Convegno Internazionale
GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2017
MILANO, 25-26 MAGGIO 2017
OSPEDALE LUIGI SACCO POLO UNIVERSITARIO – ASST FATEBENEFRATELLI SACCO
AULA MAGNA POLO LITA

Ultimi dati dai congressi e prospettive offerte da nuovi farmaci e nuove formulazioni

Gloria Taliani

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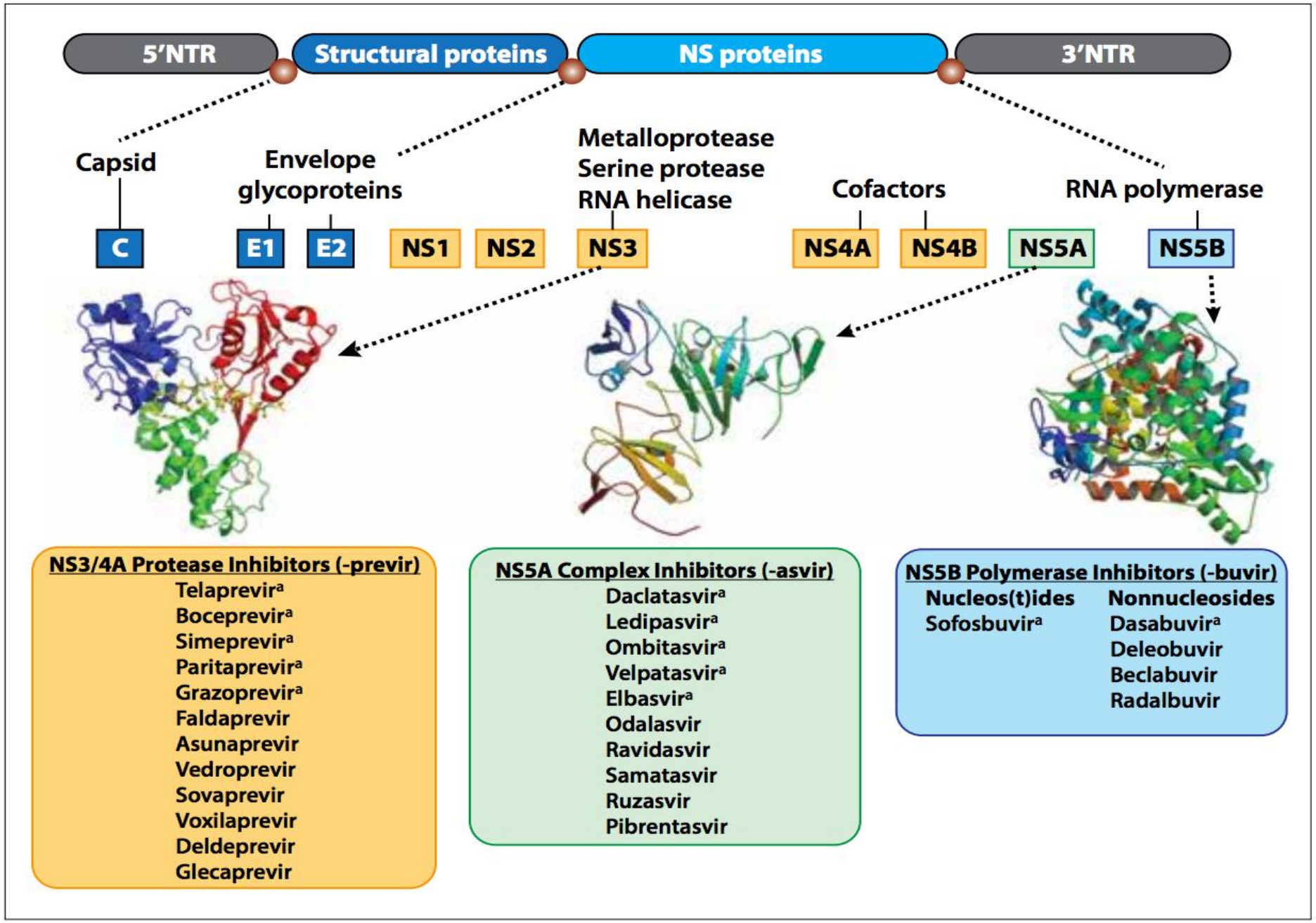
The RNA genome of hepatitis C virus (HCV) and the three classes of Inhibitors



Horsley-Silva JL, Vargas HE. Gastroenterology & Hepatology 2017; 13: 21-31

New Drugs

- New, on the block
  - Grazoprevir, Elbasvir
  - Sofosbuvir Velpatasvir

- New, on the horizon

New Drugs

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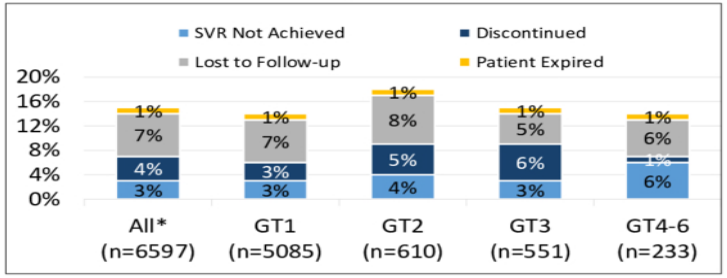
- New, on the horizon

ROBUST AND COMPREHENSIVE PHASE 2B AND 3 CLINICAL PROGRAM

Study	GT	Sample Size	Cirrhosis	Tx History	Co-Morbidity	Regimen (Weeks)
C-SURFER	1	237	± Cirrhosis	TN/PR-PTF	CKD 4-5	12, **no RBV**
C-EDGE TN	1, 4, 6	421	± Cirrhosis	TN		12, **no RBV**
C-EDGE CO-INFXN	1, 4, 6	218	± Cirrhosis	TN	HIV	12, **no RBV**
C-EDGE TE	1, 4, 6	420	± Cirrhosis	PR-PTF	±HIV	12 or 16, ±RBV
C-WORTHy G1	1b	61	No Cirrhosis	TN		8 ±RBV
C-Salvage	1	79	± Cirrhosis	PI/PR-PTF		12, + RBV
C-WORTHy G3	3	41	No Cirrhosis	TN		12/18+ RBV
C-SWIFT	3	42	± Cirrhosis	TN		12 + SOF
C-EDGE CO-STAR	1, 4, 6	300	± Cirrhosis	TN	PWID,OAT, ±HIV	12, **no RBV**
C-EDGE H2H **HEAD TO HEAD** **EBR/GZR vs PR + SOFOSBUVIR**	1	250	± Cirrhosis	TN/PR-PTF	±HIV	12, **no RBV**
C-EDGE InhBD	1, 4, 6	300	± Cirrhosis	TN/PR-PTF	InhBD	12, **no RBV**

Tot. 2369



*Includes 118 patients with Mixed (10) or Unspecified (108) genotypes.

TN: Treatment Naïve
PR-PTF: Failed Prior Peg-IFN/RBV

InhBD = Inherited Blood Disorders

CKD 4-5: Chronic Kidney Disease Grades 4-5 (incl. Hemodialysis)

OAT = Opiate Agonist Therapy
PWID= persons who inject drugs

RBV = Ribavirin

Flamm SL et al The International Liver Congress (EASL) - Amsterdam, 21 April 2017

elbasvir/grazoprevir: SVR12 rates in clinical trials

study	population	Arms (number of patients)	SVR12
C-EDGE TN [1]	GT 1, 4, 6 TN con o senza cirrosi	EBR/GZR 12 sett. (N=316) Placebo per 12 sett. (N=105)	**95%** (291/306)
C-EDGE COINFECTION [2]	GT 1, 4, 6 TN con o senza cirrosi Co-infezione HCV/HIV-1	EBR/GZR per 12 sett. (N=218)	**95%** (206/217)
C-SURFER [3]	GT 1 TN o TE con o senza cirrosi, CKD Stadio 4-5, emodialisi inclusa	EBR* + GZR* per 12 sett. (N=122) Placebo per 12 sett. (N=113)	**94%** (115/122) **99%** (115/116) mITT
C-WORTHY [4]	GT 1, 3 TN con o senza cirrosi TE null responders con o senza cirrosi TN con co-infezione da HCV/HIV-1 senza cirrosi	EBR*+ GZR* 8, 12 o 18 sett. (N=31, 136 e 63, rispettivamente) EBR*+ GZR* + RBV† 8, 12 o 18 sett. (N=60, 152 e 65, rispettivamente)	**94%** (97/103) TN 12 sett.
C-EDGE TE [5]	GT 1, 4, 6 TE con o senza cirrosi Co-infezione da HCV/HIV-1	EBR/GZR 12 o 16 sett. (N=105 e 105, rispettivamente) EBR/GZR + RBV† 12 o 16 sett. (N=104 e 106, rispettivamente)	**92%** (97/105) 12 sett. **94%** (98/104) 12 sett. + RBV **93%** (94/101) 16 sett. **97%** (101/104) 16 sett + RBV
C-SALVAGE [6,7]	GT 1 TE con regime contenente inibitore della proteasi dell'HCV‡ con o senza cirrosi	EBR* + GZR* + RBV† per 12 sett. (N=79)	**96 %** (76/79)
C-EDGE COSTAR [8]	GT 1, 4, 6 TN con o senza cirrosi Terapia con agonisti oppiacei	EBR/GZR 12 sett. (N=201) Immediate Treatment Group (ITG) Placebo 12 sett. (N=100) Deferred Treatment Group (DTG)	**91.5%** (184/201) (SVR12) ITG
C-EDGE HEAD 2 HEAD [9]	GT1, GT4 TN e TE con o senza cirrosi	EBR/GZR per 12 sett. (N=129) versus Sofosbuvir/peg-IFN/RBV per 12 sett. (N=126)	**99.2% EBR/GZR vs 90.5%** (Superiorità di EBR/GZR)
C-EDGE IBLD [10]	GT1,4,6 Pazienti TN o TE con malattie ematologiche ereditarie	Gruppo trattamento immediato (ITG; 12 sett. EBR/GZR) (N=107); Gruppo trattamento differito (DTG; 12 sett. placebo, seguito poi da EBR/GZR) (N=52)	**93.5%** EBR/GZR (SVR12) gruppo ITG

GT = genotipo TN = naïve al trattamento TE = con esperienza di trattamento (fallimento di trattamento pregresso con interferone [IFN] o peginterferone alfa [peg-IFN] con o senza ribavirina (RBV) o intolleranza a terapia pregressa) * EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-somministrati come agenti singoli † RBV è stata somministrata a una dose quotidiana totale

1) Zeuzem S. et al. Ann Intern Med. 2015;163:1-13. 2) Rockstroh JK. Et al. Lancet HIV 2015; 2: e319–27. 3) Roth D, et al. Lancet 2015. 4) Sulkowski M. et al. Lancet 2015; 385: 1087–97. 5) Kwo P. et al. ILC 2015 #P0886. 6) Forns et al. J Hepatology 2015 7) Buti M. et al. CID 2016:62 8) Dore et al. Ann Intern Med. doi:10.7326/M16-0816 www.annals.org - 9 August 2016. 9) J.Sperl et al. Journal of Hepatology S0168-8278(16)30429-9 DOI: http://dx.doi.org/10.1016/j.jhep.2016.07.050 10) Hezode, Massimo Colombo et al. J Hepatol 64(Suppl. 2):S753 Abstract SAT-128 2016. Apr 13-17 2016 - 51st EASL The International Liver Congress.

Analysis of the Real-World Treatment Effectiveness of Elbasvir/Grazoprevir

Jeffrey McCombs [1], Justin McGinnis[1,2] Steven Fox[1] and Ivy Tonnu-Mihara[2]

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2.069 Veterans

Table 1: Baseline Characteristics & SVR12

	#	%	SVR12 (%)
Overall	2,069	-	**92.9%**
Gender			
Male	2,010	97.1%	**92.8%**
Female	59	2.9%	**94.9%**
Age			
< 60	430	20.8%	**93.0%**
60 - 64	728	35.2%	**92.2%**
65+	911	44.0%	**93.4%**
Race			
Black	1138	55.0%	**93.5%**
White	753	36.4%	**91.9%**
Other/Unknown	178	8.6%	**93.3%**
Genotype			
1	1,989	96.1%	**92.8%**
Other	60	2.9%	**93.3%**
Unknown	20	1.0%	**100%**
Disease Severity			
Cirrhosis	266	12.9%	**92.9%**
Decompensated	197	9.5%	**90.4%**
Hepatocellular Carcinoma	41	2.0%	**87.8%**
Liver Transplant	16	0.8%	**81.3%**
FIB4			
< 1.45	408	19.7%	**94.1%**
1.45 - 3.25	971	46.9%	**93.5%**
> 3.25	410	19.8%	**91.2%**
Unknown	280	13.5%	**91.4%**
Comorbidities			
HIV	56	2.7%	**94.6%**
HBV	185	8.9%	**89.7%**
Diabetes	913	44.1%	**92.8%**
Obesity	106	5.1%	
Co-administered Rx			
Ribavirin	242	11.7%	**82.6%**
Sofosbuvir	37	1.8%	**89.2%**
Previous Treatment			
Naïve	1659	80.2%	**94.1%**
Experienced	410	19.8%	**88.1%**

Table 1: Baseline Characteristics & SVR12

Co-administered Rx				
Ribavirin	-1.16	0.31	[0.20 - 0.49]	<0.0001
Sofosbuvir	0.83	2.30	[0.75 - 7.10]	0.15
Prior Treatment (ref. group = naive)				
Experienced	-0.50	0.61	[0.40 - 0.92]	0.02

Approximately 13% of patients had cirrhosis, 10% decompensated, and 2% HCC.

The overall rate of SVR12 was 93% in patients using elbasvir/grazoprevir. Among patients who were co-administered ribavirin, the rate of SVR12 was 83%, and for those co-administered sofosbuvir it was 89%

Safety and Efficacy of Elbasvir/Grazoprevir in Patients With Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis

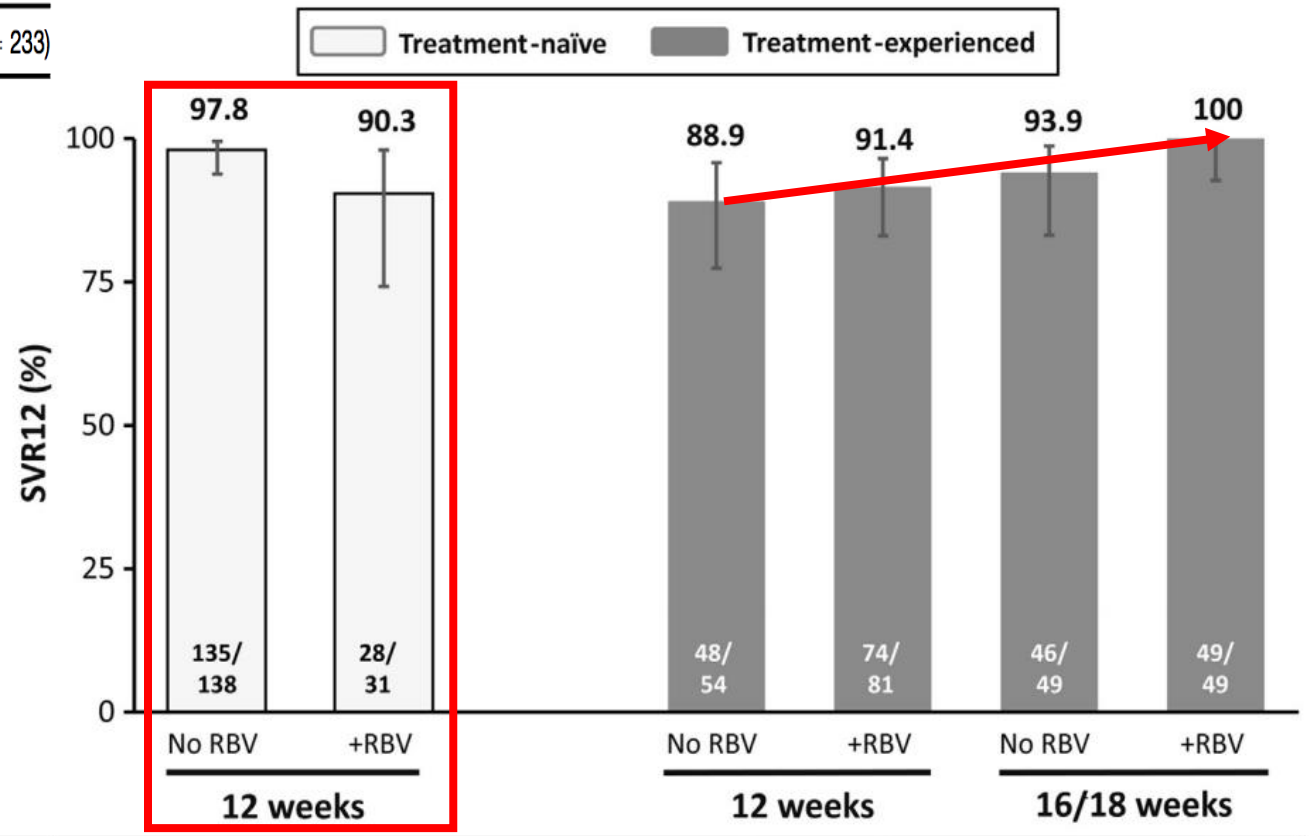
Ira M. Jacobson,[1] Eric Lawitz,[2] Paul Y. Kwo,[3] Christophe Hézode,[4] Cheng-Yuan Peng,[5] Anita Y. M. Howe,[6] Peggy Hwang,[6] Janice Wahl,[6] Michael Robertson,[6] Eliav Barr,[6] and Barbara A. Haber[6]

Characteristic	Treatment-naïve (n = 169)	Treatment-experienced (n = 233)
HCV genotype, n (%)		
1a	96 (56.8)	123 (52.8)
1b or other 1	67 (40.9)	90 (38.7)
4	6 (3.6)	17 (7.3)
6	0	3 (1.3)
Baseline viral load, n (%)		
≤800,000 IU/mL	37 (21.9)	49 (21.0)
>800,000 IU/mL	132 (78.1)	184 (79.0)
HIV co-infection, n (%)	35 (20.7)	5 (2.1)

Variable	EBR/GZR (n = 264)	EBR/GZR+RBV (n = 193)
≥1 AEs	193 (73.1)	164 (85.0)
Fatigue	40 (15.2)	59 (30.6)
Headache	44 (16.7)	40 (20.7)
Nausea	11 (4.2)	26 (13.5)
Insomnia	8 (3.0)	25 (13.0)
Drug-related AEs	111 (42.0)	141 (73.1)
Serious AEs	8 (3.0)	6 (3.1)
Serious drug-related AEs	1 (0.4)	0 (0.0)
Deaths	1 (0.4)	1 (0.5)
Discontinued due to an AE	2 (0.8)	4 (2.1)

Prior treatment response, n (%)

Prior null	120 (51.5)
Prior on-treatment failure excluding null	54 (23.1)
Prior relapse	59 (25.3)
Direct-acting antiviral agent	34 (14.6)



Breakthrough	1	1	0	0	0	0
Rebound	0	0	0	0	2	0
Relapse	1	2	4	6	1	0
LTFU/early DC	1	0	2	1	0	0

Jacobson I M et al. Gastroenterology 2017;152:1372–1382

Real-world use of elbasvir/grazoprevir and outcomes in patients with Chronic Hepatitis C: Retrospective data analyses from the TRIO Network.

B. BACON[1], M. CURRY[2], D. DIETERICH[3], S.L. FLAMM[4], K.KOWDLEY[5], S.MILLIGAN[6], C. NWANKWO[7], N. TSAI[8], Z. YOUNOSSI[9] AND N. AFDHAL[2]

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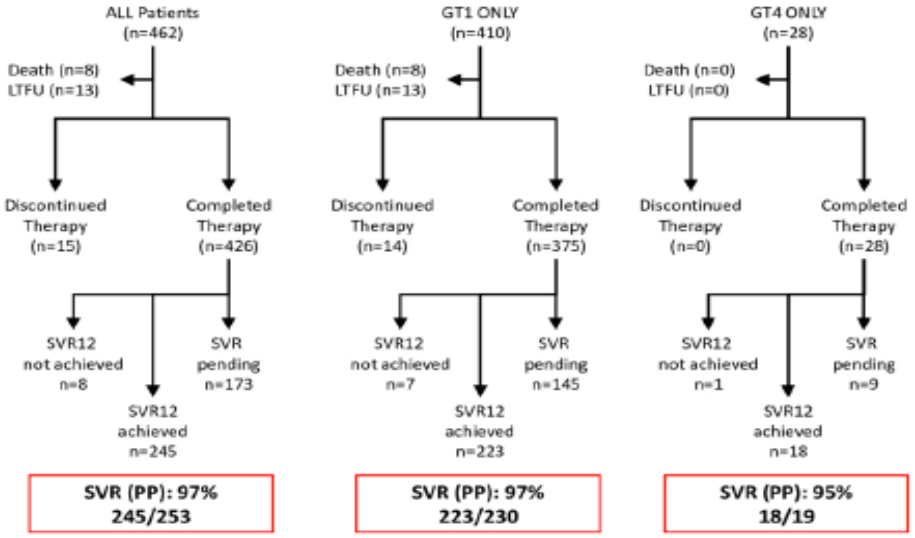
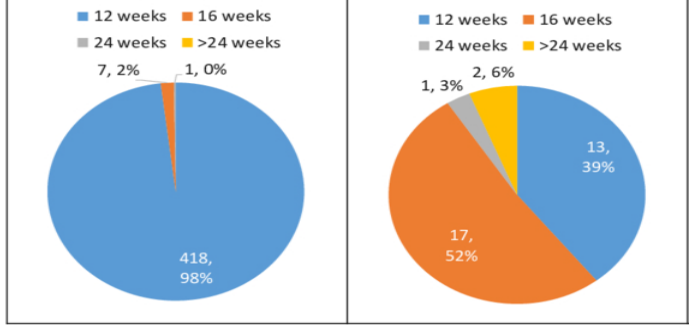
5. EBR/GZR REGIMENS PATIENT DISPOSITION



*Per Protocol (PP) denominator limited to "SVR achieved" and "SVR not achieved".

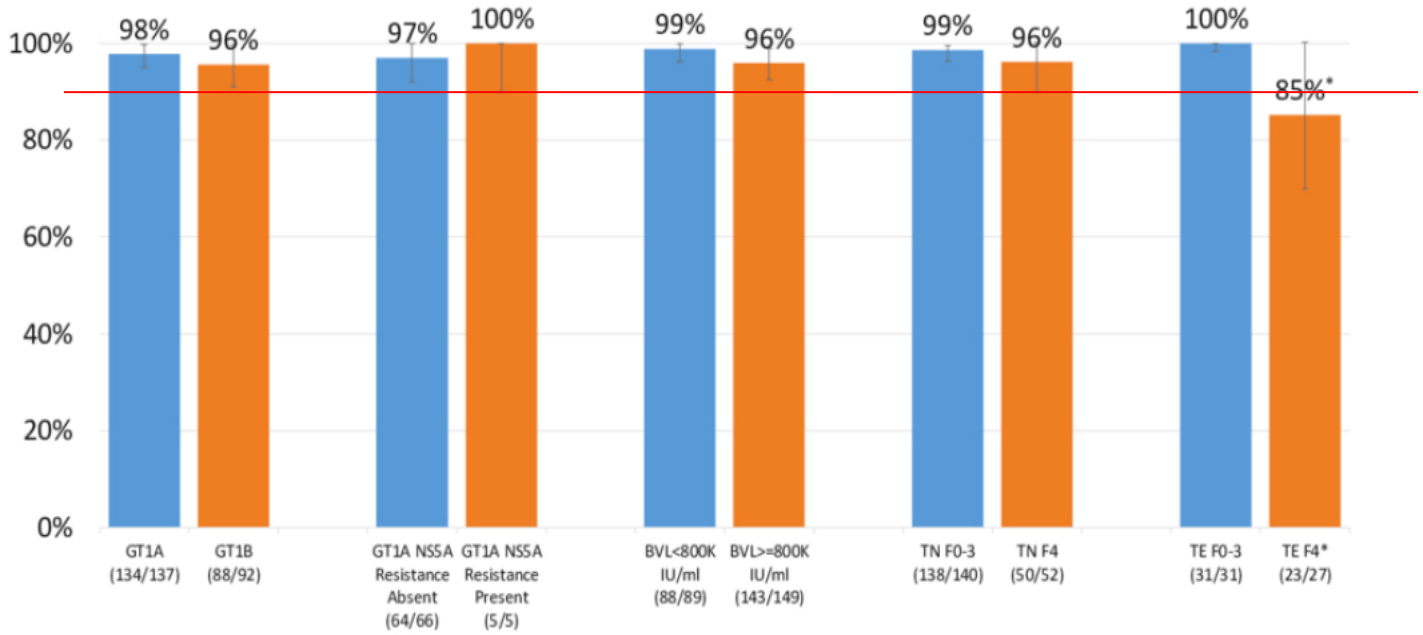
Distribution by regimen and schedule

EBR/GZR	EBR/GZR + RBV
426/462 (92%)	33/462 (7%)



6. SVR12 (PP) IN EBR/GZR-TREATED POPULATIONS

90 % 12-week No Riba 60% had CKD



*Of the four TE F4 patients who did not achieve an SVR, the prior treatment regimens received were LDV/SOF, SMV+SOF, PEG+RBV and unknown

GT=genotype, TN=Treatment Naïve, TE=Treatment Experienced, F0-3=Non-cirrhotic, F4=Cirrhosis, BVL=Baseline Viral Load.
Of the patients with NS5A Resistance Present, 6 had outcomes; 1 LTFU, 5 SVR Achieved.

Grazoprevir/Elbasvir schedules according to different SPC

	8 w	12 w	16 w + R
1b	**Canada** TN no Cirr.	Canada FDA EMA All	-

Grazoprevir/Elbasvir schedules according to different SPC

	8 w	12 w	16 w + R
1b	**Canada** TN no Cirr.	Canada FDA EMA All	-
1a	-	All Remaining pts	**Canada** Tr Exp
	-	All Remaining pts	**FDA** Resistance +
	-	All Remaining pts	**EMA** >800.000 Resistance +
4		All Remaining pts	**Canada** Tr Exp
		All Remaining pts	**FDA** Tr Exp >800.000
		All Remaining pts	**EMA** >800.000

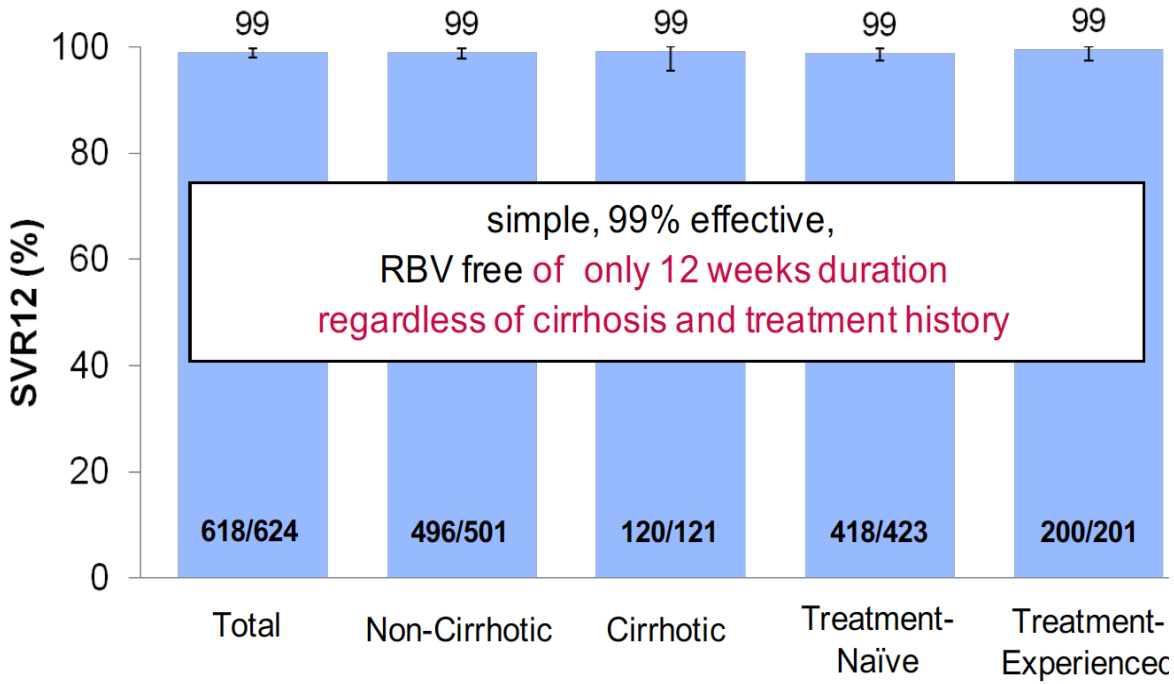
New Drugs

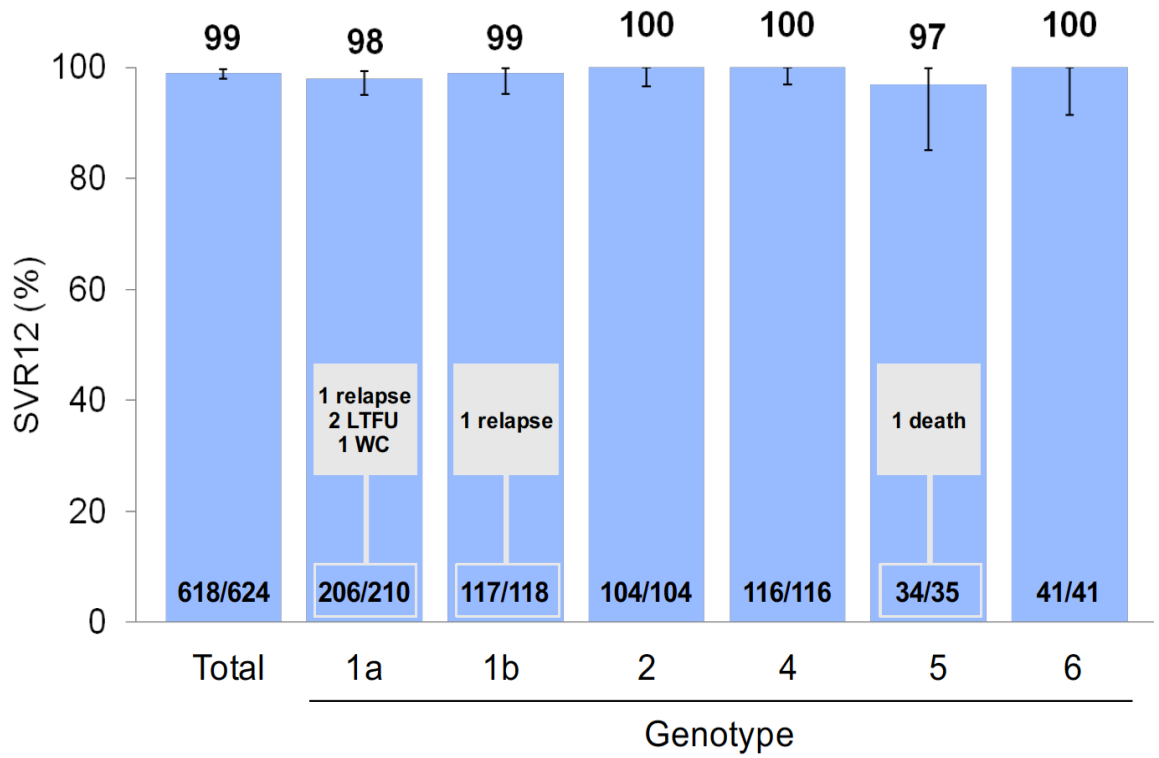
- New, on the block
  - Grazoprevir, Elbasvir
  - Sofosbuvir Velpatasvir
- New, on the horizon

ASTRAL-1: SOF/VEL STR for 12 Weeks in GT 1, 2, 4, 5, 6 HCV-Infected Patients

ASTRAL-1: SOF/VEL STR for 12 Weeks in GT 1, 2, 4, 5, 6 HCV-Infected Patients

SVR12 by Cirrhosis Status or Treatment History





Error bars represent 95% confidence intervals.

Feld, AASLD, 2015, LB-2. Feld JJ, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa15

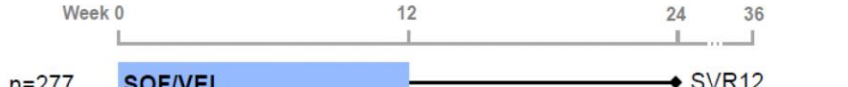
LTFU=lost to follow up; WC=withdrew consent

Feld, AASLD, 2015, LB-2. Feld JJ, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512610

ASTRAL-3 : SOF/VEL 12 weeks in GT 3

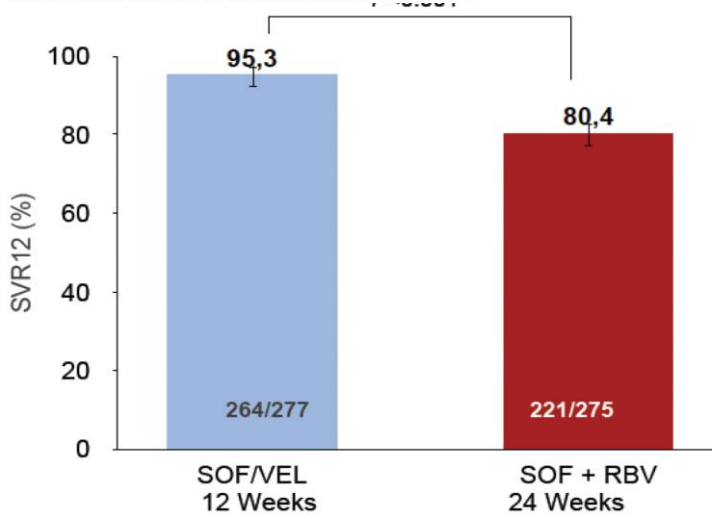
Phase 3, open-label, randomized study versus SOF/RBV for 24 wks

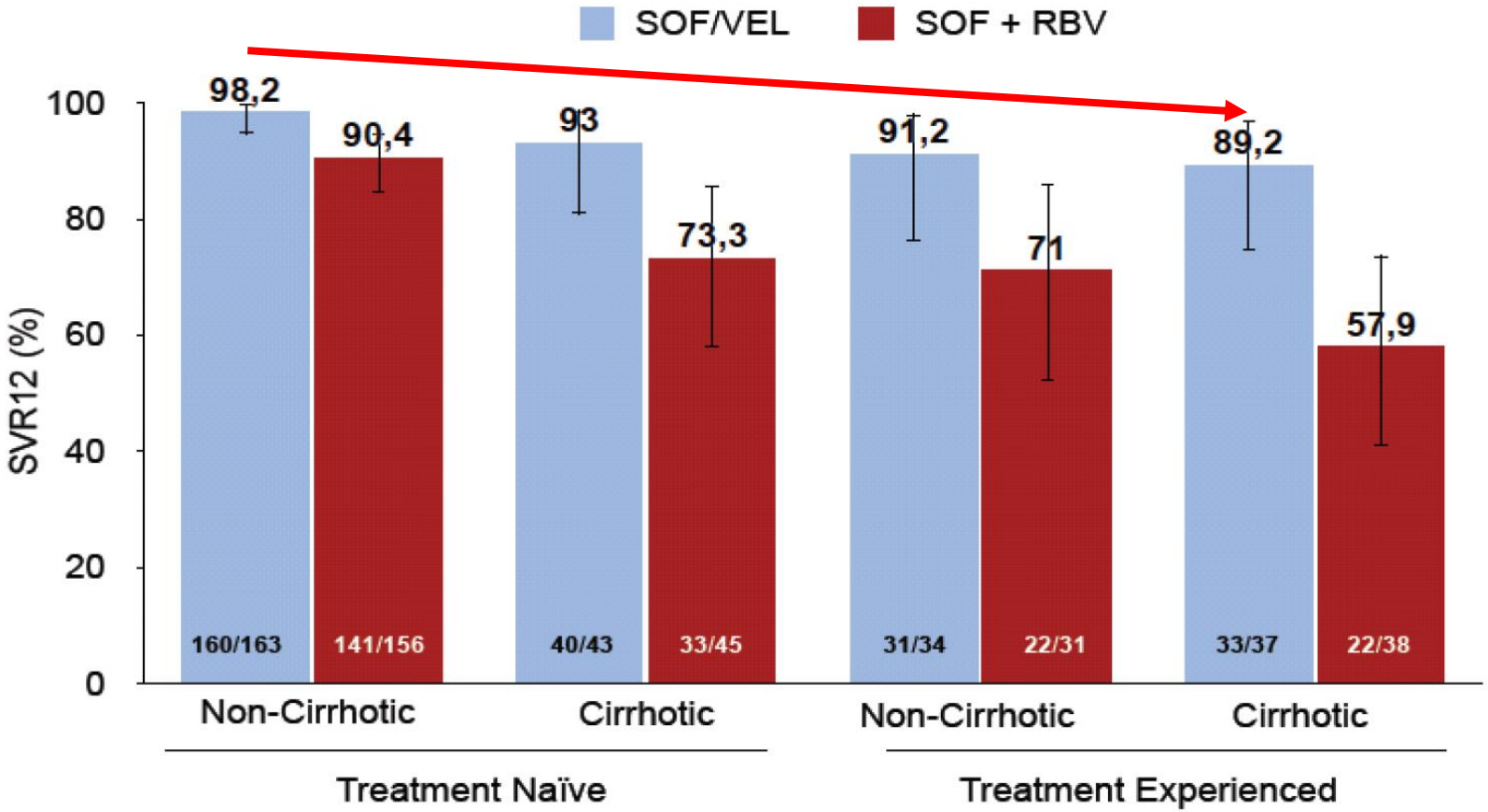
Phase 3, open-label, randomised study of SOF/VEL for 12 weeks in GT 3



	SOF/VEL 12 Weeks n=277	SOF + RBV 24 Weeks n=275
Mean age, y (range)	*49 (21–76)*	*50 (19–74)*
Male, n (%)	*170 (61)*	*174 (63)*
White, n (%)	*250 (90)*	*239 (87)*
Mean BMI, kg/m² (range)	*26.4 (16.6–48.2)*	*26.6 (16.9–56.2)*
Cirrhosis, n (%)	*80 (29)*	*83 (30)*
Treatment experienced, n (%)	*71 (26)*	*71 (26)*
IL28B CC, n (%)	*105 (38)*	*111 (40)*
HCV RNA, log_{10} IU/mL (SD)	*6.2 (0.7)*	*6.3 (0.7)*

Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612





*P-value for superiority of SOF/VEL compared with SOF+RBV.
Error bars represent 95% confidence intervals.
Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612

Safety and Efficacy of Sofosbuvir and Velpatasvir with or without Ribavirin for the Treatment of HCV Genotype 1-6: Results of the HCV-TARGET Study

Khalili, M; Welzel, TM; Terrault, N; Lim, J; Sridhar, A; Lutchman, G; Nelson, D; Borg, B; Lok AS; Ramani, A; Reau, N; Vainorius, M; Fried, MW; Landis, C

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HCV-TARGET

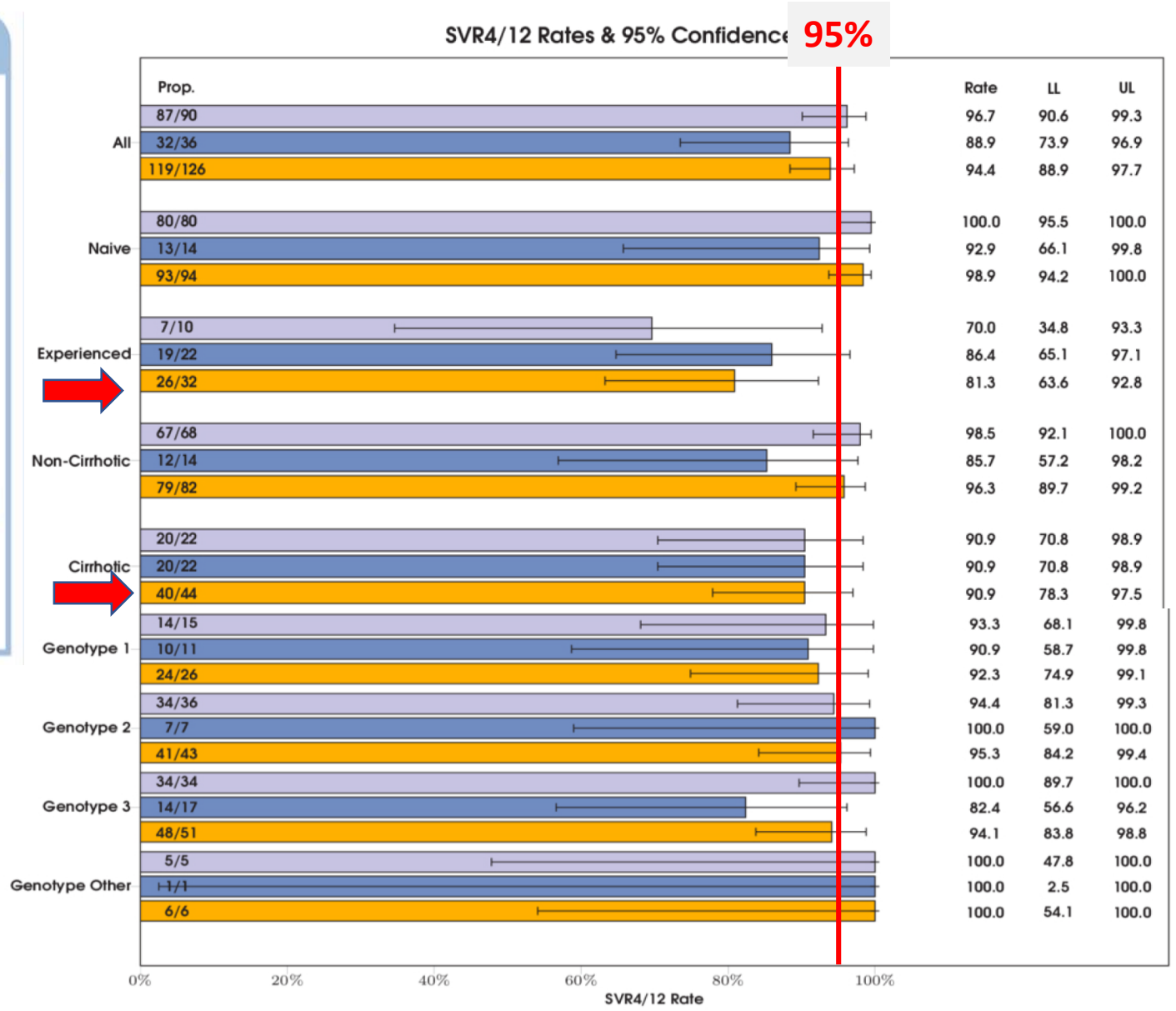
BASELINE DEMOGRAPHICS

	SOF/VEL	SOF/VEL+RBV	Total
N	387 (100.0%)	108 (100.0%)	495 (100.0%)
Demographics N (%)			
Age: 60+	156 (40.3%)	48 (44.4%)	204 (41.2%)
Sex: Male	224 (57.9%)	82 (75.9%)	306 (61.8%)
Race: White	260 (67.2%)	72 (66.7%)	332 (67.1%)
African American	46 (11.9%)	5 (4.6%)	51 (10.3%)
Other	81 (20.9%)	31 (28.7%)	112 (22.6%)
HCV Genotypes: 1	60 (15.5%)	33 (30.6%)	93 (18.8%)
2	151 (39.0%)	15 (13.9%)	166 (33.5%)
3	153 (39.5%)	53 (49.1%)	206 (41.6%)
Other	23 (5.9%)	7 (6.5%)	30 (6.1%)
Treatment Experienced	58 (15.0%)	62 (57.4%)	120 (24.2%)
Cirrhotic	89 (23.0%)	74 (68.5%)	163 (32.9%)
History of Decompensation	24 (6.2%)	46 (42.6%)	70 (14.1%)
Liver Transplant	6 (1.6%)	15 (13.9%)	21 (4.2%)
Baseline Chemistry Median (Min-Max)			
Albumin (g/dL)	4.1 (1.5-5.5)	3.7 (1.7-4.7)	4.0 (1.5-5.5)
Total Bilirubin (mg/dL)	0.6 (0-38.0)	0.8 (0.1-3.5)	0.6 (0-38.0)
Platelets (10^3/uL)	191 (25-434)	116 (21-346)	181 (21-434)
MELD (among cirrhotics)	8 (6-39)	9 (6-17)	9 (6-39)
HCV RNA (log_{10} IU/mL)	6.2 (2.2-8.2)	6.1 (2.1-8.0)	6.1 (2.1-8.2)

495 pts, mainly (79 %) GT 2, 3

23% cirrhosis

7 patients did not achieve SVR were treatment experienced and/or had advanced liver disease. 6/7 had relapse, 1 had BT

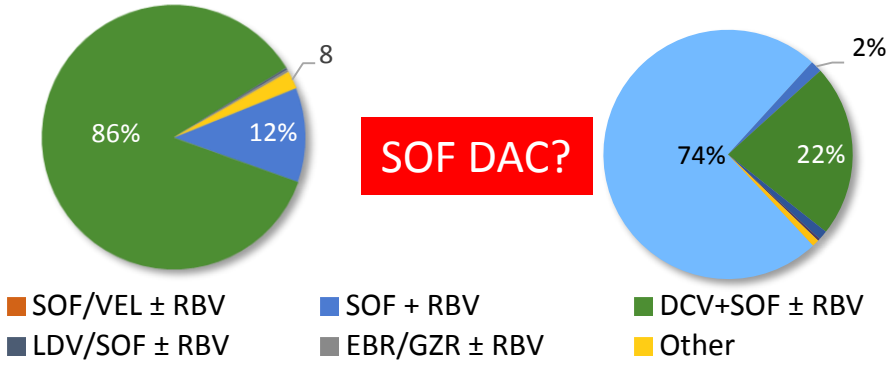


Real-World Experience of SOF/VEL ± RBV in HCV GT 3

Treatment uptake

1H 2016 (n=366) Prior to SOF/VEL Approval

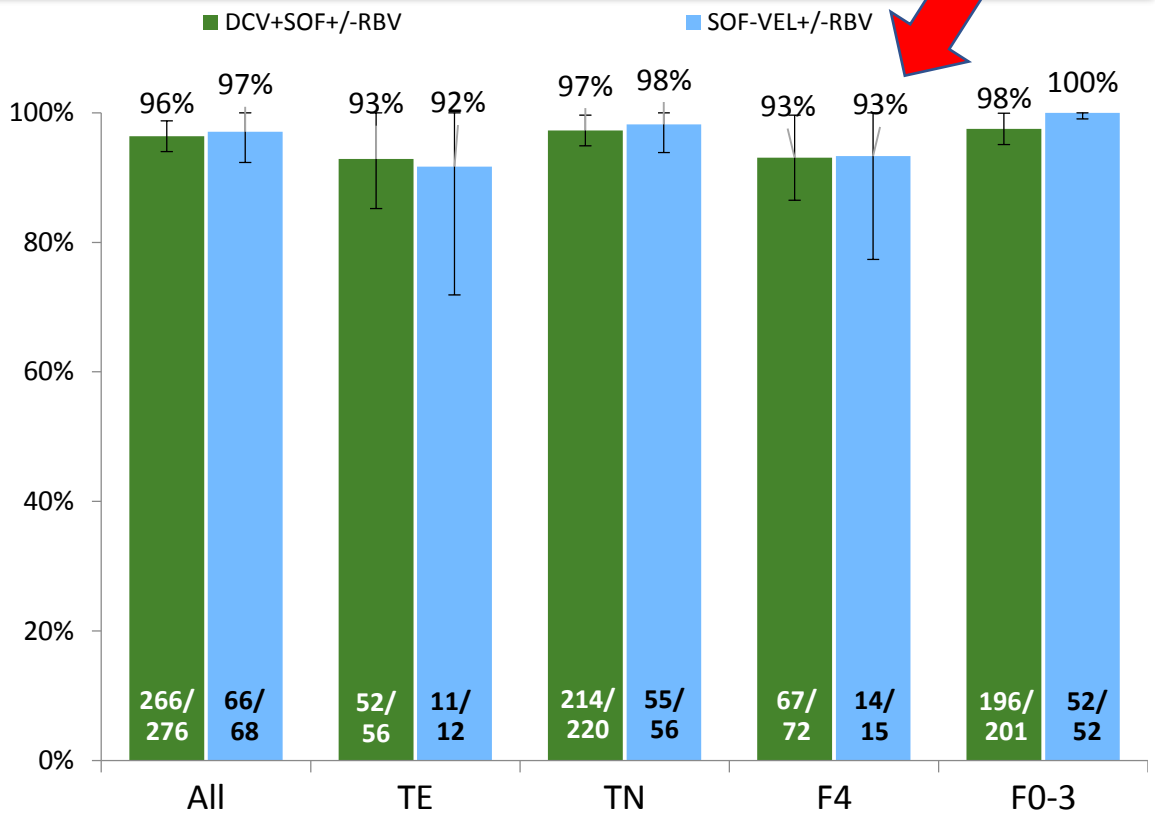
2H 2016 (n=485) After SOF/VEL Approval



Baseline Demographics

	DCV+SOF ± RBV (n=392)	SOF/VEL ± RBV (n=244)
12 week schedule, n (%)	307 (78)	238 (98)
Other schedule, n (%)	82 (21)	6 (2)
+ RBV, n (%)	78 (20)	35 (14)
Age - mean (range)	54 (22-81)	52 (21-83)
Male, n (%)	224 (57)	140 (57)
HIV coinfection, n (%)	7 (2)	5 (4)
TE, n (%)	82 (21)	54 (22)
F4, n (%)	110 (29)	69 (29)
CKD, n (%)	99 (26)	64 (27)
Diabetes, n (%)	46 (13)	33 (14)

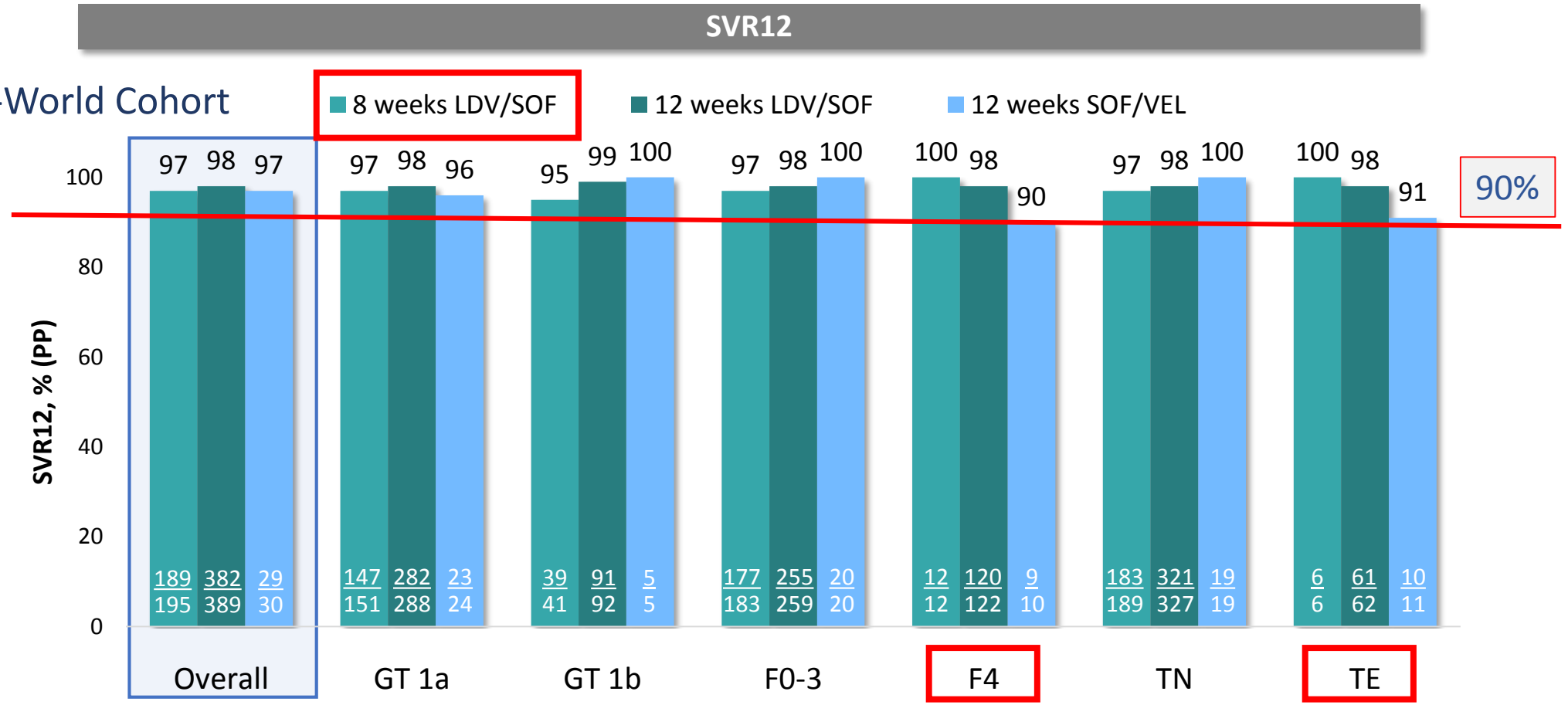
SVR12 (PP)



In this RWD cohort, high SVR results achieved with SOF/VEL in GT3 patients confirm the results observed in ASTRAL-3

Curry, EASL 2017, PS-102

Real-World Experience of LDV/SOF (8-12 wks) versus SOF/VEL (12 wks) in GT1 patients



In real-world cohort, high SVR12 rates were achieved with 8 week LDV/SOF, 12 week LDV/SOF, and 12 week SOF/VEL, regardless of genotype subtype, fibrosis or prior treatment status

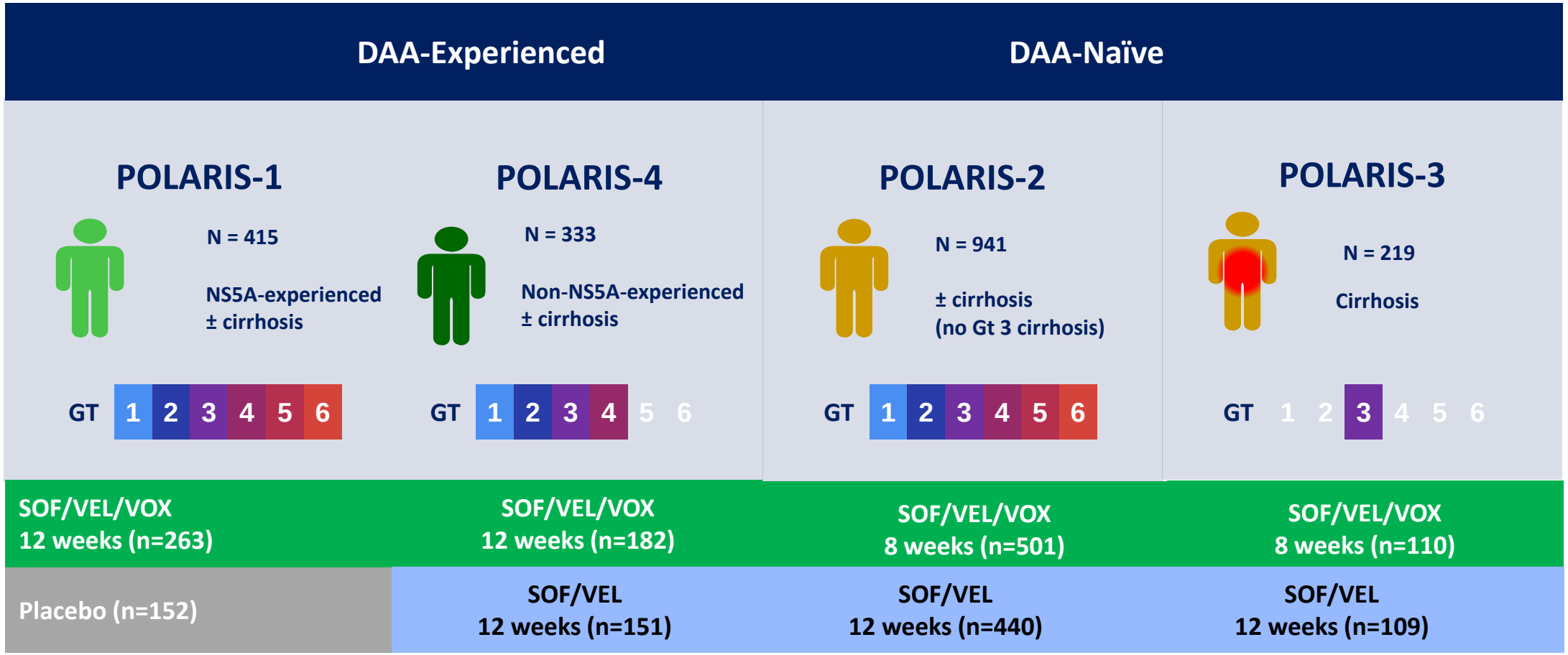
Tsai, EASL 2017, SAT-244

New Drugs

- New, on the block
  - Grazoprevir, Elbasvir
  - Sofosbuvir Velpatasvir

- New, on the horizon

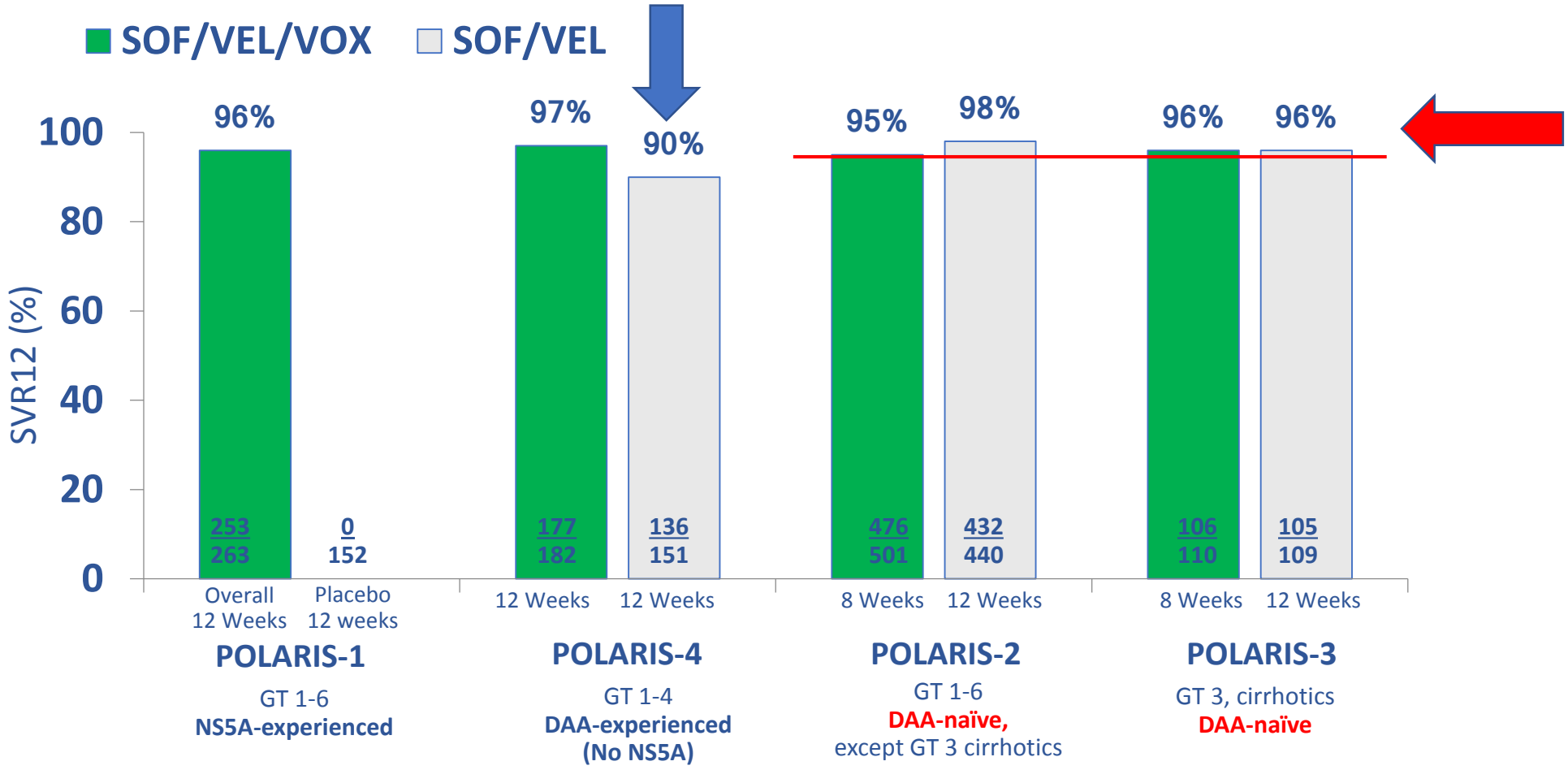
POLARIS Phase 3 Program 1.908 pts, 748 TE



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

Efficacy Summary SOF-VEL-VOX (ITT Analysis)*

*All studies included patients with compensated cirrhosis



SOF/VEL/VOX for 12 weeks provides a STR for all DAA-experienced patients and SOF/VEL for 12 weeks provides a STR for DAA-naive patients regardless of cirrhosis status

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

Negative Predictive Factors of SOF/VEL/VOX for 12 Weeks in DAA-Experienced Patients

Integrated Efficacy Analysis of POLARIS-1 and -4

% (n/N)		TOTAL	GT 1a	GT 1b	GT 2	GT 3	GT 4
Cirrhosis	Yes	**95** (195/205)	**94** (47/50)	**100** (27/27)	**100** (13/13)	**94** (82/87)	**92** (24/26)
	No	**98** (236/240)	**98** 103/105	**98** (41/42)	**100** (23/23)	**98** (44/45)	**100** (15/15)
Platelets	<100 x 10^3/µL	**100** (61/61)	**100** (16/16)	**100** (7/7)	**100** (3/3)	**100** (28/28)	**100** (7/7)
	≥100 x 10^3/µL	**96** (370/384)	**96** (370/384)	**98** (61/62)	**100** (33/33)	**94** (98/104)	**94** (32/44)
Fibroscan	<12.5 kPa	**98** (178/182)	**98** (78/80)	**97** (33/34)	**100** (16/16)	**97** (32/33)	**100** (11/11)
	≥12.5 kPa	**95** (132/139)	**92** (33/36)	**100** (20/20)	**100** (9/9)	**96** (53/55)	**88** (15/17)
Prior Experience	No prior NS5A	**98** (179/183)	**98** (53/54)	**96** (23/24)	**100** (31/31)	**96** (53/55)	**100** (19/19)
	Prior NS5A	**96** (252/262)	**96** (97/101)	**100** (45/45)	**100** (5/5)	**95** (73/77)	**91** (20/22)
Region	USA	**97** (230/236)	**97** (94/97)	**97** (35/36)	**100** (23/23)	**96** (55/57)	**100** (17/17)
	Non-USA	**96** (201/209)	**97** (56/58)	**100** (33/33)	**100** (13/13)	**95** (71/75)	**92** (22/24)

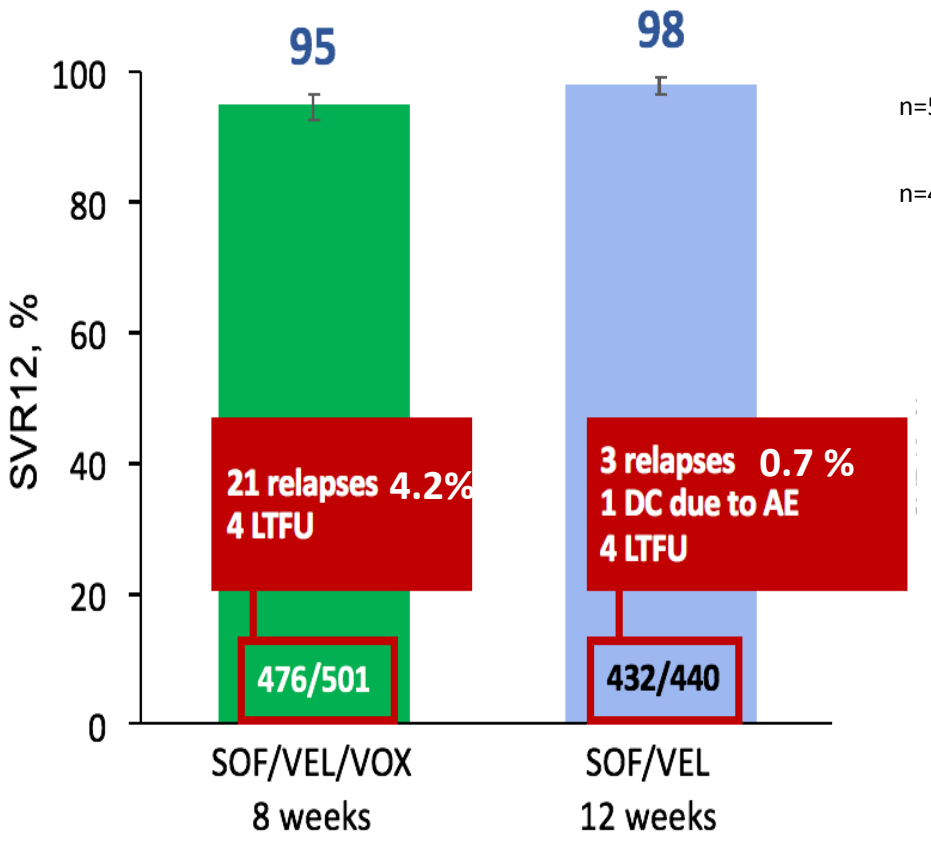
No impact of negative predictive factors on treatment outcomes in DAA-experienced patients treated with SOF/VEL/VOX for 12 weeks

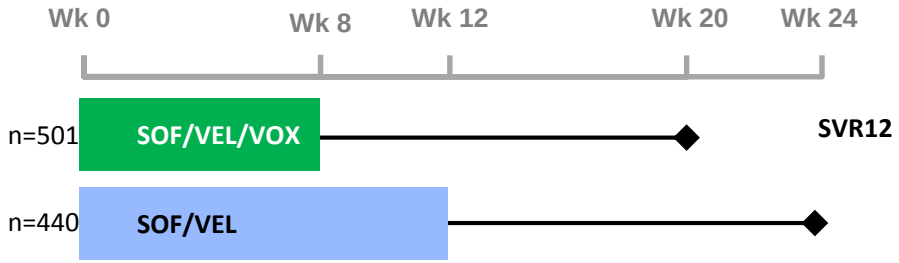
Roberts, EASL 2017, SAT-280

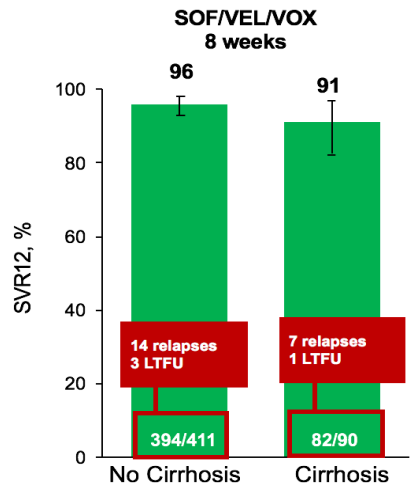
POLARIS-2: **SOF/VEL/VOX for 8 Weeks or SOF/VEL for 12 Wks**

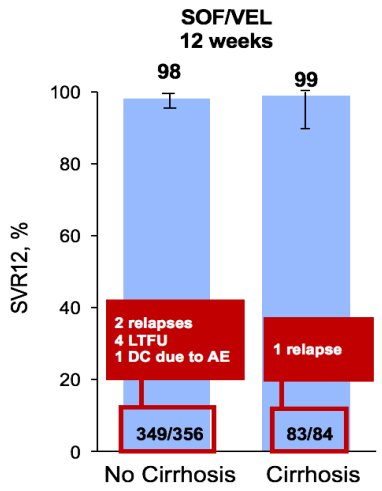
DAA-**Naïve** HCV GT 1–6 ± Cirrhosis (Except GT 3 Cirrhotics)

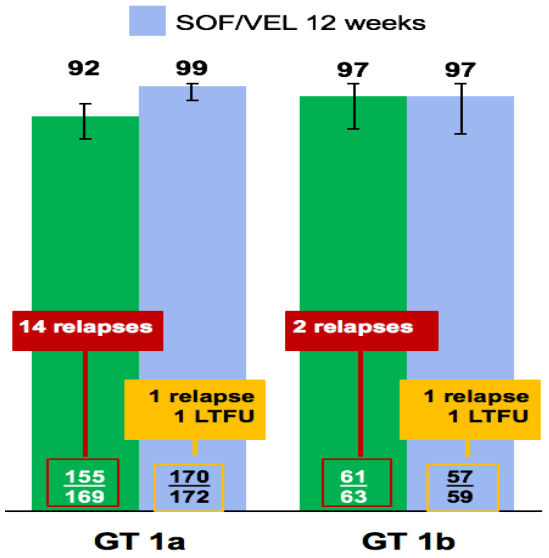
Proportional difference (2-sided 95% CI) -3.4 (-6.2% to -0.6%) noninferiority not met







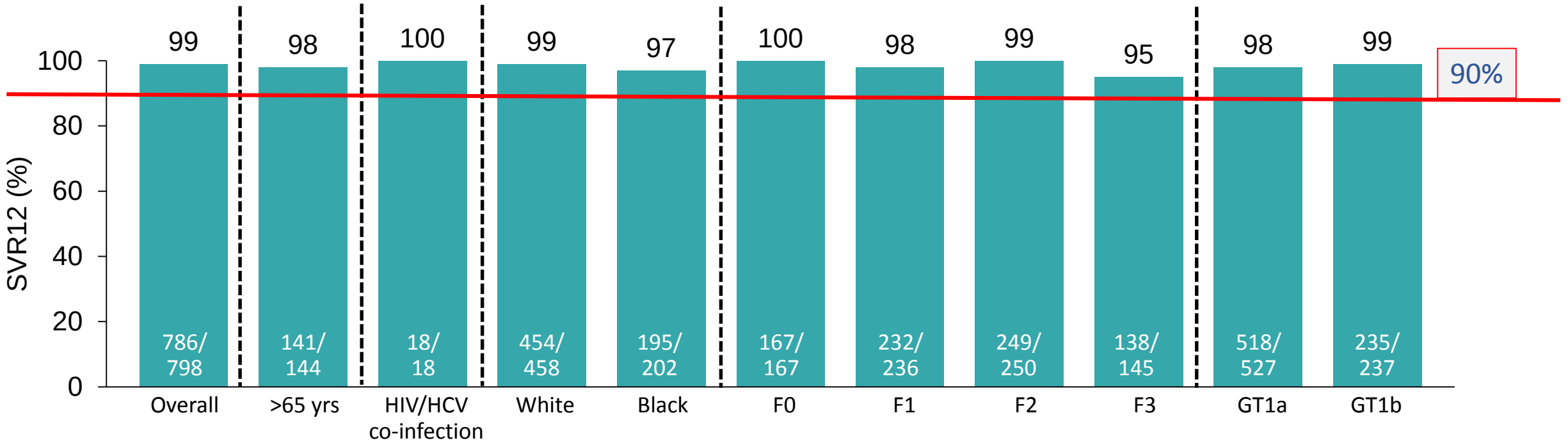




Jacobson IM, AASLD 2016, Oral LB-12

Real-World Analyses of LDV/SOF for 8 Weeks in >6,500 HCV GT1 Treatment-Naive, Non-cirrhotic Patients

Primary Analysis: Per-protocol SVR12 outcomes among patients eligible to receive 8 weeks of LDV/SOF from HCV-TRIO, IFI, Temple University/Burman's Pharmacy, and Kaiser

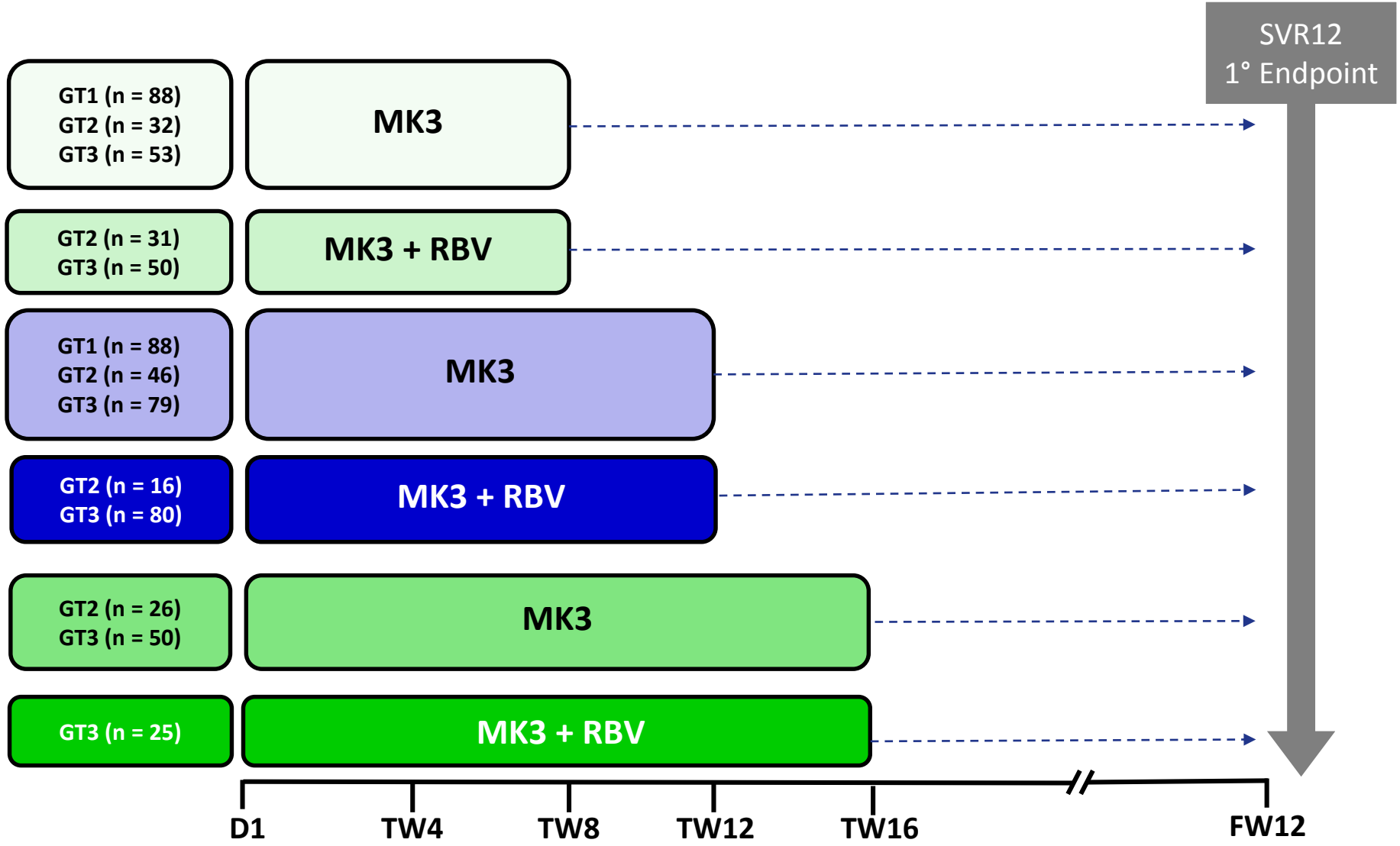


Secondary analysis: Meta-analysis of 6 additional real world cohorts (n=5,637)

- Per protocol SVR12 was 96% (2196/2293) with 8 weeks LDV/SOF and 97% (3251/3344) with 12 weeks LDV/SOF
- Similar risk for relapse between 8 and 12 weeks LDV/SOF (P=0.508)

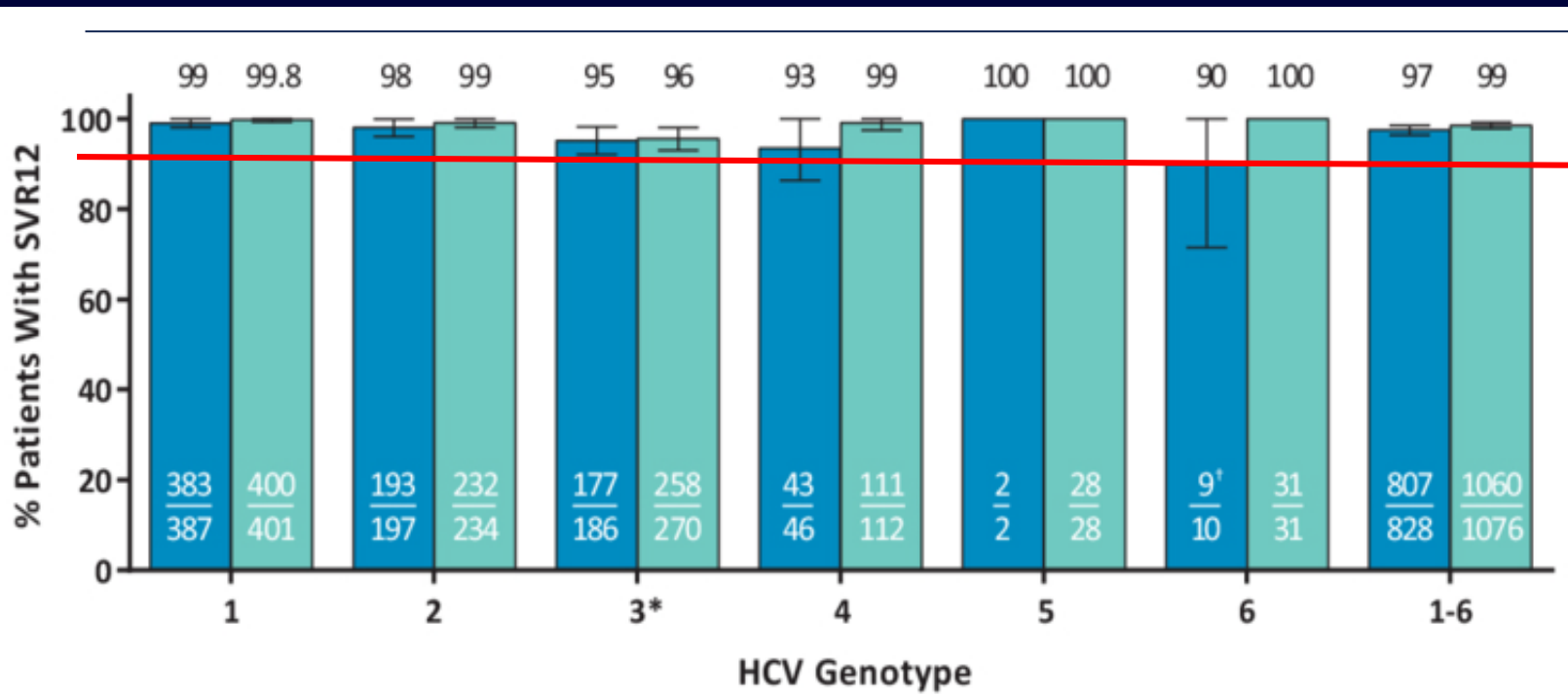
Sundaram V, AASLD 2016, Poster LB-16

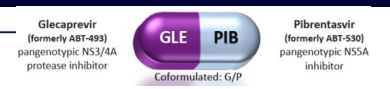
C-CREST: MK3: MK-3682 (Uprifosbuvir)/Grazoprevir/Ruzasvir; N=664



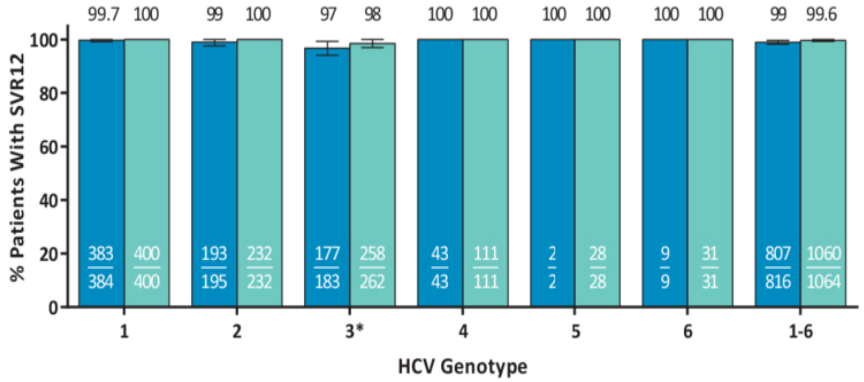
TW=treatment week; FW=follow-up week; RBV=ribavirin

High SVR Rates With Eight and Twelve Weeks of Pangenotypic Glecaprevir/Pibrentasvir: Integrated Efficacy Analysis of Genotype 1–6 Patients Without Cirrhosis





SVR 12 mITT



	8-week treatment		12-week treatment	
	N (%) pts with polymorphism N = 783	N (%) mITT SVR N = 772	N (%) pts with polymorphism N = 1013	N (%) mITT SVR N = 1001
NS3 alone	6 (0.8)	6/6 (100)	14 (1)	14/14 (100)
NS5A alone	122 (16)	119/122 (98)	184 (18)	182/183 (99)
Both NS3/NS5A	3 (0.4)	2/3 (67)	6 (0.6)	5/6 (83)
None	652 (83)	636/641 (99)	809 (80)	796/798 (99.7)

	8-week treatment N = 828	12-week treatment N = 1076
Breakthrough	2 (0.2)	1 (<0.1)
Relapse	7 (0.9)	3 (0.3)
Discontinuation	7 (0.8)	6 (0.6)
Less than 1% virologic failures, <1% Relapse in both arms		

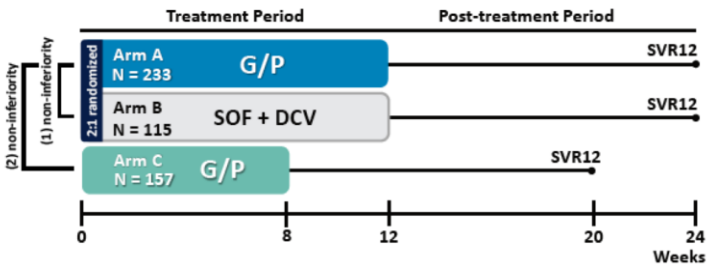
Puoti M et al. The International Liver Congress (EASL) - Amsterdam, 21 April 2017

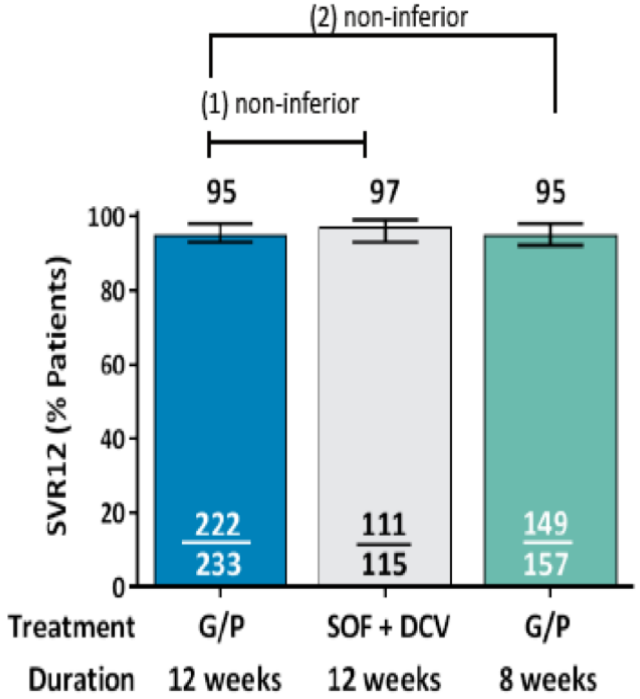
Endurance-3: Glecaprevir/Pibrentasvir versus SOF/DAC in treatment-naïve genotype 3-infected patients without cirrhosis

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

Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor

ENDURANCE-3: Objective and Study Design





Non-inferiority:
Lower bound of the confidence interval (CI) of the difference in SVR12 must be above -6%*

(1) -1.2% (95% CI -5.6 – 3.1)

(2) -0.4% (97.5% CI -5.4 – 4.6)

Both G/P treatments met non-inferiority criteria for the primary endpoint

*Conventional statistical methods were used in multiplicity comparison for determining non-inferiority

Event, n (%)	2:1 randomized G/P 12 weeks N = 233	2:1 randomized SOF + DCV 12 weeks N = 115	Non-randomized G/P 8 weeks N = 157
Any AE	177 (76)	80 (70)	98 (62)
AE with possible relation to DAA	112 (48)	50 (43)	63 (40)
Serious AE	5 (2)	2 (2)	3 (2)
AE leading to study drug d/c	3 (1)	1 (1)	0
AEs occurring in ≥10% of patients			
Headache	60 (26)	23 (20)	31 (20)
Fatigue	44 (19)	16 (14)	20 (13)
Nausea	32 (14)	15 (13)	19 (12)

AE, adverse event; d/c, discontinuation; DAA, direct-acting antiviral; G/P, coformulated glecaprevir/pibrentasvir; DCV, daclatasvir; SOF, sofosbuvir

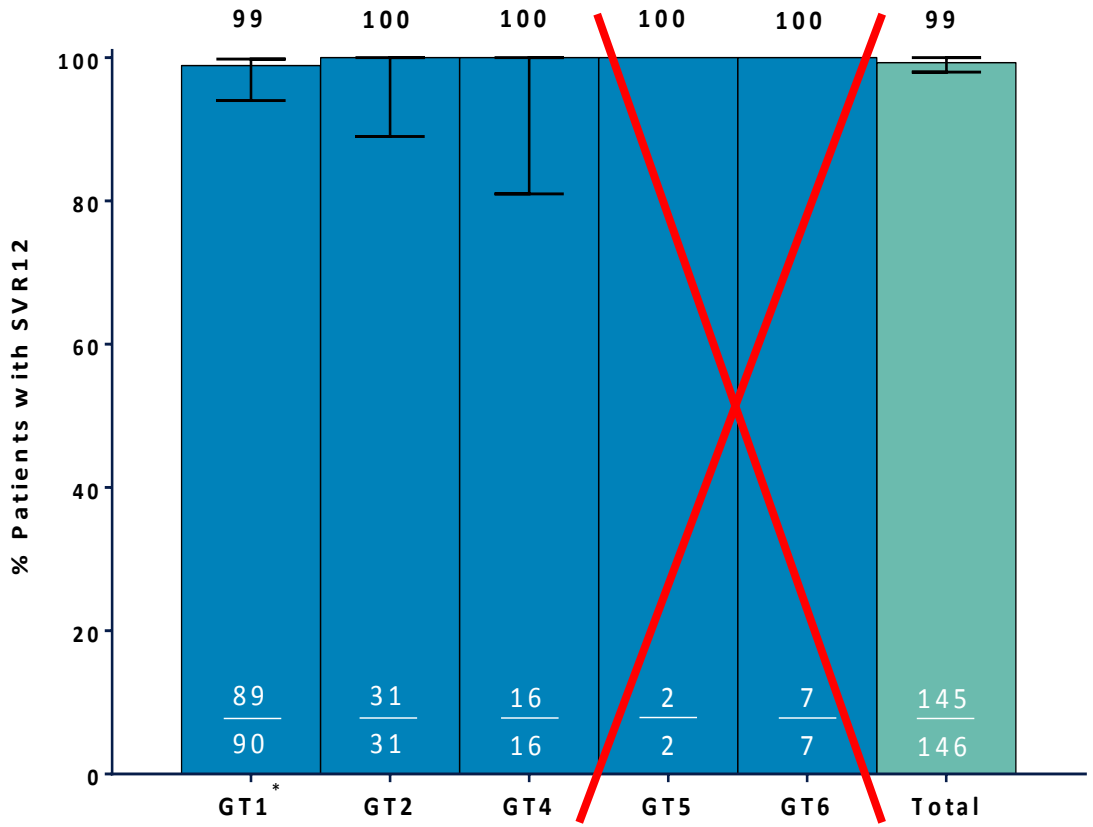
Laboratory abnormalities, n (%)	12-week G/P N=146
Haemoglobin, Grade 3* (<8 g/dL)	1 (0.7)
Alanine aminotransferase, Grade ≥3* (>5 × ULN)	0
Aspartate aminotransferase, Grade ≥3* (>5 × ULN)	0
Platelet count, Grade 3* (<50.0–25.0 x 10^9/L)	2 (1)
Total bilirubin, Grade ≥3* (>3 × ULN)	0
Neutrophil count, Grade 3* (<1.0-0.5 x 10^9/L)	0

ULN, upper limit of the normal range.
*Grade higher than baseline

EXPEDITION-I Genotype 1, 2, 4, 5 or 6 Infection in Adults with Compensated Cirrhosis. SVR12 by Intent-to-Treat (ITT) Analysis

Glecaprevir (formerly ABT-493) pangenotypic NS3/4A protease inhibitor — GLE PIB — Coformulated: G/P — Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor

12-week treatment, no Riba



*Patient with HCV GT1a infection relapsed at PTW8
- No treatment-emergent substitutions were present in NS3
- In **NS5A, Y93N was present at baseline;**
- **Y93N, Q30R and H58D** were present **at the time of failure**

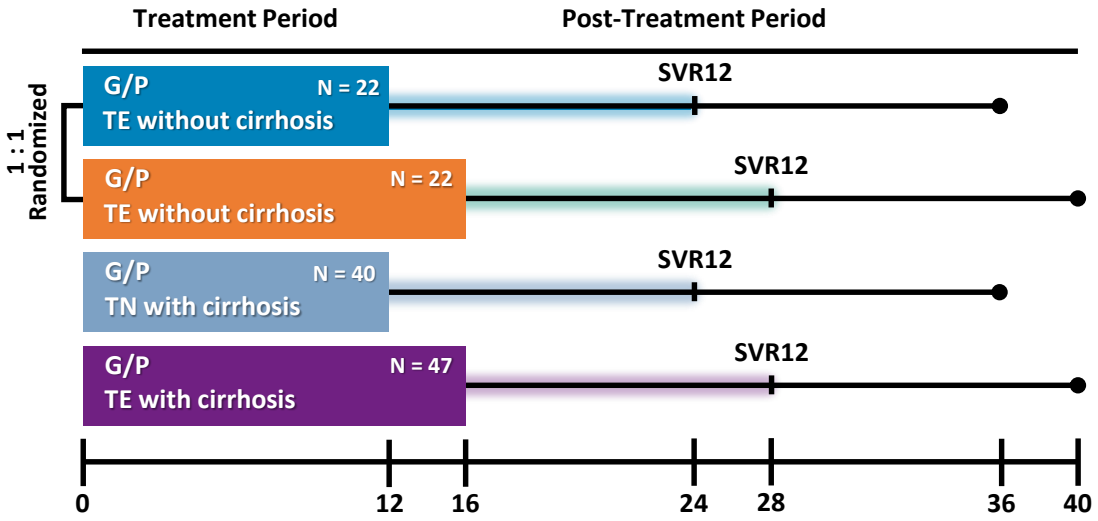
	12-week G/P N = 146
HCV RNA, median (range) log_{10} IU/mL	6.1 (3.1–7.4)
Treatment-naïve	110 (75)
Treatment-experienced	36 (25)
IFN-based (IFN/pegIFN ± RBV)	25 (69)
SOF-based (SOF + RBV ± pegIFN)	11 (31)
Platelet count <100,000, 10^9/L	29 (20)
INR <1.7	144 (99)
Total bilirubin ≥2, mg/dL	5 (3)
Albumin ≥LLN	145 (99)
Child-Pugh score at screening	
5	133 (91)
6	13 (9)

Target(s), n (%)*	12-wek G/P N = 133*
None	76 (57)
NS3 only (NS3: 155, 156, 168)	2 (2)
NS5A only (NS5A: 24, 28, 30, 31, 58, 92, 93)	53 (40)
NS3 + NS5A	2 (2)

*Baseline polymorphisms relative to appropriate subtype specific reference sequence at 15% detection threshold by next generation sequencing in samples that had sequences available for both targets (N)

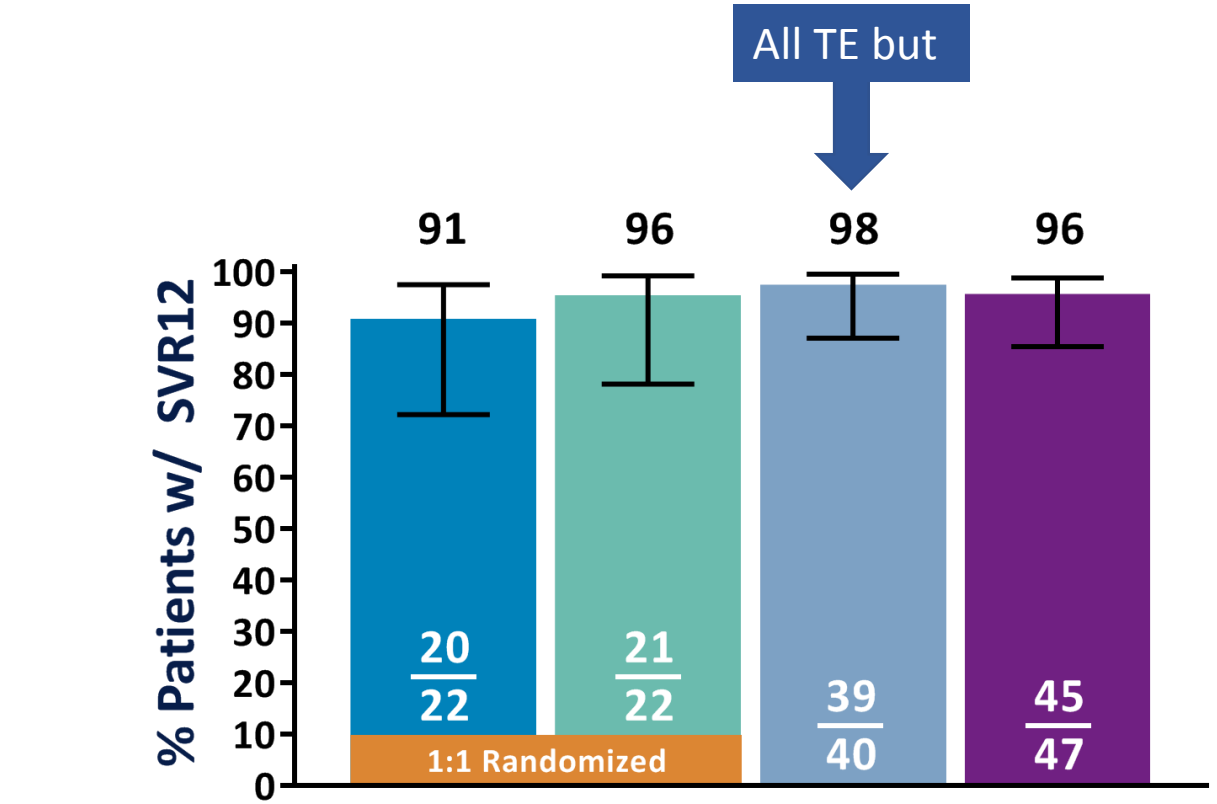
GLECAPREVIR/PIBRENTASVIR in patients with **Genotype-3 infection,** TREATMENT EXPERIENCED with or without CIRRHOSIS

Glecaprevir (formerly ABT-493) pangenotypic NS3/4A protease inhibitor — GLE PIB — Coformulated: G/P — Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor



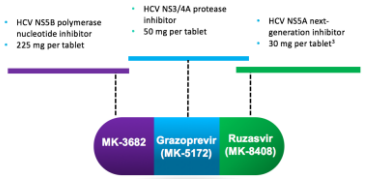
Coformulated , dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg

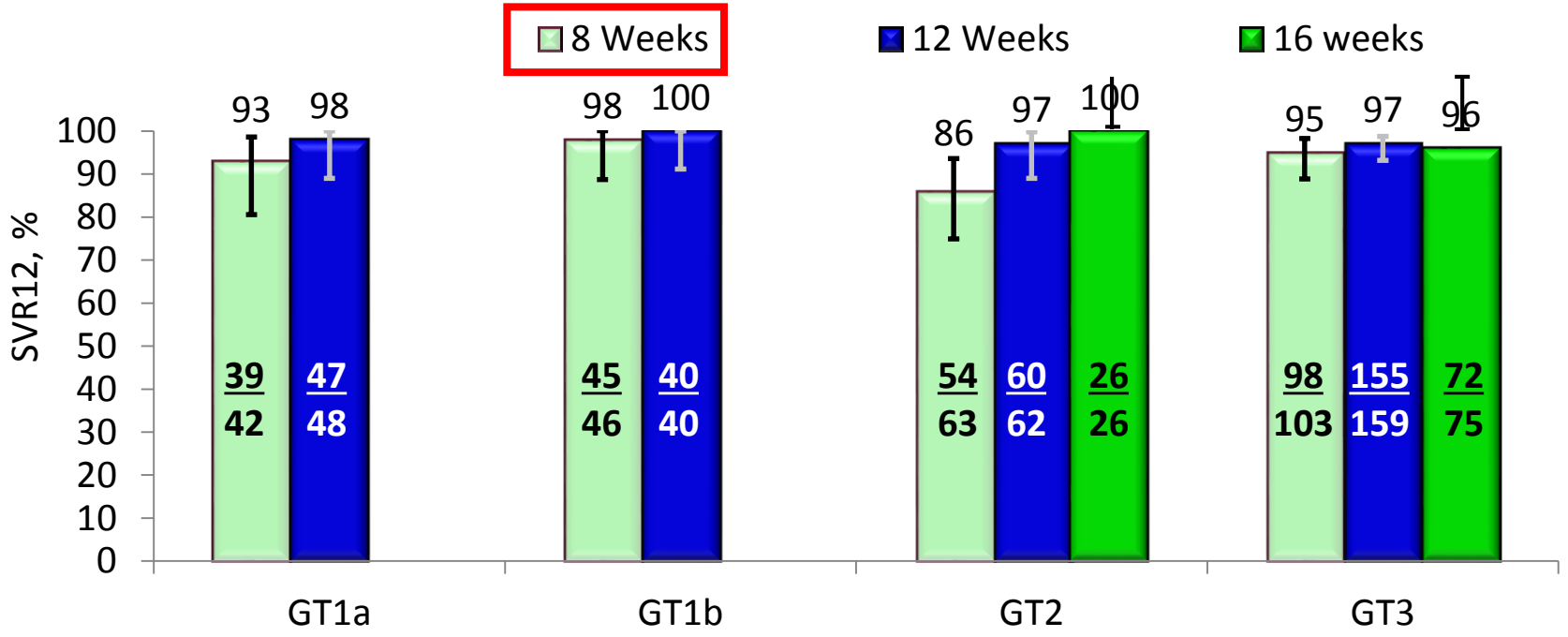
- Without cirrhosis or with compensated cirrhosis
- Treatment-naïve or treatment-experienced with interferon (IFN)/pegIFN ± RBV, or SOF + RBV ± pegIFN therapy



Weeks	12	16	12	16
Cirrhosis	-	-	+	+
T-Experience	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

MK-3682/Grazoprevir/MK-8408 (Ruzasvir) With or Without Ribavirin in **Non-cirrhotic or Cirrhotic** Patients with Chronic **HCV GT1, 2 or 3** Infection





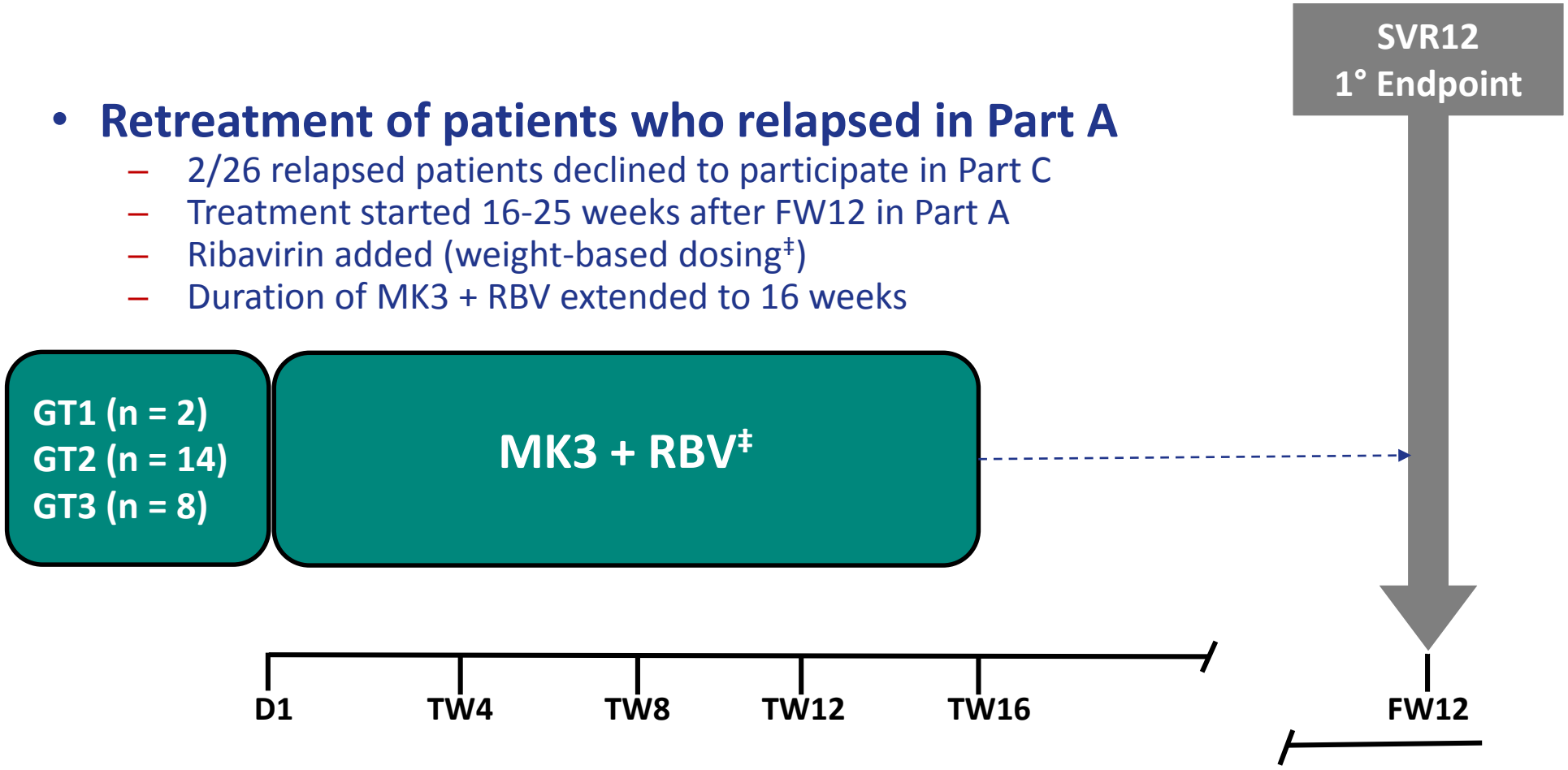
	GT1a		GT1b		GT2			GT3			Total
Relapse	**2**	**0**	**1**	**0**	**7**	**0**	**0**	**4**	**3**	**2**	**19**
Discontinuation (DR-AE)*	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**
Reinfection*	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
Non-virologic failure*	**0**	**1**	**0**	**0**	**1**	**2**	**0**	**1**	**1**	**1**	**7**

*GT1a 8 weeks, No RBV: 1 patient achieved SVR8 but was reinfected with a different HCV strain by phylogenetic analysis at FW12; GT1a 12 weeks, No RBV: 1 patient died due to study-drug unrelated bacterial sepsis; GT2 8 weeks + RBV: 1 patient discontinued at Day 5 due to drug-related AEs of fatigue, malaise; 1 patient lost to follow-up; GT2 12 weeks, No RBV: 2 patients lost to follow-up; GT3 8 weeks, RBV arm: 1 patient lost to follow-up; GT3 12 weeks, No RBV: 1 patient withdrew due to pregnancy, lost to follow-up; GT3 16 weeks arm: 1 patient lost to follow-up

Eric Lawitz et al, EASL 2017

16 Weeks of MK-3682 / Grazoprevir / Ruzasvir Plus Ribavirin in HCV GT1, 2 or 3 who failed 8 Weeks of Therapy (Part C of C-CREST-1 & 2)

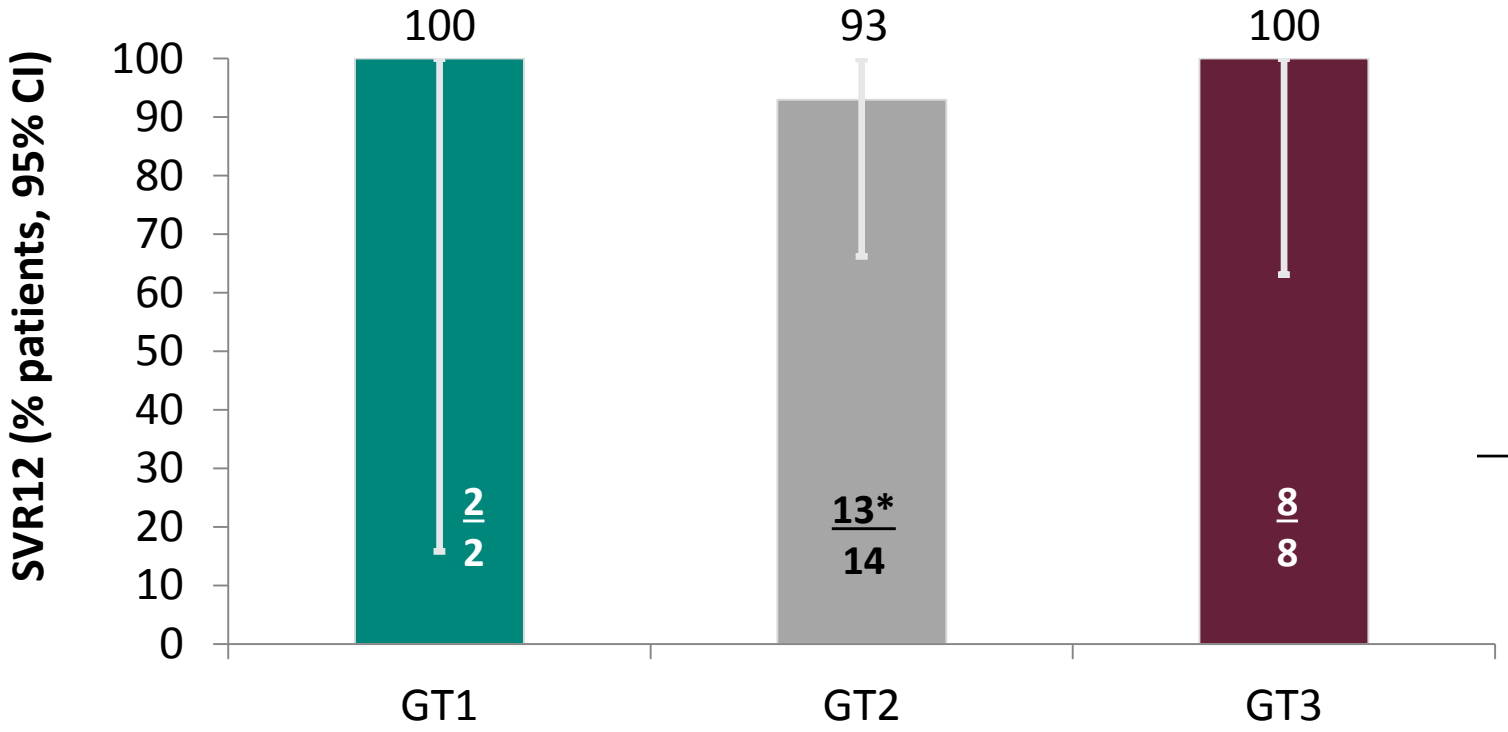
- **Retreatment of patients who relapsed in Part A**
  - 2/26 relapsed patients declined to participate in Part C
  - Treatment started 16-25 weeks after FW12 in Part A
  - Ribavirin added (weight-based dosing‡)
  - Duration of MK3 + RBV extended to 16 weeks

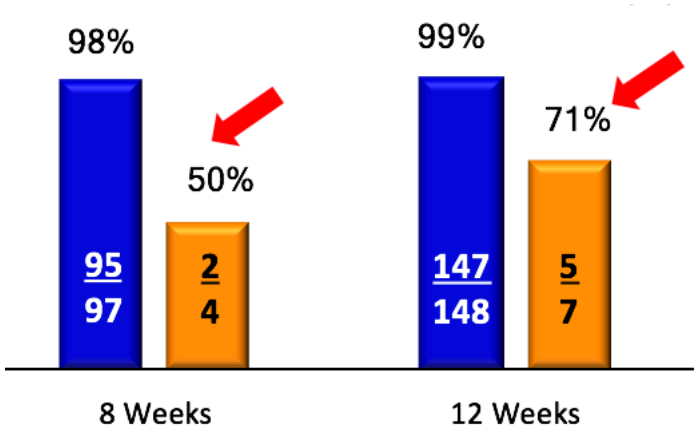


‡ RBV dose based on body weight (<65 kg=800 mg/d; 65-85 kg=1000 mg/d; >85-105 kg=1200 mg/d; >105 kg=1400 mg/d)
TW=treatment week; FW=follow-up week; RBV=ribavirin

Lawrence Serfaty et al. EASL 2017

16 Weeks of MK-3682 / Grazoprevir / Ruzasvir Plus Ribaviri in HCV GT1, 2 or 3 who failed 8 Weeks of Therapy (Part C of C-CREST-1 & 2)





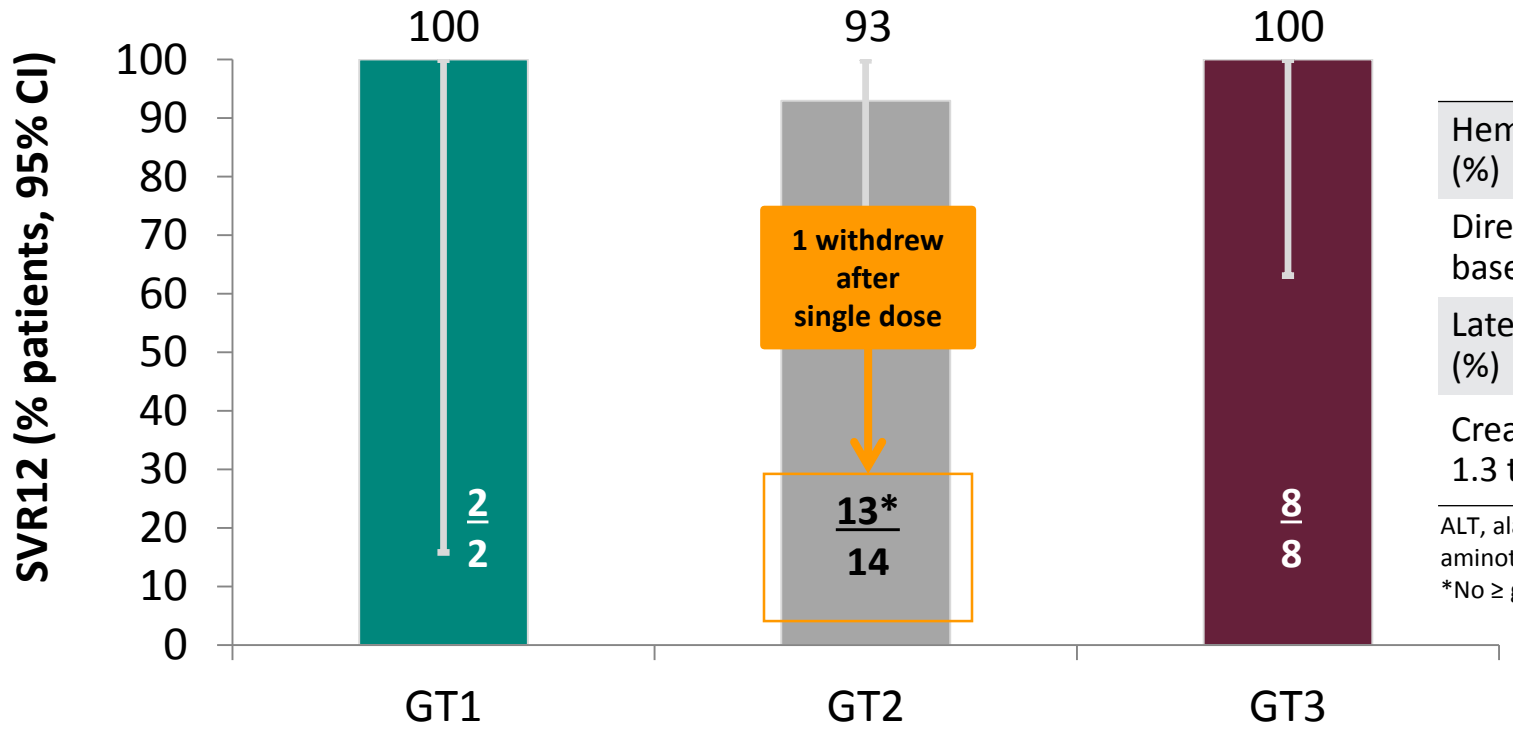
Relapse	**0**	**0**	**0**
Discontinued	**0**	**1**	**0**

†Full Analysis Set includes all patients who received ≥ 1 dose of study drug
*One GT2 patient withdrew after a single dose with SAEs of vomiting and tachycardia

Lawrence Serfaty et al. EASL 2017

16 Weeks of MK-3682 / Grazoprevir / Ruzasvir Plus Ribaviri in HCV GT1, 2 or 3 who failed 8 Weeks of Therapy (Part C of C-CREST-1 & 2)

* GT2-infected patient withdrew after a single dose with SAEs of vomiting and tachycardia considered related to MK3 + RBV.



Event, n (%)	N = 24
Hemoglobin <10 g/dL, n (%)	2 (8)
Direct bilirubin >5X baseline, n (%)	0
Late ALT/AST >5X ULN*, n (%)	0
Creatinine Grade 1 (1.1-1.3 times ULN), n (%)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal
*No ≥ grade 2 ALT/AST elevations

Relapse	**0**	**0**	**0**
Discontinued	**0**	**1**	**0**

†Full Analysis Set includes all patients who received ≥ 1 dose of study drug
*One GT2 patient withdrew after a single dose with SAEs of vomiting and tachycardia

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Conclusions

- New available regimes improve antiviral treatment
- All Genotype infections may more easily be controlled
- Future safe sgort and effective regimens will offer to easy-to-treat patients the opportunity of being cured