Hepatitis C: New Therapies in 2016-2017

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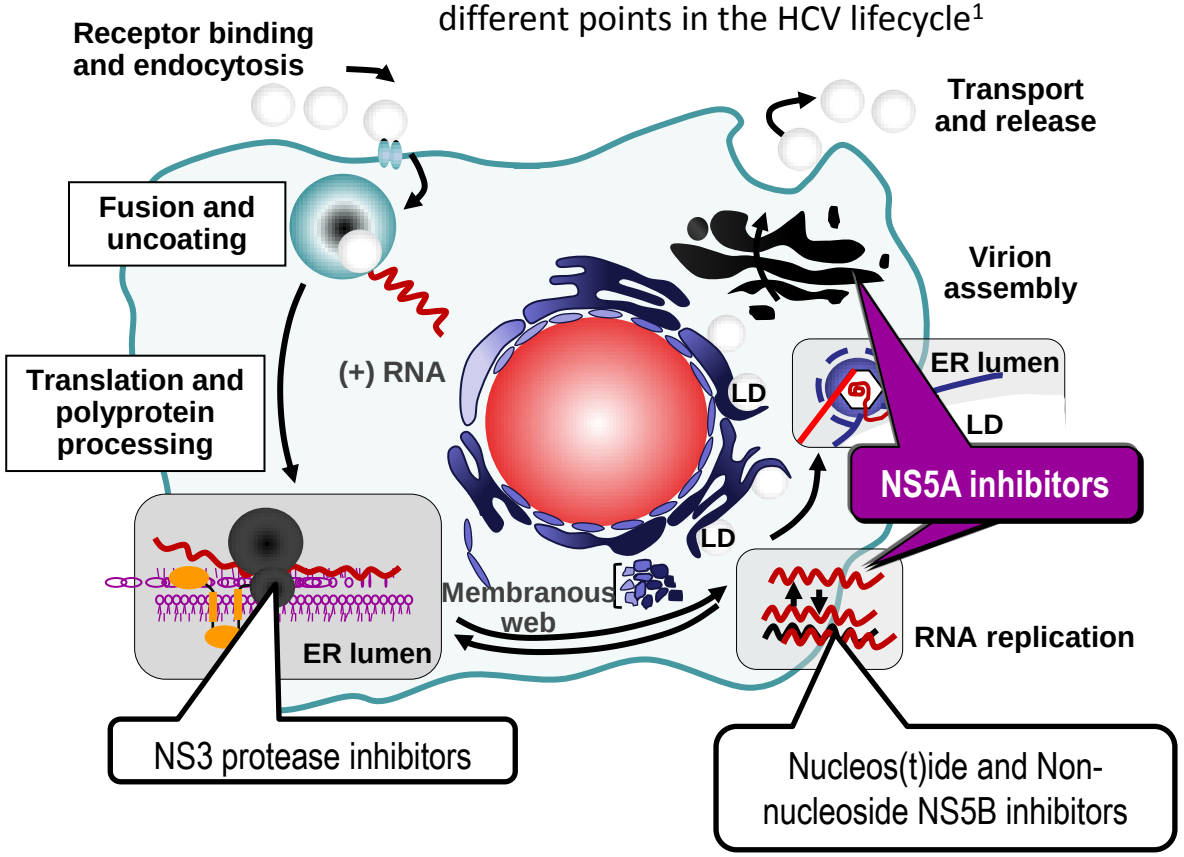
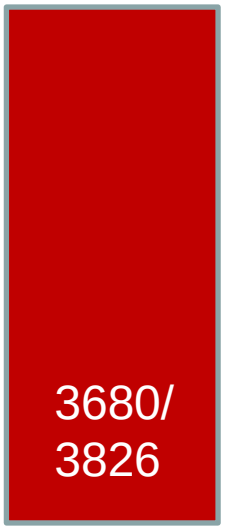
JOHNS HOPKINS
MEDICINE

Current HCV direct acting antiviral regimens cure the majority of persons treated in phase 3 trials

Highly efficacious DAAs target different points in the HCV lifecycle[1]



New England Journal of Medicine trials in GT 1 published in 2014[2]



Sustained Virologic Response [SVR]

1. Lindenbach BD, Rice CM. Nature 2005;436(Suppl):933–8;
2. Liang J, Ghany MG. N Engl J Med 2014;370:2043–7;
3. Burki T. Lancet Infect Dis 2014;14:452–3

New HCV DAAs – where is the unmet medical need?

- Access to effective HCV treatment
  - Regional registration of novel DAAs
- HCV treatment without the need for baseline assessment of genotype and/or RAVs
  - Pangenotypic
  - High barrier to emergence of resistant variants
- Shorter therapy
  - Reduce cost
  - Increase treatment capacity
- Curative treatments for persons who fail first course regimens

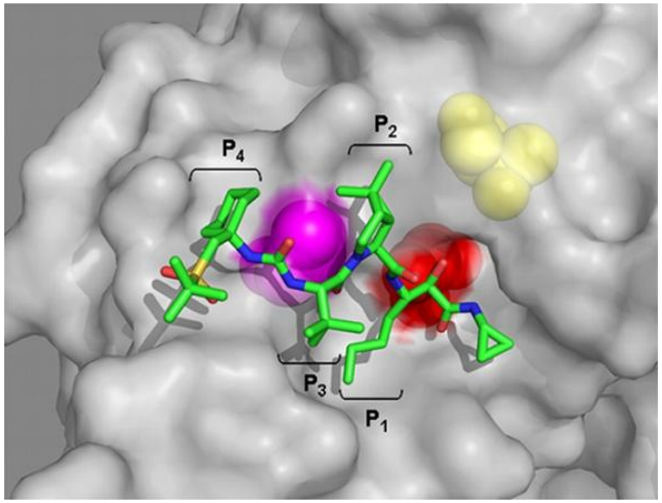
HCV treatment regimens available in 2016 – 2017

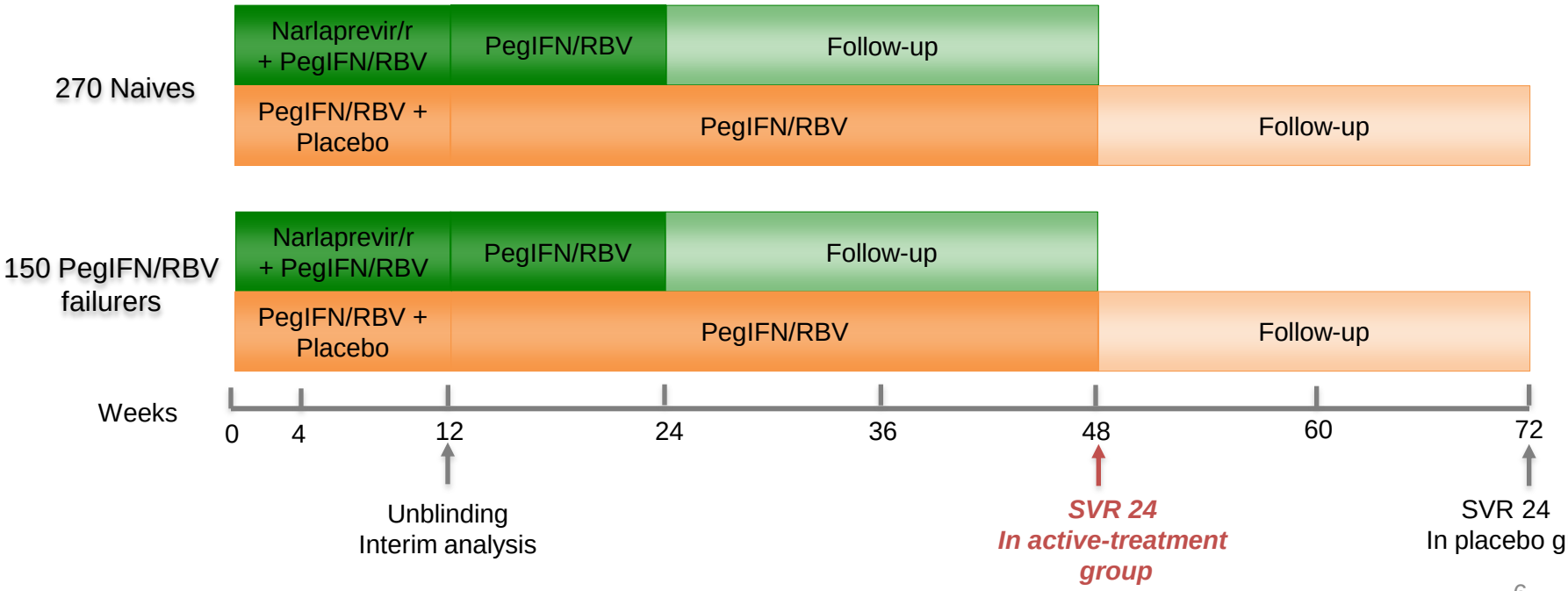
	Antiviral					
	NS3	NS5A	Non-Nuc NS5B	Nuc NS5B	RBV	IFN
Narlaprevir (2016)	●				●	●
Paritaprevir/ritonavir/Ombitasvir + Dasabuvir Asunaprevir/Daclatasvir/Beclabuvir	●	●	●		1a only ●	
Grazoprevir/Elbasvir FDC (2016) ABT493/ABT530 (2017)	●	●				
Sofosbuvir/Ledipasvir FDC Sofosbuvir/Velpatasvir FDC (2016) Sofosbuvir + Daclatasvir	●	●				
Sofosbuvir + Simeprevir	●	●				
MK3682/MK8408/Grazoprevir FDC (2018) Sofosbuvir/Ledipasvir/GS9857 FDC (2017)	●	●		●		

Novel DAAs [Registration pathway outside of the Food and Drug Administration and European Medicines Agency]

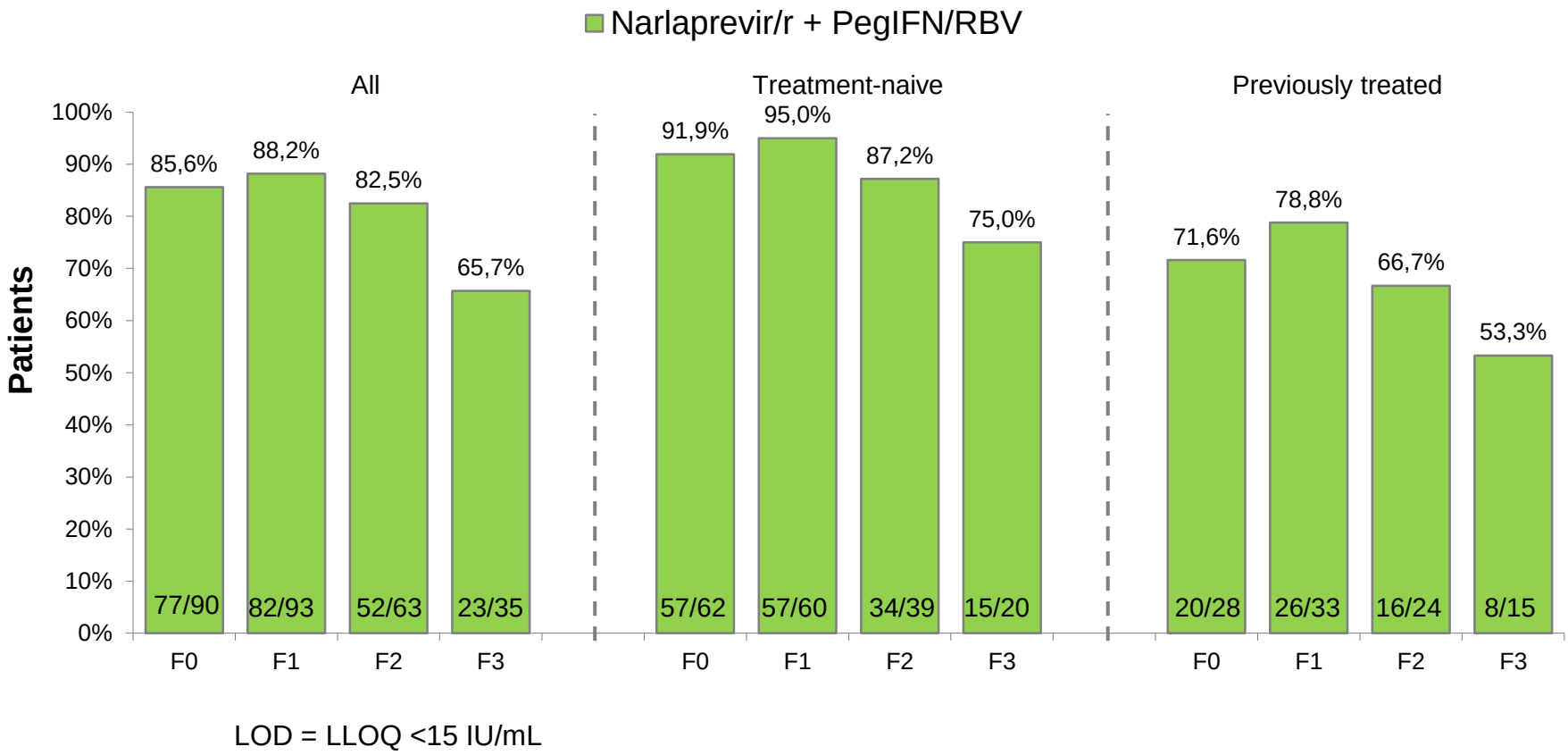
Phase III PIONEER Study: Narlaprevir + PegIFN/RBV

- International multicenter randomized placebo-controlled double-blind study
- 420 non-cirrhotic naïve and treatment-experienced patients with GT1
- 12 weeks of Narlaprevir 200 mg QD + Ritonavir 100 mg QD + PR + 12 weeks of PR
- Randomization 2:1 to Narlaprevir/Ritonavir and placebo (280 patients on Narlaprevir)





Phase III PIONEER Study SVR24 by Fibrosis Stage



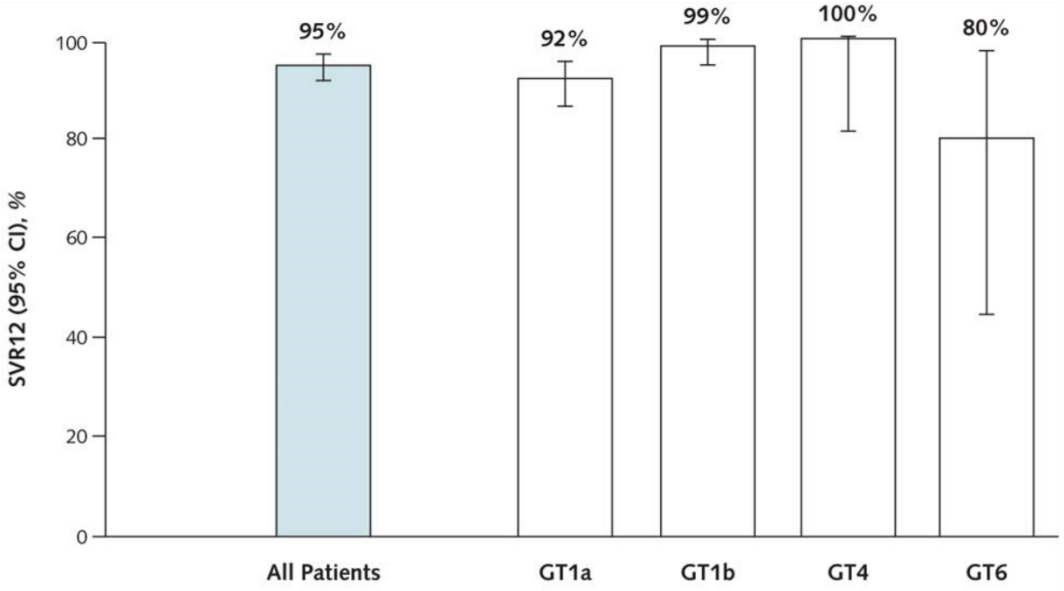
LOD = LLOQ <15 IU/mL

Phase III PIONEER Study: Safety Data

Adverse events, % (n)	Narlaprevir/r + PegIFN/RBV N=282	Placebo + PegIFN/RBV N=138
Most common adverse events list (>10% of cases)		
Neutropenia	47,5% (134)	54,4% (75)
Leukopenia	35,5% (100)	39,9% (55)
Influenza-like illness	29,1% (82)	31,9% (44)
Asthenia	27,3% (77)	26,1% (36)
Hemoglobin decrease	24,1% (68)	23,2% (32)
Pyrexia	23,4% (66)	21,7% (30)
Anaemia	22,7% (64)	22,5% (31)
Thrombocytopenia	19,5% (55)	22,5% (31)
Weight decrease	16,31% (46)	20,3% (28)
Alopecia	15,25% (43)	8,7% (12)
Headache	12,8% (36)	11,6% (16)
Cough	8,9% (25)	12,3% (17)

NS5A Inhibitor + NS3 Protease Inhibitor
[“nuke sparing”]

Grazoprevir–Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial



SVR12 (95% CI), *n/N*; %	299/316; 95% (92%–97%)	144/157; 92% (86%–96%)	129/131; 99% (95%–100%)	18/18; 100% (82%–100%)	8/10; 80% (44%–98%)
Lost to follow-up or discontinued early due to reasons other than virologic failure	4*	3	1	0	0
Virologic breakthrough	1	1	0	0	0
Virologic relapse	12	9	1	0	2

Ann Intern Med. 2015;163(1):1-13. doi:10.7326/M15-0785

Grazoprevir/Elbasvir: Impact of baseline NS5A RAVs in patients with HCV 1a and 1b infection

GT1a-infected EBR/GZR 12 Weeks (No RBV): Lower SVR with key RAVS
Population sequencing is adequate for clinical interpretation [no need for "deep" sequencing]

RAV Position	SVR12 Patients with RAVs (NGS 1% ST)	SVR12 Patients with RAVs (PopSeq)
28	61/68 (89.7%)	29/33 (87.9%)
30	14/23 (60.9%)	4/10 (40.0%)
31	15/23 (65.2%)	5/13 (38.5%)
93	9/14 (64.3%)	5/8 (62.5%)

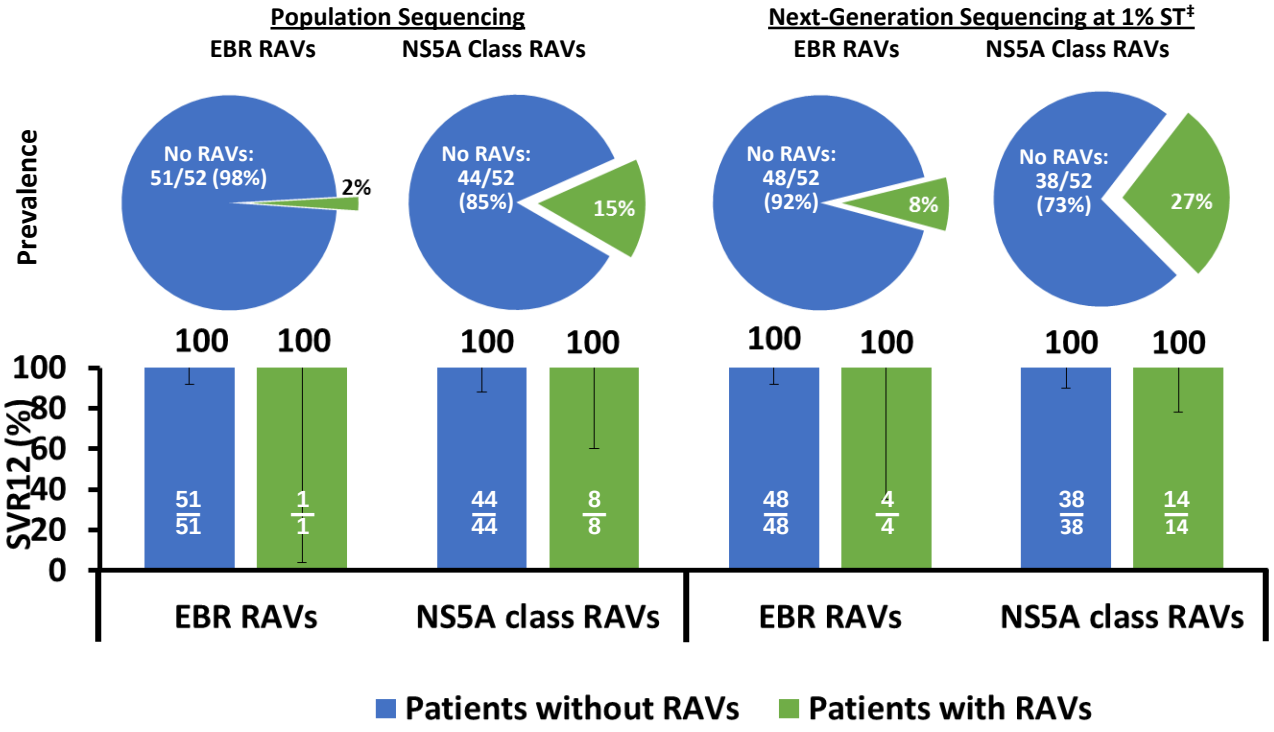
GT1b-infected EBR/GZR 12 Weeks (No RBV): No impact of RAVS

RAV Position	SVR12 Patients with RAVs (PopSeq)
28	4/4 (100.0%)
30	16/16 (100.0%)
31	17/19 (89.5%)[†]
93	21/22 (95.5%)[‡]

Jacobson I, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-22.

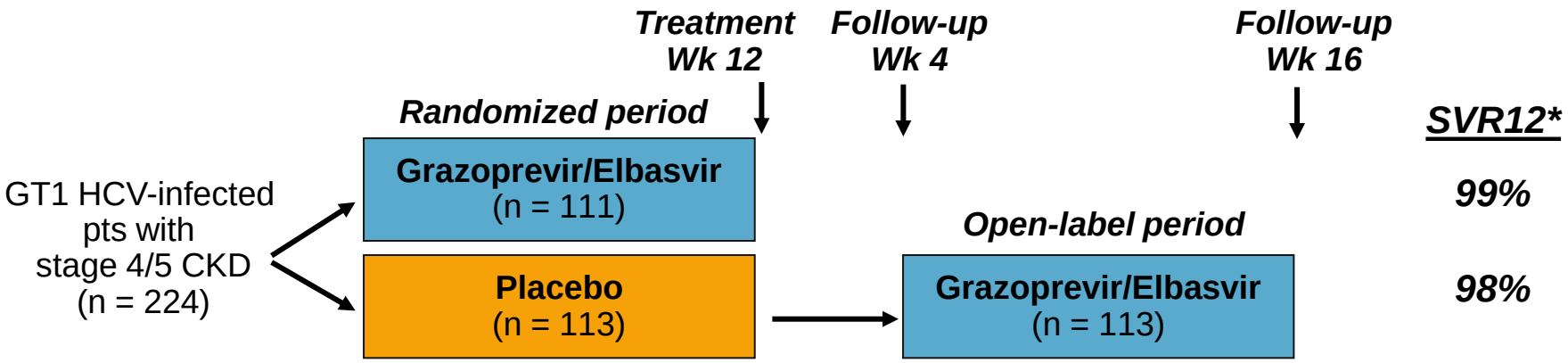
GZV/EBR: longer treatment (16 weeks) and addition of RBV lead to high SVR rate in patients with baseline NS5A RAVs (positions 28, 30, 31 and 93)

Efficacy of EBR/GZR 16/18 Weeks (+ RBV) in GT1a PR Non-responders with Baseline NS5A RAVs[†]



Jacobson I, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-22.

C-SURFER: Grazoprevir/Elbasvir in patients with Stage 4 or 5 Chronic Kidney Disease



Grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily

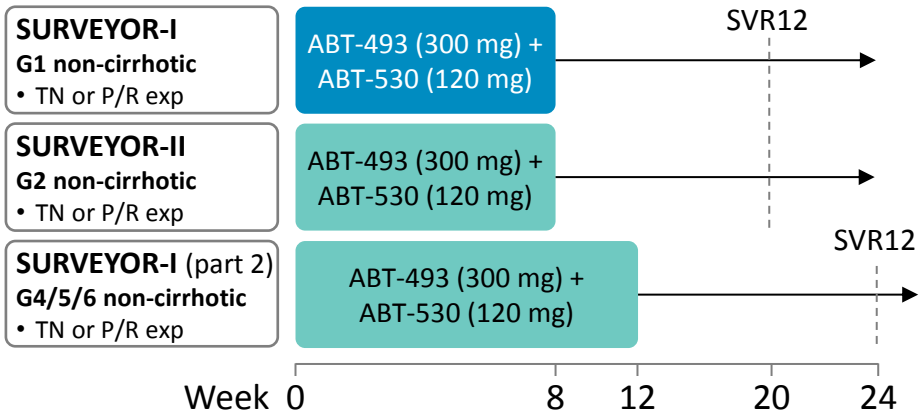
- 76% on dialysis
- 55% with diabetes
- 52% GT1a, 48% GT1b
- 6% cirrhosis

*Modified full analysis set population (mFAS).

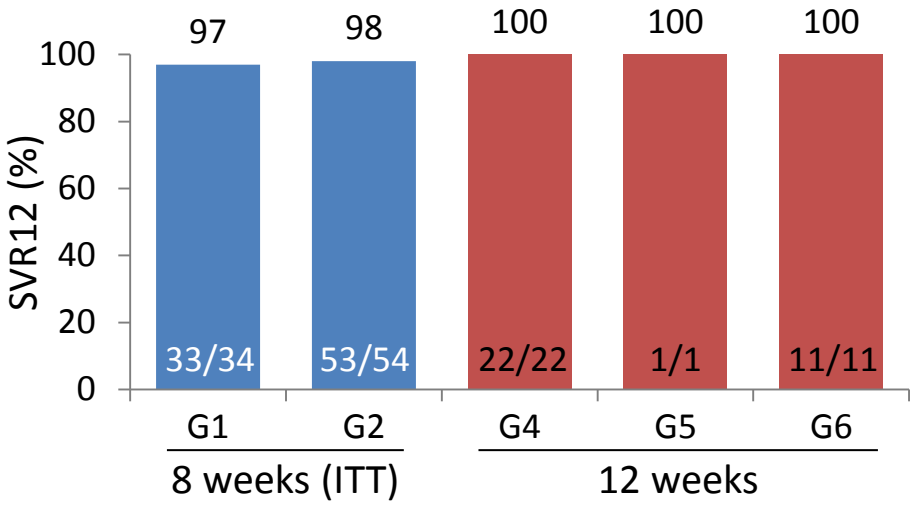
Roth D, et al. Lancet. 2015;386:1537-1545.

SURVEYOR-I and -II: High SVR in non-cirrhotic patients with ABT-493 + ABT-530 for 8 weeks in G1/2 and 12 weeks in G4/5/6

Study design



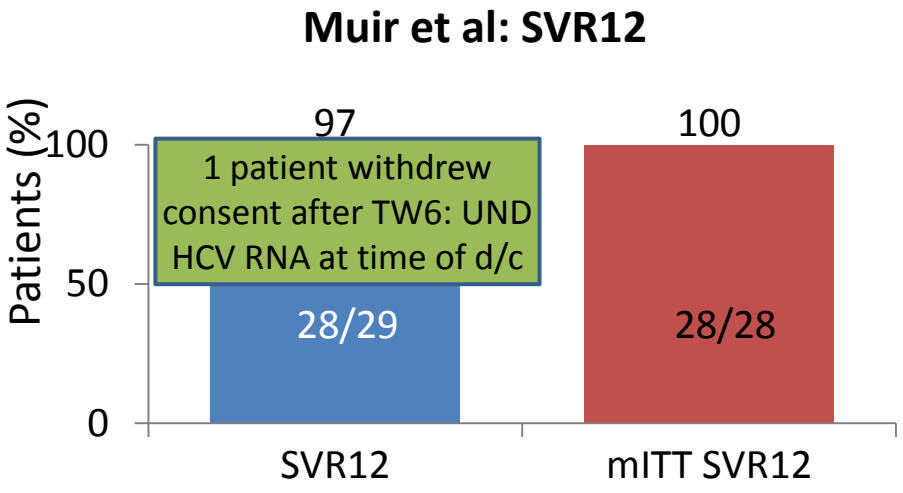
SVR12 following ABT-493 + ABT-530 for 8 weeks (G1/2) or 12 weeks (G4/5/6)

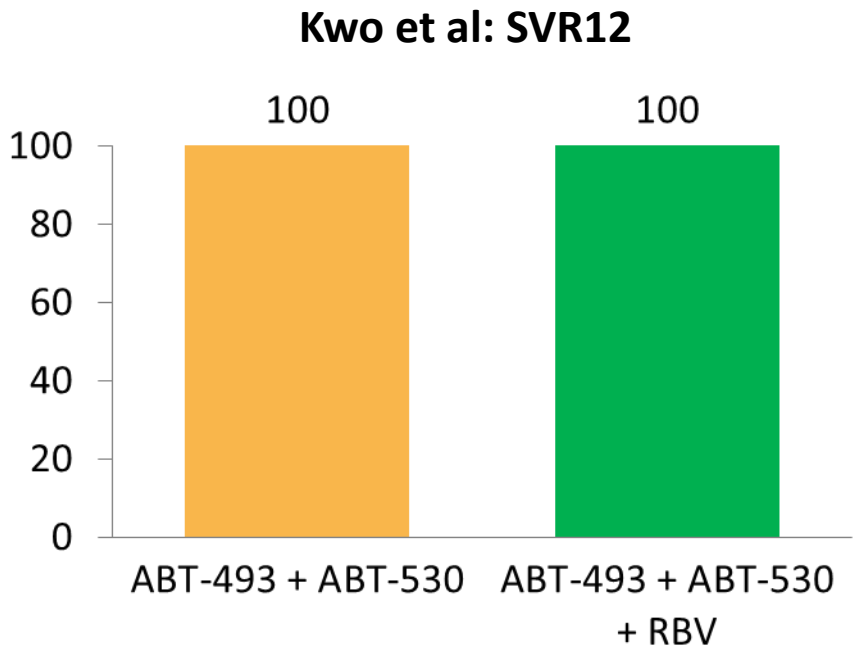


Gane E, et al. EASL 2016, Barcelona. #SAT-137; Poordad F, et al. EASL 2016, Barcelona. #SAT-157

High SVR rates with ABT-493 + ABT-530 for 8 weeks (non-cirrhotic) and 12 weeks (cirrhotic) in patients with GT3 infection

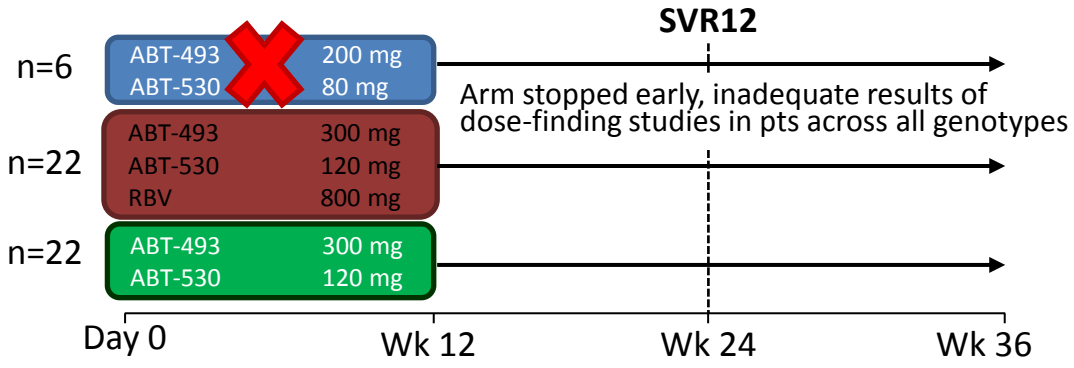
- Muir et al. 29 patients without cirrhosis treated with ABT493 + ABT530 for 8 weeks (no RBV)
  - No virologic failure
  - No SAE or DC due to AE
- Kwo et al. 48 patients with cirrhosis and no prior treatment – 12 weeks ABT 493 + 530 ± RBV
  - No virologic failure
  - No impact of baseline RAVs including Y93H/N
  - No benefit observed with RBV

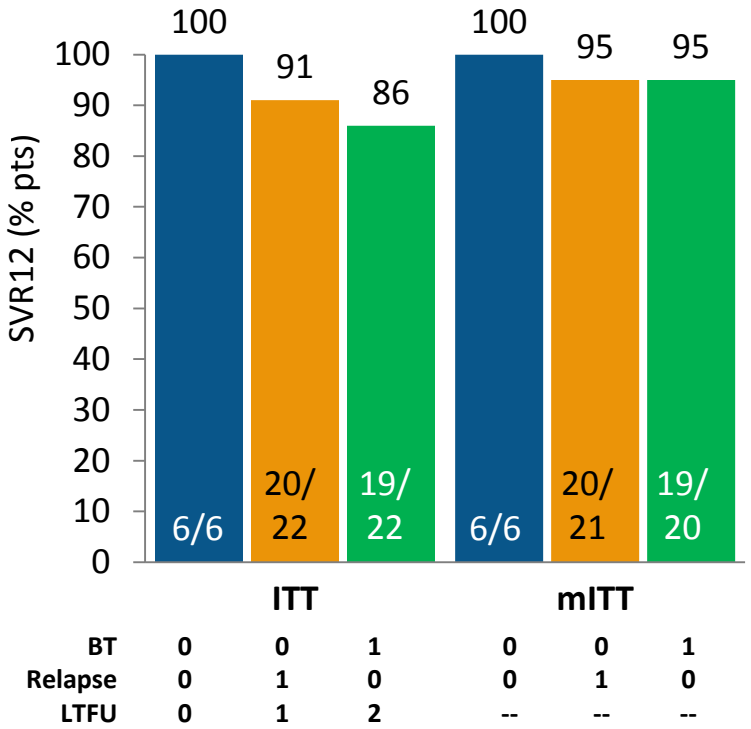


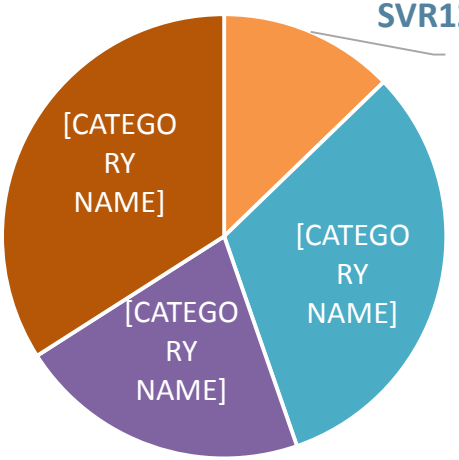


Muir A, et al. EASL 2016, Barcelona. PS098

MAGELLAN-1 Study: ABT-493 and ABT-530 in non-cirrhotic, GT1 infected patients who have failed DAA-containing regimens







SVR12 6/6 (100%)

SVR12 15/16 (94%)

1a; 3D+RBV failure
Breakthrough
NS3:Y 56H, D168A/T
NS5A:M28V, Q30L/R

SVR12 15/15 (100%)

- 100% SVR12 in 10 pts with Y93 NS5A RAVs
- 100% SVR12 in 26 pts w/ Q80 or R155 NS3 RAVs
- 100% SVR12 in 17 pts w/ prior failure of a SOF-containing regimen

SVR12 9/10 (90%)

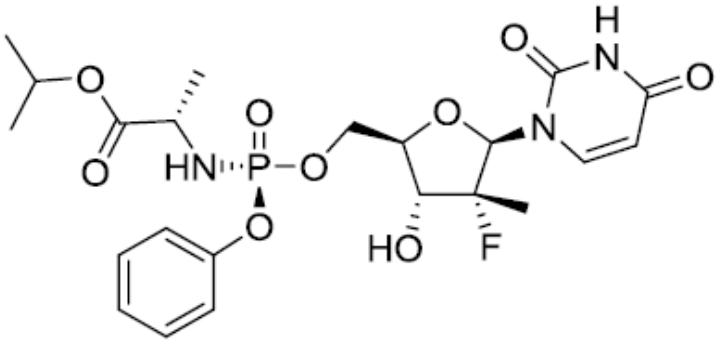
1a; DCV, TVR, PR failure
Relapse; NS5A: L31M, H58D

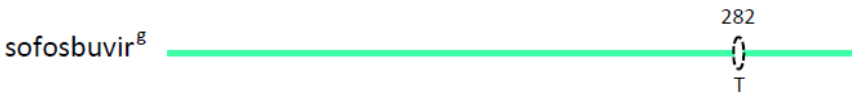
Poordad F, et al. EASL 2016, Barcelona. #GS11

NS5A inhibitor + NS5B Nucleotide Analogue Polymerase inhibitor

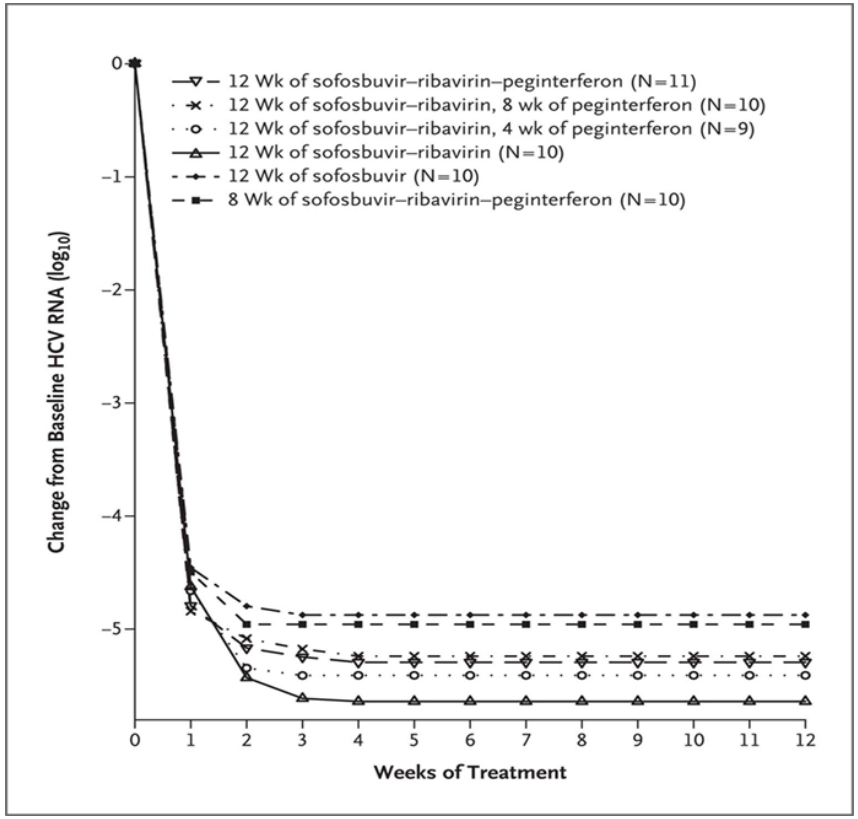
HCV suppression by nucleos(t)ide analogue NS5B polymerase inhibitors

Sofosbuvir, β-d-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (2010)





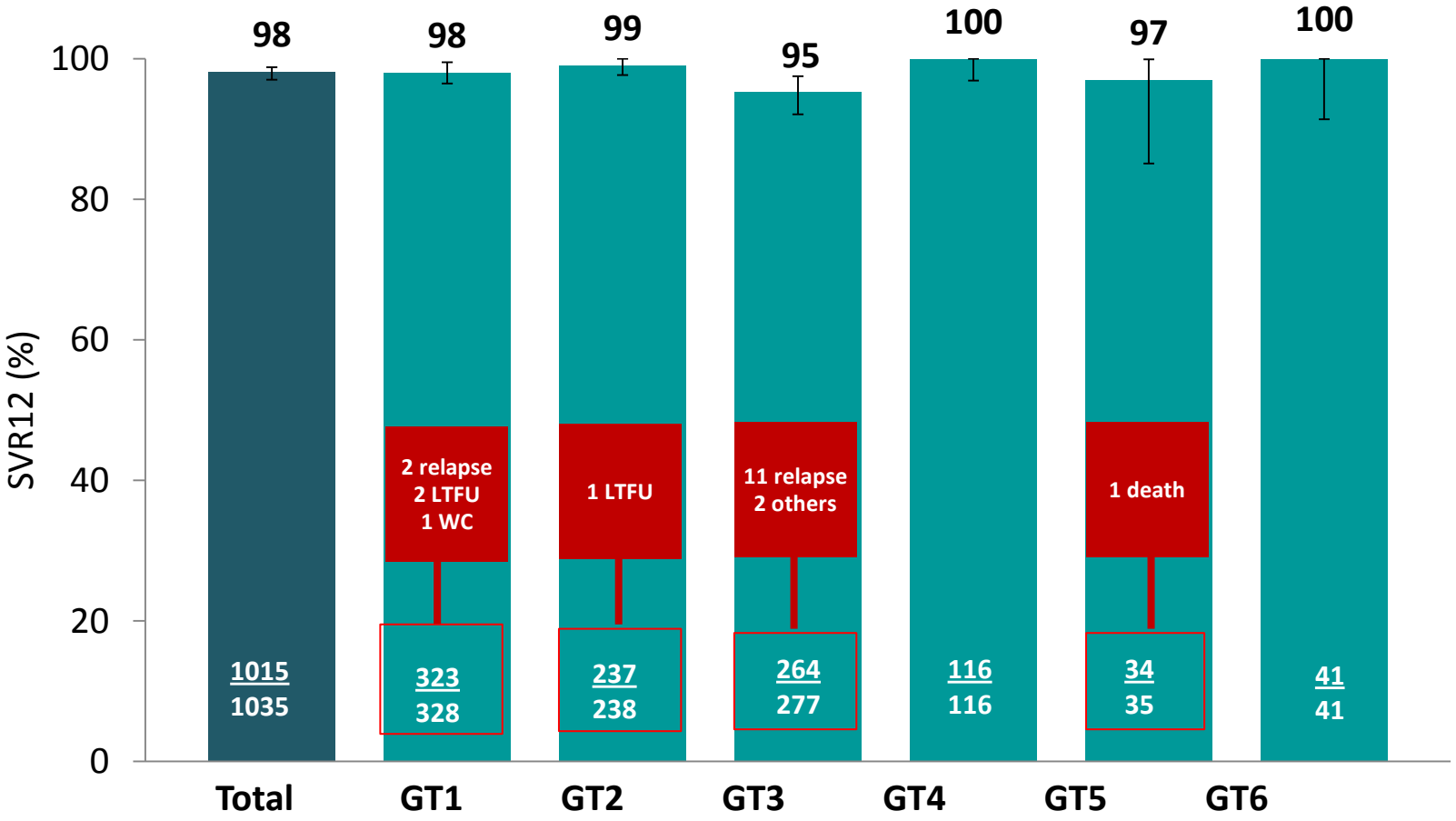
Potent HCV suppression with sofosbuvir alone, with ribavirin or with both interferon/ribavirin (2010)



Sofia J Med Chem 2010
Gane NEJM 2013
HCV Drug Development Advisory Group

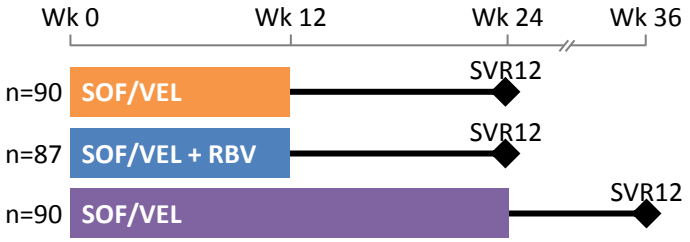
ASTRAL-1, 2, and 3: Sofosbuvir/Velpatasvir (SOF/VEL) FDC for 12 weeks

SVR12 by Genotype

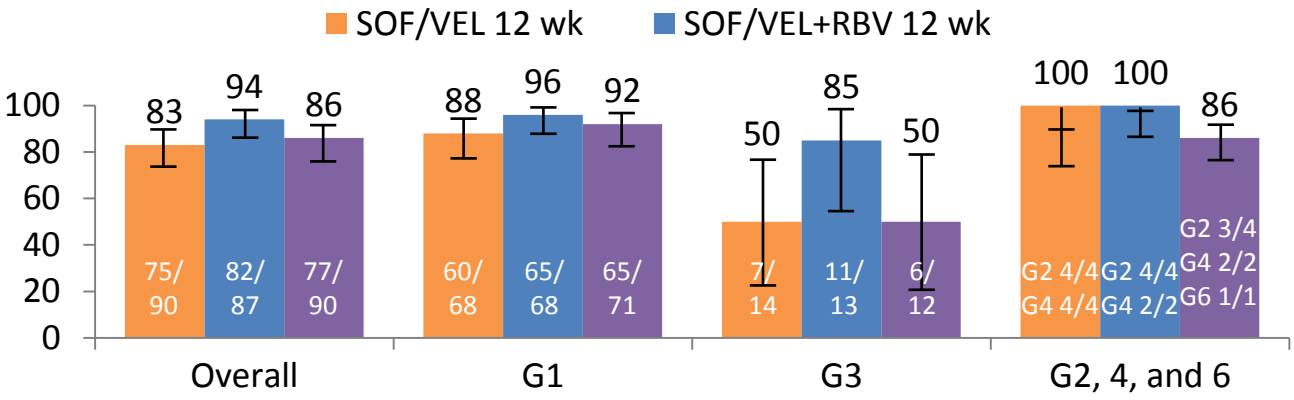


Jacobson IM. HEPDART 2015

ASTRAL-4: SOF/VEL in patients with CTP B cirrhosis



- 267 treatment-naive or -experienced G1–6 with Child B cirrhosis
  - 55% treatment-experienced
  - MELD <15 = 95%
  - Ascites 75–83%; encephalopathy 58–66%



Breakthrough, n	-	1	1	-	-	-	-	1	1	-	-	-
Relapse, n	11	2	7	5	1	3	6	1	4	-	-	-
LTFU, n	1	-	3	1	-	3	-	-	-	-	-	-
Death, n	3	2	2	2	2	-	1	-	1	-	-	1

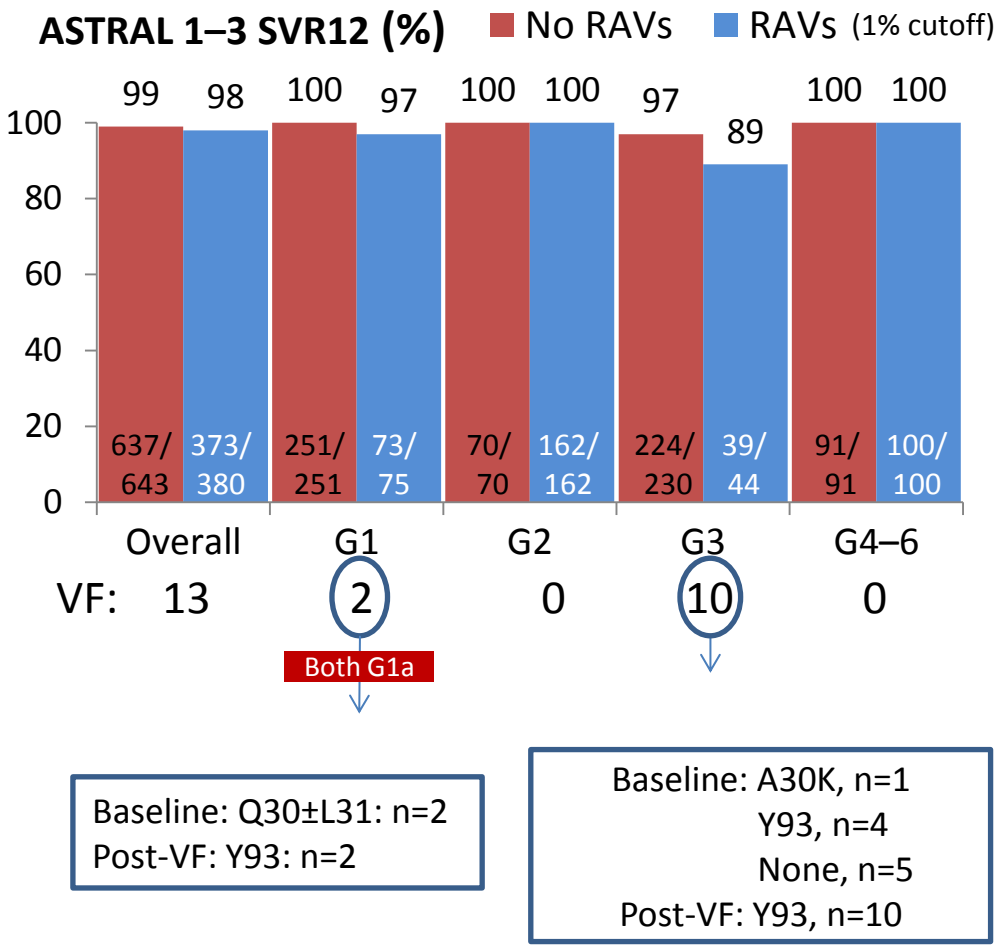
Charlton MR, et al. AASLD 2015, San Francisco. #LB-13

Resistance analysis in 1284 patients with G1–6 HCV infection treated with SOF/VEL in the ASTRAL 1-4 studies

- **Overall prevalence of RAVs:**
  - NS5A: 36%
  - Only Y93 variants considered NS5A specific RAV for velpatasvir

SVR12 in ASTRAL-4 (G1–4)

SOF/VEL	NS5A RAVs -	NS5A RAVs +
+RBV*	58/60 (97%)	24/25 (96%)



Hezode C, et al. EASL 2016, Barcelona. #THU-216

Sofosbuvir/Velpatasvir and Placebo
Adverse events occurring in >5% of patients

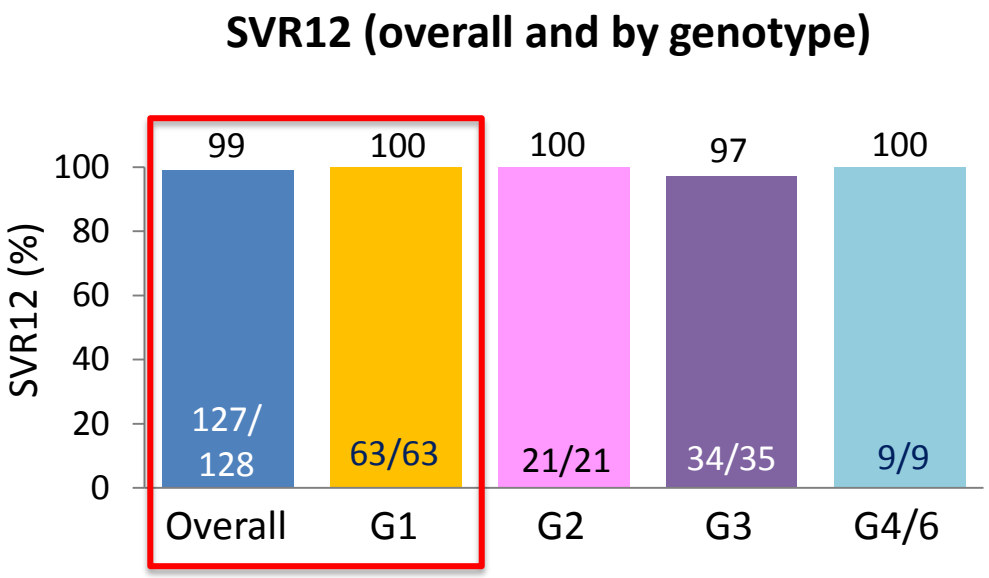
Patients, n (%)	SOF/VEL 12 wk n=1035	Placebo 12 Week (N = 116)
Headache	**296 (29)**	33 (28)
Fatigue	**217 (21)**	23 (20)
Nausea	**135 (13)**	13 (11)
Insomnia	**87 (8)**	11 (10)
Nasopharyngitis	**121 (12)**	12 (10)
Diarrhoea	**73 (7)**	8 (7)
Cough	**57 (6)**	4 (3)
Irritability	**49 (5)**	4 (3)
Arthralgia	**56 (5)**	9 (8)
Back pain	**56 (5)**	11 (10)
Asthenia	**58 (6)**	9 (8)

Jacobson IM. HEPDART 2015

NS5A inhibitor + NS3 Protease Inhibitor + NS5B Nucleotide Analogue Polymerase inhibitor

SOF/VEL + Voxilaprevir (VOX,GS-9857) for 12 weeks in treatment-experienced (including DAAs) patients with HCV GT1-6

Baseline Characteristic	VEL/SOF + GS-9857
Cirrhosis, n (%)	61 (48)
Mean HCV RNA, log_{10} IU/mL (range)	6.3 (3.8–8.1)
HCV genotype, n (%)	
1	63 (49)
2	21 (16)
3	35 (27)
4/6	9 (7)
DAA experience, n (%)	
None (G2–6 only)	27 (21)
1 DAA class	36 (28)
≥2 DAA classes	65 (51)

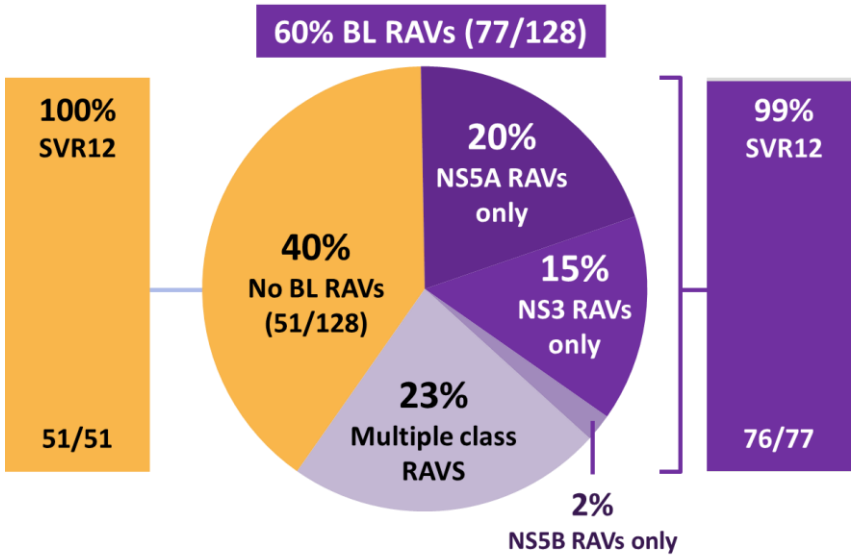


- 1 pt relapsed at post-treatment Wk 8

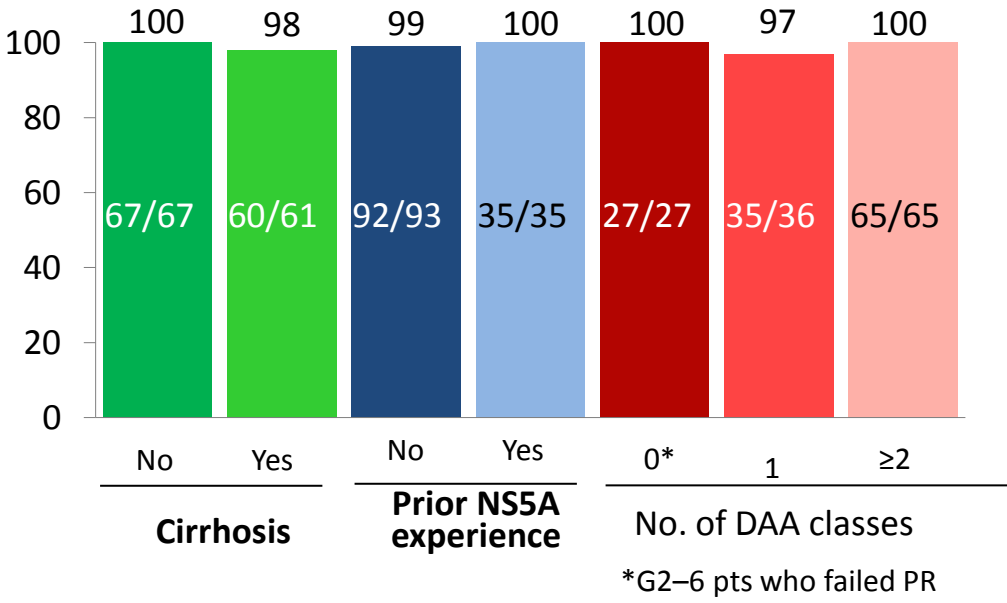
128 patients enrolled

Lawitz E, et al. EASL 2016, Barcelona. #PS008

SOF/VEL + VOX for 12 weeks in treatment-experienced G1–6 pts, including those previously treated with DAAs



Resistance analysis



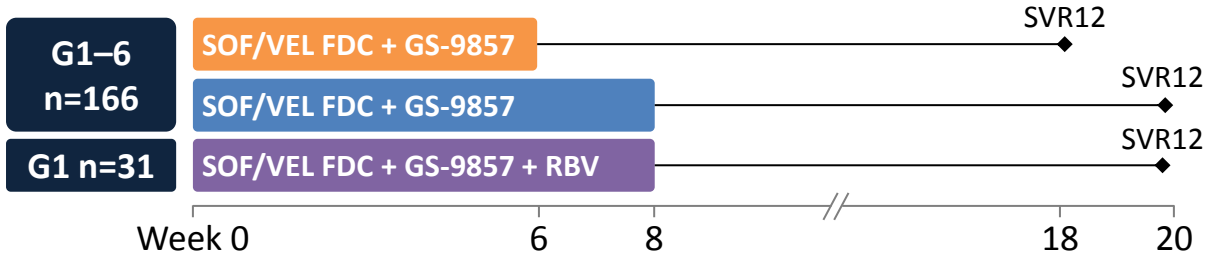
*G2–6 pts who failed PR

SVR12 (%) by subgroup

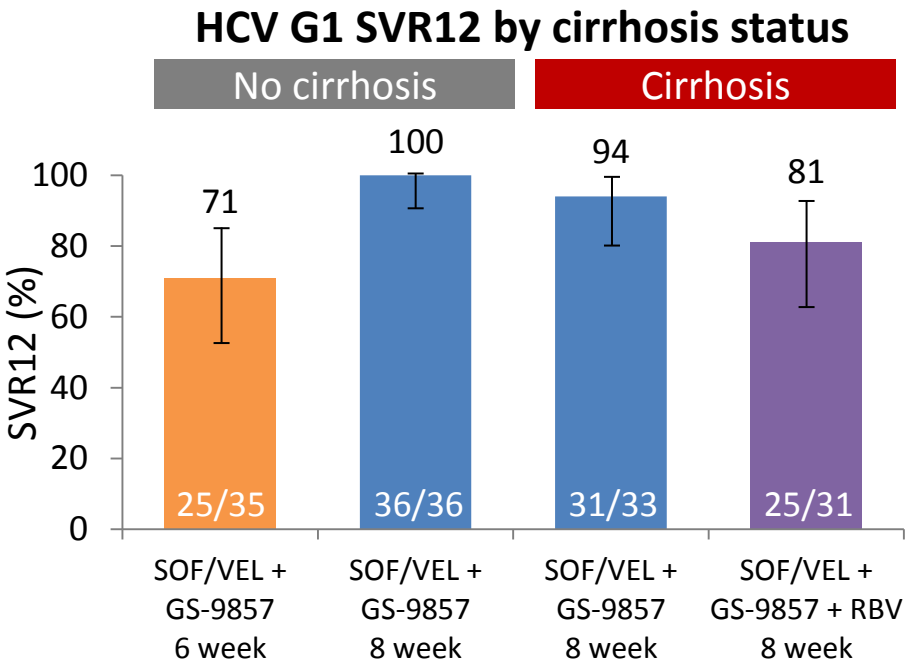
Lawitz E, et al. EASL 2016, Barcelona. #PS008

SOF/VEL + VOX for 6 or 8 weeks in treatment-naïve, HCV GT 1-6 infected patients ± cirrhosis

- Two Phase 2 studies of 6 or 8 weeks of SOF/VEL (400/100 mg) + GS-9857 (100 mg) QD
  - G1–6 (pangenotypic)
  - Treatment naive
  - US and New Zealand



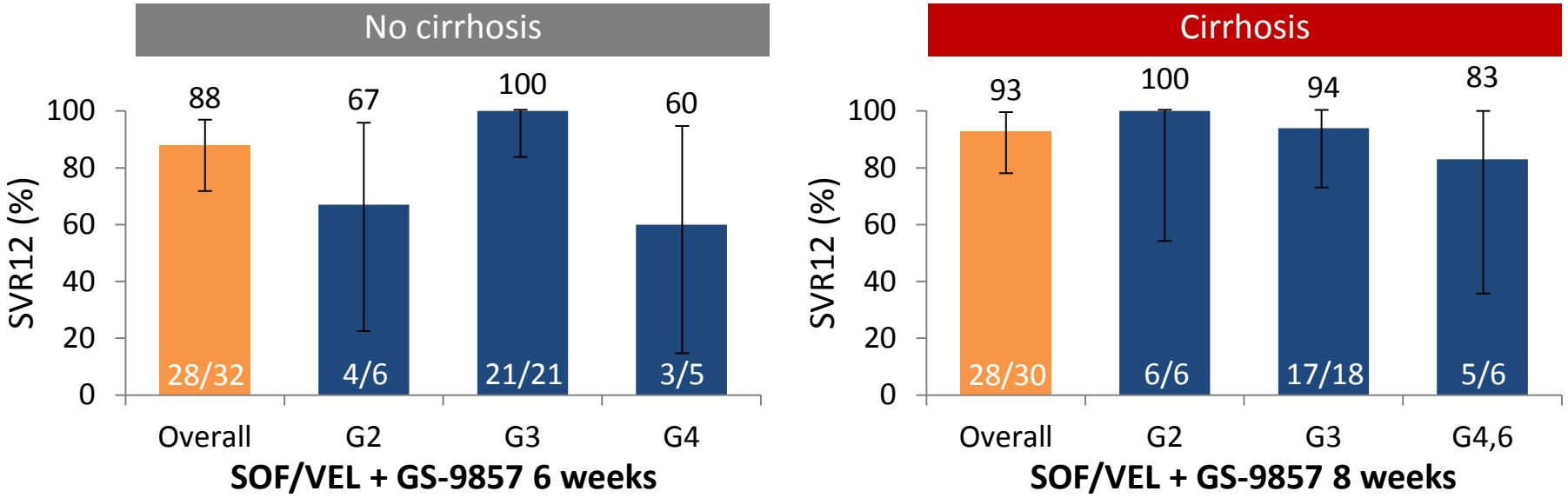
Baseline characteristics	SOF/VEL + GS-9857 6-week n=67	SOF/VEL + GS-9857 8-week n=99	SOF/VEL + GS-9857 + RBV 8-week n=31
Mean age, y (range)	53 (18–72)	55 (19–76)	59 (43–71)
Male, n (%)	35 (52)	61 (62)	19 (61)
White , n (%)	58 (87)	81 (82)	26 (84)
Mean BMI, kg/m^2 (range)	26 (18–42)	29 (19–47)	29 (19–52)
IL28B CC, n (%)	23 (34)	27 (27)	12 (39)
Cirrhosis, n (%)	0	63 (64)	31 (100)
Mean HCV RNA, log_{10} IU/mL (range)	6.2 (3.6–7.6)	6.1 (4.7–7.4)	6.3 (5.4–7.3)
G1, n (%)	35 (52)	69 (70)	31 (100)
G2, n (%)	6 (9)	6 (6)	0
G3, n (%)	21 (31)	18 (18)	0
G4, n (%)	5 (7)	5 (5)	0
G5, n (%)	0	0	0
G6, n (%)	0	1 (1)	0



Gane E, et al. EASL 2016, Barcelona. #SAT-138

Short-duration treatment with SOF/VEL + VOX in treatment-naive G1-6 HCV-infected patients with or without cirrhosis

HCV G2-6 SVR12 by genotype and cirrhosis status (all failures were HCV relapse

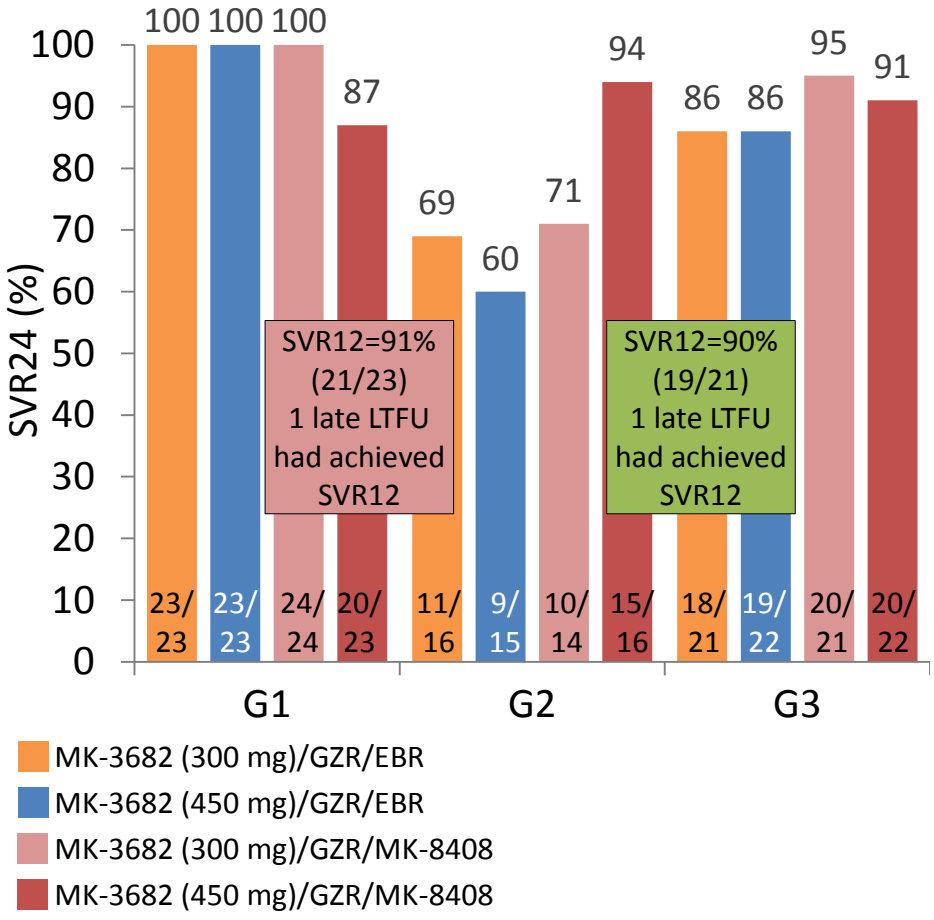


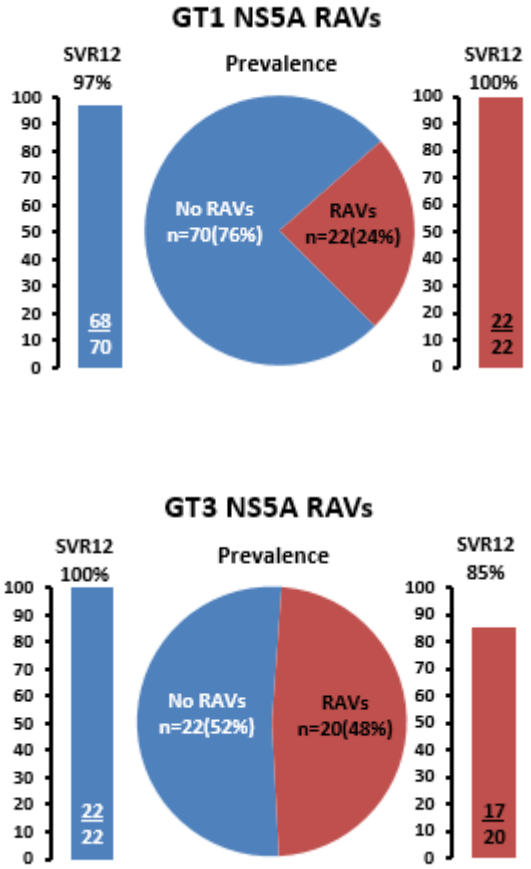
<u>Phase III, global clinical trials are ongoing (POLARIS Studies)</u>

- ✓ SOF/VEL/VOX FDC for 8 Weeks compared to SOF/VEL FDC for 12 Weeks in DAA-naïve patients
- ✓ SOF/VEL/VOX FDC for 12 Weeks in DAA-experienced patients
- ✓ SOF/VEL/VOX FDC for 12 weeks or SOF/VEL FDC for 12 weeks DAA-experienced patients without prior treatment with a NS5A inhibitor
- ✓ SOF/VEL/VOX FDC for 8 Weeks or SOF/VEL for 12 Weeks for patients with HCV GT 3 and cirrhosis

Gane E, et al. EASL 2016, Barcelona. #SAT-138

Phase 2 C-CREST 1 and 2: GZR/MK-8408/**MK-3682** (novel nucleotide NS5B inhibitor) for 8 weeks in non-cirrhotic patients with in HCV GT 1, 2 and 3





Gane E, et al. EASL 2016, Barcelona. #SAT-139

New HCV DAAs – where is the unmet medical need?

- Access to effective HCV treatment
  - Narlaprevir
  - DAAs registered regionally (e.g., Ravidasvir in Egypt)
- HCV treatment without the need for baseline assessment of genotype and/or RAVs

    + Pangenotypic

    + Shorter therapy

    + Curative treatments for persons who fail first course regimens
  - SOF/VEL with or without VOX
  - ABT-493 + ABT530
  - Grazoprevir + MK8408 + MK3682