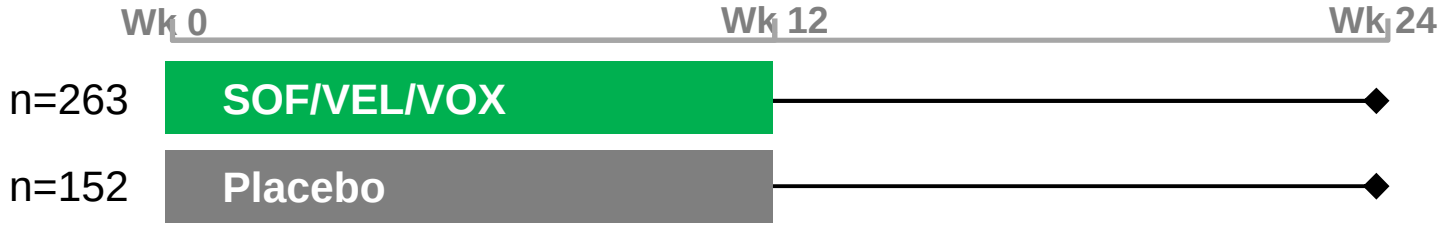


Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

POLARIS-1

SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

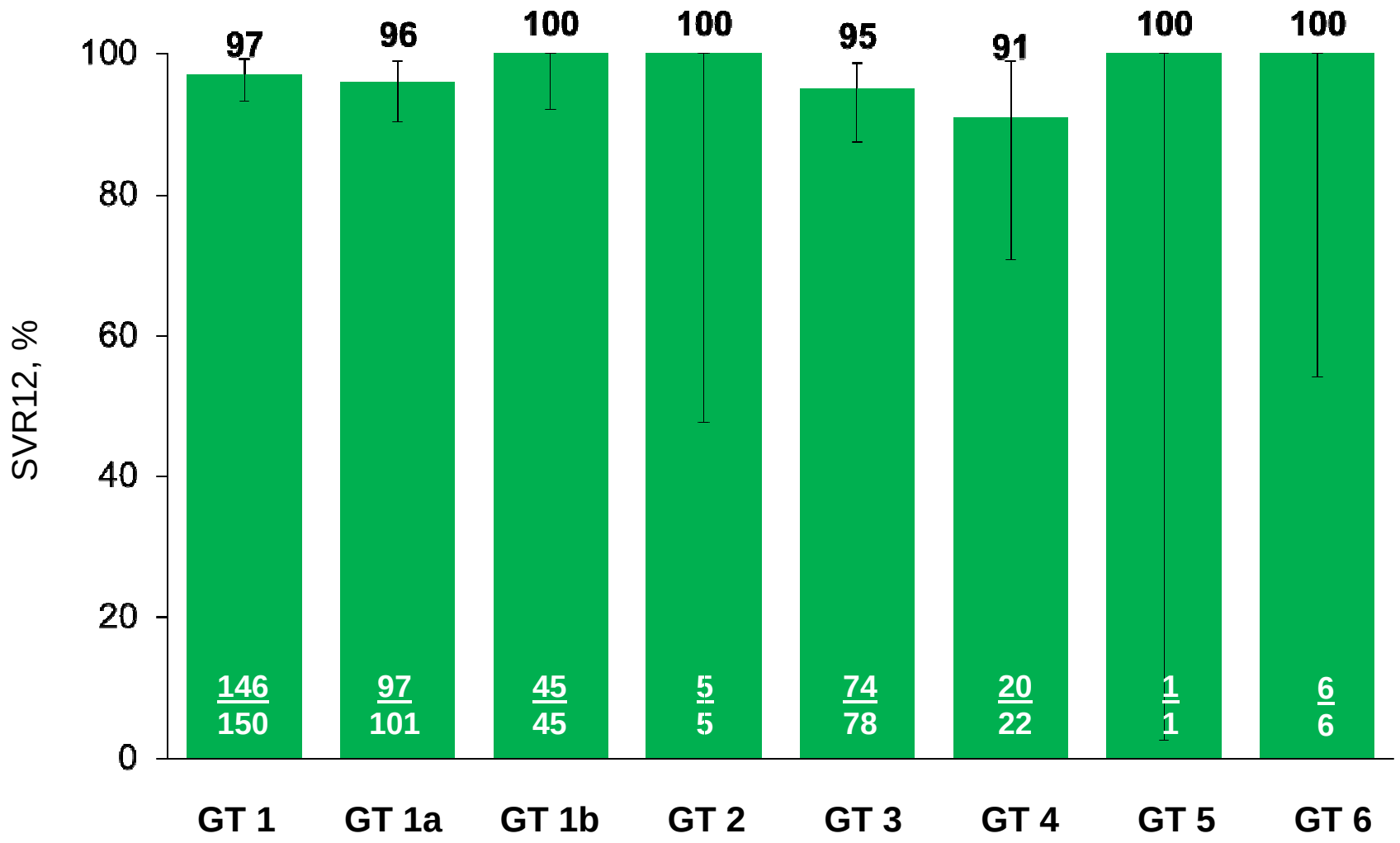
Phase 3, multicenter, randomized, double-blind, placebo-controlled in failures to LDV (51%), DCV (27%) and OMV (11%)



		SOF/VEL/VOX 12 weeks n=263	Placebo 12 weeks n=152
Mean age, years (range)		58 (27–84)	59 (29–80)
Male, n (%)		200 (76)	121 (80)
White, n (%)		211 (80)	124 (82)
Mean BMI, kg/m^2 (range)		29 (18–67)	29 (18–61)
Cirrhosis, n (%)		121 (46)	51 (34)
Genotype, n (%)	1a / 1b / Other	101 (38) / 45 (17) / 4 (2)	117 (77) / 31 (20) / 2 (1)
	2	5 (2)	—
	3	78 (30)	—
	4	22 (8)	—
	5 / 6 / Unknown	1 (<1) / 6 (2) / 1 (<1)	0 / 2 (1) /0
Mean HCV RNA, $\log_{10}$ IU/mL (range)		6.3 (1.6–7.7)	6.3 (3.7–7.6)

Bourliere M, AASLD 2016, Oral 194

SVR12 Results by Genotype



Bourliere M, AASLD 2016, Oral 194

Glecaprevir/Pribentasvir

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

Collectively: G/P

In vitro:[2,3]

- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31, and 93)
- Additive/synergistic antiviral activity

Clinical PK & metabolism:

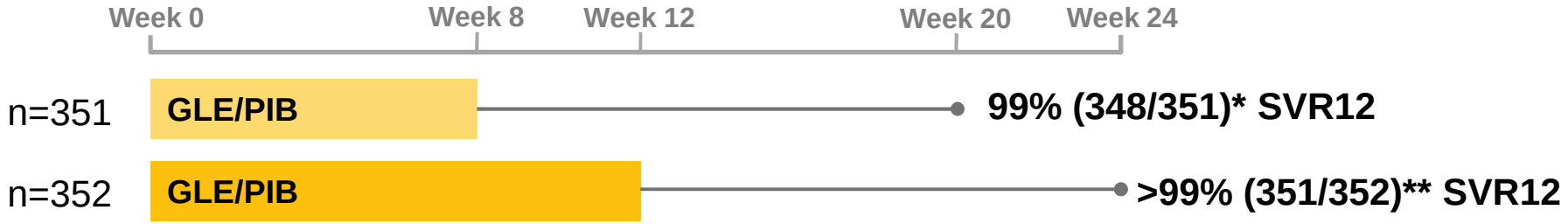
- Oral dosing of 3 pills once-daily
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

ENDURANCE-1

Glecaprevir/Pibrentasvir for 8 or 12 Weeks in TN and TE HCV GT 1 Patients without Cirrhosis, Including HIV-1 Coinfection

Phase 3, randomized, open-label, multicenter study



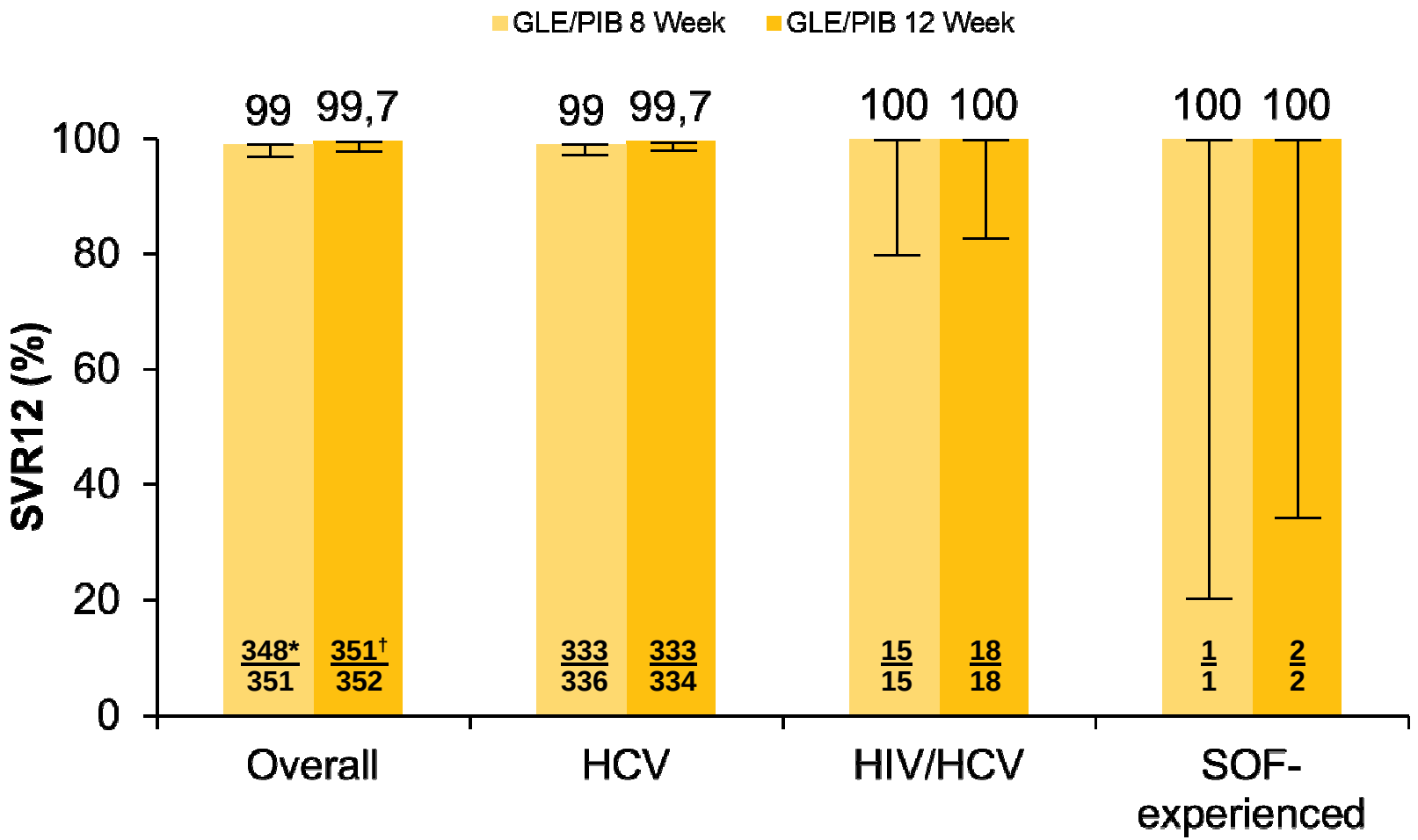
Baseline Demographics

Patients	GLE/PIB 8 weeks n=351	GLE/PIB 12 weeks n=352
Age, median (range), years	53 (19-84)	52 (21-77)
Male, n (%)	167 (48)	176 (50)
White, n (%)	289 (82)	302 (86)
HCV RNA, median (range), log_{10} IU/mL	6.11 (1.18-7.64)	6.14 (3.25-7.39)
HCV GT 1a, n (%)	152 (43)	148 (42)
Treatment experienced, n (%) SOF-based, n (%)	132 (38) 1 (0.8)	135 (38) 2 (1)
F0-F1, n (%)	297 (85)	298 (85)
F2	22 (6)	24 (7)
F3	30 (9)	29 (8)

*One patient experienced on-treatment virologic failure, 1 patient on Day 2 due to non-compliance, 1 patient missing SVR12 data; ** One patient missing SVR12 data
Treatment experienced=prior IFN or PegIFN±RBV, or SOF+RBV±PegIFN
Glecaprevir (GLE, formerly ABT-493; NS3/4A inhibitor); pibrentasvir (PIB, formerly ABT-530; NS5A inhibitor). Dosed as 3 tablets for a total of 300mg/120 mg
Zeuzem S, AASLD 2016, Oral 253

ENDURANCE-1: Glecaprevir/Pibrentasvir for 8 or 12 Weeks in TN and TE HCV GT 1 Patients without Cirrhosis, Including HIV-1 Coinfection

Secondary Efficacy Endpoints: ITT Population



*One patient experienced on-treatment virologic failure, one patient discontinued on Day 2 due to non-compliance, one patient missing SVR12 data
†One patient missing SVR12 data

ENDURANCE-1: Glecaprevir/Pibrentasvir for 8 or 12 Weeks in TN and TE HCV GT 1 Patients without Cirrhosis, Including HIV-1 Coinfection

Safety Summary

Event, n (%)	GLE/PIB 8 Weeks n=351	GLE/PIB 12 Weeks n=352
Any AE	216 (62)	234 (66)
AEs leading to study drug discontinuation	0	1 (0.3)*
Serious AEs†	5 (1)	4 (1)
Death	0	1 (0.3)‡
AEs occurring in ≥10%		
Headache	68 (19)	62 (18)
Fatigue	31 (9)	43 (12)
AST		
Grade ≥3 (>5 x ULN)	0	1 (0.3)
Grade 4	0	0
ALT		
Grade ≥3 (>5 x ULN)	0	0
Grade 4	0	0
Total Bilirubin Grade 3 (3-10 x ULN)**	2 (0.6)	1 (0.3)

- No serious AEs were deemed to be DAA-related; no SAEs led to discontinuation of GLE/PIB
- No patients prematurely discontinued treatment due to laboratory abnormalities
- Safety was similar in HCV GT1 mono-infected and HIV-1/HCV GT1 co-infected patients
- All co-infected patients maintained HIV-1 RNA suppression during the treatment period

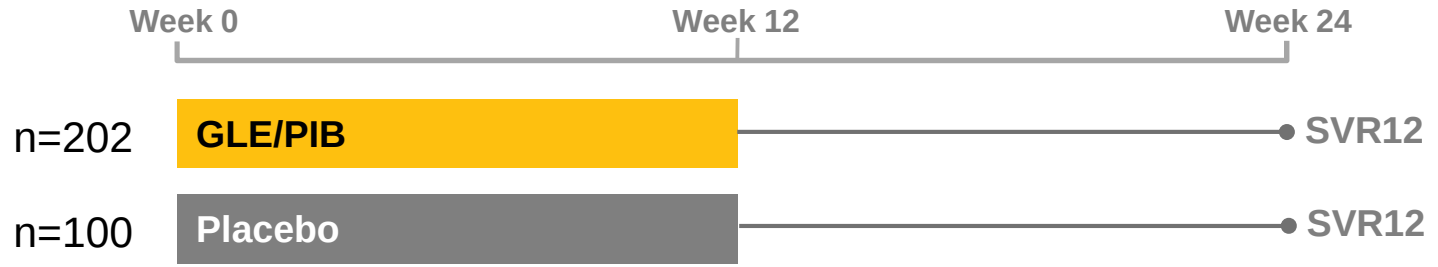
*One patient experienced dandruff, anxiety and amnesia, all deemed as having no reasonable possibility of being related to DAAs; †On treatment: pneumonia aspiration, atrial fibrillation, angina unstable, radius fracture, transient ischemic attack, irritable bowel syndrome. Post-treatment: bronchitis uterine myoma, suicide attempt; ‡Female patient died during post-treatment period due to an unknown cause considered unrelated to study drug (autopsy results pending)
**All 3 patients had bilirubin elevations at baseline; all elevations primarily indirect; no associated post-nadir ALT elevations by grade

uzem S, AASLD 2016, Oral 253

ENDURANCE-2

Glecaprevir/Pibrentasvir for 12 Weeks in TN and TE HCV GT 2 Patients without Cirrhosis

Phase 3, randomized, double-blind, placebo-controlled multicenter study

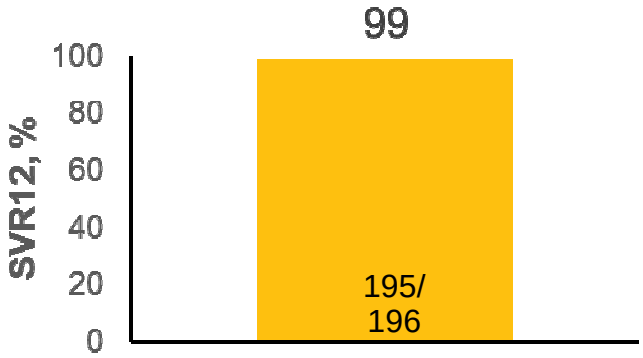


Baseline Demographics

Patients	GLE/PIB n=202	Placebo n=100
HCV RNA, median (range), log_{10} IU/mL	6.25 (2.5–7.3)	6.39 (3.4–7.2)
Treatment experienced*, n (%) SOF-based, n/N (%)	61 (30) 6 (10)	29 (29) 2 (7)
F0-F1, n (%)	154 (76)	85 (85)
F2, n (%)	18 (9)	9 (9)
F3, n (%)	30 (15)	6 (6)

*Treatment experienced=prior pegIFN+RBV or SOF+RBV
Glecaprevir (GLE, formerly ABT-493; NS3/4A inhibitor); pibrentasvir (PIB, formerly ABT-530; NS5A inhibitor).
Dosed as 3 tablets for a total of 300mg/120 mg
Kowdley K, AASLD 2016, Oral 73

Results



- AEs: 65% of GLE/PIB, 58% placebo
- AEs ≥10%
  - Headache (12% in both arms), fatigue (11% in drug arm and 10% in placebo arm)
- No D/C due to AEs
- 3 SAEs (1%); each unrelated to GLE/PIB

SURVEYOR-II, Part 4

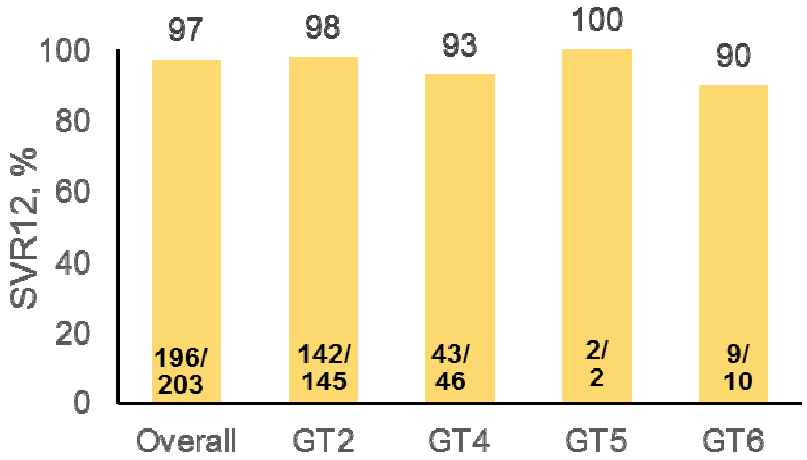
Glecaprevir/Pibrentasvir for 8 Weeks in TN or TE HCV GT 2, 4, 5, or 6 Patients without Cirrhosis

Phase 2, open-label, single-arm, multicenter study

Baseline Demographics

Patients	GLE/PIB 8 weeks N=203
Male, n (%)	98 (48)
White, n (%)	155 (76)
Age, median (range), yrs	55 (19–83)
GT 2/4/5/6, %	71 / 23 / 1 / 5
TN, n (%)	176 (87)
SOF TE, n (%)	6 (3)
HCV RNA (range), log_{10} IU/mL	6.45 (0.75–7.62)
F0–1, n (%)	170 (84)
F2, n (%)	12 (6)
F3, n (%)	21 (10)

SVR12 Results



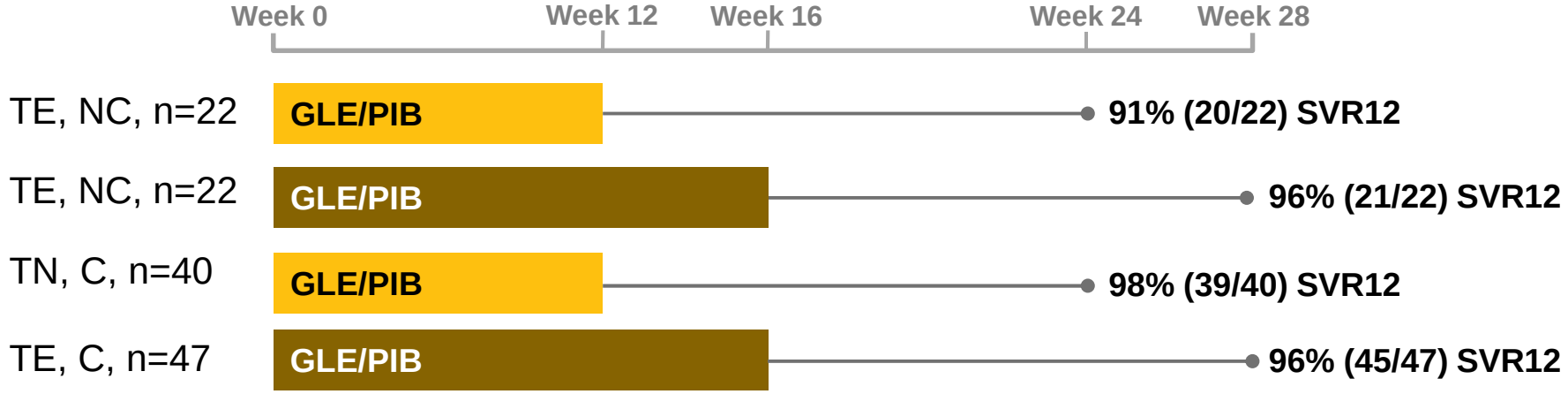
- 2 virologic failures: both GT2, TE patients, one F0-F1, one F3
- Most common AEs: fatigue (18%), headache (14%) and nausea (11%)
- No D/C due to AEs, 2 SAEs

Treatment experienced=prior pegIFN+RBV or SOF+RBV
Glecaprevir (GLE, formerly ABT-493; NS3/4A inhibitor); pibrentasvir (PIB, formerly ABT-530; NS5A inhibitor). Dosed as 3 tablets for a total of 300mg/120 mg
Hassanein TI, AASLD 2016, Poster LB-15

SURVEYOR-II, Part 3

Glecaprevir/Pibrentasvir in TN and TE HCV GT 3 Patients ± Cirrhosis

Phase 2/3, partially randomized, open-label, multicenter, adaptive study



	1:1 Randomized			
	TE w/o cirrhosis 12 Weeks n=22	TE w/o cirrhosis 16 Weeks n=22	TN w/ cirrhosis 12 Weeks n=40	TE w/ cirrhosis 16 Weeks n=47
Male, n (%)	14 (64)	14 (64)	24 (60)	36 (77)
White race, n (%)	17 (77)	20 (91)	37 (93)	42 (89)
Age, median years (range)	56 (35-68)	59 (29-66)	56 (36-70)	59 (47-70)
Prior treatment history, n (%)				
IFN/PegIFN±RBV	14 (64)	13 (59)	0	22 (47)
SOF+RBV±PegIFN	8 (36)	9 (41)	0	25 (53)
Baseline Fibrosis Stage, n (%)				
F0-F2	15 (68)	17 (77)	0	0
F3	7 (32)	5 (23)	0	0
F4	0	0	40 (100)	47 (100)

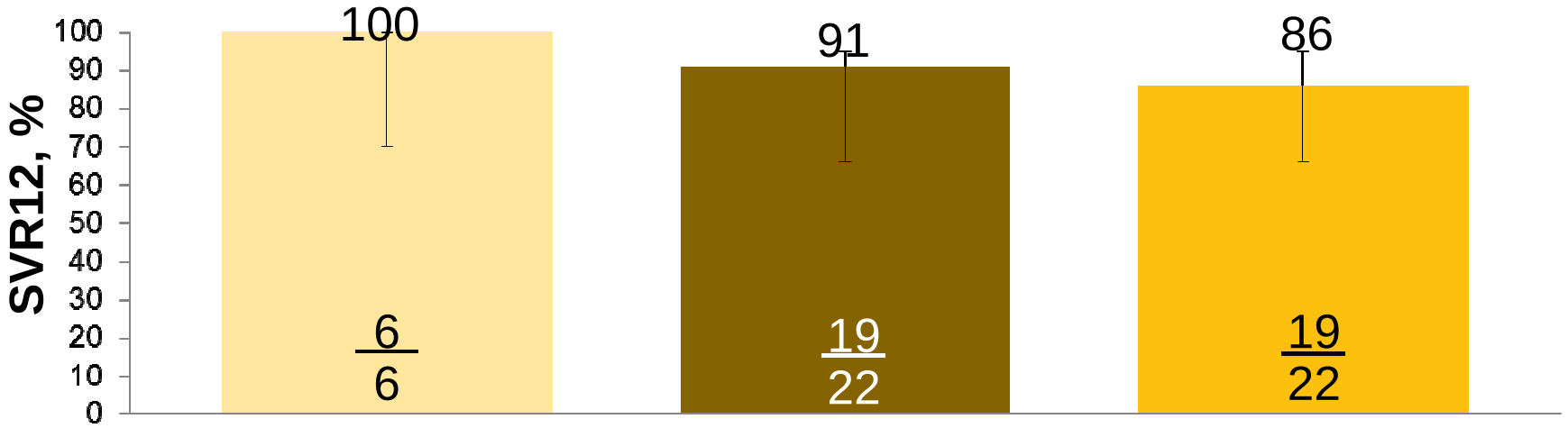
Wyles D, AASLD 2016, Oral 113

GLE/PIB is dosed as 3 tablets for a total of 300mg/120 mg

MAGELLAN-I SVR12 by ITT

Open-label, multicenter, randomized phase 2 trial in DAA-experienced patients with GT1 infection and no cirrhosis re-treated with G/P±RBV for 12 wks

25 (50%) NS5A-experienced (SOF/LDV or 3D regimen
42 (84%) PI-experienced



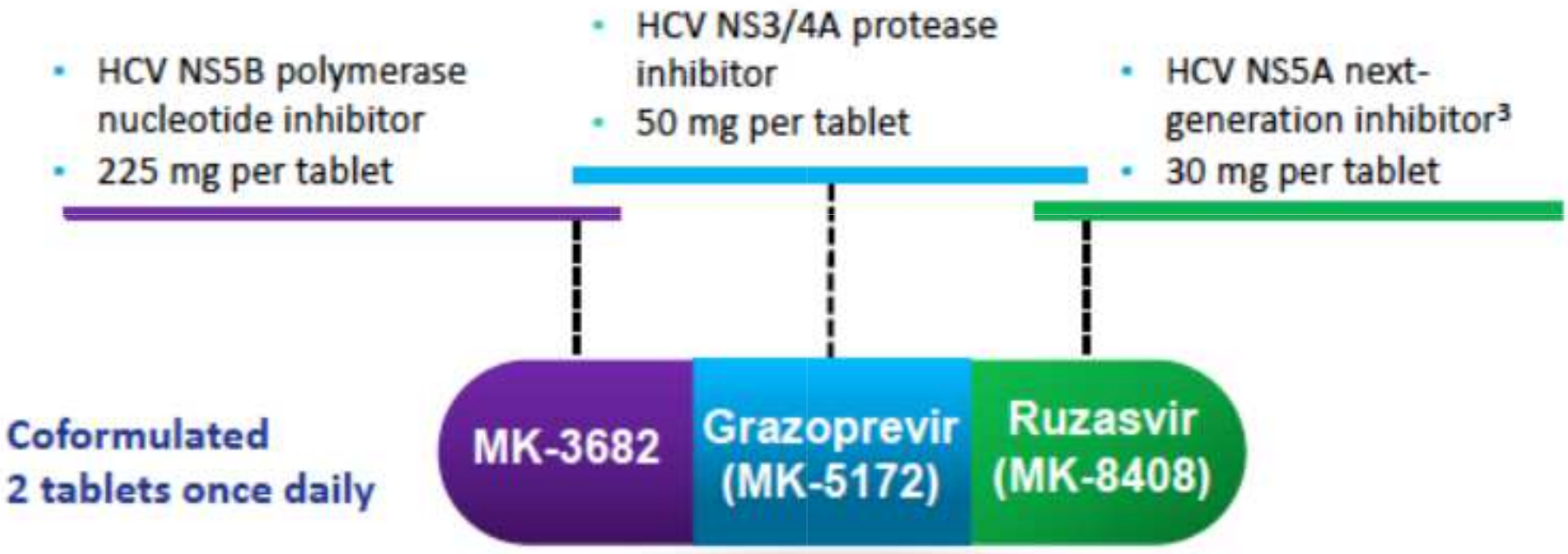
ABT-493	200	300	300
ABT-530	120	120	120
RBV		800	
Breakthrough	0	0	1
Relapse	0	1	0
LTFU	0	1	2

1 LTFU after week 6 with undetectable HCV RNA

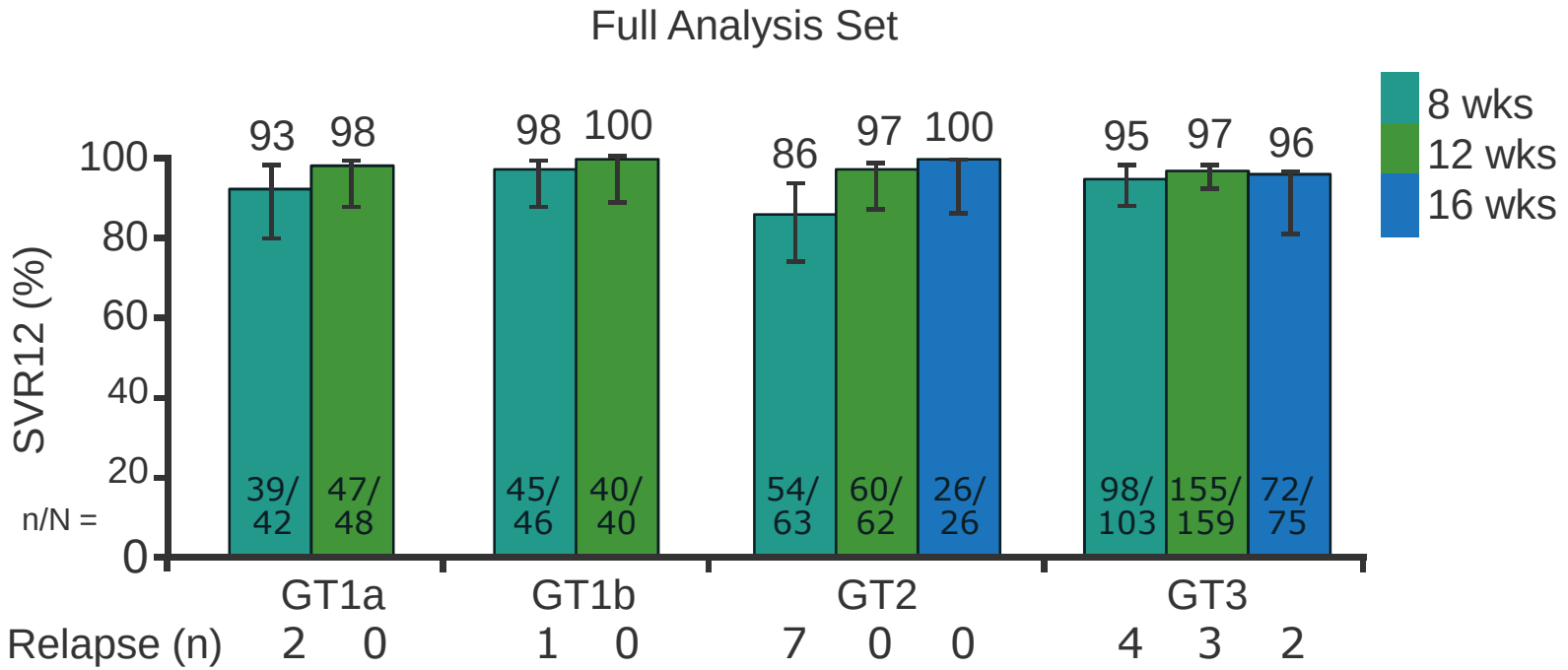
- 2 Patients LTFU after completing treatment (1 death); both achieved SVR8

Poordad, EASL 2016

MSD 3D


HCV NS5B polymerase nucleotide inhibitor
225 mg per tablet
HCV NS3/4A protease inhibitor
50 mg per tablet
HCV NS5A next-generation inhibitor[3]
30 mg per tablet
Coformulated
2 tablets once daily
MK-3682
Grazoprevir (MK-5172)
Ruzasvir (MK-8408)

C-CREST 1 & 2: Efficacy of MK-3682/ GZR/RZR ± RBV for Pts With GT1-3 HCV

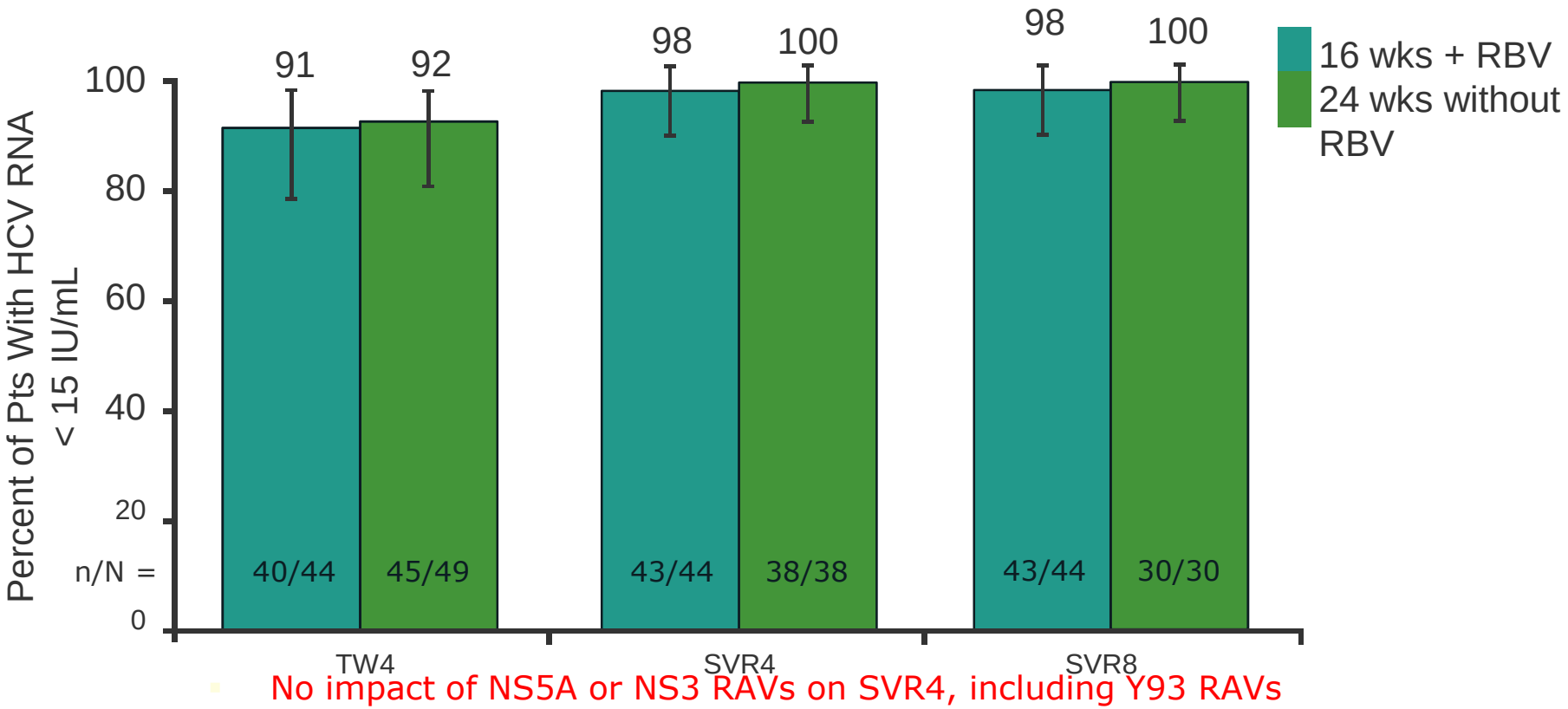


- Presence of cirrhosis, use of ribavirin, prior tx experience did not impact SVR12 rates

Lawitz E, et al. AASLD 2016, Boston. #110

C-SURGE: SVR8 Rates With MK-3682/GZR/RZR for DAA Relapses

Pts with GT1 HCV (HCV RNA ≥ 10,000 IU/mL) and relapse after SOF/LDV ± RBV or GZR/EBR ± RBV (N = 94)



No impact of NS5A or NS3 RAVs on SVR4, including Y93 RAVs

Wyles DL, et al. AASLD 2016..

Summary Novel HCV DAA Regimens

SOF/VEL is a pangenotypic regimen for 12 weeks

Phase 3 SOF/VEL/VOX for salvage therapy for 12 wks

Phase 3 GLE/PIB for 8 weeks without cirrhosis and

12 weeks with cirrhosis

Phase 2 MK3-includes nucleotide NS5B