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 CER report: 19 October 2014
Second Round CER report: 4 January 2015

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*, 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

Common abbreviations

Abbreviation	Meaning
3TC	Lamivudine
ABC	Abacavir
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
ALAG	Absorption time lag
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
ATV/r	Atazanavir and ritonavir
AUC	Area under the plasma/serum/PBMC concentration versus time curve
AUCtau	Area under the plasma/serum/PBMC concentration versus time curve over the dosing interval
BA	Bioavailability
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BID	Twice daily
BMI	Body mass index
BOC	Boceprevir
BSEP	Bile salt export pump
CatA	Cathepsin A
CES1	Carboxyl esterase 1
CHC	Chronic Hepatitis C
CI	Confidence interval

Abbreviation	Meaning
CLDQ-HCV	Chronic Liver Disease Questionnaire HCV Version
CL/F	Apparent oral clearance
Cmax	Maximum observed plasma/serum/PBMC concentration of drug
CNS	Central nervous system
COBI	Cobicistat
CPT	Child-Pugh-Turcotte classification
CRCL	Creatinine clearance
CsA	Cyclosporine (cyclosporin A; ciclosporin)
Ctau	Observed drug concentration at the end of the dosing interval
CWRES	Conditional weighted residual
CYP	Cytochrome P450 enzyme(s)
DAA	Direct-acting antiviral
DCV	Daclatasvir
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRV	Darunavir
DV	Dependent variable
EC50/90	Half-maximal/90% effective concentration
ECG	Electrocardiogram
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
Emax	Maximum effect
ESRD	End-stage renal disease
ETR	End of Treatment response (undetectable plasma HCV-RNA at the end of therapy)
EU	European Union

Abbreviation	Meaning
EVG	Elvitegravir
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FBC	Full blood count
FDA (US)	Food and Drug Administration
FDC	Fixed-dose combination
FMO	Flavin monooxygenase
FOCE	First order conditional estimation
FTC	Emtricitabine
FU-X	Follow-up visit "X" weeks after completion of all treatment
GGT	Gamma-glutamyltransferase
Gilead	Gilead Sciences, Inc.
GLSM	Geometric least squares mean
GS-5885	Ledipasvir (LDV)
GS-7977	Sofosbuvir (SOF)
GS-9451	Vedroprevir (VDV)
GT	Genotype
GT1-HCV	Genotype 1 Hepatitis C Infection
H2RA	H2-receptor antagonist
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HINT1	Histidine triad nucleotide binding protein 1
HIV	HIV-1 human immunodeficiency virus, type 1
HRV	Human rhinovirus

Abbreviation	Meaning
HTA	Host targeting antiviral
IC50	half-maximal inhibitory concentration
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IFN	Interferon
IL28	Interleukin 28
IL28B	Interleukin 28B gene
IND	Investigational New Drug (Application)
IPRED	Individual predicted concentration
IQ	Interquartile
IRES	Internal ribosome entry site
ISS	Integrated summary of safety
iVSR	Integrated virology study report
IWRES	Individual weighted residual
LC/MS/MS	Liquid chromatography/tandem mass spectrometry
LDV	Ledipasvir (GS-5885)
LiPA	Line probe assay
LLOQ	Lower limit of quantitation
LOD	Limit of detection
MATE1	Multidrug and toxin extrusion protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
mRNA	Messenger ribonucleic acid
MRP2	Multidrug resistance-associate protein 2
NI	Nucleoside inhibitor

Abbreviation	Meaning
NNI	Non-nucleoside inhibitor
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NS (3/4A/5A/5B)	Nonstructural protein (3/4A/5A/5B)
OATP	Organic anion transporting polypeptide
OC	Ortho Tri-Cyclen Lo
OCT	Organic cation transporter
PD	Pharmacodynamic(s)
PEG	Pegylated interferon
Peg-IFN	Pegylated interferon
Pgp	p-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PRED	predicted concentration
QD	Once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
QTcI	QT interval corrected for heart rate using subject-specific correction factor
QTcN	QT interval corrected for heart rate using population-specific correction factor
RAL	Raltegravir
/r	Boosted with ritonavir
RAV	Resistance-associated variant

Abbreviation	Meaning
RBV	Ribavirin
RGT	Response-guided therapy
RNA	Ribonucleic acid
RPV	Rilpivirine
RSV	Respiratory syncytial virus
RTV	Ritonavir
SAE	Serious adverse event
SD	standard deviation
SE	Standard error
SF-36	Short Form 36 Health Survey
SMV	Simeprevir
SOF	Sofosbuvir (GS-7977)
SVR	Sustained virologic response
SVRXX	Sustained virologic response "XX" weeks following completion of all treatment
TAD	Time after dose
TDF	Tenofovir disoproxil fumarate
TE	Treatment experienced
TFV	Tenofovir
TGV	Tegobuvir
TN	Treatment naïve
TND	Target not detected
TVR	Telaprevir
UGT	Uridine disphosphate glucuronosyltransferase
ULN	Upper limit of the normal range
UMP-CMP	Uridine monophosphate-cytidine monophosphate

Abbreviation	Meaning
URTI	Upper respiratory tract infection
USP	United States Pharmacopeia
VDV	Vedroprevir, GS-9451
VPC	Visual predictive check
vRVR	Very rapid virologic response
WPAI: Hep C	Work Productivity and Impairment: Hepatitis C

1. Background

1.1. Submission type

This is a Category 1, Type A application to register Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) fixed dose combination tablets.

1.2. Drug class and therapeutic indication

Ledipasvir (LDV) is a new chemical entity that inhibits HCV replication through NS5A. In cell-based replicon assays it has high potency, selectivity and specificity for HCV.

Sofosbuvir (SOF) is a pro-drug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate. It is converted to the active form in the hepatocyte. It inhibits HCV replication by inhibiting RNA replication through inhibition of NS5B.

The proposed indication is:

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

1.3. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

Harvoni (90 mg ledipasvir/ 400 mg sofosbuvir) Fixed-Dose Combination Tablets, Bottle

1.4. Dosage and administration

The recommended dose of Harvoni tablets is one tablet, taken orally, once daily with or without food.

Duration of Treatment:

- For treatment-naïve patients without cirrhosis the recommended duration of treatment with Harvoni is 8 or 12 weeks.
- For treatment-naïve patients with cirrhosis and treatment-experienced patients without cirrhosis the recommended duration of treatment with Harvoni is 12 weeks.

- For treatment experienced patients with cirrhosis the recommended duration of treatment with Harvoni is 24 weeks.

Elderly: no dose adjustment is warranted for elderly patients.

Renal impairment: no dose adjustment of Harvoni is required for patients with mild or moderate renal impairment. The safety of Harvoni has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min) or end stage renal disease (ESRD) requiring haemodialysis.

Hepatic impairment: no dose adjustment of Harvoni is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C).

2. Clinical rationale

As stated in the Clinical Summary:

"Chronic HCV infection is a global health problem with an estimated 170 million individuals infected worldwide. In the US, an estimated 3.2 million people have chronic HCV infection. Chronic HCV infection leads to approximately 16,000 deaths each year in the US. In Europe, an estimated 7.3 to 8.8 million people have chronic HCV infection leading to approximately 86,000 deaths each year. Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection: over the ensuing 20 years, as many as 20% of patients with chronic HCV infection are estimated to develop complications, including cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Complications from chronic HCV infection are responsible for approximately half of all liver transplants; HCV is therefore the most frequent indication for orthotopic liver transplantation."

"For genotype 1 HCV infection (subtypes 1a or 1b), which represents the majority of all cases of chronic HCV infection in the US (70% to 75%, predominantly subtype 1a) and Europe (69%, predominantly subtype 1b), the current standard treatment for treatment-naive patients is 12 to 24 weeks of an oral protease inhibitor (PI) combined with 24 to 48 weeks of Peg-IFN+RBV, with duration of therapy guided by on-treatment response." However, up to 50% of patients are not eligible for these treatments, and there are also serious disadvantages to these treatments, including poor tolerability, frequent adverse effects and high pill burdens.

Hence "there remains a significant unmet medical need for simplified treatment regimens that are more effective than the current standard of care, with better safety/tolerability profiles."

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- 25 clinical pharmacology studies, including 24 that provided pharmacokinetic data and one that provided pharmacodynamic data. The pharmacokinetic studies were: Study GS-US-256-0110, Study GS-US-337-0101, Study GS-US-256-0101, Study GS-US-0108, Study GS-US-334-0111, Study GS-US-256-0102, Study GS-US-248-0117, Study GS-US-344-0101, Study GS-US-344-0108, Study GS-US-119-0113, GS-US-169-0105, Study GS-US-248-0102, Study GS-US-248-0104, Study GS-US-248-0107, Study GS-US-248-0125, Study GS-US-248-0127, Study GS-US-256-0129, Study GS-US-334-0101, Study GS-US-334-0146, Study GS-US-334-0148, GS-

US-337-0127, Study GS-US-337-0128, Study GS-US-344-0102, and Study MK-5172-pn023. The pharmacodynamic study was: Study GS-US-344-0109

- The pharmacokinetic studies were supplemented by 16 reports of in-vitro studies: Study AD-256-2094, Study AD-256-2095, Study AD-256-2096, Study AD256-2097, Study AD-256-2098, Study AD-256-2109, Study AD-256-2132, Study AD-256-2133, Study AD-256-2134, Study AD-256-2139, Study AD-256-2140, Study AD-256-2143, Study AD-256-2144, Study AD-256-2146, Study AD-256-2150, and Study AD-256-2108
- Three population pharmacokinetic analyses: Pop-PK of GS331007, Pop-PK of SOF and Pop-PK of LV
- Three pivotal efficacy/safety studies: Study GS-US-337-0102, Study GS-US-337-0108 and Study GS-US-337-0109
- Three other efficacy/safety studies: GS-US-337-0118, GS-US-337-0122 and Study P7977-0523
- An Integrated Summary of Efficacy and an Integrated Summary of Safety

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

The studies submitted in the present application all appeared to have been conducted according to Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK- Single dose Mass balance, LDV	GS-US-169-0105 Study GS-US-256-0108
	Bioequivalence - Single dose: LDV Single dose SOF/LDV FDC	GS-US-256-0110 Study GS-US-337-0101
	Food effect: LDV	Study GS-US-256-0101
PK in special populations	Target population - - Multi-dose	Study GS-US-256-0102
	Hepatic impairment	Study GS-US-248-0117
		Study GS-US-344-0101
	Renal impairment	Study GS-US-344-0108
	Neonates/infants/children/adolescents	
	Elderly	
	Japanese SOF/ LDV	Study GS-US-334-0111
PK interactions	GS-9451 + LDV on the PK of GS-6620	Study GS-US-119-0113
	LDV and GS-9256, GS-9451, TGV and RBV	Study GS-US-248-0102
	LDV and famotidine and omperazole	Study GS-US-248-0104
	LDV, GS-9669 and GS-9451	Study GS-US-248-0107
	LDV and pravastatin, rosuvastatin, digoxin, rifampin, verapamil and ciclosporin	Study GS-US-248-0125
	LDV and EFV, FTC and TDF	Study GS-US-248-0127
	LDV and TMC435	Study GS-US-256-0129
	SOF and LDV	Study GS-US-334-0101
	SPF, LDV and oral contraceptive pill	Study GS-US-334-0146
	SOF and VDV	Study GS-US-334-0148
	CPA (FTC / RPV / TDF) ATR (EFV / FTC / TDF) Omeprazole and famotidine	Study GS-US-337-0127
	SOF / LDV and ABC / 3TC	Study GS-US-337-0128
	LDV and EFV, RPV and RAL SOF / LDV and EVG, COBI, ATV and RTV	Study GS-US-344-0102
	LDV and MK-5172	Study MK-5172-pn023
Population PK analyses	Pop-PK of GS331007	Pop-PK-GS331007
	Pop-PK of SOF	Pop-PK-SOF
	Pop-PK of LV	Pop-PK-LDV

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

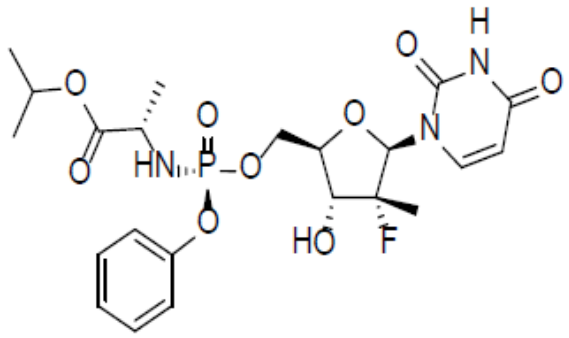
4.2. Summary of pharmacokinetics for sofosbuvir

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated. The information regarding SOF pharmacokinetics is extracted from the Clinical Evaluation Report for SOVALDI (sofosbuvir) application number PM-2013-01283-1-2 and the Product Information Document.

4.2.1. Physicochemical characteristics of sofosbuvir

The following information is derived from the Sponsor's proposed PI:

The chemical name of sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of C22H29FN3O9P and a molecular weight of 529.45. It has the following structural formula:



CAS registry number: 1190307-88-0

Sofosbuvir is a powder with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37 °C. The partition coefficient (log P) for sofosbuvir is 1.62 and the pKa is 9.3.

4.2.2. Pharmacokinetics of sofosbuvir in healthy subjects

4.2.2.1. Absorption

4.2.2.1.1. Sites and mechanisms of absorption

Following oral administration of SOF, peak SOF concentrations were generally observed 0.5 to 2 hrs post-dose, regardless of dose level, in HCV-infected subjects and healthy subjects. Peak plasma GS-331007 concentrations were generally observed 2 - 4 hrs after SOF administration. Following a single-oral dose of [14C]-SOF to healthy male subjects, SOF was well and rapidly absorbed, subsequently eliminated in urine as GS-331007; as ≈80% of administered dose was recovered in urine this indicates ≥ 80% of the administered dose is absorbed into systemic circulation and renal excretion the primary route of elimination.

4.2.3. Bioavailability

4.2.3.1.1. Absolute bioavailability

Absolute bioavailability studies were not provided for sofosbuvir because there is considered to be low systemic bioavailability because there is extensive first pass metabolism to GS-331007 which represents > 90% of systemic exposure. In dogs the systemic bioavailability was 9.89%.

4.2.3.1.2. Influence of food

Food slows the rate of absorption of SOF (a high fat meal increased Tmax for 2 to 4 hours) but did not significantly affect overall exposure (AUC).

4.2.3.1.3. Dose proportionality

There was near dose proportionality in the dose range 200 mg to 1200 mg.

4.2.3.1.4. Bioavailability during multiple-dosing

There was no apparent change in bioavailability with multiple dosing.

4.2.3.2. Distribution

4.2.3.2.1. Volume of distribution

The distribution PK of GS-331007 best fitted a two compartment model and the typical value of GS-331007 Vc/F was estimated 218 L, respectively, and the typical value of the volume of the peripheral compartment (Vp/F) was estimated to be 594 L.

4.2.3.2.2. Plasma protein binding

Plasma protein binding of SOF was ≈82-85% in healthy subjects and subjects with ESRD, respectively.

4.2.3.3. Metabolism

SOF is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203 which is then further metabolised and primarily excreted in urine as GS-331007. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [14C]-sofosbuvir, GS-331007 accounted for approximately > 90% of total systemic exposure.

4.2.3.4. Excretion

Following a single oral dose of [14C]-SOF, SOF was rapidly absorbed and eliminated in the urine as GS-331007. Mean total recovery of radioactive dose was > 92%, consisting of ≈80% recovered in urine, 14% in faeces and 2.5% in expired air.

4.2.4. Pharmacokinetics in the target population

Exposure in the HCV infected population is higher than in healthy subjects: mean SOF AUCtau was higher by 36%.

4.2.5. Pharmacokinetics in other special populations

Age, gender and ethnicity did not have any significant effects on exposure to GS-331007

4.2.6. Pharmacokinetic interactions

4.2.6.1. Pharmacokinetic interactions demonstrated in human studies

In the CER for SOVALDI (sofosbuvir), the only clinically significant drug-drug/food/herbal interaction was with potent P-gp inducers. The following additional information was included in the present submission:

There was no significant effect of SOF on the PK of GS-9669 (Study GS-US-334-0101).

GS-9669 increased the AUCinf of SOF by 35%, and Cmax by 30%, and this effect appeared to be additive to the effects of LDV (Study GS-US-334-0101). The AUCinf for GS-566500 was increased by 28%. However, the AUCinf of GS-331007 was increased to a lesser extent (15%).

In an assessment of the effects of SOF on the combined oral contraceptive pill, norelgestromin AUCtau was not significantly affected by SOF (Study GS-US-334-0146). However norgestrel AUCtau was increased by 19% and ethinyl estradiol by 9%. This would not be expected to affect the efficacy or safety of the oral contraceptive pill.

VDV increased the AUCinf of SOF by 144%, GS-566500 by 111% and GS-331007 by 19% (Study GS-US-334-0148). SOF decreased the AUCtau of VDV by 6% and the Cmax by 11% (Study GS-US-334-0148).

4.3. Summary of pharmacokinetics for ledipasvir

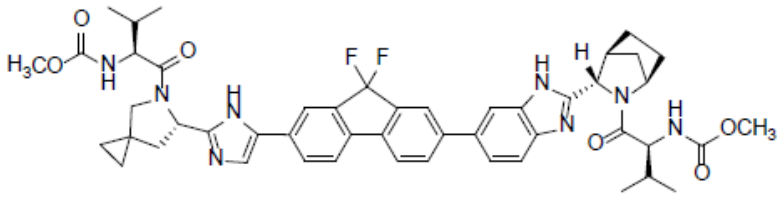
The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.3.1. Physicochemical characteristics of the ledipasvir

The following information is derived from the Sponsor's proposed PI:

The chemical name of ledipasvir is Methyl [(2S)-1-{(6S)-6-[5-(9,9-difluoro-7- {2-[(1R,3S,4S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1H-benzimidazol-6-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate.

It has a molecular formula of C49H54F2N8O6 and a molecular weight of 889.00. It has the following structural formula:



CAS registry number: 1256388-51-8

Ledipasvir is practically insoluble (< 0.1 mg/mL) across the pH range of 4.0 - 7.5 and is slightly soluble below pH 3.0 (4 mg/mL). The partition coefficient (log P) for ledipasvir is 3.8 and the pKa1 is 4.0 and pKa2 is 5.0.

4.3.2. Pharmacokinetics of ledipasvir in healthy subjects

4.3.2.1. Absorption

4.3.2.1.1. Sites and mechanisms of absorption

LDV appears to have solubility limited absorption at oral doses greater than 100 mg in the fed state (Study GS-US-169-0105). The exposure to a 100 mg and a 360 mg single oral dose was similar. For a 360 mg dose the AUCinf was 8995.7 (54.4) ng•hr/ml and for a 100 mg dose it was 7697.1 (34.3) ng•hr/ml. For a 360 mg dose the Cmax 287.2 (45.8) ng/mL and for a 100 mg dose it was 215.5 (34.6) ng/mL.

4.3.2.2. Bioavailability

4.3.2.2.1. Absolute bioavailability

Absolute bioavailability studies were not provided for ledipasvir because due to the low solubility of ledipasvir it was not possible for the sponsor to develop a formulation suitable for intravenous administration.

4.3.2.2.2. Bioequivalence of clinical trial and market formulations

LDV exposure (AUC and Cmax) increased by 23% in the spray died formulation compared with conventional tablets (Study GS-US-256-0110).

4.3.2.2.3. Influence of food

Food decreased bioavailability by 50% at the 30 mg dose level, with no effect on t½ (Study GS-US-256-0101).

4.3.2.2.4. Dose proportionality

In healthy volunteers LDV was dose proportional for Cmax and AUC in the dose range 3 mg to 100 mg (Study GS-US-256-0101).

4.3.2.3. Distribution

4.3.2.3.1. Volume of distribution

V/F is in the range of 876 to 1256 L (Study GS-US-256-0101).

4.3.2.3.2. Plasma protein binding

The mean (SD) plasma protein binding of ledipasvir was 0.05 (0.03) % at a 2 μM concentration and 0.06 (0.04) % at a 10 μM concentration (Study AD-256-2094).

4.3.2.3.3. Erythrocyte distribution

Not assessed.

4.3.2.3.4. Tissue distribution

The high volume of distribution indicates extensive tissue distribution.

4.3.2.4. Metabolism

4.3.2.4.1. Interconversion between enantiomers

Not assessed.

4.3.2.4.2. Non-renal clearance

LDV is primarily excreted in the faeces unchanged.

4.3.2.4.3. Metabolites identified in humans

4.3.2.4.3.1. Active metabolites

Ledipasvir was stable in incubations with pooled human hepatic microsomal fractions and with cryopreserved human hepatocytes (Study AD-256-2095). This indicates low hepatic metabolic clearance.

4.3.2.4.3.2. Other metabolites

LDV undergoes limited metabolism and is primarily excreted unchanged in the faeces and urine.

4.3.2.5. Excretion

4.3.2.5.1. Routes and mechanisms of excretion

LDV is predominantly excreted by the faecal route.

4.3.2.5.2. Mass balance studies

The mass balance of LDV was studied using [14C]-LDV (Study GS-US-256-0108). Over 4 days, no unchanged parent drug was detected in urine. M26 accounted for a mean of 0.632% of the dose and M27 a mean of 0.158% of the dose. All other radioactive components detected in urine each accounted for less than 0.1% of the dose. The mean (SD) total percent of dose quantified in the faeces was 77.6% (6.8%); predominantly parent drug (70.0% of the dose up to 216 hours post-dose) with oxy-LDV-3 (M19) accounting for a mean of 2.21% of the dose up to 216 hours post-dose, and the remaining unidentified components each accounted for a mean of less than 1.7% of the dose up to 216 hours post-dose.

4.3.2.5.3. Renal clearance

Renal clearance of LDV is minimal.

4.3.2.6. Intra- and inter-individual variability of pharmacokinetics

The CV% for CL/F is in the order of 40% to 80% (Study GS-US-256-0101).

4.3.3. Pharmacokinetics in the target population

At the 90 mg dose level in subjects with HCV infection, with multiple dosing, mean (CV%) CL/F was 27.7 (41.7) L/h, Cmax was 247.7 (45.4) ng/mL, Ctau was 115.9 (42.6) ng/mL and median (IQ range) t½ was 49.67 (37.76 to 54.33) h (GS-US-256-0102). LDV was dose proportional in the dose range 1 mg to 90 mg for both single dose and multiple dose.

There was an increase in CL/F of LDV of 26.7% in healthy volunteers compared to subjects with HCV (Study Pop-PK-LDV).

4.3.4. Pharmacokinetics in other special populations

4.3.4.1. Pharmacokinetics in subjects with impaired hepatic function

Compared with subjects with normal hepatic function, subjects with moderate impairment in hepatic function (Child-Pugh-Turcotte (CPT) score of 7 to 9) did not have any increase in exposure to LDV (Study GS-US-248-0117). Hence, dose adjustment would not be necessary in patients with mild or moderate hepatic impairment.

Compared with subjects with normal hepatic function, subjects with severe impairment in hepatic function (Child-Pugh-Turcotte (CPT) score of 10 to 15) had an 8% increase in AUCinf and a 35% decrease in Cmax for LDV (Study GS-US-344-0101). These changes would not be clinically significant, and dose adjustment would not be necessary in patients with severe hepatic impairment.

4.3.4.2. Pharmacokinetics in subjects with impaired renal function

There was no significant difference in exposure to LDV for subjects with severe renal impairment and subjects with normal renal function: %GLSM Ratio (Impaired/Normal) (90% CI) 92.34 (70.24 to 121.39) for Cmax and 105.60 (75.32 to 148.05) for AUCinf (Study GS-US-344-0108).

4.3.4.3. Pharmacokinetics according to age

Age did not have a clinically significant effect on PK variables (Study Pop-PK-LDV).

4.3.4.4. Pharmacokinetics related to genetic factors

There were no data relating to polymorphisms in transporters and effect on PK.

4.3.4.5. Pharmacokinetics related to gender

There was a decrease in typical CL/F for LDV of -33% in females which translated to an increase in AUC of 49% (Study Pop-PK-LDV)

4.3.5. Pharmacokinetic interactions

4.3.5.1. Pharmacokinetic interactions demonstrated in human studies

4.3.5.1.1. Effects of interactions on LDV PK

- LDV exposure decreased by over 40% when co-administered with omeprazole: AUCinf decreased by 47.7% and Cmax decreased by 47.7% (Study GS-US-256-0110). Omeprazole co-administration decreased the AUC of LDV by 50%, but there was no significant effect for famotidine (Study GS-US-248-0104).
- The AUC of LDV was increased five-fold in combination with GS-9256 and by 91% in combination with GS-9451 (Study GS-US-248-0102). TGV and RBV did not increase the exposure to LDV.

- Rifampin decreased the AUCinf of LDV by 60% (Study GS-US-248-0125). This was attributed by the Sponsor to induction of Pgp by rifampin.
- Verapamil increased the AUCinf of LDV by 67% (Study GS-US-248-0125). This was attributed by the Sponsor to inhibition of P-gp by verapamil.
- Ciclosporin increased the AUCtau of LDV by 15% (Study GS-US-248-0125). This is not likely to be clinically significant.
- In combination with ATR (a FDC of EFV 600 mg / FTC 200 mg / TDF 300 mg) the AUCtau of LDV was decreased by 33.3% (Study GS-US-0127).
- The AUCtau of LDV was increased by 92% in combination with TMC435 (Study GS-US-256-0129).
- LDV 90 mg in combination with EFV / FTC / TDF resulted in a decrease in LDV AUCtau by 24%, Cmax by 23% and Ctua by 28% (Study GS-US-344-0102).
- LDV 90 mg in combination with DRV / RTV resulted in an increase in LDV AUCtau by 39%, Cmax by 45% and Ctua by 39% (Study GS-US-344-0102).
- LDV 90 mg in combination with RAL or RPV did not result in any significant change in LDV PK (Study GS-US-344-0102).
- When LDV 90 mg daily was co-administered with MK-5172 400 mg daily, the AUC0-24 of LDV increased by 87%, Cmax by 96% and Ctau by 97% (Study MK-5172-pn023).

4.3.5.1.2. Effects of other drugs on LDV

- LDV in combination with GS-9451 had a major impact on the PK of GS-6620. The AUCinf for GS-6620 was increased by 144%, the AUCinf for the intermediary metabolite GS-465124 increased by 370% and the AUCinf for the nucleoside analogue GS-441285 increased by 42% (Study GS-US-119-0113). This effect was proposed to be due to an increase in the exposure to GS-6620 due to inhibition of intestinal transporters. GS-6620 did not have any significant effects on the PK of LDV or GS-9451.
- LDV 90 mg once daily in combination with GS 9451 200 mg once daily increased the AUC of GS-9669 by 270%, but there was no significant effect on the AUC of LDV (in combination with GS-9451) from GS-9669 (Study GS-US-248-0107)
- LDV did not significantly alter the PK of GS-9256, GS-9451, TGV or RBV (Study GS-US-248-0102).
- Pravastatin AUCinf was increased by 170% in combination with LDV, GS-9451 and TGV (Study GS-US-248-0125). This was attributed by the Sponsor to the inhibition of OATP by GS-9451.
- Rosuvastatin AUCinf was increased by 600% in combination with LDV, GS-9451 and TGV (Study GS-US-248-0125). This was attributed by the Sponsor to inhibition of OATP, BRCP and NTCP by GS-9451 and LDV.
- Digoxin AUCinf was increased by 33% in combination with LDV, GS-9451 and TGV (Study GS-US-248-0125). This was attributed by the Sponsor to inhibition of Pgp by GS-9451 and LDV.
- Ciclosporin AUCinf was not significantly affected in the combination with LDV, GS-9451 and TGV (Study GS-US-248-0125).
- LDV in combination with GS-9451 and TGV increased the AUCtau of TFV by 36% but had no significant effect on the AUCtau of FTC or EFV % (Study GS-US-0127).

- The AUCtau of TMC435 was increased by 169% in combination with LDV (Study GS-US-256-0129).
- LDV increased the AUCtau of GS-9669 by 55% and Cmax by 49% (Study GS-US-334-0101).
- LDV did not have any significant effect on the PK of GS-9669 (Study GS-US-334-0101).
- In an assessment of the effects of LDV on the combined oral contraceptive pill, norelgestromin and norgestrel AUCtau were not significantly affected by LDV (Study GS-US-334-0146). However ethinyl estradiol AUCtau was increased by 20%. This would not be expected to affect the efficacy or safety of the oral contraceptive pill.
- LDV 90 mg in combination with EFV / FTC / TFV resulted in an increase in TFV AUCtau by 38% and Ctau by 55% (Study GS-US-344-0102). There was no clinically significant effect upon EFV or FTC.
- LDV 90 mg in combination with DRV / RTV resulted in an increase in RTV AUCtau by 37%, Cmax by 33% and Ctau by 33% (Study GS-US-344-0102). There was no clinically significant effect upon DRV.
- LDV 90 mg in combination with RAL resulted in a decrease in RAL AUCtau by 15%, Cmax by 18% and Ctau by 15% (Study GS-US-344-0102).
- LDV 90 mg in combination with RPV did not have a significant effect on the PK of RPV (Study GS-US-344-0102).
- When LDV 90 mg daily was co-administered with MK-5172 400 mg daily, the AUC0-24 of MK-5172 increased by 48%, Cmax by 22% and Ctau by 77% (Study MK-5172-pn023).

4.3.5.2. Clinical implications of in vitro findings

Ledipasvir at concentrations up to 25 µM had no inhibitor effect on CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A (Study AD-256-2096).

Ledipasvir at concentrations up to 20 µM did not activate PXR or AhR regulated genes in vitro (Study AD256-2097).

Ledipasvir was not metabolised in vitro by recombinant CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 (Study AD-256-2098).

Ledipasvir was a moderate to weak inhibitor of BCRP and Pgp, only approaching 50% inhibition at near its aqueous solubility limit (Study AD-256-2109). No evidence for dose dependent MRP2 inhibition was observed for ledipasvir.

In vitro ledipasvir had a significant inhibitory effect on the activity of human UGT1A1 with an IC50 of 7.95 µM (Study AD-256-2132).

Ledipasvir had no significant inhibitory effect on the activity of human CYP2B6 in vitro (Study AD-256-2133).

Ledipasvir showed dose-dependent inhibition of OATP1B1 and OATP1B3 with IC50 values of 3.5 ± 1.0 µM and 6.5 ± 2.8 µM, respectively (Study AD-256-2134).

Ledipasvir was not a substrate for OATP1B1 or OATP1B3 (Study AD-256-2139).

Ledipasvir showed moderate inhibition of BSEP-mediated transport and weak inhibition of OCT2-mediated transport of at a concentration of 6 µM (Study AD-256-2140).

Ledipasvir showed no dose-dependent inhibition of OCT1-mediated transport at the concentrations up to 6 µM and was not a substrate of OCT1 (Study AD-256-2143).

Ledipasvir is a substrate for Pgp transport (Study AD-256-2144).

Ledipasvir demonstrated no induction of CYP1A2, CYP2C9, P-gp, and UGT1A1 at concentrations up to 10 μM, and low potential to induce CYP2B6 and CYP3A4 (Study AD-256-2146). At a clinically relevant concentration of 1 μM increases in CYP2B6 and CYP3A activities were all <2.0-fold and the relative increase in CYP2B6 and CYP3A4 mRNA was ≤ 10% of the positive control.

Ledipasvir is a substrate for BCRP transport in vitro (Study AD-256-2150).

LDV has medium to high permeability through Caco-2 cells suggesting a majority of the soluble dose should be absorbed in the intestine (Study AD-256-2108). There was no evidence of efflux transport of LDV in Caco-2 cells.

4.4. Summary of pharmacokinetics for sofosbuvir/ledipasvir

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.4.1. Physicochemical characteristics of the active substance

As per above.

4.4.2. Pharmacokinetics in healthy subjects

4.4.2.1. Absorption

As per above.

4.4.2.2. Bioavailability

4.4.2.2.1. Bioequivalence of different dosage forms and strengths

SOF/LDV FDC 400 mg/90 mg had similar exposure to GS-331007 compared to SOF 400 mg (geometric mean ratio [90% CI] 95.35 [89.99 to 101.04] for AUCinf and 98.60 [90.81 to 107.05] for Cmax) (Study GS-US-337-0101). There was also similar exposure to LDV compared to LDV 90 mg (geometric mean ratio [90% CI] 96.31 [79.21 to 117.10] for AUCinf and 98.21 [81.89 to 117.44] for Cmax).

4.4.2.2.2. Influence of food

SOF/LDV FDC 400 mg/90 mg had similar exposure to GS-331007 for fasted and following either a high calorie, high fat meal or a moderate fat meal (moderate/fasted: geometric mean ratio [90% CI] 117.42 [111.93 to 123.18] for AUCinf and 81.52 [75.56 to 87.94] for Cmax; high calorie, high fat / fasted: geometric mean ratio [90% CI] 111.96 [106.66 to 117.52] for AUCinf and 70.22 [65.03 to 75.83] for Cmax) (Study GS-US-337-0101). There was also similar exposure to LDV for fasted and following either a high calorie, high fat meal or a moderate fat meal (moderate/fasted: geometric mean ratio [90% CI] 1175.31 [99.40 to 133.76] for AUCinf and 108.61 [93.50 to 126.17] for Cmax; high calorie, high fat / fasted: geometric mean ratio [90% CI] 102.80 [88.46 to 119.4] for AUCinf and 88.21 [75.80 to 102.64] for Cmax).

4.4.2.3. Distribution

As per above.

4.4.2.4. Metabolism

As per above.

4.4.2.5. Excretion

4.4.2.5.1. Routes and mechanisms of excretion

As per above.

4.4.2.5.2. Mass balance studies

As per above.

4.4.2.5.3. Renal clearance

Renal clearance is significant for determining GS-331007 exposure. Study Pop-PK-GS-331007 concluded a covariate effect of CLCR on CL/F and Vc/F. However, there was no effect of renal clearance on LDV.

4.4.2.6. Intra- and inter-individual variability of pharmacokinetics

As per above.

4.4.3. Pharmacokinetics in the target population

As per above.

4.4.4. Pharmacokinetics in other special populations

As per above.

4.4.4.1. Pharmacokinetics in Japanese subjects

Exposure to SOF and LDV was similar in Japanese and Caucasian subjects (Study GS-US-334-0111). There was no clinically significant difference in exposure to GS-331007.

4.4.5. Pharmacokinetic interactions

4.4.5.1. Pharmacokinetic interactions demonstrated in human studies

The AUCinf of SOF, at a dose of 400 mg, was increased by 130% in combination with LDV 30 mg: %GLSM ratio (90% CI), SOF + LDV / SOF, 230.32 (191.28 to 277.33) (Study GS-US-334-0101). Cmax was increased by 121%: %GLSM ratio (90% CI), SOF + LDV / SOF, 221.20 (176.21 to 277.66). The AUCinf for GS-566500 was increased by 79% and GS-331007 by 19%.

There was a statistically significant, but not clinically significant, decrease in the AUCinf of LDV, at a dose of 30 mg, when administered with SOF 400 mg, by 4%: %GLSM ratio (90% CI), SOF + LDV / LDV, 95.75 (92.11 to 99.53) (Study GS-US-334-0101). Cmax was not significantly altered: %GLSM ratio (90% CI), SOF + LDV / LDV, 96.50 (89.91 to 103.58).

In combination with ATR (EFV 600 mg / FTC 200 mg / TDF 300 mg), the AUCtau of LDV was decreased by 34% and Cmax was also decreased by 34% (Study GS-US-337-0127). The PK parameters for SOF and its metabolites GS-566500 and GS-331007 were not significantly altered.

There was no significant effect of CPA (FTC 200 mg / RPV 25 mg / TDF 300 mg) on the PK of either SOF or LDV (Study GS-US-337-0127).

The AUCtau of TFV was increased by 98% and Cmax by 79% when administered in the FDC product ATR (EFV 600 mg / FTC 200 mg / TDF 300 mg) in combination with SOF 400 mg / LDV 90 mg (Study GS-US-337-0127). However, when administered in the FDC product CPA (FTC 200 mg / RPV 25 mg / TDF 300 mg), the AUCtau of TFV was increased by 40% and Cmax by 32% in combination with SOF 400 mg / LDV 90 mg.

Omeprazole 20 mg administered with SOF 400 mg / LDV 90 mg resulted in a decrease in LDV AUCinf of 4% and Cmax of 11%, a decrease in GS-566500 AUCinf of 15% and Cmax of 19%, but no significant effect on the PK parameters for SOF or GS-331007 (Study GS-US-337-0127).

Famotidine when co-administered with SOF 400 mg / LDV 90 mg resulted in an increase in SOF Cmax of 15% and a decrease in LDV Cmax of 20% mg (Study GS-US-337-0127). When administered the night before the SOF 400 mg / LDV 90 mg, only the Cmax of LDV was decreased by 17%.

When SOF 400 mg / LDV 90 mg was administered along with ABC /3TC the AUCtau of SOF was increased by 21%, GS-566500 by 5%, GS-331007 by 5% and LDV by 18% (GS-US-337-0128). The Cmax of LDV was also increased by 10%. These effects are not clinically significant.

When SOF 400 mg / LDV 90 mg was administered along with ABC /3TC the AUCtau of ABC was decreased by 10%, and 3TC by 6% (GS-US-337-0128). The Cmax of ABC was decreased by 8%, and 3TC by 7%. Ctau of 3TC was also increased by 12%.

SOF 400 mg /LDV 90 mg in combination with EVG and COBI resulted in an increase in EVG Ctau by 36%, COBI AUCtau by 59% and COBI Ctau by 325% (Study GS-US-344-0102).

SOF 400 mg / LDV 90 mg in combination with ATV / RTV resulted in an increase in ATV Ctau by 75% and RTV Ctau by 56% (Study GS-US-344-0102).

SOF 400 mg / LDV 90 mg in combination with EVG and COBI resulted in an increase in SOF AUCtau by 36% and Cmax by 33%; and GS-331007 AUCtau by 44%, Cmax by 33% and Ctua by 53% (Study GS-US-344-0102). There was an increase in LDV AUCtau by 78%, Cmax by 63% and Ctua by 91%. There was no significant effect on GS-566500.

SOF 400 mg / LDV 90 mg in combination with ATV / RTV resulted in an increase in LDV AUCtau by 113% and Cmax by 98% and Ctua by 136% (Study GS-US-344-0102). There was no significant effect on SOF, GS-566500 or GS-331007.

4.5. Evaluator's overall conclusions on pharmacokinetics

SOF is a pro-drug that undergoes extensive metabolism. Its active form is GS-461203 and it appears in the serum as (and is excreted as) GS-331007. Clearance of GS-331007 is primarily renal and is correlated with CLCR. Hence in ESRF there could be accumulation. The only clinically significant demonstrated drug-drug / food / herbal interaction was with potent P-gp inducers.

LDV has solubility limited absorption at doses greater than 100 mg. Bioavailability is decreased 50% with food. It has low protein binding and a high volume of distribution. It is primarily excreted unchanged in the faeces, with minimal metabolism and minimal excretion unchanged in the urine. Dose adjustment is not necessary in subjects with mild, moderate or severe hepatic impairment. Dose adjustment is not necessary in renal failure. LDV is a substrate of P-gp and BCRP. There is evidence of interactions with drugs that induce or inhibit transporters, but the clinically significant interactions were with drugs such as rifampin, EFV / FTC / TDF, and DRV / RTV (inducers of transporters) which resulted in decreased exposure to LDV. LDV was a moderate to weak inhibitor of BCRP and P-gp, and also inhibits OATP1B1 and OATP1B3. Hence there was some evidence of interactions with digoxin and with pravastatin.

The PK interactions between SOF and LDV in combination are favourable. LDV significantly increased the exposure to SOF, GS-566500 and GS-331007. SOF did not have any significant effect on exposure to LDV.

Combining treatments with SOF / LDV FDC will be complex because of the potential for drug-drug interactions. The interactions table in the PI is useful but would be of more practical value if the clinically significant drug interactions were highlighted in some way.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on HCV RNA	Study GS-US-256-0102
Secondary Pharmacology	Effect on QTc	Study GS-US-344-0109

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

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

LDV inhibits HCV replication through NS5A. SOF inhibits RNA replication through inhibition of NS5B.

There were no additional data on mechanism of action.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

In subjects with GT 1a HCV infection, when tested in the dose range 1 mg to 90 mg over 3 days, there was similar and maximal effect at doses of 10 mg, 30 mg and 90 mg per day (Study GS-US-0102). Emax modelling of effect indicated that exposures of LDV at doses of ≥ 30 mg/day would result in > 95% maximal response in subjects with GT 1a HCV infection. Onset of effect was rapid (within 12 hours) with demonstrable effects at all dose levels, and similar effect from the 10 mg dose level. Effect persisted for approximately 36 hours after the last dose and then diminished over 3 days. At Day 4, NS5A RAMs were detected in all subjects dosed at ≥ 3 mg LDV with varying degrees of reduced susceptibility to LDV.

5.2.3. Time course of pharmacodynamic effects

Time course of effect is discussed below.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

In all the clinical studies, the doses, and plasma concentrations studies would have been expected to have achieved near maximum effect (from extrapolations of in vitro data).

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Genetic-, gender- and age- related differences in pharmacodynamics were not studied.

5.2.6. Pharmacodynamic interactions

Pharmacodynamic interactions were not studied.

5.2.6.1. Secondary pharmacodynamic effects

In a thorough QT study, conducted with LDV 120 mg daily at steady state, there was no significant change in QTcF, and the maximum difference from placebo was, mean (90% CI), 1.5 (- 0.5 to 3.5) msec at 12 hours post dose (Study GS-US-344-0109). Following LDV 120 mg no subjects had a QTcF > 450 msec, compared with 3 (5.1%) with moxifloxacin 400 mg. No subject had an increase in QTc > 30 msec.

5.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic data were used to select the dose to be taken into the efficacy trials. Study GS-US-256-0102 indicated a dose of 30 mg or more would be sufficient to obtain near maximal effect.

There was no indication of QTC prolongation of regulatory interest with LDV at a dose of 120 mg. However, 120 mg is only 33% higher than the proposed dosing regimen. A study conducted at higher dose levels would be more reassuring.

6. Dosage selection for the pivotal studies

Study GS-US-256-0102 demonstrated that exposures of LDV at doses of ≥ 30 mg/day would result in > 95% maximal response in subjects with GT 1a HCV infection. Consequently, the 30 mg and 90 mg dose levels of LDV were selected for further development.

The 400 mg dose level for SOF appears to have been carried through from the development of SOVALDI (sofosbuvir), submission number PM-2013-01283-1-2.

7. Clinical efficacy

7.1. Chronic Hepatitis C Genotype 1

7.1.1. Pivotal efficacy studies

7.1.1.1. Study GS-US-337-0102

7.1.1.1.1. Study design, objectives, locations and dates

Study GS-US-337-0102 was a Phase III, multi-centre, randomized, open label study to investigate the efficacy and safety of SOF / LDV FDC with and without RBV. Although two of the four treatment groups were treated for 12 weeks and two for 24 weeks, only the 12 week data were reported. The study was conducted at 100 centres from September 2012 to November 2013.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, age ≥ 18 years
- Body mass index (BMI) ≥ 18 kg/m2
- Had HCV RNA ≥ 104 IU/mL at screening
- Were HCV treatment naïve (defined as: no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent)
- Had HCV genotype 1a, 1b, or mixed 1a/1b at screening
- Had confirmation of chronic HCV infection documented by either:
  - A positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the baseline/Day 1 visit, or
  - A liver biopsy performed prior to the baseline/Day 1 visit with evidence of chronic HCV infection
- Cirrhosis determination (up to 20% of study subjects could have had cirrhosis): Cirrhosis was defined as any one of the following:

- Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥5)
- Fibroscan showing cirrhosis or results > 12.5 kPa
- FibroTest score of > 0.75 and an AST: platelet ratio index (APRI) of > 2 during screening

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

- Liver biopsy within 2 years of screening showing absence of cirrhosis
- Fibroscan within 6 months of baseline/Day1 with a result of ≤ 12.5 kPa
- FibroTest score of ≤ 0.48 and an APRI of ≤ 1 during screening

In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy was required; liver biopsy results superseded any imaging or blood test results and were considered definitive

- Liver imaging within 6 months of baseline/Day 1 to exclude hepatocellular carcinoma (HCC) was required in subjects with cirrhosis
- Had a screening electrocardiogram (ECG) without clinically significant abnormalities
- Must have had the following laboratory parameters at screening: ALT ≤ 10xULN; AST ≤ 10xULN; direct bilirubin ≤ 1.5xULN; platelets ≥ 50,000; hemoglobin A1c (HbA1c) ≤ 8.5%; CLCR ≥ 60 mL /min, as calculated by the Cockcroft-Gault equation; haemoglobin ≥ 11 g/dL for female subjects; ≥ 12 g/dL for male subjects; albumin ≥ 3g/dL; international normalized ratio (INR) ≤ 1.5xULN unless subject had known haemophilia or was stable on an anticoagulant regimen affecting INR
- Female subject must not be pregnant or nursing; or must be of non-childbearing potential, abstinent or taking approved methods of contraception
- All male study participants must have agreed to consistently and correctly use a condom; and to refrain from sperm donation for at least 7 months after the last dose of RBV or 90 days after their last dose of study drug if not taking RBV
- Were in generally good health, with the exception of chronic HCV infection, as determined by the investigator

The exclusion criteria included:

- Clinically significant illness (other than HCV) or any other major medical disorder that may have interfered with subject treatment, assessment, or compliance with the protocol; subjects who were under evaluation for a potentially clinically significant illness (other than HCV)
- Gastrointestinal disorder or postoperative condition that could have interfered with the absorption of the study drug
- Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy
- Clinical hepatic decompensation (i.e. ascites, encephalopathy, or variceal haemorrhage)
- Solid organ transplantation
- Significant pulmonary disease, significant cardiac disease, or porphyria
- Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years
- Malignancy diagnosed or treated within 5 years (recent localized treatment of squamous or non-invasive basal cell skin cancers was permitted; cervical carcinoma in situ was allowed if

appropriately treated prior to screening); subjects under evaluation for malignancy were not eligible

- Significant drug allergy (such as anaphylaxis or hepatotoxicity)
- Had chronic liver disease of a non-HCV aetiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis)
- Infected with hepatitis B virus (HBV) or HIV
- Had clinically relevant drug abuse within 12 months of screening
- Had alcohol misuse as defined by an Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8
- Had contraindications to RBV therapy, including significant history of clinically significant haemoglobinopathy (e.g., sickle cell disease, thalassemia)
- Had chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day)
- Had known hypersensitivity to RBV, LDV, SOF, or formulation excipients

7.1.1.1.3. Study treatments

1. SOF 400 mg / LDV 90 mg FDC once daily for 24 weeks
2. SOF 400 mg / LDV 90 mg FDC once daily plus RBV 1000 mg or 1200 mg divided twice daily for 24 weeks
3. SOF 400 mg / LDV 90 mg FDC once daily for 12 weeks
4. SOF 400 mg / LDV 90 mg FDC once daily plus RBV 1000 mg or 1200 mg divided twice daily for 12 weeks

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs). HCV RNA was measured using the COBAS Taqman HCV Test v2.0 for use with the High Pure System assay. The LLOQ of the assay was 25 IU/mL.

The secondary efficacy outcome measures were:

- On-treatment virologic failure:
  - Breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA <LLOQ while on treatment, confirmed with two consecutive values (note: the second confirmation value could be post-treatment), or last available on-treatment measurement with no subsequent follow-up values
  - Rebound: > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (note: second confirmation value could be post-treatment), or last available on-treatment measurement with no subsequent follow-up values
  - Non-response: HCV RNA persistently ≥ LLOQ through 8 weeks of treatment
- Relapse:
  - HCV RNA ≥ LLOQ during the post-treatment period having achieved HCV RNA < LLOQ at EOT, confirmed with 2 consecutive values or last available post-treatment measurement
- The proportion of subjects with SVR4, defined as HCV RNA < LLOQ 4 weeks after discontinuation of therapy

- The proportion of subjects with SVR24, defined as HCV RNA < LLOQ 24 weeks after discontinuation of therapy
- The proportion of subjects with HCV RNA < LLOQ was summarized by treatment and study visit while on treatment and during the post-treatment (SVR) follow-up period.
- Summary statistics were presented for absolute values and changes from baseline in HCV RNA (log10 IU/mL) by treatment and study visit through Week 8.
- HCV resistance-associated variants (RAVs)
- Proportion of subjects with ALT normalization (defined as ALT > ULN at baseline and ALT ≤ ULN at each visit)
- Health-related quality of life questionnaires included SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C

Safety outcome measures were: AEs, laboratory tests, body weight, vital signs, and ECGs.

7.1.1.1.5. Randomisation and blinding methods

Subjects were randomized by IWRS in a ratio of 1:1:1:1 and the study was open label.

7.1.1.1.6. Analysis populations

The full analysis set (FAS) included all subjects who were randomized and received at least one dose of study drug. The efficacy and safety assessments were both performed on the FAS.

7.1.1.1.7. Sample size

A sample size of 200 subjects in each treatment group provided over 91% power to detect at least 13% improvement in SVR12 rate from the adjusted historical null rate of 60% using a 2-sided, 1-sample, binomial test at a significance level of 0.0125 based on a Bonferroni adjustment.

7.1.1.1.8. Statistical methods

An interim analysis was performed at Week 12. Hypothesis tests were performed using the 2-sided, exact, 1-sample, binomial test. Multiplicity was addressed by using the Bonferroni correction method 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. Missing data for HCV RNA were imputed according to preceding and/or following values.

7.1.1.1.9. Participant flow

A total of 1015 subjects were screened and 870 were randomised to treatment: 217 to SOF / LDV 12 weeks, 218 to SOF /LDV + RBV 12 weeks, 217 to SOF / LDV 24 weeks, and 218 to SOF /LDV + RBV 24 weeks. The FAS included 865 (99.4%) subjects; 838 (96.6%) completed study treatment and 27 (3.1%) discontinued. There were 275 subjects with no data for the SVR12 assessment, but all except 3 of these subjects were in the 24 week treatment groups. Ten (1.2%) subjects withdrew because of AE.

7.1.1.1.10. Major protocol violations/deviations

There were 67 important protocol deviations in65 subjects. There were violations of inclusion / exclusion criteria in 49 (5.7%) subjects, prohibited concomitant medications in 6 (0.7%), informed consent not obtained properly in 3 (0.3%) and study drug non-compliance in 9 (1.0%).

7.1.1.1.11. Baseline data

There were 513 (59.3%) males, 352 (40.7%) females and the age range was 18 to 80 years. The demographic characteristics were balanced between the treatment groups. There were 581 (67.2%) subjects with GT1a-HCV and 273 (31.6%) with GT1b-HCV; and 136 (15.7%) subjects

with cirrhosis. Baseline disease characteristics were similar for the four treatment groups. In the 12-week treatment groups, there was 97.2% adherence to SOF / LDV when administered alone and 95.4% when administered with RBV.

7.1.1.1.12. Results for the primary efficacy outcome

- SVR12 was achieved by 209 (97.7%) subjects in the SOF / LDV 12 week group, 95% CI 94.6% to 99.1%, p < 0.001
- SVR12 was achieved by 211 (97.2%) subjects in the SOF / LDV + RBV 12 week group, 95% CI 94.1% to 99.0%, p < 0.001

There was no effect on response for demographic characteristics. SOF / LDV FDC was equally effective for GT1a-HCV and GT1b-HCV and baseline disease characteristics did not influence efficacy. However, subjects with < 80% adherence to study treatment had reduced efficacy.

7.1.1.1.13. Results for other efficacy outcomes

- There was one subject in the SOF / LDV 12 week treatment group with overall virological failure (due to relapse). No subject in the SOF / LDV + RBV 12 week group had overall virological failure.
- SVR4 was achieved by 211 (98.6%) subjects in the SOF / LDV 12 week group, 95% CI 96.0% to 99.7%; SVR4 was achieved by 213 (98.2%) subjects in the SOF / LDV + RBV 12 week group, 95% CI 95.3% to 99.5%
- There were 197 subjects that had post-treatment week 12 and 24 data available and all of the subjects with SVR12 response also had SVR24 response.
- In all the treatment groups, near maximal response was achieved by Week 8 on-treatment
- Alt normalisation occurred for 87.1% to 93.0% of affected subjects
- RAVs were reported in 32 (15.0% subjects in the SOF / LDV 12 week group, and 36 (16.7%) in the SOF / LDV + RBV 12 week group. The one subject in the 12 week group who relapsed did not develop a RAV
- There was a decrease in quality of life scores in the SOF / LDV + RBV group relative to the SOF / LDV group on-treatment. However, the Sponsor interpreted these results with caution.

7.1.1.2. Study GS-US-337-0108

7.1.1.2.1. Study design, objectives, locations and dates

Study GS-US-337-0108 was a Phase III, multicentre, randomized, open label study to investigate the efficacy and safety of SOF / LDV FDC ± RBV for 8 weeks and SOF / LDV FDC for 12 weeks in treatment naïve subjects with chronic GT1-HCV. The study was conducted at 59 centres in the US from May 2013 to December 2013.

7.1.1.2.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria, and definitions, were the same as for Study GS-US-337-0102 except for:

- There was no requirement for US to exclude hepatocellular carcinoma
- Serum bilirubin must be < ULN
- Subjects with cirrhosis were excluded

7.1.1.2.3. Study treatments

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

2. SOF 400 mg / LDV 90 mg FDC once daily for 8 weeks
3. SOF 400 mg / LDV 90 mg FDC once daily plus RBV 1000 mg or 1200 mg divided twice daily for 8 weeks

7.1.1.2.4. Efficacy variables and outcomes

The outcome measures were the same as for Study GS-US-337-0102. The schedules of on-treatment and post-treatment visits were similar to that for Study GS-US-337-0102.

7.1.1.2.5. Randomisation and blinding methods

Subjects were randomized by IWRS in a ratio of 1:1:1, stratified by HCV genotype (1a or 1b), and the study was open label.

7.1.1.2.6. Analysis populations

The full analysis set (FAS) included subjects who were randomized and received at least one dose of study drug. The safety analysis set included subjects who were randomized and received at least one dose of study drug.

7.1.1.2.7. Sample size

A sample size of 200 subjects in each treatment group provided over 90% power to detect at least 30% improvement in the SVR12 rate from the adjusted historical null rate of 60% using a 2-sided, exact 1-sample, binomial test at a significance level of 0.025.

7.1.1.2.8. Statistical methods

The statistical methods were the same as for Study GS-US-337-0102. To adjust for multiplicity a sequential hypothesis test procedure was used.

7.1.1.2.9. Participant flow

A total of 831 subjects were screened and 647 were randomised: 215 to SOF / LDV 8 weeks, 216 to SOF / LDV + RBV 8 weeks, and 216 to SOF / LDV 12 weeks. A total of 639 (98.8%) subjects completed treatment; 8 (1.2%) discontinued, 3 (0.5%) due to AE. All randomized subjects were included in the FAS and safety datasets.

7.1.1.2.10. Major protocol violations/deviations

There were 17 important protocol violations in 16 subjects. Ten of the important protocol violations were for violation of inclusion / exclusion criteria.

7.1.1.2.11. Baseline data

There were 375 (58.0%) males, 272 (42.0%) females and the age range was 20 to 75 years. The treatment groups were similar in baseline demographic characteristics (Table 7.1.1.2.2). There were 515 (79.6%) subjects with GT1a-HCV and 131 (20.2%) with GT1b-HCV. The treatment groups were similar in baseline disease characteristics. There was greater adherence to treatment regimen in the SOF / LDV FDC only treatment groups: at least 80% adherence in 210 (97.7%) subjects in the SOF / LDV FDC 8 week group, 193 (89.4%) in the SOF / LDV + RBV 8 week, and 202 (93.5%) in the SOF / LDV 12 week group (Table 7.1.1.2.4).

7.1.1.2.12. Results for the primary efficacy outcome

- SVR12 was achieved by 202 (94.0%) subjects in the SOF / LDV FDC 8 week group, 95% CI 89.9% to 96.7%, $p < 0.001$
- SVR12 was achieved by 201 (93.1%) subjects in the SOF / LDV FDC + RBV 8 week group, 95% CI 88.8% to 96.1%, $p < 0.001$
- SVR12 was achieved by 206 (95.4%) subjects in the SOF / LDV FDC 12 week group, 95% CI 91.7% to 97.8%, $p < 0.001$

There was no statistically significant difference between the treatment groups in the primary efficacy outcome measure. There was decreased efficacy for subjects with < 80% adherence to SOF / LDV FDC. There was similar efficacy for GT1a-HCV and GT1b-HCV.

7.1.1.2.13. Results for other efficacy outcomes

- There was a higher relapse rate in the 8 week groups compared with the 12 week: 11 (5.1%) subjects in the SOF / LDV FDC 8 week group, 9 (4.2%) in the SOF / LDV + RBV 8 week, and 3 (1.4%) in the SOF / LDV 12 week group. Relapse was more likely if subjects were male and/or baseline HCV RNA was ≥ 800,000 (IU/mL).
- SVR4 rate was similar for the three treatment groups: number (rate [95% CI]) 207 (96.3 [92.8 to 98.4] %) subjects in the SOF / LDV FDC 8 week group, 205 (94.9 [91.1 to 97.4] %) in the SOF / LDV + RBV 8 week, and 208 (96.3 [92.8 to 98.4] %) in the SOF / LDV 12 week group.
- The proportion of subjects with HCV RNA < LLOQ increased to week 8 on-treatment for all three treatment groups.
- HCV RNA concentration decreased rapidly in the first two weeks of treatment in all three treatment groups.
- ALT normalisation at follow-up week 4 occurred for 115 (95.0%) subjects in the SOF / LDV FDC 8 week group, 122 (91.0%) in the SOF / LDV + RBV 8 week, and 134 (97.1%) in the SOF / LDV 12 week group.
- 116 (17.9%) subjects were identified as having at least one baseline NS5A RAV by deep sequencing with a 1% assay cut off. Of these, 104 (89.7%) subjects with baseline NS5A RAVs achieved SVR12. Of the 23 subjects that relapsed, ten had NS5A RAVs at baseline; of the 13 that did not, six had emergent NS5A RAVs at relapse.
- The addition of RBV to the treatment regimen resulted in an on-treatment decrease in SF-36 mental component score. This was also reflected in the FACIT F and WPAI:Hep C scores.
- The SVR24 data were not presented in the report.

7.1.1.3. Study GS-US-337-0109

7.1.1.3.1. Study design, objectives, locations and dates

Study GS-US-337-0109 was a Phase III, multicentre, randomised, open label study to investigate the efficacy and safety of SOF / LDV FDC ± RBV for 12 and 24 weeks in treatment experienced subjects with chronic GT1-HCV. The study was conducted at 64 centres in the US from January to December 2013. The data to week 12 were included in the report (which is an interim report).

7.1.1.3.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were the same as for Study GS-US-337-0102 except for the following inclusion criteria:

- Had prior virologic failure after treatment with a Peg-IFN + RBV regimen, including those who had failed treatment with an NS3/4A PI + Peg-IFN+RBV regimen. Subjects must not have discontinued prior therapy due to an adverse event (AE). Virologic failure included:
  - Non-response: Subject did not achieve undetectable HCV RNA levels (HCV RNA < LLOQ) while on treatment.
  - Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels (HCV RNA < LLOQ) during treatment or within 4 weeks of the end of treatment, but did not achieve SVR.

7.1.1.3.3. Study treatments

1. SOF 400 mg / LDV 90 mg FDC once daily for 24 weeks
2. SOF 400 mg / LDV 90 mg FDC once daily plus RBV 1000 mg or 1200 mg divided twice daily for 24 weeks
3. SOF 400 mg / LDV 90 mg FDC once daily for 12 weeks
4. SOF 400 mg / LDV 90 mg FDC once daily plus RBV 1000 mg or 1200 mg divided twice daily for 12 weeks

7.1.1.3.4. Efficacy variables and outcomes

The primary efficacy endpoint was SVR12 in the FAS. The test of efficacy was that the response rate was greater than the historical response rate of 25%.

The secondary efficacy outcome measures and safety outcome measures were the same as for Study GS-US-0102.

The schedule of study procedures (on-treatment and post-treatment) was the same as for Study GS-US-337-0102.

7.1.1.3.5. Randomisation and blinding methods

Randomization was by IWRS in a ratio of 1:1:1:1, stratified by HCV genotype (1a or 1b), the presence or absence of cirrhosis at screening, and response to prior HCV therapy (relapse/breakthrough or nonresponse) at screening. Enrolment was managed so that approximately 20% of randomized subjects had compensated cirrhosis and approximately 50% of randomized subjects had failed prior treatment with a protease inhibitor (PI) + Peg-IFN + RBV regimen.

7.1.1.3.6. Analysis populations

The FAS and safety analysis set included subjects who were randomised and received at least one dose of study drug.

7.1.1.3.7. Sample size

A sample size of 100 subjects in each treatment group provided over 99% power to detect at least a 45% improvement in the SVR12 rate from the adjusted historical null rate of 25% using a 2-sided exact 1-sample binomial test at a significance level of 0.0125 based on a Bonferroni correction.

7.1.1.3.8. Statistical methods

Hypothesis tests were performed using the 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method for the SVR12 rates in each of the 4 treatment groups. To adjust for multiplicity and strongly control the family-wise type I error rate at the 0.05 level, the Hochberg procedure was applied.

7.1.1.3.9. Participant flow

There were 551 subjects screened and 441 randomized to treatment: 109 subjects to the SOF / LDV FDC 12 Week group, 111 subjects to the SOF / LDV FDC + RBV 12 Week, 110 subjects to the SOF / LDV FDC 24 Week, and 111 subjects to the SOF / LDV + RBV 24 Week. A total of 437 (99.3%) subjects completed the study, and no subjects discontinued because of AE.

7.1.1.3.10. Major protocol violations/deviations

There were 28 important protocol deviations in 27 subjects, the majority (19) being for violation of inclusion / exclusion criteria.

7.1.1.3.11. Baseline data

There were 287 (65.2%) males, 153 (34.8%) females and the age range was 24 to 75 years. The treatment groups were similar in demographic characteristics. There were 347 (78.9%) subjects with GT1a-HCV and 93 (21.1%) with GT1b-HCV. The treatment groups were similar in disease characteristics and prior HCV treatment. There was ≥ 80% adherence to study treatment in 105 (96.3%) subjects in the SOF / LDV FDC 12 week group, 103 (92.8%) in the SOF / LDV FDC + RBV 12 week, 107 (98.2%) in the SOF / LDV FDC 24 week and 101 (91.0%) in the SOF / LDV FDC + RBV 24 week.

7.1.1.3.12. Results for the primary efficacy outcome

- SVR12 was achieved by 102 (93.6%) subjects in the SOF / LDV FDC 12 week group, 95% CI 87.2% to 97.4%, $p < 0.001$ (compared to the historical 25%)
- SVR12 was achieved by 107 (96.4%) subjects in the SOF / LDV FDC + RBV 12 week group, 95% CI 91.0% to 99.0%, $p < 0.001$
- SVR12 was achieved by 108 (99.1%) subjects in the SOF / LDV FDC 24 week group, 95% CI 95.0% to 100.0%, $p < 0.001$
- SVR12 was achieved by 110 (99.1%) subjects in the SOF / LDV FDC + RBV 24 week group, 95% CI 95.1% to 100.0%, $p < 0.001$

There was no effect on response for demographic characteristics. SOF / LDV FDC was equally effective for GT1a-HCV and GT1b-HCV and baseline disease characteristics did not influence efficacy. However, in the SOF / LDV FDC group, subjects with < 80% adherence to study treatment had reduced efficacy.

7.1.1.3.13. Results for other efficacy outcomes

- Overall virological failure was reported in seven (6.4%) subjects in the SOF / LDV FDC 12 week group, four (3.6%) in the SOF / LDV FDC + RBV 12 week, none in the SOF / LDV FDC 24 week and one (0.9%) in the SOF / LDV FDC + RBV 24 week. Relapse was reported in seven (6.5%) subjects in the SOF / LDV FDC 12 week group, four (3.6%) in the SOF / LDV FDC + RBV 12 week, none in the SOF / LDV FDC 24 week and none in the SOF / LDV FDC + RBV 24 week. Relapse risk was increased in subjects with cirrhosis and / or baseline thrombocytopenia.
- SVR4 was reported in 103 (94.5%) subjects in the SOF / LDV FDC 12 week group, 107 (96.4%) in the SOF / LDV FDC + RBV 12 week, 109 (100%) in the SOF / LDV FDC 24 week and 110 (99.1%) in the SOF / LDV FDC + RBV 24 week.
- Although the SVR24 data were incomplete, for the available data there was 100% concordance for SVR12 and SVR24.
- The proportion of subjects with HCV RNA < LLOQ increased to week 8 on-treatment for all three treatment groups.
- HCV RNA concentration decreased rapidly in the first two weeks of treatment in all three treatment groups.
- ALT normalisation (in those subjects with elevated ALT at baseline) occurred in 61 (89.7%) subjects in the SOF / LDV FDC 12 week group, 68 (88.3%) in the SOF / LDV FDC + RBV 12 week, 67 (93.1%) in the SOF / LDV FDC 24 week and 101 (91.7%) in the SOF / LDV FDC + RBV 24 week.
- 55 of 62 (88.7%) subjects with baseline NS5A RAVs achieved SVR12 following 12 or 24 weeks of treatment with SOF / LDV FDC ± RBV. In the SOF / LDV FDC 12 Week group, 13 of 17 (76.5%) subjects with baseline NS5A RAVs achieved SVR12 (four relapsed), and 15 of 17

(88.2%) subjects in the SOF / LDV FDC + RBV 12 Week group achieved SVR12 (two relapsed).

- Twelve subjects failed to achieve SVR12, with 11 relapses and one on-treatment failure associated with study drug non-compliance. Of the 12 subjects, 5 of 11 had no baseline RAVs, and the other 7 subjects had baseline NS5A RAVs. All 12 subjects had detectable NS5A RAVs at virologic failure, however no NS5B NI RAVs were detected. Phenotypic analysis showed a reduced susceptibility to LDV, but no change in susceptibility to SOF or RBV.
- The addition of RBV to the treatment regimen resulted in an on-treatment decrease in SF-36 mental component score for both 12 week and 24 week treatment groups. This was also reflected in the FACIT-F score. All the scores (including CLDQ-HCV and WPAI:Hep C) showed improvement during the treatment period.

7.1.2. Other efficacy studies

7.1.2.1. Study GS-US-337-0118

Study GS-US-337-0118 was a Phase II, randomized, open label study of SOF / LDV FDC ± RBV in subjects with chronic GT1-HCV. The study was conducted at one site in the US from October 2012 to July 2013. The study included males and non-pregnant females ≥ 18 years of age with chronic genotype 1 HCV infection and screening HCV RNA levels ≥ 104 IU/mL; those in Cohort 1 had no prior exposure to any interferon, RBV, or other approved or experimental HCV therapy and had documentation of absence of cirrhosis; those in Cohort 2 had previously experienced virologic failure with an approved or investigational PI + pegylated interferon (PEG) + RBV regimen and had documentation of the presence or absence of cirrhosis; all had a BMI ≥ 18 kg/m2. The study treatments were:

- Cohort 1: non-cirrhotic, treatment naïve:
  - Group 1: SOF LDV FDC once daily for 8 weeks
  - Group 2: SOF LDV FDC + RBV 1000 mg or 1200 mg as a divided dose twice daily, once daily for 8 weeks
  - Group 3: SOF / LDV FDC once daily for 12 weeks
- Cohort 2: cirrhotic and non-cirrhotic treatment experienced:
  - Group 4: SOF / LDV FDC once daily for 12 weeks
  - Group 5: SOF LDV FDC + RBV 1000 mg or 1200 mg as a divided dose twice daily, once daily for 12 week

The primary efficacy outcome measure was SVR12. Secondary efficacy outcome measures were: on-treatment virologic failure; SVR2, SVR4; SVR8, SVR24, RAVs; and the proportion of subjects with ALT normalization. The safety outcome measures were: AEs, laboratory tests, body weight, vital signs, and ECGs.

There were 100 subjects randomized to treatment: 20 to Group 1, 21 to Group 2, 19 to Group 3, 19 to Group 4 and 21 to Group 5. One subject discontinued and 99 completed. There were 66 (66.0%) males, 34 (34.0%) females and the age range was 21 to 73 years. There were 87 (87.0%) subjects with GT1a-HCV, 13 (13.0%) with GT1b-HCV and 22 (22.0%) with cirrhosis.

The results for SVR 12, n (% [95% CI]), were 19 (95.0% [75.1% to 99.9%]) for Group 1, 21 (100% [83.9% to 100.0%]) for Group 2, 18 (94.7% [74.0% to 99.9%]) for Group 3, 18 (94.7% [74.0% to 99.9%]) for Group 4 and 21 (100.0% [83.9% to 100.0%]) for Group 5. Relapse was reported for one (5.0%) subjects in Group 1 and one (5.3%) in Group 4. The results FOR Groups 2 to 5 for SVR2, SVR4, and SVR8 were in concordance with the results for SVR12, whilst the results for Group 1 indicate one subject initially responded but did not maintain response. There was concordance for SVR12 and SVR24. There were insufficient subjects to perform

subgroup analyses. For all five treatment groups HCV RNA decreased rapidly (within 1 week of treatment). Nine subjects had baseline NS5A RAVs of whom seven achieved SVR12. Two of these subjects relapsed. ALT normalization (for those subjects with elevated ALT at baseline) occurred at on-treatment week 1 for 9 (81.8%) affected subjects in Group 1, 11 (84.6%) in Group 2, 6 (85.7%) in Group 3, 7 (50.0%) in Group 4 and 14 (73.7%) in Group 5.

7.1.2.2. Study GS-US-337-0122

Study GS-US-337-0122 was a Phase II, multicentre, open-label study to evaluate safety and efficacy of SOF containing regimens administered for up to 12 weeks in subjects with chronic GT3-HCV HCV infection. The data were presented as an interim report for the two cohorts treated with SOF / LDV ± RBV. The study was conducted at two centres in New Zealand from April to November 2013. The study included males and non-pregnant, non-lactating females; ≥ 18 years with GT3-HCV infection, with or without cirrhosis. Subjects had HCV RNA ≥ 104 IU/mL and BMI ≥ 18 kg/m2 at screening. The study treatments were:

1. SOF / LDV FDC once daily
2. SPF/LDV FDC once daily + RBV 1000 mg for subjects weighing < 75 kg, 1200 mg for subjects weighing ≥ 75 kg, as a split dose twice daily.

Treatment duration was 12 weeks. The efficacy outcome measure was HCV RNA reported as SVR12. The study included 51 subjects: 25 in the SOF / LDV FDC group and 26 in the SOF / LDV FDC + RBV. There were 27 (52.9%) females, 24 (47.1%) males, and the age range was 22 to 64 years. SVR12 was achieved by 16 (64.0% [95% CI: 42.5% to 82.0%]) in the SOF / LDV FDC group and 26 (100.0% [95% CI: 86.8% to 100.0%]) in the SOF / LDV FDC group. Of the 9 subjects (36.0%) who did not achieve SVR12, 8 relapsed (5 at post-treatment Week 2, 1 at post-treatment Week 4, 1 at post-treatment Week 8, and 1 at post-treatment Week 12).

7.1.2.3. Study P7977-0523

Study P7977-0523 was a Phase IIa, multiple-dose, open-label study to evaluate different treatment regimens of SOF 400 mg alone or SOF/LDV for 6, 8, or 12 weeks administered with and without RBV and/or PEG-IFN in subjects with GT 1, 2, or 3 HCV infection and with and without LDV or GS-9669 in subjects with GT 1 HCV infection. The study was conducted at two centres in New Zealand from November 2010 to August 2013 The study included male and non-pregnant female subjects with chronic genotype 1, 2, or 3 HCV infection were enrolled in Parts 1 to 6 of this study. Subjects were between the ages of 18 and 70 years inclusive, had a BMI ≥ 18 kg/m2, determined to be non-cirrhotic (except for Groups 16, 17, and 20) by previous (within 3 years) or study-qualifying liver biopsy or FibroScan (liver elastography) within the previous 12 months, and otherwise healthy as determined during screening evaluations. Subjects in Groups 16 and 17 were cirrhotic, and subjects in Group 20 had no restrictions on their cirrhosis status. Groups 16 to 21 were treated with SOF / LDV FDC 400 mg / 90 mg once daily ± RBV twice daily. The efficacy outcome measure was HCV RNA at follow-up weeks 4, 8, 12, 24, 36 and 48. There were 68 subjects treated with SOF / LDV FDC; 48 of whom also treated with RBV. There were 46 (67.6%) males, 22 (32.3%) females, and the age range was 26 to 74 years. SVR12 was achieved by 7 (70%) of subjects with null responder GT1 treated with SOF / LDV FDC for 12 weeks; 9 (100%) of subjects with null responder GT1 treated with SOF / LDV FDC + RBV for 12 weeks; 8 (80%) of subjects with treatment naïve GT2/3 treated with SOF / LDV FDC for 12 weeks; 17 (68%) of subjects with treatment naïve GT1 treated with SOF / LDV for 6 weeks.

7.1.3. Analyses performed across trials (pooled analyses)

In the integrated summary of efficacy for Phase III studies, in treatment naïve subjects there were the following pooled results for SVR12, n/N (% [95% CI] p-value compared to 60%):

- GS-US-337-0108: SOF / LDV FDC 8 weeks treatment duration: 202/215 (94.0% [89.9% to 96.7%] < 0.001)

- GS-US-337-0108: SOF / LDV FDC + RBV 8 weeks treatment duration: 201/216 (93.1% [88.8% to 96.1%] < 0.001)
- GS-US-337-0108: SOF / LDV FDC 12weeks treatment duration: 206/216 (95.4% [91.7% to 97.8%] < 0.001)
- GS-US-337-0102: SOF / LDV FDC 12 weeks treatment duration: 209/214 (97.7% [94.6% to 99.2%] < 0.001)
- GS-US-337-0108 and GS-US-337-0102: SOF / LDV FDC 12 weeks treatment duration: 415/430 (96.5% [94.3% to 98.0%] not supplied)
- GS-US-337-0102: SOF / LDV FDC +RBV 12 weeks treatment duration: 211/217 (97.2% [94.1% to 99.0%] < 0.001)

In treatment experienced subjects for SVR12, n/N (% [95% CI] p-value compared to 25%):

- SOF / LDV FDC 12 weeks treatment duration: 102/109 (93.6% [87.2% to 97.4%] < 0.001)
- SOF / LDV FDC + RBV 12weeks treatment duration: 107/111 (96.4% [91.0% to 99.0%] < 0.001)
- SOF / LDV FDC 24 weeks treatment duration: 108/109 (99.1% [95.0% to 100.0%] < 0.001)
- SOF / LDV FDC +RBV 24 weeks treatment duration: 110/111 (99.1% [95.1% to 100.0%] < 0.001)

In treatment experienced subjects with cirrhosis, for SVR12, n/N (% [95% CI]):

- SOF / LDV FDC 12 weeks treatment duration: 19/22 (86.4% [65.1% to 97.1%])
- SOF / LDV FDC + RBV 12weeks treatment duration: 18/22 (81.8% [59.7% to 94.8%])
- SOF / LDV FDC 24 weeks treatment duration: 22/22 (100.0% [84.6% to 100.0%])
- SOF / LDV FDC +RBV 24 weeks treatment duration: 22/22 (100.0% [84.6% to 100.0%])

7.1.4. Evaluator's conclusions on efficacy

The efficacy data are supportive of efficacy in the proposed indication but in the opinion of the Evaluator the proposed treatment regimen may require modification.

In HCV treatment naïve subjects, with or without cirrhosis (Study GS-US-337-0102) SVR12 was achieved by 209 (97.7%) subjects in the SOF / LDV 12 week group, 95% CI 94.6% to 99.1%, p < 0.001. There was no additional benefit by also including RBV: SVR12 was achieved by 211 (97.2%) subjects in the SOF / LDV + RBV 12 week group, 95% CI 94.1% to 99.0%, p < 0.001.

In treatment naïve subjects with chronic GT1-HCV without cirrhosis (Study GS-US-337-0108) SVR12 was achieved by 202 (94.0%) subjects in the SOF / LDV FDC 8 week group, 95% CI 89.9% to 96.7%, p < 0.001. There was no additional benefit by also including RBV: SVR12 was achieved by 201 (93.1%) subjects in the SOF / LDV FDC + RBV 8 week group, 95% CI 88.8% to 96.1%, p < 0.001. There was no significant additional benefit with a longer, 12 week, treatment period: SVR12 was achieved by 206 (95.4%) subjects in the SOF / LDV FDC 12 week group, 95% CI 91.7% to 97.8%, p < 0.001.

In treatment experienced subjects with chronic GT1-HCV, i.e. with prior treatment failure with a Peg-IFN + RBV (Study GS-US-337-0109), SVR12 was achieved by 102 (93.6%) subjects in the SOF / LDV FDC 12 week group, 95% CI 87.2% to 97.4%, p < 0.001 (compared to the historical 25% response rate). There was better efficacy in those subjects treated with RBV and for longer treatment duration:

- SVR12 was achieved by 107 (96.4%) subjects in the SOF / LDV FDC + RBV 12 week group, 95% CI 91.0% to 99.0%, p < 0.001

- SVR12 was achieved by 108 (99.1%) subjects in the SOF / LDV FDC 24 week group, 95% CI 95.0% to 100.0%, p < 0.001
- SVR12 was achieved by 110 (99.1%) subjects in the SOF / LDV FDC + RBV 24 week group, 95% CI 95.1% to 100.0%, p < 0.001

Study GS-US-337-0118 was supportive of the pivotal studies but of too small a sample size to be pivotal.

Relapse is more likely in subjects with higher viral burden, male gender, cirrhosis and baseline thrombocytopenia. In Study GS-US-337-0108 there was a higher relapse rate in the 8 week groups compared with the 12 week: 11 (5.1%) subjects in the SOF / LDV FDC 8 week group, 9 (4.2%) in the SOF / LDV + RBV 8 week, and 3 (1.4%) in the SOF / LDV 12 week group; and relapse was more likely if subjects were male and/or baseline HCV RNA was ≥ 800,000 (IU/mL). In Study GS-US-337-0109 relapse risk was increased in subjects with cirrhosis and / or baseline thrombocytopenia.

In all three pivotal studies subjects with < 80% adherence to study treatment had reduced efficacy. However, in all three pivotal studies there was no effect on response for demographic characteristics and SOF / LDV FDC was equally effective for GT1a-HCV and GT1b-HCV. Baseline disease characteristics did not influence efficacy.

Baseline RAVs should not preclude treatment with SOF / LDV FDC. However, baseline NS5A RAVs appear to be more common in subjects that relapse and treatment emergent NS5A RAVs are more common than NS5B RAVs. In Study GS-US-337-0102 RAVs were reported in 32 (15.0% subjects in the SOF / LDV 12 week group, and 36 (16.7%) in the SOF / LDV + RBV 12 week group; and the one subject in the 12 week group who relapsed did not develop a RAV. In Study GS-US-337-0108 of the 23 subjects that relapsed, ten had NS5A RAVs at baseline; of the 13 that did not, six had emergent NS5A RAVs at relapse. In Study GS-US-337-0109 of the 12 subjects that relapsed, 5 of 11 had no baseline RAVs, and the other 7 subjects had baseline NS5A RAVs. All 12 subjects had detectable NS5A RAVs at virologic failure, but no NS5B NI RAVs were detected. Phenotypic analysis showed a reduced susceptibility to LDV, but no change in susceptibility to SOF or RBV.

In all three pivotal studies Quality of Life decreased during treatment for those subjects treated with RBV. Hence, the place of RBV as add-on therapy may be in those subjects with prior treatment failure, with or without cirrhosis.

Study GS-US-337-0122 did not support efficacy in subjects with chronic GT3-HCV. Study P7977-0523 did not support efficacy in subjects with GT2-HCV or GT3-HCV infection or a shorter treatment duration of 6 weeks in subjects with GT1-HCV.

The studies presented in the submission were mostly in accordance with the Guideline On The Clinical Evaluation Of Direct Acting Antiviral Agents Intended For Treatment Of Chronic Hepatitis C (EMEA/CHMP/EWP/30039/2008). The deficiencies in the submission are:

- Studies were open-label rather than double blind
- Long-term follow up data were not presented
- Data for SVR24 were incomplete
- Studies in subjects with HCV/HIV co-infected patients were not included

However, in the opinion of the Evaluator the potential benefits of SOF / LDV FDC outweigh the deficiencies in the study methodologies. The outcome measures were highly objective, which makes the open-label design more acceptable. Also, when available, the SVR24 data were in concordance with the SVR12 data.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Three pivotal efficacy/safety studies: Study GS-US-337-0102, Study GS-US-337-0108 and Study GS-US-337-0109
- Three other efficacy/safety studies: GS-US-337-0118, GS-US-337-0122 and Study P7977-0523
- 25 clinical pharmacology studies: Study GS-US-256-0110, Study GS-US-337-0101, Study GS-US-256-0101, Study GS-US-0108, Study GS-US-334-0111, Study GS-US-256-0102, Study GS-US-248-0117, Study GS-US-344-0101, Study GS-US-344-0108, Study GS-US-119-0113, GS-US-169-0105, Study GS-US-248-0102, Study GS-US-248-0104, Study GS-US-248-0107, Study GS-US-248-0125, Study GS-US-248-0127, Study GS-US-256-0129, Study GS-US-334-0101, Study GS-US-334-0146, Study GS-US-334-0148, GS-US-337-0127, Study GS-US-337-0128, Study GS-US-344-0102, Study MK-5172-pn023, and Study GS-US-344-0109
- An Integrated Summary of Efficacy and an Integrated Summary of Safety

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by report.
- Laboratory tests, including AST, ALT, bilirubin and FBC
- ECG and vital signs

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no studies that assessed safety as a primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by report.
- Laboratory tests, including AST, ALT, bilirubin and FBC
- ECG and vital signs

8.1.4. Other studies evaluable for safety only

There were 14 additional studies that contained clinical data. These studies used different drug combinations and/or different indications than those of the present application. These studies were: Study GS-US-248-0120, Study GS-US-248-0121, Study GS-US-248-0131, Study GS-US-248-0132, Study GS-US-256-0124, Study GS-US-256-0148, Study GS-US-334-0107, Study GS-US-334-0108, Study GS-US-334-0110, Study GS-US-334-0123, Study GS-US-334-0133, Study p2938-0721, Study p7977-1231, and Study p7977-2025. No additional safety concerns regarding SOF / LDV FDC were identified from these data.

8.1.5. Clinical pharmacology studies

No safety concerns were identified in the Clinical Pharmacology studies.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome

8.3. Patient exposure

8.3.1. Overall exposure to SOF / LDV FDC:

In the development program for SOF / LDV FDC there were 1952 subjects exposed to SOF / LDV FDC. This included:

- Subjects exposed to SOF / LDV FDC for treatment durations of 8 weeks: 215
- Subjects exposed to SOF / LDV FDC for treatment durations of 12 weeks: 539
- Subjects exposed to SOF / LDV FDC for treatment durations of 24 weeks: 326
- Subjects exposed to SOF / LDV FDC + RBV for treatment durations of 8 weeks: 216
- Subjects exposed to SOF / LDV FDC + RBV for treatment durations of 12 weeks: 328
- Subjects exposed to SOF / LDV FDC + RBV for treatment durations of 24 weeks: 328

There were 1175 (60.2%) males and 777 (39.8%) females. There were 152 (7.8%) subjects aged ≥ 65 years. There were 1234 (77.2%) subjects with confirmed GT1a-HCV and 356 (22.3%) with GT1b-HCV. There were 169 (10.6%) subjects with cirrhosis.

8.3.2. Exposure in efficacy trials:

In Study GS-US-337-0102 in the 12 Week treatment groups there were 214 subjects exposed to SOF / LDV FDC (192 for 12 weeks) and 217 to SOF / LDV FDC +RBV (194 for 12 weeks). In the 24 Week treatment groups there were 217 subjects exposed to SOF / LDV FDC (213 for 12 weeks, 186 for 24 weeks) and 217 to SOF / LDV FDC +RBV (216 for 12 weeks, 178 for 24 weeks)

In Study GS-US-337-0108, there were 215 subjects exposed to SOF / LDV FDC in the 8 week group, with 202 exposed for 8 weeks; 216 exposed to SOF / LDV FDC + RBV with 203 exposed for 8 weeks; and 216 in the SOF / LDV FDC 12 week group, with 194 exposed for 12 weeks.

In Study GS-US-337-0109, there were 109 subjects exposed to SOF / LDV FDC in the SOF / LDV FDC 12 week group (106 for 12 weeks), 111 in the SOF / LDV FDC + RBV 12 week (103 for 12 weeks), 109 in the SOF / LDV FDC 24 week (94 for 24 weeks) and 111 in the SOF / LDV FDC + RBV 24 week (99 for 24 weeks).

In Study GS-US-337-0118, there were 41 subjects exposed to SOF / LDV FDC ± RBV in the 8 week groups, 40 or whom completed 8 weeks, and 59 exposed to SOF / LDV FDC ± RBV in the 12 week groups, all of whom completed 12 weeks.

In Study GS-US-337-0122, 25 subjects were exposed to SOF / LDV FDC for up to 12 weeks and 26 to SOF / LDV FDC + RBV for up to 12 weeks.

In Study P7977-0523, summarized in Table 1.3.6, there were 10 subjects that were null responder GT1 treated with SOF / LDV FDC for 12 weeks; 9 subjects with null responder GT1 treated with SOF / LDV FDC + RBV for 12 weeks; 10 subjects with treatment naïve GT2/3 treated with SOF / LDV FDC for 12 weeks; 14 subjects with haemophilia and GT1-HCV treated with SOF / LDV FDC + RBV for 12 weeks, and 25 of subjects with treatment naïve GT1 treated with SOF / LDV for 6 weeks.

8.4. Adverse events

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

8.4.1.1. Pivotal studies

In Study GS-US-337-0102, TEAEs were reported in 168 (78.5%) subjects in the SOF / LDV 12 week group, 184 (84.8%) in the SOF / LDV + RBV 12 week, 177 (81.6%) in the SOF / LDV 24 week and 200 (92.2%) in the SOF / LDV + RBV 24 week. The commonest TEAEs were fatigue,

headache, insomnia and nausea. Fatigue and insomnia were more common in subjects co-medicated with RBV.

In Study GS-US-337-0108, TEAEs were reported in 145 (67.4%) subjects in the SOF / LDV FDC 8 week group, 165 (76.4%) subjects in the SOF / LDV FDC + RBV 8 week group, and 149 (69.0%) subjects in the SOF / LDV FDC 12 week group. The commonest TEAEs were headache, fatigue, nausea and insomnia, which were more common in the treatment group with RBV.

In Study GS-US-337-0109, TEAEs were reported in 73 (67.0%) subjects in the SOF / LDV FDC 12 week group, 96 (86.5%) in the SOF / LDV FDC + RBV 12 week, 88 (80.7%) in the SOF / LDV FDC 24 week and 100 (90.1%) in the SOF / LDV FDC + RBV 24 week. The most commonly reported TEAEs were fatigue, headache, nausea, insomnia and arthralgia. Fatigue, nausea, insomnia, arthralgia, cough, and rash were more common in the RBV treated groups.

8.4.1.2. Other studies

In Study GS-US-337-0118, TEAEs were reported in 9 (45.0%) subjects in the SOF / LDV FDC treatment naïve 8 week group; 12 (57.1%) in the SOF / LDV FDC + RBV treatment naïve 8 week group; 8 (42.1%) in the SOF / LDV FDC treatment naïve 12 week group; 7 (36.8%) in the SOF / LDV FDC treatment experienced 12 week group; and 12 (57.1%) in the SOF / LDV FDC + RBV treatment experienced 12 week group. The commonest TEAEs were nausea, anaemia and upper respiratory tract infection, which were more common in the SOF / LDV FDC + RBV treatment experienced 12 week group.

In Study GS-US-337-0122, TEAEs were reported in 25 (100%) subjects in the SOF / LDV FDC group and 23 (88.5%) in the SOF / LDV FDC + RBV group. The commonest TEAEs were headache, URTI, nausea, fatigue and insomnia.

In Study P7977-0523, TEAEs were reported in 7 (70%) subjects that were null responder GT1 treated with SOF / LDV FDC for 12 weeks; 8 (88.9%) subjects with null responder GT1 treated with SOF / LDV FDC + RBV for 12 weeks; 7 (70%) subjects with treatment naïve GT2/3 treated with SOF / LDV FDC for 12 weeks; 13 (92.9%) subjects with haemophilia and GT1-HCV treated with SOF / LDV FDC + RBV for 12 weeks, and 22 (88.0%) of subjects with treatment naïve GT1 treated with SOF / LDV for 6 weeks. The most frequently reported TEAEs were headache, nausea, fatigue and insomnia.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

In Study GS-US-337-0102, treatment related TEAEs were reported in 106 (49.5%) subjects in the SOF / LDV 12 week group, 152 (70.0%) in the SOF / LDV + RBV 12 week, 115 (53.0%) in the SOF / LDV 24 week and 170 (78.3%) in the SOF / LDV + RBV 24 week. The commonest treatment related TEAEs were fatigue, headache, insomnia and nausea. Fatigue and insomnia were more common in subjects co-medicated with RBV.

In Study GS-US-337-0108, treatment related TEAEs were reported in 82 (38.1%) subjects in the SOF / LDV FDC 8 week group, 133 (61.6%) subjects in the SOF / LDV FDC + RBV 8 week group, and 93 (43.1%) subjects in the SOF / LDV FDC 12 week group. The most commonly reported treatment related TEAEs were fatigue, headache and nausea, which were more common in the group treated with RBV.

In Study GS-US-337-0109, treatment related TEAEs were reported in 38 (34.9%) subjects in the SOF / LDV FDC 12 week group, 77 (69.4%) in the SOF / LDV FDC + RBV 12 week, 50 (45.9%) in the SOF / LDV FDC 24 week and 85 (76.6%) in the SOF / LDV FDC + RBV 24 week. The most commonly reported treatment related TEAEs were fatigue, headache, nausea, insomnia and arthralgia, all of which were more common in the RBV treated groups.

8.4.2.2. Other studies

In Study GS-US-337-0118 (Table 1.3.4) treatment related TEAEs were reported in 5 (25.0%) subjects in the SOF / LDV FDC treatment naïve 8 week group; 6 (47.6%) in the SOF / LDV FDC + RBV treatment naïve 8 week group; 2 (10.5%) in the SOF / LDV FDC treatment naïve 12 week group; one (5.3%) in the SOF / LDV FDC treatment experienced 12 week group; and 10 (47.6%) in the SOF / LDV FDC + RBV treatment experienced 12 week group. The most common treatment related TEAEs were anaemia and nausea, which were more common in the SOF / LDV FDC + RBV treatment experienced 12 week group.

In Study GS-US-337-0122, treatment related TEAEs were reported in 18 (72%) subjects in the SOF / LDV FDC group and 17 (65.4%) in the SOF / LDV FDC + RBV group.

In Study P7977-0523, treatment related TEAEs were reported in 6 (60%) subjects that were null responder GT1 treated with SOF / LDV FDC for 12 weeks; 8 (88.9%) subjects with null responder GT1 treated with SOF / LDV FDC + RBV for 12 weeks; 6 (60%) subjects with treatment naïve GT2/3 treated with SOF / LDV FDC for 12 weeks; 12 (85.7%) subjects with haemophilia and GT1-HCV treated with SOF / LDV FDC + RBV for 12 weeks, and 22 (88.0%) of subjects with treatment naïve GT1 treated with SOF / LDV for 6 weeks. Headache, fatigue, nausea and insomnia were more common in the RBV treated groups.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In Study GS-US-337-0102, there were no deaths. SAEs were reported in one (0.5%) subjects in the SOF / LDV 12 week group, seven (3.2%) in the SOF / LDV + RBV 12 week, 18 (8.3%) in the SOF / LDV 24 week and six (2.8%) in the SOF / LDV + RBV 24 week. There was no apparent pattern to the SAEs.

In Study GS-US-337-0108, there were no deaths. SAEs were reported in four (1.9%) subjects in the SOF / LDV FDC 8 week group, one (0.5%) subject in the SOF / LDV FDC + RBV 8 week group, and five (2.3%) subjects in the SOF / LDV FDC 12 week group. There was no apparent pattern to the SAEs.

In Study GS-US-337-0109, there were no deaths. SAEs were reported in no subjects in the SOF / LDV FDC 12 week group, none in the SOF / LDV FDC + RBV 12 week, six (5.5%) in the SOF / LDV FDC 24 week and three (2.7%) in the SOF / LDV FDC + RBV 24 week. There was no apparent pattern to the SAEs.

8.4.3.2. Other studies

In Study GS-US-337-0118, there were no deaths. SAEs were reported in no subjects in the SOF / LDV FDC treatment naïve 8 week group; one (4.8%) in the SOF / LDV FDC + RBV treatment naïve 8 week group (delirium); one (5.3%) in the SOF / LDV FDC treatment naïve 12 week group (peptic ulcer); one (5.3%) in the SOF / LDV FDC treatment experienced 12 week group (spinal compression fracture); and one (4.8%) in the SOF / LDV FDC + RBV treatment experienced 12 week group (anaemia and suicidal ideation).

In Study GS-US-337-0122, there were no deaths. SAEs were reported in four (16%) subjects in the SOF / LDV FDC group (abdominal pain, upper abdominal pain, diverticular perforation and choroidal effusion / lens dislocation) and none in the SOF / LDV FDC + RBV group.

In Study P7977-0523, there were no deaths. SAEs were reported in 2 (14.3%) subjects with haemophilia and GT1-HCV treated with SOF / LDV FDC + RBV for 12 weeks (syncope and cholelithiasis).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In Study GS-US-337-0102, DAEs (from SOF / LDV) were reported in no subjects in the SOF / LDV 12 week or SOF / LDV + RBV 12 week groups, four (1.8%) in the SOF / LDV 24 week and six (2.8%) in the SOF / LDV + RBV 24 week. There was no apparent pattern to the DAEs.

In Study GS-US-337-0108, DAE was reported for no subjects in the SOF / LDV FDC 8 week group, one (0.5%) subjects in the SOF / LDV FDC + RBV 8 week group (road traffic accident), and two (0.9%) subjects in the SOF / LDV FDC 12 week group (arthralgia, squamous cell carcinoma of lung).

In Study GS-US-337-0109, there were no DAEs.

8.4.4.2. Other studies

In Study GS-US-337-0118, there were no DAEs.

In Study GS-US-337-0122, DAEs were reported in one (4.0%) subject in the SOF / LDV FDC group (diverticular perforation) and none in the SOF / LDV FDC + RBV group.

In Study P7977-0523, there were no DAEs.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

In Study GS-US-337-0102, significant post-baseline elevation of AST and/or ALT was reported for one subject in the SOF / LDV group. One subject had AST or ALT > 3xULN and bilirubin > 2xULN with no signs of liver disease that resolved on treatment (and was not attributed to SOF / LDV).

In Study GS-US-337-0108, Grade 4 elevation in ALT and AST was reported in one subject in the SOF / LDV FDC 12 week group. No subjects in any treatment group had an AST or ALT > 3×ULN and total bilirubin > 2×ULN.

In Study GS-US-337-0109, grade 3 abnormalities in ALT were reported for one (0.9%) subject in the SOF / LDV FDC 12 week group, and one (0.9%) in the SOF / LDV FDC 24 week; and in AST for one (0.9%) in the SOF / LDV FDC 24 week. There were no subjects with on-treatment AST or ALT > 3xULN and total bilirubin > 2xULN.

8.5.1.2. Other studies

In Study GS-US-337-0118, no subjects had significant elevation from baseline of AST, ALT or bilirubin.

In Study GS-US-337-0122, there were no clinically significant abnormalities in ALT or AST.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

There were no reports of renal failure in the pivotal studies.

8.5.2.2. Other studies

There were no reports of renal failure in the supportive studies.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

In Study GS-US-337-0102, significant (Grade 3 or 4) elevation in serum lipase was reported in five (2.3%) subjects in the SOF / LDV 12 week group, three (1.4%) in the SOF / LDV + RBV 12 week, eight (3.7%) in the SOF / LDV 24 week and four (1.8%) in the SOF / LDV + RBV 24 week.

In Study GS-US-337-0108 (Table 1.3.2) significant (Grade 3 or 4) elevation in serum lipase was reported in two (0.9%%) subjects in the SOF / LDV FDC 8 week group, one (0.5%) in the SOF / LDV FDC + RBV 8 week, and six (2.8%) in the SOF / LDV FDC 12 week group.

In Study GS-US-337-0109 (Table 1.3.3) grade 3or 4 abnormalities in lipase were reported for no subjects in the SOF / LDV FDC 12 week group, one (0.9%) in the SOF / LDV FDC + RBV 12 week, two (0.9%) in the SOF / LDV FDC 24 week and one (0.9%) in the SOF / LDV FDC + RBV 24 week.

8.5.3.2. Other studies

In Study GS-US-337-0118, one (5.3%) subject in the SOF / LDV FDC treatment experienced 12 week group had significant elevation in serum lipase.

In Study P7977-0523, one subject had a grade 3 elevation in serum lipase.

8.5.4. Haematology

8.5.4.1. Pivotal studies

In Study GS-US-337-0102, a significant decrease in haemoglobin was reported in one (0.5%) subjects in the SOF / LDV 12 week group, 10 (4.6%) in the SOF / LDV + RBV 12 week, none in the SOF / LDV 24 week and 18 (8.3%) in the SOF / LDV + RBV 24 week. Post baseline haemoglobin < 10 g/dL was only reported in the RBV groups: 20 (9.2%) subjects in the SOF / LDV + RBV 12 week and 16 (7.4%) in the SOF / LDV + RBV 24 week.

In Study GS-US-337-0108, Grade 3 abnormalities in haemoglobin were reported no subjects in the SOF / LDV FDC 8 week group, 14 (6.5%) subjects in the SOF / LDV FDC + RBV 8 week group, and two (0.9%) subjects in the SOF / LDV FDC 12 week group. Post-baseline haemoglobin < 10 g/dL was reported in no subjects in the SOF / LDV FDC 8 week group, 11 (5.1%) subjects in the SOF / LDV FDC + RBV 8 week group, and one (0.5%) subjects in the SOF / LDV FDC 12 week group.

In Study GS-US-337-0109, grade 3 abnormalities in haemoglobin were only recorded in the RBV treated groups: 10 (9.0%) subjects in the SOF / LDV FDC + RBV 12 week group, and 22 (19.8%) in the SOF / LDV FDC + RBV 24 week. The number (%) of subjects with haemoglobin < 10 g/dL was 2 (1.8%) in the SOF / LDV FDC + RBV 12 week group, and 9 (8.1%) in the SOF / LDV FDC + RBV 24 week.

8.5.4.2. Other studies

In Study GS-US-337-0118, low haemoglobin was reported for two (9.5%) subjects in the SOF / LDV FDC + RBV treatment naïve 8 week group and two (9.5%) in the SOF / LDV FDC + RBV treatment experienced 12 week group.

In Study GS-US-337-0122, grade 3 abnormalities in haemoglobin were reported in 5 (19.2%) subjects in the SOF / LDV FDC + RBV group. Haemolytic anaemia was reported in 4 (15.4%) subjects in the SOF / LDV FDC + RBV group.

The Sponsor has reported that the four drug combination of LDV + VDV + PEG + RBV is associated with a risk of pancytopenia of 0.3%. There was also a rate of anaemia of around 20% and neutropenia of up to 17% with this combination (Study GS-US-256-0148).

8.5.5. Electrocardiograph

8.5.5.1. Pivotal studies

In Study GS-US-337-0108, one subject in the SOF / LDV FDC 8 week group had a new ECG finding of myocardial strain.

8.5.5.2. Other studies

There were no reports of significant ECG abnormalities in the supportive studies.

8.5.6. Vital signs

8.5.6.1. Pivotal studies

In Study GS-US-337-0102, there were no clinically significant abnormalities in vital signs.

In Study GS-US-337-0108, there were no reports of clinically significant changes in vital signs.

In Study GS-US-337-0109, there were no reports of clinically significant changes in vital signs.

8.5.6.2. Other studies

In Study GS-US-337-0118, there were no reports of clinically significant changes in vital signs.

8.6. Post-marketing experience

8.6.1. Post-marketing data

No post-marketing data were included in the submission.

8.6.2. Risk management plan

8.6.2.1. Important identified risks

The RMP states there are no Important Identified Risks for SOF/LDV or its components.

8.6.2.2. Important potential risks

The RMP states the following Important Potential Risks:

- Drug-drug interaction with potent intestinal Pgp inducers (SOF, LDV)
- Staggered administration of proton pump inhibitors (LDV)
- Drug-drug interaction with rosuvastatin (LDV)
- Drug-drug interaction with digoxin (LDV)

8.6.2.3. Missing information

The RMP states the following Missing Information:

- Safety in children
- Safety in pregnant or breastfeeding women
- Safety in patients with HCV/HIV co-infection
- Safety in patients with advanced liver disease
- Safety in patient who are post liver transplantation
- Safety in HCV patients with severe renal impairment or end-stage renal disease

8.7. Safety issues with the potential for major regulatory impact

There were no safety issues with the potential for major regulatory impact identified in the data.

8.8. Other safety issues

8.8.1. Safety in special populations

No safety issues in special populations were identified in the submitted data but there were no data for the following populations:

- Paediatric
- Pregnancy and lactation
- Subjects with combined HCV / HIV infections
- Subjects with significant co-morbidities
- Subjects with ESRF

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

There were no safety issues relating to interactions identified in the efficacy data, but the clinical pharmacology data indicate the potential for interactions to occur. There is particular concern with regard to statins and digoxin.

8.9. Evaluator's overall conclusions on clinical safety

SOF / LDV FDC has a favourable safety profile. The most frequently reported TEAEs were fatigue, headache, insomnia, nausea and arthralgia. These TEAEs were more frequent in the groups treated with RBV. Quality of life improved during treatment in those patients treated with SOF / LDV FDC by itself, but decreased in those subjects also treated with RBV.

There were no deaths in the efficacy studies or in the clinical pharmacology studies. SAEs were infrequent and there was no clear pattern attributable to SOF / LDV FDC. There were few DAEs.

One subject had AST or ALT > 3xULN and bilirubin > 2xULN with no signs of liver disease that resolved on treatment (and was not attributed to SOF / LDV).

Anaemia was reported in up to 9.2% of the subjects treated with RBV.

In the efficacy studies there was a higher than expected rate of significant elevation in serum lipase, but the frequency was ≤ 1.8% in any individual study. Although this may be a feature of the underlying condition, it may also be a safety signal.

The thorough QT study did not indicate any significant QTc prolongation however the dose used in that study was only 33% higher than the proposed dosing regimen.

There were no long term safety data included in the submission. Hence, it is not possible to comment on the long-term safety effects of SOF / LDV FDC.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The efficacy data are supportive of efficacy in the proposed indication but in the opinion of the Evaluator the proposed treatment regimen may require modification.

In HCV treatment naïve subjects, with or without cirrhosis (Study GS-US-337-0102) SVR12 was achieved by 209 (97.7%) subjects in the SOF / LDV 12 week group, 95% CI 94.6% to 99.1%, p < 0.001. There was no additional benefit by also including RBV: SVR12 was achieved by 211 (97.2%) subjects in the SOF / LDV + RBV 12 week group, 95% CI 94.1% to 99.0%, p < 0.001.

In treatment naïve subjects with chronic GT1-HCV without cirrhosis (Study GS-US-337-0108) SVR12 was achieved by 202 (94.0%) subjects in the SOF / LDV FDC 8 week group, 95% CI 89.9% to 96.7%, p < 0.001. There was no additional benefit by also including RBV: SVR12 was achieved by 201 (93.1%) subjects in the SOF / LDV FDC + RBV 8 week group, 95% CI 88.8% to 96.1%, p < 0.001. There was no significant additional benefit with a longer, 12 week, treatment period: SVR12 was achieved by 206 (95.4%) subjects in the SOF / LDV FDC 12 week group, 95% CI 91.7% to 97.8%, p < 0.001.

In treatment experienced subjects with chronic GT1-HCV, i.e. with prior treatment failure with a Peg-IFN + RBV, (Study GS-US-337-0109) SVR12 was achieved by 102 (93.6%) subjects in the SOF / LDV FDC 12 week group, 95% CI 87.2% to 97.4%, p < 0.001 (compared to the historical 25% response rate). There was better efficacy in those subjects treated with RBV and for longer treatment duration:

- SVR12 was achieved by 107 (96.4%) subjects in the SOF / LDV FDC + RBV 12 week group, 95% CI 91.0% to 99.0%, p < 0.001
- SVR12 was achieved by 108 (99.1%) subjects in the SOF / LDV FDC 24 week group, 95% CI 95.0% to 100.0%, p < 0.001
- SVR12 was achieved by 110 (99.1%) subjects in the SOF / LDV FDC + RBV 24 week group, 95% CI 95.1% to 100.0%, p < 0.001

Relapse is more likely in subjects with higher viral burden, male gender, cirrhosis and baseline thrombocytopenia. In Study GS-US-337-0108 there was a higher relapse rate in the 8 week groups compared with the 12 week: 11 (5.1%) subjects in the SOF / LDV FDC 8 week group, 9 (4.2%) in the SOF / LDV + RBV 8 week, and 3 (1.4%) in the SOF / LDV 12 week group; and relapse was more likely if subjects were male and/or baseline HCV RNA was ≥ 800,000 (IU/mL). In Study GS-US-337-0109 relapse risk was increased in subjects with cirrhosis and / or baseline thrombocytopenia.

In all three pivotal studies subjects with < 80% adherence to study treatment had reduced efficacy. However, in all three pivotal studies there was no effect on response for demographic characteristics and SOF / LDV FDC was equally effective for GT1a-HCV and GT1b-HCV. Baseline disease characteristics did not influence efficacy.

Baseline RAVs should not preclude treatment with SOF / LDV FDC. However, baseline NS5A RAVs appear to be more common in subjects that relapse and treatment emergent NS5A RAVs are more common than NS5B RAVs. In Study GS-US-337-0102 RAVs were reported in 32 (15.0% subjects in the SOF / LDV 12 week group, and 36 (16.7%) in the SOF / LDV + RBV 12 week group; and the one subject in the 12 week group who relapsed did not develop a RAV. In Study GS-US-337-0108 of the 23 subjects that relapsed, ten had NS5A RAVs at baseline; of the 13 that did not, six had emergent NS5A RAVs at relapse. In Study GS-US-337-0109 of the 12 subjects that relapsed, 5 of 11 had no baseline RAVs, and the other 7 subjects had baseline NS5A RAVs. All 12 subjects had detectable NS5A RAVs at virologic failure, but no NS5B NI RAVs were detected. Phenotypic analysis showed a reduced susceptibility to LDV, but no change in susceptibility to SOF or RBV.

In all three pivotal studies Quality of Life decreased during treatment for those subjects treated with RBV. Hence, the place of RBV as add-on therapy may be in those subjects with prior treatment failure, with or without cirrhosis.

Efficacy has not been demonstrated for HCV genotypes other than GT1-HCV. Study GS-US-337-0122 did not support efficacy in subjects with chronic GT3-HCV HCV. Study P7977-0523 did not support efficacy in subjects with GT2-HCV or GT3-HCV infection or shorter treatment duration of 6 weeks in subjects with GT1-HCV.

The studies presented in the submission were mostly in accordance with the Guideline On The Clinical Evaluation Of Direct Acting Antiviral Agents Intended For Treatment Of Chronic Hepatitis C (EMEA/CHMP/EWP/30039/2008). The deficiencies in the submission are:

- Studies were open-label rather than double blind
- Long-term follow up data were not presented
- Data for SVR24 were incomplete
- Studies in subjects with HCV/HIV co-infected patients were not included

However, in the opinion of the Evaluator the potential benefits of SOF / LDV FDC outweigh the deficiencies in the study methodologies. The outcome measures were highly objective, which makes the open-label design more acceptable. Also, when available, the SVR24 data were in concordance with the SVR12 data.

In the opinion of the evaluator:

- An SOF / LDV FDC 8 week treatment regimen is supported in treatment naïve subjects with chronic GT1-HCV without cirrhosis
- An SOF / LDV FDC 12 week treatment regimen is supported in treatment naïve subjects with chronic GT1-HCV with cirrhosis
- An SOF / LDV FDC 24 week treatment regimen is supported in treatment experienced subjects with chronic GT1-HCV
- In the above treatment regimens, RBV does not offer additional benefit and may decrease Quality of life

9.2. First round assessment of risks

SOF / LDV FDC has a favourable safety profile. The most frequently reported TEAEs were fatigue, headache, insomnia, nausea and arthralgia. These TEAEs were more frequent in the groups treated with RBV. Quality of life improved during treatment in those patients treated with SOF / LDV FDC by itself, but decreased in those subjects also treated with RBV.

There were no deaths in the efficacy studies or in the clinical pharmacology studies. SAEs were infrequent and there was no clear pattern attributable to SOF / LDV FDC. There were few DAEs.

One subject had AST or ALT > 3xULN and bilirubin >2xULN with no signs of liver disease that resolved on treatment (and was not attributed to SOF / LDV).

Anaemia was reported in up to 9.2% of the subjects treated with RBV.

In the efficacy studies there was a higher than expected rate of significant elevation in serum lipase, but the frequency was ≤ 1.8% in any individual study. Although this may be a feature of the underlying condition, it may also be a safety signal.

The thorough QT study did not indicate any significant QTc prolongation however the dose used in that study was only 33% higher than the proposed dosing regimen.

There were no long term safety data included in the submission. Hence, it is not possible to comment on the long-term safety effects of SOF / LDV FDC.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of register Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) FDC tablets, given the proposed usage, is favourable.

However, consideration needs to be given as to the most appropriate dosing recommendation. In the opinion of the Evaluator this should be:

In the opinion of the evaluator:

- SOF / LDV FDC once daily for 8 weeks in treatment naïve subjects with chronic GT1-HCV without cirrhosis
- SOF / LDV FDC once daily for 12 weeks in treatment naïve subjects with chronic GT1-HCV with cirrhosis
- SOF / LDV FDC once daily for 24 weeks in treatment experienced subjects with chronic GT1-HCV, with or without cirrhosis
- RBV does not offer additional benefit as add-on therapy and may decrease Quality of Life

10. First round recommendation regarding authorisation

The Evaluator has no objection to the approval of Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) FDC tablets for the indication of:

> *Harvoni is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.*

Consideration should be given to amending the dosing recommendations in line with the comments.

11. Clinical questions

11.1. Pharmacokinetics

The Evaluator has no questions relating to pharmacokinetics.

11.2. Pharmacodynamics

The Evaluator has no questions relating to pharmacodynamics.

11.3. Efficacy

Can the Sponsor please provide the SVR24 data for the pivotal studies?

Does the Sponsor have access to any long term follow-up data (1 to 2 years) with regard maintenance of efficacy?

11.4. Safety

Does the Sponsor have access to any long term follow-up data (1 to 2 years) with regard safety?

12. Second round evaluation

Can the sponsor please provide the SVR24 data for the pivotal studies?

The Sponsor has provided the final study report for Study GS-US-337-0102, and update reports for Study GS-US-337-0108 and Study GS-US-337-0109.

The final study report contained the data for SVR24 and also for the 24 week treatment regimen. There were 217 subjects randomised to SOF / LDV FDC, of whom 207 (95.4%) completed, and 217 to SOF / LDV + RBV, of whom 204 (94.0%) completed. For the primary efficacy outcome measure, the results were:

- SVR12 was achieved by 211 (98.6%) subjects in the SOF / LDV 12 week group, 95% CI 96.0% to 99.7%, $p < 0.001$
- SVR12 was achieved by 211 (97.2%) subjects in the SOF / LDV + RBV 12 week group, 95% CI 94.1% to 99.0%, $p < 0.001$
- SVR12 was achieved by 213 (97.7%) subjects in the SOF / LDV 24 week group, 95% CI 95.3% to 99.5%, $p < 0.001$
- SVR12 was achieved by 215 (97.2%) subjects in the SOF / LDV + RBV 24 week group, 95% CI 96.7% to 99.9%, $p < 0.001$

There was a similar response rate in subjects with cirrhosis treated with SOF / LDV compared to those treated with SOV / LDV + RBV. In the SOF / LDV 24 week group, 181 (98.4%) subjects without cirrhosis responded, compared with 32 (97.0%) subjects with cirrhosis. In the SOF / LDV 24 week group one subject had on treatment virological failure and one relapsed. In the SOF / LDV + RBV 24 week group there were no virological failures or relapses. SVR4 was achieved by 215 (99.1%) subjects in the SOF / LDV 24 week group, 95% CI 96.7% to 99.9%; SVR4 was achieved by 215 (99.1%) subjects in the SOF / LDV + RBV 12 week group, 95% CI 96.7% to 99.9%. All of the subjects with SVR12 response in all the study groups also had SVR24 response (i.e. the results are identical to those for SVR12).

All of the subjects with SVR12 response in Study GS-US-337-0108 also had SVR24 response (i.e. the results were identical to those for SVR12).

- SVR24 was achieved by 202 (94.0%) subjects in the SOF / LDV FDC 8 week group, 95% CI 89.9% to 96.7%
- SVR24 was achieved by 201 (93.1%) subjects in the SOF / LDV FDC + RBV 8 week group, 95% CI 88.8% to 96.1%
- SVR24 was achieved by 208 (96.3%) subjects in the SOF / LDV FDC 12 week group, 95% CI 92.8% to 98.4%, $p < 0.001$

The results for the SOF / LDV FDC 12 week group were updated as these data were incomplete in the interim report initially submitted.

The Sponsor provided the post-treatment Week 24 HCV RNA data in the S31 response. All the subjects that achieved SVR12 response also achieved SVR24 response. The results by treatment group were:

- SVR24 was achieved by 102 (93.6%) subjects in the SOF / LDV FDC 12 week group, 95% CI 87.2% to 97.4%
- SVR24 was achieved by 107 (96.4%) subjects in the SOF / LDV FDC + RBV 12 week group, 95% CI 91.0% to 99.0%
- SVR24 was achieved by 108 (99.1%) subjects in the SOF / LDV FDC 24 week group, 95% CI 95.0% to 100.0%
- SVR24 was achieved by 110 (99.1%) subjects in the SOF / LDV FDC + RBV 24 week group, 95% CI 95.1% to 100.0%

Evaluator's comments: The Sponsor's response is acceptable and has resolved the issue. All of the subjects that achieved SVR12 response in the pivotal studies also achieved SVR24 response.

Does the sponsor have access to any long term follow-up data (1 to 2 years) with regard maintenance of efficacy?

Sponsor's response: The Sponsor did not respond by providing additional long term follow up efficacy data. The Sponsor provided the protocols for two long term follow up studies that are currently being conducted:

- Study GS-US-248-0122: a long term follow-up registry study for subjects who achieve a sustained virologic response to treatment in Gilead-sponsored trials in subjects with chronic hepatitis C infection. Subjects will be followed for up to 3 years. Visits will occur at Baseline and then at Weeks 24, 48, 72, 96, 120 and 144. At each visit, subjects will have blood drawn for plasma HCV RNA quantification, liver function tests, platelets, coagulation test, α-fetoprotein, and a quality of life survey will be completed.
- Study GS-US-248-0123: a long term follow-up registry study of subjects who did not achieve sustained virologic response in Gilead-sponsored trials in subjects with chronic hepatitis C infection. The study procedures are similar to those for Study GS-US-248-0122.

The Sponsor will provide the results of these studies to the TGA once the clinical reports are available.

Evaluator's comments: The Sponsor's response is acceptable and has resolved the issue.

Does the sponsor have access to any long term follow-up data (1 to 2 years) with regard maintenance of safety?

Sponsor's response: The Sponsor did not respond by providing additional long term follow up safety data. The Sponsor provided the protocols for two long term follow up studies that are currently being conducted:

- Study GS-US-248-0122: a long term follow-up registry study for subjects who achieve a sustained virologic response to treatment in Gilead-sponsored trials in subjects with chronic hepatitis C infection. The safety data from this study will be limited as the definition for reporting an AE is: "an AE is any untoward medical occurrence in a clinical investigation subject associated with procedures mandated by this Registry protocol. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with procedures mandated by this Registry (e.g., hematoma following venipuncture)". The definition of SAE is similarly restrictive.
- Study GS-US-248-0123: a long term follow-up registry study of subjects who did not achieve sustained virologic response in Gilead-sponsored trials in subjects with chronic hepatitis C infection. The definitions for reporting AEs are the same as for Study GS-US-248-0122.

The Sponsor will provide the results of these studies to the TGA once the clinical reports are available.

Evaluator's comments: The Sponsor's response is not acceptable. The proposed studies will not identify safety data due to the restricted definitions of AE and SAE used in the studies. In the opinion of the Evaluator, the Sponsor should also use these studies to identify potential long term adverse effects of SOF / LDV.

However, consideration needs to be given as to the most appropriate dosing recommendation. In the opinion of the Evaluator this should be:

- **SOF / LDV FDC once daily for 8 weeks in treatment naïve subjects with chronic GT1-HCV without cirrhosis**
- **SOF / LDV FDC once daily for 12 weeks in treatment naïve subjects with chronic GT1-HCV with cirrhosis**

- **SOF / LDV FDC once daily for 24 weeks in treatment experienced subjects with chronic GT1-HCV, with or without cirrhosis**
- **RBV does not offer additional benefit as add-on therapy and may decrease Quality of Life**

Sponsor's response: The Sponsor intends to retain the originally proposed dosing recommendations which are:

- For treatment-naïve patients without cirrhosis the recommended duration of treatment with Harvoni is 8 weeks.
- For treatment-naïve patients with cirrhosis and all treatment-experienced patients the recommended duration of treatment with Harvoni is 12 weeks.

The reasons for retaining this dosing recommendation is to avoid over-treating those patients who respond to this shorter treatment course, and thereby exposing them to more AEs. The Sponsor quotes 95% of subjects would be over-treated in order to prevent 5% of relapses. The Sponsor also believes there would be greater cost and healthcare utilisation with the longer treatment course and lesser adherence to the treatment regimen.

Evaluator's comments: The Sponsor's response is not acceptable. Based upon the data submitted, there is greater efficacy in treatment experienced subjects with the 24 week treatment course. These data are based upon the full analysis set (which included subjects who were randomized and received at least one dose of study drug) and therefore non-adherence is taken into account in the analysis, and the longer treatment course still had greater efficacy. The adverse event profile of SOF / LDV is favourable so the argument that the longer treatment course has unacceptable risk is not valid. In the opinion of the Evaluator, the 5% of subjects that would relapse with a shorter course represents a greater burden to the healthcare system than does the longer treatment course.

Additional data included in the S31 Response

The Sponsor has provided preliminary data in the form of an interim report from Study GS-US-337-1306. This study is a Phase I drug interaction study. The key findings reported by the Sponsor with regard SOF and LDV are: "Simultaneous co-administration of a complete HIV ARV regimen of ATV/r + TVD with LDV / SOF increased systemic exposures of LDV by 96%, 68%, and 118% as assessed AUCtau, Cmax, and Ctau, respectively. A 12-hour separation of ATV/r + TVD did not minimize the interaction, as assessed by similar increases in LDV AUCtau, Cmax, and Ctau of 131%, 75%, and 164%, respectively. LDV is known to be a substrate of Pgp and BCRP drug transporters and is also subject to slow oxidative metabolism. The putative mechanism for this interaction is persistent ATV and RTV inhibition of Pgp and BCRP drug transporters". The Sponsor does not intend to make any dose change recommendations with regard SOF / LDV FDC as a result of the interaction, and does not consider the interaction to be clinically relevant.

However, LDV / SOF FDC resulted in increased exposure to TFV. AUCtau increased by 33 to 35%, Cmax by 47% to 49%, and Ctau by 47% to 38% following administration of LDV / SOF and ATV/r + TVD either simultaneously or 12-hours apart. The mechanism is likely due to inhibition of intestinal Pgp and BCRP by LDV. The Sponsor has included a warning of this interaction in the PI.

Evaluator's comments: The provision of this additional information, and the Sponsors conclusions, are acceptable. The Sponsor intends to lodge the full study report at a later date.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) FDC tablets in the proposed usage are unchanged from those identified in the first round.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) FDC tablets in the proposed usage are unchanged from those identified in the first round.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of register Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) FDC tablets, given the proposed usage, is favourable.

However, consideration needs to be given as to the most appropriate dosing recommendation. In the opinion of the Evaluator this should be:

- SOF / LDV FDC once daily for 8 weeks in treatment naïve subjects with chronic GT1-HCV without cirrhosis
- SOF / LDV FDC once daily for 12 weeks in treatment naïve subjects with chronic GT1-HCV with cirrhosis
- SOF / LDV FDC once daily for 24 weeks in treatment experienced subjects with chronic GT1-HCV, with or without cirrhosis
- RBV does not offer additional benefit as add-on therapy and may decrease Quality of Life

14. Second round recommendation regarding authorisation

The Evaluator has no objection to the approval of Harvoni (90 mg ledipasvir / 400 mg sofosbuvir) FDC tablets for the indication of:

> *Harvoni is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.*

Consideration should be given to amending the dosing recommendations in line with the comments.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au