ORIGINAL ARTICLE

Efficacy and safety of simeprevir and sofosbuvir with and without ribavirin in subjects with recurrent genotype 1 hepatitis C postorthotopic liver transplant: the randomized GALAXY study

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SUMMARY

This prospective, randomized, phase 2 study in subjects with recurrent hepatitis C virus (HCV) genotype 1 postorthotopic liver transplant evaluated once-daily simeprevir 150 mg + sofosbuvir 400 mg, with and without ribavirin 1000 mg. Primary endpoint was proportion of subjects with week 12 sustained virologic response (SVR12). Thirty-three subjects without cirrhosis were randomized 1:1:1 into three arms (stratified by genotype/subtype and Q80K): Arm 1, simeprevir + sofosbuvir + ribavirin, 12 weeks; Arm 2, simeprevir + sofosbuvir, 12 weeks; Arm 3, simeprevir + sofosbuvir, 24 weeks; 13 additional subjects (two with cirrhosis, 11 without cirrhosis) entered Arm 3. All 46 subjects received at least one dose of study drug; median age, 60 years; 73.9% male; 80.4% White; 71.7% genotype/subtype 1a [12 (36.4%) of these had Q80K]; median 4.5 years post-transplant. Among randomized subjects, SVR12 was achieved by 81.8% in Arm 1, 100% in Arm 2, and 93.9% in Arm 3; two subjects did not achieve SVR12: one viral relapse (follow-up week 4; Arm 1) and one missing follow-up week 12 data. In total, five subjects had a serious adverse event, considered unrelated to treatment per investigator. Simeprevir exposure was increased relative to the nontransplant setting, but not considered clinically relevant. Simeprevir + sofosbuvir treatment, with or without ribavirin, was efficacious and well tolerated (ClinicalTrials.gov Identifier: NCT02165189).

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Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and liver transplantation [1–3]. Compared with conventional interferon-based therapies [4–6] and boceprevir/telaprevir-based triple therapies [7–12], newer direct-acting antiviral agents have been shown to improve outcomes for liver transplant recipients with recurrent HCV infection [13–19]. In one study of 34 postliver transplant recipients without cirrhosis, treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin for 24 weeks resulted in a sustained virologic response 12 weeks after the end of treatment (SVR12) rate of 97% [13]; an SVR12 rate of 95% was seen in another study ($n = 53$) evaluating treatment with daclatasvir + sofosbuvir + ribavirin [19]. In a third study ($n = 229$), ledipasvir/sofosbuvir + ribavirin for 12 or 24 weeks demonstrated SVR12 rates ranging from 96% to 98% in subjects without cirrhosis or with Child–Turcotte–Pugh (CTP) class A cirrhosis, 85% to 88% in subjects with CTP class B cirrhosis and 60% to 75% in subjects with CTP class C cirrhosis [18]. Despite such favourable outcomes, all approved regimens require the use of ribavirin, which has been associated with safety/tolerability concerns, such as anaemia, fatigue, headache, nausea and hyperbilirubinemia [14,20–22]. In addition, the side effects of ribavirin may result in substantial healthcare costs (e.g. laboratory testing, clinic visits, medication) [23].

Simeprevir is a once-daily, oral, HCV NS3/4A protease inhibitor approved in the nontransplant setting for the treatment of chronic HCV genotype 1 infection as part of combination antiviral therapy [24,25]. Retrospective studies of simeprevir and sofosbuvir (HCV NS5B nucleotide polymerase inhibitor), with or without ribavirin, in HCV genotype 1-infected liver transplant recipients have demonstrated favourable efficacy and safety profiles over a 12-week treatment period [15–17,26,27]. The vast majority (73–100%) of subjects in these studies did not receive treatment with ribavirin; SVR12 rates ranged from 88% to 94%. In a real-world setting (HCV-TARGET registry), simeprevir and sofosbuvir treatment for 12 or 24 weeks, with or without ribavirin, in postliver transplant recipients showed an SVR12 rate of 88% [28].

In this phase 2 clinical study (GALAXY; ClinicalTrials.gov Identifier: NCT02165189), the efficacy and safety of simeprevir in combination with sofosbuvir, with or without ribavirin, were evaluated in postorthotopic liver transplant recipients with recurrent HCV genotype 1 infection. The emergence of resistance-associated HCV genotype variants and the pharmacokinetics of simeprevir and sofosbuvir were also assessed. These are the first prospective, multicenter data to be reported on postliver transplant recipients treated with simeprevir and sofosbuvir, with or without ribavirin.

Materials and methods

Study design and population

This was a phase 2, prospective, multicenter, randomized, open-label study that enrolled nonpregnant adults who were ≥18 years of age with recurrent HCV genotype 1 infection and an HCV RNA level >10 000 IU/ml at baseline (study dates: 11 August 2014 to 10 November 2015). Subjects must have had a primary orthotopic liver transplant (living or deceased donor) ≥6 months to 15 years before enrollment and were required to be on stable immunosuppression for ≥3 months before screening. Subjects' renal function, as measured by the Cockcroft Gault formula, must have been >30 ml/min. Assessment of liver fibrosis (liver graft biopsy or non-invasive procedure [29]) within 12 months of or at the screening visit, except for subjects with a diagnosis of cirrhosis, was required. Key exclusion criteria included receiving treatment with a direct-acting antiviral drug for HCV infection (prior treatment with interferon or peginterferon, with or without ribavirin, was allowed if completed ≥3 months before screening); hepatic decompensation; and HCV NS3 resistance-associated mutations identified as conferring resistance to simeprevir, except Q80K.

Initially, 33 subjects without cirrhosis were enrolled and randomized 1:1:1 using an interactive voice or web response system into one of three treatment arms; the randomization was balanced using randomly permuted blocks and was stratified by HCV genotype/subtype and NS3 polymorphism (genotype/subtype 1a with Q80K versus genotype/subtype 1a without Q80K versus genotype/subtype 1b). The study controlled for the use of ribavirin; the three treatment arms were as follows: Arm 1, once-daily simeprevir 150 mg + once-daily sofosbuvir 400 mg + weight-based ribavirin (1000 mg daily dose for subjects weighing <75 kg; 1200 mg for subjects weighing ≥75 kg) for 12 weeks; Arm 2, once-daily simeprevir 150 mg + once-daily sofosbuvir 400 mg for 12 weeks; Arm 3, once-daily simeprevir 150 mg + once-daily sofosbuvir 400 mg for 24 weeks. Upon completion of randomization, enrolment into Arm 3 was opened to all eligible subjects, regardless of the presence of cirrhosis, until a total of 46 subjects were enrolled; this allowed subjects with cirrhosis to enter the study and receive the

recommended 24 weeks of treatment [24,25]. For all subjects, the screening period was a maximum of 6 weeks and treatment was followed by a 12-week post-treatment follow-up period. Study drugs were discontinued for subjects with viral breakthrough. Choice of immunosuppressant was at the investigator's discretion, excluding cyclosporine due to a potential pharmacokinetic interaction with simeprevir [24,25]. See Supporting Information for further study design and population details.

The study protocol was reviewed by an institutional review board. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Subjects provided written informed consent to participate in the study.

Efficacy assessments

The primary efficacy endpoint was the proportion of subjects who achieved SVR12. Secondary efficacy endpoints were on-treatment virologic response at weeks 2, 4, 8 and 12 (all subjects) and weeks 16, 20 and 24 (subjects in Arm 3); the proportion of subjects who achieved sustained virologic response 4 weeks after the end of treatment (SVR4); and the incidence of virologic breakthrough and relapse. In addition, subgroup analyses were performed for SVR12 rates based on subject characteristics, including the presence of baseline HCV polymorphisms (NS3 Q80K and NS5A positions of interest; Supporting Information) and use of gastric acid-reducing agents. The latter were of interest because they may have an effect on antiviral agent pharmacokinetics [30].

Resistance monitoring

Samples were collected at baseline and at the time of virologic failure during therapy to monitor for the emergence of HCV resistance-associated variants, with sequencing of HCV NS3, NS5A and NS5B polymorphisms at baseline and NS3 and NS5B resistance-associated variants at the time of failure (Supporting Information).

Pharmacokinetic assessments

Pharmacokinetic sampling of simeprevir and GS-331007 (the major sofosbuvir metabolite [31]; hereinafter referred to as 'sofosbuvir' for simplicity) trough levels occurred on days 28, 56 and 84 for all subjects and also on Day 168 for subjects in Arm 3. The following parameters were assessed: trough plasma concentration (C_{trough}), maximum plasma concentration (C_{max}), average steady-state plasma concentration ($C_{ss,av}$), and area under the concentration–time curve from time of administration to 24 h postdose ($AUC_{24\ h}$). The model-predicted relationship between creatinine clearance at baseline and the central clearance of sofosbuvir, and the relationship between creatinine clearance at baseline and exposure to sofosbuvir (smoothing line computed using loess smoothing, implemented in R-software) were also evaluated.

Blood samples for the determination of immunosuppressant plasma concentrations were collected twice during the first week of treatment, weekly during the next 3 weeks, and per local institutional protocol thereafter. Immunosuppressant dose adjustments during therapy were also described.

Safety assessments

Safety evaluations included monitoring of adverse events (AEs; for severity grading, see Supporting Information), clinical laboratory tests, vital sign measurements and physical examinations. Diagnosis of rejection was to be made by a local pathologist per institution protocol.

Patient-reported outcomes

Patient-reported outcomes (PROs) were assessed using two validated instruments: the EuroQoL 5-Dimensions (EQ-5D) questionnaire [32] and the Hepatitis C Symptom and Impact Questionnaire version 4 (HCV-SIQv4), a new PRO tool designed specifically for HCV-infected subjects (Supporting Information).

Statistical analyses

The intent-to-treat (ITT) population was defined as all subjects who took at least one dose of study drug. Within the ITT population, randomized subjects were evaluated for efficacy and PRO outcomes. Pharmacokinetics and safety were evaluated in all ITT subjects. SVR12 rates were tabulated per treatment arm. For the determination of sample size, with a target SVR12 rate of 80%, 11 subjects would have allowed the SVR12 rate to be estimated in arms 1 and 2 with a two-sided 95% confidence interval (CI; calculated using a normal approximation with continuity correction) width of 50.8%; thus, 80% (46.3%, 97.1%) and 23 subjects in Arm 3 would have allowed the SVR12 rate to be

estimated with a two-sided 95% CI width of 35.3%, thus 80% (58.2%, 93.6%).

Secondary endpoints were summarized using descriptive statistics; SVR4, viral breakthrough, and viral relapse were tabulated per treatment arm. Relevant changes in viral sequence in the HCV NS3 and NS5B regions were summarized. Pharmacokinetic analyses included all subjects who underwent pharmacokinetic sampling at any point during the study. Descriptive statistics are provided for the pharmacokinetic parameters of immunosuppressants, simeprevir and sofosbuvir; for simeprevir and sofosbuvir, parameters were analysed using a Bayesian feedback analysis (Supporting Information). PRO endpoints were analysed using descriptive statistics; mean and median changes from baseline are reported.

Results

Study population

A total of 66 individuals were screened; 20 of these individuals were excluded due to not meeting ≥1 of the inclusion criteria, while 46 were enrolled in the study and took at least one dose of study drug (Fig. 1). Among all subjects, the median (range) age was 60.0 (49–68) years and the majority were male (73.9%) and

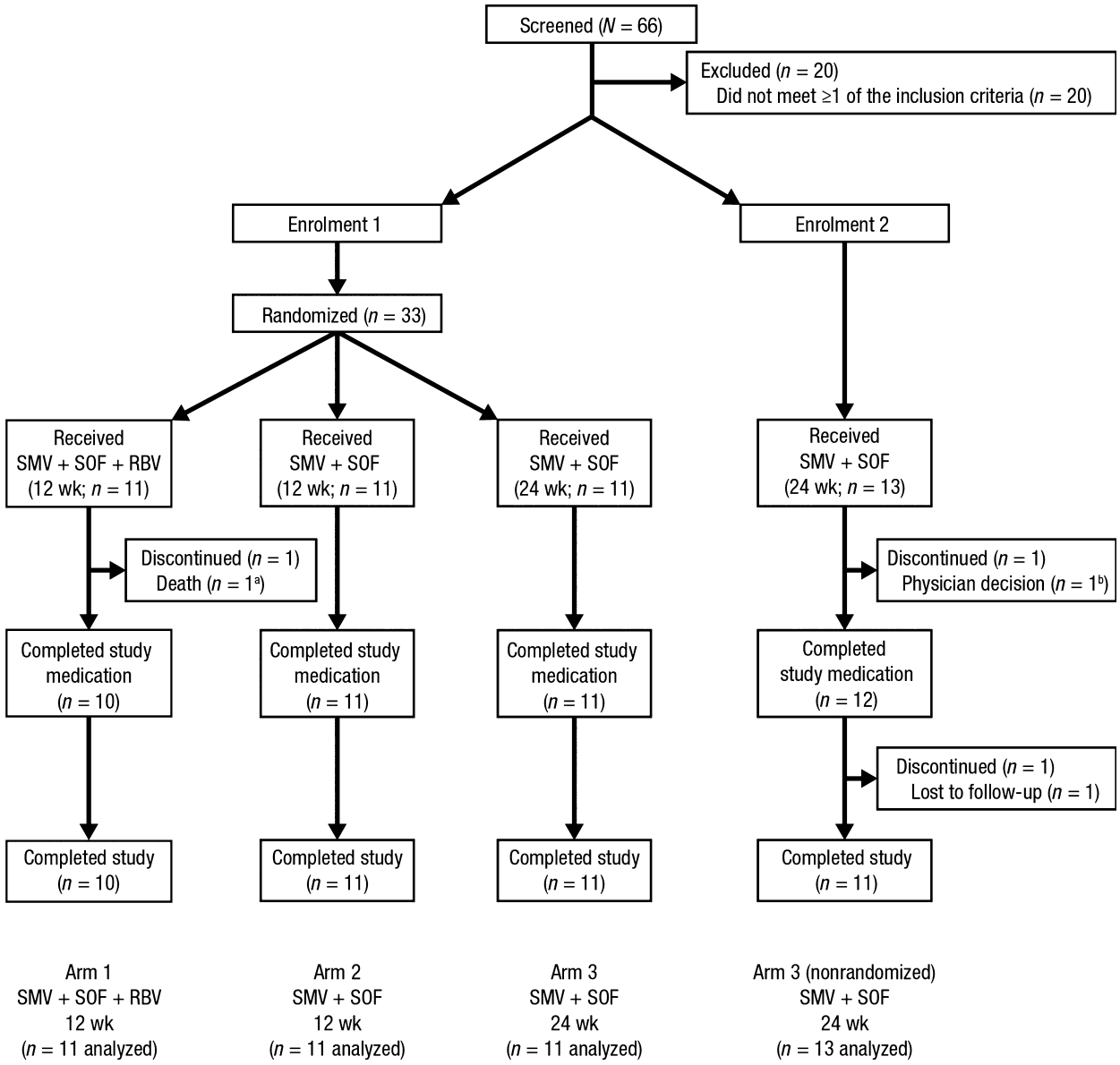

Figure 1 Subject disposition. Subject disposition during the treatment and follow-up periods of the GALAXY study. SMV, simeprevir; SOF, sofosbuvir; RBV, ribavirin. [a]Suicide, considered unrelated to study drug by the investigator. [b]Subject had metastatic prostate cancer.

Table 1. Baseline demographic and disease characteristics.

	Total (N = 46)	Arm 1: SMV + SOF + RBV, 12 weeks (n = 11)	Arm 2: SMV + SOF, 12 weeks (n = 11)	Arm 3: SMV + SOF, 24 weeks (n = 11)	Arm 3 nonrand: SMV + SOF, 24 weeks (n = 13)
Gender, *n* (%)					
Male	34 (73.9)	8 (72.7)	8 (72.7)	7 (63.6)	11 (84.6)
Female	12 (26.1)	3 (27.3)	3 (27.3)	4 (36.4)	2 (15.4)
Race, *n* (%)					
White	37 (80.4)	9 (81.8)	9 (81.8)	7 (63.6)	12 (92.3)
Black/African American	8 (17.4)	1 (9.1)	2 (18.2)	4 (36.4)	1 (7.7)
Asian	1 (2.2)	1 (9.1)	0	0	0
Ethnicity, *n* (%)*					
Hispanic/Latino	3 (6.5)	0	1 (9.1)	2 (18.2)	0
Not Hispanic/Latino	43 (93.5)	11 (100)	10 (90.9)	9 (81.8)	13 (100)
Age, median (range), years	60.0 (49–68)	60.0 (53–65)	59.0 (50–68)	61.0 (49–64)	59.0 (51–66)
BMI, median (range), kg/m^2	28.8 (20.5–43.4)	28.8 (22.5–34.5)	28.1 (24.8–40.4)	28.8 (20.5–43.4)	28.9 (23.4–39.1)
Use of gastric acid-reducing agent, *n* (%)†	28 (60.9)	5 (45.5)	8 (72.7)	7 (63.6)	8 (61.5)
Presence of cirrhosis, *n* (%)	2 (4.3)	–	–	–	2 (15.4)
METAVIR stage, *n* (%)*					
F0/F1	9 (19.6)	2 (18.2)	1 (9.1)	1 (9.1)	5 (38.5)
F2	23 (50.0)	8 (72.7)	6 (54.5)	6 (54.5)	3 (23.1)
F3	9 (19.6)	1 (9.1)	3 (27.3)	4 (36.4)	1 (7.7)
F4	1 (2.2)	0	0	0	1 (7.7)
Missing	4 (8.7)	0	1 (9.1)	0	3 (23.1)
Time since liver transplant, median (range), years	4.5 (0.8–14.3)	6.0 (1.1–10.3)	5.5 (1.9–14.3)	4.8 (2.3–7.5)	3.5 (0.8–10.6)
Use of immunosuppressant, *n* (%)‡					
Tacrolimus	41 (89.1)	10 (90.9)	10 (90.9)	9 (81.8)	12 (92.3)
Mycophenolate mofetil	19 (41.3)	4 (36.4)	4 (36.4)	6 (54.5)	5 (38.5)
Sirolimus	5 (10.9)	1 (9.1)	2 (18.2)	1 (9.1)	1 (7.7)
HCV genotype/subtype and NS3 Q80K polymorphism, *n* (%)§					
1a	33 (71.7)	8 (72.7)	7 (63.6)	8 (72.7)	10 (76.9)
Q80K	12 (36.4)	3 (37.5)	4 (57.1)	2 (25.0)	3 (30.0)
No Q80K	20 (60.6)	5 (62.5)	3 (42.9)	6 (75.0)	6 (60.0)
1b	13 (28.3)	3 (27.3)	4 (36.4)	3 (27.3)	3 (23.1)
HCV NS5A polymorphism at position of interest, *n* (%)*,¶					
No	14 (30.4)	2 (18.2)	5 (45.5)	4 (36.4)	3 (23.1)
Yes	28 (60.9)	8 (72.7)	5 (45.5)	7 (63.6)	8 (61.5)
Not available	4 (8.7)	1 (9.1)	1 (9.1)	0	2 (15.4)

Table 1. Continued.

	Total (N = 46)	Arm 1: SMV + SOF + RBV, 12 weeks (n = 11)	Arm 2: SMV + SOF, 12 weeks (n = 11)	Arm 3: SMV + SOF, 24 weeks (n = 11)	Arm 3 nonrand: SMV + SOF, 24 weeks (n = 13)
HCV NS5B polymorphism at position of interest, n (%)*,**					
No	36 (78.3)	10 (90.9)	8 (72.7)	11 (100)	7 (53.8)
Yes	5 (10.9)	0	3 (27.3)	0	2 (15.4)
Not available	5 (10.9)	1 (9.1)	0	0	4 (30.8)
HCV RNA viral load, median (range), $\log_{10}$ IU/ml	6.6 (4.1–7.6)	6.6 (5.6–7.0)	6.6 (6.3–7.1)	6.7 (6.0–7.6)	5.8 (4.1–7.5)

SMV, simeprevir; SOF, sofosbuvir; RBV, ribavirin; nonrand, nonrandomized subgroup; BMI, body mass index; HCV, hepatitis C virus.

*Percentages may not total 100% due to rounding.

†Use of prescription or over-the-counter medications at any time.

‡Immunosuppressant use at screening.

§HCV NS3 Q80K polymorphism data not available for one subject in the nonrandomized subgroup of Arm 3.

¶HCV NS5A amino acid positions of interest included 23, 24, 28, 30, 31, 32, 38, 54, 56, 58, 62, 64, 92 and 93.

**HCV NS5B amino acid positions of interest included 96, 142, 159, 282, 316, 320, 321, 390 and 415.

White (80.4%; Table 1). Two (4.3%) subjects had cirrhosis, and the median time since liver transplant was 4.5 years. Of the 33 (71.7%) subjects with HCV genotype/subtype 1a, 12 (36.4%) had Q80K. The baseline median HCV RNA was approximately 6 650 000 IU/ml and 80.4% of all subjects had plasma HCV RNA >800 000 IU/ml. Most subjects presented with less advanced liver disease [i.e. METAVIR grade A1 (45.7%) or A2 (26.1%) and METAVIR fibrosis stage F0/F1 (19.6%) or F2 (50.0%)].

Overall, 44 subjects (95.7%) completed study drug and 43 subjects (93.5%) completed the study. For the 33 randomized subjects, the median (range) actual treatment durations were as follows: Arm 1, 12.0 (8.9–12.1) weeks; Arm 2, 12.0 (11.3–13.0) weeks; Arm 3, 24.0 (24.0–25.6) weeks.

Efficacy

On-treatment virologic response over time among randomized subjects is shown in Fig. 2a. SVR12 was achieved by 31 of 33 randomized subjects (93.9%), including nine of 11 (81.8%) in Arm 1, 11 of 11 (100%) in Arm 2 and 11 of 11 (100%) in Arm 3 (Fig. 2b); the same virologic response rates were observed at the SVR4 time point. One subject did not achieve SVR12 due to viral relapse (at follow-up week 4; see below) and another for nonvirologic reasons (suicide).

For randomized subjects who had HCV genotype/subtype 1a infection and Q80K polymorphism data, the SVR12 rate was 100% (9/9; 95% CI, 66.4–100%) for those with the Q80K polymorphism and 85.7% (12/14; 95% CI, 57.2–98.2%) for those without. The SVR12 rate was 90.0% (18/20; 95% CI, 68.3–98.8%) for subjects with an NS5A polymorphism and 100% (11/11; 95% CI, 71.5–100%) for those without. The SVR12 rate was 95.0% (19/20; 95% CI, 75.1–99.9%) for subjects who used gastric acid-reducing agents and 92.3% (12/13; 95% CI, 64.0–99.8%) for those who did not.

No subjects experienced viral breakthrough. One subject in Arm 1 experienced viral relapse at the follow-up week 4 time point. This subject was a 53-year-old White male with a body mass index of 29 kg/m^2, baseline viral load of 4 130 000 IU/ml, HCV genotype/subtype 1a without NS3 Q80K and METAVIR score F2. It had been 7.7 years since transplant and the subject was treatment-experienced with prior response categorized as 'no response'; there were no emerging HCV NS3 or NS5B mutations at the time of failure. No other subjects had resistance testing performed.

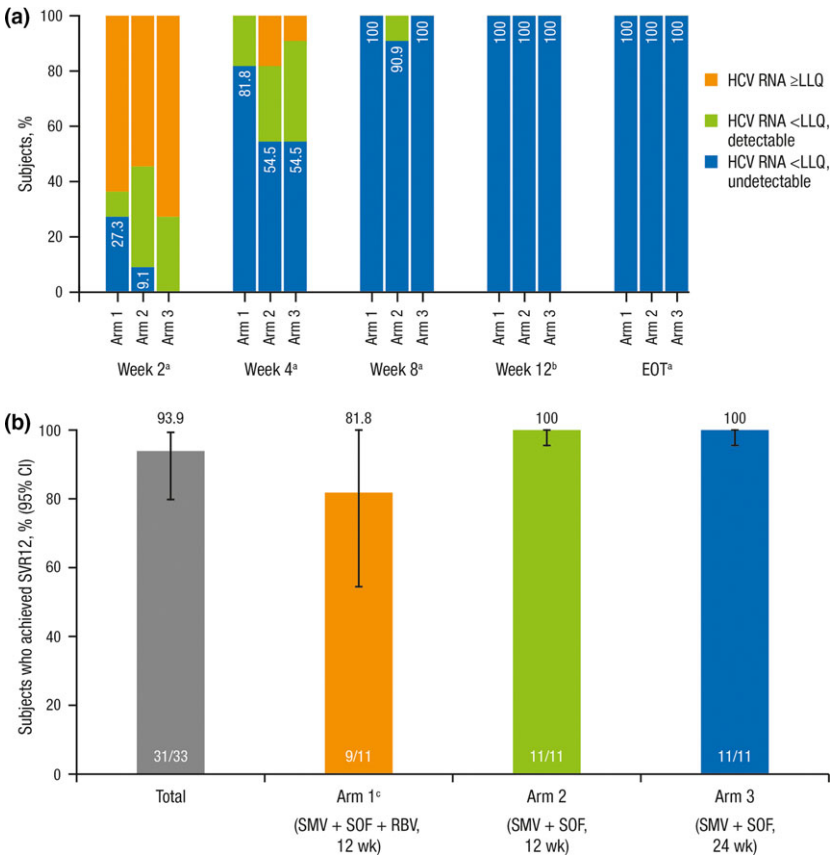

Figure 2 Virologic response over time. (a) On-treatment virologic response. (b) SVR12. Virologic response was assessed in randomized subjects at on-treatment weeks 2, 4, 8 and 12, and EOT. SVR was defined as HCV RNA <15 IU/ml (detectable or undetectable). HCV, hepatitis C virus; LLQ, lower limit of quantitation; EOT, end of treatment; SVR12, sustained virologic response 12 weeks after the end of treatment; CI, confidence interval; SMV, simeprevir; SOF, sofosbuvir; RBV, ribavirin. [a]Arm 1, $n = 11$; Arm 2, $n = 11$; Arm 3, $n = 11$. [b]Arm 1, $n = 9$; Arm 2, $n = 10$; Arm 3, $n = 11$. [c]For the two subjects who did not achieve SVR12, one committed suicide and one had viral relapse.

Pharmacokinetic assessments

Exposures to both simeprevir and sofosbuvir were similar across treatment arms among all subjects (Table 2). A correlation between sofosbuvir exposure and creatinine clearance was observed; central clearance of sofosbuvir increased with increasing creatinine clearance at baseline, and exposure to sofosbuvir (AUC/C_{max}) increased with decreasing creatinine clearance (Fig. 3).

Safety

Overall, most subjects (97.8%) reported an AE during the treatment phase; AEs were balanced across treatment groups (Table 3). The most common AEs (>25% of total population) during treatment were headache (37.0%) and fatigue (34.8%). Five (10.9%) subjects had serious AEs, including one that was fatal (suicide); none were considered by the investigator to be related to study drug. Two AEs occurred during treatment that were grade ≥2 in severity and considered possibly related to simeprevir: fatigue and increased gamma-glutamyltransferase. One transplant rejection occurred at follow-up week 12 in Arm 3. Of note, this subject's tacrolimus plasma level fell from 13.8 μg/l at baseline to 3.2 μg/l at the time of rejection. Treatment-induced resolution occurred within 6 days.

Four (8.7%) subjects had an AE of photosensitivity (one subject in Arm 2 and three subjects in Arm 3); all events were grade 1 in severity. Three (6.5%) subjects, all in Arm 1, had anaemia; no growth factors were used for treatment. There were four laboratory parameters for which at least one subject had an abnormality with grade 3 severity, including amylase level (two subjects; one each in arms 2 and 3), gamma-glutamyltransferase (one subject; Arm 3), hyperbilirubinemia (one subject; Arm 1) and hyperglycaemia (one subject; Arm 3). There were no grade 4 laboratory abnormalities.

Tacrolimus plasma levels over time are shown in Fig. 4. A dose adjustment of immunosuppressants (any time during the study) occurred in 15 of 46 (32.6%) subjects: five in Arm 1, one in Arm 2 and nine in Arm 3. For one subject in Arm 3, mycophenolate mofetil was discontinued at screening, and tacrolimus was continued unchanged. For two subjects, either the original or new dose was not known (but both were counted as having a dose adjustment). Apart from these dose adjustments, there were no other changes in immunosuppressant regimens.

Table 2. Summary of pharmacokinetic parameters.

	Total (N = 46)	Arm 1: SMV + SOF + RBV, 12 weeks (n = 11)	Arm 2: SMV + SOF, 12 weeks (n = 11)	Arm 3: SMV + SOF, 24 weeks (n = 24)
SMV*				
C_{trough}, median (range), ng/ml	1055 (110–16 400)	1010 (157–4110)	1190 (110–12 300)	1045 (163–16 400)
C_{max}, median (range), ng/ml	2945 (630–21 000)	3050 (630–7970)	3040 (975–17 100)	2690 (826–21 000)
$C_{ss,av}$, median (range), ng/ml	1846 (353–18 972)	1883 (353–5792)	1854 (416–14 542)	1702 (433–18 792)
$AUC_{24\ h}$, median (range), ng·h/ml	44 300 (8460–451 000)	45 200 (8460–139 000)	44 500 (9980–349 000)	40 850 (10 400–451 000)
Sofosbuvir†				
C_{trough}, median (range), ng/ml	518 (91–1317)	534 (249–1193)	442 (91–1061)	572 (320–1317)
C_{max}, median (range), ng/ml	1249 (354–2665)	1294 (450–2411)	1124 (354–2215)	1342 (589–2665)
$C_{ss,av}$, median (range), ng/ml	745 (295–1777)	787 (341–1612)	672 (295–1458)	829 (449–1777)
$AUC_{24\ h}$, median (range), ng·h/ml	17 884 (7087–42 647)	18 899 (8191–38 682)	16 129 (7087–34 995)	19 884 (10 777–42 647)

SMV, simeprevir; SOF, sofosbuvir; RBV, ribavirin; C_{trough}, trough plasma concentration; C_{max}, maximum plasma concentration; $C_{ss,av}$, average steady-state plasma concentration; $AUC_{24\ h}$, area under the plasma concentration–time curve from time of administration to 24 h postdose.

*In total, 152 plasma samples from 46 subjects were available for analysis (of the 159 samples in the data set, two were below the lower limit of quantitation and five were excluded because the intake time of the dose taken prior to the sample was missing).

†In total, 153 plasma samples from 46 subjects were available for analysis (of the 159 samples in the data set, one was below the lower limit of quantitation and five were excluded because the intake time of the dose taken prior to the sample was missing.

Patient-reported outcomes

The mean HCV-SIQv4 overall body system score at baseline was similar across treatment arms for randomized subjects, and there were minimal changes from baseline to follow-up week 12 (Table S1). At baseline, the mean EQ-5D visual analog scale (VAS) score was comparable across treatment arms (Table S2). These scores fluctuated over time; the changes were not considered clinically important, with the exception of a small improvement in EQ-5D VAS score at follow-up week 12 for subjects in Arm 3. Median changes from baseline over time are shown in Fig. S1. Overall, there were no clear patterns of improvement or worsening in scores over time or differences between treatment arms in PRO data.

Discussion

GALAXY is the first prospective, multicenter study that evaluated simeprevir and sofosbuvir treatment, with or without ribavirin, in the transplant setting. This regimen was efficacious in liver transplant recipients with recurrent HCV genotype 1 infection, consistent with results in a nontransplant setting [33]. SVR12 was achieved by 81.8% of subjects in Arm 1, 100% in Arm 2 and 100% in Arm 3. The relatively lower SVR12 rate in Arm 1 versus arms 2 and 3 was due to missing data from one subject (9.1%). The efficacy of simeprevir in this population was further supported by on-treatment virologic response data. No subjects had viral breakthrough, and only one subject (Arm 1) had viral relapse. For these subjects, the majority of whom did not have cirrhosis, similarly high rates of SVR12 were observed in those with HCV genotype/subtype 1a regardless of the presence of Q80K, consistent with results in the nontransplant setting [33].

It is clinically important that all subjects (11/11) treated with a ribavirin-free regimen of simeprevir and sofosbuvir for 12 weeks achieved SVR12 because most liver transplant recipients tolerate ribavirin poorly and some cannot tolerate ribavirin at any dose [14,21]. Furthermore, simeprevir and sofosbuvir, with or without ribavirin, is an HCV NS5A inhibitor-free regimen; as NS5A inhibitors have a low barrier to resistance and variants tend to persist, this regimen may be an option for individuals with HCV NS5A variants [34–36]. Notably, most GALAXY subjects had an HCV NS5A polymorphism and the presence of these polymorphisms did not have a substantial impact on SVR12 achievement.

Evaluation of potential pharmacokinetic interaction between antiviral agents and commonly used

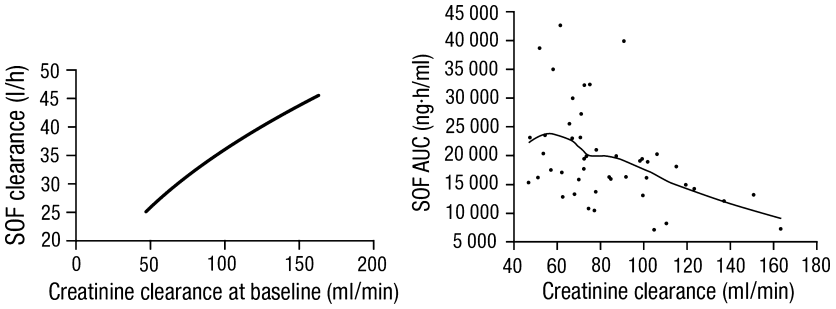

Figure 3 Correlation between sofosbuvir exposure and creatinine clearance. On the left, central clearance of sofosbuvir is plotted against creatinine clearance at baseline. On the right, sofosbuvir exposure is plotted against creatinine clearance. AUC, area under the concentration–time curve.

concomitant medications is important, and for post-transplant recipients, immunosuppressant use is of particular interest. In a previous study of postliver transplant recipients (SATURN), simeprevir exposure was increased 581% during concomitant cyclosporine A use; based on this, cyclosporine A is not recommended for coadministration with simeprevir [24]. The same study showed a 185% increase in simeprevir exposure with concomitant tacrolimus use, but this result was not considered clinically significant [24]. Based on these findings, the current study did not allow for use of cyclosporine A.

The GALAXY study is the first to describe steady-state simeprevir and sofosbuvir exposures in postliver transplant recipients with HCV genotype 1 infection. Subjects' exposures to these agents were similar regardless of treatment arm; however, compared with similar data collected in a nontransplant setting (COSMOS study) [33], exposures were numerically higher (simeprevir $AUC_{24\ h}$ values were 26 820 and 44 300 ng·h/ml, and sofosbuvir $AUC_{24\ h}$ values were 10 801 and 17 884 ng·h/ml, in COSMOS and GALAXY, respectively). Given the large variability in the current study, these exposure differences were not considered clinically relevant. It is possible that the increase in simeprevir exposure may be due, in part, to a mild pharmacokinetic interaction between simeprevir and tacrolimus [24]. The lack of a clinically relevant change in sofosbuvir exposure is consistent with previous findings in post-transplant recipients and healthy volunteers [14,31].

Simeprevir and sofosbuvir treatment, with or without ribavirin, was generally well tolerated, consistent with previous reports in this population [15–17,26,27]. Safety outcomes were comparable across arms, and not unexpectedly, anaemia was only observed in subjects treated with ribavirin [15,26,27]. There were few serious AEs and only two subjects had an AE that was grade ≥2 and considered possibly related to simeprevir. One transplant rejection occurred at follow-up week 12; consistent with this, the subject's tacrolimus level had markedly decreased from baseline to the time of rejection. A gradual downward trend in tacrolimus levels was observed in subjects using tacrolimus, similar to what has been noted in another study of simeprevir and sofosbuvir in this patient population [15]. Decreased tacrolimus levels may be explained by the reduced tacrolimus exposure with simeprevir coadministration that was previously observed in healthy volunteers [37]. It is also possible that subjects' liver function improved during effective HCV therapy, leading to HCV RNA clearance and subsequently increased tacrolimus metabolism [38]. Caution should be used when interpreting these tacrolimus pharmacokinetic results given the small numbers of subjects with available data at each time point and the overlapping CIs.

PRO endpoints were evaluated to describe the severity of symptoms associated with HCV or its treatment and health-related quality of life before and after treatment during the current GALAXY study. At baseline, subjects reported overall symptom severity and health-related quality of life measures that were similar to what's been reported in the nontransplant setting for HCV genotype 1-infected subjects without cirrhosis or with compensated cirrhosis [39]. In that study of non-transplant subjects, symptom scores improved with simeprevir and sofosbuvir treatment by the follow-up week 12 visit, sometimes by amounts considered clinically important. In the post-transplant GALAXY population, HCV-SIQv4 overall body system scores did not change relative to baseline, and the median change in EQ-5D VAS scores indicated an improvement that was slightly less than the value that has been shown to be clinically important in all cases except in Arm 3 subjects at the follow-up week 12 time point, at which point a small but clinically significant improvement was observed.

A limitation of the current study is the small sample size, which necessitated descriptive statistics and limited comparisons between treatment groups. For example, there was one subject who had missing data in the randomized population; this subject represented 9.1% of

Table 3. Summary of safety during the treatment phase.

	Total (N = 46)	Arm 1: SMV + SOF + RBV, 12 weeks (n = 11)	Arm 2: SMV + SOF, 12 weeks (n = 11)	Arm 3: SMV + SOF, 24 weeks (n = 11)	Arm 3 nonrand: SMV + SOF, 24 weeks (n = 13)
Any AE, *n* (%)	45 (97.8)	11 (100)	11 (100)	11 (100)	12 (92.3)
Any serious AE, *n* (%)*	5 (10.9)	2 (18.2)	0	1 (9.1)	2 (15.4)
Any fatal AE, *n* (%)†	1 (2.2)	1 (9.1)	0	0	0
AE at least possibly related to SMV, *n* (%)	29 (63.0)	7 (63.6)	9 (81.8)	7 (63.6)	6 (46.2)
Grade ≥2‡	2 (4.3)	0	0	0	2 (15.4)
AE leading to permanent discontinuation of ≥1 study drug, *n* (%)§	2 (4.3)	2 (18.2)	0	0	0
Most common AEs, *n* (%)¶,**					
Headache	17 (37.0)	5 (45.5)	3 (27.3)	7 (63.6)	2 (15.4)
Fatigue	16 (34.8)	3 (27.3)	3 (27.3)	5 (45.5)	5 (38.5)
Nausea	11 (23.9)	3 (27.3)	3 (27.3)	3 (27.3)	2 (15.4)
Diarrhoea	10 (21.7)	2 (18.2)	3 (27.3)	3 (27.3)	2 (15.4)
Pruritus	10 (21.7)	4 (36.4)	4 (36.4)	2 (18.2)	0
Vomiting	8 (17.4)	2 (18.2)	2 (18.2)	2 (18.2)	2 (15.4)
Dyspnoea	7 (15.2)	2 (18.2)	2 (18.2)	3 (27.3)	0
Decreased appetite	6 (13.0)	2 (18.2)	2 (18.2)	2 (18.2)	0
Insomnia	6 (13.0)	3 (27.3)	1 (9.1)	1 (9.1)	1 (7.7)
Rash††	6 (13.0)	3 (27.3)	1 (9.1)	2 (18.2)	0
Constipation	5 (10.9)	2 (18.2)	2 (18.2)	1 (9.1)	0

SMV, simeprevir; SOF, sofosbuvir; RBV, ribavirin; nonrand, nonrandomized subgroup; AE, adverse event.

*None of the serious AEs were considered to be possibly related to study drug by the investigator. The serious AEs were as follows: Arm 1, device-related infection and completed suicide; Arm 3, small intestinal obstruction (randomized subgroup), abdominal hernia (nonrandomized subgroup) and prostate cancer (nonrandomized subgroup).

†One subject committed suicide, considered unrelated to study drug by the investigator.

‡AEs were fatigue and increased gamma-glutamyltransferase.

§One subject committed suicide and discontinued all three study medications; a second subject discontinued ribavirin due to anaemia.

¶Reported by >10% of subjects in total population by preferred term.

**One (2.2%) subject had a photosensitivity reaction AE by preferred term, and a total of four (8.7%) subjects had a photosensitivity condition AE of clinical interest (including the following preferred terms: photosensitivity reaction and sunburn). All events were grade 1 in severity.

††A total of ten (21.7%) subjects had a rash AE of clinical interest (including the following preferred terms: rash, sunburn, cutaneous vasculitis, palmar erythema, photosensitivity reaction, and vesicular rash). All events were grade 1 in severity.

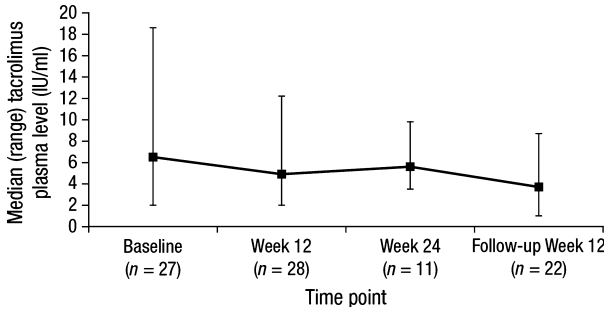

Figure 4 Tacrolimus plasma levels over time[a]. Median (range) tacrolimus plasma levels are plotted over time for subjects who used tacrolimus and had available data.
[a]Median (range) levels were as follows: baseline, 6.50 (2.0–18.6) IU/ml; week 12, 4.90 (2.0–12.2) IU/ml; week 24, 5.60 (3.5–9.8) IU/ml; follow-up week 12, 3.70 (1.0–8.7) IU/ml.

the Arm 1 population and significantly impacted the SVR12 rate in this treatment group (as noted above). Another limitation is that the majority of subjects had less advanced disease (METAVIR score F0-F2), which has been associated with higher SVR12 rates in previous studies in HCV genotype 1-infected liver transplant recipients [13,15,16]. However, it is also possible that disease severity was underestimated in some cases, as assessment of liver fibrosis could have occurred up to 12 months prior to screening.

In summary, the GALAXY study demonstrated the efficacy and safety of simeprevir and sofosbuvir treatment, with or without ribavirin, for 12 or 24 weeks in postorthotopic liver transplant recipients with recurrent HCV genotype 1. These regimens may be clinically important options for individuals with NS5A variants and, importantly, 100% of subjects treated with simeprevir and sofosbuvir for 12 weeks achieved SVR12, suggesting that this regimen may be adequate for individuals without cirrhosis. Further study is warranted to determine whether this therapy is also efficacious in patients with cirrhosis.

Authorship

JGO, RJF, KB, JRB, RF-M, AM, CO, MR, KRR and RSB: contributed to the design and/or conduct of the study, and to the acquisition and interpretation of data. RR: contributed to data analysis and interpretation. AS: contributed to data interpretation. SV: contributed to the conduct of the study and data interpretation. AP: contributed to the design and conduct of the study, and to the acquisition and interpretation of the data. All authors critically reviewed the manuscript and approved the final version.

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Conflict of interest

J.G.O. has served as a consultant for Gilead and AbbVie, and given sponsored lectures for Gilead and AbbVie. R.J.F. has received grants from Gilead, Bristol-Myers Squibb and Janssen and has given sponsored lectures for the Chronic Liver Disease Foundation. K.B. has received grants from Gilead, AbbVie, Janssen, Hyperion, Exalenz and Duke Research and has given sponsored lectures for Bristol-Myers Squibb, AbbVie and Gilead and served on advisory boards for Gilead, Merck, Janssen, AbbVie and Bristol-Myers Squibb. J.R.B. has received grants from AbbVie, Gilead and Janssen. R.F.-M. has received grants from Gilead, Intercept, Merck, AbbVie and Conatus and has served as a medical monitor for Bristol-Myers Squibb. A.M. has received grants from AbbVie, Bristol-Myers Squibb, Gilead, Janssen and Merck and served on advisory boards for AbbVie, Bristol-Myers Squibb, Gilead, Janssen and Merck. C.O. and M.R. have no disclosures to declare. K.R.R. has received grants from Janssen, Gilead, Merck, Bristol-Myers Squibb and AbbVie (money paid to institution) and served on advisory boards for Janssen, Gilead, Merck, Bristol-Myers Squibb and AbbVie. R.R., A.S., S.V. and A.P. are full-time employees of Janssen. R.S.B. has received grants from AbbVie, Bristol-Myers Squibb, Gilead, Janssen and Merck and has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead, Janssen and Merck.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Materials and methods.

Table S1. HCV-SIQv4 Overall Body System Score: Change From Baseline (randomized ITT)[a].

Table S2. EQ-5D VAS Baseline Scores (randomized ITT)[a].

Figure S1. Median change from baseline in EQ-5D VAS score over time (randomized ITT).[a,b]

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