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Simeprevir in combination with sofosbuvir in treatment-naïve and -experienced patients with hepatitis C virus genotype 4 infection: a Phase III, open-label, single-arm study (PLUTO)

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SUMMARY

Background
Hepatitis C virus (HCV) infection is a leading cause of liver cirrhosis and subsequent hepatocellular carcinoma. HCV genotype 4 is found widely in the Middle East, Egypt and Africa, and has also spread into Europe. There are limited data available regarding the use of direct-acting antiviral agents in HCV genotype 4-infected patients with cirrhosis.

Aim
To evaluate in the phase III, open-label, single-arm PLUTO study the efficacy and safety of 12 weeks of simeprevir (HCV NS3/4A protease inhibitor) plus sofosbuvir (HCV nucleotide-analogue NS5B polymerase inhibitor) in treatment-naïve and (peg)interferon ± ribavirin-experienced HCV genotype 4-infected patients, with or without compensated cirrhosis.

Methods
Adult patients with chronic HCV genotype 4 infection received simeprevir 150 mg once-daily and sofosbuvir 400 mg once-daily for 12 weeks. The primary efficacy endpoint was sustained virologic response 12 weeks after the end of treatment (SVR12). Safety was also assessed.

Results
Forty patients received treatment; the majority were male (73%) and treatment-experienced (68%). Overall, 7/40 (18%) patients had compensated cirrhosis. All patients achieved SVR12 [100% (Clopper-Pearson 95% confidence interval: 91–100%)]. Adverse events, all Grade 1 or 2, were reported in 20/40 (50%) patients. No serious adverse events were reported and no patients discontinued study treatment. Grade 3 treatment-emergent laboratory abnormalities were noted in 2/40 (5%) patients.

Conclusions
Treatment with simeprevir plus sofosbuvir for 12 weeks resulted in SVR12 rates of 100% in treatment-naïve and -experienced patients with HCV genotype 4 infection with or without compensated cirrhosis, and was well tolerated. [NCT02250807]

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INTRODUCTION

Hepatitis C virus (HCV) infection is one of the leading causes of liver disease worldwide.[1] Notably, 55–85% of patients develop chronic HCV infection and without successful treatment, 15–30% of these progress to cirrhosis within 20 years. Liver cirrhosis increases the risk of liver failure, hepatocellular carcinoma and death.[2] Complications of chronic HCV infection are among the leading indications for liver transplantation.[3] HCV is categorised into at least six major genotypes,[4] with genotype 4 accounting for 20% of global infections.[5] HCV genotype 4 is prevalent primarily in the Middle East, Egypt and Africa, but increasingly also in some European countries including Italy, France, Greece and Spain,[5, 6] where incidence rates of 10–24% have been reported. Contributing factors to the spread of HCV genotype 4 infection to these countries may include injection with glass syringes and multiple-use needles, the use of non-HCV-tested blood products, and the historical link between regions in southern Italy and Spain with the Middle East and North Africa.[7]

The previous standard of care for HCV infection was treatment with peginterferon (pegIFN) plus ribavirin (PR). However, since the recent development of direct-acting antiviral agents (DAAs), more treatment regimens have become available. Current guidelines for HCV genotype 4 infection include both interferon (IFN)-containing and IFN-free regimens; the latter consisting of DAAs with or without ribavirin.[8, 9] However, there are limited data available on the use of DAAs in HCV genotype 4-infected patients with cirrhosis.

Simeprevir, an oral, once-daily HCV NS3/4A protease inhibitor with anti-viral activity against HCV genotypes 1, 2, 4, 5 and 6, is approved as part of an IFN-free combination with sofosbuvir (a once-daily pangenotypic HCV nucleotide-analogue NS5B polymerase inhibitor) for HCV genotype 1 infection in the USA, and genotype 1 and genotype 4 infections in the European Union (EU). This combination is also approved for HCV/human immunodeficiency virus (HIV) co-infection in the EU. Furthermore, simeprevir is approved in combination with PR for chronic HCV genotype 1 and genotype 4 infections in the USA and the EU.

The approvals of simeprevir plus PR for HCV genotype 4-infected patients were primarily based on the results of the Phase III RESTORE study (NCT01567735), where simeprevir in combination with PR was shown to be effective in the treatment of HCV genotype 4-infected patients. In total, 83% of treatment-naïve patients and 57% of prior relapsers/nonresponders to PR-based treatment achieved sustained virologic response 12 weeks after the end of treatment (SVR12).[10] Similarly, sofosbuvir in combination with PR has been proven effective in this patient population.[11] The combination of simeprevir and sofosbuvir has been studied in the Phase III OPTIMIST-1 and -2 studies in HCV genotype 1-infected treatment-naïve or (peg)IFN ± ribavirin-experienced patients, in which SVR12 rates of 83% and 97% were reported with 12 weeks of treatment in patients with and without cirrhosis respectively.[12, 13]

The present study assessed for the first time in Europe the treatment combination of simeprevir and sofosbuvir for 12 weeks in treatment-naïve or (peg)IFN ± ribavirin-experienced HCV genotype 4-infected patients, with and without compensated cirrhosis.

MATERIALS AND METHODS

Patients and study design

PLUTO was a Phase III, multicentre, open-label study (NCT02250807) conducted at 10 centres in Spain, and was initiated on 7 January 2015 and completed on 23 December 2015. The study was approved by the relevant Institutional Review Board or Independent Ethics Committee at each study centre and met the principles of the Declaration of Helsinki and guidelines of Good Clinical Practice. All patients provided written, informed consent to participate.

Eligible adults (age 18–70 years) had chronic HCV genotype 4 infection confirmed at screening, with plasma HCV RNA >10 000 IU/mL and a liver biopsy within 2 years of the screening visit or a FibroScan performed within 6 months of the screening period. If a biopsy or FibroScan more than 2 years prior to screening had already demonstrated cirrhosis, the procedure did not have to be repeated. For patients with cirrhosis, hepatic imaging within 6 months before screening was required to rule out hepatocellular carcinoma.

Key exclusion criteria were evidence of hepatic decompensation (including history or current evidence of ascites, bleeding varices or hepatic encephalopathy), any liver disease of non-HCV aetiology, co-infection with HCV non-genotype 4, hepatitis B virus or HIV-1/-2 infection, or presence of other clinically significant disease. Patients with significant laboratory abnormalities, such as total serum bilirubin >1.5× upper limit of normal, albumin <3 g/dL and platelet count $<50 \times 10^3/\mu L$, were excluded. Patients previously treated with any HCV DAA (approved or investigational) were also not eligible.

Treatment-naïve and treatment-experienced patients [prior relapsers, prior nonresponders (partial responders, null responders and unknown), IFN-intolerant and 'other' (patients not classified as among any of the aforementioned categories)] were enrolled. Treatment-experienced patients must have received ≥1 documented course of (peg)IFN-based therapy with or without ribavirin.

The study consisted of a screening period of up to 4 weeks followed by a 12-week, open-label treatment phase during which patients received simeprevir (150 mg, 1 oral capsule once-daily) and sofosbuvir (400 mg, 1 oral tablet once-daily), taken with food. Patients were followed up until 24 weeks after the end of treatment (EOT).

Procedures

Blood samples for HCV RNA level determination were collected at: screening; baseline (Day 1); Day 7; end of Weeks 2, 3, 4, 8 and 12; and follow-up Weeks 4, 12 and 24. HCV RNA was measured using the Roche COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA) (with a lower limit of quantification and limit of detection of 15 IU/mL).

Population sequencing of the HCV NS3/4A and NS5B genes was performed pre-treatment in all patients to identify pre-existing sequence polymorphisms, and sequencing of post-baseline samples was to be performed in patients not achieving SVR to potentially characterise emerging viral variants (detection limit: ~20–25%). In addition, a mandatory blood sample was collected at baseline to determine *IL28B* genotype.

Adverse events (AEs) were monitored throughout the study until post-treatment follow-up Week 4. For patients who might have prematurely discontinued study treatment, AEs would be collected until EOT plus Week 4 of follow-up. AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, with severity determined according to the World Health Organization toxicity grading scale. The relationship of AEs to study treatment was assessed by the investigator. From Week 4 of follow-up onwards, reporting was limited to treatment-related AEs.

Clinical laboratory assessments, including haematology, serum chemistry and urinalysis, and safety assessments, including physical examination and vital signs, were conducted at screening, Days 1 and 7, end of Weeks 2, 4, 8 and 12, and post-treatment Week 4. Mean changes from baseline to post-treatment Week 4 for total haemoglobin, neutrophils and precursors, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lipase, amylase and platelets were plotted. Electrocardiogram assessments were performed at screening.

Outcomes

The primary objective was to demonstrate the superiority of simeprevir in combination with sofosbuvir for 12 weeks vs. a historical control derived from the Phase III RESTORE study,[10] with respect to the proportion of patients achieving SVR12 (SVR defined as HCV RNA <15 IU/mL detectable or undetectable 12 weeks after actual EOT; Table 1). The primary efficacy endpoint was the proportion of patients with SVR12.

Pre-defined secondary endpoints included: SVR at 4 and 24 weeks after EOT (SVR4 and SVR24, respectively); on-treatment virologic response [including HCV RNA <15 IU/mL detectable or undetectable at all time points, and rapid virologic response (RVR; HCV RNA <15 IU/mL undetectable at Week 4)]; 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 detectable or undetectable); viral relapse (patients not achieving SVR12, with HCV RNA 15 IU/mL undetectable at EOT and confirmed HCV RNA ≥15 IU/mL during follow-up); changes from baseline in the HCV NS3/4A and NS5B sequences in patients not achieving SVR; and safety and tolerability. Exploratory objectives included the evaluation of SVR12 in patient subgroups.

Statistical analysis

All analyses were performed on the intent-to-treat (ITT) population (all patients who received at least one dose of study drug).

The null hypothesis of this study was that the overall SVR12 rate with 12 weeks of simeprevir in combination with sofosbuvir was not superior to the derived historical control rate of 61% (Table 1). The historical control used was a composite of the SVR12 rates from the RESTORE study, in pre-defined subpopulations.[10] The historical control rate depended upon the proportion of treatment-naïve, prior relapser, prior nonresponder, IFN-intolerant and 'other' patients enrolled in this study. The SVR12 threshold for each subpopulation was based on the historical data provided in Table 1. Superiority was concluded if the lower limit of the 95% confidence interval (CI) of the SVR12 rate for simeprevir in combination with sofosbuvir was greater than the historical control SVR12 rate.

Assuming an actual SVR12 rate of 90% in this study, a sample size of 40 patients was considered sufficient to

Table 1 | Historical SVR12 rates in patients with HCV genotype 4 infection and treated with simeprevir in combination with peginterferon and ribavirin in the RESTORE study[10]

Prior HCV treatment history	Historical SVR12 rates, % (*n*/*N*)	Simeprevir 150 mg once-daily plus sofosbuvir 400 mg once-daily	
		n/*N* (%)	Derived (%)
Treatment-naïve/prior relapser	84 (48/57)	15/40 (38)	32
Prior nonresponder	44 (22/50)	21/40 (53)	23
Interferon-intolerant*	5	1/40 (3)	0
Other†	84	3/40 (8)	6
Derived historical control SVR12 rate			61%

HCV, hepatitis C virus; SVR12, sustained virologic response 12 weeks after end of treatment.

* SVR rates in interferon-intolerant patients were set to 5%.

† For conservative reasons, the SVR12 rate of the 'other' population was set to the same SVR rate for treatment-naïve patients and prior relapsers.

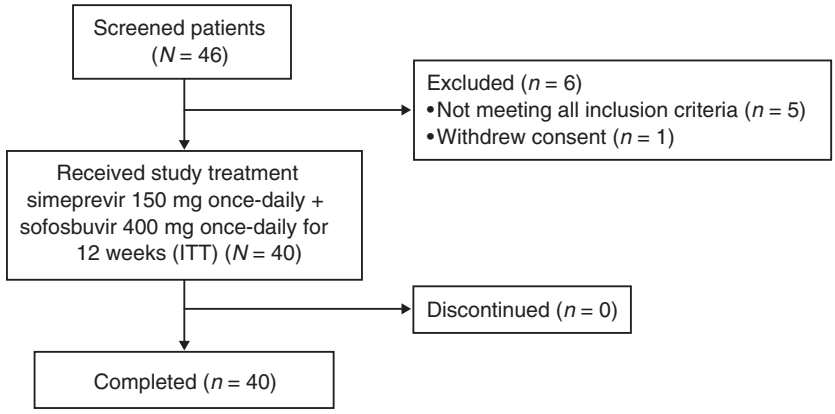

Figure 1 | Patient disposition. ITT, intent-to-treat.

provide 90% power to show superiority vs. the historical control using a one-sided binomial test at a significance level of 0.025, as long as the SVR12 threshold was no more than 70% (based on the historical control).

For the primary efficacy outcome, a Clopper-Pearson 95% CI was constructed around the SVR12 rate in this study using the Clopper-Pearson exact interval.

Secondary efficacy outcomes were analysed using descriptive statistics and SVR rates were determined overall and by subpopulation. All viral sequencing and safety data were analysed descriptively.

Data are presented from the final analysis (performed when all patients had completed their last study-related visit).

RESULTS

Patients

Forty-six patients were screened and 40 received treatment and comprised the ITT population (Figure 1). All 40 patients (100%) completed study treatment.

Baseline demographic and disease characteristics are presented in Table 2. The majority of patients were male (73%), white (95%) and treatment-experienced (68%). In total, 7/40 (18%) patients had compensated cirrhosis. Patients were infected with HCV geno/subtypes 4a (25%), 4d (73%) or 4f (3%). No NS3 simeprevir resistance-associated variants [RAVs; defined as fold change in 50% effective concentration (EC_{50}) >2, compared with wild type HCV replicon], nor the NS5B sofosbuvir RAV S282T, were observed at baseline.

Efficacy

All 40 HCV genotype 4-infected patients achieved SVR12 and SVR24 (100%; 95% CI: 91–100%). Accordingly, the primary objective of superiority to the historical control was achieved as the lower limit of the CI of the SVR12 rate exceeded the historical control rate (91 > 61%) (Figure 2a). All patients (100%) achieved SVR12 and SVR24 regardless of fibrosis stage, *IL28B* genotype or prior treatment history.

Table 2 | Patient demographics and baseline disease characteristics (ITT population)

	Simeprevir 150 mg plus sofosbuvir 400 mg (*N* = 40)
Age, years	
Median (range)	51 (29–69)
Male, *n* (%)	29 (73)
BMI, kg/m^2	
Median (range)	25 (18–39)
Race, *n* (%)	
White	38 (95)
Black/African American	2 (5)
Ethnicity, *n* (%)	
Hispanic or Latino	10 (25)
HCV geno/subtype, *n* (%)	
4a	10 (25)
4d	29 (73)
4f	1 (3)
Cirrhosis status, *n* (%)	
No	33 (83)
Yes	7 (18)
FibroScan score (kPa), median (range)	
All patients*	8 (5–44)
Patients with cirrhosis	28 (22–44)
Baseline HCV RNA, $\log_{10}$ IU/mL	
Median (range)	6 (5–7)
IL28B genotype, *n* (%)†	
CC	6 (15)
CT	19 (48)
TT	15 (38)
Treatment history	
Treatment-naïve	13 (33)
Treatment-experienced‡	27 (68)
Platelets <90 × 10^9/L, *n* (%)	4 (10)
Albumin <40 g/L, *n* (%)	3 (8)

BMI, body mass index; HCV, hepatitis C virus; ITT, intent-to-treat.

* *n* = 39; the remaining one patient had a liver biopsy only and did not have cirrhosis (METAVIR F3). The FibroScan cut-off for cirrhosis used in this study was 12.5 kPa.

† Single nucleotide polymorphism rs12979860.

‡ Treatment-experienced patients included prior relapsers, prior nonresponders, interferon-intolerant and 'other' patients (*n* = 2, 21, 1 and 3, respectively).

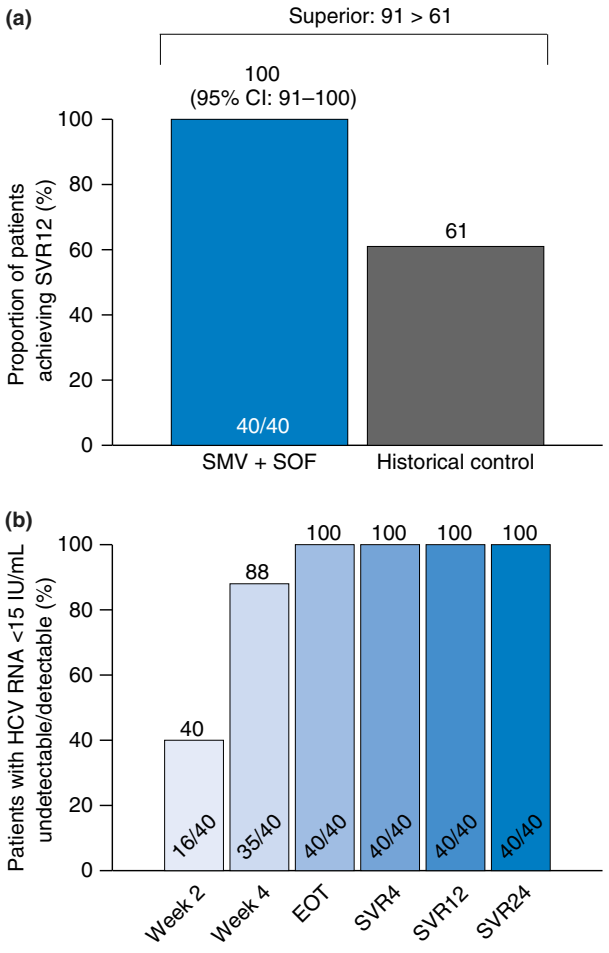

Figure 2 | (a) SVR12 rate vs. historical control rate and (b) on-treatment and post-treatment virologic response rates (ITT population). CI, confidence interval; EOT, end of treatment; HCV, hepatitis C virus; ITT, intent-to-treat; SMV, simeprevir; SOF, sofosbuvir; SVR4/12/24, sustained virologic response 4/12/24 weeks after the end of treatment.

Results for the key secondary efficacy outcomes are presented in Figure 2b. RVR was achieved by 26/40 (65%) patients. Consistent with all patients achieving SVR24, no patients experienced viral breakthrough.

Safety

A summary of AEs is presented in Table 3. AEs were reported in 20/40 (50%) patients and all were Grade 1 or 2. In total, 11/40 (28%) were considered at least possibly related to treatment with simeprevir or sofosbuvir by the investigator.

No Grade 3, Grade 4 or serious AEs were reported, and there were no treatment discontinuations. The most common AE was headache [8/40 (20%)] and this was the only AE reported in >10% of patients. No photosensitivity reactions were reported in this study.

Of the treatment-emergent laboratory abnormalities, one patient [1/40 (3%)] had both Grade 3 amylase and Grade 3 lipase increases, while another patient [1/40 (3%)] also had a Grade 3 amylase increase. All elevations were transient and asymptomatic and no cases of pancreatitis were reported.

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Table 3 | Summary of adverse events (ITT population)

	Simeprevir 150 mg plus sofosbuvir 400 mg (*N* = 40)
Any AE, *n* (%)	20 (50)
Worst Grade 1 or 2	20 (50)
Worst Grade 3 or 4	0
AEs at least possibly related to study treatment*, *n* (%)	11 (28)
Most common AEs (>5% patients), *n* (%)	
Headache	8 (20)
Asthenia	3 (8)
Erythema	2 (5)
Rash	2 (5)
Constipation	2 (5)
Catarrh	3 (8)

AE, adverse event; ITT, intent-to-treat.

* AEs at least possibly related to at least one of the study drugs.

There were no serious AEs, deaths or AEs leading to permanent discontinuation in this study.

Grade 4 hyperkalaemia, hypocalcaemia and hypomagnesaemia laboratory abnormalities were noted concurrently in the same patient [1/40 (3%)], who was clinically asymptomatic. No Grade 3 or 4 treatment-emergent ALT, AST or bilirubin elevations were observed. None of the treatment-emergent laboratory abnormalities were reported as AEs.

DISCUSSION

Treatment for 12 weeks with simeprevir in combination with sofosbuvir resulted in an SVR rate of 100% (40/40 patients) in HCV genotype 4-infected treatment-naïve and -experienced patients with and without compensated cirrhosis in the PLUTO study.

Although patient numbers were small for subgroups, all patients achieved SVR12 regardless of fibrosis stage [7/40 (18%) of patients had compensated cirrhosis], *IL28B* genotype or prior treatment history. It has been previously reported that *IL28B* genotype is strongly associated with SVR in patients with HCV genotype 4 infection receiving treatment with PR;[14] however, the results of this study demonstrate that simeprevir in combination with sofosbuvir was effective regardless of *IL28B* genotype. As expected, the NS3 Q80K polymorphism was not observed in this HCV genotype 4-infected population.

The results of this study provide support for the clinical effectiveness of simeprevir in combination with sofosbuvir for the treatment of HCV genotype 4 infection in treatment-naïve and -experienced patients with and without compensated cirrhosis. The 100% SVR12 rate in this study is complemented by the Phase IIa OSIRIS study, which investigated 12 weeks of simeprevir plus sofosbuvir in HCV genotype 4-infected patients in Egypt, and reported an SVR12 rate of 100% (43/43 patients) regardless of prior treatment history or fibrosis stage [23/43 (53%) patients had cirrhosis].[15] In contrast, the PLUTO study investigated simeprevir plus sofosbuvir in a predominantly Caucasian HCV genotype 4-infected population.

The results of this study are comparable with those of the Phase III OPTIMIST-1 study in HCV genotype 1-infected patients without cirrhosis treated with simeprevir plus sofosbuvir for 12 weeks [97% (150/155) achieved SVR12],[12] and improve upon those of the Phase III OPTIMIST-2 study in patients with cirrhosis treated with simeprevir plus sofosbuvir for 12 weeks [83% (86/103) achieved SVR12].[13] Of note, a limited number of patients with cirrhosis were included in the PLUTO study.

Real-world evidence has also highlighted 12 weeks of this treatment combination as a simple, effective and well-tolerated IFN-free regimen. Treatment-naïve and -experienced patients in a study in Egypt that included patients with cirrhosis, reported an SVR4 rate of 96% (207/215 patients).[16] In a study in Qatar, 100% (17/17) of HCV genotype 4-infected patients with cirrhosis achieved SVR12.[17] Similar results have also been reported in a study in Belgium, with 100% (23/23) of HCV genotype 4-infected patients with cirrhosis, treated with or without ribavirin, achieving HCV RNA below the lower limit of quantification at Week 12 of treatment.[18]

Similar results were observed in an open-label study that assessed the combination of sofosbuvir and ledipasvir for 12 weeks in HCV genotype 4-infected patients, reporting an SVR12 rate of 93% (41/44 patients).[19] In contrast, a lower SVR12 rate of 78% (14/18 patients) was reported in HCV genotype 4-infected patients treated with sofosbuvir and ledipasvir plus ribavirin for 12 weeks.[20] Furthermore, the treatment combination of 12 weeks of ritonavir-boosted paritaprevir and ombitasvir (without dasabuvir), with and without ribavirin, resulted in SVR12 rates of 100% (42/42) and 91% (40/44), respectively, for HCV genotype 4-infected treatment-naïve patients without cirrhosis in the Phase IIb PEARL study.[21] Ritonavir-boosted paritaprevir and ombitasvir with ribavirin for 12 weeks has also shown favourable results in HCV genotype 4-infected patients with

compensated cirrhosis in the AGATE-1 study, in which SVR12 rates of 97% (57/59 patients) were reported.[22] Another DAA treatment combination, grazoprevir in combination with elbasvir without ribavirin, was studied in the Phase 3 C-EDGE study, in which treatment-naïve and -experienced patients with HCV genotype 4 infection achieved SVR12 rates of 100% (18/18 patients) and 78% (7/9 patients), respectively, with 12 weeks of treatment.[23–25]

The safety and tolerability of DAAs has previously been described in detail. Whilst DAAs have drastically reduced side effects when compared with IFN-containing regimens, subgroup-specific contraindications and safety-related limitations are being studied further.[26] Notably, in this study, the 2-DAA regimen of simeprevir plus sofosbuvir was safe and well-tolerated, with all AEs Grade 1 or 2. Of the treatment-emergent laboratory abnormalities, no Grade 3 or 4 increases in AST, ALT or bilirubin were noted. The safety profile seen in this study is in-line with the OPTIMIST-1 and -2 studies.[12, 13]

Strengths of the PLUTO study included the short 12-week IFN-free treatment regimen without ribavirin. The benefits of ribavirin-free regimens have been further highlighted in a recent article comparing patient-reported outcomes data from multicentre, multinational, Phase 3 studies of sofosbuvir with and without IFN and ribavirin. In a multivariate analysis, the use of ribavirin was independently associated with −9.0% worsening of the patient-reported outcome scores, and ribavirin-free regimens were associated with better patient experience and work productivity during treatment.[27]

Limitations of the PLUTO study included the limited sample size overall and in the subgroups, including patients with cirrhosis, and therefore the results of this study must be interpreted with caution. Due to the small number of patients with cirrhosis, the proportions of patients with albumin <40 g/L and platelets $<90 \times 10^9$/L were limited and the use of this regimen in patients with advanced liver disease was not investigated. In addition, the patient population was predominantly Caucasian and therefore the results need to be confirmed in the HCV genotype 4-infected populations in many countries. The open-label nature of the study and the lack of a comparator arm could formally be viewed as potential limitations; however, the US Food and Drug Administration draft guidance, and guidance from the European Medicines Agency, include historical-controlled trials as one of the accepted Phase 3 study designs.[28–30]

In conclusion, the combination of simeprevir and sofosbuvir for 12 weeks resulted in a 100% SVR12 rate and was well-tolerated (with no Grade 3/4 AEs or treatment discontinuations reported) by treatment-naïve and treatment-experienced patients with chronic HCV genotype 4 infection, regardless of fibrosis stage or prior treatment history. These data are encouraging with respect to the potential use of this regimen in this patient population.

AUTHORSHIP

Guarantor of the article: Dr María Buti.

Author contributions: María Buti, José Luis Calleja, Sabela Lens, Moisés Diago, Enrique Ortega, Javier Crespo, Ramón Planas, Manuel Romero-Gómez, Francisco Gea Rodríguez and Juan Manuel Pascasio 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. Bart Fevery, Ronald Kalmeijer and Wolfgang Jessner 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. Darryl Kurland and Chris Corbett provided statistical analysis of the study data, and have been involved in the critical revision of the manuscript for important intellectual content.

All authors approved the final version of the manuscript.

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REFERENCES

1. Wilder JM, Muir AJ. Strategies for treating chronic HCV infection in patients with cirrhosis: latest evidence and clinical outcomes. *Ther Adv Chronic Dis* 2015; **6**: 314–27.
2. World Health Organization. Hepatitis C, 2015. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/ (accessed 29 June 2016).
3. Fagiuoli S, Ravasio R, Lucà MG, *et al.* Management of hepatitis C infection before and after liver transplantation. *World J Gastroenterol* 2015; **21**: 4447–56.
4. Vidal LL, Soares MA, Santos AF. NS3 protease polymorphisms and genetic barrier to drug resistance of distinct hepatitis C virus genotypes from worldwide treatment-naive subjects. *J Viral Hepatol* 2016; **23**: 840–9.
5. Kamal SM, Nasser IA. Hepatitis C genotype 4: what we know and what we don't yet know. *Hepatology* 2008; **47**: 1371–83.
6. Kamal SM. Hepatitis C virus genotype 4 therapy: progress and challenges. *Liver Int* 2011; **31**(Suppl. 1): 45–52.
7. Wantuck JM, Ahmed A, Nguyen MH. Review article: the epidemiology and therapy of chronic hepatitis C genotypes 4, 5 and 6. *Aliment Pharmacol Ther* 2014; **39**: 137–47.
8. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; **62**: 932–54.
9. European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015; **63**: 199–236.
10. Moreno C, Hezode C, Marcellin P, *et al.* Efficacy and safety of simeprevir with PegIFN/ribavirin in naive or experienced patients infected with chronic HCV genotype 4. *J Hepatol* 2015; **62**: 1047–55.
11. Gilead. SOVALDI Highlights of Prescribing Information. 2015. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf (accessed 23 June 2016).
12. Kwo P, Gitlin N, Nahass R, *et al.* Simeprevir plus sofosbuvir (12 and 8 weeks) in HCV genotype 1-infected patients without cirrhosis: OPTIMIST-1, a phase 3, randomized study. *Hepatology* 2016; **64**: 370–80.
13. Lawitz E, Matusow G, DeJesus E, *et al.* Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). *Hepatology* 2016; **64**: 360–9.
14. Asselah T, De Muynck S, Broët P, *et al.* IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol* 2012; **56**: 527–32.
15. El Raziky M, Gamil M, Hammad R, *et al.* Treatment of hepatitis C genotype 4 patients with simeprevir and sofosbuvir: results from a Phase IIa, partially randomized, open-label trial conducted in Egypt (OSIRIS). Poster 1163 presented at the American Association for the Study of Liver Disease (AASLD), San Francisco, CA, USA, 13–17 November 2015. Abstract. Available at: http://liverlearning.aasld.org/aasld/2015/thelivermeeting/110407/maissa.el.raziky.treatment.of.hepatitis.c.genotype.4.patients.with.simeprevir.html (accessed 21 November 2016).
16. Esmat G, Eldeen HG, El Kassas M, *et al.* Sofosbuvir plus simeprevir in treatment-naive and treatment-experienced Egyptian patients with hepatitis C virus infection: a real life experience. *J Hepatol* 2016; **64**: abs SAT-160.
17. Derbala M, Alkaabi S, Sultan K, *et al.* 12 W of sofosbuvir/simeprevir in genotypes 1 and 4 in HCV, cirrhotic patients: Qatar experience. *Hepatol Int* 2016; **10** (Suppl. 1): abs O–022.
18. Moreno C, Lasser L, Delwaide J, *et al.* Sofosbuvir in combination with simeprevir +/- ribavirin in genotype 4 hepatitis C patients with advanced fibrosis or cirrhosis: real-life experience from Belgium. *Hepatology* 2015; **62** (Suppl. S1): abs 1091.
19. Abergel A, Loustaud-Ratti V, Metivier S, *et al.* Ledipasvir/Sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. Oral presentation presented at the 50th Annual Meeting of the European Association for the Study of the Liver, Vienna, Austria, 22–26 April 2015. Available at: http://natap.org/2015/EASL/EASL_80.htm (accessed 21 November 2016).
20. Manns M, Samuel D, Gane EJ, *et al.* Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *Lancet Infect Dis* 2016; **16**: 685–97.
21. Hézode C, Asselah T, Reddy KR, *et al.* Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet* 2015; **385**: 2502–9.
22. Asselah T, Hézode C, Qaqish RB, *et al.* Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 25–35.
23. Zeuzem S, Ghalib R, Reddy KR, *et al.* 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. *Ann Intern Med* 2015; **163**: 1–13.
24. Kwo P, Gane E, Peng CY, *et al.* Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 or 16 weeks in patients with HCV G1, G4 or G6 infection who previously failed peginterferon/RBV: C-EDGE treatment-experienced. Poster presented at the European Association for the Study of the Liver, Vienna, Austria, 22–26 April 2015. Available at: http://www.natap.org/2015/EASL/EASL_04.htm (accessed 21 November 2016).
25. Majumdar A, Kitson MT, Roberts SK. Systematic review: current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. *Aliment Pharmacol Ther* 2016; **43**: 1276–92.
26. Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Aliment Pharmacol Ther* 2016; **43**: 674–96.
27. Younossi ZM, Stepanova M, Henry L, Nader F, Hunt S. An in-depth analysis of patient-reported outcomes in patients with chronic hepatitis C treated with different anti-viral regimens. *Am J Gastroenterol* 2016; **111**: 808–16.
28. Mishra P, Murray J, Birnkrant D. Direct-acting antiviral drug approvals for treatment of chronic hepatitis C virus infection: scientific and regulatory approaches to clinical trial designs. *Hepatology* 2015; **62**: 1298–303.
29. U.S.Food and Drug Administration. Guidance for industry: adaptive design clinical trials for drugs and biologics. 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf (accessed 7 June 2016).
30. European Medicines Agency. General considerations for clinical trials. 1998. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf (accessed 7 June 2016).