¿Existen aún pacientes infectados por Hepatitis C dificiles de curar?

Maria Buti
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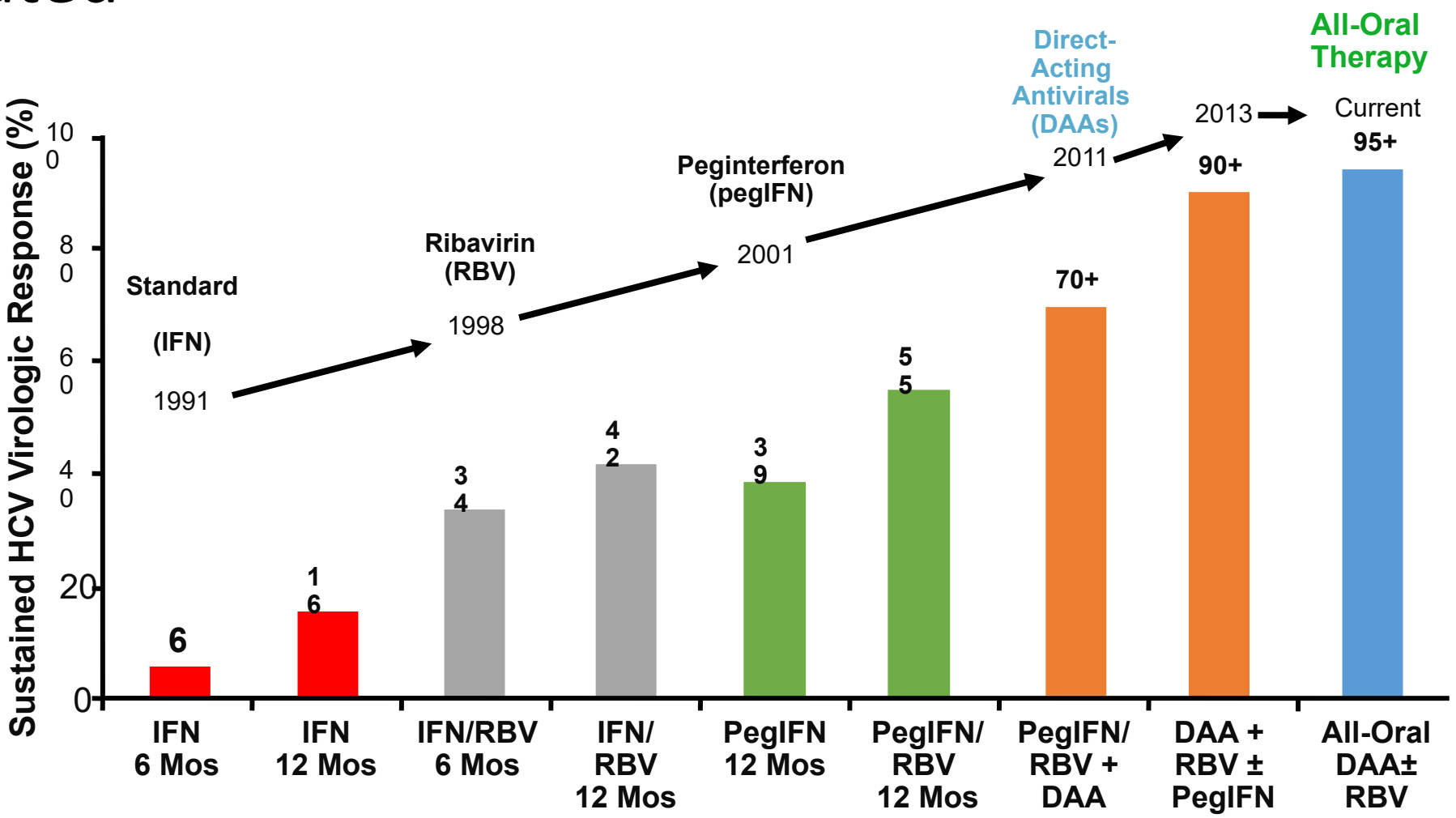
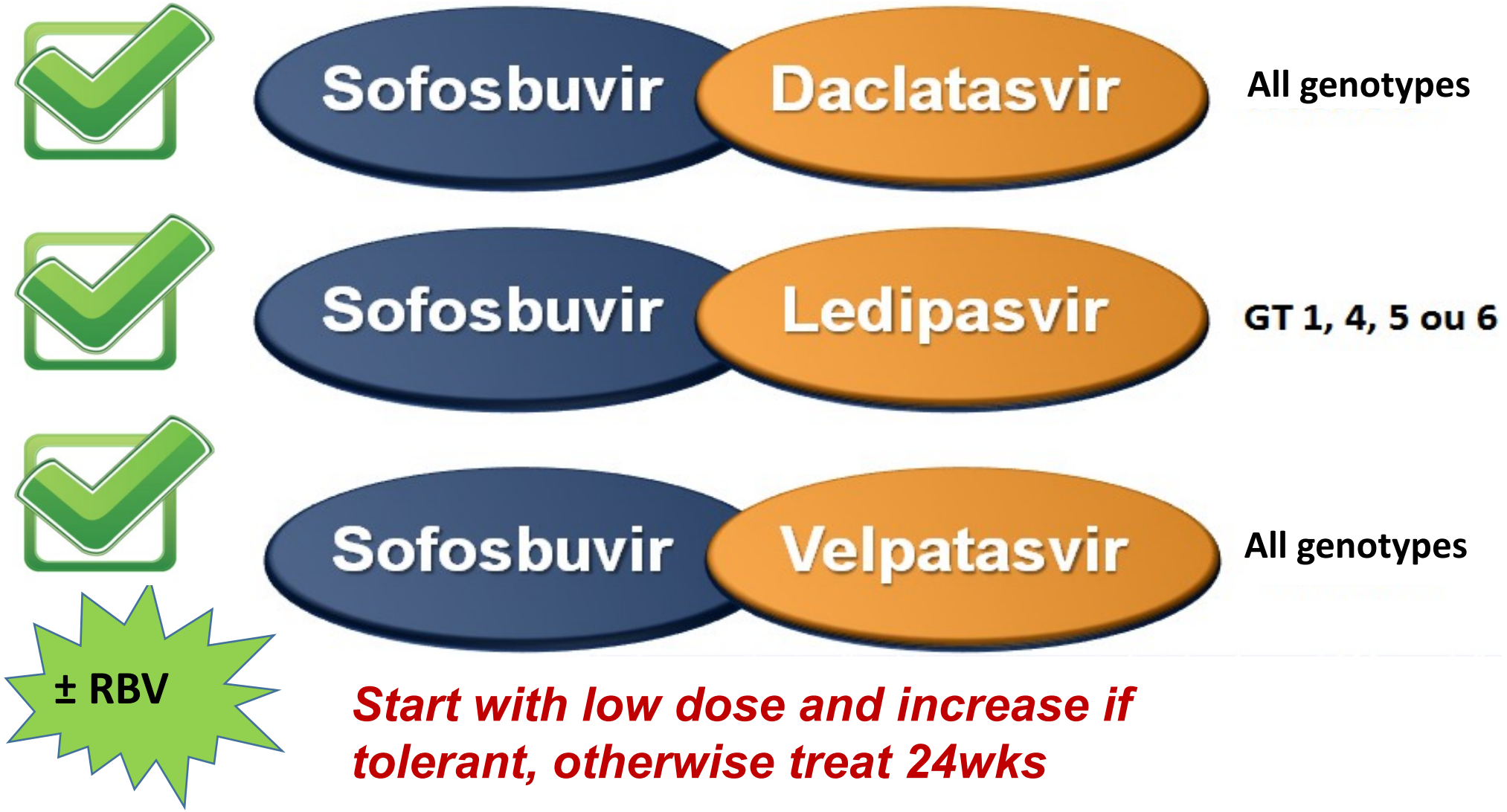
Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



HCV Positive subjects difficult to cure

- Decompensated Liver Disease
- Renal failure
- Genotype 3
- Drug-Drug Interactions
- Failure to Pangenotype Drugs

Only Combinations Without Protease Inhibitors Allowed



Start with low dose and increase if tolerant, otherwise treat 24wks

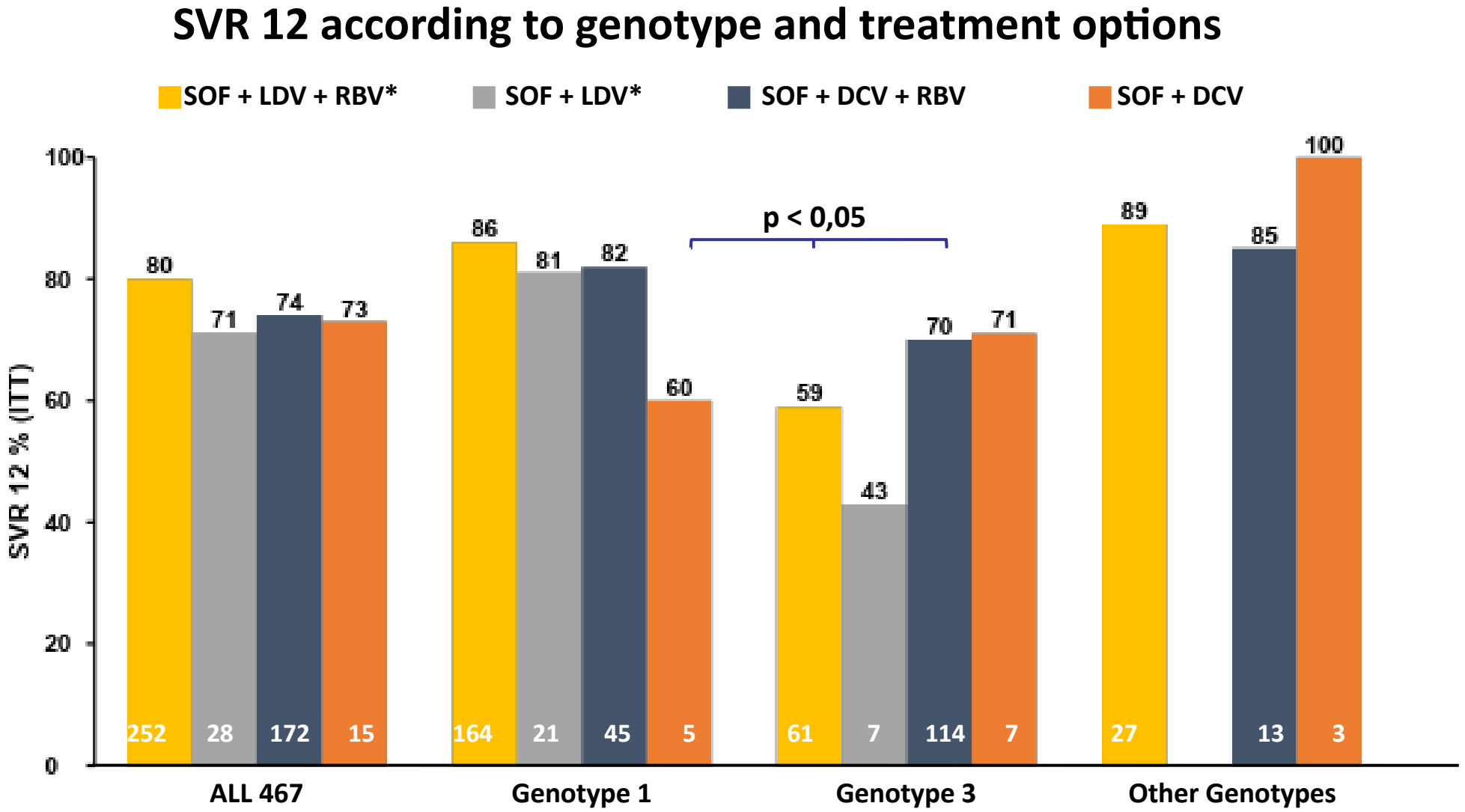
EASL Guidelines on HCV. J Hepatol 2018

SVR in Patients With Decompensated Cirrhosis

Lack of data for MELD >20

	Regimen	N	SVR-12	MELD > 15	MELD > 20
SOLAR (Gane E, et al. APASL 2016)	LDV/SOF* +/- RBV	140	57-89%	54	5
ALLY-1 (Poordad F, et al. Hepatology 2016)	SOF + DCV + RBV	60	56-94%	14	3
ASTRAL-4 (Curry MP, et al. NEJM 2015)	SOF/VEL* +/- RBV	267	50-100%	13	NA

Decompensated Cirrhosis Treated with SOF+NS5A±RBV



Foster G et al. EASL 2015, Abs. O002

SOF/VEL ± RBV for the Treatment of GT 3 Cirrhotic Patients

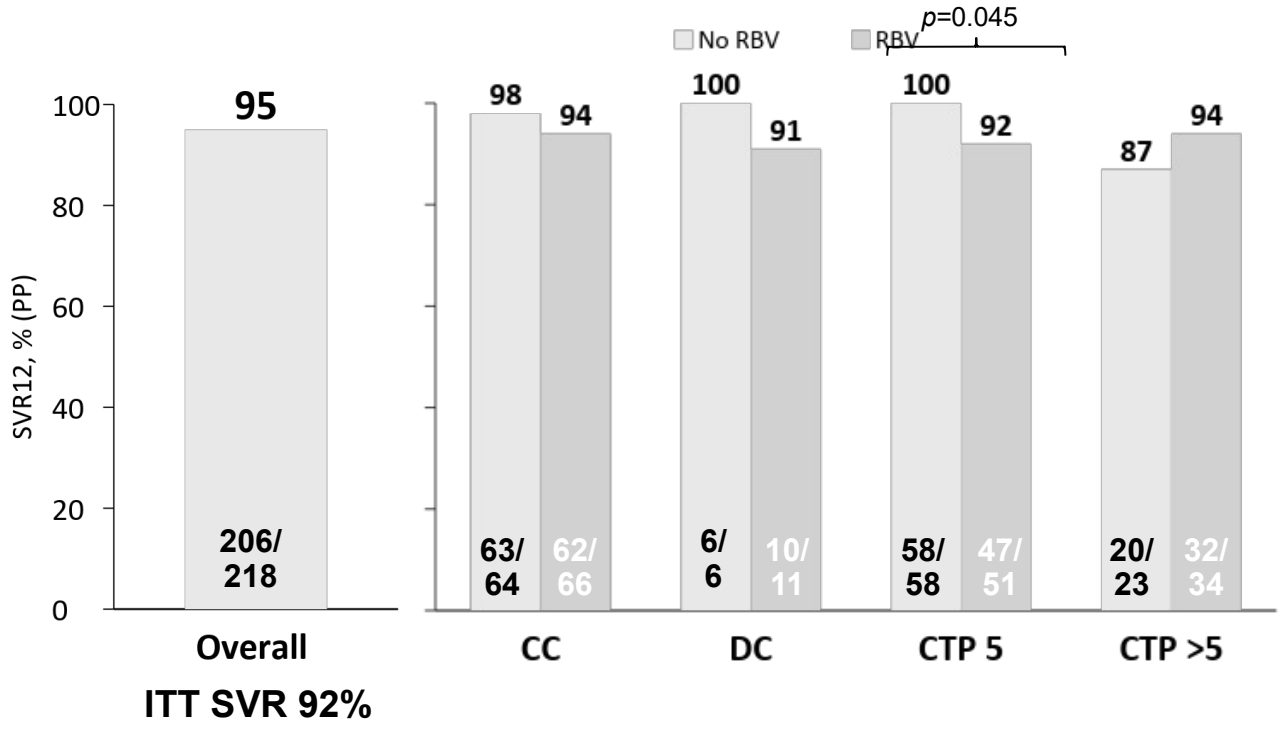
Multicentre study of SOF/VEL±RBV in patients with GT 3 with compensated and decompensated cirrhosis from 33 Italian network databases

Baseline Demographics

	n=276
SOF/VEL, %	59
SOF/VEL+RBV, %	41

11% patients had DC

- 5 patients D/C therapy for non-liver related issues



ITT SVR 92%

Overall SVR12 in GT 3 patients with CC is high

HCV Positive subjects difficult to cure

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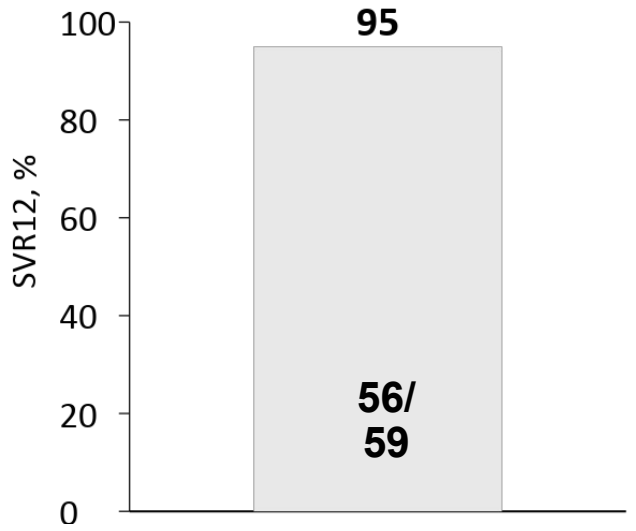
‡

SOF/VEL for 12 Weeks in Patients Undergoing Dialysis*

Baseline Demographics

	SOF/VEL n=59
Mean age, y (range)	60 (33–91)
Male, n (%)	35 (59)
White, n (%)	31 (53)
Mean BMI, kg/m^2 (range)	26 (17–39)
HCV GT, % 1 / 2 / 3 / 4-6 / Indeterminate	44 / 12 / 27 / 10 / 9
CC, n (%)	17 (29)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6 (3.1–7.7)
Prior TE, n (%)	13 (22)
Type of dialysis, n (%) Haemodialysis Peritoneal dialysis	 54 (92) 5 (8)
Mean duration of dialysis, y (range)	7 (0–40)
Prior renal transplant, n (%)	19 (32)



Safety profile of SOF/VEL in patients undergoing dialysis was consistent with advanced renal disease, with no treatment-related events

*No Dosage Recommendations in Severe Renal Impairment and End Stage Renal Disease

Borgia, AASLD 2018, LB-15

SOF/VEL for 12 Weeks in Patients Undergoing Dialysis*

Safety Summary

Patients, n (%)	SOF/VEL n=59
AE	47 (80)
Grade 3 AE	7 (12)
Treatment related	0
Serious AE	11 (19)
Treatment related	0
Treatment D/C due to AE	0
Death	2 (3)
Grade 3 or 4 lab abnormality	25 (42)

- Despite a 1719% higher AUC of the SOF metabolite GS-33107 seen in phase 2 and 3 studies, no serious, or Grade 3 or 4 AEs were reported for >1 patient
- 1 patient died of suicide after SVR4; another died of metastatic lung cancer after SVR12 (both considered not related to study drug)

Adverse Events in ≥10% of Patients

Patients, n (%)	SOF/VEL n=59
Headache	10 (17)
Fatigue	8 (14)
Nausea	8 (14)
Vomiting	8 (14)
Insomnia	6 (10)

Grade 3 or 4 Laboratory Abnormalities in >1 Patient

Patients, n (%)**	SOF/VEL n=59
Decreased haemoglobin	
Grade 3	4 (7)
Elevated creatinine	
Grade 3	1 (2)
Grade 4	14 (24)
Elevated glucose	
Grade 3	5 (8)
Elevated potassium	
Grade 3	2 (3)
Grade 4	1 (2)

Borgia, AASLD 2018, LB-15

HCV Positive subjects difficult to cure

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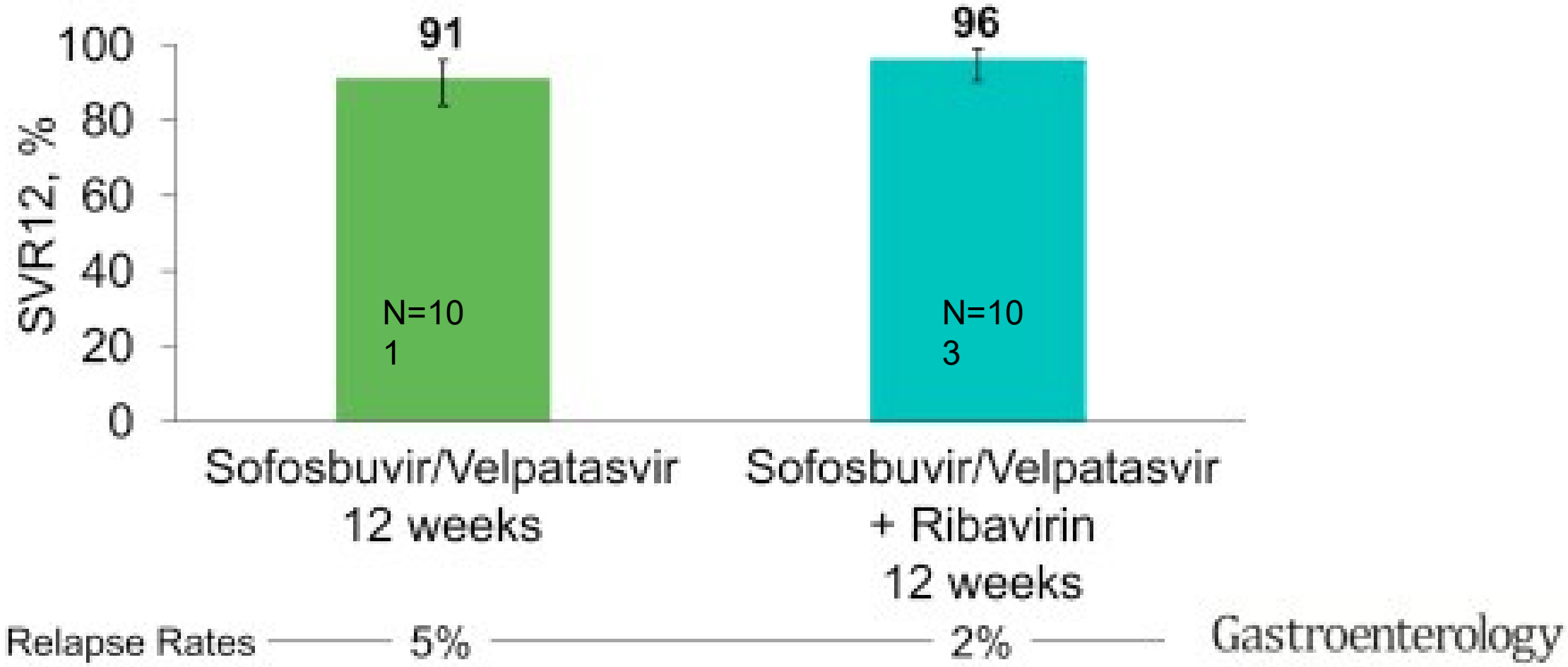
SOF/VEL IN Genotype 3 cirrhosis. With or without ribavirin?



With RAS
SVR
84%

With RAS
SVR
96%

Esteban R et al Gastronterology

SOF/VEL in GT 3 HCV with Compensated Cirrhosis

Retrospective analysis of pooled efficacy data from 337 patients treated with SOF/VEL for 12 weeks

Studies

	Description / Total patients who received SOF/VEL, (n)	GT 3/CC patients who received SOF/VEL, n (%)
Ph 2	Spain GT 3 and cirrhosis (101)	101 (100)
	POLARIS-3 GT 3 and cirrhosis (109)	109 (100)
	ASTRAL-3 GT 3 (250)	80 (32)
Ph 3	India GT 1-6 (129)	33 (26)
	Russia/Sweden GT 1-6 (119)	11 (9)
	ASTRAL-5 GT 1-6 and HCV/HIV (106)	3 (3)

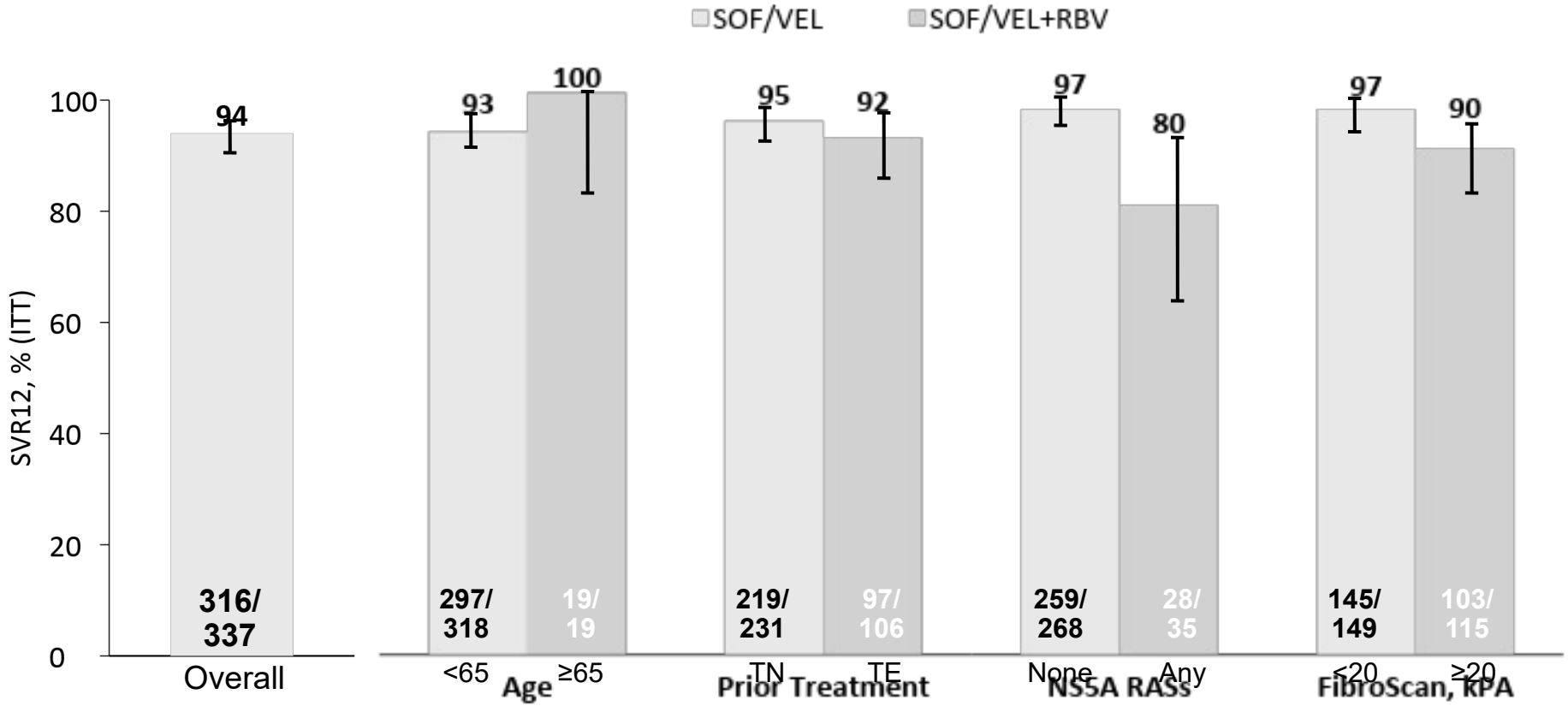
Baseline Demographics

	Total **n=337**
Mean age, y (range)	53 (21–76)
Male, n (%)	247 (73)
White, n (%)	266 (79)
HCV/HIV co-infection, n (%)	19 (6)
TE, n (%)	106 (31)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (1.9–7.5)
NS5A RASs, n (%)	35 (12)
Median FibroScan score, kPA* (Q1, Q3)	18 (14, 26)
Median platelet count, $x10^3/mm^3$ (Q1, Q3)	142 (102, 184)
Platelets ≤100 $x10^3/mm^3$, n (%)	76 (23)

kPA: kilopascals

Roberts, AASLD 2018, 628

SOF/VEL in GT 3 HCV with Compensated Cirrhosis



SOF/VEL for 12 weeks was a highly effective treatment for patients with HCV GT 3 and CC

Roberts, AASLD 2018, 628

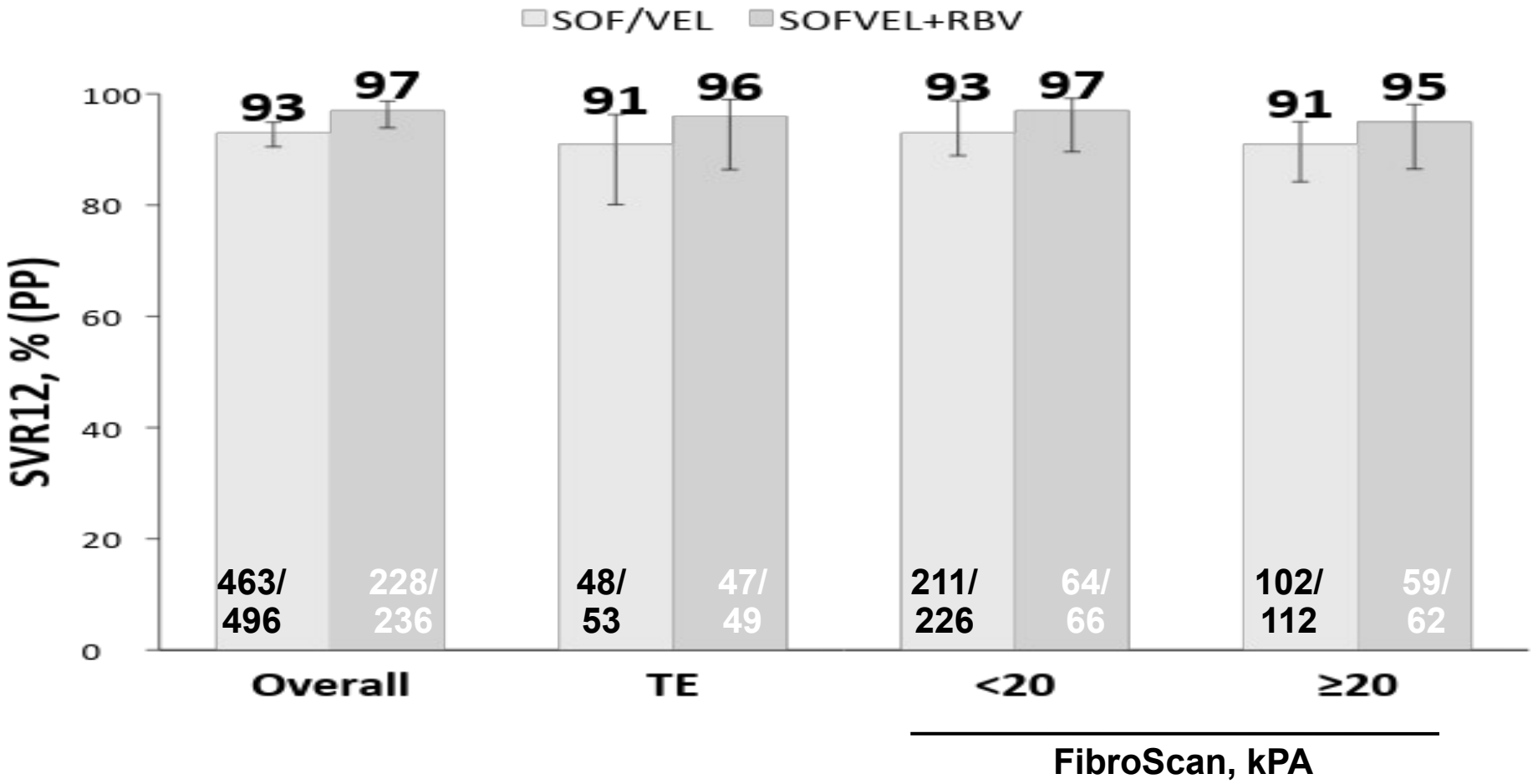
‡

SOF/VEL in GT 3 HCV with Compensated Cirrhosis

Baseline Demographics	SOF/VEL n=496	**SOF/VEL+RBV n=236**
Mean age, y (range)	55 (25-85)	53 (25-83)
Male, n (%)	334 (72)	147 (75)
White, n (%)	268 (67)	127 (76)
TE, n (%)	53 (11)	49 (21)
Median FibroScan, kPa (IQR)	16 (13-22)	19 (14-30)
Median platelets x10^3/mm^3 (IQR)	130 (94-169)	116 (76-159)
Median albumin, g/dL (IQR)	4 (3.7-4.3)	4 (3.6-4.2)

kPA: kilopascals

SOF/VEL in GT 3 HCV with Compensated Cirrhosis



GT 3 patients with CC from multiple real-world cohorts achieved a high SVR with SOF/VEL

kPA: kilopascals

Fagiuoli, AASLD 2018, 606

HCV Positive subjects difficult to cure

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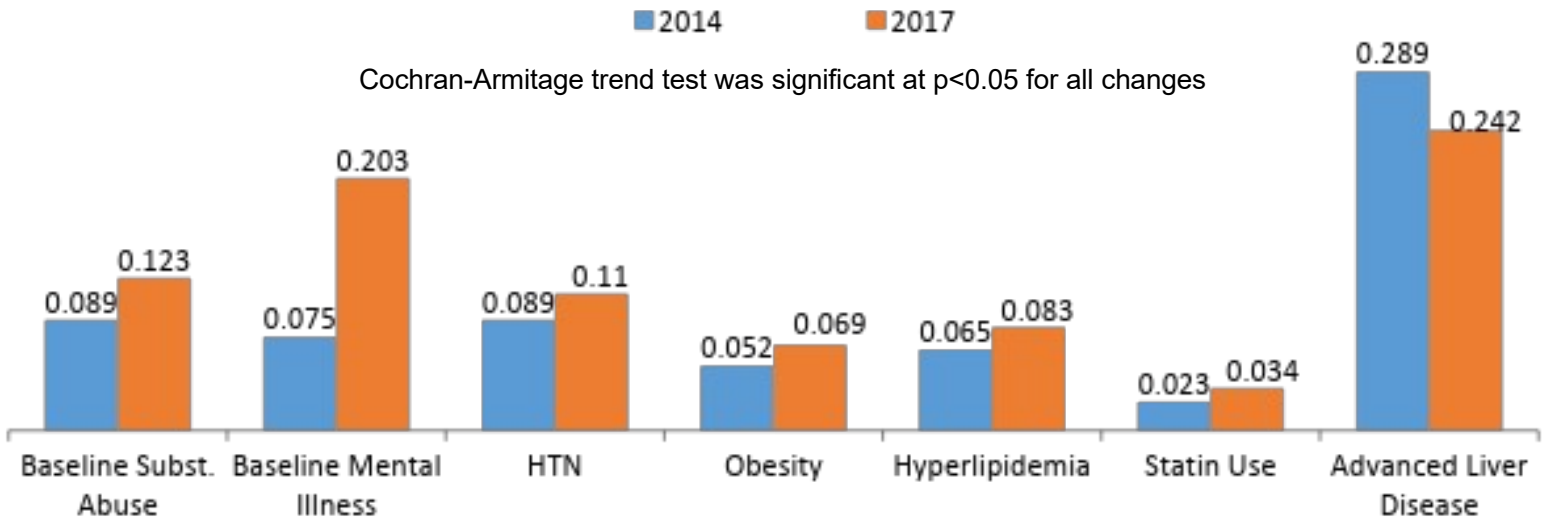
US administrative claims IQVIA PharMetrics Plus database

‡

Changes in the Characteristics of HCV Patients Treated with DAAs, 2014–2017

Study of commercially-insured HCV patients receiving any DAA

Characteristics of DAA-Treated Patients by Year of Treatment Initiation



Advanced liver disease patients still make up ~24% of the population;
Prevalence of mental illness has increased among DAA-treated patients

Singer, AASLD 2018, 621

‡

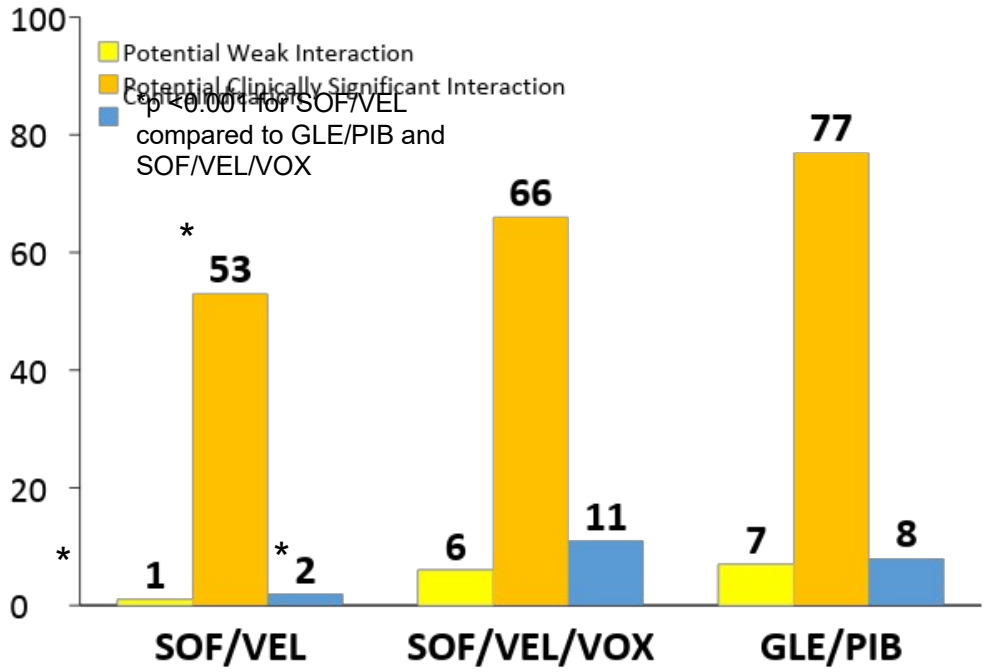
Impact of Comorbidities on Potential DDIs with Pangenotypic HCV DAAs

Retrospective, multicentre longitudinal observational study of comorbidities and DDIs among DAAs from computerised medical records

Baseline Demographics

	n=3,430
Male, %	60
Average age, years (SD)	57±13
Comorbidities, %	
Anxiety	36
Arterial hypertension	27
Active smokers	23
Dyslipidemia	20
Medications per patient per year, n (SD)	3.6 (2.7)
Time since diagnosis, years (SD)	15 (3)
BMI, kg/m^2 (SD)	28 (5)

Potential DDIs by DAA



SOF/VEL has fewer DDIs when compared to PI-containing regimens

Sicras Mainar, AASLD 2018, 650

Important drug-drug interactions* (DDI) of dual antiviral combinations

	DDI
Sofosbuvir + Ledipasvir	Amiodaron, anticonvulsants, antacids, PPI (high dose), rifampicin, St John‘s Worth, statins
Sofosbuvir + Velpatasvir	Amiodaron, anticonvulsants, antacids, PPI (high dose), rifampicin, efavirenz, St John‘s Worth, statins
Grazoprevir + Elbasvir	Dabigatran, anticonvulsants, antimycotics, bosentan, St John‘s Worth, atazanavir, darunavir, lopinavir, u.a., efavirenz, statins, ciclosporin, modafinil
Glecaprevir + Pibrentasvir	Dabigatran, anticonvulsants, rifampicin, ethinylestradiol, St John‘s Worth, atazanavir, darunavir, efavirenz, statins, ciclosporin, omeprazol

*HEP Drug Interactions, University of Liverpool: http://www.hep-druginteractions.org
*HEP Mobile Apps (Apple, Android)

But some challenges remain with e.g. anticonvulsants, herbal preparations, etc.

Successful HCV treatment of patients on contraindicated anti-epileptic drugs: Role of drug level monitoring

Patient		AED	HCV				DAA exposure $AUC_{0\text{-}24h}$ (h * g/L)^		
Gender	Age (yr)	Drug and daily dose	Genotype	Cirrhosis	Pre-treated	Treatment	DAC	SOF	GS-331007
Ref[1,2]							**14.12**	**1.01**	**7. 20**
#1 Male	56	CBZ: 400 mg	1	No	No	SOF: 400 mg QD DAC: 60 mg BID 12 weeks	4.75	0.913	7.60
#2 Male	71	CBZ: 1,000 mg	1b	No	Yes	SOF: 400 mg QD DAC: 60 mg BID	1.48	0.347	12.70
						DAC: 60 mg TID¥ 24 weeks	4.38	0.383	13.16
#3 Male	45	CBZ: 1,200 mg PHB: 225 mg	3a	Yes	No	SOF: 400 mg QD DAC: 60 mg TID RBV: 600 mg BID 24 weeks	3.98	–	–
#4 Male	53	CBZ: 1,200 mg	1a	No	No	SOF: 400 mg QD DAC: 60 mg TID 12 weeks	3.09	0.328	4.42
#5 Female	70	PHE: 225 mg	1b	Yes	Yes	SOF: 400 mg QD DAC: 60 mg TID 12 weeks	18.32	–	–
#6 Female	47	PHB: 100 mg	1b	No	No	SOF: 400 mg QD DAC: 60 mg TID 12 weeks	42.57	2.327	10.18

AED, anti-epileptic drug; $AUC_{0\text{-}24h}$, area under the concentration–time curve over the complete dosing interval; BID, twice daily; CBZ, carbamazepine; DAC, daclatasvir; HCV, hepatitis C; PHB, phenobarbital; PHE, phenytoin; QD, once daily; RBV, ribavirin; SOF, sofosbuvir; TID, 3 times daily; yr, year.

^ Extrapolated AUC.

¥ Due to suboptimal exposure the DAC dose was increased to 60 mg TID.

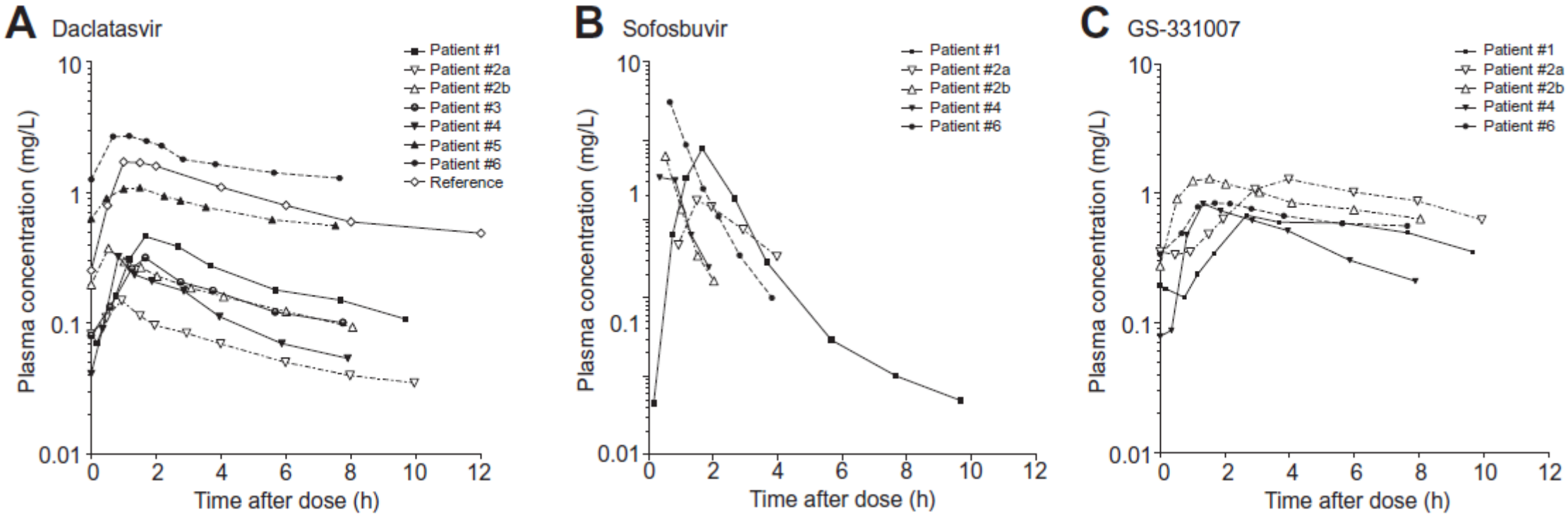
[1] Summary of Product Characteristics for daclatasvir.

[2] Summary of Product Characteristics for sofosbuvir.

Seyen M et al J Hepatol 2018

Successful HCV treatment of patients on contraindicated anti-epileptic drugs: Role of drug level monitoring

Pharmacokinetic curves of daclatasvir, sofosbuvir and GS-331007 in patients on contraindicated anti-epileptic drugs.

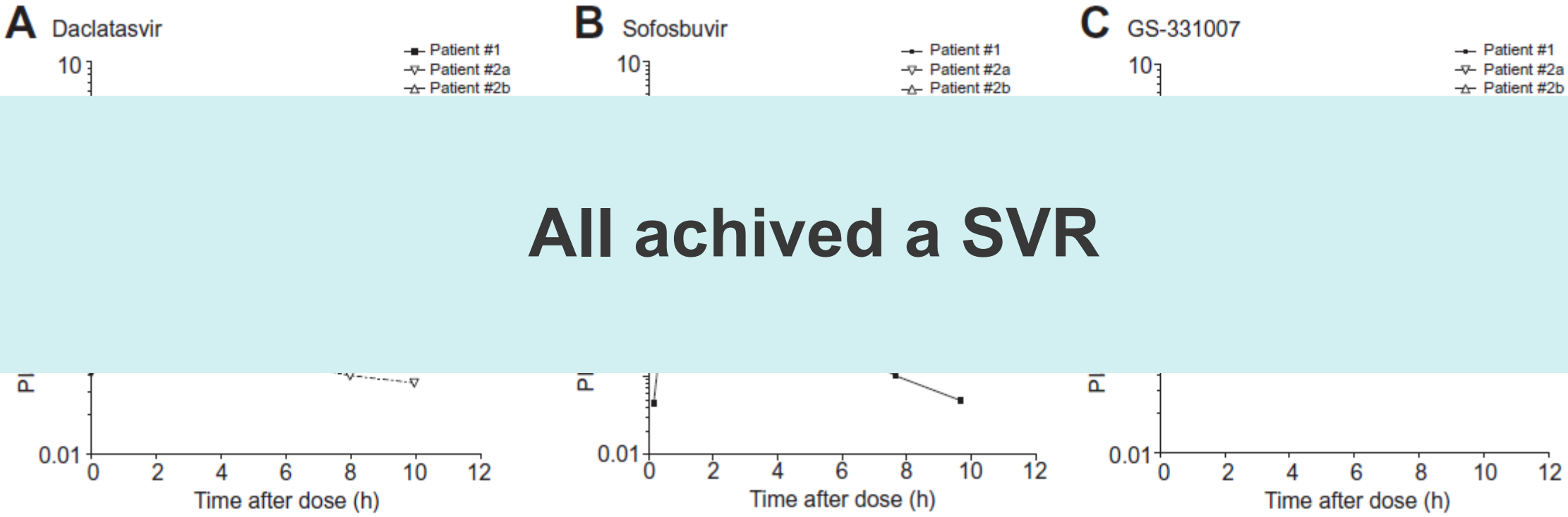


Daclatasvir Standard dose of 60 mg once daily was adjusted to 60 mg twice daily for patient 1 and 2 and 60 mg 3 times a day for patients 3–6, to compensate for the expected reduced exposure. For patient 2, the dose was further increased to 60 mg 3 times a day (curve 2b) due to low exposure on 60 mg twice daily (curve 2a). The reference curve shows daclatasvir 60 mg once daily in hepatitis C genotype 1-infected patients without cirrhosis and contraindicated medication

Seyen M et al J Hepatol 2018

Successful HCV treatment of patients on contraindicated anti-epileptic drugs: Role of drug level monitoring

Pharmacokinetic curves of daclatasvir, sofosbuvir and GS-331007 in patients on contraindicated anti-epileptic drugs.



All achived a SVR

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Seyen M et al J Hepatol 2018

HCV Positive subjects difficult to cure

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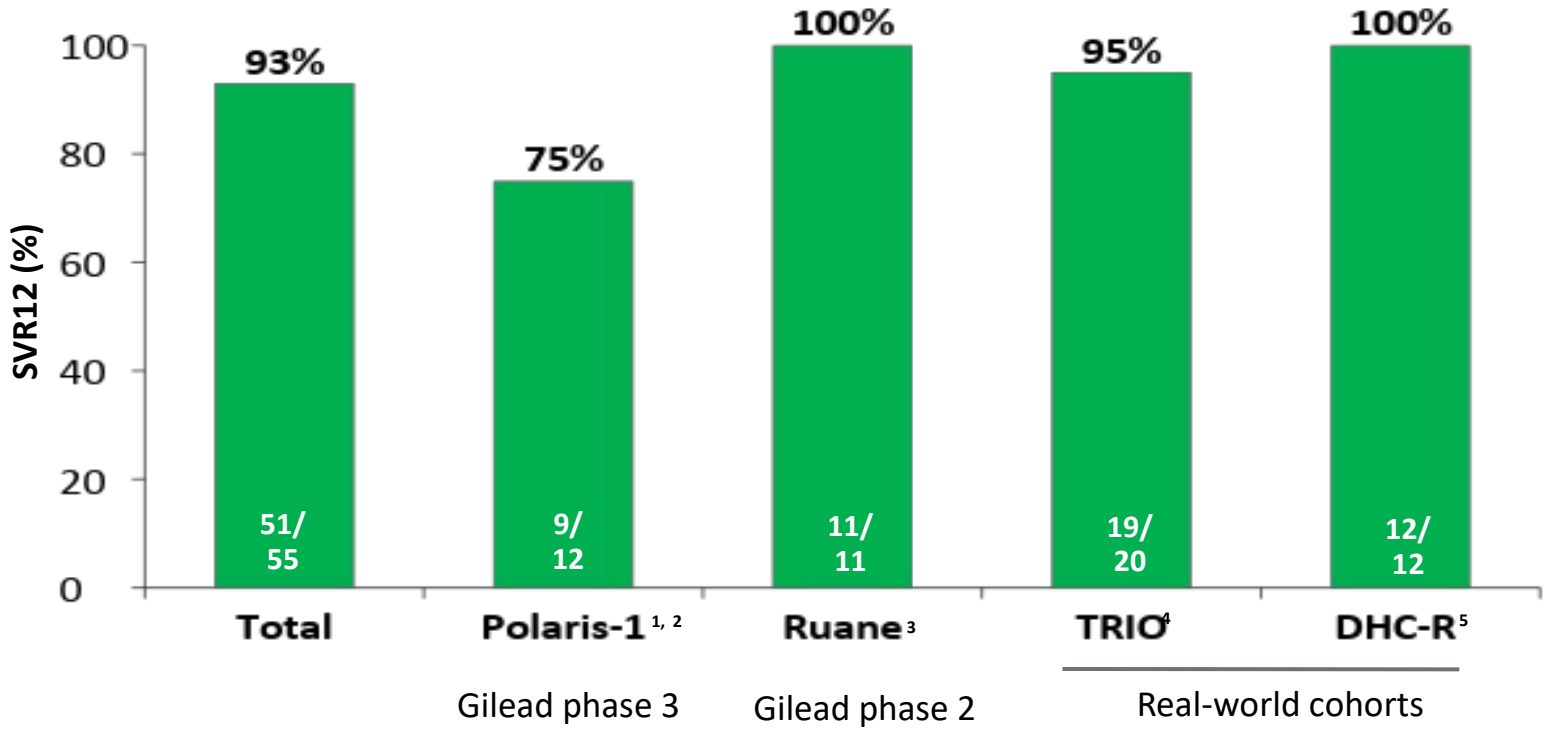
SOF/VEL/VOX in Prior SOF/VEL Failures



High SVR rates in prior SOF/VEL failures treated with SOF/VEL/VOX in clinical trials and real-world cohorts

1 - Bourliere *et al*. NEJM 2017;376:2134-46; 2 - Bourliere *et al*. Lancet Gastroenterology Hepatology 2018;3(8):559-65; 3 - Ruane *et al*. ISVHLD 2018;
4 - Bacon *et al*. AASLD 2018, poster 0706; 5 - Vermehren *et al*. AASLD 2018, poster 0676

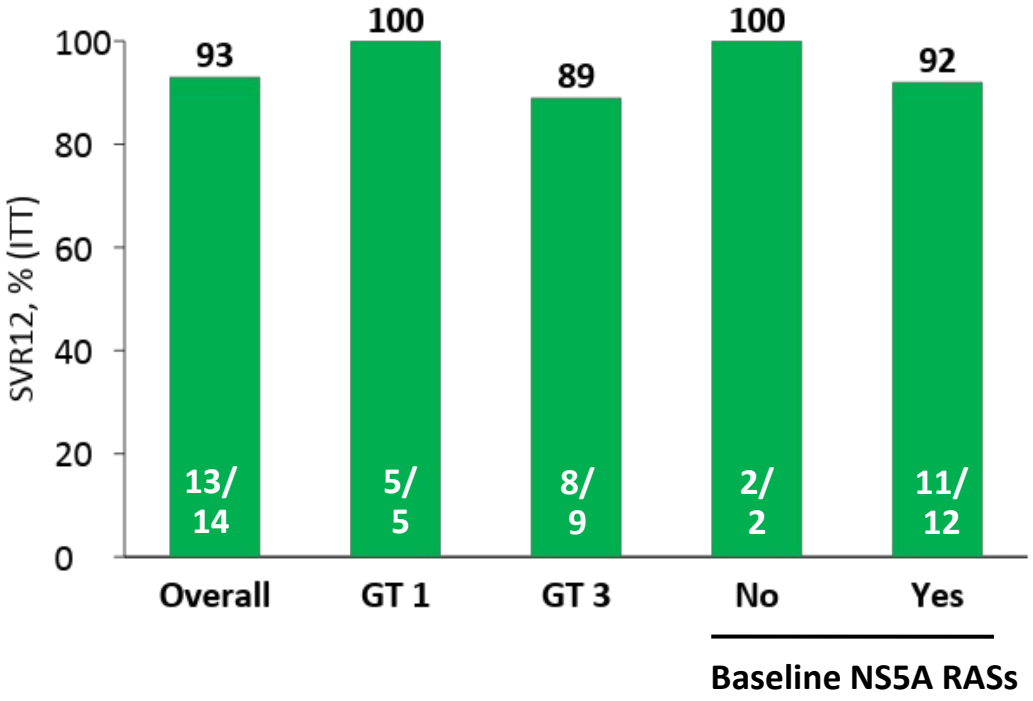
Multicentre prospective study in Atlanta, GA

‡

SOF/VEL/VOX for Prior GLE/PIB Treatment Failures

Baseline Demographics

	n=14
Treatment Naïve Prior to Receiving GLE/PIB, n (%)	12 (86)
African American, n (%)	8 (57)
Cirrhosis, n (%)	7 (50)
GT1a, n (%) Cirrhosis Prior relapse	5 (36) 2/5 5/5
GT3a, n (%) Cirrhosis Prior relapse Prior breakthrough	9 (64) 5/9 7/9 2/9
RASs, n (%)	12 (86)

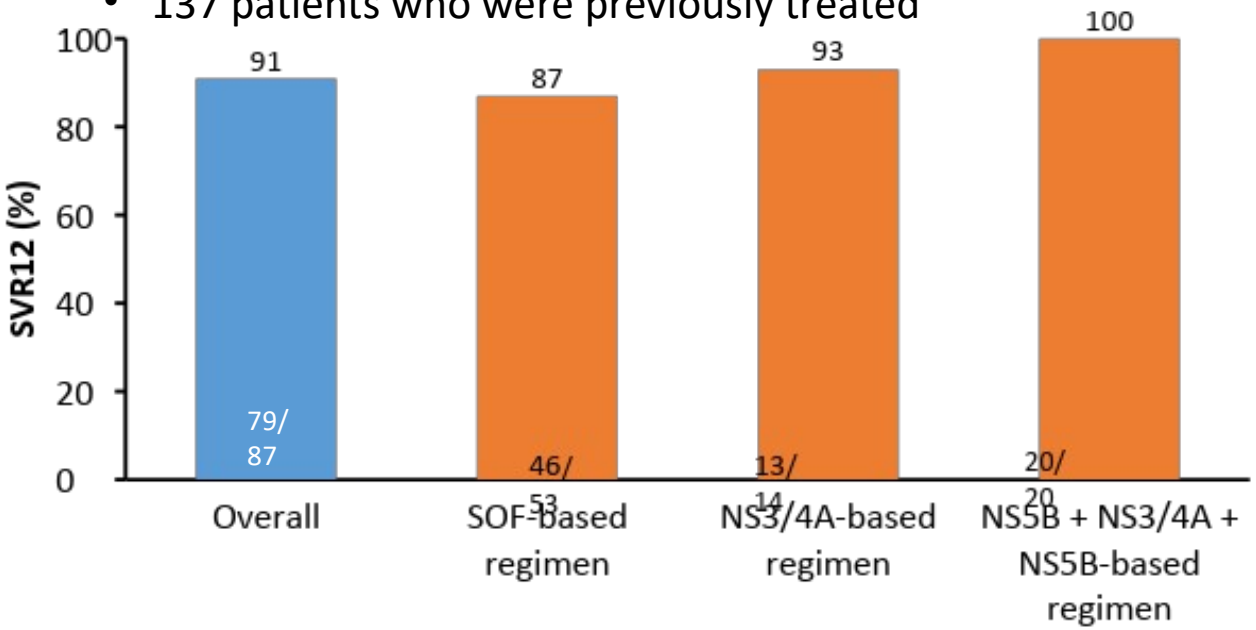


SOF/VEL/VOX for 12 weeks was well tolerated and effective for GT 1 and 3 patients who had failed GLE/PIB

Pearlman, AASLD 2018, 607

Real-world data confirm effectiveness of SOF/VEL/VOX as a rescue therapy in patients with prior DAA treatment failure

- Prospective, multicentre study in Spain
- 137 patients who were previously treated



Characteristics of patients who failed SOF/VEL/VOX (n=8)

Gender	Age (years)	GT	Fibrosis stage	Previous DAA treatment	RASs*
M	55	3	F4	SOF + DCV + RBV (24 w)	L28S, M31L, D168G
M	47	3	F4	SOF + DCV + RBV (24 w)	N/A
M	62	3	F2	SOF + DCV (12 w)	Y93H
M	54	3	F0–F1	SOF + DCV (12 w)	None detected
M	63	3	F4	SOF + DCV (12 w)	None detected
M	53	3	F4	SOF/VEL (12 w)	N/A
F	50	4	F4	EBR/GZR (12 w)	Y93H
M	43	1a	F2	LDV/SOF (8 w)	N/A

- 112 (88%) patients did not experience AEs
- AEs were mild with the most frequent being asthenia (6%) and headache (4%)†

*Analysis performed prior to receiving SOF/VEL/VOX treatment.
†One case of 'de novo' HCC was diagnosed at the EOT and the patient died before assessment of SVR12.
w: weeks

Llaneras J, et al. AASLD 2018; Poster #683

Summary

Several Challenges remain in small populations

Some of these populations such as decompensated cirrhosis,

GT3 with cirrhosis will disappear faster than the challenges

are solved