Simeprevir, daclatasvir and sofosbuvir for hepatitis C virus-infected patients with decompensated liver disease

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Abbreviations: AE, adverse event; AUC_{24h}, maximum plasma concentrations and area under the curve over the dosing interval; BMI, body mass index; BQL, below the quantification limit; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CP, Child-Pugh; DAA, direct-acting antiviral agent; EOT, end of treatment; GT, genotype; HCV, hepatitis C virus; INR, international normalized ratio; ITT, intent-to-treat; LSM, least-squares mean; MELD, model for end-stage liver disease; PK, pharmacokinetic; PR, peginterferon and ribavirin; QD, once daily; RAV, resistance-associated variant; SAE, serious adverse event; SD, standard deviation; SI, international system of units; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after end of treatment; SVR24, sustained virologic response 24 weeks after end of treatment; t_{max}, time to C_{max}; ULN, upper limit of normal.

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Summary
Approximately three million individuals in the United States are chronically infected with hepatitis C virus (HCV). Chronic HCV infection may lead to the development of compensated as well as decompensated liver cirrhosis. The Phase II IMPACT study was conducted in HCV genotype 1- or 4-infected cirrhotic patients with portal hypertension or decompensated liver disease and assessed for the first time the combination of the three direct-acting antivirals simeprevir, daclatasvir and sofosbuvir. Treatment-naïve or treatment-experienced adults with Child-Pugh (CP) score <7 (CP A) and evidence of portal hypertension, or CP score 7–9 (CP B), received 12 weeks of simeprevir 150 mg, daclatasvir 60 mg and sofosbuvir 400 mg, once daily. The primary efficacy endpoint was sustained virologic response 12 weeks after end of treatment (SVR12). Pharmacokinetics and safety were also assessed. Overall, 40 patients were enrolled (CP A: 19; CP B: 21). All 40 patients achieved SVR12. At week 8, the mean pharmacokinetic exposure to simeprevir, sofosbuvir, daclatasvir and GS-331007 (sofosbuvir metabolite) was 2.2-, 1.5-, 1.2- and 1.2-fold higher in patients with CP B than CP A, respectively. Grade 1/2 adverse events (AEs) occurred in 26 of 40 (65%) patients. One CP B patient had a Grade 3 AE (gastrointestinal haemorrhage), which was reported as a serious AE but not considered related to study drugs. Treatment for 12 weeks with simeprevir, daclatasvir and sofosbuvir was generally safe and well tolerated, and resulted in 100% of cirrhotic patients with portal hypertension or decompensated liver disease achieving SVR12.

KEYWORDS
daclatasvir, hepatitis C, simeprevir, sofosbuvir

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INTRODUCTION

An estimated three million individuals are chronically infected with hepatitis C virus (HCV) in the United States. HCV infection leads to the development of liver cirrhosis in one-fifth of patients within 20-30 years and is a leading cause of liver transplantation, hepatocellular carcinoma and death. Patients who develop decompensated liver disease, characterized by ascites, reduction in albumin, prolongation of international normalized ratio, hepatic encephalopathy and/or spontaneous bacterial peritonitis, have decreased survival rates vs patients with compensated cirrhosis.

Treating patients with advanced liver disease has been historically associated with limited success. In addition to the intrinsic fragility of these patients, decompensated liver disease may result in impaired hepatic metabolism, affecting the plasma concentrations of HCV direct-acting antiviral agents (DAAs). Therefore, treatment options must be carefully considered. Furthermore, it has been reported that some DAAs may cause liver injury in patients with underlying cirrhosis.

Until 2011, the standard of care for chronic HCV infection was peginterferon and ribavirin. However, this regimen is contraindicated in patients with decompensated cirrhosis due to poor tolerability. Since 2011, DAAs have become available, leading to the introduction of better-tolerated, interferon-/ribavirin-free, all-oral regimens. Current guidelines for patients with decompensated cirrhosis recommend the fixed-dose combination of sofosbuvir, ledipasvir and ribavirin for 12 weeks (for genotypes [GTs] 1, 4, 5 and 6), for which sustained virologic response 12 weeks after the end of treatment (SVR12) rates of 86%-89% and 85%-87% has been reported for the SOLAR-1 and SOLAR-2 studies, respectively, in nontransplant patients with Child-Pugh (CP) class B or C cirrhosis. The combination of sofosbuvir, daclatasvir and ribavirin for 12 weeks (all GTs) is also recommended, and SVR12 rates of 82% have been reported with this regimen in the ALLY-1 study in GT1-infected patients with CP A, B or C.

Furthermore, a real-world study conducted in the United Kingdom resulted in SVR12 rates of 88% and 91% with sofosbuvir, daclatasvir and ribavirin in GT1-infected patients with decompensated cirrhosis.

Simeprevir, sofosbuvir and daclatasvir are among the DAAs approved for the treatment of chronic HCV infection. Simeprevir is an HCV NS3/4A protease inhibitor with antiviral activity against GTs 1, 2, 4, 5 and 6; sofosbuvir is a pangenotypic nucleotide HCV NS5B polymerase inhibitor; and daclatasvir is a pangenotypic HCV NS5A replication complex inhibitor. Simeprevir has been evaluated in combination with sofosbuvir and/or daclatasvir in patients with compensated liver disease as part of an interferon-free regimen with/without ribavirin, leading to SVR12 rates of 69%-93%. In the SODAPI study, which evaluated three weeks of simeprevir in combination with sofosbuvir and daclatasvir in Chinese HCV GT1b-infected patients without cirrhosis, an SVR12 rate of 100% was reported. The Phase II IMPACT study assessed for the first time the combination of simeprevir, sofosbuvir and daclatasvir (DAAs with different mechanisms of action and metabolic pathways, as well as non-overlapping resistance profiles) for 12 weeks in HCV GT1- or 4-infected, treatment-naive or treatment-experienced patients with portal hypertension or decompensated liver disease.

METHODS

2.1 Patients and study design

IMPACT (NCT02262728) is an ongoing Phase II, open-label study initiated on 30 September 2014 at a single site in the United States. The primary analysis cut-off date was 28 August 2015. The study was approved by the Institutional Review Board and met the principles of the Declaration of Helsinki. All patients provided written informed consent. All authors had access to the study data, and reviewed and approved the final manuscript.

Eligible patients were adults (>18 years old) with chronic HCV GT1 or 4 infection documented more than 6 months before screening, plasma HCV RNA >10,000 IU/mL at screening and presence of cirrhosis (FibroScan® [Echosens™, Paris, France] >14.5 kPa at screening). Both treatment-naive and interferon-based (± ribavirin) HCV treatment-experienced patients were included. Liver disease was classified by CP score: CP A (panel 1): score <7 with documented portal hypertension, confirmed by the presence of oesophageal varices on gastroscopy or hepatic venous pressure gradient ≥10 mmHg; CP B (panel 2): score 7-9 (Figure 1). Stable hepatic function and absence of hepatocellular carcinoma were also required (Appendix S1).

Key exclusion criteria included evidence of liver disease of non-HCV aetiology or coinfection with multiple HCV GTs, hepatitis B or human immunodeficiency virus-1/-2. Patients previously treated with any HCV DAA (approved or investigational) were excluded (Appendix S1). The study consisted of a screening phase of approximately 4 weeks, an open-label treatment phase of 12 weeks and a post-treatment follow-up phase of 5 years after the actual end of treatment (EOT). Patients received simeprevir 150 mg once daily (QD), daclatasvir 60 mg QD and sofosbuvir 400 mg QD for 12 weeks (Figure 1).

![FIGURE 1 IMPACT study design.](image-url)
2.2 | Procedures

Blood samples for determining the HCV RNA level were collected at predefined time points. HCV RNA was measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test v2.0 (Roche; lower limit of quantification=limit of detection=15 IU/mL) (Appendix S1).

Sequencing of the HCV NS3/4A, NS5A and NS5B regions was performed pretreatment in all patients to identify pre-existing sequence polymorphisms (Appendix S1).

Liver disease status was monitored through the assessment of CP, model for end-stage liver disease (MELD), FibroTest (BioPredictive, Paris, France) and FibroScan™ scores which were assessed at either screening or baseline, and during follow-up. Change over time in CP and MELD scores from baseline to follow-up were recorded.

Pharmacokinetic (PK) data were collected as described in Appendix S1. Adverse events (AEs) were monitored throughout the treatment period up to week 4 of follow-up (Appendix S1).

2.3 | Outcomes

The primary efficacy endpoint was SVR12 (HCV RNA <15 IU/mL detectable or undetectable 12 weeks after the actual EOT) in the intent-to-treat (ITT) population (all patients who received at least one dose of the study drugs).

Key secondary endpoints included the following: SVR rate 4 weeks after EOT; SVR rate 24 weeks after EOT (SVR24); on-treatment virologic response (HCV RNA <15 IU/mL detectable or undetectable at all time points); on-treatment failure including viral breakthrough (confirmed >1.0 log_{10} increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in patients who had previously achieved HCV RNA <15 IU/mL on-treatment); viral relapse (patients not achieving SVR12, with undetectable HCV RNA at EOT and confirmed HCV RNA ≥15 IU/mL during follow-up); changes from baseline in the HCV NS3/4A, NS5A and NS5B sequences in patients not achieving SVR12; PK parameters for simeprevir, daclatasvir, sofosbuvir and GS-331007; and safety and tolerability.

Exploratory endpoints included the effect of treatment on liver disease status.

2.4 | Statistics

As this was an exploratory study, no formal sample size calculation was performed. A sample size of 20 patients per panel was determined based on considerations of estimating the SVR rate and the exact 95%, two-sided confidence intervals (CIs) with sufficient precision (Appendix S1).

All efficacy analyses were performed on the ITT population. The primary, secondary and exploratory efficacy endpoints were analyzed overall and by CP class using descriptive statistics (Appendix S1).

Noncompartmental PK analyses were conducted, and all safety data were analyzed descriptively (Appendix S1).

Results from the primary analysis of the IMPACT study, when all patients had reached the SVR12 time point or had discontinued earlier, are presented.

3 | RESULTS

3.1 | Patients

Of 74 patients screened, 40 patients were enrolled: 19 in the CP A and 21 in the CP B group (see Appendix S1 for reasons of screening failure). No patients discontinued study treatment prematurely.

Patient baseline demographics and disease characteristics are summarized in Table 1. Patients were mainly male (63%), White (98%), Hispanic or Latino (58%), with non-CC IL28B GT (83%), high body mass index (>28.5) and with HCV GT1a infection (65%). Portal hypertension was diagnosed by the presence of upper gastrointestinal varices in 100% of patients in the CP A group. In the CP B group, a mean baseline MELD score of 10.1 was reported and 95% of patients had clinical features of decompensation (ascites, 81%; hepatic encephalopathy, 67%; median albumin, 3.2 g/dl). Baseline NS3 Q80K, a naturally occurring polymorphism known to confer low-level resistance to simeprevir in vitro, was observed in 12 of 25 (48%) HCV GT1a-infected patients with sequencing data available. Table S1 presents all baseline simeprevir, daclatasvir and sofosbuvir resistance-associated variants (RAV; defined in this analysis as having a fold change in 50% effective concentration of the respective drug >2, compared with wild type). One patient (1/40 [3%]) had both simeprevir and daclatasvir RAVs at baseline (Q80R in NS3 and Y93H in NS5A). In addition, 2 of 40 (5%) further patients had the daclatasvir RAV Y93H at baseline. The S282T variant associated with resistance to sofosbuvir was not observed at baseline.

3.2 | Efficacy

All patients achieved SVR12 (Figure 2), regardless of the presence of baseline simeprevir and/or daclatasvir RAVs. All patients with SVR12 also achieved SVR24.

In CP A, 18 of 18 (100%) patients with available data at week 4 had HCV RNA <15 IU/mL (detectable or undetectable) (Figures 2 and S1). For CP B patients, 19 of 21 (90%) had HCV RNA <15 IU/mL (detectable or undetectable) at week 4. Neither the presence of a NS3 Q80K polymorphism at baseline nor prior treatment history affected on-treatment response (data not shown).

Figure 3 shows the changes in CP and MELD scores from baseline to follow-up week 12 in individual patients. CP score decreased in 11 patients, remained unchanged in 23 patients and increased in 6 patients (Figure 3A). MELD scores decreased in 20 patients, were unchanged in 13 patients and increased in seven patients (Figure 3B).

3.3 | Pharmacokinetics

At week 8, the mean PK exposure (maximum plasma concentrations and area under the curve over the dosing interval [AUC_{24h}]) to simeprevir, sofosbuvir, daclatasvir and GS-331007 was 2.2-1.5-, 1.2- and 1.2-fold higher in patients with CP B than in CP A, respectively, based on least-squares mean (LSM) ratios (Fig. S2). Further PK data are presented in Appendix S1.
During the treatment phase, there were no deaths or AEs that led to treatment discontinuation. Grade 1/2 AEs were reported in 26 of 40 (65%) patients. One patient in the CP B group had a Grade 3 AE during week 6 of treatment (gastrointestinal haemorrhage), which was also reported as a serious AE but was not considered related to the study drugs (Table 2).

The most frequently reported AEs (in ≥2 patients) were pruritus, urinary tract infection, photosensitivity reaction, nausea, hepatic encephalopathy, anaemia, insomnia and irritability (Table 2).

During the treatment phase of the study, 0 of 19 and 2 of 21 (10%) patients in the CP A and CP B groups, respectively, experienced clinical events related to hepatic decompensation (jaundice in one patient and gastrointestinal bleeding in another patient with previous history of an oesophageal bleed).
Recently reported, patients, respectively), there were no concomitant increases in alanine aminotransferase/aspartate aminotransferase in either group. Bilirubin increases were more frequent in the CP B group and correlated with higher plasma exposure of simeprevir; however, as previously reported, these increases were isolated, well tolerated and did not lead to treatment discontinuation.

Grade 3/4 laboratory abnormalities are shown in Table 2. In patients with Grade 3 or 4 bilirubin elevations (7/40 [18%] and 2/40 [5%] patients, respectively), there were no concomitant increases in alanine aminotransferase/aspartate aminotransferase in either group. Bilirubin increases were more frequent in the CP B group and correlated with higher plasma exposure of simeprevir; however, as previously reported, these increases were isolated, well tolerated and did not lead to treatment discontinuation.

4 | DISCUSSION

In the IMPACT study, treatment for 12 weeks with simeprevir, sofosbuvir and daclatasvir resulted in a 100% SVR12 rate. All of the treatment-naïve and treatment-experienced patients with cirrhosis and portal hypertension (CP A) or decompensation (CP B) achieved SVR12 and SVR24, regardless of the presence of simeprevir and/or daclatasvir RAVs at baseline.

At week 4, 18 of 18 (100%) patients with CP A and 19 of 21 (90%) patients with CP B with available data had HCV RNA <15 IU/mL (detectable or undetectable). Patients in the CP B group had slower initial viral decay; however, there was no difference in SVR12 rates versus the CP A group, reinforcing the concept that assessment of early viral dynamics may have limited value in predicting treatment outcomes with regimens that are highly potent.

The 100% SVR12 rate reported in the IMPACT study with simeprevir, sofosbuvir and daclatasvir in the absence of ribavirin, an agent that is poorly tolerated in patients with advanced liver disease, improves upon SVR rates previously reported in this patient population when treated for 12 weeks with ribavirin-containing regimens. In the ASTRAL-4 study, the combination of sofosbuvir and velpatasvir with ribavirin was investigated in CP B patients with HCV infection and decompensated cirrhosis, leading to an overall SVR12 rate of 94% in patients who received 12 weeks of treatment. Notably, both of the currently recommended treatment combinations for HCV-infected patients with decompensated cirrhosis also include ribavirin.

The combination of simeprevir and sofosbuvir for 12 weeks without ribavirin was assessed in two Phase III trials in treatment-naïve and (peginterferon±ribavirin) treatment-experienced HCV GT1-infected patients with (OPTIMIST-2) or without (OPTIMIST-1) compensated cirrhosis. The regimen demonstrated superiority in SVR12 rates over historical control data in both studies. In the presence of cirrhosis in the OPTIMIST-2 study, numerically lower SVR12 rates were observed in HCV GT1a-infected patients with a baseline NS3 Q80K polymorphism compared with HCV GT1a-infected patients without this polymorphism (74% vs 92%). In the current study, the presence of the NS3 Q80K polymorphism at baseline did not influence SVR12 rates, suggesting that the addition of a third DAA to the simeprevir/sofosbuvir regimen was beneficial in overcoming the limitations of the dual combination when treating patients with cirrhosis.

The impact of SVR on the liver function of patients with advanced and decompensated liver disease is not well understood. Results from this study, in which all patients achieved SVR12, revealed improved or stabilized CP and MELD scores from baseline to follow-up week 12 in the majority of patients. The planned 5-year follow-up period will allow clinical changes to be monitored in these patients over an extended period of time and will provide further insight into the long-term benefits of achieving SVR in patients with advanced liver disease.

Of note, simeprevir, sofosbuvir, daclatasvir and GS-331007 exposures (AUC_{24h}) were numerically higher in patients with CP B than CP A, consistent with the observation that decreased cytochrome P450 and drug transporter expression correlates with progression.
| n (%) | CP A (n=19) | CP B (n=21) | Total (N=40) |
|-------|-------------|-------------|--------------|
| Any AE | 11 (58)     | 16 (76)     | 27 (68)      |
| Grade 1 or 2 | 11 (58) | 15 (71) | 26 (65) |
| Grade 3 or 4 | 0 | 1 (5) | 1 (3) |
| SAEs | 0 | 1 (5) | 1 (3) |
| Deaths | 0 | 0 | 0 |
| Early discontinuation due to an AE | 0 | 0 | 0 |
| Treatment-related AEs | | | |
| At least possibly related to simeprevir | 3 (16) | 7 (33) | 10 (25) |
| At least possibly related to sofosbuvir | 1 (5) | 5 (24) | 6 (15) |
| At least possibly related to daclatasvir | 1 (5) | 5 (24) | 6 (15) |
| AEs in ≥2 patients | | | |
| 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) |
| Anaemia | 2 (11) | 0 | 2 (5) |
| Insomnia | 0 | 2 (10) | 2 (5) |
| Irritability | 1 (5) | 1 (5) | 2 (5) |
| Grade 3 or 4 treatment-emergent laboratory abnormalities | | | |
| Bilirubin | | | |
| Grade 3 | 2 (11) | 5 (24) | 7 (18) |
| Grade 4 | 0 | 2 (10) | 2 (5) |
| Glucose elevations | | | |
| Grade 3 | 1 (5) | 1 (5) | 2 (5) |
| Grade 4 | 0 | 1 (5) | 1 (3) |
| Lipase | | | |
| Grade 3 | 0 | 1 (5) | 1 (3) |
| Grade 4 | 1 (5) | 0 | 1 (3) |
| Neutrophils | | | |
| Grade 3 | 0 | 1 (5) | 1 (3) |
| Grade 4 | 0 | 0 | 0 |
| Platelets | | | |
| Grade 3 | 0 | 3 (14) | 3 (8) |
| Grade 4 | 0 | 0 | 0 |
| Prothrombin time | | | |
| Grade 3 | 0 | 1 (5) | 1 (3) |
| Grade 4 | 0 | 0 | 0 |

*aNot considered related to study treatment.
*bBilirubin values returned to baseline by follow-up week 12.
*cNo concomitant increases in transaminases.
*dBilirubin Grade 3 total bilirubin elevation: >2.5–≤5.0×ULN; Grade 4 total bilirubin elevation: >5.0×ULN.
*eGlucose Grade 3 Increase: 251–500 mg/dL; Grade 4 Increase: >500 mg/dL or ketoacidosis or seizures. All were observed in the nonfasting state in patients with no prior diabetes.
*fLipase Grade 3: >3.0–≤5.0×ULN; Grade 4: >5.0×ULN.
*gNeutrophils Grade 3 Decrease: 500–749/mm³.
*hPlatelets Grade 3 Decrease: 20 000–49 999/mm³.
*iProthrombin time Grade 3 Increase: >1.50–≤3.00×ULN.

AE, adverse event; CP, Child-Pugh; ITT, intent-to-treat; QD, once daily; SAE, serious adverse event; ULN, upper limit of normal.
of liver fibrosis. Despite the relatively good synthetic function of the CP B patients in this study, the 2.2-fold higher plasma exposure of simeprevir in the CP B group resulted in more frequent, isolated Grade 3/4 bilirubin increases compared with the CP A group (33% vs 11%). In spite of the high efficacy reported in this study, protease inhibitors should be used with caution in patients with decompensated cirrhosis due to PK changes in patients with CP B and the potential for liver toxicity. This has recently been highlighted in the results from C-SALT, a study which investigated the combination of the NS3/4A protease inhibitor, grazoprevir and the NSSA replication complex inhibitor, elbasvir, in HCV GT1-infected patients with CP B, in which the plasma exposure of grazoprevir was slightly higher in patients with CP B who received 50 mg compared with patients without cirrhosis who received 100 mg. However, high SVR12 rates were observed in patients with CP B (90%) regardless of the lower dose of grazoprevir. Overall, this three-DAA regimen was well tolerated. There were no discontinuations due to AEs, and only one on-treatment Grade 3 AE was reported and unrelated to the study drugs.

A major strength of this study is the inclusion of a 5-year follow-up period, which will be important in providing long-term outcomes in association with SVR. Limitations include the open-label nature of the study, the fact that it was conducted at a single centre, and the modest sample size that included a single GT4-infected patient and no CP C (CP score 10-15) patients. This is the first time that the combination of simeprevir, sofosbuvir and daclatasvir (three unique DAA with different mechanisms of action and non-overlapping resistance profiles) has been assessed in HCV GT1-4-infected patients with portal hypertension or decompensated liver disease. The results of this study provide proof of concept that combining three DAA with different mechanisms of action can enhance response rates in difficult-to-cure patients.

5 | CONCLUSION

The results from the ongoing IMPACT study indicate that the interferon-free, three-DAA combination of simeprevir, sofosbuvir and daclatasvir has the potential to become a short-duration, ribavirin-free and well-tolerated alternative regimen for the treatment of difficult-to-cure, HCV GT1-infected patients.

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CONFLICT OF INTERESTS

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AUTHORS’ CONTRIBUTIONS

EL, FP and JAG were involved in the acquisition and interpretation of study data and have been involved in the critical revision of the manuscript for important intellectual content. TNK, GP, GB, AV, PVR, BJ, SO-M, LV, VVE and MB were involved in the study concept and design, and the acquisition, analysis and interpretation of study data. They have also been involved in the critical revision of the manuscript for important intellectual content. DL provided statistical analysis of the study data and has been involved in the critical revision of the manuscript for important intellectual content. All authors have reviewed and approved the final manuscript content and agree to submit for publication.
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