THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mizokami M, Yokosuka O, Takehara T, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis* 2015; published online April 9. http://dx.doi.org/10.1016/S1473-3099(15)70099-X.

Supplement to:

Masashi Mizokami, Osamu Yokosuka, Tetsuo Takehara, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naïve and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomized, phase 3 trial

Table of Contents

Supplementary Table 1. Reasons for Screen Failure

	Total
Screened Subjects	421
Subjects Not Randomized	80/421 (19.0%)
Screen Failure Subjects Who Did Not Meet Eligibility Criteria	75/80 (93.8%)
Inclusion Criterion 11: Labs within specified ranges	54/75 (72.0%)
Inclusion Criterion 04: HCV RNA >= 10^5 IU/mL	13/75 (17.3%)
Inclusion Criterion 09: Liver imaging for HCC in patients with cirrhosis	3/75 (4.0%)
Exclusion Criterion 01: Clinically-significant illness other than HCV	2/75 (2.7%)
Inclusion Criterion 06: HCV genotype 1a or 1b at Screening as determined by the Central Laboratory	2/75 (2.7%)
Inclusion Criterion 08: Cirrhosis determination	2/75 (2.7%)
Inclusion Criterion 01: Willing and able to provide written informed consent	1/75 (1.3%)
Inclusion Criterion 03: Body weight >= 40 kg	1/75 (1.3%)
Inclusion Criterion 05: HCV Treatment Naive or Experienced	1/75 (1.3%)
Inclusion Criterion 14: Good health except HCV	1/75 (1.3%)
Subjects Not Randomized Who Met Eligibility Criteria	5/80 (6.3%)
Reasons for Subjects Not Randomized Who Met Eligibility Criteria	
Withdrew Consent	3/5 (60.0%)
Adverse Event	1/5 (20.0%)
Other	1/5 (20.0%)

Calculation of the Adjusted Historical Control Rate

The adjusted historical SVR rate was based on the expected historical SVR rate of 73% (92/126; Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naïve patients chronically infected with HCV of genotype 1 in Japan. *J Hepatol* 2012; **56**:78-84) for non-cirrhotic, treatment-naïve, Japanese subjects with GT-1 chronic hepatitis C taking Peg-IFNα+RBV+TVR. We additionally allowed for a 10% discount due to the expected improved safety profile and shorter treatment duration, resulting in a null historical SVR rate for this study of 63%.

It is important to note that this historical control rate is a conservative estimate based on available literature. A feasibility survey conducted to support this study indicated a low proportion of patients are eligible for and willing to participate in a clinical study utilizing Peg-IFNα +RBV±TVR as a control arm. In the absence of other treatment options the real-life SVR rate in these patients would be negligible.

A Hochberg procedure will be used to ensure control of the family-wise type I error rate at the 0.05 significance level.

Supplementary Table 2. Adherence to Study Drug

	Treatment Naive LDV/SOF 12 Weeks (N=83)	Treatment-Naive LDV/SOF+RBV 12 Weeks (N=83)		Treatment Experienced LDV/SOF 12 Weeks (N=88)	Treatment-Experienced LDV/SOF+RBV 12 Weeks (N=87)	
	LDV/SOF	LDV/SOF	RBV	LDV/SOF	LDV/SOF	RBV
Study Drug Adherence Rate (%)						
N	83	83	83	88	87	87
Mean (SD)	99.7 (1.04)	98.5 (10.55)	96.0 (14.84)	99.8 (0.90)	99.9 (0.41)	96.0 (11.37)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Q1, Q3	100.0, 100.0	100.0, 100.0	99.4, 100.0	100.0, 100.0	100.0, 100.0	99.4, 100.0
Min, Max	92.9, 100.0	7.1, 100.0	7.1, 100.0	92.9, 100.0	97.6, 100.0	34.5, 100.0
Study Drug Adherence Rate						
< 80%	0	2 (2.4%)	4 (4.8%)	0	0	8 (9.2%)
>= 80 to < 90%	0	0	4 (4.8%)	0	0	3 (3.4%)
>= 90%	83 (100.0%)	81 (97.6%)	75 (90.4%)	88 (100.0%)	87 (100.0%)	76 (87.4%)
At Least 80% Adherence to Each Drug	83 (100.0%)	79 (95.2%)		88 (100.0%)	79 (90.8%)	

Supplementary Table 3. SVR12 by Subgroup

	Treatment-Naive		Treatment-Experienced	
	LDV/SOF 12 Weeks (N=83)	LDV/SOF+RBV 12 Weeks (N=83)	LDV/SOF 12 Weeks (N=88)	LDV/SOF+RBV 12 Weeks (N=87)
Overall SVR12	83/83 (100.0%)	80/83 (96.4%)	88/88 (100.0%)	87/87 (100.0%)
95% CI	95.7% to 100.0%	89.8% to 99.2%	95.9% to 100.0%	95.8% to 100.0%
Age at Baseline (Years)				
< 65	60/60 (100.0%)	53/55 (96.4%)	51/51 (100.0%)	63/63 (100.0%)
95% CI	94.0% to 100.0%	87.5% to 99.6%	93.0% to 100.0%	94.3% to 100.0%
>= 65	23/23 (100.0%)	27/28 (96.4%)	37/37 (100.0%)	24/24 (100.0%)
95% CI	85.2% to 100.0%	81.7% to 99.9%	90.5% to 100.0%	85.8% to 100.0%
Sex at Birth				
Male	33/33 (100.0%)	33/34 (97.1%)	36/36 (100.0%)	39/39 (100.0%)
95% CI	89.4% to 100.0%	84.7% to 99.9%	90.3% to 100.0%	91.0% to 100.0%
Female	50/50 (100.0%)	47/49 (95.9%)	52/52 (100.0%)	48/48 (100.0%)
95% CI	92.9% to 100.0%	86.0% to 99.5%	93.2% to 100.0%	92.6% to 100.0%
Baseline Body Mass Index				
< 25 kg/m2	70/70 (100.0%)	65/67 (97.0%)	58/58 (100.0%)	51/51 (100.0%)
95% CI	94.9% to 100.0%	89.6% to 99.6%	93.8% to 100.0%	93.0% to 100.0%
>= 25 kg/m2	13/13 (100.0%)	15/16 (93.8%)	30/30 (100.0%)	36/36 (100.0%)
95% CI	75.3% to 100.0%	69.8% to 99.8%	88.4% to 100.0%	90.3% to 100.0%
Cirrhosis				
No	70/70 (100.0%)	69/71 (97.2%)	60/60 (100.0%)	64/64 (100.0%)
95% CI	94.9% to 100.0%	90.2% to 99.7%	94.0% to 100.0%	94.4% to 100.0%
Yes	13/13 (100.0%)	11/12 (91.7%)	28/28 (100.0%)	23/23 (100.0%)
95% CI	75.3% to 100.0%	61.5% to 99.8%	87.7% to 100.0%	85.2% to 100.0%
Response to Prior HCV Treatment				
Non-Responder	N/A	N/A	29/29 (100.0%)	28/28 (100.0%)
95% CI			88.1% to 100.0%	87.7% to 100.0%
Relapse/Breakthrough	N/A	N/A	44/44 (100.0%)	44/44 (100.0%)
95% CI			92.0% to 100.0%	92.0% to 100.0%
IFN Intolerant	N/A	N/A	15/15 (100.0%)	15/15 (100.0%)
95% CI			78.2% to 100.0%	78.2% to 100.0%

Interferon Eligibility Status				
Eligible	79/79 (100.0%)	71/73 (97.3%)	N/A	N/A
95% CI	95.4% to 100.0%	90.5% to 99.7%		
Ineligible	4/4 (100.0%)	9/10 (90.0%)	N/A	N/A
95% CI	39.8% to 100.0%	55.5% to 99.7%		
Baseline HCV RNA				
< 800,000 IU/mL	6/6 (100.0%)	8/8 (100.0%)	10/10 (100.0%)	13/13 (100.0%)
95% CI	54.1% to 100.0%	63.1% to 100.0%	69.2% to 100.0%	75.3% to 100.0%
>= 800,000 IU/mL	77/77 (100.0%)	72/75 (96.0%)	78/78 (100.0%)	74/74 (100.0%)
95% CI	95.3% to 100.0%	88.8% to 99.2%	95.4% to 100.0%	95.1% to 100.0%
Baseline ALT Category				
<= 1.5 x ULN	62/62 (100.0%)	49/50 (98.0%)	61/61 (100.0%)	48/48 (100.0%)
95% CI	94.2% to 100.0%	89.4% to 99.9%	94.1% to 100.0%	92.6% to 100.0%
> 1.5 x ULN	21/21 (100.0%)	31/33 (93.9%)	27/27 (100.0%)	39/39 (100.0%)
95% CI	83.9% to 100.0%	79.8% to 99.3%	87.2% to 100.0%	91.0% to 100.0%
IL28B				
CC	53/53 (100.0%)	45/46 (97.8%)	33/33 (100.0%)	33/33 (100.0%)
95% CI	93.3% to 100.0%	88.5% to 99.9%	89.4% to 100.0%	89.4% to 100.0%
non-CC	30/30 (100.0%)	35/37 (94.6%)	55/55 (100.0%)	54/54 (100.0%)
95% CI	88.4% to 100.0%	81.8% to 99.3%	93.5% to 100.0%	93.4% to 100.0%

Supplementary Table 4. Outcome of Serious Adverse Events

Subject ID	Event PT Name	Age (years)	Treatment Arm	Treatment Emergent	Causality as Reported	Event Outcome
8314-86263	Cardiac arrest	67	LDV/SOF+RBV	Yes	Related	Fatal
8322-86046	Acute myocardial infarction	71	LDV/SOF+RBV	Yes	Related	Resolved
8317-86021	Oesophageal varices haemorrhage	67	LDV/SOF	Yes	Not Related	Resolved
8714-86241	Wrist fracture	42	LDV/SOF	Yes	Not Related	Unknown
8356-86031	Hepatocellular carcinoma	70	LDV/SOF	Yes	Not Related	Resolved
8314-86273	Cardiac failure congestive *	77	LDV/SOF+RBV	No	Related	Continuing

* Nontreatment emergent SAE considered related to study treatment; reported > 30 days after the last dose of study treatment

Supplementary Table 5. Adverse Events leading to Permanent Discontinuation of Any Study Drug

	LDV/SOF 12 Weeks			LDV/SOF+RBV 12 Weeks		
	<65 Years (N=111)	**≥65 Years (N=60)**	**Total (N=171)**	**<65 Years (N=118)**	**≥65 Years (N=52)**	**Total (N=170)**
Number (%) of Subjects Experiencing any AE leading to permanent discontinuation from any study drug	0	0	0	2 (1.7)	1 (1.9)	3 (1.8)
Number (%) of Subjects Experiencing any AE leading to permanent discontinuation from any study drug by Preferred Term						
Cardiac arrest	0	0	0	0	1 (1.9)	1 (0.6)
Drug eruption	0	0	0	1 (0.8)	0	1 (0.6)
Morbilliform rash	0	0	0	1 (0.8)	0	1 (0.6)

Supplementary Table 6. Adverse Events: Summary by Cirrhosis Status

	LDV/SOF 12 Weeks		LDV/SOF+RBV 12 Weeks	
	No Cirrhosis (N=130)	Cirrhosis (N=41)	No Cirrhosis (N=135)	Cirrhosis (N=35)
Number (%) of Subjects Experiencing Any				
Treatment-Emergent Adverse Event	87 (66.9%)	25 (61.0%)	100 (74.1%)	28 (80.0%)
Grade 3 or 4 Treatment-Emergent Adverse Event	2 (1.5%)	2 (4.9%)	1 (0.7%)	1 (2.9%)
Grade 2, 3, or 4 Treatment-Emergent Adverse Event	8 (6.2%)	4 (9.8%)	24 (17.8%)	3 (8.6%)
Treatment-Emergent Treatment-Related Adverse Event	26 (20.0%)	11 (26.8%)	64 (47.4%)	20 (57.1%)
Grade 3 or 4 Treatment-Emergent Treatment-Related Adverse Event	0	1 (2.4%)	1 (0.7%)	1 (2.9%)
Grade 2, 3, or 4 Treatment-Emergent Treatment-Related Adverse Event	0	1 (2.4%)	14 (10.4%)	3 (8.6%)
Treatment-Emergent Serious Adverse Event	2 (1.5%)	1 (2.4%)	1 (0.7%)	1 (2.9%)
Treatment-Emergent Treatment-Related Serious Adverse Event	0	0	1 (0.7%)	1 (2.9%)
Adverse Event Leading to Permanent Discontinuation from Any Study Drug	0	0	2 (1.5%)	1 (2.9%)
Adverse Event Leading to Permanent Discontinuation from LDV/SOF	0	0	1 (0.7%)	1 (2.9%)
Adverse Event Leading to Modification or Interruption of Any Study Drug	3 (2.3%)	0	13 (9.6%)	7 (20.0%)
Adverse Event Leading to Interruption of LDV/SOF	3 (2.3%)	0	1 (0.7%)	0
Treatment-Emergent Death	0	0	0	1 (2.9%)

Supplementary Table 7. Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities

	LDV/SOF 12 Weeks (N=171)	LDV/SOF+RBV 12 Weeks (N=170)
Maximum Postdose Toxicity Grade	171	170
Grade 3	12 (7.0%)	14 (8.2%)
Grade 4	0	0
Hematology		
Hemoglobin	171	170
Grade 3	2 (1.2%)	5 (2.9%)
Grade 4	0	0
Lymphocytes	171	170
Grade 3	3 (1.8%)	1 (0.6%)
Grade 4	0	0
Neutrophils	171	170
Grade 3	2 (1.2%)	0
Grade 4	0	0
Platelets	171	170
Grade 3	1 (0.6%)	0
Grade 4	0	0
WBC	171	170
Grade 3	0	0
Grade 4	0	0

	LDV/SOF 12 Weeks (N=171)	LDV/SOF+RBV 12 Weeks (N=170)
Coagulation		
APTT	171	169
Grade 3	0	0
Grade 4	0	0
INR	171	169
Grade 3	0	0
Grade 4	0	0
Chemistry		
ALT	171	170
Grade 3	0	0
Grade 4	0	0
AST	171	170
Grade 3	1 (0.6%)	1 (0.6%)
Grade 4	0	0
Albumin	171	170
Grade 3	0	0
Grade 4	0	0

Supplementary Table 7. Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities (cont'd)

	LDV/SOF 12 Weeks (N=171)	LDV/SOF+RBV 12 Weeks (N=170)
Chemistry (cont)		
Alkaline Phosphatase	171	170
Grade 3	0	0
Grade 4	0	0
Creatinine	171	170
Grade 3	0	0
Grade 4	0	0
Lipase	171	170
Grade 3	1 (0.6%)	1 (0.6%)
Grade 4	0	0
Serum Glucose (Hyperglycemia)	171	170
Grade 3	1 (0.6%)	3 (1.8%)
Grade 4	0	0
Serum Glucose (Hypoglycemia)	171	170
Grade 3	0	0
Grade 4	0	0
Serum Potassium (Hyperkalemia)	171	170
Grade 3	0	0
Grade 4	0	0

Supplementary Table 7. Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities (cont'd)

	LDV/SOF 12 Weeks (N=171)	LDV/SOF+RBV 12 Weeks (N=170)
Chemistry (cont)		
Serum Potassium (Hypokalemia)	171	170
Grade 3	0	0
Grade 4	0	0
Serum Sodium (Hypernatremia)	171	170
Grade 3	0	0
Grade 4	0	0
Serum Sodium (Hyponatremia)	171	170
Grade 3	0	0
Grade 4	0	0
Total Bilirubin	171	170
Grade 3	0	0
Grade 4	0	0
Urinalysis		
Hematuria (RBC counts)	171	170
Grade 3	0	2 (1.2%)
Grade 4	0	0
Urine Glucose (Glycosuria)	171	170
Grade 3	1 (0.6%)	2 (1.2%)
Grade 4	0	0
Urinalysis (cont)		
Urine Protein (Proteinuria)	171	170
Grade 3	1 (0.6%)	0
Grade 4	0	0

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Randomized, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Treatment-Naïve and Treatment-Experienced Japanese Subjects with Chronic Genotype 1 HCV Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-337-0113
Gilead Sciences Study Director:	Name: Steven Knox Telephone: (650) 522 5001 Fax: (650) 524 9430 E-mail: steven.knox@gilead.com
Protocol Version/Date:	Original: 17 July 2013 Amendment 1: 22 August 2013

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Phase 3b, Randomized, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Treatment-Naïve and Treatment-Experienced Japanese Subjects with Chronic Genotype 1 HCV Infection
Study Centers Planned:	Approximately 20 sites in Japan
Number of Subjects Planned:	Approximately 300 subjects
Target Population:	Treatment-naïve and treatment-experienced, chronic genotype 1 HCV infected adults.
Duration of Treatment:	12 weeks
Objectives:	The primary objectives of this study are: • To determine the antiviral efficacy of combination treatment with sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) ± ribavirin (RBV) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks post treatment) • To evaluate the safety and tolerability of SOF/LDV FDC ± RBV as assessed by review of the accumulated safety data The secondary objectives of this study are: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation • To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objectives of this study are:

- To identify or validate genetic markers that may be predictive of virologic response to therapy and/or tolerability of therapy through genetic discovery research (e.g., pharmacogenomics), in subjects who provide their separate and specific consent
- To assess the effect of treatment with SOF/LDV FDC ± RBV on Health-Related Quality of Life (HRQoL)

Study Design:

Multicenter, open-label study in treatment-naïve and treatment-experienced adults with chronic genotype 1 HCV infection. Approximately 300 subjects will be enrolled.

Approximately 150 treatment-naïve subjects will be randomized (1:1) to either:

1) Group 1 (n~75):

   SOF 400 mg/LDV 90 mg FDC once daily for 12 weeks

2) Group 2 (n~75):

   SOF 400 mg/LDV 90 mg FDC once daily + RBV (weight-based dosing) for 12 weeks

Randomization into Group 1 and 2 will be stratified by the presence or absence of cirrhosis at Screening. Up to 40% of the treatment-naïve subjects enrolled may have evidence of Child's Pugh-A compensated cirrhosis at Screening.

Treatment-naïve is defined as having never received treatment for HCV with any interferon (IFN), ribavirin (RBV), or other approved or experimental HCV-specific direct acting antivirals.

Approximately 150 treatment-experienced subjects will be randomized (1:1) to either:

3) Group 3 (n~75):

   SOF 400 mg/LDV 90 mg FDC once daily for 12 weeks

4) Group 4 (n~75):

   SOF 400 mg/LDV 90 mg FDC once daily + RBV (weight-based dosing) for 12 weeks

Randomization into Group 3 and 4 will be stratified by the presence or absence of cirrhosis at Screening and by treatment-experienced category (i.e., Relapser/Breakthrough, Non-responder, or IFN-Intolerant). Up to 40% of the treatment-experienced subjects enrolled may have evidence of Child's Pugh-A compensated cirrhosis at Screening.

Of the 150 treatment-experienced subjects, it is estimated that ~90 will be Relapser/Breakthroughs, ~40 Non-Responders, and ~20 IFN-Intolerant.

Optional Substudies:	**Pharmacokinetic (PK) Substudy** All subjects, with a target of ~15 treatment-naïve and ~15 treatment-experienced subjects will be eligible to participate in an optional PK substudy if consent is obtained. An intensive serial PK sample collection (i.e., samples obtained over 24 hours post-dose) will be performed at either the Week 2 or Week 4 on-treatment visit to determine the steady-state pharmacokinetics of SOF (and its metabolites GS-566500 and GS-331007), LDV, and RBV (if appropriate). **Pharmacogenomics (PG) Substudy** All subjects will be eligible to participate in an optional PG substudy if consent is obtained. A blood sample should be drawn at the Baseline/Day 1 visit. If not obtained at Baseline/Day 1 visit, the sample may be drawn at any time during the study.
Diagnosis and Main Eligibility Criteria:	Chronic genotype 1, HCV infected, male and non-pregnant/non-lactating female subjects, aged 20 years and older, treatment-naïve or treatment-experienced, of whom up to 40% may have Child's Pugh-A compensated cirrhosis, may be eligible for the study. Reference Sections 4.2 and 4.3 for detailed Inclusion and Exclusion criteria.
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotyping. Study visits will occur at Screening, Baseline/Day 1, and on-treatment at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12. Following the last dose of study medication, all subjects will complete 4-Week, 12-Week and 24-Week Post-Treatment Visits. Screening assessments include physical examination, height, weight, vital signs, 12-lead ECG, medical history, adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, coagulation, urinalysis), HCV RNA, serology of Human Immunodeficiency Virus (HIV), HCV, and Hepatitis B virus (HBV), hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis, liver imaging to exclude Hepatocellular Carcinoma (HCC), serum β-hCG (females of child bearing potential only), thyroid stimulating hormone (TSH), HCV genotyping and IL28B genotyping. On-treatment assessments include weight, adverse events (AEs), concomitant medications, review of study drug adherence, physical examinations, vital signs, safety laboratory tests, HCV RNA, pharmacokinetic samples, and urine pregnancy tests (females of child bearing potential only).

	Single 12-lead ECGs will be collected at Screening, Baseline/Day 1 (prior to study drug administration) and on-treatment visits at the end of Weeks 1 and Week 12. Pregnancy prevention counseling will be addressed with the subject (as appropriate) at Baseline/Day 1, on-treatment at the end of Week 12, and post-treatment Week 4, 12, and 24 visits. Post-treatment assessments include physical examination, weight, AEs, concomitant medications, vital signs, safety laboratory tests, HCV RNA, and urine pregnancy tests (females of child bearing potential only). For subjects who provide their additional and specific consent, a blood sample will be collected at the Baseline/Day 1 visit for human pharmacogenomic testing (this sample may be drawn after Baseline/Day 1, if necessary). A Health Related Quality of Life (HRQoL) Survey will be conducted at Baseline/Day 1, on-treatment Weeks 4, 8, and 12, Early Termination (if appropriate), and Post-Treatment Week 4 and 12. Samples for viral RNA sequencing / phenotyping will be collected at Baseline/Day 1 and every visit thereafter. Single PK samples will be collected during on-treatment visits for PK analysis of study drug(s). Intensive PK sampling (i.e., optional PK substudy) may also be performed on-treatment at either Week 2 or Week 4. Two Archive plasma samples will be collected, one at Baseline/Day 1 and the second at the end of treatment visit for potential future testing. Subjects will have the opportunity to opt out of Archive sample collection.
Test Product, Dose, and Mode of Administration	1) SOF/LDV fixed dose combination tablet containing 400 mg SOF plus 90 mg LDV. Subjects will take 1 tablet orally daily in the morning. 2) Ribavirin 200-mg tablet. Subjects assigned to SOF/LDV FDC+RBV will take weight-based RBV every day in a divided daily dose in accordance with the approved product labeling. The morning dose of RBV will be taken with the SOF/LDV FDC tablet and with food. The evening dose of RBV will be taken alone with food.
Criteria for Evaluation:	
Safety:	AEs will be collected and clinical laboratory analyses performed throughout the study (through the 4-Week Post-Treatment Visit).
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® TaqMan® HCV Test, v2.0 for use with the High Pure System.

PK:	A single PK blood sample will be collected at each on-treatment visit for all subjects. An optional PK substudy may also be performed at either the Week 2 or Week 4 on-treatment visit in a subset of subjects (target ~15 treatment-naïve and ~15 treatment-experienced subjects). Serial PK samples will be collected over 24 hours post-dose. The PK of SOF (and its metabolites GS-566500 and GS-331007), LDV, and RBV (if appropriate) will be assessed.
Statistical Methods:	The primary efficacy endpoint is SVR12 in all randomized and treated subjects with chronic genotype-1 HCV infection.

A) Treatment-Naïve Subjects:

Approximately 150 treatment-naïve subjects will be randomized in this study with 75 in each of Group 1 and Group 2. In each group, approximately 60% (i.e., n=45) will be non-cirrhotic, and up to 40% (i.e., n=30) may have Child's Pugh-A compensated cirrhosis.

Non-Cirrhotic Subjects: The SVR12 rate in Group 1 and 2 will be compared to the adjusted historical null SVR rate of 63% using a two-sided exact one-sample binomial test. A Hochberg procedure will be used to ensure control of the family-wise type I error rate at the 0.05 level.

A sample size of 45 non-cirrhotic subjects in Group 1 and 2 will provide at least 90% power to detect a 23% improvement in SVR12 rate from the adjusted historical control rate of 63% using a 2-sided exact one-sample binomial test at a significance level of 0.025, based on a Bonferroni correction.

The adjusted historical null SVR rate is based on the expected historical SVR rate of 73% (92/126; {22064}) for non-cirrhotic, treatment-naïve, Japanese subjects with GT-1 chronic hepatitis C receiving Peg-IFNα+RBV+Telaprevir (TVR), and we allow a 10% discount due to the expected improved safety profile and shorter treatment duration which results in a null historical SVR rate for this study of 63%.

It is important to note that this historical control rate is a conservative estimate based on available literature. A feasibility survey conducted to support this study indicated a low proportion (i.e., <10%) of patients are eligible for and willing to participate in a clinical study utilizing Peg-IFNα +RBV±TVR as a control arm. In the absence of other treatment options the real-life SVR rate in these patients would be negligible.

Cirrhotic Subjects: No statistical hypothesis testing will be performed in treatment-naïve subjects with cirrhosis. A point-estimate with a two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate.

B) Treatment-Experienced Subjects:

Approximately 150 treatment-experienced subjects will be randomized in this study with 75 in each of Group 3 and Group 4.

No statistical hypothesis testing will be performed in treatment-experienced subjects including subgroups (i.e., cirrhotic or non-cirrhotic; Relapse/breakthrough, Non-responder, or IFN intolerant). A point-estimate with two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate in Group 3 and 4 and each of the subgroups.

With a sample size of 75 subjects in each of Groups 3 and 4, a two-sided 95% exact confidence interval will extend at most 24% in length.

Secondary efficacy endpoints include the proportion of subjects with SVR4, SVR24, viral breakthrough, relapse, and HCV RNA change from baseline.

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	twice a day
BLQ	below the lower limit of quantification
BMI	body mass index
BT	breakthrough
BW	body weight
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CRF	case report form(s)
CRO	Contract (or clinical) research organization
DAA	Direct acting antiviral
DCV	Daclatasvir
dL	Deciliter
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
ESA	Erythropoiesis stimulating agent
eSAE	electronic Serious Adverse Event (system)
E_{max}	maximal effect
ESLD	End Stage Liver Disease
ET	early termination
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	Fixed Dose Combination
FEV_1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

GCSF	Granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GMRs	geometric-least squares means ratios
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV Ab	Hepatitis C virus antibody
HCV	Hepatitis C virus
HDPE	high-density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
HRQoL	Health Related Quality of Life (Survey)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL28B	IL28B gene
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IU	International Units
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web Response System
JSH	Japan Society of Hepatology
kg	Kilogram
L	Liter
LDV	Ledipasvir
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
LTFU	Lost to follow up
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

MHLW	Ministry Of Health Labor and Welfare [Japan]
mL	Milliliter
mmHg	millimeters mercury
NS (3/4A/5A/5B)	Non-structural Protein
PBMC	peripheral blood mononuclear cell(s)
Peg-IFNα	pegylated interferon alpha
PG	Pharmacogenomic
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency [Japan]
PT	Preferred Term
QA	Quality Assurance
QD	once daily (use only in tables)
QTcF	QT interval corrected using Fridericia' formula
RBC	Red blood cell
RBV	Ribavirin
RNA	ribonucleic acid
RVR	rapid virologic response
SADR	Serious adverse drug reaction
SAE	serious adverse event
SD	Standard deviation
SF-36	(HRQoL) Short-Form-36
SOC	Standard of Care or System Organ Class
SOF	Sofosbuvir
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
TE	Treatment-Experienced
TGV	Tegobuvir
TN	Treatment-Naïve
TND	Target not detected
TSH	Thyroid stimulating hormone
t½	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
ULN	upper limit of the normal range
US	United States
WBC	white blood cell

1. INTRODUCTION

1.1. Background

1.1.1. HCV Infection

Infection with the hepatitis C virus (HCV) is a serious, progressive, and often life-threatening disease affecting approximately 180 million adults worldwide {13693}. The infection, if untreated, can result in progressive liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and end stage liver disease (ESLD). Transmission of HCV infection is parenteral with the majority of infections occurring through administration of contaminated blood products, unsafe medical procedures, intravenous drug use or sexual transmission {8076}. The hepatitis C virus is classified into six major genotypes (GT), i.e., 1-6, with further division to a subtype level (e.g., a, b, c) {21479}. Virologic response rates to currently available therapies vary according to host IL28B genotype, baseline levels of HCV RNA and HCV genotype. The distribution of HCV genotypes and subtypes varies according to geographic region with the most common HCV genotypes in the United States and Europe being GT-1, GT-2 and GT-3. In Japan approximately 85% of infections are associated GT-1b and 15% with GT-2 {19682}, {19705}. Genotypes 4, 5 and 6 are most prevalent in the Middle East, South Africa and Southeast Asia respectively {22110}.

Following acute infection approximately 15-20% of patients are able to clear the virus without intervention, however around 80% of patients go on to establish chronic hepatitis C {8076}. Treatment of chronic infection is currently based upon weekly subcutaneous administration of pegylated interferon (Peg-IFNα) with orally administered ribavirin (RBV) for 24 to 48 weeks dependent upon genotype and virologic response. This treatment regimen affords sustained virologic response rates (SVR) on the order of 42-46% in treatment-naïve patients with GT-1 and 76-82% in patients with GT-2/3 infection {23342}, {23351}. Recently, first generation protease inhibitors (PI) (i.e., telaprevir (TVR) and boceprevir (BOC)) have been approved in certain countries for use in patients with GT-1 infection when combined with Peg-IFNα+RBV. The Peg-IFNα +RBV+PI regimens have incrementally improved SVR rates in GT-1 treatment-naïve patients to approximately 70% however they are not approved for use in GT-2 infection and are associated with drug interactions and significant safety and tolerability concerns {17996}, {17492}. Patients with GT-1 infection failing to respond to Peg-IFNα+RBV+PI have no current treatment options with spontaneous clearance of HCV negligible in these patients.

1.1.2. HCV Infection in Japan

With published HCV prevalence estimates from blood-donor and subgroup-based studies on the order of 1-1.9% in Japan {19682}, it is estimated that there are approximately 1.3-2.4 million people chronically infected with HCV. Approximately 85% of patients are infected with HCV GT-1b and around 15% with GT-2 {22073}, {22061}. Molecular clock analyses indicate that GT-1b, the prevalent HCV genotype in Japan, started to spread within

the 1930s and was further established around World War II through injection drug use, unsafe medical practices, contaminated syringes and blood transfusions {22070}, {22061}. The highest prevalence rates of HCV antibodies in first-time blood donor studies have been reported in the 50-59 year (1.8%) and 60-69 year (3.4%) age groups {22074}. Consequently, the majority of Japanese patients with chronic hepatitis C are elderly (average age ~ 70 years) are more likely to be treatment-experienced and have progressive liver disease. Comorbid conditions (e.g., diabetes and cardiovascular disease) are common in this population and pose challenges to the use of Peg-IFNα+RBV therapy. It is estimated that approximately 15-30% of patients with chronic hepatitis C will go on to develop complications, including liver cirrhosis, HCC and ESLD; {22077}. In Japan, HCC is one of the most common causes of cancer death and represents a significant health burden particularly in an aging population {19682}. Each year it is estimated that more than 30,000 patients die from HCC, with ~70% of these deaths (i.e., ~ 21,000/year) associated with chronic HCV infection {22099}. Consensus-based clinical practice guidelines for the management of HCC have recently been updated defining the management practice in Japan {22066}. Despite such intervention, HCC is almost universally recurrent particularly in the face of ongoing HCV infection {22076} and poses a significant health and economic burden to the nation {22099}, {23808}, {22168}.

Pegylated-interferon (Peg-IFNα) plus ribavirin (RBV) combination therapy has been the standard of care (SOC) for the treatment of chronic hepatitis C in Japan since first approval in 2004, affording SVR rates of approximately 50-60% when administered for 48 weeks in treatment-naïve patients with GT-1 infection (Japan PegIntron® and Pegasys® Product Labels). In 2011 the first direct-acting antiviral (DAA) for the treatment of GT-1 chronic hepatitis C was approved in Japan (Telaprevir; Telavic®; TVR) when used in combination with Peg-IFNα-2b (PegIntron®) +RBV (Rebetol®). In Japanese patients the Peg-IFNα+RBV+TVR regimen produces a SVR rate of 73% in previously untreated patients (Kumada et al, 2012). In patients who relapsed following initial response to prior therapy and in patients who were non-responsive to prior therapy, the SVR rates following treatment with Peg-IFNα +RBV+TVR were 88.1% and 34.4% respectively {22097}. Although the addition of TVR to Peg-IFNα +RBV clearly affords incremental efficacy for the treatment of GT-1 infection it is associated with significant safety and tolerability issues including moderate to severe anemia, skin disorders (rash, Stevens-Johnson syndrome and DRESS), renal insufficiency and renal failure. The safety of TVR has been the topic of PMDA risk communications in 2012 and a ‘black box’ warning has been added to the US product label concerning rash with systemic symptoms.

Japanese treatment guidelines for chronic HCV infection have recently been updated by both the Japan Society of Hepatology and the Ministry of Health Labor and Welfare (MHLW) ‘Study Group for the Standardization of Treatment of Viral Hepatitis and Cirrhosis’ {23806}, {23807}. The revised guidelines address the use of the Peg-IFNα+RBV+TVR regimen in GT-1 infection, provide guidance on strategies to lower the risk of HCV-related HCC and considerations regarding the next generation of HCV DAAs in development. In general terms both guidelines recommend early treatment to prevent or delay development of HCC and ESLD. Treatment is selected according to various factors including HCV genotype, baseline viral load, host IL28B genotype, HCV Core70 and ISDR mutations, age, level of fibrosis and

prior treatment history. When indicated and tolerated, it is recommended that the first line therapy for GT-1 chronic hepatitis C is Peg-IFNα+RBV+TVR. Antiviral therapy with Peg-IFNα+RBV is recommended in certain subgroups, and interferon monotherapy is utilized as long term HCC preventative therapy in patients remaining viremic.

As previously described, literature reports have established that Japanese patients with chronic hepatitis C tend to be older, treatment-experienced and more likely to have progressive liver disease {22061}, {22074}, {23803}. Prior to the conduct of the present study, Gilead Sciences conducted a survey across 11 centers in Japan to confirm literature reports concerning the demographic and disease characteristics of patients with chronic hepatitis C. Centers were selected for participation on the basis of hepatitis C expertise (cumulatively clinics represented >6,000 patients) and representation of all geographic regions of the country. Summary findings for GT-1 infection indicated that the average duration of infection was 36 yrs, 65-76% of patients were aged over 60 years, and 61% of patients were treatment-experienced. The proportion of patients with advanced fibrosis/compensated cirrhosis was approximately 50%. Importantly less than 10% of patients were considered to be eligible for and willing to participate in a clinical study utilizing Peg-IFNα+RBV+TVR therapy as a control arm. The elderly patients are more likely to have comorbid conditions and a tendency toward progressive liver disease. Drug-drug interactions are an important consideration in this population. These factors and associated contraindications to interferon, ribavirin and telaprevir represent the primary reasons for the lack of treatment. Patients ineligible for, intolerant of, or unwilling to receive Peg-IFNα+RBV±TVR have no currently available antiviral treatment options. Similarly those patients who have previously failed to respond to Peg-IFNα+RBV±TVR therapy have no alternative antiviral therapy available.

There is a need for early intervention and eradication of HCV infection to reduce the burden of progressive liver disease including of HCC and ESLD. While early introduction of effective antiviral therapy is critical in order to reduce the potential future burden of advanced liver disease, safe and effective antiviral therapies that can be used in elderly patients with advanced disease is of paramount importance today. Gilead Sciences is developing the all-oral, interferon-free SOF/LDV FDC regimen to address this need in Japan for chronic genotype-1 HCV infection.

1.2. Sofosbuvir (formerly GS-7977)

Sofosbuvir (SOF), formerly GS-7977, is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication.

Please refer to the Investigator's Brochure (IB) for additional information on SOF including:

- In Vitro Anti-HCV Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.2.1. Summary of Additional Clinical Experience With SOF: Phase 1 Studies

1.2.1.1. Clinical Pharmacology Studies

A number of Phase 1 studies have been conducted with SOF and are summarized in the investigator brochure including: a relative bioavailability study (P7977-0111) to compare human exposure after administration of PSI-7851 (diastereomeric mixture of SOF and GS 491241 to SOF, a human mass balance study (P7977-0312) to evaluate routes of elimination for SOF and metabolites, a methadone interaction study (P7977-0814) which demonstrated no interaction between SOF and methadone; and a thorough QTc study (P7977-0613) demonstrating no effect of SOF upon the QT interval in humans.

A Phase I ethnic bridging study has also been conducted to compare the pharmacokinetics of single dose administration of SOF and SOF/LDV FDC in healthy Japanese and Caucasian subjects. This study which supports bridging of global clinical trial data to Japan is described below (Section 1.2.2.2).

1.2.1.2. GS-US-334-0111 Pharmacokinetic Bridging Study in Japanese Subjects

To support the conduct of clinical studies in Japan a PK bridging study was conducted in accordance with ICHE5 to compare the safety, tolerability and PK profile in Japanese and Caucasian subjects following single-dose administration of SOF at the 200 mg, 400 mg (the intended therapeutic dose) and 800 mg dose levels. This study also evaluated the pharmacokinetic parameters of the 400 mg dose of SOF and the 90 mg dose of LDV administered as a single dose of the SOF/LDV FDC. This study was conducted in accordance with ICH E5 in the United States.

1.2.1.2.1. GS-US-334-0111 Study Design

The study enrolled Japanese and Caucasian subjects with an approximately even distribution of healthy males and healthy, non-pregnant, non-lactating females between 18–45 years, inclusive, with a body mass index (BMI) 18 ≤ BMI ≤ 30, who had either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that were considered clinically insignificant by the Investigator, normal renal function, no significant medical history, and were in good general health as determined by the investigator at screening. Japanese subjects had to be of first generation. Subjects must have been born in Japan, not lived outside Japan for > 10 years, and could trace maternal and paternal Japanese ancestry of parents and grandparents. Lifestyle, including diet, must have not significantly changed since leaving Japan. To be enrolled in the study Caucasian subjects must not have been of Japanese or Asian descent; those with parents or grandparents born in Japan or in any Asian country were excluded. Following completion of screening and baseline procedures, eligible subjects received one dose of study treatment on Day 1 corresponding to their assigned group. Each group comprised of 8 Japanese and 8 Caucasian subjects and received SOF at either the 200 mg, 400 mg or 800 mg dose levels (Groups 1-3), or 400 mg SOF + 90 mg LDV administered as a single dose of the SOF/LDV FDC (Group 4). Vital signs (heart rate, blood pressure) and a 12-lead ECG were performed at Screening, Day 0, Day 1 to 5 (Groups 1-3)

or Day 7 (Group 4), or Early Termination visit (if appropriate). Vital signs were also performed at the follow up visit. Assessment of adverse events and concomitant medications occurred at screening and daily throughout the study. Plasma and urine samples were collected at selected time points to assess the PK of SOF, GS-566500, GS-331007, and LDV.

1.2.1.2.2. GS-US-334-0111 Study Results

Preliminary pharmacokinetic (plasma and urine) results are available for all subjects in Table 1-1. As seen below, the geometric-least squares means ratios (GMRs) and associated 90% confidence intervals (CIs) for SOF, GS-566500, GS-331007, and LDV exposure parameters (AUC_{inf}, AUC_{last}, and C_{max}) are similar in the Caucasian and Japanese subjects.

Table 1-1. GS-US-334-0111 Geometric Least-Squares Mean Ratios (90% Confidence Intervals) for Sofosbuvir, GS-566500, GS-331007 and Ledipasvir Primary PK Parameters in Japanese versus Caucasian Subjects

	SOF 200 mg % GLSM Ratio (90% CI)	SOF 400 mg % GLSM Ratio (90% CI)	SOF 800 mg % GLSM Ratio (90% CI)	SOF/LDV FDC (400 mg/90 mg) % GLSM Ratio (90% CI)
SOF PK Parameter				
AUC_{last} (ng•h/mL)	97.02 (63.62, 147.96)	122.62 (92.54, 162.47)	106.20 (82.63, 136.49)	90.52 (54.44, 150.50)
AUC_{inf} (ng•h/mL)	97.30 (64.77, 146.16)	121.98 (92.30, 161.20)	106.27 (82.84, 136.33)	90.77 (54.90, 150.07)
C_{max} (ng/mL)	101.56 (62.88, 164.02)	107.05 (76.31, 150.18)	96.37 (62.23, 149.23)	93.82 (64.53, 136.42)
GS-566500 PK Parameter				
AUC_{last} (ng•h/mL)	158.37 (119.80, 209.34)	149.64 (117.13, 191.17)	125.17 (103.74, 151.03)	114.13 (78.15, 166.67)
AUC_{inf} (ng•h/mL)	153.51 (117.65, 200.30)	147.47 (116.45, 186.74)	124.39 (103.30, 149.79)	113.27 (78.24, 163.98)
C_{max} (ng/mL)	154.48 (116.12, 205.51)	138.62 (108.12, 177.72)	117.59 (98.72, 140.06)	130.16 (93.88, 180.44)
GS-331007 PK Parameter				
AUC_{last} (ng•h/mL)	80.29 (64.62, 99.77)	94.44 (78.30, 113.90)	82.32 (71.98, 94.16)	85.63 (63.56, 115.36)
AUC_{inf} (ng•h/mL)	82.37 (67.59, 100.36)	95.93 (80.14, 114.82)	83.68 (74.25, 94.30)	85.40 (64.04, 113.89)
C_{max} (ng/mL)	72.72 (57.86, 91.40)	113.48 (91.12, 141.32)	102.44 (73.52, 142.73)	94.34 (68.03, 130.82)

	SOF 200 mg % GLSM Ratio (90% CI)	SOF 400 mg % GLSM Ratio (90% CI)	SOF 800 mg % GLSM Ratio (90% CI)	SOF/LDV FDC (400 mg/90 mg) % GLSM Ratio (90% CI)
LDV PK Parameter				
AUC_{last} (ng•h/mL)	—	—	—	106.07 (68.95, 163.18)
AUC_{inf} (ng•h/mL)	—	—	—	106.66 (69.13, 164.59)
C_{max} (ng/mL)	—	—	—	125.63 (83.83, 188.26)

1.2.1.2.3. GS-US-334-0111 Study Conclusions

SOF and SOF/LDV FDC were well tolerated in this study. No clinically significant differences in the PK of SOF, its metabolites GS-566500 and GS-331007, or LDV were observed between Japanese and Caucasian subjects, supporting the use of SOF 400 mg or SOF/LDV FDC (400 mg/90 mg) in Japanese and non-Japanese subjects.

1.2.2. Summary of Additional Clinical Experience with SOF: Phase 2 Studies

1.2.2.1. Study P7977-0523 (ELECTRON): Additional Efficacy data

ELECTRON is an ongoing 6-part, Phase 2 study comprising 22 treatment arms. Data from this study have previously been submitted to PMDA. Of particular importance to the efficacy and/or safety of the SOF/LDV FDC regimen the proposed for use in GS-US-337-0113 in Japan are treatment Arms 12-13 (Part 4) exploring SOF+LDV+RBV and Arms 16, 17, 20, and 21 (Part 6), exploring SOF/LDV±RBV in various patient populations:

- Arm 12: GT1, prior null responder, non-cirrhotics (12 weeks SOF+LDV+RBV; n=9)
- Arm 13: GT1, treatment-naïve, non-cirrhotics (12 weeks SOF+LDV+RBV; n=25)
- Arm 16: GT1, prior null responder, F4 cirrhotics (12 weeks SOF/LDV FDC; n=10)
- Arm 17: GT1, prior null responder, F4 cirrhotics (12 weeks SOF/LDV FDC+RBV; n=10)
- Arm 20: GT1: Hemophiliacs (12 weeks SOF/LDV FDC+RBV ~20)
- Arm 21: GT1, treatment-naïve, non-cirrhotic (6 weeks SOF/LDV FDC+RBV; n=25)

1.2.2.1.1. P7977-0523 (ELECTRON) Preliminary Safety

SOF+LDV+RBV and SOF/LDV ± RBV are generally well tolerated. One subject in the SOF+LDV+RBV groups discontinued treatment early due to a serious adverse event (colonic fistula) considered by the investigator not to be related to study drugs. No other serious adverse events have been reported. To date, no subjects receiving SOF/LDV ± RBV have discontinued treatment early. The most common adverse events were headache (44%), fatigue (23%), and nausea (22%), when safety data from Arms 12, 13, and 16-21 were pooled. No safety signal associated with treatment with SOF or LDV either separately or as a FDC has been identified.

1.2.2.1.2. P7977-0523 (ELECTRON) Preliminary Pharmacokinetic Data

An intensive PK substudy was conducted at Week 2 to examine the PK of SOF, GS-566500, GS-331007 and LDV in subjects receiving SOF+LDV+RBV (all subjects in Arms 12 and 13), and SOF/LDV FDC ± RBV who do not have hemophilia (target: up to 10 subjects in Arms 16-19, each, and up to 15 subjects in Arms 21-22).

Preliminary PK data are available for all subjects in Arms 12 (N = 9) and 13 (N = 25), and 21 (N = 15), and for the majority of subjects in Arms 16-17 (SOF: N = 11 out of 14, LDV: N = 12 out of 14). Preliminary PK data are shown in Table 1-2.

Similar plasma exposures of SOF, GS-566500, GS-331007 and LDV were achieved in all treatment groups, irrespective of presence or absence of cirrhosis.

Table 1-2. Study P7977-0523 (ELECTRON): SOF, GS-566500, GS-331007 and LDV PK Parameters Following Administration of SOF 400 mg + LDV 90 mg + RBV or SOF 400 mg/LDV 90 mg FDC ± RBV (Preliminary Data)

PK Parameter Mean (%CV)	Arm 12 GT1 SOF+LDV+RBV Prior Nulls	Arm 13 GT1 TN SOF+LDV+RBV	Arms 16-17 GT 1 FDC± RBV F4 cirrhotic (pooled)	Arm 21 GT 1 TN FDC
SOF	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	1990 (66.0)	2220 (55.3)	2300 (28.8)*	1860 (48.5)**
C_{max} (ng/mL)	1040 (108)	1100 (70.7)	1120 (64.5)	1190 (53.0)
C_{tau} (ng/mL)	BLQ	BLQ	BLQ	BLQ
GS-566500	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	2400 (22.2)	2690 (28.0)	3370 (23.7)	2530 (37.3)
C_{max} (ng/mL)	488 (25.0)	569 (29.1)	680 (21.5)	519 (42.8)
C_{tau} (ng/mL)	BLQ	BLQ	BLQ	BLQ

PK Parameter Mean (%CV)	Arm 12 GT1 SOF+LDV+RBV Prior Nulls	Arm 13 GT1 TN SOF+LDV+RBV	Arms 16-17 GT 1 FDC± RBV F4 cirrhotic (pooled)	Arm 21 GT 1 TN FDC
SOF	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	1990 (66.0)	2220 (55.3)	2300 (28.8)*	1860 (48.5)**
GS-331007	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	8110 (16.1)	11200 (28.3)	11200 (36.0)	10500 (17.2)
C_{max} (ng/mL)	630 (17.9)	757 (21.9)	805 (31.1)	768 (19.0)
C_{tau} (ng/mL)	201 (16.6)	306 (34.4)	284 (44.6)	286 (26.2)
LDV	**N=9**	**N=25**	**N=12**	**N = 15**
AUC_{tau} (hr·ng/mL)	6420 (44.1)	7030 (41.6)	8190 (58.7)	7910 (45.4)
C_{max} (ng/mL)	367 (37.3)	386 (38.1)	437 (54.7)	434 (42.0)
C_{tau} (ng/mL)	188 (54.7)	216 (46.4)	261 (59.0)	252 (51.7)

Preliminary data reported to 3 significant figures; * N = 10; **N=14; BLQ: below the limit of quantification

1.2.2.1.3. P7977-0523 (ELECTRON) Preliminary Efficacy

All available SVR data from the SOF and LDV containing arms (administered as single agents in combination or as the fixed-dose combination to genotype 1 subjects) in the ELECTRON study is provided in Table 1-3, below. This study is an ongoing study and all available data for complete cohorts at a particular time point have been reported.

All subjects (100%) in Arms 12 and 13, irrespective of HCV genotype (1A or 1B) and IL28B allele (CC, CT, or TT) had HCV RNA < LLOQ at post treatment Weeks 2, 4, 8, 12 and 24; no relapses were reported.

This contrasts with ELECTRON Arm 7 (SOF+RBV for 12 weeks in genotype 1 HCV-infected null responders) and Arm 8 (SOF+RBV for 12 weeks in genotype 1 treatment-naive subjects), where 10% and 88% of subjects, respectively, achieved SVR12. The addition of LDV increased the SVR12 rate in these populations to 100%, demonstrating the contribution of LDV to a SOF-containing regimen.

Available SVR data for all subjects enrolled in ELECTRON Arm 21 [SOF/LDV FDC tablet once daily + weight-based RBV for 6 weeks in treatment-naive genotype 1 HCV-infected subjects; n = 25] are also presented in Table 1-3 below. The 6-week treatment duration appears suboptimal, as although all 25 subjects achieved RVR, 8 subjects relapsed by the post-treatment Week 12 visit. SVR24 data is pending.

Table 1-3. Study P7977-0523 (ELECTRON): Arms 12, 13, 16, 17, 20 and 21: Available SVR Data with Subtype

Arm No.	GT1	N	Wks	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	SVR24 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
Arm 12 GT1 nulls SOF+LDV+RBV	1a	8	12	88 (7/8)	100 (8/8)	100 (8/8)	100 (8/8)	100 (8/8)	0 (0)	0 (0)	0 (0)
	1b	1	12	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	0 (0)	0 (0)	0 (0)
Arm 13 GT1 TN SOF+LDV	1a	20	12	100 (20/20)	100 (20/20)	100 (20/20)	100 (20/20)	100 (20/20)	0 (0)	0 (0)	0 (0)
	1b	5	12	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	0 (0)	0 (0)	0 (0)
Arm 16 GT1 nulls with cirrhosis SOF/LDV	1a	8	12	75 (6/8)	25 (2/8)	TBD	TBD	TBD	25 (2/8)**	0 (0)	0 (0)
	1b	2	12	100 (2/2)	100 (2/2)	TBD	TBD	TBD	0 (0)	0 (0)	0 (0)
Arm 17 GT1 nulls with cirrhosis SOF/LDV +RBV	1a	7	12	57 (4/7)	86 (6/7)	TBD	TBD	TBD	0 (0)	0 (0)	14 (1/7)
	1b	2	12	100 (2/2)	100 (2/2)	TBD	TBD	TBD	0 (0)	0 (0)	0 (0)
Arm 20 GT1 with hemophilia SOF/LDV +RBV	1a	10	12	90 (9/10)*	TBD	TBD	TBD	TBD	0 (0)	0 (0)	0 (0)
	1b	4	12	75 (3/4)	TBD	TBD	TBD	TBD	0 (0)	0 (0)	0 (0)
Arm 21 GT1 TN FDC+RBV	1a	21	6	100 (21/21)	86 (18/21)	71 (15/21)	62 (13/21)	TBD	38 (8/21)	0 (0)	0 (0)
	1b	4	6	100 (4/4)	100 (4/4)	100 (4/4)	100 (4/4)	TBD	0 (0)	0 (0)	0 (0)

BT: breakthrough; LTFU: lost to follow up; TBD: to be determined

* One subject in Arm 20 did not return at the Week 4 time point: they had HCV RNA >LLOQ at Week 3 and HCV RNA <LLOQ at Week 5.

** In addition to the 2 relapsers reported in Arm 16 at the 4 weeks post treatment time point, one additional subject had relapsed by the 8 week Post-Treatment visit. This subject will be included in the table when complete data are available on all subjects at the post-treatment week 8 time point.

The full-length NS5A region was analyzed at baseline for all 34 subjects enrolled in Arms 12 and 13 (27 genotype 1a and 7 genotype 1b) by standard population sequencing. Overall, 4/34 (11%) subjects had LDV RAVs present at baseline (Table 1-4). 3/4 subjects with baseline NS5A RAVs were genotype 1a with M28T, Q30H, or L31M variants detected. A single genotype 1b subject had a detectable LDV RAV (L31M) at baseline. Previous in vitro data demonstrates that these NS5A variants individually confer moderate to high level reductions in susceptibility to LDV in vitro (25- to 140-fold). No virologic breakthrough or relapse was observed in these subjects or any other subjects in these treatment arms, as all

achieved SVR12. This indicates that the presence of observed NS5A RAVs does not preclude the ability of subjects to achieve SVR12 on SOF+ LDV+RBV treatment. Resistance analysis of other arms containing SOF and LDV is pending.

Table 1-4. Study P7977-0523 (ELECTRON): Subjects with Baseline Ledipasvir RAVs in NS5A in Arms 12 and 13

Subject ID	Genotype	Treatment Group	NS5A RAV	NS5A Single Mutant Fold-change in LDV EC50	SVR 4 Result	SVR 8 Result	SVR 12 Result
5202	1b	Arm 13: 12 W SOF+LDV+RBV (GT1 TN)	L31M	L31M: 140	SVR	SVR	SVR
5215	1a	Arm 13: 12 W SOF+LDV+RBV (GT1 TN)	Q30H	Q30H: 73	SVR	SVR	SVR
5234	1a	Arm 13: 12 W SOF+LDV+RBV (GT1 TN)	M28T	M28T: 25	SVR	SVR	SVR
5241	1a	Arm 12: 12 W SOF+LDV+RBV (GT1 Nulls)	L31L/M	L31M: 140	SVR	SVR	SVR

1.2.2.2. Study AI444-040 (Bristol-Myers Squibb IND 79,599)

AI444-040 {20485} was designed to evaluate the potential to achieve SVR with an oral, pan-genotypic, once-daily treatment regimen combining the investigational agents SOF and a NS5A inhibitor, daclatasvir (DCV), with or without RBV, in treatment naïve subjects chronically infected with genotypes 1, 2, or 3 HCV {24592}. In the initial phase of this study, subjects were randomized into six groups, evaluating three different dosing schedules in subjects with either genotype 1 HCV (n=44) or genotype 2/3 HCV (n=44). The groups were:

- SOF 400 mg QD for 7 days then DCV 60 mg QD + SOF 400 mg QD for 23 weeks
- SOF 400 mg QD + DCV 60 mg QD for 24 weeks
- SOF 400 mg QD + DCV 60 mg QD + RBV for 24 weeks

The primary endpoint of the study was SVR12. An interim analysis for safety and antiviral activity was conducted at 12 weeks on-treatment.

The study was subsequently expanded to evaluate SOF + DCV ± RBV for 24 weeks in genotype 1 HCV infected subjects who have previously failed telaprevir or boceprevir treatment and for 12 weeks in treatment-naïve genotype 1 HCV subjects. Preliminary data on the 12 and 24 week arms are available.

Preliminary Safety

Preliminary safety data have been reported. The most frequent (greater than or equal to 15% overall) adverse events (AEs) on treatment were fatigue, headache and nausea. Adverse events were generally mild to moderate intensity and did not lead to treatment discontinuation. Grade 3-4 laboratory abnormalities included anemia in subject receiving RBV. Two subjects discontinued treatment for non-drug related AEs and both achieved SVR4. No subjects discontinued therapy due to treatment-related AEs.

Preliminary Efficacy

Preliminary efficacy data are tabulated in Table 1-5.

Table 1-5. The Proportions of Subjects Achieving Viral Load Below the Lower Limit of Quantification (HCV RNA <25 IU/mL) in Study AI444-040

	Genotype 1					Genotype 2 or 3		
Time (Week)	SOF(LI) +DCV [b] 24 weeks (Group A) (N = 15) n (%)	SOF +DCV 24 weeks (Group C) (N = 14) n (%)	SOF+ DCV+ RBV 24 weeks (Group E) (N = 15) n (%)	SOF +DCV 12 weeks (Group G) (N = 41) n (%)	SOF +DCV +RBV 12 weeks (Group H) (N = 41) n (%)	SOF(LI)+ DCV 24 weeks (Group B) (N = 16) n (%)	SOF+ DCV 24 weeks (Group D) (N = 14) n (%)	SOF +DCV +RBV 24 weeks (Group F) (N = 14) n (%)
4	15 (100)	14 (100)	15 (100)	39 (95)	41 (100)	16 (100)	14 (100)	14 (100)
EOT [a]	15 (100)	14 (100)	15 (100)	41 (100)	41 (100)	15 (94)	14 (100)	14 (100)
SVR4	15 (100)	14 (100)	15 (100)	40 (98)	39 (95)	14 (88)	14 (100)	12 (86)
SVR12	15 (100)	14 (100)	15 (100)	Pending[c]	Pending[c]	14 (88)	14 (100)	12 (86)

a EOT, End of Treatment

b LI, lead in; DCV, daclatasvir

c Pending, data collection ongoing

Preliminary HCV RNA data is also available on the SOF+DCV±RBV regimen administered for 24 weeks in GT-1 non-cirrhotics who had previously failed telaprevir or boceprevir containing regimens {24592}. Most of the subjects enrolled were HCV GT-1a (83%), IL28B non-CC (98%) and had estimated METAVIR stage ≥F2. The mean baseline HCV RNA was ≥6 log IU/mL. All subjects receiving SOF+DCV either with or without concomitant RBV, achieved rapid virologic suppression with HCV RNA <25 IU/mL by the on-treatment Week 4 visit. Early virologic suppression was maintained through the end of treatment (Week 24) with 100% (41/41) of subjects going on to achieve SVR4.

Table 1-6. Study AI444-040 HCV RNA <25 IU/mL during and post-treatment.

HCV RNA <25 IU/mL	GT1a/1b, prior Telaprevir or Boceprevir failure	
	DCV+SOF, 24 Weeks (n=21)	DCV+SOF+RBV, 24 Weeks (n=20)
On treatment Week 4	21 (100)	19 (95)[a]
End of Treatment (Week 24)	21 (100)	20 (100)
SVR4	21 (100)	20 (100)

Notes: [a]1 missing

1.2.2.3. NIAID Study 11-I-0258 (IND 112,681)

Study 11-I-0258 is a randomized controlled open-label study to assess safety, tolerability and efficacy of SOF 400 mg QD in combination with RBV in a total of 60 treatment-naïve HCV genotype 1 mono-infected individuals. The NIAID is the sponsor of the study under IND 112,681. Subjects were enrolled into 2 phases to evaluate both treatment duration as well as RBV dose. Phase 1 enrolled 10 subjects who were dosed with SOF 400 mg QD in combination with weight based RBV (1000 mg for participants weighing < 75 kg and 1200 mg for participants weighing ≥ 75kg) for 24 weeks; all subjects had ≤ stage 2 fibrosis. Upon completion of an interim safety review of these subjects at Week 12 of treatment, Phase 2 was initiated in 50 subjects with any stage of fibrosis. Phase 2 subjects were randomized in a 1:1 ratio to receive 24 weeks of SOF QD in combination with weight-based RBV (1000 mg or 1200 mg daily) or 24 weeks of SOF 400 mg QD with low dose RBV (600mg). All subjects have completed therapy in both phases of the study.

1.2.2.3.1. NIAID Study 11-I-0258 (IND 112,681) Preliminary Safety Data

The population was predominantly African American, genotype 1a, with a median baseline HCV RNA $\log_{10} \geq 6.05$. All subjects in Phase 1 were ≤ Stage 2 fibrosis while, in Phase 2, 24% of those receiving full-dose RBV and 28% of those receiving low-dose RBV had advanced fibrosis. The interim safety analysis is completed and SOF was assessed as being safe and well-tolerated. There were no SAEs and the safety profile was consistent with that expected for RBV.

1.2.2.3.2. NIAID Study 11-I-0258 (IND 112,681) Preliminary Efficacy Data

Preliminary HCV RNA data for both study phases are presented in Table 1-7.

Table 1-7. NIAID Study 11-1-0258: Percentage of Subjects with HCV RNA Achieving SVR

Time (Week)	Part 1	Part 2	
	SOF+Weight-based RBV 24 Weeks N=10 n (%)	SOF+Weight-based RBV 24 Weeks N=25 n (%)	SOF+600 mg RBV 24 weeks (N = 25) n (%)
4	9/10 (90%) [b]	24/25 (96%) [b]	24/25 (100%)
EOT [a]	9/10 (90%)	24/25 (96%) [b]	22/25 (88%) [c]
SVR4	9/10 (90%)	18/25 (72%) [b]	14/25 (56%)
SVR12	9/10 (90%)	17/25 (68%)	12/25 (48%)

a EOT, End of Treatment

b One subject discontinued therapy at Week 3

c 3 subjects dropped out before Week 8

1.2.3. Summary of Additional Clinical Experience with SOF: Phase 3 Studies

The SOF Phase 3 program includes 4 clinical studies: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO).

Studies P7977-1231, GS-US-334-0107, and GS-US-334-0108 evaluated the efficacy and safety of SOF+RBV in different genotype 2 and 3 HCV patient populations. Study GS-US-334-0110 evaluated the efficacy and safety of SOF+Peg-IFNα+RBV for 12 weeks for treatment-naive subjects with genotype 1, 4, 5, and 6 HCV infection. Preliminary safety and efficacy data for each study are summarized below.

1.2.3.1. P7977-1231 (FISSION)

This Phase 3, randomized, multicenter, open-label, active-controlled study evaluated SVR12 rates of treatment-naïve, genotype 2 or 3 HCV-infected subjects randomized 1:1 to receive either 12 weeks of treatment with SOF (400 mg once daily) +RBV (1000 or 1200 mg per day in divided [BID] doses, as determined by subject's weight) or 24 weeks of treatment with Peg-IFNα (180 µg/week) +RBV (800 mg/day).

1.2.3.1.1. P7977-1231 (FISSION) Preliminary Safety Data

Treatment with SOF+RBV was well tolerated in this study, and the overall safety profile of SOF+RBV was favorable to that of Peg-IFNα +RBV. Specifically, the SOF+RBV group had lower rates of AEs (SOF+RBV 86%; Peg-IFNα+RBV 96%); Grade 3 or higher AEs (SOF+RBV 7%; Peg-IFNα +RBV 19%); Grade 2 or higher AEs (SOF+RBV 40%; Peg-IFNα +RBV 69%); treatment-related AEs (SOF+RBV 72%; Peg-IFNα +RBV 94%); AEs leading to permanent discontinuation of any of the study drugs (SOF+RBV 1%;

Peg-IFNα +RBV 12%); and AEs leading to study drug interruption or dose modification (SOF+RBV 10%; Peg-IFNα+RBV 27%). The safety profile of SOF+RBV treatment was similar to the expected safety profile of RBV treatment.

Fatigue occurred with the highest AE incidence in both treatment groups, reported in 92 subjects (36%) in the SOF+RBV group and 134 subjects (55%) in the Peg-IFNα+RBV group. All of the other most common AEs (ie, those in ≥ 10% of subjects in either treatment group) were also reported in a lower percentage of subjects in the SOF+RBV group than the Peg-IFNα +RBV group. These AEs included events commonly associated with Peg-IFNα +RBV treatment, such as anemia, headache, nausea, insomnia, diarrhea, irritability, rash, myalgia, decreased appetite, pruritus, dizziness, influenza-like illness, arthralgia, chills, depression, pyrexia, pain, and neutropenia).

Serious AEs were infrequent in both treatment groups (SOF+RBV 3%, 7 subjects/8 events; Peg-IFNα+RBV 1%, 3 subjects/6 events). All individual SAE preferred terms were reported for only 1 subject, and no pattern was apparent in the types of events.

Most lab abnormalities in both groups were Grade 1 or 2 in severity.

1.2.3.1.2. P7977-1231 (FISSION) Preliminary Efficacy Data

Overall SVR12 rates were 67% (170/253) in the SOF+RBV group and 67% (162/243) in the Peg-IFNα+ RBV group. Since the lower bound of the 2-sided 95% confidence interval (CI) of the difference in the response rate (SOF+RBV − Peg-IFNα+ RBV) was greater than the prespecified 15% noninferiority margin, treatment with SOF+RBV for 12 weeks was determined to be noninferior to treatment with Peg-IFNα+ RBV for 24 weeks. The SVR12 rates for genotype 2 subjects were 97% versus 78% for those receiving SOF+RBV versus Peg-IFNα+ RBV, respectively, and for genotype 3 subjects were 56% versus 63% for those receiving SOF+RBV versus Peg-IFNα+ RBV, respectively. Among subjects with cirrhosis at baseline who received SOF+RBV, 47% achieved SVR12 compared with 38% of those who received Peg-IFNα+ RBV.

With the exception of one subject who was non-compliant (drug levels were undetectable), all subjects in the SOF+RBV arm became HCV negative on treatment and relapse accounted for the virologic failures.

1.2.3.2. GS-US-334-0107 (POSITRON)

Subjects (n=278) with genotype 2 and 3 HCV infection who were interferon intolerant or interferon ineligible or unwilling to take interferon were randomized (3:1) to receive 12 weeks of SOF (400 mg/day) plus RBV (1000 or 1200 mg/day) or matching placebo.

1.2.3.2.1. GS-US-334-0107 (POSITRON) Preliminary Safety Data

Treatment for 12 weeks with SOF+RBV was well tolerated in this study. The safety profile of SOF+RBV treatment was similar to the expected safety profile of RBV treatment.

The majority of subjects in both groups experienced at least 1 AE. The most frequently reported overall AEs and treatment-related AEs in both groups were fatigue, headache, and nausea. Most AEs were either Grade 1 (mild) or Grade 2 (moderate) in severity. Eight AEs leading to discontinuation of any study drug were reported in 5 (2%) SOF+RBV subjects and 4 AEs leading to discontinuation of any study drug were reported in 3 (4%) placebo subjects. No individual AE that led to discontinuation was experienced by more than 1 subject. No trends in SAE type or onset time were observed. Most laboratory abnormalities were Grade 1 or 2 in severity.

1.2.3.2.2. GS-US-334-0107 (POSITRON) Preliminary Efficacy Data

SVR12 was achieved by 78% (161/207) subjects receiving SOF+RBV compared with 0% (0/71) subjects receiving placebo ($p < 0.001$). Relapse accounted for all virologic failures in the SOF+RBV arm.

Subjects with genotype 2 HCV infection had a higher SVR12 rate than subjects with genotype 3 HCV infection (93% vs 61%). Overall 15% of subjects had cirrhosis at baseline; 61% of those receiving SOF+RBV achieved SVR12.

1.2.3.3. Study GS-US-334-0108 (FUSION)

This ongoing Phase 3, randomized, double-blind, multicenter study assessed the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment in subjects with chronic genotype 2 or 3 HCV infection who had failed prior treatment with an interferon-based regimen. Eligible subjects were randomized in a 1:1 ratio to 12 or 16 weeks of treatment with SOF (400 mg/day) plus RBV (1000 to 1200 mg/day).

1.2.3.3.1. Study GS-US-334-0108 (FUSION) Preliminary Safety Data

Treatment with SOF+RBV for 12 or 16 weeks was generally well tolerated in this study, with no deaths, no discontinuations during SOF+RBV treatment, and few SAEs or Grade 3 or 4 AEs or laboratory abnormalities. Extending treatment duration to 16 weeks did not alter the safety profile of the regimen in terms of overall frequency or severity of AEs or laboratory abnormalities. The safety profile of SOF+RBV treatment was similar to the expected safety profile of RBV treatment.

The most frequently reported overall AEs in both treatment groups were fatigue, headache, nausea, and insomnia. Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity.

Most laboratory abnormalities were Grade 1 or Grade 2 in severity.

1.2.3.3.2. Study GS-US-334-0108 (FUSION) Preliminary Efficacy Data

A total of 50% of subjects (50/100) in the SOF+RBV 12-week group and 73% of subjects (69/95) in the SOF+RBV 16-week group achieved SVR12. The study met its primary endpoint of superiority over an historical control rate of 25% ($p < 0.001$). Treatment with

SOF+RBV for 16 weeks resulted in higher SVR12 rates compared with the shorter treatment duration of 12 weeks. This difference was primarily a result of a lower response rate in subjects with genotype 3 HCV infection receiving 12 weeks of treatment. Among the 34% of FUSION participants who had compensated cirrhosis at baseline, 31% achieved SVR12 in the 12-week arm, and 66% achieved SVR12 in the 16-week arm.

Subjects with genotype 2 HCV infection had higher SVR12 rates than subjects with genotype 3 HCV infection in both the SOF+RBV 12-week group and the SOF+RBV 16-week group. Table 1-8 presents SVR12 by HCV genotype. In both treatment groups, relapse accounted for all virologic failures.

Table 1-8. GS-US-334-0108: Number (Percentage) of Subjects with SVR12 by Genotype (Full Analysis Set)

	SOF+RBV 12 Weeks + Placebo 4 Weeks Genotype 2 (N = 36)	SOF+RBV 16 Weeks Genotype 2 (N = 32)	SOF+RBV 12 Weeks + Placebo 4 Weeks Genotype 3 (N = 64)	SOF+RBV 16 Weeks Genotype 3 (N = 63)
SVR12	31/36 (86%)	30/32 (94%)	19/64 (30%)	39/63 (62%)

1.2.3.4. Study GS-US-334-0110 (NEUTRINO)

Treatment-naïve subjects with genotype 1, 4, 5, or 6 HCV infection (n= 327) were treated for 12 weeks with sofosbuvir (400 mg/day) plus RBV (1000 or 1200 mg/day) and Peg-IFNα (180 µg/week) in this Phase 3, open-label study.

1.2.3.4.1. Study GS-US-334-0110 (NEUTRINO) Preliminary Safety Results

Sofosbuvir was generally well tolerated in this study. The safety profile of SOF+Peg-IFNα+RBV treatment was similar to the expected safety profile of Peg-IFNα+RBV treatment. Five subjects (1.5%) had AEs that led to treatment discontinuation. Anemia was the only AE that led to discontinuation or all study treatment for more than 1 subject (2 subjects, 0.6%).

The most frequently reported AEs and treatment-related AEs were fatigue, headache and nausea. Most AEs were either Grade 1 or Grade 2 in severity. Approximately 15% of subjects experienced a Grade 3 AE; the most frequent Grade 3 AEs that occurred in ≥ 5 subjects were neutropenia, anemia, fatigue, and headache. No Grade 4 AEs were reported. SAEs were infrequently reported (1%) and no deaths occurred.

1.2.3.4.2. Study GS-US-334-0110 (NEUTRINO) Preliminary Efficacy Results

Twelve weeks of treatment with SOF+Peg-IFNα+RBV resulted in a high SVR12 rate of 90% in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infections. Among genotype 1 subjects, 89% achieved SVR12. Of the 35 subjects with genotypes 4, 5, or 6,

97% achieved SVR12. Seventeen percent of subjects had compensated cirrhosis; 80% of these subjects achieved SVR12. The study met its primary endpoint of superiority over an historical SVR rate of 60% ($p < 0.001$). Relapse accounted for all virologic failures.

1.2.4. Safety Evaluation of SOF in Combination with RBV or Peg-IFNα and RBV

SOF 400 mg QD administered for up to 24 weeks has been well tolerated in studies to date with the observed AEs similar to those expected for the drugs with which it is coadministered - RBV or Peg-IFNα+RBV. As such, decreased hemoglobin is the most frequent laboratory abnormality when coadministered with RBV and with Peg-IFNα+RBV. Rates of decreased hemoglobin across the Phase 3 studies are described in Table 1-9.

Table 1-9. Pooled Phase 3 Studies: Subjects with Post-Baseline Hemoglobin < 10 g/dL and < 8.5 g/dL (Safety Analysis Set)

	Genotype 2, 3				Genotype 1, 4, 5, 6
	Placebo	SOF+RBV 12 weeks	SOF+RBV 16 weeks	Peg-IFNα+RBV 24 weeks	SOF+Peg-IFNα+RBV 12 weeks
	US-GS-334-0107 (N=71)	P7977-1231 US-GS-334-0107 US-334-0108 (N=566)	US-GS-334-0108 (N=98)	P7977-1231 (N=243)	US-GS-334-0110 (N=327)
Number of subjects with any post-baseline Hb value	71	563	98	242	327
Number (%) of subjects with any post-baseline Hb value < 10 g/dL	0	48 (9%)	5 (5%)	35 (15%)	74 (23%)
Number (%) of subjects with any post-baseline Hb value < 8.5 g/dL	0	5 (1%)	0	4 (2%)	8 (2%)

1.2.5. Overall SOF SAE Summary

No SAE signal has been associated with the use of SOF.

1.3. Ledipasvir (formerly, GS-5885)

Ledipasvir (LDV), formerly GS-5885, is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype (1a and 1b) HCV infection. More than 1,200 HCV infected subjects have been dosed with LDV in ongoing Phase 2 clinical studies.

Please refer to the Investigator Brochure (IB) for additional information on LDV including:

- In Vitro Anti-HCV Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.3.1. Summary of Additional Clinical Experience with LDV

The adult safety database for LDV includes data for approximately 900 healthy volunteers and approximately 1,200 chronic HCV infected subjects exposed to at least one dose of LDV in the 6 ongoing Phase 2 studies.

1.3.2. Clinical Pharmacology Studies

1.3.2.1. GS-US-334-0111 Pharmacokinetic Bridging Study in Japanese Subjects

GS-US-334-0111 has been previously described in Section 1.2.1.2. This study evaluated SOF (and metabolites) and LDV PK parameters following single dose administration of the SOF/LDV FDC combination to healthy Japanese and Caucasian subjects. SOF and SOF/LDV FDC were well tolerated in this study. Preliminary PK results (Table 1-1, above) support the use of the 400 mg SOF dose and the SOF (400 mg)/LDV (90 mg) FDC in both Japanese and non-Japanese subjects.

1.3.2.2. Study GS-US-248-0117

GS-US-248-0117 was an open-label, Phase 1, multiple-dose, 2-cohort, pharmacokinetic (PK) study in subjects with Child-Pugh-Turcotte (CPT) B (moderate) hepatic impairment and matched healthy subjects. The PK safety and tolerability of dual or triple combination treatments of LDV 30 mg once daily plus GS-9451 (Gilead HCV NS3/4A protease inhibitor) 200 mg once daily (Cohort 1) and LDV 30 mg once daily plus GS-9451 200 mg once daily plus tegobuvir (TGV) 30 mg twice daily (Cohort 2), administered for 12 days each, were evaluated. Fifty subjects (n = 20 in Cohort 1; n = 30 Cohort 2) were enrolled and received study drugs.

Table 1-10 presents the steady state PK parameters and statistical comparisons of LDV following administration of LDV+GS-9451± TGV in subjects with moderate hepatic impairment and in subjects with normal hepatic function. Ledipasvir plasma PK parameters (AUC_{tau}, C_{max} and C_{tau}) were comparable in subjects with moderate hepatic impairment and

matched controls who received a combination of LDV + GS-9451. Ledipasvir plasma exposure was modestly lower (~34-36%) in subjects with moderate hepatic impairment, as compared to matched controls upon administration of LDV + GS-9451 +TGV. These data indicate lack of an increase in LDV plasma exposure in subjects with moderate hepatic impairment relative to subjects with normal hepatic function.

The mean % free fraction for LDV, assessed at the time of maximum concentration (T_{max}) and at the end of the dosing interval (T_{last}), was similar in subjects with moderate hepatic impairment and those with normal hepatic function, demonstrating lack of an effect of hepatic impairment on protein binding (analysis done on Cohort 2).

Table 1-10. GS-US-248-0117: LDV Steady-State Pharmacokinetic Parameters and Statistical Comparisons in Subjects with Moderate Hepatic Impairment and Matched Controls with Normal Hepatic Function Following Administration of LDV+GS-9451±TGV

LDV PK Parameters Mean (%CV)	Reference Treatment: Normal Matched Control Group	Test Treatment: Moderate Hepatic Impairment Group	GLSM Ratio (%) (90% CI) Test/Reference
Cohort 1 (N = 9)			
AUC_{tau} (ng*hr/ml)	3405.0 (50.0)	3601.1 (52.9)	100.22 (63.42, 158.40)
C_{max} (ng/ml)	208.6 (46.1)	197.9 (47.3)	90.80 (59.30, 139.04)
C_{tau} (ng/ml)	120.6 (56.4)	138.4 (59.5)	105.39 (62.21, 178.53)
Cohort 2 (N = 14)			
AUC_{tau} (ng*hr/ml)	4756.0 (41.8)	2994.8 (42.4)	63.86 (47.36, 86.11)
C_{max} (ng/ml)	271.7 (41.8)	169.7 (39.9)	63.80 (47.09, 86.45)
C_{tau} (ng/ml)	177.7 (46.0)	113.5 (41.5)	66.10 (48.96, 89.26)

A review of the safety data showed LDV was generally well tolerated when co-administered with GS-9451 and with or without TGV to CPT B (moderate) hepatic impaired subjects and matched healthy subjects. No SAEs, Grade 3 or 4 AEs, deaths, or withdrawal due to AEs were reported in the study. The frequency of treatment-emergent AEs reported in the CPT B (moderate) hepatic impaired subjects were similar to those reported in matched healthy subjects. The most frequently reported AEs (in >2 subjects) overall were diarrhea, abdominal distension, fatigue, muscle tightness, headache, and eczema. Treatment-emergent AEs were mostly mild in severity except for a moderate AE of muscle tightness reported in 2 healthy subjects during LDV+GS-9451+TGV administration. A Grade 3 hyperbilirubinemia was noted in 2 moderately hepatic impaired subjects co-administered LDV and GS-9451, a result consistent with the known inhibition of bilirubin transporters by GS-9451. No other Grade 3 or 4 laboratory abnormality was reported in >1 subject.

Based on these data, dose adjustment of LDV in moderate or mild hepatic impairment is not warranted.

1.3.2.3. Study GS-US-248-0125

GS-US-248-0125 was an open-label, Phase 1, cross-over, multiple-dose, multi-cohort study that evaluated the effect and drug interaction potential of a triple combination of DAAs, LDV 90 mg QD +GS-9451 200 mg QD+TGV 30 mg BID, on OATP, BCRP, and Pgp substrates using phenotypic probes in healthy volunteers. In addition, the drug interaction potential of DAAs with Pgp inducers, Pgp inhibitors and mixed OATP/MRP2/Pgp inhibitors was assessed.

Effect of LDV+GS-9451+TGV on OATP, BCRP, Sodium-Taurocholate Cotransporting Polypeptide (NTCP), or Pgp Substrates Using Phenotypic Probes

Administration of LDV+GS-9451+TGV with an OATP substrate pravastatin resulted in a modest increase of ~ 2.7 to 2.8-fold in AUC and C_{max} of the probe drug, as compared to pravastatin administration alone. Pravastatin t1/2 remained similar in both treatments; suggestive of the effect of DAAs on the relative bioavailability and not the systemic clearance of the probe drug. The magnitude of this interaction is comparable to that observed with clarithromycin and is likely caused by the first-pass inhibition of hepatic drug transporters OATP by GS-9451, a moderate/potent inhibitor of OATP1B1/1B3 (AD-169-2275). In accordance with the prescribing information on the use of pravastatin with clarithromycin {18314}, pravastatin dose should be limited to 40 mg once daily with LDV+GS-9451+TGV. Monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis during co-administration of these agents is recommended.

Coadministration of rosuvastatin and LDV+GS-9451+TGV resulted in increases of ~8- to 9-fold in rosuvastatin AUC and ~18-fold increase in rosuvastatin C_{max}. Considering a substantial increase in rosuvastatin exposure relative to a more modest increase in pravastatin; this interaction is likely mediated by the inhibition of several drug transporters that mediate uptake or efflux of rosuvastatin (i.e. OATP, BCRP and NTCP). These results are also consistent with GS-9451 being is a moderate/potent inhibitor of OATP, a moderate inhibitor of NTCP (AD-169-2275) and BCRP drug transporters (AD-169-2249), and of LDV being a weak to moderate inhibitor of BCRP (AD-256-2109). There were no statistically significant differences in rosuvastatin t1/2 in the two treatments, indicative of the lack of effect of LDV+GS-9451+TGV on the systemic clearance of the probe drug. The magnitude of an increase in rosuvastatin exposure by DAAs in this study is also modestly higher than that observed upon co-administration of rosuvastatin with cyclosporine {21139}. Concurrent administration of rosuvastatin and cyclosporine resulted in ~ 7-fold increase in rosuvastatin AUC and ~11-fold increase in rosuvastatin C_{max}. As such, rosuvastatin should not be co-administered with LDV+GS-9451+TGV.

Modestly higher digoxin (AUC: ~1.3- to 1.6-fold higher; C_{max}: 1.2-fold higher) exposures were observed with DAAs, indicative of intestinal inhibition of Pgp transporters by GS-9451 and/or LDV, consistent with in vitro data that show that both GS-9451 and LDV are weak Pgp inhibitors. These results from this study do not preclude administration of triple DAA

combination with Pgp substrates. However, owing to digoxin narrow therapeutic index, an increase in digoxin exposure is considered clinically relevant (exposure increase > 1.25-fold {15555}) and monitoring of subjects for the signs and symptoms of digoxin toxicity is warranted if administered with LDV+GS-9451+TGV.

Effect of Pgp Inducers, Pgp Inhibitors and Mixed OATP/MRP2/Pgp Inhibitors on LDV+GS-9451+TGV and the Effect of LDV+GS-9451+TGV on Cyclosporine

Substantial reductions in the exposure parameters of GS-9451, LDV and TGV were observed upon administration with a Pgp inducer rifampin. GS-9451 AUC and C_{max} were ~ 83% and 67% lower, respectively, with rifampin, as compared to DAAs administration alone. Similarly, LDV AUC was ~ 56% to 59% lower and C_{max} was ~ 35% lower, respectively, whereas TGV AUC was ~ 60% lower and C_{max} was ~25% lower. As such, these DAAs should not be administered with Pgp inducers.

Coadministration of LDV+GS-9451+TGV with verapamil resulted in ~ 2-fold higher AUC and ~ 1.6-fold higher C_{max} of GS-9451, ~ 1.5- 1.7-fold higher AUC of LDV, and 1.3- to 1.4-fold higher AUC of TGV. Ledipasvir and TGV C_{max} remained comparable in both treatments. These increases in DAAs exposure are likely mediated by inhibition of Pgp drug transporters by verapamil. Dose adjustment of GS-9451 when given with Pgp inhibitors is dependent on target clinical exposures. Considering only modest increase in LDV and TGV exposure upon administration with verapamil, these agents may be co-administered with Pgp inhibitors.

Coadministration of DAAs with cyclosporine resulted in ~ 2-fold higher AUC_{tau} and C_{tau}, and ~1.8-fold higher C_{max} of GS-9451. Dose adjustment of GS-9451 when given with cyclosporine is dependent on target clinical exposures. Ledipasvir and TGV primary exposure parameters AUC_{tau}, C_{max}, and C_{tau} and cyclosporine exposure parameters AUCinf, AUClast and C_{max} were comparable in both treatments. The geometric least-squares means ratios for the test versus reference treatments and their associated 90% confidence intervals remained within the predefined lack of interaction bounds of 70% to 143%. As such, LDV or TGV may be coadministered with a mixed OATP/MRP2/Pgp inhibitor cyclosporine.

The combination of LDV+GS-9451+TGV when administered alone or with probe drugs was generally well tolerated. A total of 70 treatment-emergent AEs were reported in 45 subjects. Of those 24, AEs were considered related to any study drug, which includes those considered related to probe drugs alone. The majority of treatment-emergent AEs reported were mild in severity with 12 moderate and 1 severe AE reported. The severe AE of interstitial pneumonitis was reported in a subject in Cohort 2 after completing 10 days of GS-9451+LDV+TGV treatment and 3 days after the subject was co-administered GS-9451+LDV+TGV + digoxin. The event was reported 2 days later as an SAE, when the subject was hospitalized for several days of fever, nausea, vomiting, and weakness. The subject's symptoms and CT scan findings were suggestive of atypical pneumonia. Upon admission to the hospital, the subject was administered broad spectrum antibiotics. The subject's symptoms improved and the subject was discharged from the hospital 12 days later.

Due to the inability to identify a community acquired pathogen, the severe AE and SAE were reported as interstitial pneumonitis and considered by the investigator as possibly related to GS-9451, LDV, TGV, and digoxin.

Overall, no clinically significant laboratory abnormalities consistent with drug induced organ toxicity or changes in vital signs or electrocardiogram (ECG) findings reported during LDV+GS-9451+TGV administration alone and when co-administered with the probe drugs were identified. Two subjects in Cohort 4 were withdrawn due to abnormal ECG findings after administration of a single dose of verapamil alone. In the absence of the potential drug-drug interaction data between verapamil and LDV+GS-9451+TGV, the subjects were withdrawn prior to co--administration of verapamil and LDV+GS-9451+TGV. The abnormal ECG findings of atrioventricular block are consistent with the known adverse effects of verapamil administration.

1.3.2.4. Study GS-US-169-0105 (Cohort 4)

A single supratherapeutic dose of LDV 360 mg (conventional formulation) was administered to healthy subjects (n=15) under fasted conditions in Cohort 4 of GS-US-169-0105. Preliminary PK data showed that exposures achieved at 360 mg dose were similar to those observed with a 100 mg single dose, suggesting the absorption of LDV (conventional formulation) is solubility limited.

Overall, LDV 360 mg was generally well tolerated. No SAEs, Grade 3 or 4 AEs, deaths, or withdrawals due to AEs were reported during the study. The most frequently reported AE was constipation in two subjects. No clinically significant laboratory abnormalities were observed. No subject had notable changes in mean vital sign parameters during the study, and no vital sign result was recorded as an AE. No subjects had clinically significant ECG results during the study.

1.3.2.5. Study GS-US-256-0110 (Amendment 1, cohort 2)

The PK, safety and tolerability of LDV spray-dried solid dispersion formulation, administered at supratherapeutic dose of 120 mg BID for 11 days (21 doses) to healthy volunteers are being evaluated. Fourteen subjects comprised of male and non-pregnant, non-lactating female subjects aged between 18 to 45 years old were enrolled and received study drug. Serial blood samples were collected on Days 1 and 11. Time-matched ECG measurements were obtained in duplicate at Baseline (Day 0) and on Day 11. When LDV was administered at 120 mg BID for 11 days, supratherapeutic exposures were achieved. Consistent with a long LDV half-life (T½), substantial LDV accumulation (AUC: AI 8.5, Cmax: AI 6.2) was observed upon multiple BID dosing (Day 11) relative to the first dose (Day 1). Descriptive comparisons of LDV AUC and Cmax values at 120 mg versus 30 mg revealed approximately dose proportional increases in exposure, suggestive of near linear PK of the spray-dried formulation over this dose range.

An exploratory analysis quantifying the relationship between plasma concentrations of LDV and time-matched, baseline-adjusted change in QTcF [Δ QTcF] (msec) on Day 11 was conducted. No linear relationship between Δ QTcF and LDV plasma concentrations was

observed (Pearson correlation coefficient: 0.072, p-value: 0.566). Similar analysis quantifying the relationship between Δ QTcF and the maximum plasma concentrations (C_{max}) of LDV indicated no linear relationship (Pearson correlation coefficient: 0.133; p-value 0.665).

Based on a preliminary safety data review, LDV was generally well tolerated in this cohort. No SAE, Grade 3 or 4 AEs, or deaths were reported. One subject discontinued treatment early due to streptococcal pharyngitis of moderate severity. No two subjects experienced the same AE. One Grade 3 laboratory abnormality, 3+ blood in the urine, was reported in a 35 year old female. Per the Principle Investigator, this result was non-clinically significant. No subjects had clinically significant ECG results during the study.

1.3.2.6. Study GS-US-344-0109

Study GS-US-344-0109 is a Phase 1, randomized, partially-blinded, single and multiple-dose, placebo and positive (moxifloxacin)-controlled, 3-period, crossover thorough QT/QTc study with 6 treatment sequences of LDV in 60 healthy HCV-uninfected subjects. Fifty-eight subjects completed the study.

The primary objective of this study was to evaluate the effects of supratherapeutic dose/exposure of LDV 120 mg twice daily (BID) on time-matched, baseline-adjusted, placebo-corrected QTcF. The effects of LDV on QTc using other correction methods (QTcN and QTcI) and on other ECG parameters were also to be explored.

Eligible subjects were to be randomized to 1 of 6 treatment sequences and administered each of the following 3 treatments under fed conditions.

- Treatment A (Supratherapeutic Exposure): LDV 120 mg BID X 10 days
- Treatment B (Placebo Control): 120 mg matching LDV placebo BID X 10 days
- Treatment C (Positive Control): Moxifloxacin 400 mg (single dose)

Serial blood samples were collected relative to dosing of LDV, moxifloxacin or placebo controls at the following time points: 0, 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 8, 12, 16 and 24 hours post dose. Digital ECGs using a Holter monitor were collected in triplicate at baseline (−1.5, −1.0, and −0.5 hours) prior to dosing and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 8, and 12 hours post dose.

Moxifloxacin was used as a positive control to evaluate the assay sensitivity in this study. Assay sensitivity was established if the lower limit of the 2-sided 96.67% confidence intervals (CI; Bonferroni adjustment for multiple comparisons) for the mean difference between the moxifloxacin and placebo was greater than 5 msec at one or more selected post dose points (3, 3.5 and 4 hours post dose) around pharmacodynamic T_{max} of moxifloxacin.

Pharmacodynamic analyses evaluated the effect of LDV on time-matched, baseline-adjusted, placebo-corrected QTcF (primary PD endpoint), QTcN and QTcI intervals. Non-inferiority

was concluded if the upper limits of the 2-sided 90% CIs for the baseline-adjusted mean differences between LDV and placebo were below 10 msec for all time-points.

Preliminary pharmacokinetic (PK) and pharmacodynamic (PD) results are available. Other analyses are ongoing.

Preliminary Results

Preliminary Pharmacokinetic Results: A summary of LDV preliminary PK following administration of LDV120 mg BID (single-agent; supratherapeutic dose/exposure) in this study are presented in Table 1-11.

As presented below, LDV mean exposure parameters were approximately 3.5 to 3.9- fold higher by C_{max} and AUC_{0-24}, respectively, upon administration of the supratherapeutic dose relative to the therapeutic LDV 90-mg dose (P7977-0523; ELECTRON). These exposures are deemed adequate to cover the therapeutic and supratherapeutic exposures in the case of a LDV overdose or an additional/unexpected drug-drug interaction.

Table 1-11. GS-US-344-0109: LDV Plasma PK Parameters Following Administration of LDV 120 mg BID to Healthy Subjects

	Mean (%CV)
LDV PK Parameter	**LDV 120 mg BID (N=59)**
AUC_{0-12} (h·ng/mL)	15900 (27.0)
AUC_{0-24} (h·ng/mL)**	31900 (27.0)
C_{max} (ng/ml)	1520 (27.9)
C_{tau} (ng/ml)	1280 (29.8)

Preliminary data reported to 3 significant figures; AUC_{0-24} (LDV 120 mg BID) calculated as AUC_{0-12} X 2

Preliminary Pharmacodynamic Results:

Preliminary results from this study showed the expected effect of the single dose of moxifloxacin (positive control) on the QTc intervals (QTcF, QTcN, and QTcI), indicating that the study had the sensitivity to demonstrate small QT effects. The lower bound of the 2-sided 96.67% CI was above 5 msec at all three time points (3, 3.5 and 4 hours post dose) using all QTc correction methods.

Evaluation of the baseline–adjusted mean differences between LDV and placebo and their associated 2-sided 90% CIs demonstrated a lack of effect of LDV on QTcF interval prolongation (primary PD endpoint). The upper bounds of the 90% CIs were below 10 msec at all time points after dosing. Preliminary results from the non-inferiority QTcF analysis are presented in Table 1-12, below.

Consistent with QTcF results, a lack of LDV effect on QTcN and QTcI intervals was also demonstrated.

Table 1-12. GS-US-344-0109: Mixed-Model Analysis of Change from Predose Baseline in QTcF (msec) for Non-Inferiority Evaluation

Scheduled Time (h)	LS Means		Treatment Difference (90 % CI)
	LDV 120 mg BID (N=58)	Placebo (N=59)	LDV 120 mg BID -Placebo
0.5	-8.8	-8.4	-0.4 (-2.4, 1.5)
1.0	-12.1	-11.1	-1.0 (-3.0, 0.9)
2.0	-13.2	-12.1	-1.0 (-3.0, 0.9)
3.0	-13.1	-13.2	0.0 (-1.9, 2.0)
3.5	-10.4	-10.6	0.3 (-1.7, 2.2)
4.0	-8.6	-8.2	-0.5 (-2.4, 1.5)
4.5	-6.4	-6.3	-0.1 (-2.1, 1.9)
5.0	-4.3	-3.2	-1.1 (-3.0, 0.9)
8.0	-12.5	-13.6	1.1 (-0.9, 3.1)
12.0	-10.8	-12.3	1.5 (-0.5, 3.5)

LS Means = Least Squares Means

No subject on LDV or placebo had absolute QTcF intervals > 450 msec or change from predose baseline QTc > 30 msec using any correction methods. One LDV subject had an absolute QTcN interval > 450 msec and one placebo subject had an absolute QTcI interval > 450 msec.

Preliminary Safety

LDV administration was safe and well tolerated. No Grade 3 or 4 adverse events (AEs) or serious AEs (SAEs) were observed. One patient discontinued the study prematurely due to an exacerbation of their pre-existing condition of kidney stones. Three subjects experienced clinically significant Grade 3 laboratory abnormalities. The first subject was the previously mentioned subject with the pre-existing condition of kidney stones, who was noted to have 3+ blood in the urine. Another male subject had Grade 1 blood in the urine at discharge, and a Grade 3 blood in the urine at follow up 1 month later; further workup is pending. The third subject with a Grade 3 laboratory abnormality had an elevated AST that, upon retesting, was not confirmed, possibly suggesting a laboratory error. No clinically significant ECG morphologic changes were observed.

Preliminary Conclusions

LDV administration was safe and well tolerated. No Grade 3, 4 AEs or SAEs occurred. No clinically significant changes in ECG or wave morphology were observed.

LDV exposures achieved in this study are deemed adequate to cover the therapeutic or supratherapeutic exposures of LDV in HCV-infected subjects in the case of an overdose or a drug-drug interaction.

Preliminary PD results demonstrate lack of prolongation effects of LDV 120 mg BID supratherapeutic dose/exposure on QTcF, QTcN and QTcI. Categorical analyses demonstrate that LDV 120 mg did not have marked effects on QTc intervals.

1.3.3. Other Ongoing Phase 2 Studies

Study GS-US-248-0120 is an ongoing all oral Phase 2 study that will examine the safety, tolerability and antiviral efficacy of LDV administered with GS-9451, TGV and RBV in treatment naïve, genotype 1 HCV infected subjects. Dosing is complete.

Study GS-US-248-0121 is an ongoing Phase 2 study that will examine the efficacy, safety, and tolerability of response guided therapy of combinations LDV + GS-9451 + Peg-IFNα/RBV for 6 or 12 weeks, compared to Peg-IFNα/RBV for 24 weeks in genotype 1 HCV infected, IL28B CC subjects. Dosing is complete.

Study GS-US-248-0131 is an ongoing all oral Phase 2 study that will examine the safety, tolerability and antiviral efficacy of LDV, GS-9451, TGV and RBV compared with LDV, GS-9451 with TGV or RBV in treatment-experienced subjects with chronic genotype (1a or 1b) HCV infection. Dosing is complete.

Study GS-US-248-0132 is an ongoing all oral Phase 2 study that will examine the safety, tolerability and antiviral efficacy of LDV, GS-9451, TGV and RBV; LDV, GS-9451 and TGV; LDV, GS-9451 and RBV in IFN ineligible or intolerant subjects with chronic genotype (1a or 1b) HCV infection. Dosing is complete.

Study GS-US-256-0148 is an ongoing Phase 2b study that will examine the efficacy, safety, and tolerability of response guided therapy with LDV, Peg-IFNα and RBV with or without GS-9451 in genotype 1 HCV infected, treatment-naïve subjects. Dosing is complete.

Study GS-US-256-0124 is an ongoing Phase 2b study that will examine the efficacy, safety, and tolerability of response guided therapy of combinations of oral antivirals (LDV, TGV, and/or GS-9451) with Peg-IFNα and RBV in treatment experienced subjects with chronic genotype 1 HCV infection. Dosing is complete.

1.3.3.1. Adverse Events in Ongoing Phase 2 Studies

The treatment-emergent AEs reported through September 2012 for all subjects enrolled in the GS-US-248-0120, GS-US-248-0131, GS-US-248-0132, GS-US-248-0121 (Arm 1), GS-US-256-0124, GS-US-256-0148, aggregated by treatment regimen, is shown in Table 1-13.

Table 1-13. Treatment-Emergent Adverse Events Experienced by ≥10% of Subjects in Any Interferon-Free Regimen

Preferred Terms	LDV IFN-free regimens (N=469)	LDV + GS-9451 + TGV (N=109)	LDV + GS-9451 + TGV + RBV (N=251)	LDV + GS-9451 + RBV (N=109)	LDV IFN-containing regimens (N=622)	LDV + GS-9451 + Peg-IFNα+ RBV (N=506)	LDV + Peg-IFNα+ RBV (N=116)
Subjects experiencing any AE with ≥10% incidence	85%	81%	88%	83%	96%	96%	98%
Fatigue	29%	27%	30%	27%	45%	45%	46%
Headache	28%	31%	26%	28%	37%	38%	35%
Nausea	17%	18%	16%	18%	28%	27%	34%
Rash	10%	6%	13%	9%	24%	24%	22%
Insomnia	12%	11%	12%	13%	22%	22%	22%
Pruritus	13%	10%	14%	12%	19%	18%	22%
Cough	9%	6%	10%	11%	18%	18%	17%
Diarrhea	9%	6%	11%	6%	16%	16%	15%
Anaemia	6%	0	6%	11%	16%	16%	16%
Dizziness	7%	12%	7%	3%	12%	12%	10%

1.3.4. Overall LDV SAE Summary

A preliminary review of SAEs in all completed and ongoing studies that contain LDV alone or as part of a combination regimen identified no SAE signal associated with the use of LDV.

On September 19, 2012, Gilead Sciences notified sites of the discontinuation of dosing with four drug regimens that contained pegylated interferon-alfa-2a, RBV, an investigational protease inhibitor, and another investigational agent. Three reports of severe pancytopenia among 1,003 subjects with chronic HCV infection had been received. All 3 subjects, in addition to Peg-IFNα/RBV, received a NS3 protease inhibitor (1 case with GS-9256, 2 with GS-9451) in combination with either an NS5B non-nucleoside inhibitor (2 cases with tegobuvir [TGV; GS-9190]) or an NS5A inhibitor (1 case with LDV). Subjects receiving LDV in all-oral regimens are not impacted by this decision.

1.3.5. Deaths

Across all completed and ongoing LDV containing studies (as of January 2013), one death was reported within 30 days following treatment with a regimen containing LDV. This death (hemorrhagic stroke) was considered related to study drugs.

The subject, a 59-year-old male in Study GS-US-256-0148, on LDV, GS-9451, and Peg-IFNα plus RBV with a past medical history notable for hypertension, presented with a sudden onset headache and paralysis of the left arm. The computed tomography (CT) scan on admission was notable for an 8.2 cm hemorrhagic focus, with a 1 cm midline shift. At the time of admission, the subject's laboratory results were notable for a normal complete blood count, including a platelet count of 193,000 per μL, a normal International Normalized Ratio (1.13) and activated partial thromboplastin time (0.94), as well as normal alanine aminotransferase and aspartate aminotransferase values.

1.3.6. Safety Summary

In summary, the safety and PK data support ongoing evaluation of LDV in 2 or 3 drug combination regimens. An unblinded Data Monitoring Committee (DMC), which met 3-4 times/year, monitored the Phase 2 studies listed above. The last meeting of the DMC was in August 2012, during which continued clinical development of LDV was endorsed.

1.4. SOF/LDV FDC

Sofosbuvir/LDV FDC combines these two HCV specific DAA agents into a single tablet for the treatment of chronic HCV infection.

Please refer to the Investigator's Brochure (IB) for additional information on the SOF/LDV FDC including:

- In Vitro Anti-Hepatitis C Virus Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.4.1. Summary of Additional Clinical Experience

1.4.1.1. Ongoing Clinical Pharmacology Studies

1.4.1.1.1. GS-US-334-0101

Study GS-US-334-0101 was a Phase 1 study evaluating the potential for drug-drug interaction between SOF and LDV. The study was an open-label fixed-sequence study in healthy volunteers, in which Cohort 1 subjects received single doses of SOF (400 mg, once daily) alone or in combination with multiple doses of LDV (90 mg, spray-dried dispersion, once daily), under fasted conditions.

Preliminary PK results for the combination of SOF with LDV (Cohort 1) are presented below Table 1-14, and demonstrate lack of a clinically significant interaction between SOF and LDV.

Table 1-14. Study GS-US-334-0101: Pharmacokinetic Data for SOF, Metabolites (GS-566500 and GS-331007) and LDV on Administration of Sofosbuvir (SOF) and LDV Alone or in Combination

SOF (n=17)			
Mean (%CV)	**SOF alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	794 (36.3)	1750 (27.8)	229 (191, 276)
AUC_{last} (ng.hr/mL)	787 (36.6)	1740 (27.8)	230 (191, 277)
C_{max} (ng/mL)	929 (52.3)	1870 (27.9)	221 (176, 278)
GS-566500 (n=17)			
Mean (%CV)	**SOF alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1110 (31.6)	1950 (22.8)	179 (155, 207)
AUC_{last} (ng.hr/mL)	1060 (32.7)	1890 (22.8)	182 (157, 210)
C_{max} (ng/mL)	312 (38.7)	553 (26.6)	182 (154, 216)
GS-331007 (n=17)			
Mean (%CV)	**SOF alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	10900 (17.5)	13000 (16.7)	119 (113, 126)
AUC_{last} (ng.hr/mL)	10200 (17.9)	12100 (15.5)	119 (113, 125)
C_{max} (ng/mL)	1060 (17.3)	864 (20.1)	81.2 (76.9, 85.8)
LDV (n=17)			
Mean (%CV)	**LDV alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/mL)	11900 (26.2)	11400 (27.1)	95.8 (92.1, 99.5)
C_{max} (ng/mL)	756 (24.7)	735 (27.0)	96.5 (89.9, 104)
C_{tau} (ng/mL)	375 (28.8)	360 (31.2)	95.5 (91.9, 99.1)

Data presented as 3 significant figures.

Sofosbuvir plasma exposure was increased by ~ 2.3-fold by LDV. The effect of LDV on SOF is likely due to inhibition of intestinal P-gp and/or BCRP, of which SOF is a known substrate. GS-331007 (predominant, circulating metabolite of SOF) exposure was unaffected by LDV. The increase in SOF (SOF, top panel) is not considered clinically significant due to its very low and transient exposure relative to total drug related material (DRM) exposure (DRM, calculated as the sum of the AUCs for each of the analytes, corrected for molecular weight). Based on this calculation, the AUC of SOF with LDV is only ~ 5.7% of DRM AUC.

A drug interaction study (P7977-1819) of SOF with cyclosporine (potent multi-drug transporter inhibitor) demonstrated a 4-fold increase in systemic SOF exposure on administration with cyclosporine; the AUC of SOF increased from ~3 % (SOF alone) to ~11% (SOF with cyclosporine) of DRM AUC. Safety margins for all analytes of SOF on administration with cyclosporine continue to remain adequate (AUC safety margin ranges from 1.9 to 16.0) compared to exposures obtained in toxicology studies and dose modification of SOF is not warranted.

Ledipasvir PK was not altered on co-administration with SOF. Accordingly, SOF and LDV may be co-administered without dose adjustment.

No treatment-emergent AEs were reported in Cohort 1, based on a review of preliminary data. Two Grade 3 laboratory abnormalities were observed: an unconfirmed neutrophil count of 700 µL in an African-American subject with an otherwise normal white blood cell count; and an unconfirmed 3+ blood in urine in an adult menstruating female. No Grade 4 laboratory abnormalities were observed.

1.4.1.1.2. GS-US-337-0101

Study GS-US-337-0101 is an ongoing, single-center, Phase 1, single-dose, cross-over study evaluating the relative bioavailability and the effect of food on the PK of SOF 400 mg/LDV 90 mg FDC in healthy volunteers.

In Cohort 1, the PK of SOF 400 mg/LDV 90 mg FDC was evaluated relative to that of SOF 400 mg + LDV 90 mg, coadministered as individual components. The effect of food (moderate-fat or high calorie/high-fat meals) on the PK of SOF/LDV FDC was evaluated in Cohort 2.

Preliminary PK data from Cohorts 1 and 2 are presented in Table 1-15 and Table 1-16, respectively.

Table 1-15. Study GS-US-337-0101: Preliminary Pharmacokinetic Data for SOF, Metabolites (GS-566500 and GS-331007) and LDV on Administration of SOF/LDV FDC and SOF+LDV as Individual Components

SOF (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1350 (37.7)	1560 (39.4)	87.2 (77.8, 97.6)
AUC_{last} (ng.hr/mL)	1340 (37.9)	1560 (39.6)	87.2 (77.7, 97.7)
C_{max} (ng/mL)	1320 (68.3)	1550 (46.1)	82.3 (71.2, 95.2)
GS-566500 (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1690 (30.0)	2000 (27.8)	85.4 (76.2, 95.8)
AUC_{last} (ng.hr/mL)	1650 (30.8)	1950 (28.5)	85.4 (75.6, 96.4)
C_{max} (ng/mL)	429 (33.2)	509 (28.7)	86.0 (74.8, 98.9)
GS-331007 (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	11900 (23.5)	12500 (23.1)	95.4 (89.9, 101)
AUC_{last} (ng.hr/mL)	11200 (24.4)	11800 (23.6)	95.3 (89.5, 101)
C_{max} (ng/mL)	784 (36.2)	764 (27.3)	100 (91.2, 110)
LDV (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	9570 (46.6)	9620 (45.6)	95.7 (79.1, 116)
AUC_{last} (ng.hr/mL)	7950 (41.6)	8040 (40.0)	95.3 (79.0, 115)
C_{max} (ng/mL)	314 (45.2)	314 (40.5)	98.2 (82.1, 118)

Data presented as 3 significant figures.

Similar plasma exposures of SOF, its metabolites GS-566500 and GS-331007, and LDV were achieved upon administration of SOF/LDV FDC and SOF+LDV, co-administered as individual components. The lower bounds of the 90% confidence intervals (CIs) for the primary PK parameters (AUC and C_{max}) of SOF, GS-566500 and LDV were greater than 70%. The GMR% and 90% CIs for GS-331007 primary PK parameters were contained within bioequivalence bounds of 80-125%. Based on these data, this SOF/LDV FDC tablet formulation has been selected for Phase 3 clinical development.

Table 1-16. Study GS-US-337-0101: Preliminary Pharmacokinetic Data for SOF, Metabolites (GS-566500 and GS-331007) and LDV on Administration of SOF/LDV FDC Fasted or with a Moderate-Fat Meal or with A High-Calorie/High Fat Meal

SOF (n=29)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1530 (39.2)	2880 (33.6)	194 (176, 214)
AUC_{last} (ng.hr/mL)	1520 (39.6)	2870 (33.8)	195 (1767, 215)
C_{max} (ng/mL)	1240 (49.6)	1540 (39.4)	126 (109, 147)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1530 (39.2)	2590 (34.1)	178 (161, 197)
AUC_{last} (ng.hr/mL)	1520 (39.6)	2580 (34.4)	178 (161, 197)
C_{max} (ng/mL)	1240 (49.6)	1380 (40.6)	115 (99.0, 134)
GS-566500 (n=29)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1520 (41.3)	2490 (21.1)	175 (161, 189)
AUC_{last} (ng.hr/mL)	1470 (43.3)	2440 (21.5)	180 (164, 196)
C_{max} (ng/mL)	352 (42.7)	489 (21.8)	151 (136, 167)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1520 (41.3)	2550 (22.6)	179 (165, 194)
AUC_{last} (ng.hr/mL)	1470 (43.3)	2500 (23.0)	184 (168, 201)
C_{max} (ng/mL)	352 (42.7)	507 (26.1)	154 (139, 171)
GS-331007 (n=29)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	11800 (23.0)	13800 (17.9)	117 (112, 123)
AUC_{last} (ng.hr/mL)	11300 (23.4)	12800 (18.3)	114 (108, 121)
C_{max} (ng/mL)	865 (26.6)	696 (19.7)	82.0 (76.0, 88.0)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	11800 (23.0)	12900 (19.0)	112 (107, 118)
AUC_{last} (ng.hr/mL)	11300 (23.4)	12200 (19.4)	110 (103, 116)
C_{max} (ng/mL)	865 (26.6)	597 (23.3)	70.0 (65.0, 76.0)

LDV (n=27)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	9610 (52.3)	10100 (33.8)	120 (103, 141)
AUC_{last} (ng.hr/mL)	7940 (51.0)	8220 (30.0)	118 (101, 139)
C_{max} (ng/mL)	310 (45.4)	313 (26.0)	112 (96.0, 131)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	9610 (52.3)	8740 (34.0)	107 (92.0, 126)
AUC_{last} (ng.hr/mL)	7940 (51.0)	7350 (31.3)	107 (91.0, 126)
C_{max} (ng/mL)	310 (45.4)	254 (27.5)	92.0 (79.0, 108)

Data presented as 3 significant figures.

Food slowed the rate of absorption of SOF (median T_{max}: 1.00 versus 2.00 hours) with only modest alteration in the bioavailability, as evidenced by increases of 2-fold or less in SOF and GS-566500 plasma exposure. For GS-331007, an approximately 20-30% lower C_{max} was observed upon SOF administration with food with no change in AUC. The %GMR and associated 90% CI (fed/fasted treatments) for AUC of GS-331007 were within the equivalence bounds of 70% to 143%. Since the decrease in GS-331007 C_{max} was modest and the AUC parameters met the equivalence criteria, the effect of food on GS-331007 PK was not considered clinically significant. These results are consistent with the data from previous Phase 1 studies (P7977-1318 and P7977-0111), which demonstrated that SOF could be administered without regard to food.

Similar LDV plasma exposures (AUC and C_{max}) are achieved upon administration of LDV as the FDC under fasted or fed conditions. The %GMR and associated 90% CIs (fed/fasted treatments) were within the equivalence bounds of 70-143%. While a "negative" food effect was previously observed on LDV (single agent administered as conventional formulation), the PK of LDV (spray dried formulation) administered within the SOF/LDV FDC does not appear to be altered by food.

As such, SOF/LDV FDC may be administered without regard to food.

Based on a preliminary safety data review of Cohorts 1 and 2, SOF/LDV FDC was generally well tolerated. Fifty-eight subjects were enrolled and 56 completed the study as planned. Two subjects withdrew consent in Cohort 2 for reasons not associated with an AE. The most frequently reported AEs in >1 subject were vessel puncture site pain (n=5), headache (n=5), abdominal pain (n=3), menstrual cramps (n=3), and constipation (n=3). AEs were transient and mostly mild in severity. A pregnancy was reported during the end of study follow-up visit in a 36 year old, African American female, that later resulted in a SAE of spontaneous abortion (first trimester). No other SAEs, ≥ Grade 2 AEs, or clinically significant laboratory abnormalities were reported.

1.4.1.2. Ongoing Phase 2 Studies

1.4.1.2.1. GS-US-337-0118 (LONESTAR)

LONESTAR is a single center Phase 2 study evaluating SOF/LDV±RBV in treatment-naive and treatment-experienced genotype 1 HCV-infected subjects. In summary, subjects were enrolled into 2 cohorts as follows:

- Cohort 1: Treatment-naive, non-cirrhotic subjects received SOF/LDV±RBV for 8 weeks or SOF/LDV for 12 weeks (Groups 1, 2 and 3; n ~ 20/group)
  - — Group 1 (n=20): SOF/LDV FDC once daily for 8 weeks
  - — Group 2 (n=20): SOF/LDV FDC once daily + RBV (1000 or 1200 mg/day divided BID) for 8 weeks
  - — Group 3 (n=20): SOF/LDV FDC once daily for 12 weeks
- Cohort 2: Treatment-experienced, PI-failure subjects, of whom 50% were cirrhotic, received SOF/LDV±RBV for 12 weeks (Groups 4 and 5; n ~ 20/group)
  - — Group 4 (n=20): SOF/LDV FDC once daily for 12 weeks
  - — Group 5 (n=20): SOF/LDV FDC once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

In Cohort 1, (Groups 1-3) randomization was stratified by genotype (1a or 1b). In Cohort 2 (Groups 4-5) randomization was stratified by genotype (1a or 1b) and the presence or absence of cirrhosis.

All subjects in this study have completed treatment in Groups 1 to 5. Preliminary safety, PK, and efficacy data are presented below.

1.4.1.2.1.1. Study GS-US-337-0118 (LONESTAR): Preliminary Safety

Based on a preliminary review of the data, SOF/LDV FDC was well tolerated in this study. Adverse events were generally mild or moderate. Three SAEs were reported, none of which was considered related to the study drugs. There were no discontinuations due to adverse events. The most frequent adverse events were nausea (n = 8, 8%), anemia (n = 6, 6%), and headache (n = 6, 6%). To date, no safety signal associated with SOF/LDV FDC has been identified.

1.4.1.2.1.2. Study GS-US-337-0118 (LONESTAR): Preliminary Pharmacokinetic Data

An optional intensive PK substudy was conducted at Week 2 or Week 4 on-treatment visit to examine the PK of SOF, GS-566500, GS-331007 and LDV. A total of 83 subjects

(Groups 1-3: 48 subjects; Groups 4-5: 35 subjects [21 subjects with cirrhosis and 14 subjects without cirrhosis]) participated in the PK substudy.

Preliminary pharmacokinetic data are shown in Table 1-17.

Preliminary PK data showed similar SOF, GS-566500 and GS-331007 systemic exposures in subjects who were treatment-naive and those who were PI failures with or without cirrhosis. LDV mean exposure parameters (AUC_{tau}, C_{max} and C_{tau}) were similar in PI failure subjects with or without cirrhosis and overall modestly (~ 30-40%) lower than LDV plasma exposures in non-cirrhotic treatment-naive subjects.

Table 1-17. Study GS-US-337-0118 (LONESTAR): SOF, GS-566500, GS-331007 and LDV PK Parameters Following Administration of SOF/LDV (400 mg/90 mg) ± RBV (Preliminary Data)

PK Parameter Mean (%CV)	Groups 1-3 GT1 TN FDC± RBV (pooled)	Groups 4-5 GT1 PI Failure FDC± RBV without Cirrhosis (pooled)	Groups 4-5 GT1 PI Failures FDC± RBV with Cirrhosis (pooled)
SOF	**N=48**	**N=14**	**N=21**
AUC_{tau} (hr·ng/mL)	2260 (47.8)†	2460 (42.6)*	2440 (39.3)
C_{max} (ng/mL)	1280 (60.1)	1310 (48.5)	1520 (46.4)
C_{tau} (ng/mL)	BLQ	BLQ	BLQ
GS-566500	**N=47**	**N=14**	**N=21**
AUC_{tau} (hr·ng/mL)	3420 (27.5)	4110 (37.4)	4240 (31.8)
C_{max} (ng/mL)	689 (34.2)	734 (37.1)	846 (33.2)
C_{tau} (ng/mL)	15.1 (30.5) ††	13.5 (29.5)**	13.3 (25.5)**
GS-331007	**N=47**	**N=14**	**N=14**
AUC_{tau} (hr·ng/mL)	12600 (34.6)	11600 (39.3)	11900 (36.6)
C_{max} (ng/mL)	937 (34.8)	801 (36.2)	885 (35.0)
C_{tau} (ng/mL)	336 (46.7)	327 (48.3)	301 (45.2)
LDV	**N=47**	**N= 14**	**N= 21**
AUC_{tau} (hr·ng/mL)	9470 (51.8)	6210 (44.9)	6510 (65.1)
C_{max} (ng/mL)	504 (43.9)	356 (37.4)	364 (52.7)
C_{tau} (ng/mL)	344 (63.1)	202 (57.8)	220 (72.8)

Preliminary data reported to 3 significant figures; † N =45; †† N=4; *N=13; ** N=3; BLQ: below the limit of quantification

1.4.1.2.1.3. Study GS-US-337-0118 (LONESTAR): Preliminary Efficacy

Currently available virologic response data for all subjects enrolled in LONESTAR is presented in Table 1-18, below.

All subjects in Groups 1-3 were treatment-naive and non-cirrhotic. In Group 1 (SOF/LDV FDC for 8 weeks), 95% of subjects, irrespective of HCV genotype (1A or 1B) and IL28B allele (CC, CT, or TT), had HCV RNA < LLOQ at post-treatment Week 12. A single subject relapsed by the post-treatment Week 8 assessment. In Group 2 (SOF/LDV+RBV) all subjects (100%) had HCV RNA < LLOQ at post-treatment Weeks 4, 8 and 12. In Group 3, all subjects (100%) achieved SVR8 and 95% (18/19) achieved SVR12; 1 subject was LTFU after Post-Treatment Week 8.

All subjects in Groups 4 and 5 previously failed treatment with a PI+Peg-IFNα+RBV regimen; in each group, approximately 50% of subjects have cirrhosis. In Group 4, 89% were HCV RNA < LLOQ at post-treatment Week 12; one subject experienced virologic failure while one additional subject is pending SVR12 and is considered to be a failure for the purpose of this analysis. In Group 5, 95% were HCV RNA < LLOQ at post-treatment Weeks 4, 8 and 12 (one subject in Group 5 experienced SAEs of anemia and suicidal ideation and has not yet returned during the post-treatment period).

Table 1-18. Study GS-US-337-0118 (LONESTAR): Groups 1, 2, 3, 4 and 5 Available SVR Data

Grp. No./ Population/ Regimen	Duration		N (GT1)	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
1 GT1 TN SOF/LDV	8 wks	Total	20 (20)	100 (20/20)	100 (20/20)	95 (19/20)	95 (19/20)	5 (1/20)	0 (0)	0 (0)
		GT1a	17	100 (17/17)	100 (17/17)	94 (16/17)	94 (16/17)	6 (1/17)	0 (0)	0 (0)
		GT1b	3	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	0 (0/3)	0 (0)	0 (0)
2 GT1 TN SOF/LDV+RBV	8 wks	Total	21 (21)	100 (21/21)	100 (21/21)	100 (21/21)	100 (21/21)	0 (0/21)	0 (0)	0 (0)
		GT1a	19	100 (19/19)	100 (19/19)	100 (19/19)	100 (19/19)	0 (0/19)	0 (0)	0 (0)
		GT1b	2	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	0 (0/2)	0 (0)	0 (0)
3 GT1 TN SOF/LDV	12 wks	Total	19 (19)	100 (19/19)	100 (19/19)	100 (19/19)	95*(18/19)	0 (0/18)	0 (0)	0 (0)
		GT1a	17	100 (17/17)	100 (17/17)	100 (17/17)	94 *(16/17)	0 (0/16)	0 (0)	0 (0)
		GT1b	2	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	0 (0/2)	0 (0)	0 (0)
4 GT1 PI Failures SOF/LDV	12 wks	Total	19 (19)	100 (19/19)	95 (18/19)	95 (18/19)	89** (17/19)	5 (1/19)	0 (0)	0 (0)
		GT1a	18	100 (18/18)	94 (17/18)	94 (17/18)	89 **(16/18)	6 (1/17)	0 (0)	0 (0)
		GT1b	1	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	0 (0/1)	0 (0)	0 (0)
5 GT1 PI Failures SOF/LDV+RBV	12 wks	Total	21 (21)	100 (21/21)	95 (20/21)	95 (20/21)	95 (20/21)	0 (0/21)	0 (0)	5 (1)
		GT1a	16	100 (16/16)	100 (16/16)	100 (16/16)	100 (16/16)	0 (0/16)	0 (0)	0 (0)
		GT1b	5	100 (5/5)	80 (4/5)	80 (4/5)	80 (4/5)	0 (0/5)	0 (0)	20 (1)

BT: breakthrough; LTFU: lost to follow up

* Subject 2530 in Group 3 (GT1a) achieved SVR8. SVR12 data is pending. For this analysis it is assumed that the subject did not achieve SVR12.

** Subject 2665 in Group 4 (GT1a) achieved SVR8. SVR12 data is pending. For this analysis it is assumed that the subject did not achieve SVR12.

1.4.1.2.1.4. Study GS-US-337-0118 (LONESTAR): Preliminary Resistance Analysis

The full-length NS5A region was analyzed at baseline for all 100 subjects (76 genotype 1a and 24 genotype 1b by LiPA) by deep sequencing. Baseline NS5A resistance associated variants (RAVs) were detected in a total of 9/100 (9%) subjects. Eight genotype 1a subjects and 1 genotype 1b subject had at least one LDV RAVs present at baseline, at levels ranging from 1.3% to 99.9%. Eight genotype 1a subjects with baseline NS5A RAVs had M28T, Q30L, Q30H, Q30R, L31M, Y93C, or Y93H variants detected while one genotype 1b subject had Y93H RAV. All these mutants, except Q30L, have been shown to confer significant reductions in susceptibility to LDV in vitro (Table 1-19). Of these 9 subjects, only 2/9 subjects experienced virologic relapse. One subject (subject 2504) had L31M present at 21.45% prior to treatment and experienced virologic relapse following 8 weeks of FDC treatment. Another subject (subject 2635) had >99% Q30H and >99% of Y93H (double mutants Q30H+Y93H likely) at baseline and experienced virologic relapse following 12 weeks of FDC treatment. In contrast, the remaining 7 out of 9 subjects achieved SVR4, or SVR12 (n = 5 on FDC and n=2 on FDC+RBV) despite the presence of baseline RAVs that confer a high level of reduced susceptibility to LDV. These data indicate that the presence of NS5A RAVs at baseline do not preclude the ability of subjects treated with SOF+LDV or SOF+LDV+RBV regimens from achieving a sustained virologic response.

Table 1-19. Study GS-US-337-0118 (LONESTAR): Subjects with Baseline Ledipasvir RAVs

Subject ID	Genotype	Treatment Group	NS5A Mutant (%)	NS5A Single Mutant Fold-change in LDV EC50	SVR 4 Result	SVR 8 Result	SVR 12 Result
2504	1a	Group 1	L31M (21.45%)	L31M: 140	Relapse		
2521	1a	Group 1	L31M (91.54%), Q30H (3.28%)	L31M: 140 Q30H:73	SVR	SVR	SVR
2561	1b	Group 2	Y93H (43.51%)	Y93H: 3310	SVR	SVR	SVR
2506	1a	Group 3	Y93C (14.05%)	Y93C: 2531	SVR	SVR	N/A
2519	1a	Group 3	Q30R (1.34%)	Q30R: 170	SVR	SVR	N/A
2524	1a	Group 3	Q30H (95.00%)	Q30H: 73	SVR	SVR	N/A
2635	1a	Group 4	Q30H (99.42%), Y93H (99.89%)	Q30H: 73 Y93H: 3029	Relapse		
2666	1a	Group 5	M28T (53.84%), Q30R (96.65%)	M28T: 25 Q30R: 170	SVR	N/A	N/A
2671	1a	Group 5	Q30L (98.83%), Y93H (99.56%)	Q30L: 4 Y93H: 3029	SVR	N/A	N/A

1.4.1.3. Ongoing Phase 3 Studies

1.4.1.3.1. GS-US-337-0102 (ION-1)

Study GS-US-337-0102 is a Phase 3, multicenter, randomized, open-label study investigating efficacy and safety of SOF/LDV ± RBV for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection. 207 subjects were enrolled in Part A. The study is ongoing.

1.4.1.3.2. GS-US-337-0109 (ION-2)

Study GS-US-337-0109 is a Phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of SOF/LDV FDC ± RBV for 12 and 24 weeks in treatment-experienced subjects with chronic genotype 1 HCV infection. Enrollment is complete.

1.4.1.3.3. GS-US-337-0108 (ION-3)

Study GS-US-337-0108 is a Phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of SOF/LDV FDC±RBV for 8 weeks and SOF/LDV FDC for 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection. Enrollment is complete.

1.5. Ribavirin (RBV)

Ribavirin is a guanosine analogue that inhibits the *in vitro* replication of a wide range of RNA and DNA viruses {15572}, {15668}. Ribavirin monotherapy has little or no effect on the replication of HCV *in vivo* but can result in normalization of serum ALT activity and improvement in liver histology. When combined with IFN or Peg-IFN therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy {12557}, {12558}.

Ribavirin is a known teratogen. Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment.

A comprehensive review of RBV is contained in the package insert.

1.6. Rationale for the Current Study

This Phase 3b study is designed to evaluate the efficacy and safety of the SOF/LDV FDC tablet ± ribavirin administered for 12 weeks in treatment-naïve and treatment-experienced subjects with chronic genotype 1 HCV infection. Up to 40% of subjects enrolled in the study may have Child’s Pugh-A compensated cirrhosis at screening. This study will establish the efficacy of the 12-week SOF/LDV FDC±RBV regimen compared to historical SVR control rates.

As previously described in Section 1.1.2 there is a significant unmet medical need in Japan for simple, well-tolerated, IFN-free, all-oral antiviral regimens for the treatment of chronic HCV infection. The current standard of care for these patients (Peg-IFNα+RBV±TVR) is associated with significant toxicity, with many patients unwilling to be treated with these regimens. There also exists substantial numbers of patients who cannot receive Peg-IFNα-IFN due to relative or absolute contraindications {20450}, {17893}, {17893}, {15573}, {17892}, {3291}.

Gilead has developed a FDC consisting of SOF with LDV, 2 well-tolerated, potent, once-daily antiviral agents in late phase clinical development. Based on Phase 2 data, the SOF/LDV FDC has the potential to be a simple and highly effective all-oral, once daily treatment regimen for chronic genotype 1 HCV infection, administered for a short 12-week duration.

Initial proof of concept for the efficacy of SOF administered in combination with a HCV NS5A inhibitor comes from the AI444-040 study (Section 1.2.2.2). In this study 12 weeks of SOF+DCV resulted in SVR4 rates of 95% and 98% when administered with RBV and without RBV respectively. In addition 100% (41/41) SVR4 was achieved when SOF+DCV±RBV was administered for 24 weeks in subjects who had failed to respond to Peg-IFNα+RBV+PI therapy.

Subsequently, proof of concept for the efficacy of the SOF+LDV combination comes from ELECTRON Arm 13 (n=25), in which 100% of the treatment-naïve patients who received SOF+LDV+RBV for 12 weeks achieved SVR24 (Section 1.2.2.1). Proof of concept for the efficacy of this same regimen in the most difficult-to-treat treatment-experienced patients (null responders) also came from ELECTRON Arm 12 (n=9), in which 100% of these patients achieved SVR24 after 12 weeks of therapy (Section 1.2.2.1).

Finally, recent data from the GS-US-337-0118 (LONESTAR) study reports SVR12 rates of 95% (19/20) and 100% (21/21) in GT-1 treatment-naïve subjects for SOF/LDV FDC administered for 8 weeks, with and without concomitant RBV respectively (Section 1.4.1.2.1)**.** Following administration of SOF/LDV FDC for 12 weeks in GT-1 treatment-naïve subjects 95% (18/19) achieved SVR12; 1 subject who achieved SVR8 is pending a post-treatment week 12 visit and for the purpose of this analysis is assumed to be a failure at post-treatment week 12. In GT-1 protease-inhibitor failures, SOF/LDV FDC administered for 12 weeks achieved an SVR8 rate of 95% (18/19) and SVR12 rate of 89% (17/19); one subject experienced virologic failure and another, who achieved SVR8, is pending a post-treatment week 12 visit and for the purpose of this analysis is assumed to to be a failure at post-treatment week 12. Finally SOF/LDV FDC +RBV administered for 12 weeks in GT-1 protease-inhibitor failures achieved SVR8 and SVR12 rates of 95% (20/21). Notably, 50% of the treatment-experienced subjects in this study had compensated cirrhosis (Section 1.4.1.2.1).

The ongoing, blinded GS-US-337-0102 (ION-1) Phase 3 study (Section 1.4.1.3.1) is evaluating the same SOF/LDV FDC±RBV regimens proposed for the study in Japan. The Data Monitoring Committee met on 25 March 2013 to evaluate the safety and predefined interim futility criteria, and indicated the study was safe to proceed unchanged. Neither Group 3 (SOF/LDV FDC, 12 weeks) nor Group 4 (SOF/LDV FDC + RBV, 12 weeks) met protocol defined futility criteria.

Current data for the SOF/LDV FDC indicates the regimen to be safe, well-tolerated and associated high degrees of antiviral efficacy supporting the conduct of the proposed Phase 3 study in Japanese subjects with GT-1 chronic hepatitis C.

The proposed Phase 3b study will include treatment-naïve and treatment-experienced subjects, of which up to 40% may have Child's Pugh-A compensated cirrhosis at screening.

1.7. Rationale for Dose Selection of Sofosbuvir/Ledipasvir Fixed Dose Combination (FDC)

Sofosbuvir 400 mg, once daily, when dosed in combination with RBV with or without Peg-IFNα has demonstrated broad genotypic efficacy and favorable safety profile in over 3300 HCV-infected subjects across multiple patient populations in Phase 2 and 3 trials. This dose is the proposed marketed dose of sofosbuvir for the treatment of HCV-infection and as such, has been selected for co-formulation with LDV into a fixed-dose combination tablet.

The ledipasvir (LDV) has been administered in combination with other direct-acting antiviral agents including RBV, with or without Peg-IFNα to over 1,200 HCV-infected subjects in Phase 2 studies. LDV 90 mg was selected for co-formulation with SOF and evaluation in this study based on the safety, PK and antiviral activity data (studies GS-US-256-0102 and GS-US-248-0120). Study GS-US-256-0102 established the anti-HCV activity of LDV and indicated that the exposures achieved following administration of the 30 mg dose provides >95% of maximal antiviral response in genotype 1a HCV infected subjects. It was also observed that 30 mg or greater of LDV likely provided coverage of some drug related mutations that doses less than 30 mg did not, based on an analysis of NS5A mutants that arose in response to exposure to LDV. Therefore, 30 mg and 90 mg of LDV were selected for further clinical evaluation.

In the Peg-IFNα-free Study GS-US-248-0120, 30 mg of LDV (Arm 1) is being compared to 90 mg of LDV (Arm 2), on a background of 3 other antivirals, vedroprevir (VDV), tegobuvir, and RBV. When comparing these 2 arms, the breakthrough (BT) rate (number of subjects with HCV RNA > LLOQ after having achieved very rapid virologic response [vRVR]/total number of subjects who achieved vRVR), is higher in Arm 1 (BT = 27%, 9 of 33 subjects; LDV 30 mg), than Arm 2 (BT = 12%, 9 of 74 subjects; LDV 90 mg). vRVR was defined as HCV RNA < LLOQ at week 2. The 12% breakthrough rate in the 90 mg arms compared to a 27% breakthrough rate in the 30 mg arm supports the further development of the 90 mg dose of LDV.

The combination of SOF 400 mg and LDV 90 mg has been administered in on-going Phase 2 and Phase 3 studies to over 2,200 patients. The favorable safety and efficacy profiles of SOF 400 mg and LDV 90 mg support further evaluation of this combination and doses in clinical development.

1.8. Overall Risk/Benefit Assessment

The SOF/LDV FDC product combines a potent HCV nucleotide NS5B inhibitor and a potent HCV NS5A inhibitor.

The potential benefits of SOF/LDV FDC±RBV for the treatment of chronic HCV are:

- Greater antiviral efficacy (i.e., rapid and durable eradication of HCV) compared to the current standard of care (Peg-IFNα+RBV±TVR)
- A reduction in the AEs currently associated with the use of Peg-IFNα and the approved NS3 protease inhibitor, telaprevir (Telavic®)
- A simple, well-tolerated regimen to replace the current complex, response-guided PEG IFNα +RBV±TVR regimens.
- The potential benefit of a shortened SOF/LDV FDC±RBV therapy of 12 weeks is a decrease in the burden of treatment for both patients and physicians, through a reduction in the overall number of patient visits.

The safety profile of SOF includes approximately 3,300 chronic HCV-infected subjects that have been administered SOF in combination with a DAA, Peg-IFNα, with or without RBV. No clinical safety issues related to SOF have been identified to date. The safety profile of LDV includes approximately 1,200 chronic HCV-infected subjects, which was given in combination with other DAAs, Peg-IFNα, with or without RBV. No clinical safety issues related to LDV have been identified to date.

Furthermore, there is no expectation of significant overlapping or new, unexpected toxicities upon administration of SOF/LDV together as an FDC. To date, the SOF/LDV FDC ± RBV has been administered to over 2,200 HCV infected subjects in ongoing phase 2/3 trials. No clinical safety issues related to the SOF/LDV FDC have been identified to date.

During the conduct of the study the Sponsor will perform ongoing safety data review.

In summary, there is no currently approved all-oral treatment available for HCV-infected patients. This study will support the registration of the SOF/LDV FDC±RBV in treatment-naïve and treatment-experienced Japanese subjects with chronic genotype 1 HCV infection including those with Child’s Pugh-A compensated cirrhosis.

2. OBJECTIVES

The primary objectives of this study are:

- To determine the antiviral efficacy of combination treatment with SOF/LDV FDC ± RBV as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks post treatment)

- To evaluate the safety and tolerability of SOF/LDV FDC ± RBV as assessed by review of the accumulated safety data

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objectives of this study are:

- To identify or validate genetic markers that may be predictive of virologic response to therapy and/or tolerability of therapy through genetic discovery research (e.g., pharmacogenomics), in subjects who provide their separate and specific consent

- To assess the effect of treatment with SOF/LDV FDC ± RBV on HRQoL

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is a multicenter, open-label study in Japan that will evaluate the safety, tolerability and antiviral efficacy of SOF/LDV FDC ± RBV administered for 12 weeks in treatment-naïve and treatment-experienced subjects with chronic genotype 1 HCV infection.

Approximately 150 treatment-naïve subjects will be randomized (1:1) to either:

1) Group 1 (n~75):
   SOF 400 mg/LDV 90 mg FDC once daily for 12 weeks

2) Group 2 (n~75):
   SOF 400 mg/LDV 90 mg FDC once daily + RBV (weight-based dosing) for 12 weeks

Randomization into Group 1 and 2 will be stratified by the presence or absence of cirrhosis at Screening. Up to 40% of the treatment-naïve subjects enrolled may have evidence of Child's Pugh-A compensated cirrhosis at Screening.

Approximately 150 treatment-experienced subjects will be randomized (1:1) to either:

3) Group 3 (n~75):
   SOF 400 mg/LDV 90 mg FDC once daily for 12 weeks

4) Group 4 (n~75):
   SOF 400 mg/LDV 90 mg FDC once daily + RBV (weight-based dosing) for 12 weeks

Randomization into Group 3 and 4 will be stratified by presence or absence of cirrhosis at Screening, and by treatment-experienced category (i.e., Relapser/Breakthrough, Non-responder, or IFN-Intolerant). Up to 40% of the treatment-experienced subjects enrolled may have evidence of Child's Pugh-A compensated cirrhosis at Screening.

Of the 150 treatment-experienced subjects, it is estimated that ~90 will be Relapser/Breakthroughs, ~40 Non-Responders, and ~20 IFN-Intolerant.

3.2. Visit Schedule

All subjects will complete screening, on-treatment, and post-treatment assessments. Screening assessments will be completed within 28 days of the Baseline/Day 1 visit or within 42 days if a liver biopsy or additional HCV genotyping is required. All subjects will complete all post-treatment visits.

The assessments performed at each visit are described in Section 6.

3.3. Virologic Response-Based Stopping Criteria

The following on-treatment virologic response-based treatment stopping criteria will be utilized:

- Confirmed HCV RNA ≥ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 $\log_{10}$ increase in HCV RNA from nadir
- HCV RNA ≥ LLOQ through 8 weeks of treatment

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure during the on-treatment phase.

3.4. Treatment Discontinuations

When medically feasible, the Medical Monitor must be consulted prior to the premature discontinuation of treatment in a given subject.

Study drug(s) must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 7 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Pregnancy of female subject
- Efficacy failure as defined in Section 3.3
- Significant protocol violation
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

If a subject meets discontinuation criteria during treatment, an Early Termination visit will be required (Section 6.2.10). Following completion of the Early Termination visit, all subjects must complete the all Post-Treatment visits.

3.5. Substudies

3.5.1. Pharmacokinetic (PK) Substudy

All subjects, with a target of approximately ~15 treatment-naïve and
~15 treatment- experienced subjects, will be eligible to participate in the PK substudy if

consent is obtained. An intensive serial PK sample collection (i.e., samples obtained over 24 hours post-dose) will be performed at either the Week 2 or Week 4 on-treatment visit to determine the steady-state pharmacokinetics of SOF (and its metabolites GS-566500 and GS-331007), LDV and RBV (if appropriate).

3.5.2. Pharmacogenomic (PG) Substudy

All subjects will be eligible to participate in the PG substudy if consent is obtained. A blood sample should be drawn at the Baseline/Day 1 visit. If not obtained at Baseline/Day 1 visit, the sample may be drawn at any time during the study.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 300 subjects will be enrolled in this study with approximately 150 treatment-naïve subjects and approximately 150 treatment-experienced subjects. Up to 40% of enrolled subjects (i.e., treatment-naïve or treatment-experienced) may have Child's Pugh-A compensated cirrhosis at screening.

In order to manage the total study enrollment, Gilead Sciences at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study.

1) Willing and able to provide written informed consent

2) Male or female, age ≥ 20 years

3) Body weight ≥ 40 kg

4) HCV RNA ≥ 10^5 IU/mL at Screening

5) HCV treatment-naïve, as defined as no prior exposure to any IFN, RBV or other approved or experimental HCV-specific direct-acting antiviral agent; OR HCV treatment-experienced with medical records that include sufficient detail of prior treatment with IFN to allow for categorization of prior response as either:

    a) IFN Intolerant: Subject discontinued IFN treatment due to development or significant worsening of at least one of the conditions listed below. The last dose of IFN must have been administered ≥3 months prior to Screening.

        - Significant local or systemic adverse reaction to IFN (e.g., hypersensitivity, injection site reactions)
        - Psychiatric disease necessitating hospitalization or period of disability or psychosis, schizophrenia, bipolar disorder, depression, schizoaffective disorder, suicidal ideation, or suicide attempt
        - Significant cognitive impairment
        - Neuropathy
        - Disabling flu-like symptoms (arthralgias, fatigue, pyrexia, myalgia)
        - Gastrointestinal toxicity with nausea, vomiting or diarrhea

- Thrombocytopenia (platelets < 25,000/μL)
- Neutropenia (ANC < 500/μL)
- Development of colitis, non-alcoholic pancreatitis or ophthalmologic disorders
- Autoimmune disorder including but not limited to: myositis, hepatitis, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, immune (idiopathic) thrombocytopenic purpura, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, thyroiditis.
- AE related to IFN that is not listed after consultation with the Medical Monitor

Note: Subjects considered to be IFN-intolerant must (according to investigator judgment) have sufficiently recovered from IFN-related clinical adverse events and/or laboratory abnormalities prior to Screening. In addition, all other protocol eligibility criteria must be met.

b) Non-Response: Subject did not achieve undetectable HCV RNA levels on treatment

c) Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels during treatment or at the completion of administration of therapy but did not achieve a sustained virologic response (SVR)

Note: For treatment-experienced subjects, prior exposure to approved or experimental HCV-specific direct-acting antiviral agent(s) other than NS3/4A protease inhibitors is prohibited.

6) Genotype 1 HCV at Screening as determined by the Central Laboratory. Any non-definitive results will exclude the subject from study participation

7) Confirmation of chronic infection documented by either:

a) A positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Baseline/Day 1 visit, or

b) A liver biopsy performed prior to the Baseline/Day 1 visit with evidence of chronic infection

8) Cirrhosis determination [up to 40% of treatment-naïve subjects and up to 40% of treatment-experienced subjects may have Child's Pugh-A compensated cirrhosis]:

a) Cirrhosis is defined as any one of the following:

i) Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥ 5, see Appendix 4)

ii) Fibroscan indicative of cirrhosis as evidenced by a result > 12.5 kPa

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

i) Liver biopsy within 2 years of Screening showing absence of cirrhosis

ii) Fibroscan within 6 months of Baseline/Day 1 with a result of ≤ 12.5 kPa

9) Liver imaging (e.g., ultrasound or CT scan, at the discretion of the investigator) performed within 4-6 months prior to Baseline/Day 1 to exclude hepatocellular carcinoma (HCC) is required in all patients; i.e., within 4 months for subjects with cirrhosis and within 6 months for subjects without cirrhosis

10) Screening ECG without clinically significant abnormalities

11) Subjects must have the following laboratory parameters at screening:

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

b) AST ≤ 10 × ULN

c) Direct bilirubin ≤ 1.5 × ULN

d) Platelets ≥ 50,000/µL

e) Creatinine clearance (CL_{cr}) ≥ 60 mL /min, as calculated by the Cockcroft-Gault equation {2202}

f) Hemoglobin ≥ 11 g/dL for female subjects; ≥ 12 g/dL for male subjects.

g) Albumin ≥ 3g/dL

h) INR ≤ 1.5 × ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR.

12) Females of childbearing potential (as defined in Appendix 5) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Baseline/Day 1 prior to randomization.

13) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5.

14) Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator.

15) Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Current or prior history of any of the following:

    a) Clinically-significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol; subjects currently under evaluation for a potentially clinically-significant illness (other than HCV) are also excluded.

    b) Gastrointestinal disorder or post operative condition that could interfere with the absorption of the study drug.

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

    d) Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal hemorrhage, Child's-Pugh B or C cirrhosis).

    e) Solid organ transplantation.

    f) Significant pulmonary disease, significant cardiac disease or porphyria.

    g) Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Subjects with psychiatric illness (without the prior mentioned conditions) that is well-controlled on a stable treatment regimen for at least 12 months prior to Baseline/Day 1 or has not required medication in the last 12 months may be enrolled.

    h) Malignancy (other than hepatocellular carcinoma (HCC)) within the 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are not eligible. Patients with a history of HCC are not eligible for study participation.

    i) Uncontrolled diabetes mellitus.

    j) Significant drug allergy (such as anaphylaxis or hepatotoxicity).

2) If treatment-naïve, prior exposure to approved or experimental HCV-specific direct-acting antiviral agent(s). If treatment-experienced, prior exposure to approved or experimental HCV-specific direct-acting antiviral agent(s) other than NS3/4A protease inhibitors.

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

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

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

6) Donation or loss of more than 400 mL blood within 2 months prior to Baseline/Day 1

7) Contraindications to RBV therapy, including significant history of clinically significant hemoglobinopathy (e.g., sickle cell disease, thalassemia).

8) Use of any prohibited concomitant medications as described in Section 5.6 within 28 days of the Baseline/Day 1 visit; this washout period does not apply to Proton Pump Inhibitors (PPI) which can be taken up to 7 days before Baseline/Day 1.

9) Chronic use of systemically administered immunosuppressive agents including corticosteroids (e.g., prednisone equivalent > 10 mg/day) azathioprine or monoclonal antibodies such as infliximab. The Gilead Medical Monitor will be available to address questions from investigators regarding permissible corticosteroid use for this trial.

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Blinding

An Interactive Web Response System (IWRS) will be employed to manage subject randomization and treatment assignment. Randomization into Groups 1 and 2 will be stratified by the presence or absence of cirrhosis at Screening. Randomization into Groups 3 and 4 will be stratified by the presence or absence of cirrhosis at Screening and by treatment-experienced category (i.e., Relapser/Breakthrough, Non-responder or IFN-Intolerant). The study is an open-label study, and no blinding will be required.

5.2. Description and Handling of Sofosbuvir/Ledipasvir Fixed-Dose Combination

5.2.1. Formulation

Sofosbuvir/LDV FDC tablets are orange, diamond-shaped, film-coated tablets containing 400 mg of SOF and 90 mg of LDV. The tablets are debossed with “GSI” on one side and “7985” on the other side. The SOF/LDV FDC tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol and FD&C yellow # 6 /sunset yellow FCF aluminum lake.

5.2.2. Packaging and Labeling

Sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant canister or sachet and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

SOF/LDV FDC bottles to be distributed shall be labeled to meet applicable requirements of the Pharmaceuticals and Medical Devices Agency (PMDA) and/or other local regulations as applicable.

Sufficient quantities of SOF/LDV FDC tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Sciences Materials & Logistics (or its designee).

5.2.3. Storage and Handling

Sofosbuvir/LDV FDC bottles should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C (77°F); excursions are permitted between 15 °C and 30 °C (59°F to 86°F).

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling SOF/LDV FDC.

5.2.4. Dosage and Administration of Sofosbuvir/Ledipasvir FDC

Sofosbuvir/LDV FDC tablet is to be administered once daily either with or without food. However, for subjects receiving RBV, in order to maintain compliance with the treatment regimen, SOF/LDV FDC should be administered with the morning dose of RBV (Section 5.3.4) and consequently with food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the same day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

Study medications should not be cut or split.

5.3. Description and Handling of RBV

5.3.1. Formulation

Ribavirin will be provided in the course of this study as Copegus® tablets (Chugai Pharmaceuticals). Copegus® tablets are debossed with RIB 200 on one side and ROCHE on the other, light pink-colored, film-coated tablets. Each tablet contains 200 mg of ribavirin.

5.3.2. Packaging and Labeling

Copegus® tablets are packaged in blister packaging of 140 tablets. The ribavirin package shall be labeled for clinical use to meet all applicable requirements of the Pharmaceuticals and Medical Devices Agency (PMDA) and/or other local regulations as applicable.

5.3.3. Storage and Handling

Copegus® tablets should be stored at controlled room temperature. Controlled room temperature is defined as 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

5.3.4. Dosage and Administration of RBV

RBV will be administered in accordance with approved Copegus® labeling in Japan, see Table 5-1 below.

Table 5-1. Dosing and Administration of RBV in Japan

Body weight	Ribavirin dose		
	Daily dosage	After breakfast	After evening meal
≤ 60 kg	600 mg	200 mg	400 mg
> 60 kg to ≤ 80 kg	800 mg	400 mg	400 mg
> 80 kg	1,000 mg	400mg	600 mg

Source: Japan product label for Copegus®

RBV dose modification or discontinuation should be performed in accordance with the Copegus® package insert.

RBV should be dosed with food and SOF/LDV FDC when appropriate.

RBV tablets (200 mg) will be supplied by Gilead Sciences for all subjects.

5.4. Co-administration of SOF/LDV FDC and RBV

For subjects randomized to the SOF/LDV FDC + RBV treatment groups (Group 2 and 4), each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses.

For **morning doses**, subjects will be instructed to take study drugs with food as follows:

- One SOF/LDV FDC tablet: contains 400 mg SOF plus 90 mg LDV
- Weight-based RBV (as per Section 5.3.4).

For **evening doses**, subjects will be instructed to take study drug with food as follows:

- Weight-based RBV (as per Section 5.3.4).

If a subject does not take the SOF/LDV FDC dose at the usual time, it may be taken up to 16 hours later; however, no more than one tablet should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day.

Ribavirin should be administered as a divided daily dose (i.e., morning and evening) as per the Copegus® product label (Protocol Section 5.2.4). If the subject misses a dose of ribavirin and remembers the same day, the missed dose should be taken as soon as possible. However, if the subject missed taking the morning dose with lunch or if more than 6 hours have passed since the usual morning dose time, the subject should only take the prescribed evening dose of ribavirin. Subjects should be instructed not to take 2 doses of ribavirin at the same time.

Study medications should not be cut or split. No food restrictions apply to SOF/LDV FDC, however, SOF/LDV FDC should be taken with the morning dose of RBV and with food for optimal adherence.

5.5. Study Drug Adherence and Drug Accountability

Subjects must be instructed to bring back all bottles/blister packs of study medication in the original container at every post-baseline study visit through the end of treatment.

Study medication will be reconciled using medication pill counts at every post-baseline visit by the investigator or designee (e.g., pharmacist, study coordinator) in order to monitor the subject's adherence with the medication regimen.

Sites must review subject diary data at each visit.

5.6. Concomitant Medications

Concomitant medications taken within 30 days prior to Screening, up to and including 30 days after the last dose of study drug need to be recorded in the source documents and electronic case report form(s) (eCRFs).

Administration of interferon or any HCV treatment, other than study drug, is prohibited from 12 weeks prior to screening until completion of the final post treatment follow-up visit.

The following medications are prohibited during the screening period and for a minimum of 28 days prior to the Baseline/Day 1 visit through the end of treatment:

- Hematologic stimulating agents (e.g., erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- Chronic use of systemically administered immunosuppressive agents including, but not limited to corticosteroids (e.g., prednisone equivalent > 10 mg/day) azathioprine or monoclonal antibodies such as infliximab. The Gilead Medical Monitor will be available to address questions from investigators regarding permissible corticosteroid use for this trial.
- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information of RBV

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s). Examples of representative medications which are prohibited from 21 days prior to Baseline/Day 1 through the end of treatment are listed below:

Table 5-2. Disallowed and Concomitant Medications to be used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]	Proton-Pump Inhibitors	H2-Receptor Antagonists Antacids
Antiarrhythmics[b]		Quinidine
Anticonvulsants[c]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[c]	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications[b]		Valsartan, Olmesartan, Telmisartan, Ranolazine, Bosentan, Digoxin
Herbal/Natural Supplements	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[d]	Rosuvastatin	Atorvastatin (≤ 10 mg per day), Simvastatin, Pravastatin, Pitavastatin, Fluvastatin, Lovastatin
Other	Modafinilc	

a The 21 day washout period does not apply to PPIs, which can be taken up to 7 days before Baseline/Day 1. H2-receptor antagonists must not exceed a daily dose of 20 mg of famotidine or equivalent. Antacids that directly neutralize stomach pH (i.e., Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/LDV FDC administration.

b May result in an increase in the concentration of study drugs and/or concomitant medications

c May result in a decrease in the concentrations of study drugs

d Use with study drugs may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

6. STUDY PROCEDURES

Study visits will occur at Screening, Baseline/Day 1, and on-treatment at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12. All subjects will complete 4-week, 12-week and 24-week Post-Treatment visits. The end of study will occur at the 24-week Post-Treatment visit.

Information on the specific laboratory parameters to be measured and clinical assessments to be performed are provided below.

6.1. Screening Assessments

6.1.1. Screening Visit (Day -28 to Day -1)

Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotype testing.

The following procedures will be performed and documented:

- Obtain signed informed consent
  - A separate informed consent will be required from subjects participating in the pharmacokinetic and/or pharmacogenomic sub-studies.
- Determine inclusion eligibility (Reference Section 4.2 and 4.3)
- Liver imaging (CT or Ultrasound) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Baseline/Day 1. For subjects with cirrhosis, imaging must have been performed within 4 months of Baseline/Day 1.
- Obtain medical history
- Perform complete physical examination
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Perform 12-lead ECG
- Obtain details of adverse events related to screening procedures
- Obtain details of concomitant medications

- Obtain blood samples for tests
  - — Hematology & Chemistry
  - — Coagulation tests
  - — HCV RNA
  - — Serum β-hCG pregnancy test for females of childbearing potential only
  - — IL28B genotype
  - — Determination of genotype and subtype of HCV infection
  - — HCV antibody, HIV 1/2 antibody, and HBV surface antigen (HBsAg)
  - — HbA_{1c}
  - — TSH
- Obtain urine sample for:
  - — Urinalysis

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 visit assessments.

6.2. Treatment Assessments

6.2.1. Baseline/Day 1 Visit

The following baseline tests and procedures must be completed prior to dosing/dispensing:

- Confirm eligibility
- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling

- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
  - Archive Sample (for subjects who have consented)
  - Pharmacogenomic testing (for subjects who have consented to participate in the Pharmacogenomic Substudy)
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Drug Administration
  - Dispense study drugs as directed by the IWRS
  - Instruct the subject on the packaging, storage and administration of study drugs
  - Instruct the subject on how to complete the subject diary
  - Observe the subject taking the first dose of study drugs with food and record the time of first dose.

6.2.2. Week 1 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 1.

- Perform complete physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications

- Obtain blood samples for:
  - — Hematology & Chemistry
  - — HCV RNA
  - — Single PK sample
  - — Viral RNA Sequencing / Phenotyping Sample
- Complete medication pill count and review patient diary data with subject

6.2.3. Week 2 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 2:

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - — Hematology & Chemistry
  - — HCV RNA
  - — Single PK sample
  - — Viral RNA Sequencing / Phenotyping Sample
  - — If appropriate at Week 2, collect serial PK substudy samples (for subjects who have consented to participate in the PK substudy)
- Complete medication pill count and review dosing diary data with subject

6.2.4. Week 3 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 3.

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications

- Obtain blood samples for:
  - — Hematology & Chemistry
  - — HCV RNA
  - — Single PK sample
  - — Viral RNA Sequencing / Phenotyping Sample
- Complete medication pill count and review patient diary data with subject

6.2.5. Week 4 (± 3 days)

The following procedures/assessments are to be completed at the end of Weeks 4:

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - — Hematology & Chemistry
  - — HCV RNA
  - — Single PK sample
  - — Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - — β-hCG pregnancy test for females of childbearing potential only
  - — Urinalysis
  - — If appropriate at Week 4, collect serial PK substudy samples (for subjects who have consented to participate in the PK substudy)
- Complete medication pill count and review patient diary data with subject
- Dispense study drugs as directed by the IWRS

6.2.6. Weeks 5 and 6 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 5 and Week 6.

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK sample
  - Viral RNA Sequencing / Phenotyping Sample
- Complete medication pill count and review patient diary data with subject

6.2.7. Week 8 (± 3 days)

The following procedures/assessments are to be completed at the end of Weeks 8:

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK sample
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
  - Urinalysis
- Complete medication pill count and review patient diary data with subject

- Dispense study drugs as directed by the IWRS

6.2.8. Week 10 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 10.

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK sample
  - Viral RNA Sequencing / Phenotyping Sample
- Complete medication pill count and review patient diary data with subject

6.2.9. Week 12 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 12:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA

- Single PK sample
- Viral RNA Sequencing / Phenotyping Sample
- Archive Sample (for subjects who have consented)

- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
  - Urinalysis
- Complete medication pill count and review patient diary data with subject

6.2.10. Early Termination (ET)/Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments at the unscheduled visits are at the investigator's discretion. At all unscheduled visits initiated for the purpose of confirming virologic failure a Viral RNA Sequencing / Phenotyping Sample must be collected.

The Sponsor (e.g. Medical Monitor and Clinical Program Manager)/CRO must be informed, as soon as possible, when a subject prematurely discontinues treatment. The primary reason for premature treatment discontinuation must be provided to the Sponsor/CRO.

If a subject discontinues treatment early for any reason then the following assessments for the Early Termination (ET) Visit must be performed:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes a Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA

- — Single PK sample
- — Viral RNA Sequencing / Phenotyping Sample
- — Archive Sample (for subjects who have consented)

- Obtain urine sample for:
  - — β-hCG pregnancy test for females of childbearing potential only
  - — Urinalysis
- Complete medication pill count and review dosing diary data with subject

6.3. Post-Treatment Assessments

All subjects must complete the Post-Treatment Week 4, Week 12 and Week 24 visits. For subjects who have completed an ET visit, the post-treatment Week 4, Week 12 and Week 24 follow-up visits will be scheduled at 4, 12 and 24 weeks after the last dose of study drug.

6.3.1. Post Treatment Week 4 (± 5 days)

The following procedures/assessments are to be completed for all subjects, 4 Weeks after taking the last dose of study drug:

- Perform complete physical examination
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes a Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - — Hematology & Chemistry
  - — HCV RNA
  - — Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - — β-hCG pregnancy test for females of childbearing potential only

All subjects, including those who prematurely discontinue study drug, must return for Post Treatment Visit at Week 12 and Week 24.

6.3.2. Post Treatment Weeks 12 and 24 (± 5 days)

The following procedures/assessments are to be completed for all subjects at the Post-treatment Week 12 and 24 Visits:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Pregnancy prevention counseling (only for subjects in Groups 2 and 4)
- Subject completes a Health Related Quality of Life Survey, SF-36 (Post treatment Week 12 only)
- Obtain blood samples for:
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only (only for subjects in Groups 2 and 4)

Female subjects of child-bearing potential in Groups 2 and 4 (RBV-containing regimen), including those who do not need to continue to return for subsequent visits, should be provided with Urine Pregnancy Test-kits, instructed on their use and requested to continue to self-monitor for pregnancy every 4 weeks, for 6 months after their last dose of RBV. If required by regulations, additional pregnancy tests beyond 6 months may be added. The subject will be contacted every 4 weeks and asked to report results of their urine pregnancy tests. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.4. Procedures and Specifications

6.4.1. Clinical Laboratory Analytes

Hematology: Hematocrit, Hemoglobin (Hb), Platelet count, MCV, Reticulocyte count, Red blood cell (RBC) count, White blood cell (WBC) count with differential (absolute and percentage) including Lymphocytes, Monocytes, Neutrophils, Eosinophils and Basophils.

Coagulation: INR, Prothrombin time (PT), Activated partial thromboplastin time (APTT).

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Direct Bilirubin at Screening only, Glucose, Lipase, Potassium, Sodium; Gamma-glutamyl transferase (GGT) at Baseline only.

Urinalysis: Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Virological Tests: Serologies for HCV, HBV and HIV. HCV RNA will be measured using the COBAS® TaqMan® HCV Test, v2.0 for Use with the High Pure System. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or are not definitive.

IL28B genotype will be determined by polymerase chain reaction (PCR) amplification of the SNP, rs12979860, with sequence specific forward and reverse primers and allele specific fluorescently labeled TaqMan® MGB probes. Gilead reserves the rights to use an alternate assay for IL28B determination should the above assay become unavailable.

Pregnancy Tests: Serum β-hCG or Urine β-hCG (if positive, requires immediate confirmation with Serum β-hCG)

Additional Tests: Hemoglobin A1c (HbA_{1c}), and TSH (reflex free T4).

6.4.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during screening. Additionally, for treatment-naïve subjects, any relative or absolute contraindications to interferon treatment ("IFN ineligible") should be identified. Information related to HCV infection will also be collected.

For treatment-experienced subjects, the subject's medical record must include sufficient detail of prior treatment to allow for categorization as either IFN-Intolerant, Non-Responder or Relapse/Breakthrough, defined as:

- IFN Intolerant: Subject discontinued IFN treatment due to development or significant worsening of at least one of the conditions in Inclusion Criteria #5a.
- Non-Response: Subject did not achieve undetectable HCV RNA levels on treatment
- Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels during treatment or within 4 weeks of the end of treatment but did not achieve a SVR

6.4.3. Complete Physical Examination

A complete physical examination must include source documentation of general appearance, and the following body systems: head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

6.4.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

- Subject should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.4.5. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {2202} using actual body weight (BW).

Male: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg)}{72 \times S_{cr}}$$

Female: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg) \times 0.85}{72 \times S_{cr}}$$

S_{cr} = serum creatinine (mg/dL)

6.4.6. 12-Lead ECGs

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. On-treatment ECGs should be compared to the subject's Baseline as part of routine safety monitoring.

6.4.7. Viral RNA Sequencing / Phenotyping Sample

Plasma samples will be collected at Baseline/Day 1 and each visit for viral sequence analysis. At any unscheduled visit initiated for the purpose of confirming virologic breakthrough, a plasma sample for viral sequence analysis must be collected. Untested samples may be archived.

Details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.4.8. Archive Sample

A plasma sample will be obtained from all subjects at the Baseline/Day 1 visit and at the end of treatment (i.e., Week 12) or Early Termination visit for future research use. Unlike the other samples drawn from subjects, this protocol does not specifically define the type of research that may be conducted using this sample. This research could involve the use of the sample for HCV genotyping/phenotyping assays (as applicable) or their development, for retesting the amount of HCV in the blood, for measurement of antiviral drug levels in the blood, for future laboratory testing to provide additional clinical data. No human genetic testing will be performed. This plasma sample will be stored for up to 10 years after the study closure. Subjects enrolled in the study will have the opportunity to withdraw consent from storage and use of the Archive sample for future research.

Details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.4.9. Single Pharmacokinetic (PK) Sample

Single PK blood samples will be collected for all subjects at each on-treatment visit after Baseline/Day 1 and archived for PK analysis of SOF (and its metabolites GS-566500 and GS-331007), LDV, and RBV (if appropriate).

Details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.4.10. Intensive Pharmacokinetic (PK) Substudy

An optional intensive PK substudy may be performed. A target of ~15 treatment-naïve and ~15 treatment-experienced subjects may be included. A separate informed consent form is required to be signed for any subjects participating in the optional PK substudy. Intensive serial PK sample collection (i.e., samples obtained at pre-dose, and 15 min, 30 min and 1, 2, 4, 8, 12 and 24 hours post-dose) would be performed at either the Week 2 or Week 4 on-treatment visit to determine the steady-state pharmacokinetics of SOF (and its metabolites GS-566500 and GS-331007), LDV and RBV (if appropriate).

Approximately 55 mL of whole blood will be collected.

Subjects who participate in this substudy need to take study drugs in the morning at the same time of the day for every day at least 5 days before the visit for this substudy.

Participants will fast (except for water) for at least 8 hours before the PK substudy visit. Participants also need to bring their assigned study drug(s) to the clinic for this visit. On the day of the PK sub-study visit, subjects will be instructed to not take their morning dose of SOF/LDV FDC and ribavirin, if appropriate, before coming to the clinic. They will take their morning dose when told by the study doctor or study staff at the site. If the subject is assigned to Groups 2 or 4, the subject will take their morning dose of RBV with food. All subjects must wait to eat again (subjects may drink only water during this time period) until after the 4-hour blood draw.

After the last blood draw of the PK sub-study visit, the subject may leave the clinic when the study doctor or study staff believes it is safe for him/her to do so and return the next day for the 24 hour blood sample collection (overnight stay is allowed if necessary).

Additional details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.4.11. Pharmacogenomic (PG) Substudy

This study also includes the optional collection of a whole blood sample for human Pharmacogenomic testing. This sample may only be collected following approval of the national and local regulatory bodies and Ethical Committees. In addition to the study-specific informed consent to be signed by each subject participating in the study, a separate, specific signature will be required to document a subject's agreement to provide this additional sample for optional Pharmacogenomic research. Provision of the Pharmacogenomic sample is optional and is not required in order for a subject to participate in the study.

From subjects who agree to participate and provide their additional specific consent, one blood sample of approximately 6 mL of whole blood will be collected. This sample should be collected at the Baseline/Day 1 visit, but may be collected at any time during the study or at a separate post study visit, if necessary. The specimens collected for optional Pharmacogenomic research will be used to identify or validate genetic markers that may increase our knowledge and understanding of the biology of the study disease and related diseases and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, adverse events, and the processes of drug absorption and disposition. These specimens may also be used also to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional future research specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The subject's identity will be protected, and the subject's name will not be attached to the sample. The sample may be stored for up to 10 years before being destroyed.

Details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.4.12. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and for a minimum of 6 months following the last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy test result, subjects will be instructed to stop study drugs immediately (if appropriate) and return to the clinic as soon as possible for a confirmatory serum pregnancy test.

Pregnancy test kits will be dispensed to female subjects of childbearing potential at the 4 Week Post-Treatment visit to self-monitor for pregnancy between scheduled study visits, every 4 weeks, for 6 months after their last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. The subject will be contacted every 4 weeks and asked to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.4.13. Health Related Quality of Life Survey

A health related quality of life survey, SF-36 will be completed by patients at Baseline/Day 1, On-treatment Weeks 2, 4, 8, 12, Post-treatment Weeks 4 and 12 and Early Termination (if appropriate). The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire.

7. TOXICITY MANAGEMENT

7.1. Modification of Dose/Schedule Due to Toxicity

7.1.1. RBV Dose Adjustments

Dose reduction or discontinuation of RBV due to toxicity should be performed according to the Japanese Copegus® product label. Information is provided in Table 7-1 and Table 7-2.

RBV may be permanently discontinued due to toxicity without stopping SOF/LDV FDC. In the event a female partner of a male subject becomes pregnant, the male subject must permanently discontinue RBV.

Table 7-1. RBV Dose Reduction Guidelines for Non-Cirrhotic Subjects

Test items	Value	Ribavirin
Neutrophil count	< 750 /μL	No change
	< 500 /μL	Discontinue
Platelet count	< 50,000 /μL	Discontinue
	< 25,000 /μL	Discontinue (Not resumable)
Hemoglobin (no cardiac disease or history thereof)	< 10 g/dL	Reduce dose 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1,000 mg/day → 600 mg/day
	< 8.5 g/dL	Discontinue
Hemoglobin (with cardiac disease or history thereof)	<10 g/dL, or a 4-week continuous decrease of 2 g/dL or more from baseline during treatment	Reduce dose 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1,000 mg/day → 600 mg/day
	< 8.5 g/dL, or <12 g/dL even after 4 weeks from dose reduction	Discontinue

Source: Japan Copegus® Product Label

Table 7-2. RBV Dose Reduction Guidelines for Cirrhotic Subjects

Test items	Value	Ribavirin
Neutrophil count	< 1,000 /μL	No change
	< 750 /μL	No change
	< 500 /μL	Discontinue
Platelet count	< 50,000 /μL	Discontinue
	< 35,000 /μL	Discontinue
	< 25,000 /μL	Discontinue (Not resumable)
Hemoglobin (no cardiac disease or history thereof)	< 11 g/dL after 1 to 4 weeks of administration	Reduce dose 600 mg/day → 200 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 400 mg/day
	< 10 g/dL after 5 to 48 weeks of administration	Reduce dose 600 mg/day → 200 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 400 mg/day
	< 8.5 g/dL	Discontinue
Hemoglobin (with cardiac disease or history thereof)	< 11 g/dL after 1 to 4 weeks of treatment, or a 4-week continuous decrease of 2 g/dL or more from baseline during treatment	Reduce dose 600 mg/day → 200 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 400 mg/day
	< 10 g/dL after 5 to 48 weeks of treatment, or 4-week continuous decrease of 2 g/dL or more from baseline during treatment	Reduce dose 600 mg/day → 200 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 400 mg/day
	<8.5 g/dL, or <12 g/dL even after 4 weeks from dose reduction	Discontinue

Source: Japan Copegus® Product Label

Once RBV has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart RBV at a lower daily dose with subsequent step-wise increase in the daily dose as clinically indicated. However, it is not recommended that the RBV daily dose be increased to the original assigned dose.

7.2. Subject Stopping Rules

The Medical Monitor must be consulted prior to dose discontinuation of SOF/LDV FDC unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Due to a clinical or laboratory event, administration of all study drug(s) may be discontinued. There is no option for SOF/LDV FDC dose reduction. If SOF/LDV FDC is stopped due to

toxicity, it must not be restarted; if SOF/LDV FDC is discontinued then RBV must also be discontinued, the subject must complete an ET visit. Post-treatment 4-Week, 12-Week and 24-Week visits must also be scheduled, 4, 12 and 24 weeks from the last dose of study drug.

In Group 2 and 4, subjects that require discontinuation of only RBV should continue with SOF/LDV FDC for the remainder of the treatment period and complete all the scheduled study visits as planned.

Subjects who meet any of the following laboratory criteria must stop all study medication(s):

- Elevation of ALT and/or AST > 5x Baseline/Day 1 or nadir, confirmed by immediate repeat testing
- Abnormal elevation of ALT > 3 x Baseline/Day 1 *and* total bilirubin > 2 x ULN, confirmed by immediate repeat testing
- Elevation of ALT > 15 x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 adverse event or laboratory abnormality assessed as related to SOF/LDV

8. ADVERSE EVENTS MANAGEMENT

8.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g. such as venipuncture, biopsy) during or after screening (before the administration of study investigational medicinal product).

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE.

- Complications and termination of pregnancy (see Section 8.6 for additional information)

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event

- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the Screening visit that do not worsen

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Overdose without clinical sequelae (see Section 8.6.1)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

- Uncomplicated pregnancy.

- An induced elective abortion to terminate a pregnancy without medical reason.

8.2. Assessment of Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded on the AE CRF page. The AE entry should indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to investigational medicinal product or to a study procedure, the action taken with investigational medicinal product due to the AE, and the severity of the AE. The investigator is responsible for final review and confirmation of accuracy of events, relationship and severity confirmed by the signature on the CRF book. The relationship to investigational medicinal product therapy should be assessed using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

If the investigator cannot establish a definite cause other than the study medication, the adverse event should be classified as related.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol-mandated procedures such as venipuncture or biopsy.

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

8.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **immediate** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Examples of such events are as follows:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the investigational medicinal product(s).
- The subject may not have been on investigational medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 8.3.

8.4. Serious Adverse Event Reporting Requirements

8.4.1. All Serious Adverse Events

Gilead Sciences is required to expedite to worldwide regulatory authorities reports of SAEs, Serious Adverse Drug Reactions (SADRs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) in line with relevant legislation, including the applicable US FDA Code of Federal Regulation, the European Commission Clinical Trials Directive (2001/20/EC); therefore, Gilead Sciences (or the CRO on the behalf of Gilead Sciences) must be notified immediately regarding the occurrence of any SAE or SADR that occurs after the subject consents to participate in the study, including SAEs/SADRs resulting from protocol-associated procedures as defined in relevant legislation including 2001/20/EC. The procedure for reporting all SAEs, regardless of causal relationship, is as follows:

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form (see following bullet). During the study conduct sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the serious adverse event report form and submitted by faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of the CRO Pharmacovigilance Representative (see below for contact information).

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to CRO Pharmacovigilance Representative.

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- CRO Pharmacovigilance Representative contact information is as follows:

CRO Pharmacovigilance Representative:	Name:	Miyu Nakano
	Phone:	+81 3 3537 5838
	Fax:	+81 3 6888 5377
	E-mail:	Gilead_JP_Medical@parexel.com
Medical Monitor:	Name:	Yukiya Sasaki
	Phone:	+81 6 6201 7120
	Fax:	+81 3 6888 5377
	E-mail:	Sasaki.Yukiya@parexel.com

- For fatal or life-threatening events, also e-mail or fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable. Transmission of such documents should occur with Personal Subject Details de-identified, without losing the traceability of a document to the Subject Identifiers.

- Gilead Sciences may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF and the event description section of the SAE form.

Follow-up of AEs will continue through the last day on study (including the follow-up off-study medication period of the study) and/or until a conclusive outcome (e.g., resolved, resolved with sequelae, lost to follow-up, fatal) is achieved.

8.4.2. Investigator and Sponsor Reporting Requirements for SAEs

An SAE may qualify for reporting to regulatory authorities. Expectedness of SAEs will be determined by Gilead Sciences using reference safety information specified in the Investigator's Brochure.

All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the IRB as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead will notify worldwide regulatory authorities and the relevant Ethics Committees (EC) in concerned Member States of applicable SUSARs.

8.4.3. Reporting Requirements

All AEs regardless of cause or relationship, must be reported for subjects from the Baseline/Day 1 visit through the 4-Week Post-Treatment Visit.

All SAEs, including deaths, regardless of cause or relationship, must be reported from signing of the informed consent through the end of the study. Investigators are not obligated to actively seek SAEs beyond this point. However, if the investigator learns of any SAEs that occur after study participation and the event is deemed relevant to the use of investigational medicinal product(s), he/she should promptly document and report the event to the CRO Pharmacovigilance Representative (Reference Section 8.4.1 or to Gilead Sciences, DSPH (Safety_FC@gilead.com and/or Fax: +1 (650) 522-5477) if the study has been completed.

8.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or Serious AEs

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 8.2 and 8.4. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of AEs and Laboratory Abnormalities (Appendix 3). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

8.6. Special Situations Reports

8.6.1. Definitions of Special Situations

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse, or overdose, reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints.

A pregnancy report is used to report pregnancies occurring in subjects or their partners during the study whether or not maternal or paternal exposure to the product occurred.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while the medication is in the control of a healthcare professional, patient or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects.

Misuse is defined as any use of a medicinal product in a way that the product is intentionally and inappropriately used not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labelling (as it applies to the daily dose for the subject/patient in question).

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

8.6.2. Instructions for Reporting Special Situations

8.6.2.1. Instructions for Reporting Pregnancies

The Investigator should report all pregnancies that occur in subjects or their partners from the signing of informed consent to the CRO Pharmacovigilance Representative using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the Investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the Investigator.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the adverse event term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in the Adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to the CRO Pharmacovigilance Representative using the Pregnancy Outcome Report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead Sciences or other study drugs must also be reported, and relevant information should be submitted to the CRO Pharmacovigilance Representative using the Pregnancy and Pregnancy Outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Sciences DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

8.6.2.2. Reporting Other Special Situations

All other Special Situation reports must be reported on the Special Situations Report Form and forwarded to the CRO Pharmacovigilance Representative within 24 hours.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Objectives and Endpoints

9.1.1. Analysis Objectives

The primary objectives of this study are:

- To determine the antiviral efficacy of treatment with sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) ± Ribavirin (RBV) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks post treatment)

- To evaluate the safety and tolerability of SOF/LDV FDC ± RBV as assessed by review of the accumulated safety data

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objectives of this study are:

- To identify or validate genetic markers that may be predictive of virologic response to therapy and/or tolerability of therapy through genetic discovery research (e.g., pharmacogenomics), in subjects who provide their separate and specific consent

- To assess the effect of treatment with SOF/LDV FDC ± RBV on Health-Related Quality of Life (HRQoL)

9.1.2. Primary Endpoint

The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 weeks after discontinuation of therapy) in the Full Analysis Set (FAS) population.

9.1.3. Secondary Endpoint

Secondary efficacy endpoints include the proportion of subjects with: HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24); viral breakthrough; and relapse.

9.1.4. Safety Endpoint

The primary safety endpoint is any AE leading to permanent discontinuation of study drug(s).

9.1.5. Other Endpoints of Interest

Additional efficacy evaluations may include HCV RNA change from baseline; ALT normalization; viral kinetic parameters, and the health related quality of life endpoints.

9.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

The study drugs in this study include SOF/LDV FDC and RBV. Last dose of study drug refers to the last dose of any of the study drugs in a treatment group and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various post-treatment time points.

9.2.1. Analysis Sets

9.2.1.1. Efficacy

The analysis set for antiviral activity analyses will be the Full Analysis Set (FAS) which includes subjects who were randomized and received at least one dose of study drug and have chronic genotype (1a, 1b, or mixed 1a/1b) HCV infection.

9.2.1.2. Safety

The primary analysis set for safety analyses will include subjects who were randomized and received at least one dose of study drug.

Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of the last dose of study drug plus 30 days.

9.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who are randomized and have received at least one dose of study drug and for whom concentration data of analytes SOF, and metabolite(s), as appropriate, LDV, and/or RBV (if appropriate) are available. The PK analysis set will be used for analyses of general PK.

9.2.2. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed.

For the analysis of post-baseline categorical efficacy endpoints, if a data point is missing and is immediately preceded and followed in time by values that are deemed successes, then the missing data point will be termed a success; otherwise the data point will be termed a failure.

Any subject with missing data due to premature discontinuation of the study will be considered a failure at the time points on, or following, the date of discontinuation. If no HCV RNA values are obtained after the last dose of study medication, the subject will be considered a treatment failure for the SVR endpoints.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics. For example,

- If a subject received study medication, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary.

- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

Values for missing vital signs data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available.

HCV RNA values below the LLOQ for the assay will be set to the lower limit minus 1 for calculation of summary statistics for the actual HCV RNA values and the change from baseline values by study visit. The reported values will be provided in the HCV RNA listing.

For selected analyses of early time point data, HCV RNA data (IU/mL) may be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

PK concentration values below the lower limit of quantification (BLQ) will be treated as zero for determination of summary and order statistics. Individual values that are BLQ will be presented as “BLQ” in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLQ for the time point, then the

minimum value will be displayed as "BLQ". If more than 50% of the subjects have a concentration data value BLQ for the time point, then the minimum and median values will be displayed as "BLQ". If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will be displayed as "BLQ".

Exposure parameters that are selected for statistical analysis will be natural log-transformed. Concentration values that are BLQ will be excluded for any ratio or natural log-transformed statistical analysis.

9.2.3. Interim Analysis

No formal interim analyses are planned for this study.

9.3. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods by group.

Demographic data will include sex, self-identified race/ethnicity, and age.

Baseline characteristic data will include body weight/body mass index, HCV RNA level (log_{10} IU/mL), HCV genotype (1a or 1b, or mixed 1a/1b), IL28B genotype, presence/absence of cirrhosis, baseline ALT level, creatinine clearance estimated by Cockcroft-Gault, and additional endpoints as necessary.

9.4. Efficacy Analysis

9.4.1. Primary Analysis

The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 weeks after discontinuation of therapy) in the FAS population. The primary analysis will be performed after all randomized subjects have been followed through 12 weeks post-treatment or discontinued from study.

A point estimate with a two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate by group.

Treatment-Naïve Subjects

Non-Cirrhotic Subjects: In the primary efficacy analysis the SVR12 rate in Group 1 and 2 non-cirrhotic subjects will be compared to the adjusted historical SVR null rate of 63% using a two-sided exact one-sample binomial test.

The hypothesis for superiority is:

H0: SVR12 rate = 63%,

H1: SVR12 rate ≠ 63%.

The adjusted historical SVR rate is based on the expected historical SVR rate of 73% (92/126; Kumada et al. J Hepatol 2012; 56:78-84) for non-cirrhotic, treatment-naïve, Japanese subjects with GT-1 chronic hepatitis C taking Peg-IFNα+RBV+TVR, and we allow a 10% discount due to the expected improved safety profile and shorter treatment duration which results in a null historical SVR rate for this study of 63%.

It is important to note that this historical control rate is a conservative estimate based on available literature. A feasibility survey conducted to support this study indicated a low proportion of patients are eligible for and willing to participate in a clinical study utilizing Peg-IFNα +RBV±TVR as a control arm. In the absence of other treatment options the real-life SVR rate in these patients would be negligible.

A Hochberg procedure will be used to ensure control of the family-wise type I error rate at the 0.05 significance level.

Details of the Hochberg testing procedure will be presented in the Statistical Analysis Plan (SAP) {17876}.

Cirrhotic Subjects: No statistical hypothesis testing will be performed in treatment-naïve subjects with cirrhosis. A point-estimate with two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate.

Treatment-Experienced Subjects:

No statistical hypothesis testing will be performed in treatment-experienced subjects nor each subgroup (i.e., cirrhotic or non-cirrhotic; Relapse/breakthrough, Non-responder, or IFN intolerant). A point-estimate with two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate in Group 3 and 4 and each of the subgroups.

9.4.2. Secondary Analysis

A point-estimate with two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the difference in SVR12 rate between Group 1 and 2, and between Group 3 and 4.

The proportion of subjects with HCV RNA below LLOQ over time (including SVR12) will be presented by group in tabular and graphical form.

Descriptive summaries and listings will be provided for additional efficacy evaluations including the proportion of subjects who experience virologic failure, ALT normalization, serum HCV RNA actual values and change from baseline and health related quality of life endpoints.

Resistance analysis will be performed for all subjects who experience virologic failure.

Virologic failure is defined as follows:

- On-treatment breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values (second confirmation value could be post-treatment), or last available on-treatment measurement with no subsequent follow-up values;

- On-treatment rebound: > 1 log10 increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (second confirmation value could be post-treatment), or last available on-treatment measurement with no subsequent follow-up values;

- On-treatment non-responsive: HCV RNA persistently ≥ LLOQ through 8 weeks of treatment;

- Relapse: HCV RNA ≥ LLOQ during the post treatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available post treatment measurement.

All subjects meeting any of the above criteria with HCV RNA ≥1000 IU/ml will undergo viral sequencing to identify resistance-associated mutations. Sequence analysis will be performed on an ongoing basis throughout the trial as subjects meeting any of the above criteria are identified. HCV NS5A and NS5B regions will be amplified and deep-sequenced at Baseline and at the timepoint(s) of virologic failure. Deep-sequence data will be processed and aligned using internally-developed software via a multi-step method. Emergent resistance-associated variants will be determined by comparing the amino acid sequences from post-Baseline samples to those from Baseline for the same subject along with wild-type reference samples of the corresponding HCV genotype.

Exploratory analyses may be performed to assess the relationship between demographic, baseline characteristics, (including Baseline viral load, genotype 1a vs. 1b, Age, Sex, Race, Ethnicity, presence/absence of cirrhosis, baseline ALT level and bodyweight/BMI) and antiviral activity (HCV RNA reduction, proportion of subjects with HCV RNA below the limit of quantification and target not detected at various time points during and following discontinuation of study drugs). Predictive factors of antiviral activities may be examined using regression type of analysis.

Details on efficacy analyses will be described in the statistical analysis plan.

9.5. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements, at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized by treatment (SOF/LDV FDC and

SOF/LDV FDC + RBV) according to the study drug received**.** Safety endpoints will be summarized as the number (proportion) of subjects with events or abnormalities for categorical data or as an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

9.5.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the CRF. Exposure data will be summarized.

9.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and preferred term) will be provided by treatment (SOF/LDV FDC and SOF/LDV FDC + RBV):

- All AEs,
- All study drug-related AEs,
- Combined Grade 2, 3 and 4 AEs,
- Combined Grade 3 and 4 AEs,
- Combined Grade 2, 3 and 4 study drug-related AEs,
- Combined Grade 3 and 4 study drug-related AEs,
- All AEs that caused permanent discontinuation from study drug,
- All AEs that caused change in dose or temporary interruption of study drug,
- All SAEs (including death), and
- All study drug-related SAEs

All AEs collected during the course of the study will be presented in data listings.

9.5.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment (SOF/LDV FDC and SOF/LDV FDC + RBV) and study visit along with corresponding change from baseline.

Graded laboratory abnormalities will be defined using the laboratory toxicity grading scheme defined in Appendix 3 of this protocol. The incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least one toxicity grade from baseline at any time post-baseline up to the date of last dose of study drug plus 30 days will be summarized by treatment (SOF/LDV FDC and SOF/LDV FDC + RBV). If baseline data are missing, then any post-baseline graded abnormality (i.e., at least Grade 1) will be considered treatment emergent.

All laboratory abnormalities will be included in the listings of laboratory data.

9.6. Pharmacokinetic Analysis

Plasma concentrations of the study drug and metabolite(s) over time, if analyzed, will be summarized using descriptive statistics. Details of the analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

9.7. Sample Size

9.7.1. Treatment-Naïve Subjects:

Approximately 150 treatment-naïve subjects will be randomized in this study with 75 in each of Group 1 and Group 2. Approximately 60% (i.e., n=45) will be non-cirrhotic, and up to 40% (i.e., n=30) may have Child's Pugh-A compensated cirrhosis in each group.

Non-Cirrhotic Subjects: A sample size of 45 non-cirrhotic subjects in Group 1 and 2 will provide at least 90% power to detect a 23% improvement in SVR12 rate from the adjusted historical control rate of 63% using a 2-sided exact one-sample binomial test at a significance level of 0.025, based on a Bonferroni correction.

Cirrhotic Subjects: No formal sample size calculations were provided for cirrhotic subjects. Up to 40% (i.e., n=30) of randomized subjects in Group 1 and 2 may have compensated cirrhosis. With a sample size of 30 subjects in each of Group 1 and 2, a two-sided 95% exact confidence interval will extend at most 38% in length.

9.7.2. Treatment-Experienced Subjects:

Approximately 150 treatment-experienced subjects will be randomized in this study with 75 in each of Group 3 and Group 4. Approximately 60% (i.e., n=45) will be non-cirrhotic, and up to 40% (i.e., n=30) may have Child's Pugh-A compensated cirrhosis in each group.

Among the 75 subjects in each of Group 3 and 4, approximately 45 subjects will be Relapsers, ~20 subjects will be Non-Responders, ~10 subjects will be IFN intolerant.

For Treatment Experienced subjects, a confidence interval approach will be used to justify the sample size given that our goal is to characterize the SVR rate in a population with limited treatment options and not to test a specific hypothesis.

With a sample size of 75 subjects in each of Group 3 and 4, a two-sided 95% exact confidence interval will extend at most 24% in length.

With a sample size of 30 cirrhotic subjects in each of Group 3 and 4, a two-sided 95% exact confidence interval will extend at most 38% in length.

With a sample size of 45 Relapse/breakthrough, 20 Non-responder and 10 IFN-intolerant subjects in each of Groups 3 and 4, a two-sided 95% exact confidence interval will extend at most 31%, 46% and 63% in length respectively.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

Since this is a "covered" clinical trial, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all subinvestigators must provide documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify Gilead Sciences of any change to reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

This study is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

10.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). Approval from the IRB or IEC must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent.

10.1.4. Subject Identification Card

A Subject Identification Card is provided to each subject to carry (e.g. in a wallet) at all times while the subject is participating in the trial. The Subject Identification Card will be provided to the subject prior to study drugs being dispensed to the subject. The Subject Identification Card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;

2. The subject's identification number;

3. A statement identifying the card-carrier as a participant in a clinical trial (e.g. "This person is participating in a clinical research trial");

4. A statement indicating the person might be taking an investigational drug (e.g. "This person is taking an experimental drug which could have interactions with other medications"); and

5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather than a contact at the sponsor.

The cards may also include other trial-specific information to assist with treatment decisions in the event of an emergency, such as types of concomitant therapies that may, or may not be, permitted as part of emergency treatment. As with any other information provided to subjects, the Subject Identification Card must be approved by the IRB/IEC. CRAs will request that Investigators provide the Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them at all times while they are participating in the trial. The Investigator/site should collect the cards at the end of the trial and retain them with other clinical trial documents.

10.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Gilead Sciences, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data are listed in the Source Data verification Plan, and should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);
- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;

- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- Concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- Date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead Sciences. The investigator must notify Gilead Sciences before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead Sciences must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead Sciences to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years for purposes of this study.

10.1.7. Case Report Forms

For each subject enrolled, a CRF (or eCRF) must be completed and signed by the principal investigator or subinvestigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a prerandomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Drug Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, and comparators. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead Sciences requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead Sciences' requirements for disposal, arrangements will be made between the site and Gilead Sciences or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.1 Sponsor Responsibilities

10.2.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

10.2.2 Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Gilead Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Gilead Sciences, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead Sciences in an abstract, manuscript, or presentation form; or

- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 10.1.5).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.3 Joint Investigator/Sponsor Responsibilities

10.3.1 Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3 Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead Sciences and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11. REFERENCES

2202 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

3291 Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med 2002;136 (4):288-92.

5008 Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22 (6):696-9.

8076 Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345 (1):41-52.

12557 Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352 (9138):1426-32.

12558 McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339 (21):1485-92.

13693 Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49 (4):1335-74.

15555 Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, et al. Membrane transporters in drug development. Nat Rev Drug Discov 2010;9 (3):215-36.

15572 COPEGUS® (ribavirin, USP) TABLETS. US Prescribing Information. Roche Laboratories Inc., Nutley, NJ. Revised: January 2010.

15573 PEGASYS® (peginterferon alfa-2a). US Prescribing Information. Roche Pharmaceuticals. Nutley, NJ. March 2010.

15668 Copegus 200mg and 400mg Film-coated Tablets. Summary of Product Characteristics. Roche Products Limited, Welwyn Garden City, United Kingdom. Revised: March 2010.

17492 Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364 (13):1195-206.

17876 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75 (4):800-2.

17892 Muir AJ, Provenzale D. A descriptive evaluation of eligibility for therapy among veterans with chronic hepatitis C virus infection. J Clin Gastroenterol 2002;34 (3):268-71.

17893 Backus LI, Boothroyd DB, Phillips BR, Mole LA. Predictors of response of US veterans to treatment for the hepatitis C virus. Hepatology 2007;46 (1):37-47.

17996 Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364 (25):2405-16.

18314 PRAVACHOL® (pravastatin sodium) tablets. US Prescribing Information. Bristol-Myers Squibb Company. Princeton, NJ. May 2011.

19682 Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int 2011;31 Suppl 2:61-80.

19705 Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 2008;48 (1):148-62.

20450 Alter HJ, Liang TJ. Hepatitis C: the end of the beginning and possibly the beginning of the end. Ann Intern Med 2012;156 (4):317-8.

20485 Sulkowski M, Gardiner D, Lawitz E, Hinestrosa F, Nelson D, Thuluvath P, et al. Potent Viral Suppression With the All-Oral Combination of Daclatasvir (NS5A Inhibitor) and GS-7977 (Nucleotide NS5B Inhibitor), +/- Ribavirin, in Treatment-Naive Patients With Chronic HCV GT1, 2, or 3 [Poster 1422]. 47th Annual Meeting of the European Association for the Study of the Liver (EASL); 2012 April 18 - 22; Barcelona, Spain.

21139 CRESTOR (rosuvastatin calcium) tablets. US Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. February 2012.

21479 Nakano T, Lau GM, Sugiyama M, Mizokami M. An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region. Liver Int 2012;32 (2):339-45.

22061 Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology 2010;53 (1):39-43.

22064 Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol 2012;56 (1):78-84.

22066 Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29 (3):339-64.

22070 Mizokami M, Tanaka Y, Miyakawa Y. Spread times of hepatitis C virus estimated by the molecular clock differ among Japan, the United States and Egypt in reflection of their distinct socioeconomic backgrounds. Intervirology 2006;49 (1-2):28-36.

22073 Tanaka E, Kiyosawa K, Matsushima T, Ishikawa K, Hino K, Tanaka S, et al. Epidemiology of genotypes of hepatitis C virus in Japanese patients with type C chronic liver diseases: a multi-institution analysis. J Gastroenterol Hepatol 1995;10 (5):538-45.

22074 Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, et al. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. Intervirology 2004;47 (1):32-40.

22076 Sasaki Y, Yamada T, Tanaka H, Ohigashi H, Eguchi H, Yano M, et al. Risk of recurrence in a long-term follow-up after surgery in 417 patients with hepatitis B- or hepatitis C-related hepatocellular carcinoma. Ann Surg 2006;244 (5):771-80.

22077 Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48 (2):418-31.

22097 Hayashi N, Okanoue T, Tsubouchi H, Toyota J, Chayama K, Kumada H. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. J Viral Hepat 2012;19 (2):e134-42.

22099 Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res 2007;37 (9):676-91.

22110 Negro F, Alberti A. The global health burden of hepatitis C virus infection. Liver Int 2011;31 Suppl 2:1-3.

22168 Liu GG, DiBonaventura M, Yuan Y, Wagner JS, L'Italien GJ, Langley P, et al. The burden of illness for patients with viral hepatitis C: evidence from a national survey in Japan. Value Health 2012;15 (1 Suppl):S65-71.

23342 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347 (13):975-82.

23351 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358 (9286):958-65.

23803 Asahina Y, Tsuchiya K, Tamaki N, Hirayama I, Tanaka T, Sato M, et al. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology 2010;52 (2):518-27.

23806 Chayama K, Hayes CN, Ohishi W, Kawakami Y. Treatment of chronic hepatitis C virus infection in Japan: update on therapy and guidelines. J Gastroenterol 2013;48 (1):1-12.

23807 Guidelines for the Management of Hepatitis C Virus Infection: First edition, May 2012, The Japan Society of Hepatology. Hepatol Res 2013;43 (1):1-34.

23808 Tomoda T, Nouso K, Sakai A, Ouchida M, Kobayashi S, Miyahara K, et al. Genetic risk of hepatocellular carcinoma in patients with hepatitis C virus: a case control study. J Gastroenterol Hepatol 2012;27 (4):797-804.

24219 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24 (2):289-93.

24592 Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, et al. Sustained Virologic Response With Daclatasvir Plus Sofosbuvir ± Ribavirin (RBV) in Chronic HCV Genotype (GT) 1-Infected Patients Who Previously Failed Telaprevir (TVR)or Boceprevir (BOC) [Abstract 1417]. J Hepatol 2013;58:S570.

12. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3b, Randomized, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Treatment-Naïve and Treatment-Experienced Japanese Subjects with Chronic Genotype 1 HCV Infection

GS-US-337-0113, Amendment 1, 22 August 2013

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Phil Pang
Phil Pang, MD (Printed)
Medical Monitor

Signature

22 AUG 2013
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Appendix Table 1. Screening and On-Treatment Study Visits

	Screening[a]	On Treatment Period										
Clinical Assessments	**Day -28 to Day -1**	**Baseline/ Day 1[b]**	**Week 1 (±3 days)**	**Week 2 (±3 days)**	**Week 3 (±3 days)**	**Week 4 (±3 days)**	**Week 5 (±3 days)**	**Week 6 (±3 days)**	**Week 8 (±3 days)**	**Week 10 (±3 days)**	**Week 12 (±3 days)**	**ET**
Informed Consent	X											
Determine Eligibility	X	X										
Liver Imaging	X[c]											
Medical History	X											
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Weight	X	X									X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X	X								X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X									X	X
Health Related Quality of Life		X				X			X		X	X
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X									X	X
Serum HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X

Clinical Assessments	Screening[a]	On Treatment Period										
	Day -28 to Day -1	Baseline/ Day 1[b]	Week 1 (±3 days)	Week 2 (±3 days)	Week 3 (±3 days)	Week 4 (±3 days)	Week 5 (±3 days)	Week 6 (±3 days)	Week 8 (±3 days)	Week 10 (±3 days)	Week 12 (±3 days)	ET
Single PK			X	X	X	X	X	X	X	X	X	X
Viral RNA Sequencing /Phenotyping Sample (Plasma)[f]		X	X	X	X	X	X	X	X	X	X	X
*Archive Sample[g]		X									X	X
Serum or Urine Pregnancy Test[h]	X	X				X			X		X	X
Urinalysis	X					X			X		X	X
IL28B Genotype, HCV Genotype	X											
HCV Ab, HIV Ab and HBsAg	X											
Hemoglobin A1c, TSH	X											
PK Substudy Collection[i]				X		X						
Single Pharmacogenomic Sample[j]		X										
Review of Study Drug Adherence and Drug Accountability[k]			X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing[l]		X				X			X			

a The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotype testing.

b Baseline/Day 1 assessments must be performed prior to dosing.

c Liver imaging (CT or Ultrasound) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Baseline/Day 1. For subjects with cirrhosis, imaging must have been performed within 4 months of Baseline/Day 1.

d Vital signs include resting blood pressure, pulse, respiratory rate and temperature.

e Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for gross abnormalities.

f Serum samples will be collected and stored for potential HCV sequencing and other virology studies.

g Archive plasma samples will be collected at Baseline/Day 1 visit and at the end of treatment for subjects who do not opt out of Archive sample collection

h Females of childbearing potential only. Serum pregnancy test performed at Screening and for confirmation of positive urine pregnancy test. All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period.

i Subjects that consent to the optional PK substudy will have serial PK samples drawn at Week 2 or Week 4 visit.

j Only for subjects who have provided consent for this sample and testing. This sample can be obtained at a subsequent visit if not obtained at Day 1.

k Study medication and dosing diary, will be reconciled at every post-baseline visit by the investigator or designee in order to monitor the subject's adherence with the medication regimen.

l Study Drug will be dispensed per IWRS directions. Subjects must be instructed to bring back all bottles of study medication(s) in the original container at every post baseline study visits through the end of treatment.

Appendix Table 2. Post Treatment Study Visits

Clinical Assessments	Post Treatment Period[a]		
	Post Treatment Week 4 (±5 days)	**Post Treatment Week 12 (±5 days)**	**Post Treatment Week 24 (±5 days)**
Physical Examination	X	X	X
Weight		X	X
Vital Signs[b]	X	X	X
Adverse Events	X		
Concomitant Medications	X		
Pregnancy Prevention Counseling	X	X	X
Health Related Quality of Life	X	X	
Hematology & Chemistry	X		
Serum HCV RNA	X	X	X
Viral Sequencing Sample (Plasma)[c]	X	X	X
Serum or Urine Pregnancy Test[d]	X	X	X

a All subjects will complete all Post-Treatment visits regardless of the treatment duration. The end of study will occur at the 24-week Post-Treatment visit.

b Vital signs include resting blood pressure, pulse, respiratory rate and temperature.

c Plasma samples will be collected and stored for potential HCV sequencing and other virology studies.

d Females of childbearing potential in Groups 1 and 3 (without RBV) will have a urine pregnancy test at the post-treatment Week 4 visit only. Females of childbearing potential in Groups 2 and 4 (with RBV) will have additional urine pregnancy testing every 4 weeks for a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. Pregnancy test kits will be dispensed to female subjects of child bearing potential in Groups 2 and 4 (with RBV) after the post-treatment Week 4 visit. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed post-treatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

Appendix 3. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18June2012

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE) **Infant, 22–35 Days** (HIV POSITIVE OR NEGATIVE) **Infant, 1–21 Days** (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L 9.5 to 10.5 g/dL 95 to 105 g/L 12.0 to 13.0 g/dL 120 to 130 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L 8.0 to < 9.5 g/dL 80 to < 95 g/L 10.0 to < 12.0 g/dL 100 to < 120 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L 7.0 to < 8.0 g/dL 70 to < 80 g/L 9.0 to < 10.0 g/dL 90 to < 100 g/L	< 6.0 g/dL < 60 g/L < 7.0 g/dL < 70 g/L < 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC)	1000 to 1300/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
Adult and Pediatric, > 7 Days	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric** **≥ 1 Month** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric** **≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.14 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below				
Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.

With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year** **Pediatric < 1 Year**	 Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr Liquid stools (more unformed than usual) but usual number of stools	 Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs. Liquid stools with increased number of stools OR Mild dehydration	 Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated Liquid stools with moderate dehydration	 Life-threatening consequences (eg, hypotensive shock) Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc

Appendix 4. Ishak and Metavir Scoring System

Description	Ishak Score	Metavir Score
No Fibrosis	0	0
Few Portal tracts	1	1
Many Portal Tracts	2	1
Occasional Bridges	3	2
Numerous Bridges	4	3
Early or Incomplete Cirrhosis	5	4
Complete Cirrhosis	6	4

{5008}, {24219}

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1. Background

Ribavirin is contraindicated in pregnancy as significant teratogenic and embryocidal effects have been demonstrated in all animal species tested. Pregnancy must be excluded before the start of treatment with study drugs and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study. Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment. Please refer to the latest version of the product insert for additional information.

Non-clinical toxicity studies of sofosbuvir and ledipasvir demonstrated no adverse effect on embryo-fetal development. However, there are no clinical studies of SOF/LDV in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

2. Definition of Female of Childbearing Potential and Contraceptive Requirements for Female Subjects (and their male partners)

Women > 54 years of age with cessation for ≥ 12 months of previously occurring menses, or women of any age who have had a hysterectomy, or have had both ovaries removed, or have had medically documented ovarian failure will be considered to be of non-childbearing potential.

Women ≤ 54 years of age (including those with amenorrhea of any duration) who have not had a hysterectomy, and have not had both ovaries removed, and have not had medically documented ovarian failure will be considered to be of childbearing potential.

Women of childbearing potential must have 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 agree 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 the last dose of study drug if not taking RBV:

- Complete abstinence from intercourse. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom, from the date of Screening until 6 months after the last dose of RBV, or 30 days after study drug if not taking 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

3. Contraceptive Requirements for Male Subjects (and their female partners)

All male study participants must agree to consistently and correctly use a condom from Baseline until 6 months after the last dose of RBV, or 90 days after the last dose of study drug if not taking RBV. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 6 months after last dose of RBV, or 90 days after the last dose of study drug if not taking RBV.

Male subjects must agree to refrain from sperm donation for at least 6 months after the last dose of RBV or 90 days after their last dose of study drug, if not taking RBV.

4. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they (or their partner) become pregnant at any time during the study, or if they become pregnant within 30 days (90 days for partners of male subjects, or 6 months for partners of males subjects taking RBV). Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 8.6.2.1.