SVR12 results from the Phase II, open-label IMPACT study of simeprevir (SMV) in combination with daclatasvir (DCV) and sofosbuvir (SOF) in treatment-naïve and -experienced patients with chronic HCV genotype 1/4 infection and decompensated liver disease

Reported by Jules Levin
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IMPACT: Conclusions

- Treatment for 12 weeks with SMV, SOF, and DCV resulted in 100% response rate; all 19 Child-Pugh A patients and all 21 Child-Pugh B patients achieved SVR12
  - High virologic response was observed regardless of Child-Pugh class (<7 or 7–9) or the presence of resistance-associated variants at baseline
- This 3-DAA combination was generally safe and well tolerated
  - No discontinuations due to adverse events
  - No deaths

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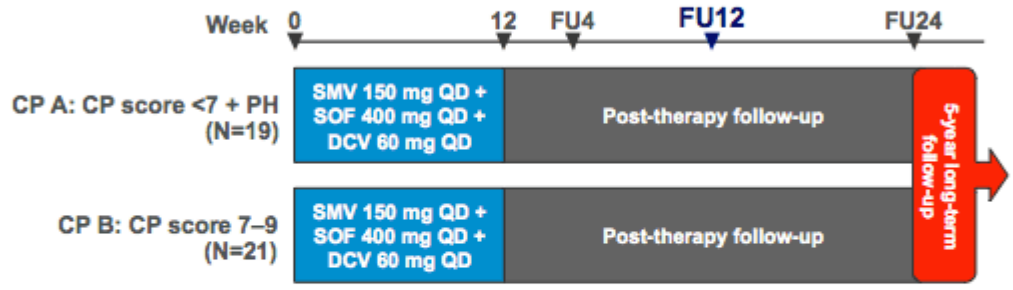
Introduction

- Effective and well-tolerated treatments are needed for HCV-infected patients with decompensated cirrhosis
  - Regimens that do not contain ribavirin are highly desirable in this patient population
- The IMPACT study assessed for the first time the combination of SMV, SOF, and DCV, three DAAs with different mechanisms of action and non-overlapping resistance profiles, for 12 weeks in HCV genotype 1- or 4-infected patients with portal hypertension or decompensated liver disease
- Results are presented from the primary analysis of IMPACT

DAA, direct-acting antiviral agent; DCV, daclatasvir; HCV, hepatitis C virus; SMV, simeprevir; SOF, sofosbuvir

IMPACT: SMV + SOF + DCV for 12 weeks in patients with decompensated liver disease (N=40)



- Patient population: treatment-naïve and treatment-experienced (prior pegIFN ±RBV therapy) patients with chronic HCV GT1 or 4 infection with either evidence of portal hypertension or decompensation
- Intensive PK analysis performed at Week 2 and Week 8
- Primary efficacy endpoint: SVR12 (intent-to-treat population)

CP, Child-Pugh; DCV, daclatasvir; FU, follow up; GT, genotype; HCV, hepatitis C virus; pegIFN, peginterferon; PH, portal hypertension; PK, pharmacokinetics; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after actual end of treatment

IMPACT: Key entry criteria

- Absence of co-infection with HBV or HIV-1/-2
- No prior treatment with a DAA
- Absence of HCC
- Total serum bilirubin ≤3 x ULN
- Platelet count ≥30,000/mm^3
- Albumin ≥2.5 g/dL
- INR ≤2.5
- eGFR ≥30 mL/min (Cockcroft-Gault equation)

DAA, direct-acting antiviral agent; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; ULN, upper limit of normal

Additional participation requirements:

- Stable hepatic function
- CP A: CP score <7 with documented portal hypertension, confirmed by the presence of esophageal varices on gastroscopy or HVPG ≥10 mm Hg
- CP B: CP score 7–9
- Hemoglobin ≥10 g/dL
- ALT and/or AST ≤10 x ULN

IMPACT: Baseline demographics

	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
Median age, years (range)	56.0 (30–64)	61.0 (50–75)	58.5 (30–75)
Male, n (%)	14 (74)	11 (52)	25 (63)
White, n (%)	18 (95)	21 (100)	39 (98)
Black/African-American, n (%)	1 (5)	0	1 (3)
Hispanic or Latino, n (%)	13 (68)	10 (48)	23 (58)
BMI, median (range)	26.80 (22.7–35.5)	31.80 (21.2–47.0)	28.45 (21.2–47.0)

BMI, body mass index; CP, Child-Pugh; DCV, daclatasvir; SMV, simeprevir; SOF, sofosbuvir

IMPACT: Baseline disease characteristics

	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
Median HCV RNA, $\log_{10}$ IU/mL (range)	5.78 (4.8–6.8)	5.60 (4.0–6.7)	5.72 (4.0–6.8)
Treatment-experienced, n (%)	9 (47)	10 (48)	19 (48)
HCV genotype, n (%)			
1a	15 (79)	11 (52)	26 (65)
NS3 Q80K[a]	9/15 (60)	3/10 (30)	12/25 (48)
1b	3 (16)	10 (48)	13 (33)
4	1 (5)	0	1 (3)
IL28B, non-CC, n (%)	15 (79)	18 (86)	33 (83)
Median albumin, g/dL	4.1	3.2	3.6
Median platelets $\times 10^3/mm^3$	106.0	79.0	89.5

[a]Calculated among HCV genotype 1a-infected patients in CP B, one genotype 1a-infected patient had no NS3 protease sequencing data available

CP, Child-Pugh; DCV, daclatasvir; HCV, hepatitis C virus; SMV, simeprevir; SOF, sofosbuvir

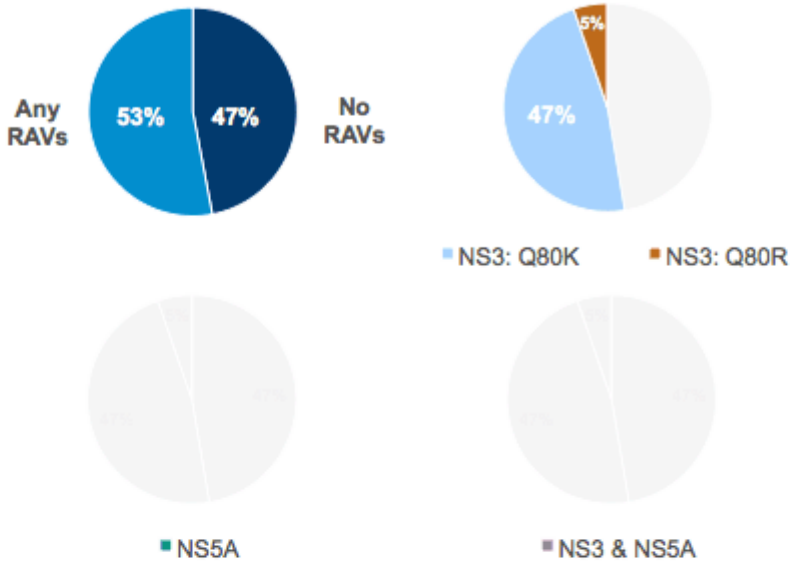
IMPACT: Baseline disease characteristics

	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
Median fibroscan score, kPa (range)	21.80 (14.9–43.5)	30.80 (16.8–75.0)	27.00 (14.9–75.0)
CP score, n (%)			
5	14 (74)	-	14 (35)
6	5 (26)	-	5 (13)
7	-	9 (43)	9 (23)
8	-	8 (38)	8 (20)
9	-	4 (19)	4 (10)
MELD score, n (%)			
<10	12 (63)	10 (48)	22 (55)
≥10–<15	7 (37)	9 (43)	16 (40)
≥15	0	2 (10)	2 (5)

CP, Child-Pugh; DCV, daclatasvir; MELD, model for end-stage liver disease; SMV, simeprevir; SOF, sofosbuvir

- There were two patients with MELD score of 16
- The transplantation evaluation is typically initiated once a patient has a MELD score >10, and as such this cut-off is widely used in clinical practice and frequently reported in the field

IMPACT: Baseline resistance-associated variants (RAVs): Child-Pugh A



- RAVs with fold change (FC) in 50% effective concentration (EC_{50}) >2, compared with wild type, for SMV (NS3 RAVs), DCV (NS5A RAVs), or SOF (NS5B RAVs) are considered
- No SOF RAVs at positions 159, 282, 316, 320, or 321 were observed at baseline

DCV, daclatasvir; SMV, simeprevir; SOF, sofosbuvir

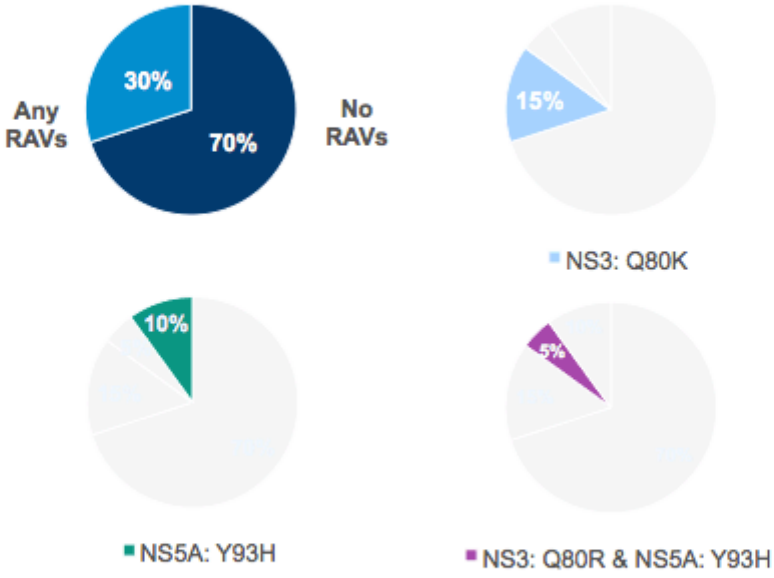
•One subject (CP-B) did not have sequencing data available in all 3 regions.
•No patient had more than one NS5A polymorphism at baseline (considering NS5A positions 28, 30, 31, 32, and 93)
•The patient with GT4 did not carry any NS3 or NS5A RAVs at the considered positions

•All three subjects with NS5A Y93H had GT1b
•NS5A: In addition, M28V (n=2; both GT1a) and R30Q (n=1; GT1b) were observed at NS5A positions 28, 30, 31, 32, or 93
•NS3: In addition, Q80L (n=1), Q80N (n=1), S122G (n=1), and S122N (n=1) were observed at NS3 positions 43, 80, 122, 155, 1
•NS3 Q80R and Q80K: SMV FC in EC_{50} <50 (both in GT1a and GT1b)
•NS5A Y93H: DCV FC in EC_{50} = 24 in GT1b and 5,432 in GT1a (Fridell et al., Hepatology, 2011)

In vitro data for the observed baseline polymorphisms from SDM analyses in literature

•NS3 Q80K: SMV median FC in EC_{50} = 7.7
•NS3 Q80R: SMV median FC in EC_{50} = 6.9
•NS3 Q80K & NS5A M28V: SMV median FC in EC_{50} = 7.7
•NS3 S122N & NS5A Y93H: DCV median FC in EC_{50} = 19
•NS3 Q80R & NS5A Y93H: DCV median FC in EC_{50} = 19
•NS5A Y93H: DCV median FC in EC_{50} = 19

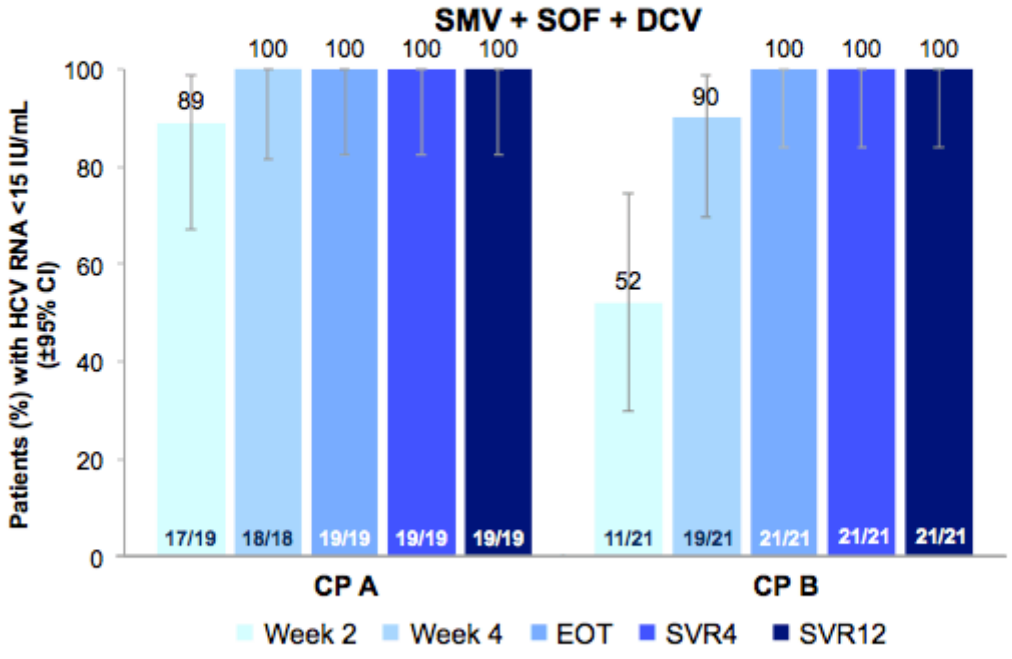
IMPACT: Baseline resistance-associated variants (RAVs): Child-Pugh B



- RAVs with fold change (FC) in 50% effective concentration (EC_{50}) >2, compared with wild type, for SMV (NS3 RAVs), DCV (NS5A RAVs), or SOF (NS5B RAVs) are considered
- No SOF RAVs at positions 159, 282, 316, 320, or 321 were observed at baseline

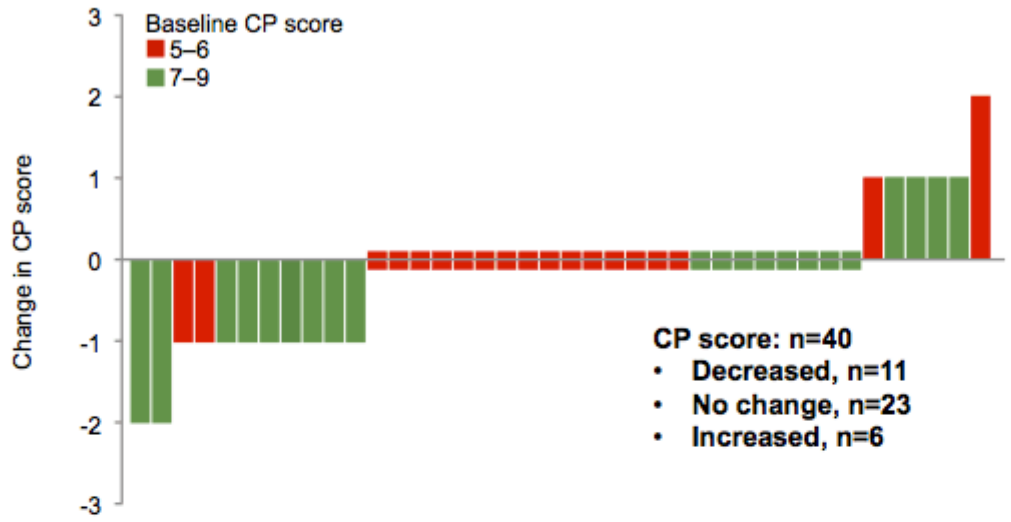
DCV, daclatasvir; SMV, simeprevir; SOF, sofosbuvir

IMPACT: On-treatment and sustained virologic response

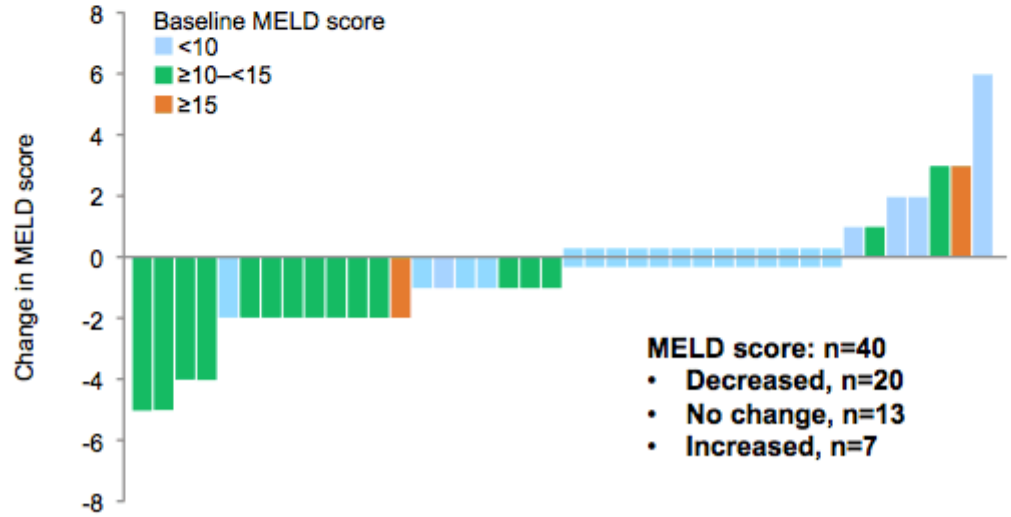


CI, confidence interval; CP, Child-Pugh; DCV, daclatasvir; EOT, end of treatment; HCV, hepatitis C virus; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response 4 (SVR4) or 12 (SVR12) weeks after actual end of treatment

IMPACT: Change in Child-Pugh scores from baseline to follow-up Week 12



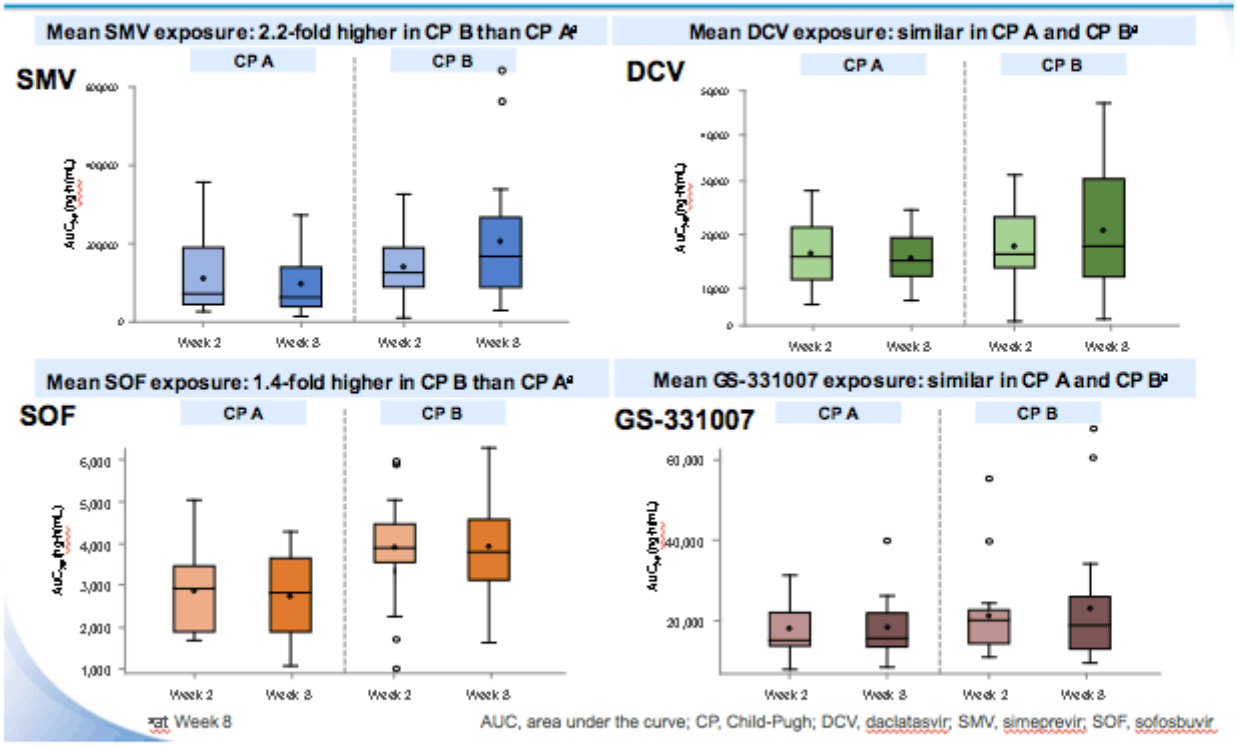
IMPACT: Change in MELD scores from baseline to follow-up Week 12



MELD, model for end-stage liver disease

•The observed overall trends in MELD scores were similar to those seen for SOF/LDV + RBV (SOLAR-2 data) and EBR/RBV in patients with liver decompensation

IMPACT: SMV, SOF, and DCV pharmacokinetics following administration of SMV + SOF + DCV



DDI

•No DDI analyses performed in this study

•SOF has no effect on SMV levels

•When SMV/SOF are co-administered, there is an increase in SOF levels (C_{max}: 1.91-fold increase; AUC: 3.2-fold increase), but not in GS-33107 levels; therefore, no dose-adjustment is required (see COSMOS)

•In healthy volunteers, SMV increased DCV AUC by approximately 2-fold (DCV USPI), but this did not translate in the LEAGUE s

•DCV increased SMV exposure by approximately 40% (also confirmed in clinical trials)

IMPACT: Summary of on-treatment adverse events

Parameter, n (%)	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
Any AE	11 (58)	16 (76)	27 (68)
Grade 1/2	11 (58)	15 (71)	26 (65)
Grade 3/4	0	1 (5)[a]	1 (3)
Treatment-related AEs	3 (16)	7 (33)	10 (25)
Serious AE	0	1 (5)[a]	1 (3)
Early discontinuation due to AE	0	0	0
Death	0	0	0

[a]Grade 3 gastrointestinal hemorrhage, not related to study drugs

IMPACT: Most common on-treatment adverse events (≥2 patients)

Parameter, n (%)	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
Pruritus	1 (5)	2 (10)	3 (8)
Urinary tract infection	1 (5)	2 (10)	3 (8)
Photosensitivity reaction	2 (11)	1 (5)	3 (8)
Nausea	1 (5)	2 (10)	3 (8)
Hepatic encephalopathy	0	2 (10)	2 (5)
Anemia	2 (11)	0	2 (5)
Insomnia	0	2 (10)	2 (5)
Irritability	1 (5)	1 (5)	2 (5)

IMPACT: Grade 3/4 treatment-emergent laboratory abnormalities

Parameter, n (%)	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
Bilirubin[a,b]			
Grade 3	2 (11)	5 (24)	7 (18)
Grade 4	0	2 (10)	2 (5)
Lipase			
Grade 3	0	1 (5)	1 (3)
Grade 4	1 (5)	0	1 (3)
Glucose elevations			
Grade 3	1 (5)	1 (5)	2 (5)
Grade 4	0	1 (5)	1 (3)

[a]Bilirubin values returned to baseline by follow up Week 12
[b]No concomitant increases in transaminases

Bilirubin Grade 3 total bilirubin elevation: >2.5–≤5.0 x ULN; Grade 4 total bilirubin elevation: >5.0 x ULN

Glucose Grade 3 increase: 251–500 mg/dL; Grade 4 increase: >500 mg/dL or ketoacidosis or seizures

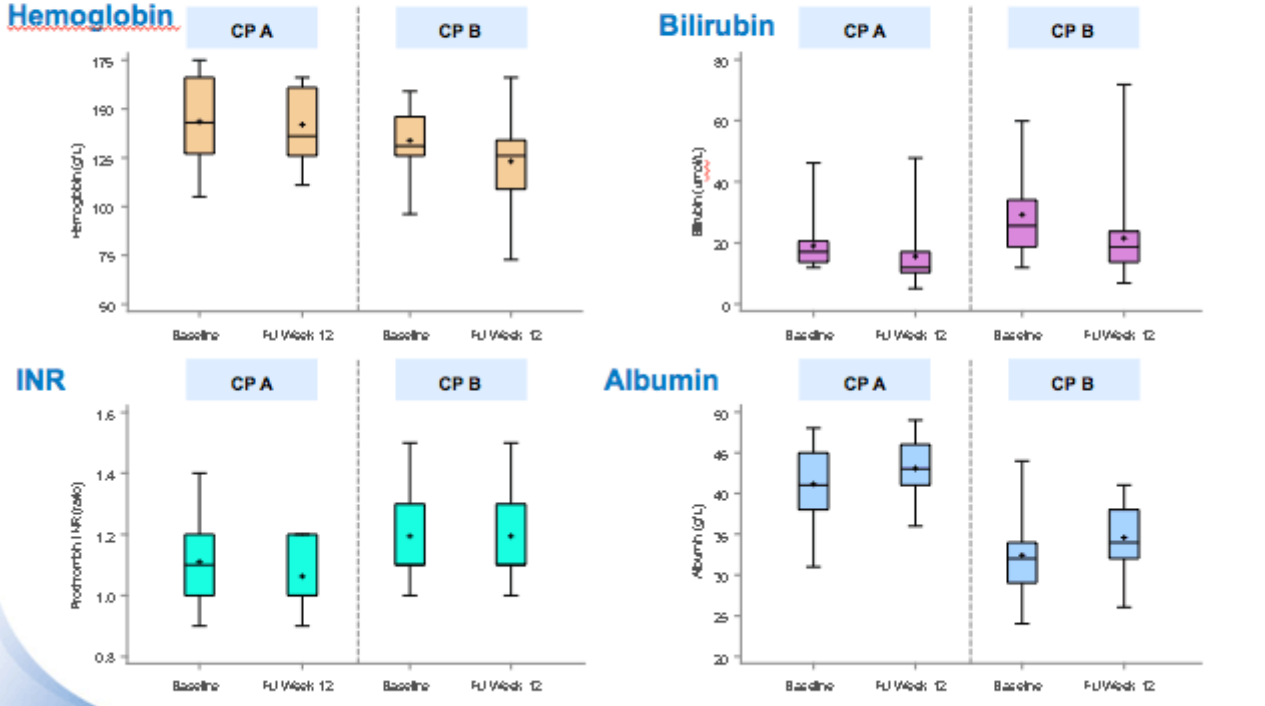
Lipase Grade 3: >3.0–≤5.0 x ULN; Grade 4: >5.0 x ULN

Platelets Grade 3: 20,000–49,000/mm^3; Grade 4: <20,000/mm^3

Back-up slides

IMPACT: Median total hemoglobin, bilirubin, INR and albumin with SMV + SOF + DCV

Change from baseline to follow up Week 12

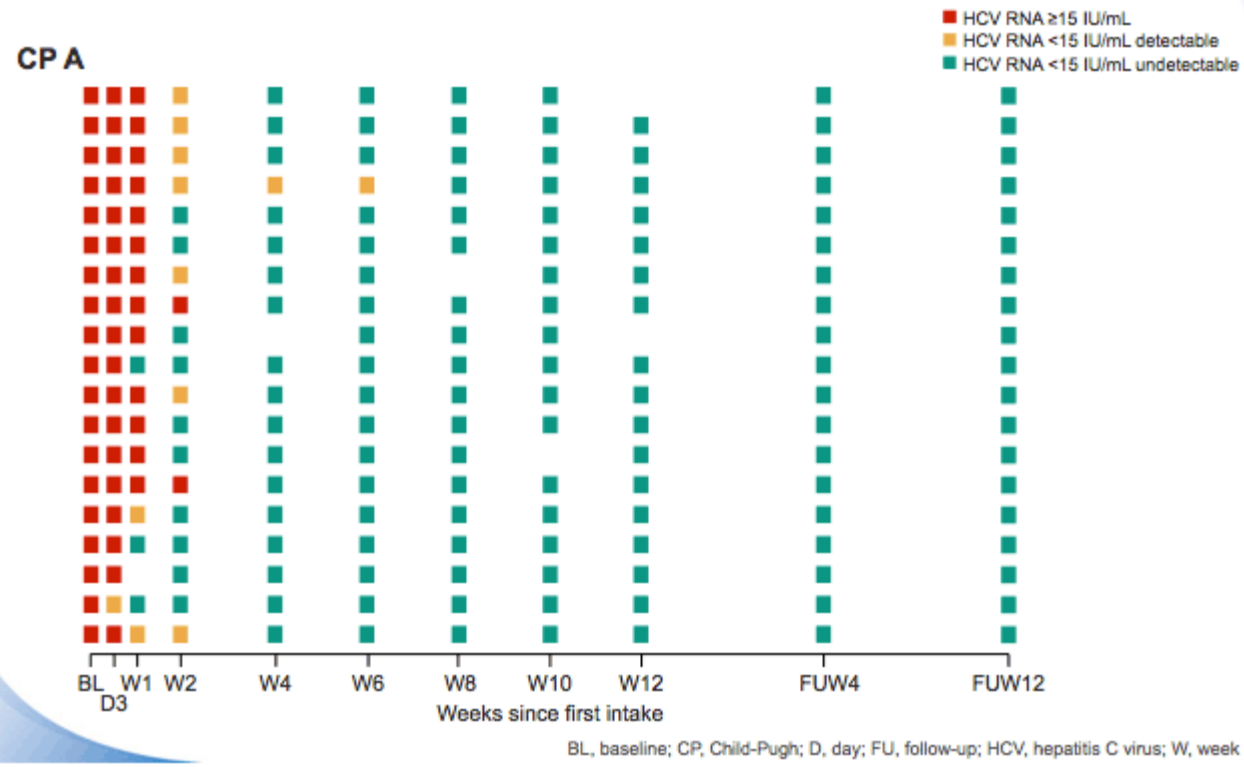


CP, Child-Pugh; DCV, daclatasvir; FU, follow-up; INR, international normalized ratio; SMV, simeprevir; SOF, sofosbuvir

IMPACT: Baseline disease characteristics

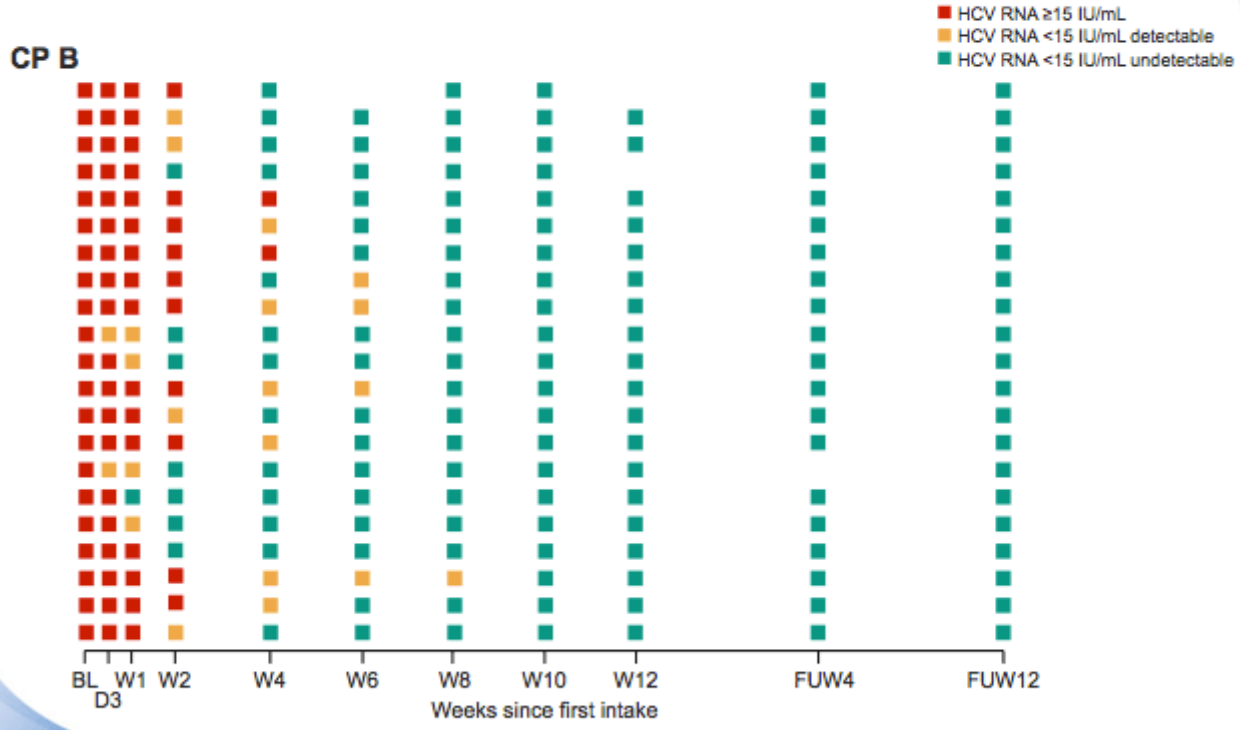
Parameter, n (%)	SMV + SOF + DCV		
	CP A (N=19)	CP B (N=21)	Total (N=40)
HCV RNA level (IU/mL)			
<400,000	8 (42)	11 (52)	19 (48)
≥400,000–≤800,000	4 (21)	0	4 (10)
>800,000	7 (37)	10 (48)	17 (43)
<6,000,000	18 (95)	21 (100)	39 (98)
≥6,000,000	1 (5)	0	1 (3)

IMPACT: Virologic response over time



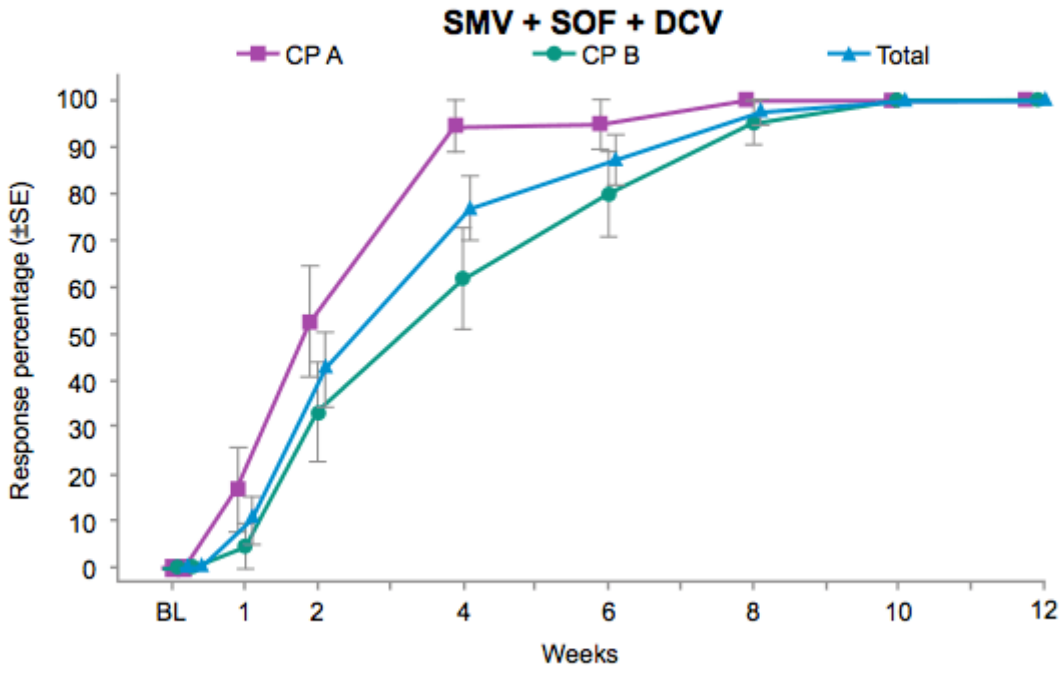
BL, baseline; CP, Child-Pugh; D, day; FU, follow-up; HCV, hepatitis C virus; W, week

IMPACT: Virologic response over time



BL, baseline; CP, Child-Pugh; D, day; FU, follow-up; HCV, hepatitis C virus; W, week

IMPACT: On-treatment virologic response (HCV RNA <15 IU/mL undetectable) over time



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