SYNOPSIS

Name of Sponsor/Company	Janssen Scientific Affairs, LLC
Name of Finished Product	OLYSIO™
Name of Investigational Product	TMC435 (simeprevir)

Status: Approved
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Prepared by: Janssen Scientific Affairs, LLC

Protocol No.: TMC435HPC2009

Title of Study: A Phase 2 Open-label Study in Patients With Recurrent Genotype 1 Hepatitis C Post-orthotopic Liver Transplant to Explore the Safety and Efficacy of Simeprevir and Sofosbuvir With and Without Ribavirin.

Study Name: TMC435HPC2009 (GALAXY)

NCT No.: NCT02165189

Clinical Registry No.: CR104281

Coordinating Investigator(s): Jacqueline O'Leary, MD - Baylor University / [redacted]; United States

Study Center(s): This study was initiated at 10 sites in the United States.

Publication (Reference): none

Study Period: 11 August 2014 - 10 November 2015

Phase of Development: Phase 2

Objectives:

The primary objective was to evaluate sustained virologic response 12 weeks after the end of treatment (SVR12) with simeprevir (SMV) plus sofosbuvir (SOF) for 12 weeks with ribavirin (RBV) (Arm 1), SMV plus SOF for 12 weeks without RBV (Arm 2), and SMV plus SOF for 24 weeks without RBV (Arm 3), in post-orthotopic liver transplant patients with recurrent hepatitis C virus (HCV) genotype 1 infection.

The secondary objectives were:

- To describe safety, tolerability, and rates of rejection during the entire study period;
- To describe drug levels for immunosuppressants during HCV therapy with SMV plus SOF with or without RBV;
- To describe the dose adjustment schedule of all immunosuppressants (according to local standard of care) during and after HCV therapy with SMV plus SOF with or without RBV;
- To describe on-treatment virologic response at Weeks 2, 4, 8, and 12 for all subjects and at Weeks 16, 20, and 24 for subjects in Arm 3;
- To evaluate the incidence of viral breakthrough and relapse;

- To evaluate SVR4 (ie, sustained virologic response 4 weeks post treatment);
- To evaluate the impact of HCV and its treatment on patient-reported symptoms, functioning, and health-related quality of life using 2 patient-reported outcome (PRO) tools: the Hepatitis C Symptom & Impact Questionnaire version 4 (HCV-SIQv4) and the EuroQol 5-Dimension questionnaire (EQ-5D).

Note that exploratory objectives are not included in the synopsis.

Methodology: This was a Phase 2, partially randomized, open-label study conducted at multiple sites in the United States that evaluated the safety and efficacy of SMV 150 mg once daily plus SOF 400 mg once daily for 12 weeks (with or without RBV) and 24 weeks (without RBV) in post-orthotopic liver transplant patients with recurrent HCV genotype 1 infection.

Subjects at least 6 months post-liver transplant with compensated liver disease and on a stable immunosuppressive regimen were enrolled if eligible, and were randomized or assigned to a treatment arm at baseline. The first 33 enrolled non-cirrhotic subjects were randomized in a 1:1:1 ratio to Arms 1, 2 or 3 (defined below). After randomization of non-cirrhotic subjects was completed, all subsequent subjects were then assigned (without randomization) to Arm 3. Up to a maximum of 12 cirrhotic subjects could be enrolled and were assigned to Arm 3. Cirrhotic subjects were excluded from randomization because of a suspected higher risk of viral relapse if treated for 12 weeks; therefore, all cirrhotic subjects were assigned to 24 weeks of treatment. Enrollment continued until a target total of 45 subjects were enrolled into the study.

- Arm 1: SMV plus SOF and RBV for a 12 week treatment phase;
- Arm 2: SMV plus SOF without RBV for a 12-week treatment phase;
- Arm 3: SMV plus SOF for a 24-week treatment phase.

Randomized subjects were stratified by HCV genotype subtype and NS3 polymorphism at screening (genotype 1a with Q80K versus [vs.] genotype 1a without Q80K vs. genotype 1b).

The study consisted of a screening phase (maximum 6 weeks), an open-label treatment phase for up to 24 weeks (12 or 24 weeks depending on the treatment arm) and a 12-week post-treatment phase for follow-up. During the open-label treatment phase, subjects received SMV 150 mg once daily and SOF 400 mg once daily. Subjects receiving RBV received weight-based dosing of 400 mg once daily (for subjects <75 kg) or 600 mg once daily (for subjects ≥75 kg). RBV dose was increased monthly by 200 mg as tolerated up to a weight-based dose of 1,000 mg per day (<75 kg) or 1,200 mg per day (≥75 kg). As the RBV dose increased, RBV could be taken twice daily in divided doses. RBV dose for subjects with creatinine clearance between 30 and 50 mL/min consisted of alternating doses, 200 mg and 400 mg every other day (and no dose increase).

Study drugs were discontinued for subjects with viral breakthrough (ie, confirmed >1.0 $\log_{10}$ increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in subjects who had previously achieved HCV RNA <15 IU/mL). HCV RNA ≥15 IU/mL after previously being <15 IU/mL had to be confirmed by repeat HCV RNA testing done within 3 weeks.

SMV is a mild inhibitor of intestinal cytochrome P450 3A (CYP3A). Co-administration of SMV with substances that are moderate or strong inducers or inhibitors of CYP3A was not recommended as this may have led to significantly lower or higher exposure of SMV, respectively. Drugs that are potent P-glycoprotein (P-gp) inducers in the intestine (eg, rifampin or St. John's wort) may significantly decrease SOF plasma concentrations leading to reduced therapeutic effect of SOF and thus should not be used with SOF. Disallowed prior or concomitant medication included, but was not limited to, treatment

with FDA approved interferon (IFN) and/or pegylated IFN (PegIFN) based therapy and cyclosporine from 3 months prior to screening onwards and during the entire treatment phase.

A pre-specified interim analysis was performed when all 22 subjects enrolled in Arms 1 and 2 reached the SVR12 time point (or discontinued earlier) to assess safety and efficacy, but no report was written. Futility criteria for viral failure were installed in Arms 1 and 2 to allow the addition of RBV and/or extension of therapy to 24 weeks if the response in the 12-week treatment groups was inadequate. Viral failure was defined as a combination of viral breakthrough and/or relapse (and not to be confused with the broader term 'failure [virologic or non-virologic]', ie, SVR12 not achieved [or missing HCV RNA at time point of SVR12] or viral relapse) No futility criterion was met, and enrollment in both arms continued as planned. The final analysis described in this report was performed when all subjects had completed the last study-related visit (at Week 24 for Arms 1 and 2 and at Week 36 for Arm 3) or discontinued earlier.

The relatively small total sample size is a potential limitation of the study and reflects the Phase 2 proof-of-concept design. This is the first study of SMV+SOF conducted by the sponsor in post-liver transplant patients for whom the optimal treatment duration and the need for RBV were not yet known.

Number of Subjects (planned and analyzed): The planned total sample size was approximately 45 subjects. A total of 46 subjects were enrolled; 33 non-cirrhotic subjects were randomized (11 per treatment arm) and 11 non-cirrhotic and 2 cirrhotic subjects were assigned without randomization to Arm 3. All enrolled subjects received at least 1 dose of study drug.

Data Sets Analyzed: All Subjects Analysis Set

	Arm 1: SMV+SOF+RBV 12 Wks (N=11) n (%)	Arm 2: SMV+SOF 12 Wks (N=11) n (%)	Arm 3: SMV+SOF 24 Wks Total (N=24) n (%)	Overall Total (N=46) n (%)
Planned	11	11	23	45
Enrolled	11	11	24	46
Not randomized	-	-	13 (54.2%)	13 (28.3%)
Randomized	11 (100%)	11 (100%)	11 (45.8%)	33 (71.7%)
Intent-to-treat population[a]	11 (100%)	11 (100%)	24 (100%)	46 (100%)
Completed treatment	10 (90.9%)	11 (100%)	23 (95.8%)	44 (95.7%)
Completed study	10 (90.9%)	11 (100%)	22 (91.7%)	43 (93.5%)

[a] Intent-to-treat population includes all enrolled subjects who took at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion: Men or women, aged 18 years or above, infected with HCV genotype 1 (1a or 1b) with baseline HCV RNA of >10,000 IU/mL, on a stable immunosuppressive regimen following primary orthotopic liver transplant ≥6 months to 15 years prior to enrollment without evidence of clinically significant rejection within 12 months of screening were eligible. The subjects' renal function as measured by the Cockcroft Gault formula had to be >30 mL/min.

Subjects with hepatic decompensation, past or present diagnosis of fibrosing cholestatic hepatitis or plasma cell hepatitis, any liver disease of non-HCV etiology (except liver steatosis), a hepatitis B co-infection (hepatitis B surface antigen positive) and/or human immunodeficiency virus (HIV) co-infection or another organ transplant in the past were excluded. Subjects willing to participate, who signed the informed consent form (ICF), and found eligible for the study at screening were required to discontinue specified disallowed medication.

Test Product, Dose and Mode of Administration, Batch No.: SMV 150-mg oral gelatin capsules (Batch No. DATK01E and DCTK02N) at a dose of 150 mg once daily. SOF 400-mg oral tablets (Batch No. 3ATK01A, 3ATK01M and 3ATK02U) at a dose of 400 mg once daily. Ribavirin (Copegus®) 200-mg oral tablet (Batch No. DATK01F) at a starting dose of 400 or 600 mg once daily, increased

monthly by 200 mg up to a dose of 1,000 or 1,200 mg per day (twice daily regimen), depending on the body weight (<75 or ≥75 kg).

Duration of Treatment: 12 weeks in Arms 1 and 2 and 24 weeks in Arm 3 (followed by a 12-week follow-up in each arm).

Criteria for Evaluation:

Efficacy Evaluations: Blood samples for the determination of plasma HCV RNA levels were taken at predefined time points. Plasma HCV RNA was determined using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 (lower limit of quantification = limit of detection = 15 IU/mL).

Resistance Determinations: Blood samples for sequencing of the HCV NS3/4A and NS5B regions were collected at predefined time points to determine the viral NS3/4A and NS5B sequences pre-treatment (at screening or baseline) in all subjects and post-baseline in subjects not achieving SVR. In addition to HCV NS3/4A and NS5B sequencing, NS5A sequencing was performed in the screening samples. Sequencing of the HCV NS3/4A and NS5B regions in the post-baseline samples could be triggered at the sponsor's discretion and was performed for subjects with virologic failure. Viral sequencing was performed using population sequencing.

Patient-Reported Outcomes Evaluations: The impact of HCV infection and its treatment on patient-reported symptoms, functioning, and health related quality of life was evaluated using the HCV SIQv4 and EQ-5D, which were completed by subjects at predefined time points.

Pharmacokinetic (PK) Evaluations: Blood samples for determination of plasma concentrations (trough levels [C_{0h}] only) of SMV, SOF and GS-331007 (the primary systemic metabolite of SOF) were collected on Days 28, 56, and 84 (all subjects) and Day 168 (Arm 3) and analyzed using validated, specific, and sensitive analytical methods. Plasma concentrations of immunosuppressants were checked twice during the first week of treatment, weekly during the next 3 weeks, and per local institutional protocol thereafter according to the established method at the local laboratories. PK parameters (C_{0h}, average steady-state plasma concentration [C_{av}], maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve from time of administration to 24 hours post-dose [AUC_{24h}]) of SMV and GS-331007 were determined using population PK analysis. No PK parameters were derived for SOF as the majority of samples were below the lower limit of quantification.

Safety Evaluations: Safety and tolerability were evaluated from signing of the informed consent onwards until the last study-related activity. The evaluations of safety and tolerability included monitoring of adverse events (AEs), including AEs of interest and serious AEs (SAEs), clinical laboratory tests, electrocardiogram (screening only), vital sign measurements, and physical examinations. Specific toxicity management plans were incorporated in line with known toxicities for the study drugs evaluated. Diagnosis of liver allograft rejection was made by a local pathologist per institution protocol. Any clinically significant abnormalities persisting at the end of the study/early withdrawal were followed by the investigator until resolution or until a clinically stable endpoint was reached.

Statistical Methods: This report describes the results of the final analysis, performed when all subjects had completed the last study-related visit (at Week 24 for Arms 1 and 2 and at Week 36 for Arm 3) or discontinued earlier. All analyses were performed on the intent-to-treat (ITT) population, which included all enrolled subjects who took at least 1 dose of study drug (SMV or SOF or RBV in the arms with RBV; SMV or SOF in the arms without RBV).

Sample Size Determination: It was expected that SVR12 would be achieved in 80% of the subjects receiving HCV therapy of 12 to 24 weeks of SMV plus SOF with or without RBV. Therefore, a target of 45 subjects were to be enrolled in the study. With a target SVR12 rate of 80%, 11 subjects allowed the

SVR12 rate to be estimated in Arms 1 and 2 with a 2-sided 95% confidence interval (CI) width of 50.8%, thus 80% (46.3%, 97.1%) and 23 subjects in Arm 3 allowed the SVR12 rate to be estimated with a 2-sided 95% CI width of 35.3%, thus 80% (58.2%, 93.6%).

Efficacy Analyses: No statistical testing was conducted for this study. All CIs were computed at the 5% significance 2-sided level.

The primary efficacy parameter was the proportion of subjects who achieved SVR12.

The secondary efficacy parameters included the following:

- the proportion of subjects with SVR4;
- the proportion of subjects with undetectable HCV RNA (on-treatment virologic response) at Weeks 2, 4, 8, and 12 (Arms 1, 2, 3) and at Weeks 16, 20, and 24 (Arm 3);
- the proportion of subjects with viral breakthrough;
- the proportion of subjects with viral relapse;
- the time to on-treatment failure, time to viral breakthrough and time from last dose to viral relapse.

The efficacy parameters were summarized per treatment arm using descriptive statistics (n, mean, standard error [SE], standard deviation [SD], median, interquartile range, range) for continuous parameters and tabulations (numbers and proportions and 95% CI) for categorical parameters. The reason for success/failure was explored by type of failure and completion of study treatment. The "time to" analysis was to be conducted if more than 10 subjects per arm had an event. Subgroup analyses were performed for genotype subtype 1a and 1b, by the presence of NS3 Q80K polymorphism at screening, and the presence of NS5A polymorphisms at screening, and other baseline characteristics as defined in the Statistical Analysis Plan.

Resistance Analyses: Pre-treatment polymorphisms in the HCV NS3/4A and NS5B regions in all subjects and relevant changes in the HCV NS3/4A and NS5B regions in subjects with virologic failure were tabulated and described. The effect of NS3/4A and NS5B polymorphisms on treatment outcome was explored.

Patient-Reported Outcomes Analyses: The PRO parameters included the changes from baseline in HCV-SIQv4 body symptom score, HCV-SIQv4 time missed from work/school score, HCV-SIQv4 impact on daily life score, EQ-5D valuation index and EQ-5D visual analog scale (VAS) scores. HCV SIQv4 and EQ-5D data were summarized per treatment arm using descriptive statistics and tabulations. Duration of decreased EQ-5D VAS (change from baseline ≤-10) was also summarized descriptively.

Pharmacokinetic Analyses: Descriptive statistics were provided for the PK parameters of SMV and GS-331007. The plasma concentrations of the immunosuppressants were summarized. Subjects who changed their immunosuppressant regimen (drugs and/or dosage) during the study were listed.

Safety Analyses: The safety parameters were analyzed, as appropriate, by means of descriptive statistics, frequency tabulations and listings.

RESULTS:

Note that for readability the data for the randomized and non-randomized subgroups of the SMV+SOF+RBV 24 Wks arm are excluded from the synopsis tables. Relevant differences between these subgroups are mentioned in the text, as appropriate.

STUDY POPULATION: Of the 46 enrolled subjects, 44 (95.7%) completed the study treatment, ie, completed planned treatment with SMV+SOF with or without RBV for 12 or 24 weeks. Of the

44 subjects who completed treatment, 43 (93.5%) completed the study and attended the Follow-up Week 12 visit. Reasons for study/treatment discontinuation are provided in the table below.

Study and Treatment Completion/Discontinuation

	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total
Analysis Set: Intent-To-Treat	11	11	24	46
Number of subjects who:				
Completed the study	10 (90.9%)	11 (100.0%)	22 (91.7%)	43 (93.5%)
Discontinued the study	1 (9.1%)	0	2 (8.3%)	3 (6.5%)
Death (patient committed suicide)	1 (9.1%)	0	0	1 (2.2%)
Lost to follow-up	0	0	1 (4.2%)	1 (2.2%)
Physician Decision (patient developed metastatic prostate cancer)	0	0	1 (4.2%)	1 (2.2%)
Number of subjects who:				
Completed treatment	10 (90.9%)	11 (100.0%)	23 (95.8%)	44 (95.7%)
Discontinued the medication	1 (9.1%)	0	1 (4.2%)	2 (4.3%)
Death (patient committed suicide)	1 (9.1%)	0	0	1 (2.2%)
Physician Decision (patient developed metastatic prostate cancer)	0	0	1 (4.2%)	1 (2.2%)

Information presented in the table is based upon "End of Trial" eCRF page and "End of Treatment" eCRF page.
Discontinuation refers to permanent stop of study medication.

Overall, the majority of the subjects were male (73.9%), white (80.4%) and not of Hispanic or Latino ethnicity (93.5%). The median age at screening was 60.0 years, and the median BMI at baseline was 28.80 kg/m². The proportion of subjects using acid reducing agents was higher in the SMV+SOF 12 Wks arm (72.7%) when compared with the other treatment arms (45.5% and 62.5%). The majority of subjects (80.4%) had plasma HCV RNA >800,000 IU/mL. Most subjects presented with less advanced liver disease, ie, METAVIR grade A1 (45.7%) or A2 (26.1%) and METAVIR fibrosis stage F0/F1 (19.6%) or F2 (50.0%). The majority of subjects had HCV genotype 1a infection (71.7%). The baseline disease characteristics were reasonably well balanced across the treatment arms; however, when comparing the randomized and non-randomized subgroups in the SMV+SOF 24 Wks arm, the non-randomized subjects presented with relatively lower HCV RNA (median 5.79 vs. 6.73 $\log_{10}$ IU/mL) and were diagnosed more frequently with METAVIR fibrosis stage F0/F1 (38.5% vs. 9.1%). Per protocol, the subjects with cirrhosis (4.3% of all subjects) were only enrolled in the SMV+SOF 24 Wks arm.

Demographic and Baseline Disease Characteristics

	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total
Analysis Set: Intent-To-Treat	11	11	24	46
Gender				
Female	3 (27.3%)	3 (27.3%)	6 (25.0%)	12 (26.1%)
Male	8 (72.7%)	8 (72.7%)	18 (75.0%)	34 (73.9%)
Race				
White	9 (81.8%)	9 (81.8%)	19 (79.2%)	37 (80.4%)
Black or African American	1 (9.1%)	2 (18.2%)	5 (20.8%)	8 (17.4%)
Asian	1 (9.1%)	0	0	1 (2.2%)
Ethnicity				
Hispanic or Latino	0	1 (9.1%)	2 (8.3%)	3 (6.5%)
Not Hispanic or Latino	11 (100.0%)	10 (90.9%)	22 (91.7%)	43 (93.5%)
Age (years)				
Mean (SD)	59.9 (3.45)	58.9 (5.77)	58.8 (4.87)	59.1 (4.73)
Median	60.0	59.0	60.0	60.0
Range	(53; 65)	(50; 68)	(49; 66)	(49; 68)
Body Mass Index (kg/m2)				
Mean (SD)	27.80 (4.202)	29.52 (4.685)	30.49 (5.293)	29.61 (4.933)
Median	28.80	28.10	28.85	28.80

Demographic and Baseline Disease Characteristics				
	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total
Range	(22.5; 34.5)	(24.8; 40.4)	(20.5; 43.4)	(20.5; 43.4)
Use of Acid Reducing Agents				
Yes	5 (45.5%)	8 (72.7%)	15 (62.5%)	28 (60.9%)
No	6 (54.5%)	3 (27.3%)	9 (37.5%)	18 (39.1%)
HCV RNA level (log_{10} IU/mL)				
Mean (SD)	6.51 (0.454)	6.66 (0.318)	6.29 (0.964)	6.43 (0.753)
SE	0.137	0.096	0.197	0.111
Median	6.61	6.58	6.60	6.60
Range	(5.6; 7.0)	(6.3; 7.1)	(4.1; 7.6)	(4.1; 7.6)
HCV RNA category (IU/mL)				
<=800000	2 (18.2%)	0	7 (29.2%)	9 (19.6%)
>800000	9 (81.8%)	11 (100.0%)	17 (70.8%)	37 (80.4%)
Metavir Stage				
F0/F1	2 (18.2%)	1 (9.1%)	6 (25.0%)	9 (19.6%)
F2	8 (72.7%)	6 (54.5%)	9 (37.5%)	23 (50.0%)
F3	1 (9.1%)	3 (27.3%)	5 (20.8%)	9 (19.6%)
F4	0	0	1 (4.2%)	1 (2.2%)
Missing	0	1 (9.1%)	3 (12.5%)	4 (8.7%)
Metavir Grade				
A0	0	1 (9.1%)	2 (8.3%)	3 (6.5%)
A1	7 (63.6%)	3 (27.3%)	11 (45.8%)	21 (45.7%)
A2	3 (27.3%)	4 (36.4%)	5 (20.8%)	12 (26.1%)
A3	1 (9.1%)	2 (18.2%)	3 (12.5%)	6 (13.0%)
Missing	0	1 (9.1%)	3 (12.5%)	4 (8.7%)
Cirrhosis				
Yes	-	-	2 (8.3%)	2 (4.3%)
No	-	-	22 (91.7%)	44 (95.7%)
HCV geno/subtype and Q80K polymorphism (Genotype)				
1a	8 (72.7%)	7 (63.6%)	18 (75.0%)	33 (71.7%)*
Q80K	3 (37.5%)	4 (57.1%)	5 (27.8%)	12 (36.4%)
No Q80K	5 (62.5%)	3 (42.9%)	12 (66.7%)	20 (60.6%)
1b	3 (27.3%)	4 (36.4%)	6 (25.0%)	13 (28.3%)

* For 1 HCV genotype 1a subject, no NS3 sequencing data were available.

Baseline NS3 polymorphisms (considering the 6 positions of interest: 43, 80, 122, 155, 156 and 168) were observed in 16 (37.2%) of 43 subjects with NS3 sequencing data. A baseline Q80K polymorphism was present in 12 (37.5%) of 32 HCV genotype 1a subjects with NS3 sequencing data (for 1 HCV genotype 1a subject, no NS3 sequencing data were available). Baseline NS5B polymorphisms (considering the 9 positions of interest: 96, 142, 159, 282, 316, 320, 321, 390 and 415) were observed in 5 (12.2%) of 41 subjects with NS5B sequencing data. The NS5B S282T polymorphism, associated with in vitro resistance to SOF, was not observed at baseline.

Major protocol deviations were identified for 2 subjects. One subject received RBV at a dose of 1,200 mg daily since baseline. Per protocol, the RBV dose should start at 400 or 600 mg with monthly increases of 200 mg per tolerance up to a maximum of 1,000 or 1,200 mg per day (depending on body weight). The principal investigator lowered the dose to 800 mg daily. The other subject experienced an SAE which the site did not report to the sponsor within 24 hours of knowledge of the event.

All 46 enrolled subjects received treatment with at least one dose of study drug and were included in the ITT population.

EFFICACY RESULTS: The primary efficacy parameter was the proportion of subjects with SVR12, ie, subjects with HCV RNA <15 IU/mL detectable or undetectable at 12 weeks after the end of treatment (EOT). SVR12 was achieved in 81.8% (9/11), 100.0% (11/11) and 91.7% (22/24) of subjects in the

SMV+SOF+RBV 12 Wks, SMV+SOF 12 Wks and SMV+SOF 24 Wks arms, respectively. Comparable results were observed for SVR4. Two subjects in the SMV+SOF 24 Wks arm achieved SVR4 but not SVR12.

Sustained Virologic Response 12 Weeks After the End of Treatment; Intent-to-Treat Analysis Set

	SMV+SOF+RBV 12 Wks		SMV+SOF 12 Wks		SMV+SOF 24 Wks Total		Overall Total	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
SVR12	9/11 (81.8%)	54.5 - 100.0	11/11 (100.0%)	95.5 - 100.0	22/24 (91.7%)	78.5 - 100.0	42/46 (91.3%)	82.1 - 100.0
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
SVR4	9/11 (81.8%)	54.5 - 100.0	11/11 (100.0%)	95.5 - 100.0	24/24 (100.0%)	97.9 - 100.0	44/46 (95.7%)	88.7 - 100.0

There were no cases of viral breakthrough. Four post-treatment failures were observed, 2 in the SMV+SOF+RBV 12 Wks arm and 2 in the SMV+SOF 24 Wks arm. One of these 4 subjects experienced virologic failure (viral relapse detected at 4 weeks after the end of treatment in a subject enrolled in the SMV+SOF+RBV 12 Wks arm who completed the assigned treatment as planned); for the other 3 subjects, data were missing at the SVR12 time point (discontinued study before SVR time point, see above under 'Study Population' for reasons for discontinuation). The subject with viral relapse was infected with HCV genotype 1a without the NS3 Q80K polymorphism at baseline and had no emerging NS3 or NS5B mutations at the positions of interest at the time of failure.

Apart from the observed numerical differences in RVR rate (81.8% [9/11], 54.5% [6/11] and 62.5% [15/24] in the SMV+SOF+RBV 12 Wks, SMV+SOF 12 Wks and SMV+SOF 24 Wks arms, respectively), no clear differences between the 12 and 24 Wks arms or between the treatment arms with or without RBV were observed for the virologic response parameters evaluated in this study.

The subgroup analyses showed that, in general, the SVR4 and SVR12 rates were high and comparable across the subgroups tested. However, due to the small sample sizes within the categories, the findings should be interpreted with caution and no firm conclusions can be drawn.

PATIENT-REPORTED OUTCOMES RESULTS: Results for PRO measuring the severity of symptoms or impairments in daily activities and health-related quality of life indicated that the majority of subjects were in a relatively good health state at baseline and remained so throughout the treatment and follow-up phases. There were no clear patterns of improvement or worsening in scores over time or differences between the treatment arms in PRO data. A clinically relevant improvement in median EQ-5D VAS score was observed in the randomized subgroup of the SMV+SOF 24 Wks arm at Follow-up Week 12 (change from baseline of +8.5). However, given the small sample size, no firm conclusions can be drawn.

PHARMACOKINETIC RESULTS: The exposures were similar in all treatment groups for both SMV and GS-331007. In the population PK model applied to obtain individual PK parameters for GS-331007, a relationship between creatinine clearance at baseline and the central clearance of GS-331007 is considered. Subjects with a higher baseline creatinine clearance will have a lower exposure of GS-331007. Tacrolimus was the most commonly used immunosuppressant (in 42/46, 91.3%). Overall, 15 (32.6%) of 46 subjects required an adjustment of the immunosuppressant dose during the study (ie, 5/11, 1/11 and 9/24 subjects in the SMV+SOF+RBV 12 Wks, SMV+SOF 12 Wks and SMV+SOF 24 Wks arms, respectively). Since the impact of SMV on immunosuppressants was already established in previous studies, no extensive analysis was performed.

Summary of the Pharmacokinetic Parameters of SMV

	Median (range)		
	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total
PK Data Analysis Set	11	11	24
PK Parameters			
C_{0h}, ng/mL	1,010 (157-4,110)	1,190 (110-12,300)	1,045 (163-16,400)
C_{max}, ng/mL	3,050 (630-7,970)	3,040 (975-17,100)	2,690 (826-21,000)
C_{av}, ng/mL	1,883 (353-5,792)	1,854 (416-14,542)	1,702 (433-18,792)
AUC_{24h}, ng·h/mL	45,200 (8,460-139,000)	44,500 (9,980-349,000)	40,850 (10,400-451,000)

Summary of the Pharmacokinetic Parameters of GS-331007

	Median (range)		
	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total
PK Data Analysis Set	11	11	24
PK Parameters			
C_{0h}, ng/mL	534 (249-1,193)	442 (91-1,061)	572 (320-1,317)
C_{max}, ng/mL	1,294 (450-2,411)	1,124 (354-2,215)	1,342 (589-2,665)
C_{av}, ng/mL	787 (341-1,612)	672 (295-1,458)	829 (449-1,777)
AUC_{24h}, ng·h/mL	18,899 (8,191-38,682)	16,129 (7,087-34,995)	19,884 (10,777-42,647)

SAFETY RESULTS: During the treatment phase, the overall incidence of subjects (all treatment arms combined) with at least 1 AE was 97.8%. The most frequently reported AEs (in >25.0% of all subjects) were headache (37.0%) and fatigue (34.8%). The majority of AEs were grade 1 or 2 in severity. There were no grade 4 AEs; grade 3 AEs occurred in 8.7% of subjects. All grade 3 AEs by preferred term were isolated cases. Five (10.9%) subjects experienced at least 1 SAE; none of these events were considered at least possibly related to any of the study drugs. One (2.2%) subject died due to an SAE [redacted]). By preferred term, all SAEs occurred in at most 1 subject. Study drugs (SMV, SOF and RBV) were permanently discontinued due to an AE in 1 (2.2%) subject (ie, the fatal event). RBV only was stopped in 1 subject (due to anemia). No relevant differences in the overall incidence of AEs, AEs with worst grade 3 or 4, deaths or other SAEs, or AEs leading to permanent discontinuation of study drug were noted between the treatment arms.

Adverse Events Summary Table – During the Treatment Phase

	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total
Analysis set: Intent-To-Treat	11	11	24	46
Any AE	11 (100.0%)	11 (100.0%)	23 (95.8%)	45 (97.8%)
Most frequent AEs by preferred term during the treatment phase (ie, in >10.0% of all subjects), n (%)				
Headache	5 (45.5%)	3 (27.3%)	9 (37.5%)	17 (37.0%)
Fatigue	3 (27.3%)	3 (27.3%)	10 (41.7%)	16 (34.8%)
Nausea	3 (27.3%)	3 (27.3%)	5 (20.8%)	11 (23.9%)
Diarrhea	2 (18.2%)	3 (27.3%)	5 (20.8%)	10 (21.7%)
Pruritus	4 (36.4%)	4 (36.4%)	2 (8.3%)	10 (21.7%)
Vomiting	2 (18.2%)	2 (18.2%)	4 (16.7%)	8 (17.4%)
Dyspnea	2 (18.2%)	2 (18.2%)	3 (12.5%)	7 (15.2%)
Decreased appetite	2 (18.2%)	2 (18.2%)	2 (8.3%)	6 (13.0%)
Insomnia	3 (27.3%)	1 (9.1%)	2 (8.3%)	6 (13.0%)
Rash	3 (27.3%)	1 (9.1%)	2 (8.3%)	6 (13.0%)

Adverse Events Summary Table – During the Treatment Phase				
	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total
Constipation	2 (18.2%)	2 (18.2%)	1 (4.2%)	5 (10.9%)
Any SAE	2 (18.2%)	0	3 (12.5%)	5 (10.9%)
Any AE with fatal outcome	1 (9.1%)	0	0	1 (2.2%)
Worst grade 3 or 4 AE	2 (18.2%)	0	2 (8.3%)	4 (8.7%)
AE leading to permanent stop of All Study Medication	1 (9.1%)	0	0	1 (2.2%)
AE leading to permanent stop of SMV+SOF[a]	1 (9.1%)	0	0	1 (2.2%)
AE leading to permanent stop of SMV	1 (9.1%)	0	0	1 (2.2%)
AE leading to permanent stop of SOF	1 (9.1%)	0	0	1 (2.2%)
AE leading to permanent stop of RBV	2 (18.2%)	0	0	2 (4.3%)

[a] Permanent stop of at least one drug.

Some AEs were pre-specified as being of special interest (increased bilirubin) or of clinical interest (rash [any type], pruritus [any type], dyspnea, photosensitivity conditions, anemia, and neutropenia). Pruritus (any type), rash (any type), and dyspnea occurred in 11 (23.9%), 10 (21.7%) and 8 (17.4%) subjects, respectively. The incidence of any other type of event of interest was infrequent. These events were grade 1 or 2 and none were considered serious. One event led to permanent discontinuation of study drug (RBV only for anemia, see above). When comparing the treatment arms, there was a higher (>20.0%) proportion of subjects with pruritus (any type) in the 12 Wks arms and with anemia in the SMV+SOF+RBV 12 Wks arm. The non-randomized subgroup of the SMV+SOF 24 Wks arm experienced no AEs of interest.

No AEs related to lipase or amylase increased and no cases of pancreatitis were reported during the course of the study.

Adverse Events of Special/Clinical Interest During the Treatment Phase				
	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total
Analysis set: Intent-To-Treat	11	11	24	46
Events of special interest				
Increased bilirubin	0	1 (9.1%)	0	1 (2.2%)
Events of clinical interest				
Rash (Any Type)	3 (27.3%)	1 (9.1%)	6 (25.0%)	10 (21.7%)
Pruritus (Any Type)	4 (36.4%)	4 (36.4%)	3 (12.5%)	11 (23.9%)
Photosensitivity conditions	0	1 (9.1%)	3 (12.5%)	4 (8.7%)
Dyspnea	3 (27.3%)	2 (18.2%)	3 (12.5%)	8 (17.4%)
Neutropenia	0	0	0	0
Anemia	3 (27.3%)	0	0	3 (6.5%)

Adverse Events of Special/Clinical Interest During the Treatment Phase				
	SMV+SOF+RBV 12 Wks	SMV+SOF 12 Wks	SMV+SOF 24 Wks Total	Overall Total

Subjects are counted only once for any given event, regardless of the number of times they actually reported the same event.
Adverse events are coded using MedDRA version 17.1.
Increased bilirubin includes MedDRA PT: Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin excretion disorder, Bilirubinuria, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinaemia, Icterus increased index, Jaundice, Jaundice cholestatic, Jaundice extrahepatic obstructive, Jaundice hepatocellular, Ocular icterus, Urine bilirubin increased, Yellow skin.
Rash (Any Type) includes MedDRA HLTs: “Erythemas” , “Papulosquamous conditions” , “Rashes, eruptions and exanthems NEC” , PT: Hutchinson's summer prurigo,
Photosensitivity allergic reaction, Photodermatosis, Photosensitivity reaction, Polymorphic light eruption, Solar dermatitis and “Sunburn”, MedDRA SMQ “Severe cutaneous adverse reaction”: narrow scope and selected terms of the broad scope.
Pruritus includes MedDRA HLT “Pruritus NEC”
Photosensitivity conditions includes MedDRA PT: Hutchinson's summer prurigo, Photosensitivity allergic reaction, Photodermatosis, Photosensitivity reaction, Polymorphic light eruption, Solar dermatitis and Sunburn.
Dyspnea: MedDRA PT Acute respiratory distress syndrome, cardiorespiratory arrest, dyspnea, dyspnea exertional, dyspnea at rest, dyspnea paroxysmal nocturnal, hyperventilation, nocturnal dyspnea, orthopnea, respiratory arrest, respiratory distress, tachypnea.
Neutropenia includes MedDRA PT “Neutropenia“,“Neutrophil count decreased”.
Anemia includes MedDRA PT “Anaemia“,“Haemoglobin decreased”, “Haemolytic anemia”.

In the SMV+SOF+RBV 12 Wks arm, a decrease from baseline in median hemoglobin values was observed during the first 4 weeks of treatment and gradually decreased further until EOT. After the EOT, median hemoglobin values increased to baseline levels. No relevant decrease in hemoglobin was observed in the treatment arms without RBV. Similar observations were made for erythrocytes, mean corpuscular hemoglobin concentration and hematocrit. A transient increase in median bilirubin (direct, indirect, and total) up to Week 8 was observed in the SMV+SOF+RBV 12 Wks arm only. Median direct bilirubin were below the baseline values in all treatment arms after SMV+SOF dosing with or without RBV was complete. There were no other clinically relevant differences between the treatment arms for any of the other laboratory parameters. During the treatment phase, treatment-emergent laboratory abnormalities with grade 4 (worst outcome) were not observed, the incidence of those with grade 3 (worst outcome) were low (ie, <5.0% of all subjects), and no consistent trends or relevant differences between the treatment arms were seen.

There were no clinically relevant changes over time, and no meaningful differences between the treatment arms regarding the values over time or incidence of treatment-emergent abnormalities in vital signs. Adverse events related to abnormalities in vital signs were infrequent. A single case of liver allograft rejection occurred in the SMV+SOF 24 Wks arm during the follow-up phase, which responded to medical treatment and resolved within 6 days after onset.

STUDY LIMITATIONS: The majority of subjects enrolled in the study had less advanced liver disease (METAVIR fibrosis stage F0-F2), which has been associated with higher SVR12 rates in previous studies of SMV and SOF in HCV genotype 1-infected liver transplant recipients. Another limitation of this study is the low total sample size.

CONCLUSION(S): The study demonstrated the efficacy and safety of a treatment regimen consisting of SMV 150 mg and SOF 400 mg once daily with or without RBV for 12 or 24 weeks in post-orthotopic liver transplant subjects with recurrent hepatitis C genotype 1 infection. The primary efficacy endpoint SVR12 was achieved by 81.8%, 100.0%, and 91.7% of subjects in the SMV+SOF+RBV 12 Wks, SMV+SOF 12 Wks and SMV+SOF 24 Wks arms, respectively. One subject enrolled in the SMV+SOF+RBV 12 Wks arm experienced viral relapse (detected at 4 weeks after the end of treatment). The beneficial effect was supported by the secondary virologic efficacy endpoints. Apart from the observed numerical differences in RVR rate, no clear differences between the 12 and 24 Wks arms or

between the treatment arms with or without RBV were observed for the virologic response parameters. PRO data showed no clear changes over time or differences between the treatment arms.

The exposures were similar in all treatment groups for both SMV and GS-331007. Considering variability, both SMV and GS-331007 exposure in this patient population (post liver transplant) were similar to the results obtained in the COSMOS study conducted in non-post transplant patients. Tacrolimus was the most frequently used immunosuppressant; 32.6% of subjects required a dose modification of their immunosuppressant.

Treatment with SMV 150 mg and SOF 400 mg once daily with or without RBV for 12 or 24 weeks was generally safe and well tolerated. One subject enrolled in the SMV+SOF+RBV 12 Wks arm died due to suicide, considered unrelated to study treatment. A single case of liver allograft rejection (which responded to medical treatment) occurred in the SMV+SOF 24 Wks arm during the follow-up phase. The safety profile of each treatment regimen was consistent with previous studies in this at risk population.

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