Supplementary Appendix S1: Detailed inclusion/exclusion criteria

Patients must have met all of the following inclusion criteria to be eligible for participation in this study.

Inclusion Criteria

1) Willing and able to provide written informed consent.
2) Male or female, age ≥ 18 years.
3) Cohorts 1 and 3: HCV RNA ≥ 10_4 IU/mL at Screening; Cohort 2: HCV RNA >lower limit of quantification (LLOQ).
4) Chronic HCV infection (≥ 6 months) documented by medical history or liver biopsy.
5) HCV genotype 4 at screening as determined by the Central Laboratory. Any non-definitive results excluded the patient from study participation. Historical result from prior participation in this study was acceptable, if applicable.
6) Cohort 1 only: HCV treatment naïve, defined as no prior exposure to any interferon (IFN), ribavirin (RBV), or other approved or experimental HCV-specific direct-acting antiviral agent. Cohort 2 only: Patient participated in GS-US-334-0138 and did not achieve SVR12, or, patient participated in Cohort 1 and did not achieve SVR with 8 weeks of LDV/SOF +/-RBV. Patient must not have withdrawn consent or have been terminated early due to investigator discretion. Cohort 3 only: HCV treatment-experienced: Patient had previously received therapy for HCV infection with an IFN-containing regimen, with or without RBV and/or an HCV NS3/NS4A PI, and had a minimum of 12 weeks washout from prior HCV treatment, with a response that could be categorized as:

a) IFN-intolerant: patient had documented intolerance to IFN during prior IFN therapy of up to 12 weeks duration.

b) Non-response: patient did not achieve undetectable HCV RNA levels on treatment.

c) Relapse/Breakthrough: patient achieved undetectable HCV RNA levels during treatment or within 4 weeks after treatment and later showed detectable HCV RNA.

7) For patients with cirrhosis: Results from liver imaging, done within 6 months of Baseline/Day 1, that excluded hepatocellular carcinoma (HCC).

For Cohorts 1 and 3, up to approximately 25% of patients may have compensated cirrhosis. Patients in Cohort 2 may have compensated cirrhosis.

Cirrhosis is defined as any one of the following:

a) Liver biopsy showing cirrhosis.

b) Fibroscan® showing cirrhosis or results >12.5kPa.

c) FibroTest® score of >0.75 AND an AST:platelet ratio index (APRI) of >2 performed during Screening.

Absence of cirrhosis is defined as any one of the following:

d) Liver biopsy within 2 years of Screening showing absence of cirrhosis.

e) Fibroscan with a result of ≤ 12.5 kPa ≤ 6 months of Baseline/Day 1.

f) FibroTest score of ≤ 0.48 AND APRI of ≤ 1 performed during Screening.

In the absence of a definitive diagnosis of the presence or absence of cirrhosis by the above criteria, a liver biopsy is required. Liver biopsy results supersede the results obtained by Fibroscan or Fibrotest and APRI.

8) Body mass index (BMI) ≥18 kg/m^2.

9) Screening electrocardiogram (ECG) without clinically significant abnormalities

10) Patients must have the following laboratory parameters at screening:

a) Alanine aminotransferase (ALT) ≤10 × upper limit of normal (ULN)

b) Aspartate aminotransferase (AST) ≤10 × ULN

c) Hemoglobin ≥12 g/dL for male, ≥11 g/dL for female patients

d) Platelets ≥ 50,000/mm^3.

e) International normalized ratio (INR) ≤1.5 × ULN unless patient has known haemophilia or is stable on an anticoagulant regimen affecting INR.

f) Albumin ≥3g/dL.

g) Direct bilirubin ≤1.5 × ULN

h) HbA_{1c} ≤10.0%

i) Creatinine clearance (CLcr) ≥60 mL/min, as calculated by the Cockcroft-Gault equation.

Patients who received prior treatment in GS-US-334-0138 or Cohort 1 of this study and who currently do not fulfil all of the above requirements may be enrolled in Cohort 2 at the request of the Investigator and with the approval of the Medical Monitor or Study Director.

11) Patient had not been treated with any investigational drug or device within 30 days of the screening visit.

12) A female patient was eligible to enter the study if it was confirmed that she was:

a) Not pregnant or nursing.

b) Of non-childbearing potential (ie, women who have had a hysterectomy, both ovaries removed or medically documented ovarian failure, or are postmenopausal women >50 years of age with cessation [for ≥12 months] of previously occurring menses).

c) Of childbearing potential (ie, women who have not had a hysterectomy, both ovaries removed, or no medically documented ovarian failure). Women ≤50 years of age with amenorrhea were considered to be of childbearing potential. These women must have had a negative serum pregnancy test at screening and a negative urine pregnancy test on the Baseline/Day 1 visit prior to randomization. They must also have agreed to one of the following from 3 weeks prior to Baseline/Day 1 until 6 months after last dose of RBV or 30 days after last dose of LDV/SOF (if not exposed to RBV):

i) Complete abstinence from intercourse. Periodic abstinence from intercourse (eg, calendar, ovulation, symptothermal, post-ovulation methods) was not permitted.

Or

ii) Consistent and correct use of 1 of the following methods of birth control listed below in addition to a male partner who correctly used a condom from the date of screening until 3 weeks prior to Baseline/Day 1 until 6 months after last dose of RBV or 30 days after last dose of LDV/SOF (if not exposed to RBV):

- intrauterine device (IUD) with a failure rate of < 1% per year
- female barrier method: cervical cap or diaphragm with spermicidal agent
- tubal sterilization
- vasectomy in male partner
- implants of levonorgestrel
- injectable progesterone
- oral contraceptives (either combined or progesterone only)
- contraceptive vaginal ring
- transdermal contraceptive patch

13) All male study participants must have agreed to consistently and correctly use a condom from Baseline until 90 days after the last dose of LDV/SOF or 7 months after the last dose of RBV. If their female partner was of childbearing potential (as defined above), their female partner must have used 1 of the methods of birth control listed above from the date of Screening until 90 days after the last dose of LDV/SOF or 7 months after last dose of RBV.
14) Male patients must have agreed to refrain from sperm donation for at least 7 months after the last dose of RBV or 90 days after their last dose of study drug if not taking RBV.
15) Patient must have been of generally good health as determined by the Investigator.
16) Patient must have been able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

Exclusion Criteria

Patients with any of the following were not eligible for participation in the study:
1) Current or prior history of any of the following:

a) Clinical hepatic decompensation (ie, ascites, encephalopathy or variceal hemorrhage)

b) Clinically-significant illness (other than HCV) or any other major medical disorder that may have interfered with patient treatment, assessment or compliance with the protocol, or, currently under evaluation for a potentially clinically-significant illness (other than HCV).

c) Gastrointestinal disorder or postoperative condition that could have interfered with the absorption of the study drug.

d) Solid organ transplantation.

e) Significant pulmonary disease, significant cardiac disease or porphyria

f) Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Patients with psychiatric illness (without the prior mentioned conditions) that was well-controlled on a stable treatment regimen for at least 6 months prior to baseline/Day 1 or that had not required medication in the last 12 months were eligible.

g) Malignancy within the 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (eg, basal cell skin cancer). Patients under evaluation for possible malignancy were not eligible.

h) Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.

i) Significant drug allergy (such as anaphylaxis or hepatotoxicity)

2) Chronic liver disease of a non-HCV etiology (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis).

3) Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).

4) Contraindications to RBV therapy, including significant history of clinically significant hemoglobinopathy (eg, sickle cell disease, thalassemia).

5) Use of any prohibited concomitant medications.

6) Pregnant or nursing female or male with pregnant female partner.

7) In the judgment of the investigatory, any clinically-relevant drug or alcohol abuse within 12 months of screening that may have interfered with patient treatment, assessment of compliance with the protocol.

8) Known hypersensitivity to RBV, SOF, LDV or formulation excipients.

9) For treatment-experienced patients: prior exposure to a NS5a inhibitor, NS5b nucleotide inhibitor, or NS5b non-nucleotide inhibitor targeting HCV.