Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ledipasvir / Sofosbuvir

Proprietary Product Name: Harvoni

Sponsor: Gilead Sciences Pty Ltd

First round report 3 January 2016
Second round report 25 June 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au> .

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website < https://www.tga.gov.au/product-information-pi> .

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATV/r	ritonavir-boosted atazanavir
AZT	zidovudine
BD	Two times daily
BMI	Body Mass Index
BCRP	breast cancer resistance protein
CFR	Code of federal regulations
CHC	Chronic hepatitis C virus infection
CI	Confidence interval
Clcr	creatinine clearance
CLDQ-HCV	Chronic Liver Disease Questionnaire-HCV
CMI	Consumer Medicine Information
CPT	Child-Pugh Turcotte score
CRF	case report form
CSR	clinical study report
CsA	cyclosporin
CYP	cytochrome P450 enzymes
DAA	Direct Acting Antiviral
DDI	Drug-drug interaction
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee

Abbreviation	Meaning
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
EASL	European Association for the Study of the Liver
ECG	electrocardiograph
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eGFRCG	estimated glomerular filtration rate Cockgroft Gault
EMA or EMEA	European Medicines Agency
EOT	End Of Therapy
EVG	elvitegravir
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	US Food and Drug Administration
FDC	Fixed dose combination
FTC	emtricitabine
FU	follow-up
gp	group
GS-331007	A metabolite of SOF
GS-5816	Velpatasvir
GT	genotype
Hb	haemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Abbreviation	Meaning
hr	hour
INSTI	integrase inhibitor
ICH	International Conference on Harmonisation
IFN	interferon
ITT	Intent to treat
LC-MS/MS	liquid chromatography with tandem mass spectroscopy
LDV	ledipasvir
LL	lower limit
LTransplant	liver transplant
LLOQ	Lower limit of quantification
LTFUP	lost to follow up
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
NDA	New Drug Application
NI	nucleoside inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NS5B	nonstructural protein5B
OD	once daily
PCR	polymerase chain reaction
PEG	PEGylated interferon
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetics
PO	per oral (taken orally)
PP	Per protocol

Abbreviation	Meaning
pTVR	post transplant virological response
QoL	Quality of Life
RAL	raltegravir
RAP	resistance-associated polymorphism
RAV	resistance-associated variant
RBV	ribavirin
RPV	rilpivirine
RT-PCR	Reverse transcription polymerase chain reaction
RTV	ritonavir
SAE	Serious adverse event
SAS	Safety Analysis Set
SF-36	Short Form Health Survey
SOF	Sofosbuvir
SVR	sustained virological response
SVR4	sustained virological response 4 weeks after EOT
SVR12	sustained virological response 12 weeks after EOT = cure
SVR24	sustained virological response 24 weeks after EOT
3TC	lamivudine
TAF	Tenofovir Alafenamide
TDF/FTC	Truvada = FDC of tenofovir Disoproxil Fumarate+ emtricitabine
TDF/FTC/EFV	Atripla - the FDC of tenofovir Disoproxil Fumarate, emtricitabine and efavirenz
TEV	treatment emergent variant
TGA	Therapeutic Goods Administration
t1/2	apparent plasma half-life
TR	Treatment related

Abbreviation	Meaning
UL	upper limit
US	United States
WPAI: Hep C	Work Productivity and Activity Impairment: Hepatitis
wk	week
yr	year

1. Introduction

This is a Category 1 extension of indication submission for the fixed dose combination (FDC) oral tablet ledipasvir (LDV)/sofosbuvir (SOF) (Harvoni). Harvoni, is an all oral, once daily (OD) FDC of LDV, a Hepatitis C (HCV) nucleotide nonstructural protein 5A (NS5A) inhibitor, and SOF, a HCV NS5B polymerase inhibitor, that has shown a favourable safety profile and efficacy in treatment naive and treatment experienced subjects with chronic Hepatitis C (CHC), with and without compensated cirrhosis. In Australia, Harvoni is approved for the treatment of hepatitis C virus (HCV) genotype 1 (GT) infection. This application proposes to extend the indication to:

Harvoni for the treatment of chronic Hepatitis C (CHC) infection in adults.

In support of this application, the sponsor provides further data on:

- Patients with HCV infection who are post transplantation with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status
- Patients with chronic GT 2, 3, 4, 5 or 6 HCV infection as there is currently no approved of an all oral, IFN and RBV free therapy for such patients
- Patients with HCV/human immunodeficiency virus (HIV) co-infection
- Patients who have previously failed a SOF + ribavirin (RBV) ± Pegylated interferon (PEG) regimen as there is currently no approved therapy for those patients who have previously failed a SOF containing regimen.

In this application Gilead proposes to extend the indication and update the prescribing information (PI) of Harvoni based on data generated from a number of Phase II and III studies as well as 4 Phase I studies exploring drug-drug interactions (DDI).

2. Clinical rationale

HCV is a global health challenge and untreated, can lead to liver cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC) and death. Currently, approximately 170 million individuals worldwide are chronically infected with HCV. [1] In the US, > 3 million are estimated to be chronically infected with HCV (Kershenobich), with > 800,000 estimated to have cirrhosis and > 100,000 of these estimated with decompensated cirrhosis (Davis).

In a systematic review, the rate of transition from compensated cirrhosis (CPT A) to decompensated cirrhosis (CPT B or CPT C) was 5% to 7% per year. Once decompensated, the 1 year mortality for CPT B decompensated cirrhosis is approximately 20%, while the 1 year mortality for CPT C decompensated cirrhosis is > 50% (D'Amico). In the US, there are currently no approved therapies for the treatment of HCV patients with decompensated liver disease. The poor adverse event (AE) profile of interferon (IFN) based regimens has limited their use in this sick patient population to specialised centres and clinical trials. Instead, the mainstay of treatment in the US for patients with decompensated liver disease due to HCV has been liver transplantation.

Accordingly, liver failure and HCC secondary to HCV infection are the most common indications for liver transplantation in the US, accounting for > 30% of liver transplants (Brown). Unfortunately, of the > 100,000 with decompensated liver disease due to HCV, only approximately 4,500 are listed in a given year for transplantation, and only approximately 1,500 liver transplantations for HCV are performed annually. Furthermore, the odds of being

[1] http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003

transplanted once on the waiting list (1:3) are similar to those of dying/becoming too sick to undergo transplantation (1:5) (Kim).

Need for medical treatment and the long-term benefits of achieving sustained virological response (SVR) = HCV cure in cirrhotics and those with decompensated liver disease.

The large number with decompensated disease due to HCV, the small number able to obtain a liver transplant, and limited prognosis even in those who receive a transplant, highlight the need for safe and efficacious HCV therapy for decompensated disease as well as those with recurrent HCV post liver transplantation. IFN free treatment regimens have created an opportunity to address this unmet medical need. The purpose of SOLAR-1 and SOLAR-2 is;

a. to assess the efficacy of LDV/SOF FDC+RBV in post transplantation subjects with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status; and

b. demonstrate the safety of LDV/SOF+RBV in a population with very high morbidity and mortality.

2.1. Treatment of genotypes other than GT1

The most common HCV GT in the US, Australia and EU is GT 1 (Backus); GT 2 and 3 HCV represent the majority of the remaining cases of chronic HCV infection in the US and EU (Fattovich). GT 4, 5, and 6 HCV infections are most prevalent in the Middle East, South Africa, and Southeast Asia, respectively (Nguyen). While SOF+RBV for 12 weeks is approved for GT 2 a RBV free treatment regimen would likely be less toxic and allow treatment of those in whom RBV is contraindicated. A currently approved regimen for treatment naive GT 3 is SOF+RBV for 24 weeks, a shorter treatment duration would be of benefit. There is currently no approved all oral, IFN and RBV free therapy for patients with GT 4, 5, or 6 HCV. For patients with GT 4, 5 and 6 HCV, SOF+Peg-IFN+RBV for 12 weeks is an option. Thus, there is an unmet medical need for IFN free treatment regimens in these groups.

2.2. Treatment; if HIV/HCV co-infection

There are currently 2 approved regimens for this group.

Sovaldi (SOF) is approved for patients with GT 1,4, 5 and 6 HCV infection (SOF +PEG+ RBV for 12 weeks), and patients with GT 2 or 3 HCV infection (SOF+RBV for 12 or 24 weeks, respectively) (Sovaldi AU PI).

Viekira Pak (ombitasvir, paritaprevir, and ritonavir (RTV) tablets; dasabuvir tablets) is also approved in the US for patients with GT 1 HCV (Viekira ± RBV for 12 or 24 weeks for patients ± cirrhosis) (Viekira Pak AU PI). Efficacy ranged from 76% to 92%, based on small numbers of subjects. Additionally, due in part to the inclusion of the potent CYP3A4 inhibitor, RTV, in Viekira Pak, this regimen has the potential for numerous DDI that may require alteration of the patient's antiretroviral (ARV) regimen which not always be feasible or desirable.

2.3. Prior SOF failures

There is currently no approved therapy for patients with HCV infection who have previously failed a SOF+RBV±PEG regimen. Although SOF-based regimens are efficacious, the extensive number of patients being treated with these regimens has resulted in a pool of patients who have nevertheless failed these regimens. Thus, there is an unmet medical need for regimens that are effective in patients who have failed a prior SOF+RBV±PEG regimen.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

Nine clinical studies were provided in support of Gilead's application to extend the indication:

- GS-US-337-0102 (ION-1): A Phase III, multi-centre, randomized, open label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic Genotype 1 HCV infection.
- GS-US-337-0115 (ION-4): A Phase III, multi-centre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination for 12 weeks in subjects with chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 co-infection
- GS-US-337-0121 (SIRIUS): A Phase II, multi-centre, randomized, double blind, placebo controlled study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination for 12 weeks with ribavirin or for 24 weeks without ribavirin in treatment experienced cirrhotic subjects with chronic Genotype 1 HCV infection.
- GS-US-337-0122 (ELECTRON 2): A Phase II, multi-centre, open label study to assess the efficacy and safety of sofosbuvir containing regimens for the treatment of chronic HCV infection
- GS-US-337-1118 (RETREATMENT): An Open label, multi-centre study to evaluate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination ± ribavirin for 12 or 24 weeks in chronic Genotype 1 HCV infected subjects who participated in a prior Gilead sponsored HCV treatment study
- GS-US-337-1119: A Phase II, multi-centre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination in treatment naïve and treatment experienced subjects with chronic Genotype 4 or 5 HCV infection
- GS-US-337-1468 (LEPTON): A Phase II, multi-centre, open label study to assess the efficacy and safety of oral regimens for the treatment of chronic HCV infection
- GS-US-337-0123 (SOLAR-1): A Phase II, multi-centre, open label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post-liver transplant.
- GS-US337-0124 (SOLAR-2): A Phase II, multi-centre, open label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post-liver transplant.

Studies providing further supporting data but not key to this application

- CO-US-337-0117 (SYNERGY): A pilot study to evaluate the safety and efficacy of multiple anti-HCV combination therapy; supports retreatment; genotype 4.

Integrated summaries:

- PC-337-2006
- PC-337-2007

Extrinsic Factor PK Study Reports (n = 4)

- GS-US-334-1344: A Phase I Study in healthy volunteers to evaluate transporter-mediated drug-drug interactions between rifampin (RIF) and sofosbuvir (SOF)

- GS-US-337-1306: A Phase I Study to evaluate pharmacokinetic drug-drug interaction potential between sofosbuvir/ledipasvir (SOF/LDV) fixed dose combination (FDC) tablet and HIV antiretroviral regimens ritonavir-boosted atazanavir (ATV plus RTV) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or ritonavir-boosted darunavir (DRV plus RTV) plus FTC/TDF or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)
- GS-US-337-1501: A Phase I Study to evaluate pharmacokinetic drug-drug interaction potential between ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination (FDC) tablet and HIV antiretroviral regimen dolutegravir (DTG) plus emtricitabine/tenofovir df (FTC/TDF)
- GS-US-337-1624: A Phase I Study to evaluate pharmacokinetic drug-drug interaction potential between ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination (FDC) tablet with HIV antiretroviral regimen elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) FDC tablet.

Integrated summaries of virology, efficacy, and safety.

Population PK Study reports;

- Population PK report - GS-US-337-0115 (ION4)
- Population PK Report - GS-US-337-0123 & GS-US-337-0124

Clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

3.2. Paediatric data

The submission did not include paediatric data.

3.1. Good clinical practice

All included studies were conducted in accordance with good Clinical Practice Guidelines (ICH-GCP), considerations for the ethical treatment of human subjects were in place at the time the trials were performed and informed consent was obtained from all trial participants.

4. Pharmacokinetics

Table 1 shows the studies relating to each PK topic.

Table 1: Submitted PK studies

PK topic	Subtopic	Study ID
PK interactions	interaction with rifampicin	GS-US-334-1344
	interaction with Elvitegravir/Cobicistat/Emtricitabine/TDF	GS-US-337-1306
	interaction with dolutegravir and Truvada (TRU)	GS-US-337-1501

PK topic	Subtopic	Study ID
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide	GS-US-337-1624
Population PK analyses	Target population	Population PK

None of the PK studies had deficiencies that excluded their results from consideration.

4.1. Summary of pharmacokinetics

This application included 4 extrinsic PK studies exploring DDI between Harvoni -rifampicin; and new ARVs and Harvoni. Population PK was provided from 2 studies in the target population.

4.2. Pharmacokinetics in the target population that is CHC

4.2.1. Intrinsic factors

4.2.1.1. HIV/HCV co-infection (ION-4)

LDV/SOF PK was evaluated in HCV/HIV co-infected subjects on NNRTI based regimens EFV/FTC/TDF or RPV/FTC/TDF (or components), or INSTI based regimen RAL plus FTC/TDF in the ION-4.

LDV, SOF and GS-331007 exposure parameters were generated for all with measurable plasma concentrations using previously established population PK models. Exposures of LDV, SOF and GS-331007; comparable across ARV regimens, race and treatment outcome. Comparison of LDV/SOF PK between HCV/HIV co-infected versus HCV mono-infected subjects revealed similar SOF and GS-331007 exposures, as evidenced by the 90% CIs for the %GMRs for these parameters falling between 95% and 117%. LDV geometric mean exposure parameters were approximately 25% to 29% lower in HCV/HIV co-infected subjects; mechanism unclear. When assessed relative to the previously established E_{max} model (LDV/SOF, 0000), LDV plasma exposures in HCV/HIV subjects continued to reside in the near-maximum portion of the dose response curve. Considering high SVR12 rates > 95%, these decreases are not considered clinically relevant.

4.2.1.2. Liver dysfunction in SOLAR-1 and SOLAR-2

Cirrhosis status and hepatic impairment on SOF, GS-331007, and LDV PK was evaluated. Exposure values for SOF, GS-331007, and LDV similar among the groups of subjects with decompensated cirrhosis, regardless of liver transplantation status, and thus for subsequent analyses, subjects were pooled according to degree of hepatic impairment without regard to transplantation status. Relative to the LDV/SOF NDA Population, SOF AUC_{tau} was increased approximately 2 fold in post-transplantation subjects ±compensated liver disease and in subjects with decompensated liver disease regardless of transplantation status. The increase in SOF AUC_{tau} in subjects with any degree of hepatic impairment (Groups 1, 2, 4, 5, 6) consistent with results of a Phase I single agent study of SOF in subjects with moderate and severe hepatic impairment (Study P2938-0515). Compensated cirrhosis was not identified as a clinically relevant covariate during population PK analyses of SOF, GS-331007, and LDV within the LDV/SOF NDA Population; no clear explanation for the increased SOF exposure observed in post-transplantation subjects without hepatic impairment (Group 3) relative to the NDA Population. Based on established efficacy, PK, and safety data for SOF, the 2 fold increase in exposure not considered clinically relevant. GS-331007 and LDV PK were not affected by

cirrhosis status or hepatic impairment. Compared to the LDV/SOF NDA population no clinically relevant changes in LDV/SOF PK in the 11 post transplantation subjects with recurrent disease.

4.2.1.3. Effect of BMI

In order to identify potential predictors of relapse, a logistic regression analysis of baseline factors was performed in those with GT 1 HCV and decompensated cirrhosis. BMI ≥ 30 kg/m^2 was significantly associated with relapse. To understand drug exposure in subjects with decompensated cirrhosis across ranges of BMI, LDV/SOF exposures in the pooled group of subjects with decompensated cirrhosis were summarised by quartile of BMI. The range of baseline BMI values in subjects with decompensated cirrhosis (18.7 to 48.5 kg/m^2) was similar to the range from the LDV/SOF NDA Population (18.0 to 56.2 kg/m^2).

4.2.1.4. SOF

In the NDA Population, body weight not identified as a statistically significant covariate of SOF (or GS-331007) exposure in population PK models. In agreement with these results, across quartiles of BMI, similar PK of SOF and GS-331007 observed in the decompensated cirrhotics.

4.2.1.5. LDV

PK of LDV in the decompensated cirrhotics was similar across quartiles of BMI. In the NDA Population PK analyses, body weight had been identified as a statistically significant covariate for LDV; LDV exposure exhibited modest mean decreases of approximately 25% to 31% between midpoints of lower and highest quartiles of BMI. Differences in LDV exposure due to BMI in the NDA Population were not considered clinically relevant based on the known PK of LDV, including exposure relationships and underlying variability in the population (NDA Population AUC_{tau} range: 416 to 49,100 ng.h/mL). In this analysis the smaller difference in LDV exposures across BMI quartiles was noted.

4.3. Pharmacokinetic interactions

Refer also to the original application for LDV/SOF.

4.3.1. Extrinsic Factors in SOLAR-1 and SOLAR-2

Patients undergoing liver transplantation require immunosuppressants typically including cyclosporin A [CsA]), a known P-gp and BCRP inhibitor. SOF and LDV are P-gp and BCRP substrates. No clinically relevant differences in LDV/SOF PK with CsA versus non-CsA immunosuppressant regimens following liver transplantation. No dose modification of LDV/SOF required in post-transplantation patients on CsA containing regimens.

4.4. Evaluator's overall conclusions on pharmacokinetics

The application explored the DDI between LDV/SOF-ARV regimens (ATV+RTV, DRV+RTV or DTG plus FTC/TDF, or E/C/F/TAF); Harvoni-rifampicin in healthy volunteers. Rifampicin cannot be administered with Harvoni. Importantly, results of this rifampicin DDI study inform on DDI with other P-gp inducers for example carbamazepine, rifabutin, St. John's wort. Like rifampicin, other P-gp inducers are expected to decrease LDV and SOF exposure and have limited or no impact on GS-331007 concentrations. In terms of ARVs, higher tenofovir exposures observed, unclear what the clinical consequences might be, no dose adjustment needed but should have closer monitoring of renal function during co-administration. There is no data on bone health during co-administration of TDF-Harvoni. In exploring the effects of liver dysfunction on LDV/SOF PK, SOF AUC_{tau} was increased approximately 2 fold in post-transplantation subjects ± compensated liver disease and in subjects with decompensated liver disease regardless of transplantation status. This increase is not likely to have safety consequences and no dose adjustment is recommended in this setting.

5. Pharmacodynamics

5.1. SOLAR-1 and SOLAR-2

Relative to the LDV/SOF NDA Population, SOF and its metabolite GS-331007, and LDV exposures were only modestly altered in SOLAR-1 and SOLAR-2 in subjects ± compensated liver disease and in subjects with decompensated liver disease regardless of transplantation status. Given the high SVR12 rate and relatively small number of relapsers, an analysis of LDV/SOF exposure in relapsers versus those achieving SVR12 should be interpreted with caution.

5.2. Evaluator's overall conclusions on pharmacodynamics

Not Applicable. All new clinical studies have been reviewed in the efficacy section.

6. Dosage selection for the pivotal studies

As currently approved that is FDC containing 90 mg LDV/400 mg SOF taken orally OD ± food.

7. Clinical efficacy

Pivotal studies for SOF in the treatment of HCV infection.

7.1. Pivotal efficacy studies

7.1.1. Study GS-US-337-0102 (ION-1)

A Phase III, multi-centre, randomized, open label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed dose combination ± ribavirin for 12 and 24 Weeks in treatment naïve subjects with chronic Genotype 1 HCV infection.

7.1.1.1. Study design, objectives, locations and dates

Sites: 100: USA (n = 62), Germany (n = 10), France (n = 7), UK (n = 7), Spain (n = 6), Italy (n = 8).

First subject screened: 26 September 2012; 30 April 2014 (Last subject observation).

Publications arising

1. Afdhal N, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. *NEJM* 2014; 370: 1889-1898.
2. Mangia A, et al. All oral fixed dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naïve genotype 1 HCV-infected patients: the Phase III ION-1 study. *J Hepatol* 2014; 60 (1): S523-524.

Protocol amendments

None; only v 1.0 29 August 2012 was utilised.

Design

Phase III, randomised, open label, multicentre study assessed antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment naive subjects with chronic GT 1 HCV infection.

7.1.1.2. Inclusion and exclusion criteria

Key inclusion criteria

1. Willing and able to provide written informed consent.
2. Male or female, age ≥ 18 years.
3. Confirmation of chronic HCV infection(at least 6 months) GT-1a/b/mixed 1a/1b.
4. HCV RNA ≥ 10^4 IU/mL.
5. BMI ≥ 18 kg/m^2.
6. HCV treatment naïve no prior IFN/RBV/DAA.
7. Cirrhosis determination, in up to 20% of enrolees; protocol defined as;
    i. Liver biopsy showing cirrhosis
    ii. Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa
    iii. FibroTest score of > 0.75 and an AST:platelet ratio index (APRI) of > 2 during Screening.
8. Liver imaging within 6 months of Baseline/Day 1 to exclude hepatocellular carcinoma (HCC) is required in patients with cirrhosis.
9. Normal ECG.
10. Laboratory parameters at screening:
    a. ALT ≤ 10 x ULN
    b. AST ≤ 10 x ULN
    c. Direct bilirubin ≤ 1.5 x ULN
    d. Platelets ≥ 50,000
    e. HbA1c ≤ 8.5%
    f. Creatinine clearance (CLcr) ≥ 60 mL /min, as calculated by the Cockcroft-Gault Equation
    g. Hb ≥ 11 g/dL for female subjects; ≥ 12 g/dL for male subjects
    h. Albumin ≥ 3 g/dL,
    i. INR ≤ 1.5 x ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR.
11. No investigational agents within 30 days of screening.
12. Avoidance of pregnancy including partner for durations in men and women as per SPC for RBV.

Key exclusion criteria

Current medical problems including:

1. Clinical hepatic decompensation (that is, ascites, encephalopathy or variceal haemorrhage); solid organ transplantation; significant pulmonary disease, significant cardiac disease or porphyria; psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 year; malignancy diagnosed/treated within 5 years.
2. Pregnant or nursing female or male with pregnant female partner.

3. Chronic liver disease of a non-HCV aetiology.
4. HBV or HIV.
5. Contraindications for any of the study drugs.
6. Laboratory parameters outside protocol defined limits.
7. Clinically-relevant drug abuse within 12 months of screening.
8. Alcohol misuse as defined by a Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8.
9. Chronic use of systemically administered immunosuppressive agents (for example, prednisone equivalent > 10 mg/day).

7.1.1.3. Study treatments

Approximately 800 subjects were randomised in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- Group 1; LDV/SOF 24 week group; FDC taken OD 24 weeks
- Group 2; LDV/SOF+RBV 24 week group; FDC taken OD + RBV (weight based dosing that is 1000 or 1200 mg/day divided BD) both for 24 weeks
- Group 3; LDV/SOF 12 week group: FDC taken OD for 12 weeks
- Group 4; LDV/SOF+RBV 12 week group: FDC taken OD + RBV (weight based dosing) both for 12 weeks.

Duration of treatment

Duration of treatment was 24 weeks for Groups 1 and 2; 12 weeks for Groups 3 and 4; stratified by GT (1a, 1b, or mixed 1a/1b) and presence/absence of cirrhosis. Approximately 20% can have compensated cirrhosis. Post treatment HCV RNA results blinded to investigator and sponsor.

Subject enrolment occurred in 2 parts. Part A enrolled and randomised approximately 200 subjects (50 subjects per treatment group; up to 20% with compensated cirrhosis).

Enrolment halted in all 4 treatment groups once Part A was fully enrolled. After subjects in Groups 3 and 4 (12 week treatment groups) reached post treatment Week 4, the DMC reviewed safety data from the first 12 weeks of dosing for all subjects (Groups 1 to 4) and SVR4 efficacy data for Groups 3 and 4. If the predefined interim futility criteria were met, Groups 3 and/or 4 were to be discontinued. As futility criteria were not met, the study was continued as planned.

Part B commenced enrolment after this interim futility analysis was complete. Approximately 600 additional subjects (approximately 150 subjects per group) enrolled in Part B. During a Type C meeting with the US FDA on 03 June 2013, agreed that if 12 weeks of LDV/SOF±RBV achieved an SVR12 ≥ 90% in subjects ± cirrhosis separately, efficacy data from the 24 week treatment groups would not be necessary for the initial LDV/SOF NDA filing. Based upon meeting the prespecified criteria in the interim analysis, results from the primary efficacy analysis for Groups 3 and 4 and all subjects in Part A were summarised in the interim CSR. This final CSR summarises the results of the final analysis, conducted when all subjects completed Post treatment Week 24 visit or prematurely discontinued from the study. After completing ION-1, eligible subjects could enrol into 1 of 2 follow-on studies: SVR Registry (GS-US-248-0122) or Sequence Registry (GS-US-248-0123).

7.1.1.4. Efficacy variables and outcomes

Study visits occurred at Screening, Baseline/Day 1, and On-treatment at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. Subjects in Groups 1 and 2 will have additional On-Treatment visits at end of Weeks 16, 20, and 24. Post treatment visits at Weeks 4, 12, and 24 following last dose of study medications. All subjects to complete a 4 Week and 12 Week post treatment visits regardless of

treatment duration. Subjects with HCV RNA < LLOQ at the 12 Week post treatment visit continued to complete at 24 Week post treatment visit unless viral relapse is determined. The end of study occurred at the 24 Week post treatment visit.

Criteria for evaluation

- Safety: AEs and safety laboratory, vital signs, ECGs, and physical examinations collected throughout the study (through the 4 Week post treatment visit).
- Efficacy: scheduled assessments of HCV RNA using COBAS TaqMan HCV Test, v2.0 for use with the High Pure System (LLOQ < 25 IU/mL)
- Genetics: IL28B genotype by PCR amplification of the SNP, rs12979860, with sequence specific forward and reverse primers and allele specific fluorescently labelled TaqMan MGB probes
- PK: single PK blood sample collected at each on-treatment visit for all. Optional PK sub-study at the Week 2 or Week 4 on-treatment visit in a subset of subjects (target 15 per group).
- QoL surveys; Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hep C) questionnaire completed at Day 1 (baseline), Weeks 2, 4, 8, 12 and 24 (if applicable), early termination (if applicable), and Post treatment Weeks 4, 12, and 24 (if applicable).

Primary objective

Proportion with SVR12; safety and tolerability of each treatment regimen.

Other efficacy outcomes

Other efficacy outcomes included: SVR4 and 24; quantitative HCV RNA kinetics; ALT normalisation; QoL; virologic failure and resistant variants; steady state PK; identify/validate genetic markers predictive of natural history of disease, response and/or tolerability of DAA.

7.1.1.5. Randomisation and blinding methods

Open label. An interactive web and voice response system employed to manage subject randomisation and treatment assignment. Stratified by GT (1a, 1b, mixed) and ± cirrhosis.

7.1.1.6. Analysis populations

ITT population: all randomised subjects receiving ≥ 1 dose study drug. This will be the primary population for efficacy analyses (= Full Analysis Set or FAS). For all analyses based on the ITT Population, subjects analysed in the treatment group to which they are randomised, regardless of what treatment is actually received.

Per-Protocol Population: excludes subjects with no post baseline HCV RNA data or with major protocol deviations. This population includes all subjects who have received ≥ 1 dose study drug. Subjects analysed according to the treatment received.

The primary analysis set for safety analyses (SAS) will include subjects who received ≥ 1 dose study drug.

PK analysis set: The PK analysis set includes all subjects who are randomised and have received ≥ 1 dose of study drug and for whom concentration data of analytes are available. PK analysis set will be used for analyses of general PK.

The PK Sub-study analysis set will include all subjects who were randomised and received ≥ 1 dose study drug and for whom steady state PK parameters of the analytes of interest are available. The PK Sub-study analysis set will be used for detailed PK analyses of these analytes.

7.1.1.7. Sample size

Planned: approximately 800 subjects (200 in each treatment group); see below under statistical methods.

7.1.1.8. Statistical methods

In the primary efficacy analysis, SVR12 rates in each of the 4 treatment groups compared with the adjusted historical SVR null rate of 60% using a 2 sided exact 1 sample binomial test. The Bonferroni correction method used to strongly control the family wise type I error rate at the 0.05 level and individual type I error rate at the 0.0125 level for each primary hypothesis.

Secondary efficacy endpoints included SVR4 and SVR24. After the first 200 subjects were enrolled (Part A), futility in the 12 Week treatment groups (Groups 3 and 4), was assessed using an interim futility stopping procedure that utilised a conditional power approach under the observed trend. Stopping for futility was triggered when the conditional power was < 5% (equivalent to an observed response rate of ≤ 60%).

Based on meeting the prespecified criteria agreed at a Type C meeting with the FDA, an interim analysis was conducted when all subjects in the 12 Week treatment groups completed the post treatment Week 12 visit or prematurely discontinued from the study. The final analysis was conducted when all subjects completed the post treatment Week 24 visit or prematurely discontinued from the study. All continuous endpoints summarised using descriptive statistics by treatment group. All categorical endpoints summarised by numbers and % who met the endpoint.

PK: Steady-state PK over a 24 hour dosing interval determined in the PK sub-study at the Week 2 or 4 on-treatment visit. Standard statistical methods for PK used. In addition, a population PK model was developed to characterise the PK of LDV, SOF, and SOF's major metabolite GS-331007.

Safety: Safety data analysed by treatment group and included all data collected on or after the first dose of any study drug up to the last dose + 30 days. AE coded using MedDRA, Version 16.0.

Quality of Life: A Wilcoxon signed rank test explored within treatment group changes from baseline to each of the time points, and from EOT to each Post treatment time point. A Wilcoxon rank sum test explored between-treatment group differences in change from baseline to each of the time points.

7.1.1.9. Participant flow

Table 2: Participant flow in GS-US-337-0102 (ION-1)

Subject Disposition	LDV/SOF 12 Weeks	LDV/SOF+ RBV 12 Weeks	LDV/SOF 24 Weeks	LDV/SOF+ RBV 24 Weeks	Total
Subjects Screened					1015
Subjects Not Randomized					145
Subjects Randomized	217	218	217	218	870
Subjects Randomized but Never Treated	3	1	0	1	5
Subjects in Safety Analysis Set	214	217	217	217	865
Subjects in Full Analysis Set	214	217	217	217	865
Study Treatment Status					
Completed Study Treatment	212 (99.1%)	213 (98.2%)	208 (95.9%)	205 (94.5%)	838 (96.9%)
No FU-4 HCV RNA Assessment	1	1	0	1	3
With FU-4 but no FU-12 HCV RNA Assessment	0	1	1	0	2
Discontinued Study Treatment	2 (0.9%)	4 (1.8%)	9 (4.1%)	12 (5.5%)	27 (3.1%)
No FU-4 HCV RNA Assessment	1	3	1	1	6
With FU-4 but no FU-12 HCV RNA Assessment	0	1	0	0	1
Reason for Premature Discontinuation of Study Treatment					
Adverse Event	0	0	4 (1.8%)	6 (2.8%)	10 (1.2%)
Withdrew Consent	0	1 (0.5%)	3 (1.4%)	3 (1.4%)	7 (0.8%)
Lost to Follow-Up	1 (0.5%)	2 (0.9%)	0	1 (0.5%)	4 (0.5%)
Protocol Violation	1 (0.5%)	1 (0.5%)	0	2 (0.9%)	4 (0.5%)
Lack Of Efficacy	0	0	1 (0.5%)	0	1 (0.1%)
Pregnancy	0	0	1 (0.5%)	0	1 (0.1%)

Note: The denominator for percentages is based on the number of subjects in the safety analysis set.
Note: Safety analysis set includes subjects who were randomized and received at least 1 dose of study drug.
Note: Full analysis set includes subjects who were randomized and received at least 1 dose of study drug.
Source: Section 15.1, Table 3

7.1.1.10. Major protocol violations/deviations

Table 3: Study GS-US-337-0102 (ION-1); important protocol deviations (SAS)

Protocol Deviation	LDV/SOF 12 Weeks (N=214)	LDV/SOF+ RBV 12 Weeks (N=217)	LDV/SOF 24 Weeks (N=217)	LDV/SOF+ RBV 24 Weeks (N=217)	Total (N=865)
Violation of Inclusion/Exclusion Criteria	21 (9.8%)	7 (3.2%)	11 (5.1%)	11 (5.1%)	50 (5.8%)
Received Prohibited Concomitant Medication[a]	1 (0.5%)	2 (0.9%)	4 (1.8%)	0	7 (0.8%)
Initial Informed Consent Not Obtained Properly	1 (0.5%)	1 (0.5%)	2 (0.9%)	0	4 (0.5%)
Study Drug Noncompliance[b]	0	4 (1.8%)	3 (1.4%)	4 (1.8%)	11 (1.3%)
Study Assessment Not Done Per Protocol	0	1 (0.5%)	1 (0.5%)	0	2 (0.2%)

Note: Subjects may have been counted more than once.
a This category is for subjects who started a prohibited concomitant medication after Day 1 (baseline).
b This category is for subjects who had adherence to study drug of < 80%.
Source: Appendix 16.2, Important Protocol Deviation Log

There were 74 important protocol deviations in 71 subjects. The majority (50 of 74) were for 'violation of inclusion/exclusion criteria'; most commonly use of prohibited concomitant medications within 28 days of the baseline/Day 1 visit. None affected overall quality or interpretation of the study data.

7.1.1.11. Baseline data

Extent of exposure

Mean (SD) duration of exposure was 12.1 (0.84) weeks in the LDV/SOF 12 Week group, 12.0 (0.69) weeks in the LDV/SOF+RBV 12 Week group, 23.6 (2.58) weeks in the LDV/SOF 24 Week group, 23.7 (1.90) weeks in the LDV/SOF+RBV 24 Week group. The majority of subjects (82.0% to 89.7%) in all 4 treatment groups received study drug for 84 days (12 Week groups) or 168 days (24 Week groups).

Subject disposition and demographics

Of the 870 randomised, 865 received ≥ 1 dose of study drug and were included in the SAS and FAS. Twenty seven (3.1%) prematurely discontinued study treatment.

Demographics generally balanced across the 4 treatment groups: 59.3% male, White (85.0%), and non-Hispanic/Latino (88.1%), mean age of 52 years (ranging 18 to 80 years). Overall, 12.5% were Black or African-American race. Of the subjects enrolled in the US, 19.5% were Black or African-American race. Overall mean (SD) baseline BMI value for subjects was 26.5 (5.00) kg/m^2, and 20.0% of subjects had a BMI ≥ 30 kg/m^2.Baseline disease characteristics (Table 4) generally balanced across the 4 treatment groups. Majority in the SAS had GT 1a (67.2%), non-CC (CT or TT) IL28B alleles (70.4%), HCV RNA ≥ 800,000 IU/mL (79.0%), mean (SD) baseline HCV RNA of 6.4 (0.66) $\log_{10}$ IU/mL; 15.7% had cirrhosis. Mean (SD) ALT was 81 (62.6) U/L, 53.2% with ALT > 1.5 the ULN.

Table 4: GS-US-337-0102 (ION-1): Baseline disease characteristics (SAS)

Disease Characteristics	LDV/SOF 12 Weeks (N=214)	LDV/SOF+RBV 12 Weeks (N=217)	LDV/SOF 24 Weeks (N=217)	LDV/SOF+RBV 24 Weeks (N=217)	Total (N=865)
Interferon Eligibility Status					
Eligible	200 (93.5%)	197 (90.8%)	198 (91.2%)	203 (93.5%)	798 (92.3%)
Ineligible	14 (6.5%)	20 (9.2%)	19 (8.8%)	14 (6.5%)	67 (7.7%)
HCV Genotype					
Genotype 1a	144 (67.3%)	148 (68.2%)	146 (67.3%)	143 (65.9%)	581 (67.2%)
Genotype 1b	66 (30.8%)	68 (31.3%)	68 (31.3%)	71 (32.7%)	273 (31.6%)
Genotype 1 (no confirmed subtype)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	4 (0.5%)
Genotype 4	1 (0.5%)	0	0	1 (0.5%)	2 (0.2%)
Missing	2 (0.9%)	0	2 (0.9%)	1 (0.5%)	5 (0.6%)
Cirrhosis					
No	178 (83.2%)	183 (84.3%)	184 (84.8%)	181 (83.4%)	726 (83.9%)
Yes	34 (15.9%)	33 (15.2%)	33 (15.2%)	36 (16.6%)	136 (15.7%)
Missing	2 (0.9%)	1 (0.5%)	0	0	3 (0.3%)
IL28B					
CC	55 (25.7%)	76 (35.0%)	52 (24.0%)	73 (33.6%)	256 (29.6%)
Non-CC	159 (74.3%)	141 (65.0%)	165 (76.0%)	144 (66.4%)	609 (70.4%)
CT	113 (52.8%)	107 (49.3%)	119 (54.8%)	112 (51.6%)	451 (52.1%)
TT	46 (21.5%)	34 (15.7%)	46 (21.2%)	32 (14.7%)	158 (18.3%)
Baseline HCV RNA ($\log_{10}$ IU/mL)					
N	214	217	217	217	865
Mean (SD)	6.4 (0.69)	6.4 (0.64)	6.3 (0.68)	6.3 (0.65)	6.4 (0.66)
Median	6.5	6.5	6.4	6.4	6.5
Q1, Q3	6.0, 6.8	6.0, 6.9	6.0, 6.8	6.0, 6.8	6.0, 6.8
Min, Max	1.6, 7.5	4.4, 7.6	3.7, 7.4	3.2, 7.5	1.6, 7.6
Baseline HCV RNA Category					
< 800,000 IU/mL	45 (21.0%)	44 (20.3%)	49 (22.6%)	44 (20.3%)	182 (21.0%)
≥ 800,000 IU/mL	169 (79.0%)	173 (79.7%)	168 (77.4%)	173 (79.7%)	683 (79.0%)
Baseline ALT (U/L)					
N	214	217	217	217	865
Mean (SD)	87 (76.5)	82 (60.0)	79 (59.8)	77 (51.9)	81 (62.6)
Median	63	62	59	62	62
Q1, Q3	42, 98	47, 97	41, 92	39, 103	42, 97
Min, Max	16, 557	16, 485	17, 360	7, 321	7, 557
Baseline ALT Category					
≤ 1.5 x ULN	94 (43.9%)	98 (45.2%)	108 (49.8%)	105 (48.4%)	405 (46.8%)
> 1.5 x ULN	120 (56.1%)	119 (54.8%)	109 (50.2%)	112 (51.6%)	460 (53.2%)

7.1.1.12. Results for the primary efficacy outcome

Efficacy results: All 4 treatment groups met the primary efficacy endpoint of an SVR12 rate that was superior to the historical control rate of 60% ($p < 0.001$). The SVR12 rates were:

- LDV/SOF 12 Week group: 98.6% (95% CI: 96.0% to 99.7%) of subjects (211 of 214)
- LDV/SOF+RBV 12 Week group: 97.2% (95% CI: 94.1% to 99.0%) of subjects (211 of 217)
- LDV/SOF 24 Week group: 98.2% (95% CI: 95.3% to 99.5%) of subjects (213 of 217)
- LDV/SOF+RBV 24 Week group: 99.1% (95% CI: 96.7% to 99.9%) of subjects (215 of 217).

Cirrhotic subjects in all 4 treatment groups achieved SVR12 rates of 94% to 100%. The addition of RBV to LDV/SOF and/or extending the duration of the regimen to 24 Weeks did not impact on the SVR12 rate. Furthermore, no clinical impact on SVR12 whether LDV/SOF ± food.

Fifteen subjects failed to achieve SVR1, 12 subjects were lost to follow-up or withdrew consent and three were virologic failures. One subject in the LDV/SOF 24 Week group had on-treatment virologic failure (breakthrough) at Week 8, associated with study drug noncompliance confirmed by PK results. Post treatment virologic failure (relapse) observed in 2: 1 in the LDV/SOF 12 Week group relapsed at post treatment Week 4 and 1 in the LDV/SOF 24 Week group relapsed at post treatment Week 12. SVR12 and SVR24 was 100% with SVR12 in all treatment groups. Several host/viral factors traditionally predictive of or associated with lower SVR had no impact on SVR12 rates, including baseline LDV associated NS5A RAVs detected in 140 subjects.

Table 5: GS-US-337-0102 (ION-1): SVR12 (FAS)

	LDV/SOF 12 Weeks (N = 214)	LDV/SOF+RBV 12 Weeks (N = 217)	LDV/SOF 24 Weeks (N = 217)	LDV/SOF+RBV 24 Weeks (N = 217)
SVR12	211/214 (98.6%)	211/217 (97.2%)	213/217 (98.2%)	215/217 (99.1%)
95% CI	96.0% to 99.7%	94.1% to 99.0%	95.3% to 99.5%	96.7% to 99.9%
P-value (compared to 60%)	< 0.001	< 0.001	< 0.001	< 0.001

Table 6: GS-US-337-0102 (ION-1): SVR12 for subjects with and without cirrhosis (FAS)

SVR12	LDV/SOF 12 Weeks (N = 214)	LDV/SOF+RBV 12 Weeks (N = 217)	LDV/SOF 24 Weeks (N = 217)	LDV/SOF+RBV 24 Weeks (N = 217)
Cirrhosis				
No	179/180 (99.4%)	178/184 (96.7%)	181/184 (98.4%)	179/181 (98.9%)
95% CI	96.9% to 100.0%	93.0% to 98.8%	95.3% to 99.7%	96.1% to 99.9%
Yes	32/34 (94.1%)	33/33 (100.0%)	32/33 (97.0%)	36/36 (100.0%)
95% CI	80.3% to 99.3%	89.4% to 100.0%	84.2% to 99.9%	90.3% to 100.0%

Note: HCV RNA analyzed using Roche TaqMan v2.0 assay for use with the High Pure System assay with an LLOQ of 25 IU/mL.
Note: SVR12 is sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
Note: A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (i.e., '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR12 value is imputed as a failure. TND = target not detected.
Note: The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.
Note: The summary is based on eCRF (cirrhosis status) data reported at the time of analysis.
Note: If cirrhosis status was missing, then CIRRHOSIS = NO for purposes of analysis.
Source: Section 15.1, Table 12.1

7.1.1.13. Results for other efficacy outcomes

1. Viral kinetics: HCV RNA declined rapidly in all 4 treatment groups irrespective of inclusion of RBV.
2. ALT normalisation: observed in most in all 4 treatment groups during treatment (87.1% to 93.0% by EOT), coincident with HCV suppression.
3. Resistance: 140 of 861 (16.3%) had ≥ 1 baseline NS5A RAV by deep sequencing. Of these 140, 100 (71.4%) had ≥ 1 NS5A RAV conferring > 100 fold reduced susceptibility to LDV. Despite NS5A RAVs, 97.1% achieved SVR12. Of the 4 not achieving SVR12, 2 relapsed and 2 LTFUP. Among 865 enrolled, only 2 relapsed. Both relapsers were cirrhotic, no additional NS5A RAVs detectable at failure time point. Phenotypic analysis showed a reduced susceptibility to LDV (but not SOF) at both baseline and at relapse. Additionally, 1 subject in the LDV/SOF 24 Week group with GT 1b had on-treatment virologic failure (breakthrough), associated with study drug noncompliance.

Table 7: GS-US-337-0102 (ION-1): Number of subjects with baseline NS5A and NS5B RAVs

		LDV/SOF 12 Weeks (N = 214)				LDV/SOF+RBV 12 Weeks (N = 217)				LDV/SOF 24 Weeks (N = 217)				LDV/SOF+RBV 24 Weeks (N = 217)					
Gene with RAVs	Genotype	Subjects with RAVs n/N	SVR12 for Subjects with RAVs n/N	Total Subjects with RAVs n/N (%)	Total SVR12 for Subjects with RAVs n/N (%)	Subjects with RAVs n/N	SVR12 for Subjects with RAVs n/N	Total Subjects with RAVs n/N (%)	Total SVR12 for Subjects with RAVs n/N (%)	Subjects with RAVs n/N	SVR12 for Subjects with RAVs n/N	Total Subjects with RAVs n/N (%)	Total SVR12 for Subjects with RAVs n/N (%)	Subjects with RAVs n/N	SVR12 for Subjects with RAVs n/N	Total Subjects with RAVs n/N (%)	Total SVR12 for Subjects with RAVs n/N (%)	Overall Subjects with RAVs n/N (%)	Overall SVR12 for Subjects with RAVs n/N (%)
NS5A RAVs	GT 1a	17/144	16/17	32/213 (15.0)	31/32 (96.9)	27/151	27/27	36/216 (16.7)	35/36 (97.2)	19/146	19/19	34/216 (15.7)	33/34 (97.1)	25/142	24/25	38/216 (17.6)	37/38 (97.4)	140/861 (16.3)	136/140 (97.1)
	GT 1b	13/67	13/13			8/64	7/8			14/69	13/14			12/73	12/12				
	Others	2/2	2/2			1/1	1/1			1/1	1/1			1/1	1/1				
NS5B RAVs (NI)	GT 1a	0/66	–	7/102 (6.9)	7/7 (100)	0/72	–	5/102 (4.9)	5/5 (100)	0/69	–	7/106 (6.6)	7/7 (100)	0/72	–	9/113 (8.0)	9/9 (100)	28/423	28/28[b] (100)
	GT 1b	7/33	7/7			5/30	5/5			7/36	7/7			9/40	9/9				
	Others	0/1	–			–	–			0/1	-			0/1	–				

GT = genotype
a One subject LTFU
b 25 subjects had L159F (NI) + C316N (NNI) and 3 subjects had N142T (NI)
Source: Appendix 16.2, GS-US-337-0102 Virology Listings 1 and 2

4. QoL: Overall, results from the SF-36 (Part B only), CLDQ-HCV, FACIT-F, and WPAI: Hep C quality of life questionnaires indicated that, in contrast to the RBV free (LDV/SOF) groups, which had no on-treatment decrements in QoL, the RBV containing (LDV/SOF+RBV) 12 and 24 Week treatment groups had a statistically significant ($p < 0.05$) worsening in health related quality of life between baseline and the EOT for most responses. Mean scores for all scales generally improved from EOT to 4, 12, and 24 Weeks following treatment.
5. Safety: Overall, LDV/SOF ± RBV was generally safe and well tolerated. See further in the safety Section.

7.1.2. Study GS-US-337-0115 (ION-4)

Study GS-US-337-0115 (ION-4): A Phase III, multi-centre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination for 12 weeks in subjects with chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 co-infection

7.1.2.1. Study design, objectives, locations and dates

Sites: 60: USA (n = 53 including 2 in Puerto Rico), Canada (n = 5), New Zealand (n = 2)

First subject screened: 24 February 2014; 14 January 2015 (Last subject observation).

Publications/presentations arising:

1. Naggie S, et al. Ledipasvir/Sofosbuvir for 12 Weeks in Patients Coinfected With HCV and HIV-1. 22nd CROI; 2015 February 23-26; Seattle, WA.

Protocol amendments: none; v 1.0 25 November 2013.

Design

Phase III, open label, non-randomised, multicentre study assessed the antiviral efficacy, safety, and tolerability of LDV/SOF administered for 12 weeks in HCV treatment naïve and treatment experienced (including treatment intolerant) subjects with chronic GT 1 or 4 HCV infection co-infected with HIV-1. Approximately 300 subjects treated with LDV/SOF FDC OD for 12 weeks. Subject subgroups will include: approximately 50% of the subjects who are HCV treatment experienced (including treatment intolerant); approximately 20% with cirrhosis. All subjects were to complete the post treatment Week 4, 12, and 24 visits regardless of their treatment duration. Eligible subjects who experienced post treatment virologic failure at or before post treatment Week 24 may enrol in the Retreatment Sub study and retreated with LDV/SOF FDC OD + weight based RBV for 24 weeks.

Interim analysis: report date 12 March 2015.

7.1.2.2. Inclusion and exclusion criteria

Key inclusion criteria

1. Willing and able to provide written informed consent.
2. Male or female, age ≥ 18 years.
3. confirmation of chronic HCV infection(≥ 6 months) GT-1a/b/mixed 1a/1b or GT 4.
4. HCV RNA ≥ 10^4 IU/mL.
5. BMI ≥ 18 kg/m^2.
6. HCV treatment status as follows:
    a. HCV Treatment naive: No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA agent
    b. HCV Treatment-Intolerant: Subjects that discontinued HCV treatment due to development or significant worsening of a treatment related adverse event
    c. HCV Treatment experienced: Virologic failure after treatment with PEG-IFN+RBV, NS3 protease inhibitor plus PEG-IFN/RBV regimen or SOF ±RBV±PEG-IFN regimen. Subjects in this category must not have discontinued prior therapy due to an AE.
7. HIV-1 infection.
8. HIV treatment status:
    a. Completed at least 6 months of any prior HIV ARV therapy and maintained HIV RNA < 50 copies/mL (or < LLOQ if the local laboratory assay's LLOQ is ≥ 50 copies/mL) prior to Screening. Subjects with an isolated or unconfirmed HIV RNA > 50 copies/mL (or > LLOQ if the local laboratory assay's LLOQ is ≥ 50 copies/mL) are not excluded
    b. On a stable, protocol approved, ARV regimen for ≥ 8 weeks prior to Screening and expected to continue the current ARV regimen through the end of study. FTC/TDF standard of care backbone plus EFV, RPV or RAL. Single tablet regimens containing Truvada plus EFV or RPV (Atripla and Complera, respectively) permitted.
9. Liver imaging within 6 months of Baseline/Day 1 to exclude HCC is required in patients with cirrhosis.
10. Cirrhosis determination, in up to 20% of enrolees; protocol defined as

i. Liver biopsy showing cirrhosis

ii. Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa

iii. FibroTest score of > 0.75 and an AST:platelet ratio index (APRI) of > 2 during Screening.

11. Normal ECG.
12. laboratory parameters at screening:
    a. HIV-1 RNA < 50 copies/mL
    b. CD4 T-cell count > 100 cells/mm^3
    c. ALT ≤ 10 x ULN
    d. AST ≤ 10 x ULN
    e. Direct bilirubin ≤ 1.5 x ULN
    f. Platelets ≥ 50,000
    g. HbA1c ≤ 8.5%
    h. Creatinine clearance (CLcr) ≥ 60 mL /min, as calculated by the Cockcroft-Gault Equation
    i. Hb ≥ 10 g/dL
    j. Albumin ≥ 3 g/dL
    k. INR ≤ 1.5 x ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR.
13. non-pregnant, agree to use adequate contraception throughout the study.

Key exclusion criteria

Current medical problems including:

1. Clinical hepatic decompensation (that is, ascites, encephalopathy or variceal haemorrhage); solid organ transplantation; significant pulmonary disease, significant cardiac disease or porphyria; psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 2 years; malignancy diagnosed/treated within 5 years of screening.
2. OI within 6 months of screening.
3. Pregnant or nursing female.
4. Any IFN-containing regimen within 8 weeks prior to Screening or any prior exposure to HCV-specific direct acting antiviral agent(s), other than a NS3/4A protease inhibitor and sofosbuvir.
5. Chronic liver disease of a non-HCV aetiology.
6. HB.
7. Contraindications for any of the study drugs and/or use of any prohibited concomitant medications.
8. Laboratory parameters outside protocol defined limits.
9. Clinically relevant alcohol or drug abuse within 12 months of screening; a positive drug screen during screening will exclude patients.

10. Chronic use of systemically administered immunosuppressive agents (for example, prednisone equivalent > 10 mg/day).

7.1.2.3. Study treatments

LDV/SOF FDC (90/400 mg) tablet OD for 12 weeks.

7.1.2.4. Efficacy variables and outcomes

Subjects will complete all of the following visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 6, 8, 10, 12 and post treatment visits at Weeks 4, 12 and 24. Screening assessments completed within 28 days of Baseline/Day 1 visit. For the Retreatment Sub-study, visits: Day 1, On Treatment visits at the end of Weeks 2, 4, 8, 12, 16, 20, and 24 and post treatment visits at Weeks 4, 12, and 24.

Criteria for evaluation

- Safety: AEs and safety laboratory tests vital signs measurements, ECGs, and physical examinations collected throughout the study (through the 4 week post treatment visit). Includes HIV plasma viral load; change from baseline of serum creatinine at EOT and at post treatment Week 12 and 24.
- 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 (LLOQ < 25 IU/mL).
- Genetics: IL28B genotype as described before.
- PK: Single PK blood sample collected at each on-treatment visit for all subjects (but not in the retreatment protocol). Optional PK sub-study (Weeks 2, 4, 6 and 8) in a subset of subjects.
- QoL surveys; SF-36, CLDQ-HCV, the FACIT-F questionnaire, and WPAI: Hep C questionnaire at Day 1 (baseline), Weeks 4, 8, 12, Post treatment Weeks 4, Early Termination (if applicable) visits.
- Primary objective: proportion of subjects with SVR12; safety and tolerability.
- Other outcomes: SVR4 and 24; quantitative HCV-RNA kinetics; proportion with HIV-1 RNA < 50 copies/mL; change from baseline in CD4 T-cell count; efficacy of LDV/SOF FDC+RBV for 24 weeks in subjects entering the Retreatment Sub-study; steady state PK; identify/validate genetic markers predictive of the natural history of disease, response and/or tolerability of DAA.

7.1.2.5. Randomisation and blinding methods

Non-randomised; open label.

7.1.2.6. Analysis populations

The FAS, SAS and PK analysis sets are as defined previously.

7.1.2.7. Sample size

N = 300.

7.1.2.8. Statistical methods

Single arm study; with approximately 300 GT 1 or 4 subjects enrolled, a two sided 95.0% CI of the SVR12 rate will extend at most 3.4% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 90%. The point estimate of the SVR12 rate calculated and the 2 sided 95% CI constructed using the Clopper-Pearson method. Subgroup analyses performed to assess relationship between SVR12 and baseline demographic and disease characteristics, and ARV regimen. Point estimates and 95% exact CIs of SVR12 rates calculated for each subgroup by ARV regimen.

PK

Population PK model derived PK parameters for SOF, GS-331007, LDV, and tenofovir were summarised by HIV ARV regimen at enrolment, by treatment outcome (relapse by Post treatment Week 12 and SVR12 success), and race. GMR and its 90% CI were provided to compare the PK exposure by treatment outcome and race. PK parameters compared in subjects with HCV/HIV co-infection in this study and HCV mono infection in the LDV/SOF Phase II/III population. PK parameters for RAL, EFV, RPV, FTC and GS-566500 computed for all with evaluable PK profiles who participated in the PK sub-study. Standard PK parameters were presented.

Safety

Safety data analysed by treatment group and included all data collected on or after the first dose of any study drug up to the last dose + 30 days. AE coded using MedDRA, Version 17.1.

7.1.2.9. Participant flow

Analysed: All enrolled subjects: 335 subjects; FAS: 335 subjects; SAS: 335 subjects; PK Analysis Set: 335 subjects; PK Sub-study Analysis Set: 56 subjects.

7.1.2.9.1. Major protocol violations/deviations

Table 8: Protocol deviations in Study GS-US-337-0115 (ION-4)

	LDV/SOF 12 Weeks (N = 335)
Deviation of Inclusion/Exclusion Criteria	18 (5.4%)
Not Managed According to Protocol	2 (0.6%)
Incorrect Dispensing or Dosing of Study Drug	3 (0.9%)

7.1.2.10. Baseline data

335 enrolled and received ≥ 1 dose. Of these, 9 (2.7%) discontinued treatment early: 2 (0.6%) lack of efficacy, 1 (0.3%) died, 6 (1.8%) 'coded' as prematurely discontinuing: 1 with treatment duration < 81 days (protocol specified treatment duration of 84 days ± 3) and 5 completed 81 days of therapy but were incorrectly documented as not completing.

Majority male (82.4%, n = 276), White (60.6%, n = 203) or Black (34.3%, n = 115), of non-Hispanic or non-Latino ethnicity (82.4%, n = 276), with a mean age of 52 years (range: 26 to 72). Mean (SD) baseline BMI was 27.3 (5.21) kg/m^2, 22.7% had a BMI ≥ 30 kg/m^2.

All subjects in the SAS had GT 1a (74.6%, n = 250), 1b (23.0%; majority non-CC (CT or TT) IL28B GT (75.8%). 22% (67 subjects) had cirrhosis. Mean (SD) baseline HCV RNA was 6.7 (0.64) $\log_{10}$ IU/mL, most had baseline HCV RNA ≥ 800,000 IU/mL (89.3%, n = 299).

185 HCV treatment experienced subjects (55.2%); most recent HCV treatment was PEG + RBV for 113 (61.1%), DAA + PEG+RBV for 53 (28.6%), DAA+RBV for 14 (7.6%, 13 of whom failed SOF+RBV), 'other' for 5 (2.7%). Mean (SD) estimated GFR was 101.6 (30.79) mL/min.

Overall median (Q1, Q3) baseline CD4 count was 628 (469, 823) cells/μL, and 70.7% of subjects had CD4 counts > 500 cells/μL. Per protocol, all subjects were on a stable ARV regimen at enrolment: 47.8% (n = 160 subjects) on Atripla, 43.6% (n = 146) were on RAL+Truvada, and 8.7% (n = 29) were on RPV+Truvada.

Table 9: HCV disease characteristics in Study GS-US-337-0115 (ION-4)

Disease Characteristics	LDV/SOF 12 Weeks (N = 335)
HCV Genotype	
Genotype 1a	250 (74.6%)
Genotype 1b	77 (23.0%)
Genotype 4	8 (2.4%)
Cirrhosis	
No	268 (80.0%)
Yes	67 (20.0%)
Treatment-Naive	20 (29.9%)
Treatment-Experienced	47 (70.1%)
IL28B	
CC	81 (24.2%)
Non-CC	254 (75.8%)
CT	185 (55.2%)
TT	69 (20.6%)
Baseline HCV RNA (log10 IU/mL)	
N	335
Mean (SD)	6.7 (0.64)
Median	6.9
Q1, Q3	6.3, 7.2
Min, Max	4.1, 7.8
Baseline HCV RNA Category	
< 800,000 IU/mL	36 (10.7%)
≥ 800,000 IU/mL	299 (89.3%)
Baseline HCV RNA Category	
< 6,000,000 IU/mL	154 (46.0%)
≥ 6,000,000 IU/mL	181 (54.0%)

7.1.2.11. Results for the primary efficacy outcome

Mean adherence rate to LDV/SOF (tablet counts), was 97.4%.

Efficacy results

Overall SVR12 rate was 95.8% (95% CI: 93.1% to 97.7%). Of the 14 who did not achieve SVR12, 10 relapsed, 2 had on-treatment virologic failure (both non-compliance), 1 died (sepsis), and 1 was LTFUP.

SVR4 = SVR12 results with the exception of 3 subjects: 2 achieved SVR4 but did not achieve SVR12 (relapsed), and 1 achieved SVR4 but was then LTFUP.

High SVR12 rates observed in most subgroups, including treatment experienced (96.8%, 179 of 185), treatment experienced with cirrhosis (97.9%). High and similar SVR12 rates observed irrespective of ARV regimen. However, Black subjects (103 of 115, 89.6%, 95% CI: 82.5% to 94.5%) and those with IL28B TT allele (61 of 69, 88.4%, 95% CI: 78.4% to 94.9%) had lower SVR12. In multivariate analysis (Table 10) only Black race was associated with increased relapse.

Table 10: GS-US-337-0115 (ION-4): Multivariate logistic regression to assess association of race, IL28B, and ARV regimen with virologic relapse (FAS)

Variable	Odds Ratio	95% Confidence Limit	2-Sided P-Value
Race: black vs non-black	17.734	(2.657, Infinity)	**0.0012**
IL28B: TT vs non-TT	4.269	(0.888, 27.494)	0.0751
Baseline ARV regimen: EFV vs non-EFV	3.259	(0.587, 33.633)	0.2411

The 3 subjects with "Not Permitted" race were excluded.
The 2 subjects with on-treatment failure were excluded.

7.1.2.11.1. Results for other efficacy outcomes

In ION-4, there were 13 treatment experienced subjects enrolled who had failed a SOF+RBV regimen. All 13 of these subjects achieved SVR12. Of the only 8 subjects with GT 4 all achieved an SVR12. HCV RNA levels (log_{10} IU/mL) declined rapidly irrespective of ARV regimen. After 1 week of treatment, mean (SD) log_{10} IU/mL change from baseline was −4.68 log_{10} IU/mL.

Virologic resistance results

A total of 83 of 325 subjects (25.5%) with GT 1 HCV infection and with available sequencing data had NS5A RAPs at Pre-treatment. Seventy-eight of the 83 subjects with Pre-treatment NS5A RAPs achieved SVR12 (94.0%), and 235 of 242 (97.1%) subjects without Pre-treatment NS5A RAPs achieved SVR12. All subjects with GT 4 HCV infection had NS5A RAPs and achieved SVR12. Two subjects who experienced on-treatment virologic failure developed NS5A resistance associated variants (RAVs) at the time of virologic failure. Seven of the 10 (70%) who experienced virologic relapse had Pre-treatment NS5A RAPs, 4 of the 10 had Pre-treatment NS5A RAVs, and 8 of the 10 who relapsed had Post treatment NS5A RAVs. No NS5A RAVs were detected at Pre-treatment and Post treatment in 2 of the 10 subjects who relapsed. The 3 (0.9%) with the SOF treatment emergent variant (TEV) L159F at Pre-treatment achieved SVR12. The SOF RAV S282T and SOF TEVs L320F and V321A were not detected by deep sequencing in any subjects Pre-treatment. Only 1 had L159F (9.86%) at the time of relapse, observed together with the NS5B RAV Y93N (> 99%).

PK

Population PK model derived exposure parameters (AUC_{tau}, C_{max}, and C_{tau}) generated as applicable for all subjects with measureable plasma concentrations of SOF, GS-331007, LDV, and TFV. Steady state PK parameters were also calculated for GS-566500, EFV, RAL, RPV, and FTC in subjects with evaluable plasma profiles who participated in the intensive PK sub-study. Exposures of SOF, its metabolites (GS-331007 and GS-566500), LDV, FTC, TFV was generally comparable across the 3 ARV regimens. TFV exposure was moderately higher than those observed historically in HIV mono infection studies with NNRTI or INSTI regimens that contain Truvada. These results are in agreement with the findings from Phase I evaluations, which revealed higher TFV exposure with LDV/SOF. EFV, RAL, and RPV PK were consistent with historical data. LDV/SOF PK was similar in subjects who achieved SVR12 and those with virologic relapse; no difference in SOF, GS-331007, or LDV PK by race (Black versus non-Black). No clinically relevant differences in SOF, GS-331007, LDV exposure parameters in HCV/HIV versus HCV mono-infection in the Phase II/III population.

Safety results

Overall, LDV/SOF generally safe and well tolerated. See safety section.

7.1.3. Study GS-US-337-0121 (SIRIUS)

A Phase II, multi-centre, randomized, double blind, placebo controlled study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination for 12 weeks with ribavirin

or for 24 weeks without ribavirin in treatment experienced cirrhotic subjects with chronic Genotype 1 HCV infection.

7.1.3.1. Study design, objectives, locations and dates

Sites: 20 sites in France.

First subject screened: 26 September 2013; 12 November 2014 (Last subject observation for this interim).

Protocol amendments: original protocol 14 June 2013; Amendment 1 Date: 10 Jan 2014: key changes; addition of exploratory objective of transient elastography and addition of an additional transient elastography in order to assess cirrhosis status 24 weeks post treatment

Publications/presentations arising:

1. Bourlière M, et al. An Integrated Safety and Efficacy Analysis of > 500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir with or without Ribavirin. Hepatology (2014), 60: 4 (suppl) 239A.
2. Bourlière M, et al. Ledipasvir/ Sofosbuvir Fixed Dose Combination is Safe and Efficacious in Cirrhotic Patients Who Have Previously Failed Protease-Inhibitor Based Triple Therapy. Hepatology (2014), 60: 6(suppl) 1270A.

Design: Phase II, randomised, double blind, placebo controlled, multicentre study assessed the antiviral efficacy and safety of LDV/SOF for 12 weeks with RBV or 24 weeks without RBV in treatment experienced cirrhotic subjects with chronic GT 1 HCV. All subjects eligible to participate in a pharmacogenomics sub-study. Subjects not achieving SVR were eligible for enrolment in the Sequence Registry Study (GS-US-248-0123). Subjects who achieved SVR24 eligible for enrolment in the SVR Registry Study (GS-US-248-0122) to evaluate durability of SVR for up to 3 years after treatment.

7.1.3.2. Inclusion and exclusion criteria

Key inclusion criteria

1. Willing and able to provide written informed consent
2. Male or female, age ≥ 18 years;
3. confirmation of chronic HCV infection(at least 6 months) GT-1
4. HCV RNA ≥ 10^4 IU/mL
5. BMI ≥ 18 kg/m^2
6. HCV treatment experienced that is Prior virologic failure after treatment with Peg-IFN, RBV, and a PI following documented prior virologic failure after treatment with a Peg-IFN+RBV regimen. The subject's medical records must have included sufficient detail of prior virologic failure to allow for categorization of prior response during both prior treatment periods as one of the following:
    a. Non-responder: Subject did not achieve undetectable HCV RNA levels while on treatment.
    b. Breakthrough: Subject achieved undetectable HCV RNA levels during treatment but subsequently had detectable HCV RNA while continuing treatment.
    c. Relapse: Subject achieved undetectable HCV RNA levels during treatment, maintained undetectable HCV RNA for the duration of treatment, or achieved undetectable HCV RNA within 4 weeks of the end of treatment but did not achieve SVR.
    d. Stopped due to AE

7. Cirrhosis - protocol defined as:
    i. Liver biopsy showing cirrhosis
    ii. Fibroscan showing cirrhosis or results > 12.5 kPa
    iii. FibroTest score of > 0.75 AND anAPRI of > 2 during Screening
8. Liver imaging within 6 months of Baseline/Day 1 to exclude HCC
9. Normal ECG
10. laboratory parameters at screening:
    a. ALT ≤ 10 x ULN
    b. AST ≤ 10 x ULN
    c. Direct bilirubin ≤ 1.5 x ULN
    d. Platelets ≥ 50,000
    e. HbA1c ≤ 10.0%
    f. Creatinine clearance (CLcr) ≥ 50 mL /min, as calculated by the Cockcroft-Gault Equation
    g. Hb ≥ 11 g/dL
    h. Albumin ≥ 3g/dL
    i. INR ≤ 1.5 x ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR
11. No investigational agents within 30 days of screening
12. Avoidance of pregnancy including partner for durations in men and women as per SPC for RBV.

Key exclusion criteria

Current medical problems including:

1. Clinical hepatic decompensation; solid organ transplantation; significant pulmonary disease, significant cardiac disease or porphyria; serious psychiatric illness within the last 2 years; malignancy within 5 years
2. Pregnant/nursing female or male with pregnant female partner
3. HBV or HIV
4. Prior HCV specific DAAs, other than a nonstructural protein 3/4a PI.

7.1.3.3. Study treatments

Group 1: LDV/SOF + placebo RBV 24 weeks (= LDV/SOF 24 week group): LDV/SOF FDC OD + matched RBV placebo tablet (divided BD) for 24 weeks.

Group 2: placebo 12 weeks followed by LDV/SOF+RBV 12 weeks (= LDV/SOF+RBV 12 week group): Matched LDV/SOF placebo tablet OD + matched RBV placebo (divided BD) for 12 weeks followed by LDV/SOF FDC OD + RBV (weight-based dosing 1000 or 1200 mg/day divided BD) for 12 weeks.

7.1.3.4. Efficacy variables and outcomes

Treatment procedures/assessments: Weeks 1, 2, 4, 8, 12, 13, 14, 16, 20, and 24; post treatment Weeks 4 and 12. Subjects with HCV RNA < LLOQ at the 12 Week post treatment visit completed 24 Week post treatment visit, unless viral relapse is determined.

Criteria for evaluation

Safety: AEs and safety laboratory parameters, vital signs, ECGs, physical examinations collected throughout the study.

- Efficacy: scheduled assessments of HCV RNA performed using COBAS TaqMan HCV Test, v2.0 for use with the High Pure System (LLOQ < 25 IU/mL)
- Genetics: IL28B genotype as described before
- QoL surveys: SF-36, CLDQ-HCV, the FACIT-F questionnaire, and WPAI: Hep C questionnaire completed at Day 1 (baseline), Weeks 4, 12, 16, and 24, early termination (if applicable), and post treatment Weeks 4, 12, and 24 (if applicable)
- Primary objective: SVR12; safety and tolerability of each treatment regimen
- Other outcomes:
  - SVR4 and 24; quantitative HCV-RNA kinetics
  - evaluate safety and tolerability during the first 12 weeks of treatment of the 24 week LDV/SOF treatment group with the 12 week placebo control treatment period
  - To compare, in the deferred start group, the safety profile during the first 12 weeks of the study (placebo period) with the second 12 weeks (LDV/SOF+RBV period) of the study
  - ALT normalisation
  - QoL; virologic failure and resistant variants; identify/validate genetic markers predictive of natural history of disease, response and/or tolerability of DAA
  - evaluate effect of treatment on liver cirrhosis markers for example LOXL-2, Fibrotest/APRI, transient elastography.

7.1.3.5. Randomisation and blinding methods

1:1 randomisation stratified by GT (1a or 1b; mixed or other GT 1) and prior response to HCV treatment therapy (never achieved HCV RNA < LLOQ or achieved HCV RNA < LLOQ). Study treatment assignment and on treatment HCV RNA results were double blinded.

7.1.3.6. Analysis populations

The FAS, SAS and PK analysis sets are as defined previously.

7.1.3.7. Sample size

N = 155.

7.1.3.8. Statistical methods

A sample size of 75 subjects in each treatment group provided 80% power to detect a difference of 15% in SVR12 rates (80% versus 95%) between the 2 treatment groups. SVR12 in each of the 2 treatment groups estimated with 2-sided 95% exact CI using the binomial distribution (Clopper-Pearson method). Secondary endpoints: SVR4, SVR24, proportion with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through Week 12, proportion with virologic failure.

Safety: as above; AE coded using MedDRA, Version 17.1.

Quality of Life: Wilcoxon signed rank test explored within-treatment group changes from baseline to each of the time points, and from EOT to each Post treatment time point. A Wilcoxon rank sum test explored group differences between LDV/SOF for 24 weeks and placebo by time-point. A Wilcoxon signed rank test explored group differences between placebo and LDV/SOF+RBV for 12 weeks by time point.

7.1.3.9. Participant flow

Analysed: All randomised subjects: 155 subjects; FAS: 154 subjects; SAS: 155 subjects.

Table 11: GS-US-337-0121 (SIRIUS): Subject disposition (screened subjects)

Subject Disposition	LDV/SOF + Placebo RBV 24 Weeks	Placebo 12 Weeks Followed by LDV/SOF+RBV 12 Weeks	Total
Subjects Screened			172
Subjects Not Randomized			17
Subjects Randomized	77	78	155
Subjects in Safety Analysis Set	78	77	155
Subjects in Full Analysis Set	77	77	154
Study Treatment Status			
Completed Study Treatment	78 (100.0%)	76 (98.7%)	154 (99.4%)
Discontinued Study Treatment	0	1 (1.3%)	1 (0.6%)
Reason for Premature Discontinuation of Study Treatment			
Adverse Event	0	1 (1.3%)	1 (0.6%)

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
Safety Analysis Set includes subjects who were randomized and received at least 1 dose of study drug.
Full Analysis Set includes subjects with genotype 1 HCV infection who were randomized and received at least 1 dose of active study drug.

7.1.3.10. Major protocol violations/deviations

Twenty five important protocol deviations occurred in 22. Majority (13 of 25) were for violation of inclusion/exclusion criteria. Of these 13, 6 deviations were for liver imaging to exclude HCC. Overall quality/interpretation of study data was not affected by these deviations.

7.1.3.11. Baseline data

Majority male (73.5%), White (97.4%), and not Hispanic or Latino (97.4%), mean age of 56 years (range: 23 to 77 years). Mean BMI 27.1 kg/m^2 (19.1 to 47.1 kg/m^2), 20.6% of subjects had a BMI ≥ 30 kg/m^2.

All subjects in the SAS had GT 1a (63.2%), GT 1b (35.5%), or GT 1 no confirmed subtype (1.3%). All subjects met the protocol defined definition of cirrhosis, with the exception of 1. 93.5% had non-CC (CT or TT) IL28B alleles. Overall mean baseline HCV RNA 6.5 $\log_{10}$ IU/mL (3.9 to 7.7 $\log_{10}$ IU/mL), 85.8% had baseline HCV RNA ≥ 800,000 IU/mL.

Overall mean (SD) ALT was 103 (60.4) U/L, 77.4% had ALT > 1.5 x ULN. Overall mean baseline eGFR was 115.3 mL/min (range: 50.7 to 335.9 mL/min); 56.8% had achieved HCV RNA < LLOQ during prior HCV treatment.

Treatment adherence: Majority had a ≥ 90% adherence rate.

7.1.3.12. Results for the primary efficacy outcome

Efficacy results

- 149 of 154 achieved SVR12; 97.4% of the LDV/SOF 24 week group and 96.1% of the LDV/SOF+RBV 12 week group achieved SVR12. The difference in SVR12 between the two treatment groups was not statistically significant (p = 0.63). All 5 subjects who did not achieve SVR12 relapsed.

- All subjects in the FAS completed study treatment and no subject in either treatment group had on-treatment virologic failure (that is, breakthrough, rebound, or nonresponse).
- SVR4 = SVR12 with exception of 1 who achieved SVR4, but relapsed at post treatment Week 12.
- All subjects who achieved SVR12 also achieved SVR24.

Table 12: GS-US-337-0121 (SIRIUS): SVR12

	LDV/SOF + Placebo RBV 24 Weeks (N = 77)	Placebo 12 Weeks Followed by LDV/SOF+RBV 12 Weeks (N = 77)
SVR12	75/77 (97.4%)	74/77 (96.1%)
95% CI	90.9% to 99.7%	89.0% to 99.2%
LDV/SOF 24 Weeks vs. LDV/SOF+RBV 12 Weeks		
p-value	0.63	
Prop Diff (95% CI)	1.4% (−5.9% to 8.6%)	

HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.
SVR12 was sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR12 value was imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

Table 13: GS-US-337-0121 (SIRIUS): SVR4 and SVR24 (FAS)

	LDV/SOF + Placebo RBV 24 Weeks (N = 77)	Placebo 12 Weeks Followed by LDV/SOF+RBV 12 Weeks (N = 77)
Number of Subjects Who Were < LLOQ at Their Last Observed On-Treatment HCV RNA Value	77	77
SVR4	75/77 (97.4%)	75/77 (97.4%)
95% CI	90.9% to 99.7%	90.9% to 99.7%
SVR12	75/77 (97.4%)	74/77 (96.1%)
95% CI	90.9% to 99.7%	89.0% to 99.2%
SVR24	75/77 (97.4%)	74/77 (96.1%)
95% CI	90.9% to 99.7%	89.0% to 99.2%

HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.
SVRx was sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.
A missing SVR value was imputed as a success if it was bracketed by values that were termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR value was imputed as a failure. A missing SVR24 was imputed as a success if SVR12 was a success; otherwise, the missing SVR24 value was imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

7.1.3.13. Results for other efficacy outcomes

Viral kinetics

Potent and rapid suppression of HCV RNA observed in both treatment groups irrespective of RBV in the treatment regimen.

ALT normalisation

Coincident with suppression of viral replication, decreases from baseline in median ALT values observed in the LDV/SOF±RBV treatment groups for the duration of treatment and at the post treatment Week 4 visit. No decrease seen with placebo.

Resistance

19.5% had Pre-treatment NS5A RAPs; 8.2% with GT 1a had Pre-treatment NS5A RAPS, 36.4% with GT 1b had Pre-treatment NS5A RAPs, and 2 of 2 with GT 1e had Pre-treatment NS5A RAPs. Among the 30 with NS5A RAPs, all 15 (100.0%) in the LDV/SOF+RBV 12 week group achieved SVR12 while 13 of 15 subjects (86.7%) in the LDV/SOF 24 week group achieved SVR12. Six subjects (4%) had Pre-treatment NS5B RAPs; 5 of 6 achieved SVR12 including 4 of 5 subjects with GT 1b HCV infection with L159F and 1 subject with GT 1b HCV infection with V321I.

34.4% had baseline NS3 RAV. All 52 achieved SVR12. The 5 not achieving SVR12 experienced virologic relapse. Both relapse subjects treated with LDV/SOF for 24 weeks had Pre-treatment NS5A RAPs that were maintained or enriched Post treatment. No Pre-treatment RAPs were observed in the 3 relapse subjects treated with LDV/SOF+RBV; however, all 3 had ≥ 1 NS5A RAVs or RAPs emerge post treatment. Relapse was associated with single class NS5A resistance. No SOF RAV S282T or TEVs emerged in any subjects who relapsed in this study.

Table 14: GS-US-337-0121 (SIRIUS): SVR12 in subjects with pre-treatment NS3 RAVs

	LDV/SOF + Placebo RBV 24 Weeks (N = 77)	Placebo 12 Weeks Followed by LDV/SOF+RBV 12 Weeks (N = 77)
Subjects with Pretreatment NS3 Sequence Data	74	77
Subjects (%) with Pretreatment NS3 RAVs	25/74 (33.8%)	27/77 (35.1%)
SVR12 in Subjects with NS3 RAVs	25/25 (100.0%)	27/27 (100.0%)
SVR12 in Subjects without NS3 RAVs	47/49 (95.9%)	47/50 (94.0%)

Safety

See safety Section below. In summary, comparing these 2 regimens, higher frequency of AEs and TRAEs observed with LDV/SOF+RBV for 12 weeks versus LDV/SOF for 24 weeks; attributable to a higher incidence in RBV associated AEs. Other than the 2 SAEs (bacterial arthritis and hepatic cirrhosis) no SAEs led to treatment discontinuation. No deaths or pregnancies reported in the study.

Quality of life

Mean scores for all scales improved from EOT to Post treatment Week 24 both groups.

7.1.4. Study GS-US-337-0122 (ELECTRON 2)

A Phase II, multi-centre, open label study to assess the efficacy and safety of sofosbuvir containing regimens for the treatment of chronic HCV infection.

7.1.4.1. Study design, objectives, locations and dates

Sites: 2 sites in New Zealand

First subject screened: 03 April 2013 (First Subject Screened) Study End Date 16 December 2014 (Last subject observation for this interim).

Protocol amendments: original protocol 04 February 2013; Amendment 5 Date: 15 May 2014. Main changes in:

Amendment 2 increased enrolment numbers up to 375 from the original 200 and capturing the addition of Cohort 2, groups 5 and 6 and Cohort 4

Amendment 3, Allowed inclusion of cirrhotics in Cohort 2, Groups 5 and 6, to allow these patients at high medical need to be included. A 40% cap for cirrhotics included

Amendment 4 key changes; Addition of Part C to the protocol, including: Cohort 5: This cohort will offer additional IFN free options to previous participants in Study P7977-0523 or GS-US-337-0122 (except Cohort 4) and who did not achieve SVR. Up to 25 subjects to be enrolled to receive SOF/LDV+ weight based RBV for 24 weeks. Cohort 6: utility of treatment of HBV/HCV co-infected subjects. Up to 10 subjects co-infected with HBV and GT 1 HCV to receive SOF/LDV FDC tablet OD for 12 weeks. Plus increased enrolment up to 410 subjects.

Publications/presentations arising:

1. Gane EJ, et al. Once Daily Sofosbuvir/Ledipasvir Fixed dose Combination with or without Ribavirin: the ELECTRON Trial. Hepatology, 58: 4 (suppl) 243A. October 2013 (AASLD 2013).
2. Gane EJ, et al. High Efficacy of LDV/SOF Regimens for 12 Weeks for Patients with HCV GT 3 or 6 Infection. Hepatology, 60: 6 (suppl) 1274A-1275A. December 2014 (AASLD 2014).
3. Gane EJ, et al. Once Daily Sofosbuvir with GS-5816 for 8 weeks with or without Ribavirin in Patients with HCV Genotype 3 without Cirrhosis Result in High Rates of SVR12: The ELECTRON2 Study. Hepatology, 60: 4 (suppl) 236A. October 2014 (AASLD 2014).
4. Bourlière M, et al. An Integrated Safety and Efficacy Analysis of > 500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir with or without Ribavirin. Hepatology, 60: 4 (suppl) 239A. October 2014 (AASLD 2014).
5. Gane EJ, et al. Sofosbuvir/Ledipasvir Fixed Dose Combination is Safe and Effective in Difficult-To-Treat Populations Including Genotype-3 Patients, Decompensated Genotype-1 Patients, and Genotype-1 Patients with Prior Sofosbuvir Treatment Experience. Hepatology, 60: 4 (suppl) S3-S4. April 2014 (EASL 2014).

Design: Ongoing Phase II multicentre, open label study evaluated the safety, tolerability and antiviral efficacy of SOF containing treatment regimens administered for up to 24 weeks in subjects with chronic HCV infection. This study was conducted in 3 parts: Part A (Cohorts 1, 2, and 3), Part B (Cohort 4), and Part C (Cohorts 5 and 6). All subjects who achieve SVR24 eligible for enrolment in the SVR Registry Study (GS-US-248-0122).

7.1.4.2. Inclusion and exclusion criteria

Key inclusion criteria

1. Willing and able to provide written informed consent
2. Male or female, age ≥ 18 years
3. confirmation of chronic HCV infection(at least 6 months)
4. HCV RNA ≥ 10^4 IU/mL
5. BMI ≥ 18 kg/m^2
6. Cirrhosis determination (where cohort/group allowed inclusion of cirrhosis) defined as
    i. Liver biopsy showing cirrhosis
    ii. Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa
    iii. iii) FibroTest score of > 0.75 and APRI of > 2

7. Liver imaging within 6 months of Baseline/Day 1 to exclude HCC) in cirrhotics
8. Normal ECG
9. No investigational agents within 28 days of screening
10. Avoidance of pregnancy including partner for durations in men and women as per SPC for RBV.

Key exclusion criteria

Current medical problems including:

1. Clinically significant illness including - solid organ transplantation, significant pulmonary disease, significant cardiac disease; psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years; malignancy diagnosed/treated within 5 years
2. Pregnant or nursing female or male with pregnant female partner
3. Chronic liver disease of a non-HCV aetiology
4. HBV or HIV; (note: Cohort 6 did allow enrolment of HBV co-infected patients as a pilot study)
5. Contraindications for any of the study drugs
6. Laboratory parameters outside protocol defined limits
7. Clinically relevant drug abuse within 12 months of screening
8. Alcohol misuse/abuse within 12 months that would interfere with participation
9. Chronic use of systemically administered immunosuppressive agents.

Additional inclusion criteria for Cohort 1, Group 1

1. HCV GT 1
2. Subjects must have been treated in study P7977-0523 and did not achieve SVR
3. Laboratory parameters at screening:
    a. ALT ≤ 10 x the upper limit of normal (ULN)
    b. AST ≤ 10 x ULN
    c. Direct bilirubin ≤ 1.5 x ULN
    d. HbA1c ≤ 8.5%
    e. Creatinine clearance (CLcr) ≥ 60 mL /min, as calculated by the Cockcroft-Gault equation
    f. Albumin ≥ 3g/dL
    g. INR ≤ 1.5 x ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR
    h. Platelets ≥ 50,000
    i. Haemoglobin ≥ 11 g/dL for female subjects; ≥ 12 g/dL for male subjects

Additional Exclusion Criteria for Cohort 1, Group 1

1. Clinical hepatic decompensation
2. Contraindications to RBV
3. Received another therapy for HCV after completion of treatment P7977-0523

4. Prior HCV treatment with FDC tablet OD for 12 weeks.

Additional Inclusion Criteria for Cohort 1, Group 2

1. HCV GT 2 or 3
2. treated in study P7977-0523 and did not achieve SVR
3. Laboratory parameters at screening as above except Platelets ≥ 90,000/μL (≥ 75,000/μL in subjects with cirrhosis) and White blood cell count ≥ 2,500/μL, ANC ≥ 1,500/μL (or ≥ 1,000/μL if considered a physiologic variant in those of African descent); TSH ≤ ULN.

Additional Exclusion Criteria for Cohort 1, Group 2

1. Clinical hepatic decompensation
2. Contraindications for PEG or RBV therapy
3. Received another therapy for HCV infection after completion of treatment on study P7977-0523

Additional Inclusion Criteria for Cohort 2, Groups 1 and 2

1. HCV GT 1
2. Cirrhosis as determined by Inclusion Criteria (see above) At least 50% will be cirrhotic
3. Subjects must have documentation of their prior treatment experience and fulfil the following: a. least one previous course of treatment for HCV infection which included PEG and was not stopped due to an AE. Sufficient information to classify the subjects as a previous non-responder or responder must be available.
4. Laboratory parameters as for Cohort 1, Group 1.

Additional Exclusion Criteria for Cohort 2, Group 1

1. Clinical hepatic decompensation
2. Contraindication to RBV therapy

Additional Exclusion Criteria for Cohort 2, Group 2

1. Clinical hepatic decompensation

Additional Inclusion Criteria for Cohort 2, Groups 3 and 4

1. HCV GT 3
2. Laboratory parameters as for Cohort 1, Group 1.

Additional Exclusion Criteria for Cohort 2, Group 3

1. Clinical hepatic decompensation
2. Prior treatment for HCV with an interferon or RBV

Additional Exclusion Criteria for Cohort 2, Group 4

1. Clinical hepatic decompensation (that is, ascites, encephalopathy or variceal haemorrhage)
2. Contraindication to RBV therapy
3. Prior treatment for HCV with an IFN or RBV.

Additional Inclusion Criteria for Cohort 3

1. HCV GT 1
2. Subjects must have cirrhosis with moderate hepatic decompensation (Child-Pugh B; score 7 to 9) at Screening

3. Laboratory parameters at screening as for Cohort 1, Group 1 except threshold for platelets and Hb lower that is Platelets ≥ 30,000; Haemoglobin ≥ 10 g/dL for males and ≥ 9 g/dL for females.

Additional Exclusion Criteria for Cohort 3, Group 1

1. Prior treatment for HCV with SOF-containing regimen
2. Any current signs or symptoms of severe hepatic encephalopathy, that may affect ability of the subject to provide initial and continuing consent to participate
3. History of gastric or oesophageal variceal bleeding not adequately medically or surgically treated or any history of variceal bleeding in the last 6 months
4. Prior placement of a portosystemic shunt (such as TIPS), unless vascular imaging studies indicate that shunt has clotted and has no current blood flow
5. History of hepatorenal, or hepatopulmonary syndrome
6. Current signs or symptoms consistent with spontaneous bacterial peritonitis, known active spontaneous bacterial peritonitis, or a history of spontaneous bacterial peritonitis within the last 6 months
7. Recent hospitalisation (within last 2 months) related to cirrhosis or its complications
8. Confirmed hypotension at screening
9. Refractory ascites
10. Expected survival of < 1 yr
11. Requiring dose adjustment or change of beta blockers within 3 months.

7.1.4.3. Study treatments

Cohort 1

Cohort 1 consisted of 2 treatment groups to evaluate safety and efficacy of LDV/SOF +RBV or SOF + PEG + RBV treatment in subjects with GT 1, 2, or 3 HCV infection who had been previously treated in Study P7977-0523 (ELECTRON) and did not achieve SVR.

For Cohort 1, up to 50 and 30 subjects were planned to be enrolled into Groups 1 and 2, respectively, to receive:

· Cohort 1, Group 1 LDV/SOF+RBV 12 weeks in GT-1 HCV previously treated in Study P7977-0523 and did not achieve SVR;

· Cohort 1, Group 2 SOF+PEG+RBV 12 weeks in subjects with GT 2 or 3 HCV previously treated in Study P7977-0523 and did not achieve SVR;

Cohort 2

Cohort 2 consisted of 6 treatment groups to evaluate the safety and efficacy of LDV/SOF with GS-9669 or RBV in treatment experienced subjects with GT 1 HCV infection;

· LDV/SOF ±RBV in treatment naive subjects with GT3 HCV infection

· LDV/SOF in treatment naive or treatment experienced subjects with GT 6 HCV infection

· LDV/SOF+RBV in treatment experienced subjects with GT 3 HCV infection.

Within this cohort, up to 40% of enrolled subjects in each group may have compensated cirrhosis. For Cohort 2, Groups 1 and 2, approximately 50 subjects with GT 1 HCV infection and advanced liver fibrosis/compensated cirrhosis to be enrolled and randomised (1:1) into one of the following 2 treatments:

- Cohort 2, Group 1: LDV/SOF+RBV 12 weeks in treatment experienced GT-1 and advanced liver fibrosis or compensated cirrhosis
- Cohort 2, Group 2: LDV/SOF+GS-9669 12 weeks in treatment experienced GT-1 and advanced liver fibrosis or compensated cirrhosis.

For Cohort 2 Groups 3 and 4, approximately 50 treatment naive subjects with GT 3 HCV infection planned to be enrolled and randomised (1:1) into one of the following 2 treatments:

- Cohort 2, Group 3: LDV/SOF 12 weeks in treatment naive subjects with GT 3 HCV
- Cohort 2, Group 4: LDV/SOF+RBV 12 weeks in treatment naive subjects with GT 3 HCV

For Cohort 2, Groups 5 and 6, approximately 25 treatment naive or treatment experienced subjects with GT 6 HCV infection and 50 treatment experienced subjects with GT 3 HCV infection were planned to be enrolled in Cohort 2, Group 5 and Cohort 2, Group 6, respectively, and assigned to receive the following:

- Cohort 2, Group 5 LDV/SOF 12 weeks in subjects with GT 6 HCV
- Cohort 2, Group 6 LDV/SOF+RBV 12 weeks in treatment experienced subjects with GT 3 HCV.

Cohort 3

Cohort 3 comprised 1 treatment group to evaluate safety and efficacy of LDV/SOF in GT 1 HCV and CPT B cirrhosis. Approximately 20 subjects planned to receive:

Cohort 3, Group 1 LDV/SOF 12 weeks in GT 1 HCV and CPT B cirrhosis.

Cohort 4

Cohort 4 comprised 4 treatment groups to evaluate the safety and efficacy of SOF and one of 2 doses of GS-5816 (25 and 100 mg) ±RBV. This Cohort is not applicable to this Harvoni application.

Cohort 5

Cohort 5 comprised 1 treatment group to evaluate safety and efficacy of LDV/SOF+RBV. Approximately 25 with prior exposure to a SOF-containing regimen in either Study P7977-0523 or GS-US-337-0122 who did not achieve SVR were planned to receive:

- Cohort 5, Group 1 LDV/SOF+RBV 24 weeks in subjects with prior exposure to a SOF-containing regimen in Study P7977-0523 or GS-US-337-0122 who did not achieve SVR.

Cohort 6

Cohort 6 comprised 1 treatment group to evaluate safety and efficacy of LDV/SOF in HCV/HBV-co-infected subjects. Approximately 10 subjects with GT 1 HCV and HBV co-infection were planned for:

- Cohort 6, Group 1 LDV/SOF 12 weeks in GT 1 HCV and HBV co-infection.

For this second interim CSR, the efficacy and safety analyses were conducted when all subjects in Cohorts 1 (Groups 1 and 2), 2 (Groups 1-4), 3 (Group 1), and 4 (Groups 1-4) completed the Post treatment Week 24 visit, all subjects in Cohorts 2 (Groups 5 and 6) and 6 (Group 1) had completed the Post treatment Week 12 visit, and all subjects in Cohort 5 (Group 1) had completed the EOT visit or when a subject had prematurely discontinued from the study.

7.1.4.4. Randomisation and blinding methods

Open label study.

The FAS, SAS and PK analysis sets are as defined previously.

7.1.4.5. Efficacy variables and outcomes

Primary objectives were to: SVR12; safety and tolerability.

Secondary objectives: SVR4 and SVR24; viral resistance to SOF, LDV, GS-5816, and GS-9669; viral dynamics; steady state PK of study drugs; pharmacogenomics.

Efficacy

HCV RNA at screening and Day 1(predose) (all cohorts) and Weeks 1, 2, 4, 6, 8, 10, and 12 (Cohorts 1-3), Weeks 1, 2, 4, 6, and 8 (Cohort 4), Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 (Cohort 5), and Weeks 1, 2, 4, 6, 8, 10, and 12 (Cohort 6) during treatment (or upon early termination), and Post treatment Weeks 2, 4, 8, 12, and 24 (all cohorts) and Weeks 16 and 20 (Cohort 6). COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0. LLOQ was 15 IU/mL.

PK

A single PK blood sample collected at each on-treatment visit for all subjects. Optional PK sub-study performed anytime on or between the Week 2 or Week 4 on treatment visit in a subset of subjects. Only subjects in Cohorts 2, 3, 4, and 6 were eligible to participate. Serial PK samples were collected over 24 hours post dose. The PK of SOF (and its metabolites GS-566500 and GS-331007), LDV, GS-9669 (if applicable), GS-5816 (if applicable), and RBV (if appropriate) was assessed.

Safety

AEs and safety laboratory parameters, vital signs, ECGs, physical examinations collected throughout the study.

7.1.4.6. Sample size

N = 410.

7.1.4.7. Statistical methods

This study was not designed to evaluate formal statistical hypotheses. Primary efficacy endpoint was SVR12 in the FAS. The 2 sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rates in each efficacy analysis group. Secondary efficacy endpoints included SVR4, SVR24, proportion with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through Week 8; virologic failure, and HCV drug resistance.

PK: PK parameters derived using non compartmental methods using WinNonlin, Version 6.3 or equivalent. Standard PK parameters were calculated.

Safety: AE coded using MEDRA Version 17.1.

7.1.4.8. Participant flow

Planned: 410 subjects overall.

Analysed: SAS: 358 subjects; FAS: 358 subjects.

7.1.4.9. Baseline data

Subject Disposition and Demographics

Cohort 1

Cohort 1 (n = 29): 19 GT 1 received LDV/SOF+RBV for 12 weeks in Gp 1; 10 GT 3 received SOF+PEG+RBV for 12 weeks in Group 2. All subjects completed study treatment.

Baseline: majority male (68.4% to 80.0%), White (90.0% to 94.7%), 100% non-Hispanic/Latino; mean age 49 to 55 years (range 28 to 65 years); mean (SD) baseline BMI 25.7 (3.97) to 26.8 (4.59) kg/m^2, 26.3% -30.0% BMI ≥ 30 kg/m^2. Of treatment experienced with GT 1 who received LDV/SOF+RBV for 12 weeks, 84.2% GT 1a.

Of treatment experienced with GT 3 HCV who received SOF+PEG+RBV for 12 weeks, 100.0% GT3. Most did not have cirrhosis (90.0% to 94.7%); 21.1% to 30.0% IL28B CC; mean (SD) HCV RNA 6.3 (0.51) to 6.5 (0.63) $\log_{10}$ IU/mL. 84.2% to 90.0%) had HCV RNA ≥ 800,000 IU/mL; 58% of GT 1 had ALT ≤ 1.5 x ULN, 70% of GT 3s had baseline ALT > 1.5 x ULN.

Cohort 2, Groups 1 and 2

Cohort 1 (n = 51 Treatment experienced GT 1 with advanced liver fibrosis/compensated cirrhosis): 25 received LDV/SOF+RBV for 12 weeks; 26 received LDV/SOF+GS-9669 for 12 weeks.

All subjects completed study treatment.

Baseline: majority male (57.7% to 60.0%) and White (88.0% to 92.3%); mean age 55-56 years - range of 43 to 71 years; mean (SD) baseline BMI was 27.1 (4.17) to 28.5 (5.48) kg/m^2, 26.9% to 32.0% of subjects had a BMI ≥ 30 kg/m^2. 60-84.6% had the GT 1a; 65.4% to 72.0% had cirrhosis; 15.4% to 24.0% had IL28B CC alleles; mean (SD) baseline HCV RNA 6.1 (0.69) to 6.5 (0.39) $\log_{10}$ IU/mL. Most had HCV RNA ≥ 800,000 IU/mL (65.4% to 92.0%). 56% of those treated with LDV/SOF+RBV had bALT ≤ 1.5 x ULN; in those receiving LDV/SOF+GS-9669 53.8% had ALT > 1.5 x ULN.

Cohort 2, Groups 3 to 6

Cohort 2, Groups 3 to 6 (n = 127): 25 treatment naive GT 3 who received LDV/SOF for 12 weeks; 26 treatment naive GT 3 who received LDV/SOF+RBV for 12 weeks; 25 treatment naive or treatment experienced GT 6 who received LDV/SOF for 12 weeks; 51 treatment experienced GT 3 who received LDV/SOF+RBV for 12 weeks. 92.0% to 100.0% completed all study drug.

Baseline: majority male (52.0% to 78.0%) except for the treatment naive GT 3 who received LDV/SOF+RBV for 12 weeks who were mostly female (57.7%). GT3 subjects were mainly White (80.0% to 88.5%) while those with GT 6 HCV infection were mainly Asian (88.0%). 100% non-Hispanic/Latino; mean age 43to 52 years with a range of 22 to 76 years; mean (SD) baseline BMI was 23.6 (3.24) to 28.0 (6.08) kg/m^2, and 8.0% to 30.8% of subjects had a BMI ≥ 30 kg/m^2. Of the GT3s, 92-96.2% were GT 3a; of the GT 6, 68% subtype c. 56.0 to 92.0% did not have cirrhosis; of the GT3s, 36.0% to 57.7% had IL28B CC alleles in the GT6s, 80% were CC. Mean (SD) baseline HCV RNA was 6.3 (0.88) to 6.7 (0.69) $\log_{10}$ IU/mL. Most had HCV RNA ≥ 800,000 IU/mL (64.0% to 92.0%). 68.0% and 52% of the treatment naive GT3 receiving LDV/SOF for 12 weeks and GT 6 received LDV/SOF for 12 weeks had baseline ALT ≤ 1.5 x ULN, 53.8% treatment naive with GT 3 receiving LDV/SOF+RBV for 12 weeks and 64% treatment experienced GT 3s who received LDV/SOF+RBV for 12 weeks had baseline ALT > 1.5 x ULN.

Cohort 3

Cohort 3 (n = 20) - All completed study treatment. Baseline: 85.0% male and 85.0% White, and 100% non-Hispanic/Latino; mean age 56 years with a range of 47 to 72 years; mean (SD) baseline BMI 31.1 (7.70), 50% had BMI ≥ 30 kg/m^2. 90.0% had the GT 1a; 100% had cirrhosis; 35.0% IL28B CC alleles; mean (SD) baseline HCV RNA 6.0 (0.48) $\log_{10}$ IU/mL. 75% had baseline HCV RNA ≥ 800,000 IU/mL; 60% had baseline ALT > 1.5 x ULN.

Cohort 4

Cohort 4 (n = 104): not applicable to this Harvoni application.

Cohort 5

Cohort 5 (n = 20) - 19 subjects (95.0%) completed study treatment; 1 subject withdrew consent.

Baseline: 90.0% male and 90.0% White, 100% non-Hispanic/Latino; mean age 54 years with a range of 33 to 62 years; mean (SD) baseline BMI was 32.2 (9.06) , 50% had a BMI ≥ 30 kg/m^2. 50.0% had the GT 3a subtype; 45% had GT1a. 70% had cirrhosis; 35.0% IL28B CC alleles; mean

(SD) baseline HCV RNA was 6.0 (1.09) $\log_{10}$ IU/mL. 70% had baseline HCV RNA ≥ 800,000 IU/mL; 60% had baseline ALT > 1.5 x ULN.

Cohort 6

Cohort 6 (n = 8) - All subjects (100.0%) completed study treatment. Baseline: 75.0% male; 50% native Hawaiian or other Pacific Islander ethnicity; mean age 53 years with a range of 43 to 64 years; mean (SD) BMI was 28.8 (3.94) , 25% had BMI ≥ 30 kg/m^2. 75.0% had GT 1a subtype, 25% GT1b; 25% had cirrhosis; 87.5% IL28B CC alleles; mean (SD) baseline HCV RNA was 6.5 (0.49) $\log_{10}$ IU/mL. 75% had HCV RNA ≥ 800,000 IU/mL. All hepatitis B e antigen (HBeAg) negative. Hepatitis B surface antigen ranged from 1.58 to 7384 IU/mL. HBV DNA ranged from not detected to 1028 IU/mL. 50.0% had baseline ALT > 1.5 x ULN.

7.1.4.10. Results for the primary efficacy outcome

Cohort 1, Groups 1 and 2

- LDV/SOF+RBV for 12 weeks in GT 1 previously treated in ELECTRON → 100% SVR12;
- SOF+PEG+RBV for 12 weeks in GT 3 previously treated in ELECTRON → 90% SVR12 (9 of 10)

No resistance detected in the 1 subject with GT 3a HCV infection who relapsed post treatment.

- High SVR rates following retreatment of subjects who have previously failed SOF containing regimens, together with the lack of detection NS5B RAVs or TEVs, supports the lack of selection of clinically meaningful SOF resistance during prior therapy
- safe and well tolerated, no new safety signals.

Cohort 2, Groups 1 and 2

- LDV/SOF+RBV or LDV/SOF+GS-9669 for 12 weeks in treatment experienced subjects with GT 1 and advanced liver fibrosis or compensated cirrhosis resulted in a high SVR12 rate of 100.0%.
- PK of SOF, GS-566500, GS-331007, and LDV within the range of historical data.
- No new safety signal.

Cohort 2, Groups 3 to 6

- Treatment with LDV/SOF+RBV for 12 weeks → 100.0% SVR12, whereas treatment with LDV/SOF resulted in a 64.0% SVR12, suggesting an advantage to the inclusion of RBV when treating subjects with GT 3 HCV infection with LDV/SOF
- Treatment with LDV/SOF+RBV for 12 weeks in treatment experienced subjects with GT 3 HCV infection → SVR12 rate of 82.0%. One subject experienced on treatment breakthrough.
- Treatment with LDV/SOF for 12 weeks in subjects with GT 6 HCV infection →SVR12 rate of 96.0%; all subjects who completed study drug achieved SVR12.
- Of all the subjects with GT 3 HCV infection who relapsed, NS5A RAPs and NS5B S282T were detected in 7 of 17 and 1 of 17 subjects, respectively. The on treatment breakthrough in 1 subject was associated with the emergence of low levels of NS5B L159F only.
- NS5B S282T emerged in 1 subject with GT 6 HCV infection who completed 8 weeks of treatment and relapsed.
- The PK of SOF, GS-566500, GS-331007, and LDV similar to historical data
- No new safety signals.

Cohort 3, Group 1

- Treatment with LDV/SOF for 12 weeks in treatment naive or treatment experienced subjects with GT 1 HCV infection and decompensated CPT B cirrhosis resulted in an SVR12 rate of 65.0%. Pre-treatment NS5A RAPs had no apparent effect on treatment outcome. Viral relapse was associated with the detection of a single class of NS5A RAVs.
- The PK of SOF, GS-566500, GS-331007, and LDV were similar to historical data observed in subjects with decompensated cirrhosis receiving LDV/SOF.
- Safe and well tolerated in these cirrhotics.
- No new safety signals.

Cohort 5, Group 1

Cohort 5, Group 1 (incomplete data): No SVR12 data is available.

Cohort 6, Group 1

- LDV/SOF for 12 weeks in these 8 subjects →100% SVR12
- PK not affected by the HBV co-infection
- Safe and well tolerated.
- No new safety signals. Some experienced increases in HBV DNA and HBsAg; however, no clinical hepatitis flares. No treatment for HBV required.

7.1.4.11. Results for other efficacy outcomes

Resistance

See above.

PK Results

Cohort 2

PK of SOF, its metabolites, and LDV were similar regardless of treatment regimen (± GS-9669 or RBV), treatment history (treatment naive or treatment experienced with compensated cirrhosis), or HCV GT(1, 3, or 6), and were similar to that observed in other Phase II and 3 studies (for example, Studies GS-US-337-0118, GS-US-337-0133, GS-US-337-0102, and GS-US-337-0109). Mean plasma PK parameters for GS-9669 were also similar to those observed in another Phase II study (Study GS-US-337-0133) following administration of GS-9669 500 mg with LDV/SOF.

Cohort 3

Mean plasma PK parameters for SOF, GS-566500, and GS-331007 were similar to those observed for subjects with decompensated cirrhosis (CPT B) receiving treatment with LDV/SOF in Study GS-US-337-0123. Mean plasma PK parameters for LDV similar to those in the Phase II and 3 studies, regardless of hepatic function. Collectively, these data are in agreement with results from Phase I studies evaluating the effect of hepatic impairment on SOF and metabolites (P2938-0515) and LDV (GS-US-344-0101 and GS-US-248-0117).

Cohort 4

Not relevant to this Harvoni application.

Cohort 6

Exposures of SOF, GS-566500, GS-331007, LDV similar to the LDV/SOF Phase II and III studies in subjects mono-infected with HCV.

7.1.5. Study GS-US-337-1118 (RETREATMENT)

An Open label, multi-centre study to evaluate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination ± ribavirin for 12 or 24 weeks in chronic Genotype 1 HCV infected subjects who participated in a prior Gilead sponsored HCV treatment study.

7.1.5.1. Study design, objectives, locations and dates

Sites: 24 in the USA (for Group 1).

First subject screened: 05 November 2013; Study End Date: 16 September 2014.

Publications/presentations arising:

- Wyles DL, et al. Retreatment of patients who failed prior sofosbuvir-based regimens with all oral fixed dose combination ledipasvir/sofosbuvir plus ribavirin for 12 weeks [Abstract 235]. Presented at: The 65th Annual Meeting of the AASLD; 2014 November 07-11; Boston, MA, United States.

Protocol amendments

Original 24 September 2013; Amendment 1 6 Jan 2014; added a second treatment that is, Subjects in Group 1 will be treated for 12 weeks. Subjects in Group 2 will be treated for 24 weeks; Amendment 2, 09 April 2014.

Design

Non-randomised open label study that will investigate the safety, tolerability and antiviral efficacy of SOF/LDV with or without RBV for 12 or 24 weeks in chronic GT 1 HCV infected subjects that failed prior treatment in a previous Gilead sponsored HCV treatment study. After completing the current study, eligible subjects could enrol into 1 of 3 follow-on studies: GS-US-248-0122, the Sequence Registry Study (GS-US-248-0123), or Cirrhosis SVR Registry Study (GS-US-337-1431).

7.1.5.2. Inclusion and exclusion criteria

Key inclusions: Eligible subjects were males or non-pregnant/non-lactating females ≥ 18 years of age, with chronic GT 1 HCV infection, who had screening HCV RNA levels > LLOQ, were HCV treatment experienced, and had participated in a previous Gilead sponsored HCV treatment study. For the LDV/SOF+RBV 12 week group (Group 1), subjects were enrolled from the following Gilead sponsored studies: P7977-0221, P7977-0422 (PROTON), P7977-0724 (ATOMIC), GS-US-334-0110 (NEUTRINO), and P2938-0721 (QUANTUM).

7.1.5.3. Study treatments

Group 1: LDV/SOF+RBV 12 Week group in subjects who failed a prior SOF+RBV±PEG regimen.

Group 2: LDV/SOF 24 Week group in subjects who failed a prior LDV/SOF±RBV regimen.

Group 3: LDV/SOF+RBV 24 Week group in subjects with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen.

7.1.5.4. Efficacy variables and outcomes

Serum HCV RNA levels at screening, Day 1 (predose), Weeks 1, 4, 8, 12 during treatment (or on early termination); post treatment Weeks 4, 12 (if applicable), and 24 (if applicable).

Safety

AEs and safety laboratory tests, vital signs, ECGs, physical examinations collected throughout the study (through the 4 week post treatment visit).

Efficacy

HCV RNA using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v2.0. LLOQ of the assay was 15 IU/mL.

Primary objective

- SVR12
- Safety and tolerability.

Other outcomes

- SVR4 and 24; HCV-RNA kinetics
- Virologic failure and resistant variants.

7.1.5.5. Analysis populations

The FAS, SAS and PK analysis sets are as defined previously.

7.1.5.6. Sample size

N = 100. Non-randomised; open label.

7.1.5.7. Statistical methods

The point estimate of SVR12 rate and the 2 sided 95% exact CI based on Clopper-Pearson method will be provided for Group 1. SVR12 summarised by categories of early viral response by cirrhosis status, prior treatment to explore possible early on treatment predictors of SVR12. Relationship between SVR12 and study drug dose reduction and modification will also be explored.

7.1.5.8. Participant flow

Analysed: 51 subjects in the LDV/SOF+RBV 12 Week group (Group 1) were included in the FAS and SAS.

7.1.5.9. Major protocol violations/deviations

One cirrhotic patient did not have an USS to exclude HCC.

One other patient did not have all the required screening safety blood at screen.

Nil impact on results.

7.1.5.10. Baseline data

Majority male (60.8%), White (84.3%), non-Hispanic/Latino (92.2%), mean age of 54 years (range: 27 to 68). The mean (SD) BMI value for subjects was 30.4 (5.21) kg/m^2; GT 1a (58.8%). Majority had a non-CC (CT or TT) IL28B GT (92.2%). 27.5% of subjects had cirrhosis.

Overall mean (SD) HCV RNA value was 6.2 (0.58) $\log_{10}$ IU/mL, 75% had baseline HCV RNA ≥ 800,000 IU/mL. All subjects had been treated in a prior Gilead sponsored HCV study; 25 (49.0%) previously received SOF+PEG+RBV, 20 (39.2%) previously received SOF+RBV, and 6 (11.8%) previously received treatment without SOF (GS-0938 monotherapy [n = 1] and SOF placebo +PEG+RBV [n = 5], respectively). 92.2% had experienced virologic failure (relapse/nonresponse), 1 discontinued treatment due to an AE, and 3 (5.9%) had an outcome categorised as “other”.

7.1.5.11. Results for the primary efficacy outcome

Fifty (98.0%) completed study treatment. One subject discontinued study treatment after Week 10 of treatment due to an AE of worsening of bipolar disorder.

Efficacy results (Group 1 only for this interim): 98.0% achieved SVR12. The 1 subject not achieving SVR12 relapsed at post treatment Week 4 after completing study treatment. This patient had been misclassified as GT-1 when in fact they had GT 3a.

In summary, retreatment of prior SOF failures with LDV/SOF+RBV resulted in a durable SVR: all who achieved SVR12 also achieved SVR24.

Table 15: Study GS-US-337-1118 (RETREATMENT): Proportion of subjects with SVR12 and virologic outcomes (FAS)

	LDV/SOF+RBV 12 Weeks (Group 1) (N = 51)
SVR12	50/51 (98.0%)
95% CI	89.6% to 100.0%
Overall Virologic Failure	1/51 (2.0%)
Relapse	1/51 (2.0%)
Completed Study Treatment	1/50 (2.0%)
Discontinued Study Treatment	0/1
On-Treatment Virologic Failure	0/51
Other	0/51

7.1.5.12. Results for other efficacy outcomes

Resistance

All GT 1 with NS5A RAVs (n = 6) or NS5B L159F (n = 2) at baseline achieved SVR12.

Table 16: Study GS-US-337-1118 (RETREATMENT): Presence of NS5A and NS5B variants at Baseline and SVR outcome

Subject ID	Genotype	NS5A RAVs at Baseline	NS5B RAVs or TEVs at Baseline	SVR24
3060-86008	1a	A92T (1.3%)	none	yes
5518-86051	1a	Q30H (> 99%)	none	yes
3060-86002	1b	L31M (3.6%)	none	yes
4139-86030	1b	L31M (98.1%)	none	yes
4308-86029	1b	Y93H (>99%)	none	yes
5369-86037	1b	Y93H (>99%)	none	yes
3060-86006	1b	none	L159F (> 99%)	yes
6844-86018	1b	none	L159F (> 99%)[a]	yes

a In Subject 6844-86018, NS5B L159F was present in combination with C316N.

Safety Results

Overall, LDV/SOF+RBV safe and well tolerated.

7.1.6. Study GS-US-337-1119

A Phase II, multi-centre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination in treatment naïve and treatment experienced subjects with chronic Genotype 4 or 5 HCV infection.

7.1.6.1. Study design, objectives, locations and dates

Sites: 5 sites in France.

First subject screened: 07 Mar 2014; 25 November 2014 (Last Subject Observation for this Report).

Publications/presentations arising: none.

Protocol amendments: none, Original protocol: 09 October 2013.

Design: non-randomised, Phase II, multicentre, open label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed dose combination in treatment naïve and treatment experienced subjects with chronic GT 4 or GT-5 HCV infection.

7.1.6.2. Inclusion and exclusion criteria

Key inclusions criteria

1. Willing and able to provide written informed consent
2. Male or female, age ≥ 18 years
3. confirmation of chronic HCV infection(at least 6 months) GT-4 or GT-5
4. HCV RNA ≥ 10^4 IU/mL
5. BMI ≥ 18 kg/m^2
6. HCV treatment status of one of the following:
    a. Treatment-naïve, defined as no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA; or,
    b. Treatment experienced, defined as having received treatment with an IFN-containing regimen, ±RBV and/or an HCV NS3/NS4A PI, and which can be further categorized as
        i. Treatment intolerant
        ii. Non response; did not achieve undetectable HCV RNA levels while on treatment
        iii. Relapse/breakthrough; achieved undetectable HCV RNA levels during treatment or within 4 weeks of the EOT but did not achieve a SVR.
7. Cirrhosis determination, in up to 50% of enrolees; protocol defined as before.

Key exclusion criteria

1. Current medical problems including: current or prior history of clinical hepatic decompensation; solid organ transplantation; significant pulmonary/cardiac disease; psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 2 years; malignancy diagnosed/treated within 5 years; HCC
2. Pregnant or nursing female
3. Chronic liver disease of a non-HCV aetiology
4. HBV or HIV.

7.1.6.3. Study treatments

LDV/SOF FDC tablet OD for 12 weeks.

7.1.6.4. Efficacy variables and outcomes

HCV RNA at baseline/Day 1; on treatment Weeks 1, 2, 4, 8, 12; post treatment Week 4; post treatment Weeks 12 and 24 as applicable, using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v2.0 with LLOQ of 15 IU/mL.

Primary objective

SVR12; safety and tolerability of each treatment regimen

Other outcomes

SVR4 and 24; viral kinetics; virologic failure and resistant variants; identify/ validate genetic markers predictive of natural history of HCV, response and/or tolerability of DAA.

7.1.6.5. Analysis populations

The FAS, SAS analysis sets are as defined previously.

7.1.6.6. Sample size

n = 80.

7.1.6.7. Statistical methods

The proportion achieving SVR12 by GT and prior HCV treatment status estimated; exact 2 sided 95% CIs were constructed using the Clopper-Pearson method.

Primary efficacy endpoint was also analysed for select demographic, baseline, disease characteristics subgroups. Point estimates and 95% exact CIs for SVR12 rates for each subgroup calculated as described above.

Safety: as described before. AE coding used MedDRA, Vn 17.1.

7.1.6.8. Participant flow

Eighty-five subjects (44 GT 4, 41 GT 5) were included in the FAS and SAS.

7.1.6.9. Major protocol violations/deviations

One patient did not have a pregnancy test at screening.

7.1.6.10. Baseline data

Eighty-five enrolled (44 GT 4; 41 with GT 5). All completed 12 weeks of treatment.

Genotype 4

81.8% White and 95.5% not Hispanic or Latino; 68.2% of European descent, 18.2% of Egyptian descent. Mean age 51 years (range: 21 to 69), 63.6% male. Mean [SD] BMI value for 24.8 (3.75) kg/m^2, 90.9% had BMI < 30 kg/m^2.

56.8% had GT4a subtype; 81.8% non-CC IL28B allele.

Mean (SD) HCV RNA 6.2 (0.47) log_{10} IU/mL. 22.7% cirrhosis; mean (SD) ALT 57 (35.7) U/L.

Genotype 5

All were White and not Hispanic/Latino; 95.1% of European descent. Mean age 63 years (range: 40 to 79), 51.2% male. Mean (SD) baseline BMI of 25.4 (4.11) kg/m^2, 92.7% had BMI < 30 kg/m^2.

All were subtype 5a, except for one subject with undetermined subtype; 53.7% non-CC IL28B allele. Mean (SD) HCV RNA 6.4 (0.47) log_{10} IU/mL. 22.0% had cirrhosis; mean (SD) ALT 61 (43.6) U/L.

7.1.6.11. Results for the primary efficacy outcome

Efficacy Results

Table 17 presents a summary of the efficacy results.

- SVR12 rate = 93.2% (41 of 44) for GT 4 and 92.7% (38 of 41) for GT 5;
- SVR12 similar in treatment naive and experienced.

- For GT 4, 95.5% treatment naive and 90.9% experienced achieved SVR12.
- For GT 5, 90.5% treatment naive and 95.0% treatment experienced subjects achieved SVR12.

· No on-treatment virologic failure. Each of the 3 GT 4 subjects not achieving SVR12 relapsed. Two of the 3 GT 5s not achieving SVR12 relapsed. One GT 5 subject not achieving SVR12 had HCV RNA < LLOQ at last on treatment visit; however, the subject was then LTFUP

· No apparent differences in SVR12 rates for subgroups. 100% GT 4 subjects with cirrhosis achieved SVR12; 88.9% GT 5 cirrhotics achieved SVR12.

· Rapid suppression of HCV RNA observed in all groups. All with SVR4 also achieved SVR12.

7.1.6.12. Results for other efficacy outcomes

Virologic resistance

Virologic resistance is summarised in Tables 18 and 19.

Of the 5 with virologic relapse, NS5B S282T emerged at virologic relapse for 1 with GT 4r and 1 with GT 5a.

At relapse, post treatment NS5B sequencing showed that the NS5B V321I RAP was retained or enriched in 2 with GT 4r infection, and the M289I RAP emerged in 1 GT 5a subject with post treatment NS5B sequencing data.

High SVR were achieved despite the presence of NS5A RAPs. Virologic relapse associated with retained NS5A and NS5B RAPs and emergence of NS5A Y93C (n = 1), NS5B S282T (n = 2) or M289I (n = 1).

Safety

See also Section 8. LDV/SOF FDC was well tolerated with low rates of SAEs and clinical laboratory abnormalities, and no discontinuations due to AEs, pregnancies, or death.

Table 17: GS-US-337-1119: SVR12 (FAS)

	Group 1 GT 4 TN (N = 22)	Group 2 GT 4 TE (N = 22)	Total GT 4 (N = 44)	Group 3 GT 5 TN (N = 21)	Group 4 GT 5 TE (N = 20)	Total GT 5 (N = 41)
SVR12	21/22 (95.5%)	20/22 (90.9%)	41/44 (93.2%)	19/21 (90.5%)	19/20 (95.0%)	38/41 (92.7%)
95% CI	77.2% to 99.9%	70.8% to 98.9%	81.3% to 98.6%	69.6% to 98.8%	75.1% to 99.9%	80.1% to 98.5%

GT = genotype; TN = treatment naive; TE = treatment experienced
HCV RNA was analyzed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The LLOQ of the assay was 15 IU/mL.
SVR12 = sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (ie, '<LLOQ TND' or '<LLOQ detected'); otherwise, the missing SVR12 value was imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

Table 18: GS-US-337-1119 resistance analysis in GT 4

Number of Pretreatment RAPs	GT 4 Number of Subjects	SVR12 for Subjects with NS5A RAPs
1 RAP[a]	16	16/16 (100%)
2 RAPs[b]	18	18/18 (100%)
3 RAPs[c]	10	7/10 (70%)

GT = genotype; RAP = resistance associated polymorphism
a All subjects (n = 16) with a single RAP had L31M.
b Two-RAP combinations included K24S/R+L31M (n = 2), L28I+L30R (n = 1), L28M+L31M (n = 3), L30R+L31M (n=7), L30R+P58T (n = 1), L30S+L31M (n = 1), L31M+P58L/T (n = 2), and L31M+Y93H (n = 1).
c Three-RAP combinations included K24Q+L30R+M31M (n = 1), L28M+L30T/R+ M31M/V (n = 4), L28M+M31M+P58T (n = 1), and L30R+M31M+P58T (n = 4).

Table 19: GS-US-337-1119 resistance analysis in GT 5

Pretreatment NS5A RAPs	GT 5 N = 39[a,b,c]	SVR12 for Subjects with NS5A RAPs
L31F/M	3/39 (7.7%)	2/3 (66.7%)
P58S	1/39 (2.6%)	1/1 (100%)

GT = genotype; RAP = resistance-associated polymorphism

a NS5A amplification failed for Subject 8575-92064. No baseline NS5A sequence was available and the subject was excluded from this analysis.

b Subject 6359-92074 did not have a posttreatment Week 12 visit and was excluded from this analysis.

c Subjects with multiple RAPs were counted once in each category.

7.1.7. Study GS-US-337-1468 (LEPTON)

A Phase II, multi-centre, open label study to assess the efficacy and safety of oral regimens for the treatment of chronic HCV infection.

7.1.7.1. Study design, objectives, locations and dates

Sites: 2 in New Zealand.

First subject screened: 04 Aug 2014; 13 February 2015 (Last Subject Observation for this Report).

This interim synoptic CSR presents efficacy and safety outcomes for subjects with GT 2 HCV infection who received LDV/SOF FDC OD for 12 weeks (Cohort 2, Group 1).

Publications/presentations arising: none.

Protocol amendments: original 18 June 2014; Amendment 1 22 Aug 2014; Amendment 2, 16 December 2014; Amendment 3 12 February 2015.

Design: Phase II, multicentre, non-randomised, open label study to assess efficacy and safety of oral regimens for the treatment of chronic HCV infection.

7.1.7.2. Inclusion and exclusion criteria

Key inclusion criteria

Eligible subjects were:

- males and non-pregnant, non-nursing females aged ≥ 18 years of age with GT 2 HCV.
- HCV RNA ≥ 10^4 IU/mL at screening and BMI ≥ 18 kg/m^2.
- Up to 40% of subjects HCV treatment experienced, and up to 25% with cirrhosis.

7.1.7.3. Study treatments

LDV/SOF FDC OD for various treatment durations. For Group 1 (GT 2), duration was12 weeks, or 8 weeks.

7.1.7.4. Efficacy variables and outcomes

Efficacy evaluated by measuring serum HCV RNA at Day 1; at on-treatment Weeks 1, 2, 4, 8, 12; and at Post treatment Weeks 2, 4, 8, and 12.

The primary objectives

SVR12; safety and tolerability.

Secondary objectives

To evaluate virologic failure; viral resistance to LDV, SOF, and other DAAs.

Safety assessments

As detailed before.

7.1.7.5. Analysis populations

The FAS, SAS are as defined previously.

7.1.7.6. Sample size

N = 25 (for GT 2) (REF this interim report)

- Up to 295 subjects will be enrolled into one of five cohorts.
- Cohort 1 will consist of 2 groups each with up to 25 enrolled subjects.
- Cohort 2 will consist of 2 groups each with up to 25 enrolled subjects.
- Cohort 3 will consist of 1 group with up to 25 enrolled subjects.
- Cohort 4 will consist of 1 group with 15 enrolled subjects.
- Cohort 5 will consist of 8 groups.
  - Groups 1 and 2 will consist of 15 enrolled subjects in each group.
  - Groups 3, 4, and 5 will consist of up to 20 enrolled subjects in each group.
  - Groups 6 and 7 will consist of 30 enrolled subjects in each group.
  - Group 8 will consist of up to 5 enrolled subjects.

7.1.7.7. Statistical methods

SVR12 rates calculated with 2 sided 95% exact CIs based on the Clopper-Pearson method.

No statistical hypothesis testing was performed for the primary endpoint. Safety: as described before.

7.1.7.8. Participant flow

Analysed: Twenty-six subjects each in the SAS and FAS.

7.1.7.9. Baseline data

All of the enrolled subjects received ≥ 1 dose of study drug and were included in the SAS and FAS. 96.2% (25 of 26) completed 12 weeks of treatment with LDV/SOF; 1 subject withdrew consent and prematurely discontinued from the study after receiving 1 dose of study drug.

Baseline characteristics

Majority were male (65.4%) and White (92.3%), none Hispanic or Latino. Mean age was 53 years (range: 28 to 75 years). Mean (SD) BMI of 25.9 (3.84) kg/m^2.

Mean (SD) HCV RNA was 6.1 (0.66) $\log_{10}$ IU/mL; 57.7% had HCV RNA ≥ 800,000 IU/mL.

All GT 2 HCV (61.5% subtype 2b). 61.5% had non-CC IL28B alleles. Two cirrhotics; 80.8% were naive to prior HCV treatment.

7.1.7.10. Results for the primary efficacy outcome

Twenty-five of 26 subjects (96.2%) achieved SVR12. The only subject who did not achieve SVR12 withdrew consent and prematurely discontinued from the study after receiving a single dose of LDV/SOF.

7.1.7.11. Results for other efficacy outcomes

Viral kinetics

HCV RNA decreased rapidly by on-treatment Week 2.

Resistance

Deep sequencing results obtained for 26/26 and 25/26 for NS5A and NS5B, respectively. Of the 26, 11 GT 2a, and 15 GT 2b.

Pre-treatment NS5A RAPs (T24A, F28L, K30R, or L31M) detected in all 11 GT 2a subjects, with L31M present in 10 of 11 GT 2a.

Pre-treatment NS5A RAPs (L28F, L31M) detected in 5/15 with HCV GT 2b. The NS5B RAPs (M289I/V) detected in 2 GT 2a and 2 GT 2b subjects.

High SVR rates despite NS5A and NS5B RAPs.

Safety

LDV/SOF FDC well tolerated; no new safety signals.

7.1.8. Study GS-US-337-0123 (SOLAR-1)

A Phase II, multi-centre, open label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post liver transplant.

7.1.8.1. Study design, objectives, locations and dates

Sites: 29 in the USA.

Dates: 06 September 2013 (First Subject Screened); Study End Date: 09 Jan 2015 (Last Subject Observation for this Interim Report nos 2); date of report: 20 March 2015.

Publications/presentations arising:

- Flamm SL, et al. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients With Decompensated Cirrhosis: Preliminary Results of a Prospective, Multi-centre Study [Presentation #239]. The 65th Annual Meeting of the AASLD; 2014 November 07-11; Boston MA United States.
- Reddy KR, et al. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients With Post-Transplant Recurrence: Preliminary Results of a Prospective, Multi-centre Study [Presentation #8]. The 65th Annual Meeting of the AASLD; 2014 November 07-11; Boston MA United States

Protocol amendments: none, Original: 14 June 2013.

Design

Ongoing Phase II, randomised, open label, multicentre study evaluating efficacy and safety of LDV/SOF+RBV GT 1 and 4 HCV infected subjects with advanced liver disease and/or who had undergone liver transplantation.

Randomised: 1:1 ratio within each Group of approximately 50 subjects (or 100 for Group 3) so equal numbers receive LDV/SOF+RBV for 12 weeks and LDV/SOF+RBV for 24 weeks, as follows:

- Cohort A: approximately 100 with decompensated cirrhosis (CPT Class B or C [CPT A or CPT B]), as follows:
  - Group 1: approximately 50 cirrhotics and moderate hepatic impairment (CPT B; severity score of 7-9)

- Group 2: approximately 50 subjects with cirrhosis and severe hepatic impairment (CPT C; severity score 10-12)

· Cohort B: approximately 300 subjects who had undergone liver transplantation (liver Transplant), as follows:

- Group 3: approximately 100 without cirrhosis (fibrosis stage F0-F3) and no evidence of hepatic decompensation
- Group 4: approximately 50 cirrhotics and mild hepatic impairment (CPT A; score 5-6 [compensated])
- Group 5: approximately 50 cirrhotics and moderate hepatic impairment (CPT B; score 7-9 [decompensated])
- Group 6: approximately 50 cirrhotics and severe hepatic impairment (CPT C; score of 10-12 [decompensated])
- Group 7: approximately 50 with aggressive recurrent disease after liver transplantation with evidence of cholestasis (fibrosing cholestatic hepatitis)

Subjects who did not achieve SVR or with HCV recurrence after the Post treatment and/or post-transplant Week 4 visit were eligible to participate in GS-US-248-0123.

Those achieving SVR or pTVR at the Post treatment and/or post-transplant Week 24 visit were eligible for GS-US-248-0122).

7.1.8.2. Inclusion criteria

Key inclusion criteria

1. Willing and able to provide written informed consent
2. Male or female, age ≥ 18 years
3. chronic HCV infection GT-1 of GT-4 with advanced liver disease or who had undergone liver transplantation, including those with decompensated cirrhosis
4. non-pregnant, non-lactating
5. treatment naive or treatment experienced and had documentation of the presence or absence of cirrhosis
6. No serious or active medical or psychiatric illnesses at screening, including HCC
7. No history of prior organ transplantation other than liver or kidney allowed
8. Treatment experienced subjects must not have received IFN, RBV, telaprevir, or boceprevir or any other approved or experimental medication with known anti- HCV activity within 1 month prior to screening, nor have any prior exposure to an HCV nonstructural protein 5A (NS5a) specific inhibitor.

7.1.8.3. Study treatments

LDV/SOF FDC OD + weight based RBV (BD) for 12 or 24 weeks within each group. The initial RBV dose was selected based on liver disease status, as follows:

· Post-transplantation with stage F0-F3 fibrosis, CPT A cirrhosis, or FCH (Groups 3, 4, and 7): -RBV 1000 or 1200 mg divided BD for 12 or 24 weeks according to the prescribing information

· Decompensated cirrhosis (CPT B or CPT C) regardless of transplantation status (Groups 1, 2, 5, and 6): RBV 600 mg/day. If this dose as well tolerated and the subject maintained a Hb > 10.0 g/dL without the need for significant growth weigh factor support, dose titrated

to a max of 1000 or 1200 mg divided BD. If 600 mg/day not well tolerated, dose could be reduced.

7.1.8.4. Efficacy variables and outcomes

Primary objective

SVR12; safety and tolerability of LDV/SOF+RBV for 12 or 24 weeks

Secondary objectives

SVR2, SVR4, SVR8, SVR24; determine if LDV/SOF+RBV to HCV infected subjects undergoing liver transplantation can prevent post-transplant recurrence as determined by sustained post-transplant virological response (pTVR: HCV RNA < LLOQ) at 12 weeks post-transplant (in those subjects who underwent liver transplantation while on study); change of CPT score and Model for End Stage Liver Disease (MELD) score; viral resistance; viral kinetics; identify/validate genetic markers that may predict natural history of disease, response and/or tolerability of DAA.

Efficacy

HCV RNA Day 1 (baseline), at the Week 1, 2, 4, 6, 8, 10, and 12 visits; and at the Post treatment/post transplantation Week 2, 4, 8, 12, and 24 visits for all subjects.

HCV RNA at the Week 16, 20, and 24 visits for subjects receiving 24 weeks of LDV/SOF+RBV. COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0 for use with the High Pure System assay, LLOQ of < 15 IU/mL.

PK

Single PK blood sample collected at each on-treatment visit (except Week 6). Optional intensive PK sub-study. PK of SOF, GS-566500, GS-331007, LDV were assessed.

Safety

As described previously.

7.1.8.5. Analysis populations

The FAS, SAS and PK analysis sets are as defined previously.

7.1.8.6. Sample size

N = 400 with 100 in Cohort A and 300 in Cohort B

7.1.8.7. Statistical methods

Primary efficacy endpoint was SVR12 in the FAS. Point estimates and 2-sided exact 90% CIs using the Clopper-Pearson method displayed for the proportion of subjects < LLOQ at each visit. No hypothesis testing was performed. Secondary: SVR4; on-treatment virologic failure.

PK: Steady-state PK from PK sub-study. Standard PK parameters determined.

Safety: as described above. AE coded using MedDRA, Version 16.1.

7.1.8.8. Participant flow

Analysed

All randomised subjects: 339 subjects; FAS = 337; SAS = 337; PK sub-study: 52 subjects.

Exposure

Of the 337 who received ≥ 1 dose of study drug, 7.4% prematurely discontinued treatment that is 12/25 discontinued due to an AE; 4 subjects each died or underwent transplantation; and 1 subject each (0.3%) discontinued for a variety of reasons.

7.1.8.9. Major protocol violations/deviations

Reference was made to the important deviations log in the body of the interim report provided. Deviations included laboratory parameters at screening (for example use of local CrCl not centrally obtained), incorrect dosing of RBV on study.

7.1.8.10. Baseline data

Demographics

The demographics were generally balanced across all groups. 60.9% to 100% male, 80% to 100% White, mean age ranged from 57 to 62 years and the mean (SD) baseline BMI 23.2 (1.06) to 31.4 (6.88) kg/m^2.

98.5% had GT 1 HCV infection; 5 subjects (1.5%) had GT4. 81.6% non-CC (CT or TT) IL28B alleles. Mean (SD) baseline HCV RNA ranged from 5.6 (0.62) to 7.1 (0.90) log_{10} IU/mL.

Cohort A

Cohort A (n = 108 with decompensated cirrhosis)

Prior treatment: 64.8% had received prior HCV treatment, of whom 46 received PEG + RBV, 19 received HCV PI + PEG+RBV treatment, and 5 received unspecified ("other") treatment. 70.0% were prior non-responders and 30.0% relapsed or had breakthrough. The majority of subjects (61.1%) had a baseline MELD score of 10 to 15.

Cohort B, Group 3

Cohort B, Group 3 (n = 112 post liver Transplant with F0 to F3 fibrosis)

Prior treatment: 78.4% had received prior HCV treatment.

Cohort B, Groups 4, 5, and 6

Cohort B, Groups 4, 5, and 6 (n = 111, post liver transplant subjects with compensated cirrhosis (CPT A) and

Prior treatment: 87.5% had received prior HCV treatment. For post-transplantation subjects with compensated (CPT A) cirrhosis, 54.9% had baseline MELD score of < 10. For the CPT B or CPT C cirrhosis group, 62.3% had a baseline MELD score of 10 to 15.

Cohort B, Group 7

Cohort B, Group 7 (n = 6, aggressive recurrent disease after liver transplant, with cholestasis)

Prior treatment: 5of 6 had received PEG+RBV before and were non-responders.

7.1.8.11. Results for the primary efficacy outcome

Table 20: GS-US-337-0123 (SOLAR-1): Proportion of subjects achieving SVR12 for all treatment groups (FAS)

Cohort	Liver Disease Status (Group)	Study Treatment	SVR12[a] (n/N [%])	90% CI
A	CPT B Cirrhosis (Group 1)	LDV/SOF+RBV 12 Weeks	26/30 (86.7%)	72.0% to 95.3%
		LDV/SOF+RBV 24 Weeks	24/27 (88.9%)	73.7% to 96.9%
	CPT C Cirrhosis (Group 2)	LDV/SOF+RBV 12 Weeks	19/22 (86.4%)	68.4% to 96.2%
		LDV/SOF+RBV 24 Weeks	20/23 (87.0%)	69.6% to 96.3%
B	Stage F0-F3 Fibrosis (Group 3)	LDV/SOF+RBV 12 Weeks	53/55 (96.4%)	89.0% to 99.4%
		LDV/SOF+RBV 24 Weeks	55/56 (98.2%)	91.8% to 99.9%
	CPT A Cirrhosis (Group 4)	LDV/SOF+RBV 12 Weeks	25/26 (96.2%)	83.0% to 99.8%
		LDV/SOF+RBV 24 Weeks	24/25 (96.0%)	82.4% to 99.8%
	CPT B Cirrhosis (Group 5)	LDV/SOF+RBV 12 Weeks	22/26 (84.6%)	68.2% to 94.6%
		LDV/SOF+RBV 24 Weeks	23/26 (88.5%)	72.8% to 96.8%
	CPT C Cirrhosis (Group 6)	LDV/SOF+RBV 12 Weeks	3/5 (60.0%)	18.9% to 92.4%
		LDV/SOF+RBV 24 Weeks	3/4 (75.0%)	24.9% to 98.7%
	Fibrosing Cholestatic Hepatitis (Group 7)	LDV/SOF+RBV 12 Weeks	4/4 (100.0%)	47.3% to 100.0%
		LDV/SOF+RBV 24 Weeks	2/2 (100.0%)	22.4% to 100.0%

Efficacy results

- Post-transplantation subjects with F0-F3 fibrosis or FCH had SVR12: 96.0% to 100.0%
- In those with decompensated (CPT B or CPT C) cirrhosis (no Liver Transplant) SVR rates similar across groups and treatment durations (range: 86.4% to 88.9%)
- Post-transplantation subjects with CPT A or CPT B cirrhosis had SVR12 ranging: 84.6% to 96.2%) those with CPT C cirrhosis has SVR12 range: 60.0% to 75.0%
- SVR12 rates similar across all groups between the 12 and 24 week treatment durations. No on-treatment virologic failure. Thirteen across all groups relapsed. Majority of relapses (84.6%, 11 of 13 subjects) occurred by Post treatment Week 8
- For the 5 with GT 4, 3 achieved SVR12. The 2 failures included 1 death due to cirrhosis complications on Post treatment Day 1; 1 achieved SVR4, but was LTFUP
- Of 7 who underwent liver Transplant on study and had HCV RNA < LLOQ at the last measurement prior, 6 achieved pTVR12. The 1 not achieving pTVR died 1 day after post-transplantation Week 2 visit.

7.1.8.12. Results for other efficacy outcomes

Changes in MELD and CPT

- Of 48 subjects with CPT A with a Post treatment Week 4 MELD score, 20 (41.7%) improved, 13 (27.1%) no change, and 15 (31.3%) worsened. Of 143 subjects with CPT B or CPT C cirrhosis Week 4 MELD score, 95 (66.4%) improved, 21 (14.7%) no change, 27 (18.9%) worsened. 66.7% of those treated for 24 weeks versus 54.1% of those treated for 12 weeks had improvements in MELD score. Of those with baseline MELD score ≥ 15, 56% had MELD score < 15 Post treatment Week 4.
- Majority of cirrhotics (> 85% in all groups) had an improvement or no change in CPT score from baseline to Post treatment Week 4, largely due to improvements in bilirubin and albumin.

PK

Higher SOF exposures in those with advanced liver disease versus non cirrhotics using Phase II or III population PK. See also 7.1.3.2.

ALT changes

Decreases in median ALT observed across groups coincident with HCV suppression.

Viral resistance

See Section describing analyses performed across trials (pooled analyses and meta-analyses) Safety: See Section 8.

7.1.9. Study GS-US337-0124 (SOLAR-2)

A Phase II, multi-centre, open label study to investigate the safety and efficacy of sofosbuvir/ledipasvir fixed dose combination + ribavirin administered in subjects infected with chronic HCV who have advanced liver disease or are post-liver transplant.

7.1.9.1. Study design, objectives, locations and dates

Sites: Australia (n = 2), France (n = 4), Germany (n = 4), Italy (n = 2), Switzerland (n = 2), Austria (n = 2), Belgium (n = 2), Canada (n = 6), The Netherlands (n = 2), Spain (n = 4), UK (n = 3), New Zealand (n = 1).

Dates: 14 Jan 2014 (First Subject Screened); 15 May 2015 (Last Subject Observation for this Interim).

Publications/presentations arising:

- Manns M, et al. Ledipasvir/Sofosbuvir with Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients with HCV Infection: Preliminary Results of the Prospective SOLAR-2 Trial [Presentation]. Presented at EASL 50th International Liver Congress 2015, April 22-26, 2015, Vienna, Austria.
- Samuel D, et al. Ledipasvir/Sofosbuvir with Ribavirin is Safe in > 600 Decompensated and Post-Liver Transplantation Patients with HCV Infection: An Integrated Safety Analysis of the SOLAR-1 and SOLAR-2 Trials [Poster P0774]. Presented at EASL 50th International Liver Congress 2015, April 22-26, 2015, Vienna, Austria.
- Forns X, et al. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of Fibrosing Cholestatic Hepatitis C after Liver Transplantation [Poster P0779]. Presented at EASL 50th International Liver Congress 2015, April 22-26, 2015, Vienna, Austria.

Protocol amendments

Original: 12 Jul 2013; Amendment 1: 24 Jan 2014 – main change, ALT, AST, or ALP ≥ 10 ULN parameters no longer to be used to determine eligibility for group 7.

Design

Ongoing Phase II, randomised, open label, multicentre study evaluating efficacy and safety of LDV/SOF+RBV GT 1 and 4 HCV with advanced liver disease and/or undergone liver transplant.

Randomised: 1:1 ratio within each Group of approximately 50 subjects (or 100 for Group 3) so equal numbers receive LDV/SOF+RBV for 12 weeks and LDV/SOF+RBV for 24 weeks, as follows:

Cohorts A and B: as per SOLAR-1.

7.1.9.2. Inclusion criteria

As per SOLAR-1.

7.1.9.3. Study treatments

LDV/SOF FDC OD + weight-based RBV (BD) for 12 or 24 weeks within each group.

7.1.9.4. Efficacy variables and outcomes

See SOLAR-1.

7.1.9.5. Analysis populations

The FAS, SAS and PK analysis sets are as defined previously.

7.1.9.6. Sample size

N = 400 with 100 in Cohort A and 300 in Cohort B.

7.1.9.7. Statistical methods

See SOLAR-1.

7.1.9.8. Participant flow

Analysed: All randomised subjects: 334 subjects; FAS = 330; SAS = 333 subjects. 3 excluded from the FAS due to not meeting entry criteria.

Exposure: Of 333 randomised and treated, 17 (5.1%) prematurely discontinued treatment. Of these, 7 (2.1%) discontinued due to AE; 4 died; 3 underwent transplant; 2 due to investigator's discretion, 1 due to study drug noncompliance.

7.1.9.9. Major protocol violations/deviations

125 Important protocol deviations occurred in 96 subjects. None affected overall quality/interpretation of study data.

7.1.9.10. Baseline data

Demographics

Demographics were generally balanced across all groups. 50.0% to 100.0% male and White (80.0% to 100.0%). Mean age 54 to 62 years; mean (SD) baseline BMI 22.4 (4.17) to 28.8 (6.48) kg/m^2.

88.9% had GT 1 HCV; 37 (11.1%) had GT 4. 79.9% non-CC (CT or TT) IL28B alleles. Mean (SD) baseline HCV RNA 5.6 (0.58) to 7.3 (0.72) $\log_{10}$ IU/mL. 79.6% had received prior treatment.

Cohort A (decompensated cirrhosis)

61.7% had a baseline MELD score of 10 to 15.

Cohort B, Groups 4, 5, and 6 (post liver Transplant)

Subjects with compensated cirrhosis (CPT A) and decompensated cirrhosis (CPT B and C): 58.5% of the CPT B and Cs, had MELD score 10 to 15.

7.1.9.11. Results for the primary efficacy outcome

Efficacy results

(See Table 21)

- Among those with GT 1 with decompensated cirrhosis (no Liver Transplant), SVR12 was 86.5%;
- Among liver Transplant without cirrhosis with GT 1 SVR12 was 96.6%;
- Among liver Transplant with compensated (CPT A) or decompensated (CPT B or C) cirrhosis with GT 1, SVR12 rate was 96.2%;
- Among liver Transplant with GT 1 HCV infection with FCH, SVR12 was 100.0%;
- Overall, among the 35 with GT 4, SVR12 was 85.7%.

- SVR12 rates similar across all groups between the 12 and 24 week treatment durations. No on-treatment virologic failure. Ten across all groups relapsed (7 GT 1 and 3 GT 4). Nine of the 10 subjects who relapsed had decompensated cirrhosis.

7.1.9.12. Results for other efficacy outcomes

Changes in MELD and CPT

68.3% versus 58% of 24 weeks versus 12 week treatment groups respectively had improvements in MELD score.

Of 137 with CPT B or CPT C cirrhosis, 71.5% had improvement, 12.4% no change, 16.1% worsening. Of those with MELD score ≥ 15 59.5% had a MELD score < 15 at post treatment Week 4.

Majority of cirrhotics (> 90% in all groups) had an improvement or no change in CPT score. Improvements were largely due to improvements in total bilirubin and albumin.

PK

Similar findings to SOLAR-1.

Resistance: See Section describing analyses performed across trials (pooled analyses and meta-analyses). Safety: See Section 8.

Table 21: GS-US-337-0124 (SOLAR-2): Proportion of subjects achieving SVR12 for all treatment groups (FAS)

Cohort	Liver Disease Status (Group)	Study Treatment	Genotype 1				Genotype 4			
			SVR12 (n/N [%])	90% CI	Relapse (n/N [%])[a]	90% CI	SVR12 (n/N [%])	90% CI	Relapse (n/N [%])[a]	90% CI
A	CPT B Cirrhosis (Group 1)	LDV/SOF+RBV 12 Week	20/23 (87.0%)	69.6% to 96.3%	3/23 (13.0%)	3.7% to 30.4%	2/3 (66.7%)	13.5% to 98.3%	1/3 (33.3%)	1.7% to 86.5%
		LDV/SOF+RBV 24 Week	22/23 (95.7%)	81.0% to 99.8%	1/23 (4.3%)	0.2% to 19.0%	2/2 (100.0%)	22.4% to 100.0%	0/2	0.0% to 77.6%
	CPT C Cirrhosis (Group 2)	LDV/SOF+RBV 12 Week	17/20 (85.0%)	65.6% to 95.8%	1/18 (5.6%)	0.3% to 23.8%	0/1	0.0% to 95.0%	1/1 (100.0%)	5.0% to 100.0%
		LDV/SOF+RBV 24 Week	18/23 (78.3%)	59.6% to 91.0%	1/19 (5.3%)	0.3% to 22.6%	1/2 (50.0%)	2.5% to 97.5%	0/1	0.0% to 95.0%
B	Stage F0-F3 Fibrosis (Group 3)	LDV/SOF+RBV 12 Week	42/45 (93.3%)	83.7% to 98.2%	1/43 (2.3%)	0.1% to 10.6%	7/7 (100.0%)	65.2% to 100.0%	0/7	0.0% to 34.8%
		LDV/SOF+RBV 24 Week	44/44 (100.0%)	93.4% to 100.0%	0/44	0.0% to 6.6%	5/5 (100.0%)	54.9% to 100.0%	0/5	0.0% to 45.1%
	CPT A Cirrhosis (Group 4)	LDV/SOF+RBV 12 Week	30/30 (100.0%)	90.5% to 100.0%	0/30	0.0% to 9.5%	3/4 (75.0%)	24.9% to 98.7%	0/3	0.0% to 63.2%
		LDV/SOF+RBV 24 Week	27/28 (96.4%)	84.1% to 99.8%	0/27	0.0% to 10.5%	5/5 (100.0%)	54.9% to 100.0%	0/5	0.0% to 45.1%
	CPT B Cirrhosis (Group 5)	LDV/SOF+RBV 12 Week	19/20 (95.0%)	78.4% to 99.7%	0/19	0.0% to 14.6%	2/2 (100.0%)	22.4% to 100.0%	0/2	0.0% to 77.6%
		LDV/SOF+RBV 24 Week	20/20 (100.0%)	86.1% to 100.0%	0/20	0.0% to 13.9%	3/3 (100.0%)	36.8% to 100.0%	0/3	0.0% to 63.2%
	CPT C Cirrhosis (Group 6)	LDV/SOF+RBV 12 Week	1/2 (50.0%)	2.5% to 97.5%	0/1	0.0% to 95.0%	0/1	0.0% to 95.0%	1/1 (100.0%)	5.0% to 100.0%
		LDV/SOF+RBV 24 Week	4/5 (80.0%)	34.3% to 99.0%	0/4	0.0% to 52.7%	NA	NA	NA	NA
	Fibrosing Cholestatic Hepatitis (Group 7)	LDV/SOF+RBV 12 Week	3/3 (100.0%)	36.8% to 100.0%	0/3	0.0% to 63.2%	NA	NA	NA	NA
		LDV/SOF+RBV 24 Week	2/2 (100.0%)	22.4% to 100.0%	0/2	0.0% to 77.6%	NA	NA	NA	NA

a The Full Analysis Set excluding subjects who had "other" virologic failure and subjects who had undergone transplantation prior to SVR12 with HCV RNA < LLOQ was used for the relapse analysis.
HCV RNA was analyzed using the Roche COBAS Ampliprep/COBAS Taqman HCV Test, v2.0 with lower limit of quantitation 15 IU/mL.
SVR12 was sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
Relapse to posttreatment Week 12 was confirmed HCV RNA ≥ LLOQ during the posttreatment period up to Posttreatment Day 146 after having HCV RNA < LLOQ at last on-treatment visit.
A subject was a success if their latest observed HCV RNA value in the visit window was < LLOQ, or if they had a missing value for the visit window bracketed by observed HCV RNA values that were termed successes (ie, '< LLOQ TND' or '< LLOQ detected'). TND = target not detected.
The exact 90% CI for the proportion within group and treatment duration was based on the Clopper-Pearson method.

7.2. Other efficacy studies

7.2.1. Study CO-US-337-0117 (SYNERGY)

A Pilot Study to evaluate the safety and efficacy of multiple anti-HCV combination therapy; supports retreatment; Genotype 4.

Study sponsor: NIAID. Multi centre US sites only.

Study Start Date: 16 September 2013 (First Subject Screened); 23 February2015 (Last Subject Observation)

7.2.1.1. Design

Open label Phase IIa study to assess safety, tolerability, and efficacy of a LDV/SOF FDC OD for 12 weeks. This is a multipart study, containing 8 groups (A-H). The focus of this clinical study report will be group E, which evaluated treatment with LDV/SOF in GT 4.

7.2.1.2. Objectives

Assess the safety, tolerability, and efficacy of a fixed dose combination (FDC) of GS-5885/GS-7977 tablets for 12 weeks for the treatment of HCV GT 4, in both treatment naïve and interferon treatment experienced patients.

7.2.1.3. Diagnosis and main criteria for inclusion

Men and women, ≥ 18 years of age, CHC GT 4.

Planned: 21 subjects receiving FDC for 12 weeks.

Analysed: 21 subjects receiving FDC for 12 weeks.

Efficacy: SVR12 using an HCV assay with LLOQ (< 43 IU/mL).

Safety: as above.

7.2.1.4. Statistical analysis

Based on an ITT population. Analyses performed using PRISM 6.0.

7.2.1.5. Results

Subject disposition and demographics: 40% treatment experienced, 29% had cirrhosis; 19 % were both treatment experienced and had cirrhosis.

29% Egyptian origin; 38% from other African countries.

67%; (14/21) male, plasma HCV RNA levels (> 800,000 IU/mL) (62%; (13/21)). 9% (2/21) had HAI Stage 3 liver disease and 33% (7/21) had cirrhosis.

Efficacy Results: Twenty out of 21 (20/21; 95%CI: 76 to 100%) achieved SVR12. The 1 failure was non-adherent.

In a further analysis from the SYNERGY study, a small amount of retreatment data was provided for GT 1 subjects who previously relapsed after 24 weeks of SOF+RBV on study 11-I-0258 (SPARE). SUMMARY OF RESULTS: All 14 of 14 patients (100%) treated with LDV/SOF for 12 weeks achieved SVR12. Well tolerated and safe; no deaths or discontinuations due to AE observed.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

7.3.1. PC-337-2006

Integrated Virology study report for ledipasvir/sofosbuvir containing regimens for the treatment of HCV Genotype 1 special populations and HCV Genotypes 2-6 infection. PC-337-2006.

A full description of the resistance analysis methodologies is summarised in the virology analysis plan (PC-337-2004).

Baseline deep sequencing of the full-length HCV NS3 (where applicable), NS5A, and NS5B coding region was performed by DDL (DDL Diagnostic Laboratory, Rijswijk, The Netherlands) or the WuXi Genome Center (Shanghai, China) using RT-PCR and then deep sequencing using the Illumina MiSeq deep sequencing platform.

The NS3, NS5A, and NS5B sequence was utilised to confirm the results of genotyping/subtyping by the INNO-LiPA assay (Innogenetics) performed at screening. Sequencing only attempted if HCV RNA ≥ 1000 IU/mL.

Data for this integrated report is derived from the LDV/SOF Phase II or III clinical studies: GS-US-337-0115 (ION 4), GS-US-337-0121 (SIRIUS), GS-US-337-1118 (Group 1), GS-US-337-0122 (ELECTRON 2; Cohort 1, Group 1; Cohort 2, Groups 3, 4, 5, and 6), GS-US- 337-1468 (LEPTON; Cohort 2, Group 1), and GS-US-337-1119.

In summary:

- high SVR rates in subjects with HCV GT 1, 2, 3, 4, 5, and 6;
- high SVR12 achieved in the presence of baseline NS5A or NS5B NI RAVs, irrespective of patient population or GT. This is similar to the findings from the previous LDV/SOF Phase III studies (ION-1, ION-2, ION-3) conducted in GT 1 HCV;
- The lack of a high predictive value between baseline viral sequence and treatment outcome also appears to preclude the clinical utility of baseline HCV sequencing;
- Of the limited number who experienced virologic failure, NS5A RAVs observed in the majority. With regard to NS5B NI RAVs, S282T emerged in 1 subject each for GT 4, 5, and 6, whereas S282T was not observed in any GT 1 HCV-infected subject with relapse.

7.3.2. Study PC-337-2007

Integrated virology study report for ledipasvir/sofosbuvir containing regimens in subjects infected with chronic HCV who have advanced liver disease or are post liver transplant (SOLAR-1 and SOLAR-2 Studies).

Full description of the resistance analysis and virological analysis plan methodologies are found in the analysis plan PC-337-2004.

Overall results:

- when pooling all GT 1 subjects irrespective of group or duration, high SVR12 rates in the presence of baseline NS5A RAPs or RAVs: 143 of 148 (96.6%) with NS5A RAPs (15% cut off) achieved SVR12 versus 424 of 439 (96.6%) with no NS5A RAPs; and 96 of 101 (95.0%) with NS5A RAVs (1% cut off) achieved SVR12 versus 471 of 486 (96.9%) with no NS5A RAVs.
- When subjects were analysed according to their group and treatment duration, except for subjects in group 2 (CPT C), no clear differences in SVR12 rates observed by the presence or absence of NS5A RAPs or RAVs. For the small number of CPT C subjects who received LDV/SOF+RBV for 12 weeks: 7 of 9 subjects (77.8%) and 6 of 8 (75.0%) with RAPs (15% cut off) and NS5A RAVs (1% cut off), respectively, achieved SVR12 versus subjects who received

LDV/SOF+RBV for 24 weeks: 9 of 9 (100%) and 10 of 10 (100%) subjects with no NS5A RAPs or RAVs, respectively.

- When pooling subjects by stage of liver disease, in GT 1, NS5A RAP did not have a meaningful impact on outcome; conversely, a statistically significant difference was observed for the subset with decompensated disease with NS5A RAVs known to confer > 100 fold resistance to LDV in vitro: SVR12 rates were 75% (12/16) and 100% (18/18), respectively, for those treated with SOF/LDV+RBV for 12 weeks versus for 24 weeks (p value: 0.039; 2 sided Fisher's Exact test). However, all four subjects with a Pre-treatment NS5A RAV that confers > 100 fold shift in EC_{50} who relapsed, also had BMI > 30. Subsequent logistic regression analyses demonstrated that, when accounting for BMI, presence of NS5A RAVs conferring > 100 fold shift in EC_{50} was not associated with relapse. No effect on SVR12 with Pre-treatment NS5B NI RAVs. For GT 4, no subjects without RAPs (n = 11) or RAVs at 1% cut off (n = 10) relapsed. Of those with NS5A RAPs (n = 24) or RAVs (n = 25), 3 relapsed; all 3 had decompensated disease and were treated for 12 weeks. No GT 4 subjects with NS5A RAPs or RAVs who were not decompensated relapsed. No subjects treated for 24 weeks relapsed, irrespective of the presence or absence of NS5A RAPs or RAVs. No effect on SVR12 rate observed with NS5B NI RAVs at Pre-treatment. Virologic failure associated with single class LDV resistance in the majority of subjects. The NS5B NI RAVs S282T, L159F and V321A, not detected in any at virologic failure. E237G, a conserved site substitution in NS5B, was detected in 3 GT 1a subjects and 1 GT 4d subject at time of relapse. E237G showed a small reduction in susceptibility to SOF (1.3 fold change) in a GT 1a replicon assay. The clinical significance of E237G is unknown.

7.4. Evaluator's conclusions on clinical efficacy for Harvoni for extended use

In Australia, Harvoni is approved for the treatment of hepatitis C virus (HCV) GT 1 infection. This application proposes to extend the indication to: Harvoni for the treatment of CHC infection in adults to include patients with HCV infection who are post liver transplantation with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status; patients with chronic GT 2, 3, 4, 5 or 6 HCV infection as there is currently no approved all oral, IFN and RBV free therapy for these genotypes; HCV/HIV co-infection; and those who have previously failed a SOF+RBV±PEG regimen as there is currently no approved therapy for those who have previously failed a SOF containing regimen. The sponsor has provided a comprehensive swathe of Phase II and III studies and 4 PK studies in support of this extension of indication request. Overall, in all settings, this FDC is highly efficacious and safe, with no new safety signal of concern revealed even in the very sick populations of patients enrolled in SOLAR-1 and SOLAR-2.

The extension of indication seeks to meet unmet medical need. Overall the data supports the extension of indication with the caveat that there is a paucity of data for retreatment with Harvoni ± RBV for non-Genotype 1 patients who have previously failed sofosbuvir. The data from ELECTRON-2, suggests that adjunctive ribavirin may important to achieve high rates of SVR12 when using 12 week courses of Harvoni for Genotype 3, especially in treatment experienced patients where even with ribavirin, SVR12 was 82%. In addition SOLAR-1 and SOLAR-2 did not include patients with genotypes other than 1 and 4, so there is very little data about the efficacy and safety of Harvoni with these other genotypes in those with varying degrees of liver impairment including pre and post liver transplantation. All studies enrolled a majority of male subjects (most especially true of ION-4), and in most, the majority ethnicity was White and this was even the case in GS-US-337-1119 which enrolled GT-4 and GT-5 subjects.

8. Clinical safety

8.1. Studies providing evaluable safety data

For the purpose of this safety section, the reviewer has considered all the studies defined as 'pivotal' in Section 7, as pivotal in Section 8, this includes the two Phase II clinical studies included of LDV/SOF, with RBV, in subjects with HCV infection who were post-transplantation with compensated liver disease as well as those with decompensated liver disease, regardless of transplantation status (SOLAR-1 and SOLAR-2). Three of the pivotal studies are highlighted because of their particular populations:

- Treatment experienced with Cirrhosis (GS-US-337-0121 [SIRIUS])
- HCV/HIV Co-infection (GS-US-337-0115 [ION-4])
- SOLAR-1 and SOLAR -2 (pooled data).

8.1.1. Safety reporting

Treatment related adverse events (TRAEs) defined in the individual study statistical analysis plans and met one of the following criteria:

- AE with onset dates on or after start of treatment and up to 30 days after the discontinuation of all the study drugs
- Continuing AEs diagnosed prior to the start of treatment and worsening in severity grade
- non-serious AEs at baseline which become serious
- AEs resulting in treatment discontinuation after the start of treatment.

TRAEs were assessed using clinical judgment (related/not-related and degree of certainty using Gilead Grading Scale for Severity. Grade 1, 2, 3, and 4 AEs are considered mild, moderate, severe, and life-threatening, respectively).

8.1.2. Pivotal efficacy studies

See summary of these in Table 22 below.

Table 22: Summary of studies reviewed for safety data in Section 7

Study	Study Design	Treatment Regimen	N[a]	Subject Population	Location
Gilead-Sponsored Phase 2 and 3 Studies					
GS-US-337-0115 (ION-4)	Phase 3, open-label, multicenter	LDV/SOF for 12 weeks	335	Treatment-naive and treatment-experienced subjects with genotype 1 or 4 HCV infection who are coinfected with HIV-1	m5.3.5.1, GS-US-337-0115 (ION-4) Interim CSR
GS-US-337-0121 (SIRIUS)	Phase 2, randomized, double-blind, placebo-controlled, multicenter	LDV/SOF for 24 weeks or placebo for 12 weeks followed by LDV/SOF+RBV for 12 weeks	154[b]	Treatment-experienced cirrhotic subjects with genotype 1 HCV infection	m5.3.5.1, GS-US-337-0121 (SIRIUS) Final CSR
GS-US-337-0122 (ELECTRON-2; Cohort 1, Group 1 and Cohort 2, Groups 3,4, 5 and 6)	Phase 2, open-label, multicenter	LDV/SOF or LDV/SOF+RBV for 12 weeks	145	Treatment-experienced subjects with genotype 1 HCV infection who had failed a prior LDV/SOF+RBV, SOF+RBV, or SOF+GS-9699+RBV regimen and treatment-naive and treatment-experienced subjects with genotype 6 HCV infection	m5.3.5.1, GS-US-337-0122 (ELECTRON-2) Interim 2 CSR
GS-US-337-1118 (Group 1)	Phase 2, open-label, multicenter	LDV/SOF+RBV for 12 weeks	51	Subjects with genotype 1 HCV infection who failed a prior SOF+RBV+Peg-IFN regimen	m5.3.5.1, GS-US-337-1118 (Group 1) Interim CSR
GS-US-337-1468 (LEPTON; Cohort 2, Group 1)	Phase 2, open-label, multicenter	LDV/SOF for 12 weeks	26	Treatment-naive and treatment-experienced subjects with genotype 2 HCV infection	m5.3.5.1, GS-US-337-1468 (LEPTON; Cohort 2, Group 1)
GS-US-337-1119	Phase 2, open-label, multicenter	LDV/SOF for 12 weeks	85	Treatment-naive and treatment-experienced subjects with genotype 4 or 5 HCV infection	m5.3.5.1, GS-US-337-1119 Interim CSR
NIAID-Sponsored Phase 2 Study					
CO-US-337-0117[e] (SYNERGY; Groups D and E)	Phase 2, open-label	LDV/SOF for 12 weeks	35	Treatment-naive and treatment-experienced subjects with genotype 4 HCV infection and treatment-experienced subjects with genotype 1 HCV infection who had failed a prior SOF+RBV regimen	m5.3.5.4, CO-US-337-0117 (SYNERGY; Group D) Interim CSR and CO-US-337-0117 (SYNERGY; Group E) Interim CSR
Phase 1 Studies					
GS-US-337-1306	Phase 1 randomized, open-label, multiple-dose, single-center	LDV/SOF QD; Reyataz® QD or Prezista® QD +Norvir QD + Truvada® QD; LDV/SOF QD + Reyataz QD or Prezista QD +Norvir QD + Truvada QD[d,+]	96	Healthy subjects	m5.3.3.4, GS-US-337-1306 Final CSR
GS-US-337-1501	Phase 1 randomized, open-label, multiple-dose, single-center	LDV/SOF QD; Truvada QD +Tivicay® 50 mg QD; LDV/SOF QD + Truvada QD +Tivicay 50 mg QD[d]	30	Healthy subjects	m5.3.3.4, GS-US-337-1501 Final CSR
GS-US-337-1624	Phase 1 randomized, open-label, multiple-dose, single-center	LDV/SOF QD; E/C/F/TAF QD; and LDV/SOF+E/C/F/TAF QD[d]	30	Healthy subjects	m5.3.3.4, GS-US-337-1624 Final CSR

Study	Study Design	Treatment Regimen[a]	N[b]	Region	Subject Population	Location
GS-US-337-0123 (SOLAR-1)	Phase 2, randomized, open-label, multicenter study	LDV/SOF+RBV for 12 or 24 weeks	337	US	Treatment-naive and treatment-experienced adult subjects with chronic genotype 1 or 4 HCV infection, who were posttransplantation with compensated liver disease or with decompensated liver disease regardless of transplantation status	m5.3.5.1, GS-US-337-0123 (SOLAR-1) Interim 2 CSR and Interim 2 CSR Amendment
GS-US-337-0124 (SOLAR-2)	Phase 2, randomized, open-label, multicenter study	LDV/SOF+RBV for 12 or 24 weeks	333	Europe, Canada, Australia, New Zealand	Same as above	m5.3.5.1, GS-US-337-0124 (SOLAR-2) Interim CSR

8.2. Patient exposure

Some 987 subjects have received ≥ 1 dose of LDV/SOF FDC in the studies supporting this extension of indications application

- 335 in a Phase III study
- 496 in Phase II studies
- 156 in Phase I.

Patient exposure in the following specific populations was:

a. SIRIUS. Of 155 randomised, 155 (100.0%) received ≥ 1 dose and were included in the SAS

b. ION-4. 335 enrolled and received ≥ 1 dose of study drug

c. SOLAR-1 and SOLAR-2: of 673 randomised, 670 received ≥ 1 dose of LDV/SOF+RBV and were included in the SAS.

Mean exposure 11.6 to 12.2 weeks (12 week Group) and 21.3 to 24.1 weeks (24 Week Group).

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

Overall AE profile of LDV/SOF±RBV in the 342 (excludes SIRIUS, ION-4, SOLAR-1 and SOLAR-2) in other Phase II studies similar to the 1,952 in LDV/SOF Phase III Safety Population in the original (Category 1) application. Generally well tolerated, no safety signal identified in these studies.

SIRIUS

SIRIUS (Table 23) The LDV/SOF+RBV overall group had a higher % of subjects with any AE (96.1%, 74 subjects) and treatment related AE (88.3%, n = 68) during the overall treatment period versus the LDV/SOF 24 week group (87.2%, n = 68 and 69.2%, n = 54, respectively). No AEs leading to permanent discontinuation reported in the LDV/SOF 24 week group. One subject (1.3%) in the LDV/SOF+RBV 12 week group permanently discontinued all study drugs (placebo) due to AEs of bacterial arthritis and hepatic cirrhosis. The only AEs reported more frequently in first 12 weeks of LDV/SOF versus first 12 weeks of placebo were headache and fatigue. All headache and fatigue events were Grade 1 or 2.

Table 23: GS-US-337-0121 (SIRIUS): Adverse events: brief summary (SAS)

	LDV/SOF + Placebo RBV 24 Weeks		Placebo 12 Weeks Followed by LDV/SOF+RBV 12 Weeks		
Number (%) of Subjects Experiencing Any	Overall Period (N = 78)	LDV/SOF + Placebo RBV First 12 Weeks (N = 78)	Placebo First 12 Weeks (N = 77)	LDV/SOF +RBV Second 12 Weeks (N = 76)	Overall Period (N = 77)
AE	68 (87.2%)	66 (84.6%)	63 (81.8%)	66 (86.8%)	74 (96.1%)
Grade 3 or 4 AE	10 (12.8%)	2 (2.6%)	1 (1.3%)	5 (6.6%)	6 (7.8%)
Treatment-Related AE	54 (69.2%)	51 (65.4%)	46 (59.7%)	58 (76.3%)	68 (88.3%)
Grade 3 or 4 Treatment-Related AE	3 (3.8%)	1 (1.3%)	0	3 (3.9%)	3 (3.9%)
SAE	8 (10.3%)	3 (3.8%)	1 (1.3%)	3 (3.9%)	4 (5.2%)
Treatment-Related SAE	0	0	0	1 (1.3%)	1 (1.3%)
AE Leading to Permanent Discontinuation from Any Study Drug	0	0	1 (1.3%)	0	1 (1.3%)
AE Leading to Permanent Discontinuation from LDV/SOF or LDV/SOF Placebo	0	0	1 (1.3%)	0	1 (1.3%)
AE Leading to Modification or Interruption of Any Study Drug	2 (2.6%)	0	0	1 (1.3%)	1 (1.3%)
AE Leading to Modification or Interruption of LDV/SOF or LDV/SOF Placebo	1 (1.3%)	0	0	0	0
Death	0	0	0	0	0

Data were included to last dose date of any study drug + 30 days.
The denominator for percentages was based on the number of subjects in the Safety Analysis Set.

HCV/HIV Co-infection (ION-4)

HCV/HIV Co-infection (ION-4) (Table 24 and 25). Adverse event profile consistent with previous Phase III studies evaluating mono-infected subjects (ION-1,ION-2 and ION-3) and similar across different ARV regimens. The three most commonly reported AEs: headache (24.8%, n = 83), fatigue (21.2%, n = 71), diarrhoea (10.7%, n = 36). Most AEs were Grade 1 or 2. Some 4.2% experienced any Grade 3 or 4 AE. Headache and HCC (2 subjects each) were the only Grade 3 AEs reported in > 1 subject. The two with HCC were cirrhotic, baseline imaging negative. Only 1 subject had a Grade 4 AE of sepsis, reported as serious, considered not related.

Table 24: GS-US-337-0115 (ION-4): Overall summary of adverse events (SAS)

Number (%) of Subjects Experiencing Any	LDV/SOF 12 Weeks (N = 335)
AE	257 (76.7%)
Grade 3 or 4 AE	14 (4.2%)
Treatment-Related AE	153 (45.7%)
Grade 3 or 4 Treatment-Related AE	4 (1.2%)
SAE	8 (2.4%)
Treatment-Related SAE	1 (0.3%)
AE Leading to Permanent Discontinuation from LDV/SOF	0
AE Leading to Interruption of LDV/SOF	3 (0.9%)
Death	1 (0.3%)

Data were included to last dose date of study drug + 30 days.
The denominator for percentages was based on the number of subjects in the Safety Analysis Set.

Table 25: GS-US-337-0115 (ION-4): Adverse events reported for at least 5% of subjects (SAS)

Number (%) of Subjects Experiencing	LDV/SOF 12 Weeks (N = 335)
Any AE	257 (76.7%)
Headache	83 (24.8%)
Fatigue	71 (21.2%)
Diarrhoea	36 (10.7%)
Nausea	33 (9.9%)
Arthralgia	22 (6.6%)
Upper respiratory tract infection	18 (5.4%)

Adverse events were mapped according to MedDRA Version 17.1.
Subjects were counted once for each AE preferred term.
Data were included to last dose date of study drug + 30 days.

SOLAR-1 and SOLAR-2

SOLAR-1 and SOLAR-2: Most reported ≥ 1 AE (88.3% to 100.0%) and 1 TRAE (55.6% to 86.7%). Across all groups, the 3 most frequently reported AEs were fatigue (42.5%), anaemia (33.6%) and headache (27.3%). Analysis of AEs by pre transplantation versus post transplantation status demonstrated similar AE profile among decompensated subjects, irrespective of transplantation. Similar proportions of pre and post transplantation subjects experienced AEs, TRAEs, Grade 3 or 4 AEs, TR Grade 3 or 4 AEs, SAEs, AEs leading to discontinuation of LDV/SOF, and deaths. Those with CPT C decompensated cirrhosis had an overall worse AE profile than CPT B; likely due to greater degree of hepatic impairment.

Table 26: GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2): Overall summary of AEs (SAS)

	Liver Disease Status (Group)	Duration of Treatment	N	Number (%) of Subjects Experiencing Any				
				AE	Grade 3 or 4 AE	SAE	AE Leading to Discontinuation from LDV/SOF	Treatment-Emergent Death
Pretransplantation	CPT B Cirrhosis (Group 1)	12 Weeks	58	56 (96.6%)	4 (6.9%)	6 (10.3%)	1 (1.7%)	1 (1.7%)
		24 Weeks	57	55 (96.5%)	12 (21.1%)	16 (28.1%)	3 (5.3%)	2 (3.5%)
	CPT C Cirrhosis (Group 2)	12 Weeks	48	47 (97.9%)	15 (31.3%)	19 (39.6%)	1 (2.1%)	3 (6.3%)
		24 Weeks	52	51 (98.1%)	22 (42.3%)	20 (38.5%)	4 (7.7%)	4 (7.7%)
Posttransplantation	Stage F0-F3 Fibrosis (Group 3)	12 Weeks	107	106 (99.1%)	24 (22.4%)	15 (14.0%)	1 (0.9%)	1 (0.9%)
		24 Weeks	105	103 (98.1%)	25 (23.8%)	17 (16.2%)	2 (1.9%)	0
	CPT A Cirrhosis (Group 4)	12 Weeks	60	53 (88.3%)	11 (18.3%)	6 (10.0%)	1 (1.7%)	2 (3.3%)
		24 Weeks	58	55 (94.8%)	16 (27.6%)	11 (19.0%)	1 (1.7%)	1 (1.7%)
	CPT B Cirrhosis (Group 5)	12 Weeks	48	46 (95.8%)	10 (20.8%)	10 (20.8%)	2 (4.2%)	2 (4.2%)
		24 Weeks	49	46 (93.9%)	17 (34.7%)	17 (34.7%)	3 (6.1%)	2 (4.1%)
	CPT C Cirrhosis (Group 6)	12 Weeks	8	8 (100.0%)	2 (25.0%)	2 (25.0%)	0	1 (12.5%)
		24 Weeks	9	9 (100.0%)	4 (44.4%)	5 (55.6%)	1 (11.1%)	1 (11.1%)
	FCH (Group 7)	12 Weeks	7	7 (100.0%)	1 (14.3%)	3 (42.9%)	0	0
		24 Weeks	4	4 (100.0%)	1 (25.0%)	2 (50.0%)	0	0

8.3.2. AE of interest

8.3.2.1. Cardiac

5 experienced AEs in the cardiac failure/cardiomyopathy category. None considered related.

- Arrhythmia: 18 experienced AEs of cardiac arrhythmia, including bradycardia. Of these, 6 experienced only AEs of atrial fibrillation or atrial/cardiac flutter.
- Beta-blocker and calcium-channel blocker use: Of those receiving a beta blocker during the first 2 weeks of LDV/SOF+RBV, a total of 15 subjects experienced any AE of interest. For 12 of these 15 subjects, the AE of interest was either syncope or dizziness, all of which were Grade 1 (n = 11) or Grade 2 (n = 1) in severity. A review of the heart rates of each of these 12 showed no clinically meaningful changes. No subjects receiving a calcium-channel blocker experienced any AEs within these categories.

8.3.2.2. Dermatological events

Two post-transplantation subjects experienced Grade 3 AEs in this category: skin ulcer and pruritus, respectively. Neither event considered related to study drug.

8.3.2.3. Pancytopenia

Two subjects experienced AEs of pancytopenia during LDV/SOF+RBV treatment.

8.3.2.4. Psychiatric events relevant to suicidal ideation or attempt

Nil.

8.3.2.5. Pancreatitis events

One subject experienced an AE of pancreatitis during LDV/SOF+RBV.

8.3.2.6. Rhabdomyolysis/myopathy events

Nil.

8.3.3. Treatment related adverse events (adverse drug reactions)

8.3.3.1. Pivotal studies

Of the 952 subjects who received LDV/SOF across the Gilead sponsored Phase II and III studies in this supplemental marketing application, 1 treatment emergent death was reported in ION-4. Table 27 below presents a summary of the SAEs. Overall, SAEs were rare, irrespective of the patient group, and were generally considered unrelated to treatment. No pattern of SAEs observed.

SIRIUS

During the overall treatment period, RBV containing treatment group had a higher % of subjects with TRAEs versus RBV free treatment group (LDV/SOF+RBV overall group, 88.3%, n = 68; LDV/SOF 24 week group, 69.2%, n = 54). When comparing the three 12 week treatment periods, there was a higher % of subjects with TRAEs during treatment with LDV/SOF+RBV (76.3%, n = 58) versus LDV/SOF (65.4%, n = 51) and placebo (59.7%, 46 subjects). The only TRAEs reported more frequently (> 10%) in first 12 weeks of LDV/SOF treatment versus first 12 weeks of placebo were headache and fatigue.

ION-4

Table 27: GS-US-337-0115 (ION-4): TRAE Reported for at Least 5% of Subjects (SAS)

Number (%) of Subjects Experiencing	LDV/SOF 12 Weeks (N = 335)
Any Treatment-Related Adverse Event	153 (45.7%)
Headache	66 (19.7%)
Fatigue	56 (16.7%)
Nausea	23 (6.9%)
Diarrhoea	22 (6.6%)

Adverse events were mapped according to MedDRA Version 17.1.
Subjects were counted once for each system organ class, and once for each AE preferred term.
AEs were related to treatment if Related to Study Treatment = 'Related' on the AE CRF.
Data were included to last dose date of study drug + 30 days.

SOLAR-1 and SOLAR-2

Table 28: GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2): Overall summary of TRAEs (SAS)

	Liver Disease Status (Group)	Duration of Treatment	N	Number (%) of Subjects Experiencing Any Treatment-Related AE	Grade 3 or 4 AE	SAE
Pretransplantation	CPT B Cirrhosis (Group 1)	12 Weeks	58	39 (67.2%)	1 (1.7%)	1 (1.7%)
		24 Weeks	57	46 (80.7%)	4 (7.0%)	1 (1.8%)
	CPT C Cirrhosis (Group 2)	12 Weeks	48	33 (68.8%)	4 (8.3%)	2 (4.2%)
		24 Weeks	52	38 (73.1%)	9 (17.3%)	1 (1.9%)
Posttransplantation	Stage F0-F3 Fibrosis (Group 3)	12 Weeks	107	89 (83.2%)	15 (14.0%)	2 (1.9%)
		24 Weeks	105	91 (86.7%)	17 (16.2%)	2 (1.9%)
	CPT A Cirrhosis (Group 4)	12 Weeks	60	45 (75.0%)	7 (11.7%)	2 (3.3%)
		24 Weeks	58	45 (77.6%)	8 (13.8%)	4 (6.9%)
	CPT B Cirrhosis (Group 5)	12 Weeks	48	34 (70.8%)	3 (6.3%)	0
		24 Weeks	49	39 (79.6%)	9 (18.4%)	4 (8.2%)
	CPT C Cirrhosis (Group 6)	12 Weeks	8	5 (62.5%)	1 (12.5%)	0
		24 Weeks	9	5 (55.6%)	1 (11.1%)	0
	FCH (Group 7)	12 Weeks	7	5 (71.4%)	1 (14.3%)	0
		24 Weeks	4	3 (75.0%)	0	1 (25.0%)

Data were included to last dose date of any study drug + 30 days.
The denominator for percentages was based on the number of subjects in the Safety Analysis Set.
Adverse events were related to treatment if "Related to Study Treatment" = 'Yes' on the AE CRF.

8.3.4. Deaths and other serious adverse events

8.3.4.1. Pivotal studies

Study GS-US-337-0122 (ELECTRON-2)

Study GS-US-337-0122 (ELECTRON-2; Cohort 1, Group 1 and Cohort 2, Groups 3, 4, 5, and 6): No deaths; 5 subjects experienced any Grade 3 or 4 AE, 6 subjects any SAE. Two subjects experienced Grade 3 AEs of abdominal pain considered serious and study drug related. No other Grade 3 or 4 AEs or SAEs considered related.

Study GS-US-337-1118

Study GS-US-337-1118 (Group 1): No deaths. Grade 3 and 4 AEs and SAE were rare: 3 subjects experienced any Grade 3 or 4 AE and 2 experienced any SAE. One subject experienced Grade 3

AE of anaemia and chest pain considered serious and study drug related. No other Grade 3 or 4 AEs or SAEs considered related. One subject with AE (Grade 3, serious) experienced a worsening of bipolar disorder leading to permanent cessation of LDV/SOF.

Study GS-US-337-1119

Study GS-US-337-1119: No deaths or AEs leading to permanent discontinuation of LDV/SOF reported. One subject experienced Grade 3 AE of depression that was considered serious and not related to study treatment. No other Grade 3 or 4 AEs or SAEs reported.

Study GS-US-337-1468 (LEPTON Cohort 2, Group 1)

Study GS-US-337-1468 (LEPTON; Cohort 2, Group 1): No deaths or AEs leading to permanent discontinuation of LDV/SOF. One subject experienced a Grade 3 AE of gastro-oesophageal reflux considered serious and not related to study treatment. No other Grade 3 or 4 AEs or SAEs.

Table 29: Summary of SAE in Subjects with HCV Infection Who Received LDV/SOF from Gilead sponsored Phase II and III Studies Included in this application

	Treatment Regimen	SAEs % (n/N)	Treatment-Related SAEs % (n/N)	SAE Preferred Terms in > 1 Subject
GS-US-337-0121 (SIRIUS)[a]	LDV/SOF 24 weeks	10.3% (8/78)	0	None
	Placebo 12 weeks followed by LDV/SOF+RBV 12 weeks	3.9% (3/77)	1.3% (1/77)	None
GS-US-337-0115 (ION-4)	LDV/SOF 12 weeks	2.4% (8/335)	0.3% (1/335)	Hepatocellular carcinoma, portal vein thrombosis
GS-US-337-0122 (ELECTRON-2; Cohort 1, Group 1 and Cohort 2, Groups 3, 4, 5, and 6)	LDV/SOF 12 weeks	10.0% (5/50)	4.0% (2/50)	None
	LDV/SOF+RBV 12 weeks	1.1% (1/95)	0	None
GS-US-337-1118	LDV/SOF+RBV 12 weeks	3.9% (2/51)	2.0% (1/51)	None
GS-US-337-1119	LDV/SOF 24 weeks	1.2% (1/85)	0	None
GS-US-337-1468 (LEPTON; Cohort 2, Group 1)	LDV/SOF 24 weeks	3.8% (1/26)	0	None

a The subject from Study GS-US-337-0121 (SIRIUS) who had SAEs while on placebo treatment was excluded from this summary.
Two SAEs (influenza A infection and coronary artery disease) were reported in the NIAID-sponsored Study CO-US-337-0117 (SYNERGY). Both events were considered not related to study drug

Treatment experienced with cirrhosis (SIRIUS)

SAEs rare in both treatment groups during the overall treatment period: LDV/SOF 24 week group, 10.3%, 8 subjects; LDV/SOF+RBV overall group, 5.2%, 4 subjects. No trends in SAE type or onset time. All SAEs considered unrelated to study drug with the exception of anaemia reported in 1 subject on Day 111 during treatment with LDV/SOF+RBV. Two SAEs reported in 1 subject in the LDV/SOF+RBV group led to treatment discontinuation. Subject [information redacted] had a Grade 2 SAE of bacterial arthritis on Day 2 and a Grade 4 SAE of hepatic cirrhosis on Day 30 during placebo treatment. The subject discontinued study treatment on Day 32 and received an emergency liver transplantation.

HCV/HIV Co-infection (ION-4)

One subject died. This 59 year old male subject, on a stable regimen of RAL+FTC+TDF died on Post treatment Day 16, after discontinuing treatment early on Day 41. This subject, with confirmed IVDU, developed Staphylococcus aureus endocarditis and sepsis on Day 41 of

treatment and eventually died; the event was assessed as not related to study treatment. Overall, SAEs were rare; 8 subjects (2.4%) experienced 14 SAEs. The only SAEs reported in > 1 subject were HCC and portal vein thrombosis. All events considered not related to study drug. A Grade 2 AE of diarrhoea was the only treatment related SAE. No subjects permanently discontinued from LDV/SOF due to an AE.

SOLAR-1 and SOLAR-2 (pooled data)

SAEs occurred more frequently (22.2%; 149 of 670 subjects) in this subject population compared with the RBV-containing groups within previous Phase III studies (1.9%) (ION-1, ION-2 and ION-3). Notably, however, majority of SAEs were not treatment related; only 20 of 670 subjects (3.0%) experienced treatment related SAEs. Few subjects (3.0%; 20 of 670) experienced AEs leading to LDV/SOF discontinuation. 30 deaths occurred, 10 died > 30 days after the EOT (= non treatment emergent); 20 deaths were treatment emergent (that is, within 30 days Post treatment). Majority of these deaths associated with clinical progression of end-stage liver disease and all with treatment emergent deaths had decompensated cirrhosis, except for 4 subjects: 3 with compensated cirrhosis and 1 with F0-F3 fibrosis. Cause of death: progressive multifocal leuko-encephalitis, MI, infection (food poisoning/pneumonia), graft rejection, respectively.

Liver transplantation

17 liver transplantations occurred. Six underwent transplantation > 30 days after the end of treatment. Treatment emergent liver transplantations were reviewed as part of the overall review of potential cases of DILI. None of the treatment emergent liver transplantations were considered due to LDV/SOF induced liver injury. 10 of these 11 achieved post-transplant virologic response at 12 weeks post transplantation. The 1 subject who did not achieve pTVR died 15 days after receiving a liver transplantation.

8.3.5. Discontinuation due to adverse events

8.3.5.1. Pivotal studies

Two of 952 subjects experienced an AE leading to permanent discontinuation of LDV/SOF.

SIRIUS

Two SAEs in Subject [information redacted] (see above) in the LDV/SOF+RBV group led to treatment discontinuation.

HCV/HIV Co-infection (ION-4)

None.

SOLAR-1 and SOLAR -2

Of the 20 who experienced AEs resulting in treatment discontinuation, 5 were post transplantation with stage F0-F3 fibrosis or CPT A cirrhosis (Groups 3 and 4); the remaining 15 had decompensated cirrhosis regardless of transplantation status. The only AEs leading to discontinuation that occurred in > 1 subject overall were sepsis, HCC, acute renal failure, and dyspnoea (2 subjects each).

8.4. Laboratory tests

The clinical laboratory safety profile for the 342 subjects from other Phase II studies, including subjects with non GT 1 HCV who received LDV/SOF±RBV for 12 weeks and subjects who received re-treatment with LDV/SOF±RBV for 12 weeks, was similar to the clinical laboratory safety profile of the 1,952 subjects in the LDV/SOF Phase III Safety Population in the original Category 1 submission. For these subjects, no additional safety signals identified. The clinical

laboratory safety profile for the 156 in the Phase I studies showed LDV/SOF was safe and well tolerated.

8.4.1. Liver function and other chemistries

8.4.1.1. Pivotal studies

Treatment experienced with cirrhosis (SIRIUS)

All Grade 3 or 4 chemistry laboratory abnormalities were observed in < 10% of subjects. As expected with untreated HCV, 9.1% and 7.8% receiving placebo experienced Grade 3 or 4 ALT/AST elevations, respectively. Grade 3 increased serum glucose reported for 6 (7.7%) during treatment with LDV/SOF and 5 (6.5%) during placebo. All subjects with Grade 3 increased serum glucose had diabetes or increased baseline serum glucose/HbA1c. Grade 3 or 4 increased lipase reported for 7 9.0%) during treatment with LDV/SOF and 3 (3.9%, 1 subject during placebo and 2 during LDV/SOF+RBV). All lipase elevations were asymptomatic. Grade 3 or 4 increased total bilirubin observed in 3 (3.9%, 1 placebo; 2 LDV/SOF+RBV).

HCV/HIV Co-infection (ION-4)

Grade 3 or 4 laboratory abnormalities were rare across all chemistry parameters (< 4.0% of subjects for any chemistry parameter). Grade 3 or 4 increased lipase observed in 13 (3.9%). Grade 3 or 4 increased creatine kinase observed in 5 (1.5%); transient and resolved by the post treatment Week 4 visit, confirmed due to excessive exercise, except for 1 who experienced rhabdomyolysis after using cocaine.

SOLAR-1 and SOLAR -2 (pooled data)

Grade 3 or 4 chemistry abnormalities were generally infrequent, except increased total bilirubin and increased glucose. The former consistent with advanced liver disease and RBV haemolysis. Hyperglycaemia only in known diabetics or impaired glucose tolerance. At baseline 16 had a Grade 3 or 4 increased lipase, none had an associated AE of pancreatitis.

8.4.1.2. Hepatic safety of LDV/SOF+RBV: independent adjudication committee (IAC) review

A review of all cases meeting the revised criteria for identifying DILI in advanced liver disease, as well as a review of all AE cases meeting the criteria (for example, deaths, transplantations, serious hepatic events), was performed by the IAC. In total, 82 cases in 61 subjects reviewed. After excluding a subject whose events were confounded by co-administration of lamotrigine, only a single case of clinical concern was identified for which DILI could not be excluded, a marked increase in direct bilirubin at Week 20. No deaths or transplantation events were the result of DILI.

Adjustment of immunosuppression in post-transplant patients

7.0%; 24 of 341 subjects needed adjustment in frequency of dosing of immunosuppressive agents as hepatic function improved, likely as the result of the suppression of HCV viraemia.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

HCV/HIV Co-infection (ION-4)

A specific evaluation of renal events/laboratory abnormalities was performed.

Overall, 11 (3.3%) reported an AE under the Renal/Urinary Disorders system organ class. In 10 of the 11, these AEs were Grade 1 or 2 and not considered typical of TFV induced renal toxicity. No Grade 3 or 4 serum creatinine laboratory abnormalities, 11 subjects (3.3%) had a change from baseline in serum creatinine ≥ 0.4 mg/dL. With the exception of 2 cases, the remaining 9 were not deemed clinically concerning. Subject [information redacted] a 47 year old male, with

baseline serum creatinine of 1.42 mg/dL and 1+ proteinuria, developed increasing serum creatinine 1.88 mg/dL (Week 10) and confirmed 2+ proteinuria during treatment. Study treatment completed without modification of ARVs; Subject [information redacted] a 55 year old male, had diabetes mellitus type 1 since 1965, hypertension, on Atripla since 2007. Following the Week 4 retest laboratory results, showed serum creatinine 1.88 mg/dL, TDF discontinued and regimen was changed to EFV+RAL + renally dose adjusted FTC. Subject completed treatment with close follow-up.

Urine Renal Biomarkers: Median urine retinol binding protein/serum creatinine ratio, urine beta-2 microglobulin/serum creatinine ratio did not change significantly during treatment.

SOLAR-1 and SOLAR -2 (pooled data)

Minor, non-clinically relevant changes in mean and median serum creatinine during treatment through Post treatment Week 4; no trend suggesting a longer treatment duration was associated with greater increases in serum creatinine. Across all groups in the pooled SAS, 34.0% of subjects had an eGFRCG < 60 mL/min. Since RBV is renally eliminated, RBV exposures in subjects with an eGFRCG < 60 mL/min may have been increased. Among the post-transplantation subjects with stage F0-F3 fibrosis and CPT A cirrhosis, 141 of 330 subjects (42.7%) had an eGFRCG < 60 mL/min. The findings were as follows:

- % with any AE (97.9% versus 94.7%), SAE (15.6% versus 14.3%), and AEs leading to discontinuation of LDV/SOF (1.4% versus 1.6%) similar for eGFRCG < 60 mL/min and ≥ 60 mL/min, respectively.
- Rates of Grade 3 or 4 AEs (31.2% versus 16.9%) higher for those with eGFRCG < 60 mL/min versus ≥ 60 mL/min, respectively, largely due to more anaemia in eGFRCG < 60 mL/min (56.7% versus 29.1%).
- The % who experienced Grade 3 and 4 laboratory abnormalities higher in those with an eGFRCG < 60 mL/min (70.2% versus 57.1%).

Among the pre-transplantation and post transplantation subjects with CPT B or CPT C cirrhosis, 85 of 329 subjects (25.8%) had an eGFRCG < 60 mL/min. The findings were as follows:

- % of subjects with any AE (96.5% versus 96.7%) and AEs leading to discontinuation of LDV/SOF (7.1% vs 3.7%) similar for those with eGFRCG < 60 mL/min and ≥ 60 mL/min, respectively.
- Rates of Grade 3 or 4 AEs (32.9% versus 23.8%) and SAEs (35.3% versus 26.6%) were higher with eGFRCG < 60 mL/min versus eGFRCG ≥ 60 mL/min, respectively. Any Grade anaemia reported at an increased rate in subjects with an eGFRCG < 60 mL/min (42.4% versus 20.5%).

8.4.3. Haematology

8.4.3.1. Pivotal studies

SIRIUS

Most common Grade 3 haematology laboratory abnormality was decreased Hb. All Grade 3 decreases in Hb observed in LDV/SOF+RBV group (5.2%). No subjects in the RBV-free group had Grade 3 decreased Hb. No clinically meaningful changes in white cells, neutrophils, lymphocytes, reticulocytes, platelets.

ION-4

No clinically meaningful changes from baseline for reticulocytes, white blood cells, neutrophils, lymphocytes, platelets were observed across ARV regimens.

No Grade 4 haematology laboratory abnormality; 2 subjects had a Grade 3 haematology laboratory abnormalities (decreased Hb and decreased neutrophils, 1 subject each).

SOLAR-1 and SOLAR -2

Most commonly observed Grade 3 or 4 abnormalities were decreased Hb, lymphocytes, and platelet counts. Decreased Hb was most pronounced in post-transplantation subjects with stage F0-F3 fibrosis (Group 3), who had received the highest dose of RBV and had the greatest renal insufficiency.

For all subjects (Groups 1 to 7) no clinically meaningful changes from baseline in the mean or median lymphocyte, platelet, or reticulocyte counts observed during LDV/SOF+RBV treatment for 12 or 24 weeks, regardless of liver disease or transplantation status. Overall, 36 of 670 subjects (5.4%) received a blood transfusion and 55 of 670 subjects (8.2%) received medication to treat anaemia.

A substantial percentage of subjects required a reduction of RBV dose or discontinuation of RBV. Among subjects with decompensated cirrhosis (CPT B or CPT C) regardless of transplantation status (Groups 1, 2, 5, and 6), who began treatment with a starting daily dose of 600 mg of RBV, 42 of 162 subjects (25.9%) in the 12 week group and 58 of 167 (34.7%) in the 24 week group required a RBV dose reduction for ≥ 3 consecutive days. RBV was prematurely discontinued for 22 subjects in the 12 week group and 37 subjects in the 24 week group.

Among post-transplantation subjects with stage F0-F3 fibrosis or CPT A cirrhosis (Groups 3 and 4), who began RBV at 1000 to 1200 mg/day, 84 of 167 subjects (50.3%) in the 12 week group and 88 of 163 (54.0%) in the 24 week group required a RBV dose reduction for ≥ 3 consecutive days. RBV was prematurely discontinued for 14 subjects in the 12 week group and 24 subjects in the 24 week group.

Among post-transplantation subjects with FCH (Group 7), who began treatment with a starting daily dose of 1000 to 1200 mg of RBV, 9 of 11 subjects (5 in the 12 week group and 4 in the 24 week group) required a RBV dose reduction for ≥ 3 consecutive days and 3 of the 11 subjects (1 in the 12 week group and 2 in the 24 week group) prematurely discontinued RBV.

Table 30: GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2): Post baseline Hb Levels < 8.5 and < 10.0 g/dL (SAS)

	Liver Disease Status (Group)	Duration of Treatment	Initial RBV Dose[a]	N	Hemoglobin Level, n (%)	
					< 8.5 g/dL	< 10.0 g/dL
Pretransplantation	CPT B Cirrhosis (Group 1)	12 Weeks	600 mg	58	1 (1.7%)	6 (10.3%)
		24 Weeks		57	4 (7.0%)	12 (21.1%)
	CPT C Cirrhosis (Group 2)	12 Weeks	600 mg	48	6 (12.5%)	19 (39.6%)
		24 Weeks		52	5 (9.6%)	17 (32.7%)
Posttransplantation	Stage F0-F3 Fibrosis (Group 3)	12 Weeks	1000 or 1200 mg	107	20 (18.7%)	52 (48.6%)
		24 Weeks		105	12 (11.4%)	44 (41.9%)
	CPT A Cirrhosis (Group 4)	12 Weeks	1000 or 1200 mg	60	10 (16.7%)	24 (40.0%)
		24 Weeks		58	9 (15.5%)	27 (46.6%)
	CPT B Cirrhosis (Group 5)	12 Weeks	600 mg	47	5 (10.6%)	17 (36.2%)
		24 Weeks		49	10 (20.4%)	30 (61.2%)
	CPT C Cirrhosis (Group 6)	12 Weeks	600 mg	8	1 (12.5%)	6 (75.0%)
		24 Weeks		9	1 (11.1%)	5 (55.6%)
	FCH (Group 7)	12 Weeks	1000 or 1200 mg	7	1 (14.3%)	2 (28.6%)
		24 Weeks		4	2 (50.0%)	2 (50.0%)

a For posttransplantation subjects with stage F0-F3 fibrosis, compensated (CPT A) cirrhosis, or FCH (Groups 3, 4, and 7), subjects received RBV 1000 or 1200 mg (1000 mg for subjects < 75 kg or 1200 mg for ≥ 75 kg) divided BID. For subjects with decompensated (CPT B or CPT C) cirrhosis regardless of transplantation status (Groups 1, 2, 5, and 6), subjects received RBV 600 mg/day divided BID.

Data are included to last dose date of any study drug + 30 days.

8.4.3.2. Immunological and HIV markers in ION-4

98.8% had HIV RNA < 50 copies/mL, with similar proportions across ARV regimens. No subjects had HIV rebound during study. No clinically meaningful changes from baseline in CD4 count observed.

8.4.4. Genotypic and/or phenotypic resistance

See Section 7 for the integrated summaries.

8.4.5. ECG and vital signs

8.4.5.1. Pivotal studies

Consistent with the observations in the LDV/SOF Phase III Safety Population in the original Category 1 application, no safety signal was identified in any of the Gilead sponsored Phase II and III studies in this Category 1 application with respect to vital signs, physical findings, or ECGs.

8.5. Post-marketing experience

A few cases of symptomatic bradycardia, including 1 fatal cardiac arrest and 1 requiring pacemaker insertion, have been reported in patients taking amiodarone and LDV/SOF. Bradycardia was observed within hours to days of starting LDV/SOF. Co-administration of amiodarone with LDV/SOF is not recommended. TGA was notified and updated LDV/SOF labelling submitted on 23 Mar 2015.

8.6. Safety issues with the potential for major regulatory impact

None identified for liver toxicity, haematological toxicity, serious skin reactions, cardiovascular safety and unwanted immunological events

8.6.1. Safety in special populations

8.6.1.1. HCV/HIV-1 co-infection; Cirrhotics; Liver transplant

All discussed above.

8.6.1.2. HBV/HCV co-infection

Eight patients only enrolled (ELECTRON-2), no safety concerns identified with the caveat that numbers were very small, no clinical hepatitis flares.

8.6.1.3. Age

Pooled age analysis for this application only performed in SOLAR-1/2:

17.3% of subjects were ≥ 65 years of age. Among the post-transplantation subjects with stage F0-F3 fibrosis and CPT A cirrhosis, 67 of 330 subjects (20.3%) were ≥ 65 years of age. Age appeared to have no clinically relevant effect on the incidence of any abnormality observed in these subjects.

In summary:

- % with any AE (95.5% versus 96.2%), Grade 3 or 4 AE (20.9% versus 23.6%), SAE (19.4% versus 13.7%), AEs leading to LDV/SOF discontinuation (3.0% versus 1.1%) similar in ≥ 65 years and < 65 years, respectively.
- No notable differences in the reported AEs of any Grade between those aged ≥ 65 years and < 65 years.

- % experiencing Grade 3 and 4 laboratory abnormalities similar for ≥ 65 years and < 65 years (59.7% versus 63.5%).

Among the pre transplantation and post transplantation subjects with CPT B or CPT C cirrhosis, 48 of 329 subjects (14.6%) were ≥ 65 years of age. The findings were as follows:

- % with any AE (100.0% vs 96.1%) similar for ≥ 65 years and < 65 years, respectively. However, rates of Grade 3 or 4 AEs (35.4% versus 24.6%), SAEs (37.5% versus 27.4%), and AEs leading to discontinuation of LDV/SOF (10.4% versus 3.6%) were higher for subjects aged ≥ 65 years.
- In contrast, the only differences in AEs of any Grade were observed for fatigue (41.3% versus 31.3%) and headache (29.2% versus 14.6%), majority of which were Grade 1 or 2 in severity and were reported at increased rates in subjects aged < 65 years.
- % experiencing Grade 3 and 4 laboratory abnormalities similar for ≥ 65 years and < 65 years (64.6 versus 69.6%).

8.7. Safety related to drug-drug interactions and other interactions

LDV/SOF cannot be co-administered with rifampicin.

The interactions between LDV/SOF and HIV ARV regimens (ritonavir boosted ATV or DRV plus FTC/TDF, DTG plus FTC/TDF and E/C/F/TAF have been evaluated. No dose adjustment is necessary for any of these drugs or regimens.

Higher TFV exposures observed following administration of LDV/SOF with TDF-based ARV regimens; suggests closer monitoring for TFV-associated AEs is required.

8.8. Evaluator's overall conclusions on clinical safety

The data presented in this application demonstrate that Harvoni has an overall highly acceptable safety profile.

This application provides clinical trial (many open label and several un-randomised, single arm) data in a number of different populations that is treatment experienced subjects with cirrhosis, HCV/HIV co-infection, prior treatment failures with a SOF containing regimen, and chronic HCV infection with Genotypes other than GT-1 (Harvoni is already approved in GT-1 CHC).

The safety profile of LDV/SOF for 12 or 24 weeks and LDV/SOF+RBV for 12 weeks was consistent with that observed for LDV/SOF±RBV in previous Phase III studies (Studies GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], and GS-US-337-0108.

Overall, the safety profile of LDV/SOF+RBV treatment was similar to the expected safety profile of RBV. The safety profile of LDV/SOF for 12 weeks in HCV/HIV-1 co-infected subjects stable on ARVs and with suppressed plasma HIV RNA, was consistent with the safety profile of LDV/SOF in the HCV mono-infected population. There was no negative impact on surrogate markers of ARV efficacy that is HIV viral load and CD4 T-cell count during treatment with Harvoni.

The elevated levels of TFV with TDF-containing regimens are of uncertain significance, especially as co-administration of these drugs will be relatively short. However, this DDI merits closer renal monitoring especially in patients with some degree of renal impairment and probably some attention to bone health (see summary comments).

Another special population with data presented in this application for extension of indications are Liver Transplant (for HCV) Recipients where HCV recrudescence is universal and associated with poorer graft and patient survival compared with non-HCV related liver transplants. SOLAR-1 and SOLAR-2 evaluated LDV/SOF+RBV for 12 or 24 weeks across the spectrum of patients who are pre and post-liver transplantation including those without cirrhosis, and those

with compensated and decompensated cirrhosis. This is a varying sick population of patients with overall high morbidity and mortality especially those with decompensated cirrhosis. Other all oral regimens are available in some countries but AbbVie's Viekira Pak ("3D" regimen), whilst of proven efficacy and well tolerated, including in cirrhotic patients with GT-1, contains ritonavir as a PK booster for the component DAAs. Unfortunately, ritonavir is a drug fraught with the potential for multiple DDI. This might be challenging in some of these patients with end-stage liver disease who are frequently on multiple medications with the potential for DDI (for example beta-blockers). That said, Harvoni is not free of DDI and cannot be co-administered with potent P-gp inducers like rifampicin.

As discussed in Section 8, anaemia was the predominant treatment related safety finding in the post-transplant subjects, which is associated with RBV and likely exacerbated by the relatively low eGFRCG in some of these subjects. Most patients were successfully managed with dose reduction, and haemoglobin recovered quickly after end of treatment. Paradoxically, and reflecting efficacy against HCV, dose adjustment (frequency of dosing) for some immunosuppressants as liver function improved.

8.8.1. Decompensated cirrhosis

Consistent with the underlying severity of the liver disease in these subjects AEs, including SAEs, occurred more frequently compared with the rates observed in subjects in previous Phase III studies that excluded decompensated subjects. However, the AEs were consistent with decompensated liver disease or the known toxicity profile of RBV, including anaemia. Decreases in haemoglobin to < 10.0 g/dL and < 8.5 g/dL during treatment occurred in just over 1/3 and 1/10 of subjects, respectively. Most episodes were successfully managed with RBV dose reduction, although just fewer than 20% had to discontinue RBV. Reassuringly, haemoglobin declines reversed rapidly after completion of treatment.

The Independent Adjudication Committee after formal review of hepatic safety including the impact of longer exposure to Harvoni, determined that LDV/SOF+RBV was safe and well tolerated, with a low potential for causing DILI. However, the IAC and sponsor propose that for patients treated with LDV/SOF+RBV, monthly liver tests, including direct bilirubin, be performed. The latter would align with standard-of-care monitoring for this patient population.

In summary, the data provided in this extension shows Harvoni is safe (and effective) in the populations providing clinical trial data included in this extension application without any new and/or concerning safety signal.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Harvoni in the extended usage are:

- High rates of SVR12 that is cure in all genotypes, in patients who had previously failed a SOF containing regimen (GT-1) and in those with severe compensated and decompensated liver disease with/without liver transplant and (the evaluator) agrees many of these scenarios are areas of 'unmet medical need'
- Safe and well tolerated, no new safety signal of concern revealed
- Low risk for drug-drug interactions
- Safe and well tolerated at the proposed therapeutic dose
- Much of the data suggests treatment without ribavirin can be used, a great advantage in terms of certain populations where RBV is absolutely/relatively contraindicated.

9.2. First round assessment of risks

The risks of Harvoni in the proposed usage are:

- It will not protect against re-infection (same for all the DAA, and not unique to this FDC), and this is not clearly stated in the PI or CMI
- This is not a risk per se but the evaluator noted that there were frequent transcription errors in this application that is "*LDV/SOF was administered to all subjects orally at a dose of 400 mg/90 mg (1 tablet once daily)*". This is not correct; it should read LDV/SOF (90/400 mg). Please ensure consistency.
- There is still a relative paucity of data from those with Genotype 4, although the data provided does not suggest that the SVR12 or safety profile differs substantially from GT-1
- Lower SVR12 for GT-3 when not partnered with RBV and given for short course (12 weeks) true for both treatment naïve and treatment experienced (refer to ELECTRON-2)
- Very little data on non-GT-1 cirrhotics, and no data on non GT-1 pre and post liver transplant subjects
- Paucity of data from populations other than those of White ethnicity
- Relative paucity of women enrolled in these studies, all studies are majority male (especially true of ION-4 the study in HIV/HCV co-infection), this may reflect the demographics of HCV in some countries or may reflect the almost universal difficulties in enrolling women into studies (a similar issue is seen in many of the licensing studies for ARVs) or enrolment restrictions placed around pregnancy/breast-feeding
- Paucity of data presented on retreatment of genotypes other than GT-1 in patients previously treated with SOF-containing regimens; further data from LEPTON and ELECTRON-2 may be informative
- Paucity of data from patients with cirrhosis CPT C category
- High rates of SVR12 in most subjects irrespective of baseline RAPs and RAVs. The predictors of virological failure are not currently completely understood; some trends in some settings (related to high BMI for example). Even though suggested otherwise in this application, clinicians are likely to conduct expensive and largely pointless genotypic (and even phenotypic) resistance tests before/after use of Harvoni.

9.3. First round assessment of benefit-risk balance

Favourable.

10. First round recommendation regarding authorisation

Recommend authorisation with one caveat. The evaluator did not think there is enough data (yet) to recommend the use of Harvoni for retreatment of patients with HCV genotypes other than GT1 and who have been previously treated with sofosbuvir. The evaluator had particular concerns with respect to Genotype 3.

11. Clinical questions

There were no clinical questions.

12. Second round evaluation of clinical data submitted in response to questions

Gilead Sciences have provided responses/clarifications to those raised in the first round clinical evaluation of this request to extend the indications for Harvoni.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Harvoni are unchanged from those identified in the first round assessment of benefits.

13.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Harvoni are unchanged from those identified in first round assessment of risks.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Harvoni, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

Recommend authorisation. The evaluator no longer had any caveats as the evaluator did following the Round 1 evaluation. This is because Gilead Sciences have now clarified their intentions with respect to the evaluator's particular concerns regarding retreatment of patients with HCV genotypes other than Genotype 1, who have received sofosbuvir previously. The evaluator's concerns extended particularly to Genotype 3. The reasons the evaluator's concerns have been allayed is that Gilead in their response dated 24-May-2016 have provided the following clarifications:

"*Gilead wishes to clarify that it was never the intent to recommend use of Harvoni with ribavirin for the treatment of treatment experienced patients with Genotype 3. As stated (in the submission), the totality of evidence suggests that LDV/SOF+RBV for 12 weeks has comparable efficacy with SOF+RBV for 24 weeks. Nevertheless, Gilead acknowledges that in treatment experienced, genotype 3 patients, the duration of LDV/SOF+RBV for 12 weeks is not optimal. Gilead, therefore, proposes that LDV/SOF+RBV for 12 weeks be indicated for use only in patients with Genotype 3 HCV infection who are treatment-naïve.*

The proposed PI has been revised to clarify that treatment with Harvoni and ribavirin is recommended for Genotype 3 patients that are treatment naïve only. This revision will remove the ambiguity around the product's use in previously treated Genotype 3 patients, including patients previously treated with sofosbuvir. The PI has been modified.

15. References

Backus LI, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011; 9: 509-516.

Brown RS, Jr. Hepatitis C and liver transplantation. *Nature* 2005; 436 :973-978.

Davis GL, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; 138: 513-521.

D'Amico G, et al. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies*. J Hepatol* 2006; 44:217-231.

Fattovich G, et al. Hepatitis C virus genotypes: distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centres in *Europe. J Viral Hepat* 2001; 8: 206-216.

Kershenobich D, et al. Applying a system approach to forecast the total hepatitis C virus-infected population size: model validation using US data. *Liver Int* 2011; 31 Suppl 2:4-17.

Kim WR, et al. OPTN/SRTR 2013 Annual Data Report: liver. *Am J Transplant* 2013; 15 Suppl 2: 1-28.

Nguyen MH, Keeffe EB. Prevalence and treatment of hepatitis C virus genotypes 4, 5, and 6. *Clin Gastroenterol Hepatol* 2005; 3:S97-S101.

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