Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for sofosbuvir

Proprietary Product Name: Sovaldi

Sponsor: Gilead Sciences Pty Ltd

First round CER: September 2013

Second round CER: February 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ATV/r	ritonavir-boosted atazanavir
AUC	area under the curve
$AUC_{0\text{-}last}$, AUC_{last}	area under the concentration-time curve from time of dosing (0 hour) to the last time point with measurable plasma concentration
AUC_{inf}	area under the plasma concentration-time curve extrapolated to infinity
AUC_{tau}	AUC to the end of the dosing period
AZT	zidovudine
BID	two times daily
BMI	body mass index
BOC	boceprevir
CBP	child bearing potential
CER	clinical evaluation report
CFR	code of federal regulations
CHC	chronic hepatitis C virus infection
CI	confidence interval
CK	creatine phosphokinase
Clcr	creatinine clearance
CL/F	CL/F apparent oral clearance
CLSI	clinical and laboratory standards institute
C_{max}	maximum plasma concentration
CMI	consumer medicine information
C_{min}	minimum plasma concentration
CPT	Child-Pugh Turcotte score

Abbreviation	Meaning
CRF	case report form
CsA	cyclosporin
CYP	cytochrome P450 enzymes
DAA	Direct Acting Antiviral
DAIDS	Division of AIDS
D-D	Drug-drug
DDQ	desires for drugs questionnaire
DRV/r	ritonavir-boosted darunavir
ECG	electrocardiograph
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA or EMEA	European Medicines Agency
ESLD	end-stage liver disease
ESRD	end-stage renal disease
ETR	end of treatment response
EVR	early virological response
EU	European Union
FDA	US Food and Drug Administration
FMO	flavin monooxygenase
FU	follow-up
λz	apparent first order terminal elimination rate constant
group	group
GT	genotype
Hb	haemaglobin
HBV	hepatitis B virus

Abbreviation	Meaning
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCV N-R	hepatitis C virus non-responders
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model of assessment-insulin resistance
HPLC	High performance liquid chromatography
hr	hour
II	integrase inhibitor
ICH	International Conference on Harmonisation
ILI	influenza like illness
ITT	Intent to treat
IVDU	injecting drug use
LC-MS/MS	liquid chromatography with tandom mass spectroscopy
LL	lower limit
LTx	liver transplant
LLOQ	Lower limit of quantification
LS	least square
LTFUP	lost to follow up
MedDRA	medical dictionary for regulatory activities
MELD	model for end-stage liver disease
MOX	moxifloxacin
NNRTI	non-nucleoside reverse transcriptas inhibitor
NS5B	nonstructural protein 5B
OD	once daily
PEG	PEGylated interferon

Abbreviation	Meaning
PI	product information
PK	pharmacokinetics
PO	per oral (taken orally)
PMN	polymorphonuclear leukocytes=neutrophil
PP	per protocol
PSP	primary safety population
QoL	quality of life
QTc	QC interval corrected
RAL	raltegravir
RBV	ribavirin
RPV	rilpivirine
RNA	ribonucleic acid
RVR	rapid virological response
SAE	serious adverse event
SAS	safety analysis set
SOC	standard of care
SOF	Sofosbuvir (GS-7977; formerly PSI-7977)
SOrgC	system organ class
SOWS	short opiate withdrawal scale
SSP	secondary safety population
SVR	sustained virological response
3TC	lamivudine
TDF/FTC	Truvada = FDC of tenofovir disoproxil fumarate+ emtricitabine
TDF/FTC/EFV	Atripla - the FDC of tenofovir disoproxil fumarate, emtricitabine and efavirenz
$t_{1/2}$	apparent plasma half-life

Abbreviation	Meaning
t_{max}	the time after dosing at which Cmax was achieved
TNV	tenofovir
TPV	telaprevir
TR	treatment-related
UGT	uridine diphosphate glucuronosyltransferase
UL	upper limit
US	United States
wk	week
Vz/F	apparent volume of distribution in the terminal phase

1. Clinical rationale

Globally, 130-150 million people have CHC infection.[1] The prevalence of hepatitis C virus (HCV) is highest in Egypt at >10% of the general population; China has the most people overall with HCV (29.8 million);[2] approximately 3.2 million are infected in the US.[3] Of those with CHC, ≤20% develop serious morbidities ± mortality, that is, cirrhosis, end stage liver disease (ESLD), hepatocellular carcinoma (HCC).[4] CHC infection leads to approximately 10,000 deaths per year in the US[5] and has surpassed human immunodeficiency virus (HIV) as a cause of death.[6]

HCV is a single stranded ribonucleic acid (RNA) virus transmitted primarily through blood/blood product exposure[7] in particular through injecting drug use (IVDU). HCV has significant genetic (RNA sequence) variability and is classified on this basis into at least 6 genotypes (GTs). Genotype 1 (GT-1) is the most common in North America (70-75%),[8] Europe (69%)[9] and Australia (55%).[10] Until recently, the standard of care (SOC) treatment for GT-1 was 48 weeks of therapy with maximum doses of weight based dosing of ribavirin (RBV) in

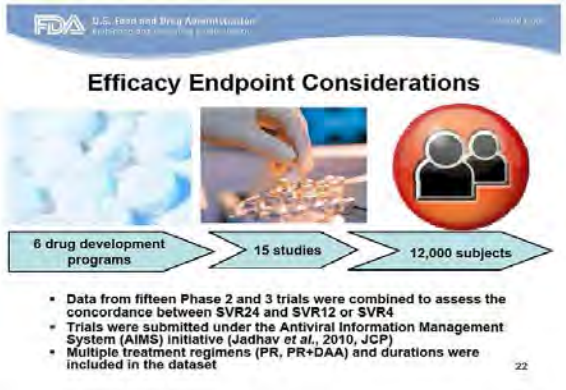
[1] World Health Organisation, "Fact sheet No. 164: Hepatitis C", April 2014.
[2] Hajarizadeh B, et al. (2013) Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 10: 553-562.
[3] Naggie S, et al. (2010) Hepatitis C virus directly acting antivirals: current developments with NS3/4A HCV serine protease inhibitors. J Antimicrob Chemother. 65: 2063-2069.
[4] Naggie S, et al. (2010) Hepatitis C virus directly acting antivirals: current developments with NS3/4A HCV serine protease inhibitors. J Antimicrob Chemother. 65: 2063-2069.
[5] Naggie S, et al. (2010) Hepatitis C virus directly acting antivirals: current developments with NS3/4A HCV serine protease inhibitors. J Antimicrob Chemother. 65: 2063-2069.
[6] Ly KN, et al. (2012) The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 156: 271-278.
[7] Naggie S, et al. (2010) Hepatitis C virus directly acting antivirals: current developments with NS3/4A HCV serine protease inhibitors. J Antimicrob Chemother. 65: 2063-2069.
[8] Carey W. (2003) Tests and screening strategies for the diagnosis of hepatitis C. Cleve Clin J Med. 70 (Suppl 4): S7-S13.
[9] Fattovich G, et al. (2001) Hepatitis C virus genotypes: distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centres in Europe. J Viral Hepat. 8: 206-216.
[10] Hajarizadeh B, et al. (2013) Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 10: 553-562.

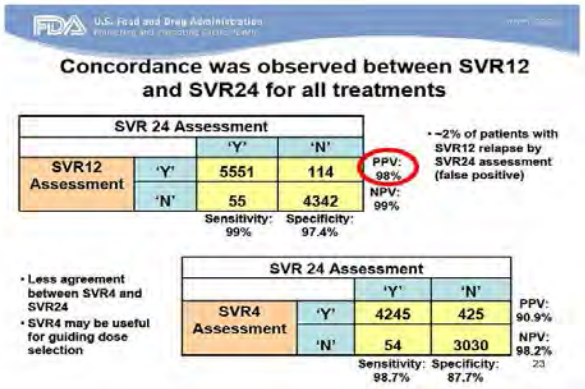
combination with weekly subcutaneous (SC) pegylated interferon alfa (PEG).[11] However, <50% of patients with CHC GT-1 achieve sustained virologic response (SVR) after initial PEG+RBV.[12] Moreover, non-responders or relapsers retreated with PEG+RBV had low SVR (8-42%).[13]

In 2011, two new HCV non-structural protein 3/4A (NS3/4A) protease inhibitors, telaprevir (TPV) and boceprevir (BOC), were approved for treatment of CHC GT-1. The rationale was the improvement in SVR rates to 63% and 79% when these drugs were combined with PEG+RBV.[14] These regimens also allow treatment options for patients previously failing to achieve SVRs, with SVR approximately 70-86% for prior relapsers, 40-59% for partial responders, and 32% for null responders (TPV only).[15] Despite the efficacy of these combined regimens, downsides are additional toxicities: anaemia for BOC, and rash for TPV.[16] In addition, BOC and TPV are approved only for GT-1, leaving PEG+RBV as the treatment for GT-2, 3, 4, 6.[17]

SOF is a novel nucleotide **prodrug** inhibitor of the HCV nonstructural protein 5B (NS5B) RNA-dependent RNA polymerase, essential for HCV replication and as such is a direct-acting antiviral agent (DAA). When used in combination with RBV ±PEG, results in high SVR rates in subjects with CHC. SOF has the potential to offer a safe, shorter, effective alternative to the current SOC regimens, including PEG-free regimens. Moreover, there is a Fixed Dose Combination (FDC) of SOF + the inhibitor of the HCV NS5A protein inhibitor, ledipasvir (GS-5885) currently in Phase 3 studies ±RBV. These PEG and potentially RBV-free regimens represent a real potential shift in the treatment of CHC. In this application, a new SVR endpoint has been accepted. At the present time, the TGA utilises the 2009 EMEA guideline "*Guideline on the Clinical Evaluation of Direct Acting Antiviral Agents Intended for Treatment of Chronic Hepatitis C*". In this application, the standard as the duration for determining SVR **is shorter** than in the EMEA 2009 guidelines. This was discussed during the pre-submission meeting with TGA and the shorter **SVR of 12 weeks**, was pre-agreed with TGA, US FDA and EMA. Further data is provided in Figure 1.[18]

Table 1: Slides from FDA Perspective on Direct Acting Antiviral Trials.





[11] Ghany MG, et al. (2009) Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49: 1335-1337.
[12] Dienstag JL, McHutchison JG. (2006) American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 130: 231-264; quiz 214-217.
[13] Jacobson IM, et al. (2005) A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. Am J Gastroenterol. 100: 2453-2462.
[14] Victrelis (boceprevir) Product Information; Incivek (telaprevir) Product Information.
[15] Victrelis (boceprevir) Product Information; Incivek (telaprevir) Product Information.
[16] Ghany MG, et al. (2011) An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 54: 1433-1444.
[17] Ghany MG, et al. (2009) Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49: 1335-1337; Ghany MG, et al. (2011) An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 54: 1433-1444.
[18] Carter W. (2012) FDA Perspective on Direct Acting Antiviral Trials. HCV Drug Development Workshop, Baltimore, MD USA, US Food and Drug Administration Division of Antiviral Products.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical submission was presented in Common Technical Document format and contained 81 volumes not the original 110 planned. The sponsor has given assurance to the TGA that there is no impact on the integrity or quality of data of the data submitted as a consequence of this reduction in the amount of information submitted. The submission contained the following clinical information:

- 25 clinical pharmacology studies, including 12 that provided pharmacokinetic data and
- 17 that provided pharmacodynamic data, that is, healthy volunteer pharmacokinetic studies (n = 4).

These included:

- Module 5.3.1:
  - P7977-0111: A Single Dose, Randomised, 3-Period, Crossover Study to Evaluate the Relative Bioavailability of a PSI-7851 Capsule Formulation to a PSI-7977 Tablet Formulation and Food Effect
  - P7977-1318: A Single-Dose, Randomised, 3-Period, Crossover Study to Evaluate the Relative Bioavailability of a 200 mg PSI-7977 Tablet Formulation to a 400 mg PSI-7977 Tablet Formulation and the Effect of Food on the Bioavailability of the 400 mg Tablet
  - P7977-0312: An Open Label, Non-Randomised, Single Dose, Mass Balance Study to Investigate the Pharmacokinetics, Excretion and Recovery of [14C]PSI-7977 Administered as a Single Oral Dose to Healthy Adult Subjects
  - P7851-1101: A Double-Blind, Parallel, Randomised, Placebo-Controlled, Single Ascending Dose Study to Investigate the Safety, Tolerability and Pharmacokinetics Following Oral Administration of PSI-7851 to Healthy Volunteers.
- Module 5.3.4.1
  - P7977-0613: A Single-Dose, Randomised, Blinded, Placebo- and Positive-Controlled, Four-Period Cross-Over Study to Investigate the Effect of PSI-7977 at a Projected Therapeutic and Supratherapeutic Dose on the QT/QTc Interval in Healthy Volunteers.
- Module 5.3.3.2 Patient pharmacokinetics/pharmacodynamics and dose finding (n = 2)
  - P7851-1102: A Double-Blind, Parallel, Randomised, Placebo-Controlled, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7851 to Patients with Chronic Hepatitis C Infection of Genotype 1.
- Module 5.3.3.3 Intrinsic Factor Pharmacokinetic Study Reports (n = 2)
  - P7977-0915: An Open-Label Study of Pharmacokinetics of Single Oral Doses of PSI-7977 in Subjects with Varying Degrees of Renal Function
  - P2938-0515: An Open-Label Study to Characterize the Pharmacokinetics and Pharmacodynamics of Multiple Oral Doses of PSI-7977 or PSI-352938 in HCV-infected Subjects with Varying Degrees of Hepatic Impairment.
- Module 5.3.3.4 Extrinsic Factor Pharmacokinetic Study Reports (n = 4)
  - GS-US-334-0131: A Phase I, Open-label, Pharmacokinetic Drug-Drug Interaction Study Between GS-7977 and antiretrovirals efavirenz/emtricitabine/tenofovir Disoproxil Fumarate (TDF/FTC/EFV), a Boosted Protease Inhibitor, darunavir/ritonavir (DRV/r)

an Integrase Inhibitor (II), raltegrevir (RAL), and Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), Rilpivirine (RPV)

  - P7977-0814: A Phase I, Open-Label, Single-Sequence Drug-Drug Interaction Trial in Healthy Subjects Receiving Stable Methadone Maintenance Therapy to Investigate the Potential Interaction at Steady State between PSI-7977 400 mg QD and Methadone
  - P7977-1819: An Open-Label, Randomised, Three Period, Cross-Over, Drug Interaction Study to Assess the Effect on Pharmacokinetics of Co-administration of PSI-7977 and Cyclosporine or Tacrolimus in Healthy Subjects
  - P7977-1910: Part A: Drug Interaction Study between GS- 7977 and Antiretroviral Therapy (ARV) Combinations of efavirenz, tenofovir and emtricitabine; efavirenz, zidovudine and lamivudine; atazanavir/ritonavir, tenofovir and emtricitabine; darunavir/ritonavir, tenofovir and emtricitabine; raltegravir, tenofovir and emtricitabine in HIV and Hepatitis C Virus (HIV/HCV) Co-infected Patients.

- Module 5.3.3.5.
  - A population pharmacokinetic analyses.
- Module 5.3.5.1 4 pivotal efficacy/safety studies (n = 4)
  - P7977-1231 (FISSION): A Phase III, Multicenter, Randomised, Active-Controlled Study to Investigate the Safety and Efficacy of PSI-7977 and Ribavirin for 12 Wks Compared to PEGylated Interferon and Ribavirin for 24 Wks in Treatment-Naïve Patients with Chronic Genotype 2 or 3 HCV Infection
  - GS-US-334-0107 (POSITRON): A Phase III, Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Wks in Subjects with Chronic Genotype 2 or 3 HCV Infection who are Interferon Intolerant, Interferon Ineligible or Unwilling to Take Interferon
  - GS-US-334-0108 (FUSION): A Phase III, Multicenter, Randomised, Double-Blind Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 or 16 Wks in Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection
  - GS-US-334-0110 (NEUTRINO): A Phase III, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of GS-7977 with PEGinterferon Alfa 2a and Ribavirin for 12 Wks in Treatment-Naïve Subjects with Chronic Genotype 1, 4, 5, or 6 HCV Infection.
- Module 5.3.4.2 – Dose finding studies (n = 6)
  - P2938-0212 (NUCLEAR): A Two-Part, Double-Blind, Parallel, Randomised, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Ascending Doses of PSI-352938 and the Combination of PSI-352938 and PSI-7977 in Patients with Genotype 1 Chronic Hepatitis C Infection
  - P7977-0221: A Multi-center, Double-Blind, Parallel Group, Randomised, Placebo-Controlled, Dose Ranging Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 in Combination with Standard of Care (PEGylated Interferon and Ribavirin) in Treatment-Naïve Patients with Chronic HCV Infection Genotype 1
  - P7977-0422 (PROTON): A Multi-center, Placebo-Controlled, Dose Ranging Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 in Combination with PEGylated Interferon and Ribavirin in Treatment-Naïve Patients with Chronic HCV Infection Genotype 1, and an Open Label Assessment of PSI-7977 in Patients with HCV Genotypes 2 or 3

  - P7977-0724 (ATOMIC): A Multicenter, Open-label, Randomised, Duration Finding Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 in Combination with PEGylated Interferon and Ribavirin in Treatment-Naïve Patients with Chronic HCV Infection Genotype 1, 4, 5, or 6
  - P7977-0523 (ELECTRON): A Multi-center, Open-Labeled Exploratory Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 400 mg and Ribavirin for 12 Wks With and Without Pegylated Interferon in Treatment-Naïve Patients with Chronic HCV Infection Genotype 2 or Genotype 3
  - P2938-0721 (QUANTUM): An International, Multicenter, Blinded, Randomised Study to Investigate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Administration of Regimens Containing PSI-352938, PSI-7977, and Ribavirin in Patients with Chronic HCV Infection.
- Module 5.3.5.4. Other efficacy/safety studies (n = 3)
  - P7977-2025: An Open-Label Study to Explore the Clinical Efficacy of PSI-7977 with Ribavirin Administered Pre-Transplant in Preventing Hepatitis C Virus (HCV) Recurrence Post-Transplant
  - GS-US-334-0123 (PHOTON-1): A Phase III, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects
  - NIH Study 11-I-0258 (IND 112,681): A Randomised Controlled Study to Assess Safety, Tolerability and Efficacy of GS-7977 in Combination with full or low dose RBV in HCV Genotype 1, Monoinfected Treatment Naive Participants (NIAID Study).
- Integrated Summaries of Virology, Efficacy, Safety

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

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

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

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

Table 2: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	P7977-0312	*
	- Multi-dose	P7851-1101 P7977-0613	* *
	Bioequivalence† - Single dose - Multi-dose		
	Food effect	P7977-0111 P7977-1318	* *
PK in special populations	Target population § - Single dose - Multi-dose	 P7851-1102	 *
	Hepatic impairment in CHC (multiple doses)	P2938-0515	*
	Renal impairment	P7977-0915	*
	Neonates/infants/children/adolescents/Elderly	not applicable	
Genetic/gender -related PK	Males vs. females		
	@ {other genetic variable}		
PK interactions	GS-7977 and antiretrovirals TDF/FTC/EFV FDC, DRV/r, RAL RPV	GS-US-334-0131	*
	methadone	P7977-0814	*
	Cyclosporine or Tacrolimus	P7977-1819	*
	with ARV combination in HIV/HCV coinfected patients	P7977-1910	
Population PK analyses	Healthy subjects		
	Target population	Population PK	

* Indicates the primary aim of the study; † Bioequivalence of different formulations; § Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies.

3.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries. The chemical name of SOF 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-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. The molecular formula is $C_{22}H_{29}FN_3O_9P$ and it has molecular weight (mw) of 529.45. SOF is a potent pan-genotypic nucleotide analog HCV NS5b polymerase inhibitor, with comparable in vitro activity against all HCV genotypes. In the *in vitro* HCV replicon assays, the half-maximal effective concentrations (EC50) of SOF against the full length replicon range from 0.014 to 0.11 µM. SOF is active in the GT- 1a and 2a infectious cell culture systems, with EC50 values of 0.03 µM and 0.02 µM, respectively. The active uridine triphosphate form (GS-461203) directly inhibits NS5B polymerase activity *in vitro* at concentrations that result in 50% inhibition (IC_{50} values) between 0.7 to 2.1 µM. GS-331007 is the primary analyte of interest, demonstrating relationship with antiviral activity and accounting for ~90% of study drug systemic exposure.

Results from preclinical studies identified GS-9851 (PSI-7851) as a potent and selective inhibitor of NS5B-directed HCV replicon RNA replication *in vitro*. Pre-clinical *in vitro* studies with rat, dog, monkey, primary hepatocytes and *in vivo* metabolism study in rats showed PSI-7851 is hydrolysed to PSI-352707 (GS-566500), which is further metabolised to PSI-6206 or PSI-7411 (GS-606965), then phosphorylated to the di- and tri-phosphate metabolites, PSI-7410 and PSI-7409 (GS-461203), respectively. The active triphosphate metabolite shows potent, selective inhibition of recombinant NS5B RNA-dependent RNA polymerase activity and native HCV replicase activity. The diastereoisomeric mixture GS-9851 was used in 3 early development clinical studies (P7851-1101, P7851-1102, P7977-0111) but the single diastereoisomer SOF (GS-7977) was eventually chosen for further development. As the metabolites and active moiety of GS-9851 and SOF were similar, GS-9851, used in initial studies, still informs the clinical PK of

SOF. The end product of SOF metabolism across species is the nucleoside metabolite, GS-331007 representing >90% of systemic exposure. In a human mass balance study, recovery of SOF, as unchanged drug, in urine and faeces was low; ~80% administered dose was recovered in urine, primarily as GS-331007. Bioanalytical methods used for SOF, GS-566500, GS-331007 concentrations during the clinical development programme are described; a detailed summary is beyond the scope of this clinical review.

3.2.2. Pharmacokinetics in healthy subjects

3.2.2.1. Absorption

3.2.2.1.1. Sites and mechanisms of absorption

SOF was well absorbed in nonclinical species; oral administration resulting in high exposure to GS-566500 and GS-331007 across all species tested. Examination of plasma PK to formation of the pharmacologically active nucleoside analog triphosphate, GS-461203, in dog liver revealed this was efficiently formed and was the dominant metabolite observed at all assessed time points ($t_{1/2}$ ~17.8hrs). The absolute BA of SOF was not evaluated in humans. Clinical studies examining SOF absorption in healthy subjects include the human mass balance study (P7977-0312) and food effect studies (P7977-0111; P7977-1318). Following oral administration of SOF, peak SOF concentrations were generally observed ~0.5 to 2 hrs postdose, 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.

3.2.2.2. Bioavailability

3.2.2.2.1. Absolute bioavailability

Absolute BA of SOF was not specifically evaluated. Specifically, following a single oral dose of [^{14}C]-SOF, SOF was rapidly absorbed and eliminated in the urine as GS-331007 (Study P7977-0312). Mean total recovery of radioactive dose was >92%, consisting of ~80% (76% by LSC; 85% by LC/MS/MS), 14% (by LSC), and 2.5% (by LSC) recovered in urine, faeces, expired air, respectively. Study P7851-1101 evaluated PK of single ascending doses of GS-9851, the racemic mixture of SOF and GS-491241, (25-, 50-[capsule **and solution**], 100-, 200-, 400-, 800-mg capsules) in fasted healthy subjects. GS-9851 exposure was generally low, with most systemic drug exposure from GS-331007. Indications of reduced GS-9851 intestinal solubility or saturable/reduced absorption were observed with less than dose proportional increases in GS-9851 and GS-331007 (AUC_{inf} and C_{max}) and decreased urinary % of dose recovered as the dose increased above 100 mg, despite relatively unchanged CLr. To investigate dose linearity of SOF, cross-study analyses of SOF and GS-331007 AUC_{inf} and C_{max} from Study P7977-0613 (evaluating PK of single 400- and 1200-mg doses of SOF in fasted healthy subjects) and Study P7977-0111 (200mg dose in fasted healthy subjects) were evaluated using a power model regression. The power model mean slope and 90% CIs indicated that near dose linearity was observed for SOF AUC_{inf} and C_{max}, and GS331007 AUC_{inf} with GS-331007 C_{max} showing modestly **less** than dose proportional increases. Additionally, data comparing single & multiple dosing in P7977-0814 (**methadone interaction study**), showed SOF and GS-331007 exhibited similar PK on single- and multiple-dosing with SOF (AUC_{inf} on Day 1 comparable to AUC_{tau} on Day 7) with minimal SOF or GS-331007 accumulation.

3.2.2.2.2. Bioavailability relative to an oral solution or micronised suspension

See above, this was investigated with the racemic mixture of SOF and GS-491241 i.e. P7851, in study P7851-1101.

3.2.2.2.3. Bioequivalence of clinical trial and market formulations

SOF has had a complex development with multiple formulations to optimise PK i.e. powdered GS-9851 in capsules, SOF Form I 100-mg tablets, SOF Form I 200-mg tablets (in Study 7977-1231 [FISSION]), SOF Form I 400-mg tablets (in Study GS-US-334-0107 [POSITRON]), SOF Form II 400-mg tablets (in Studies GS-US-334-0131 [Cohort 5], GS-US-334-0108 [FUSION], GS-US-334-0110 [NEUTRINO]).

Table 3: SOF Single-Dose Fasted PK Parameters Across Formulations in Healthy Subjects.

				SOF or GS-9851		GS-331007	
study	formulation	dose (mg)	N	AUC_{inf} (ng•h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	C_{max} (ng/mL)
P9799-0111	GS-9851 capsule	200	24	134(79.0)	81.0(92.1)	4330(31.9)	388(38.3)
P9799-0111	SOF Form I 100mg tab	200	24	263 (41.3)	267(41.3)	6260(25.3)	781(32.8)
P9799-1318	SOF Form I 200mg tab	400	39	736 (38.9)	737(48.2)	14,100(24.0)	1250(31.7)
P9799-1318	SOF Form I 400mg tab	400	39	646 (40.2)	675(46.9)	13,500(28.4)	1230(32.1)
GS-US-334-0131	SOF Form II 400mg tab	400	16	765 (36.1)	994(47.4)	11,600(19.1)	1220(37.8)

3.2.2.2.4. Influence of food

Effect of food on rate and extent of SOF absorption evaluated in 2 Phase 1 studies: Study P7977-0111 (as GS-9851) & Study P7977-1318 (as SOF). The findings of both were in agreement; compared with the fasted state, food, specifically a high-fat meal, resulted in a slower rate of absorption of SOF (high-fat meal vs. fasted; prolonged T_{max}: 1.5 vs. 0.5 hrs) **with no substantial alteration in the extent of absorption** (high-fat meal vs. fasted; mean AUC_{inf} increased 67-91%). When evaluated as GS-331007, prolonged T_{max} (high-fat meal vs. fasted; 4.00 vs. 2.00 hrs) and modestly lower C_{max} (high-fat meal vs. fasted; GLSM ratio for C_{max} 24−30% decreased) were observed. $AUC_{0\text{-}last}$ and AUC_{inf} of GS-331007 were unaltered in the presence of a high-fat meal. The equivalence criterion **for a lack of food effect was not met**; however, C_{max} decrease was not considered clinically significant. Moreover, whilst SOF dosing in Phase 2 and 3 clinical studies was recommended **without regard** to food, in reality, SOF when co-administered with RBV in Phase III studies, was dosed with food, as required in the RBV prescribing information.

3.2.2.2.5. Dose proportionality

A cross-study analysis of SOF and GS-331007 AUC_{inf} and C_{max} was performed to investigate the dose linearity of SOF (power model regression) using data from Study P7977-0613 that evaluated the PK of single therapeutic (400mg) and supratherapeutic (1200mg) doses of SOF in fasted healthy subjects and Study P7977-0111 that evaluated the 200mg single-dose SOF in fasted healthy subjects. The power model mean slope and 90% CIs indicated that near-dose linearity was observed for SOF AUC_{inf} and C_{max}, and GS-331007 AUC_{inf} with GS-331007 C_{max} showing modestly less than dose proportional increases.

3.2.2.2.6. Bioavailability during multiple-dosing

See above.

3.2.2.2.7. Effect of administration timing

Not formerly assessed in any studies, aside from dosing with or without food.

3.2.2.3. Distribution

3.2.2.3.1. Volume of distribution

The final population PK model for GS-331007 best described the plasma concentration data with a 2-compartment mammillary PK model with a first-order absorption rate constant (KA), a zero order absorption component and absorption lag time, with interindividual variability terms on CL/F, KA, volume of the central compartment (Vc/F), and included the effect of creatinine clearance (Clcr) and HCV status on CL/F (GS-331007 Population PK Report). The typical values of GS-331007 CL/F and Vc/F were estimated to be 39.5 L/h, and 218 L, respectively, while the volume of the peripheral compartment (Vp/F) was estimated to be 594

L. GS-331007 was absorbed with a typical KA of 0.05 h−1, a zero order absorption duration of 4.4 hrs, and a lag time of 0.28 hrs. Primary parameters for population PK analyses were AUC_{tau} and C_{max} for GS-331007.

3.2.2.3.2. Plasma protein binding (PPB)

Based on ultrafiltration studies, *in vitro* protein binding of SOF was low in dog and human plasma (<70%) and constant regardless of protein concentration in human plasma; ex vivo PPB of SOF was ~82-85% in healthy subjects and subjects with ESRD, respectively (P7977-0915). SOF was not stable in mouse, rat, rabbit plasma, and plasma binding in those matrices was not determined. GS-331007 protein binding was minimal in mouse, rat, rabbit, dog, human plasma. After a single 400mg dose of [^{14}C]-SOF in healthy male subjects, blood to plasma ratio of ^{14}C-radioactivity was ~0.71, indicating SOF and its metabolites were predominantly distributed to plasma.

3.2.2.3.3. Erythrocyte distribution

See above.

3.2.2.3.4. Tissue distribution

Pre-clinical data indicates that following single dose [^{14}C]-SOF to male rats, drug-derived radioactivity was absorbed and widely distributed, with high radiocarbon concentrations in alimentary canal, excretory organs (liver, bladder, renal cortex/medulla), lymphatic system; low radiocarbon concentrations in central nervous system, bone, eye lens, white adipose tissue.

3.2.2.4. Metabolism

3.2.2.4.1. Interconversion between enantiomers

Not applicable, no enantiomers of SOC. The single diastereoisomer, SOF, was chosen for further development, although the diastereoisomeric mixture GS-9851 was used in studies P7851-1101, P7851-1102, P7977-0111.

3.2.2.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Combined results from nonclinical pharmacology and PK studies led to the proposed pathway of SOF (a prodrug) metabolism. SOF is potentially activated to GS-461203, by a sequential metabolic activation pathway: 1) hepatically expressed CES1 and CatA catalyze removal of the ester, resulting in the release of isopropanol; 2) following a chemical step that releases phenol, HINT1 cleaves the phosphoramidate bond liberating the nucleoside analog monophosphate and alanine; 3) uridine monophosphate-cytidine monophosphate kinase and nucleoside diphosphate kinase catalyse conversion to the **active triphosphate, GS-461203**. Dephosphorylation of GS-606965 leads to formation of the nucleoside analog, GS-331007, which cannot be efficiently rephosphorylated **and lacks anti-HCV activity in vitro**. In P7977-0312 (human mass balance) the primary metabolic route of SOF was hydrolase cleavage, ultimately leading to GS-331007 formation. Following administration of [^{14}C]-SOF, mean total recovery of the radioactive dose was >92%, consisting of ~80% (76% by LSC; 85% by LC/MS/MS), 14% (LSC), and 2.5% (LSC) recovered in urine, faeces, expired air, respectively. The results indicated that at least ≥80% of the administered dose was absorbed into systemic circulation with elimination through urine as the major elimination pathway. Mean recovery of SOF in urine was low (3.47%). Mean CL/F and CLr values for SOF were 7.32 and 0.238 L/min, respectively, indicating that the majority of elimination of SOF (in contrast to the major metabolite, GS-331007), was potentially via the nonrenal route of elimination. In vitro studies suggest that **SOF is a substrate for Pgroup** and BCRP but not the renal transporters OCT1, OATP1B1, OATP1B3; **GS-331007 is not a substrate for Pgroup**, BCRP, OAT1, OAT3, OCT2, MATE1. In vitro studies indicated that SOF, GS-9851, GS-566500, GS-331007 were not inhibitors (IC_{50} >50−100μM) of human CYP isozymes CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2C8, CYP2D6. No significant inhibition (IC_{50} >50μM) of UGT1A1 observed for SOF, or GS-331007. SOF

at 100 μM caused little or no induction in CYP activities and caused little or no increases in CYP messenger RNA in primary human hepatocytes. SOF and GS-331007 showed little/no inhibition of the transport of probe substrates by Pgroup, BCRP, OATP1B1, OATP1B3, OCT1, BSEP (IC_{50} >approx.100 μM). GS-331007 showed little or no inhibition of the renal transporters OAT1, OAT3, OCT2, MATE1 (IC_{50} >100μM).

3.2.2.4.3. Non-renal clearance

As described above, data from the mass balance study confirm mean CL/F and CLr values for SOF were 7.32 and 0.238 L/min, respectively, indicating that the majority of its elimination was potentially via the nonrenal route of elimination. The majority of the dose recovered in the urine measured by LC/MS/MS was as the main metabolite, GS-331007 (77.7%) with 3.5% as SOF; confirming CLr was a major pathway for elimination of the nucleoside. Renal clearance for GS-331007 was estimated as 0.242 L/min, approx. 2.0-fold higher than the GFR (0.120 L/min), suggesting a role of active secretion in renal elimination of GS-331007 (study P7977-0312). Consistent with substantial elimination of GS-331007 in urine, clinically significant changes in its PK noted with declining renal function (Study P7977-0915).

3.2.2.4.4. Metabolites identified in humans

The primary metabolic route of SOF, hydrolase cleavage, results in GS-331007 formation. Sequential activation by generally low affinity, high capacity hydrolases (CES1, CatA, HINT1) and nucleotide phosphorylation (UMP-CMP kinase, NDP kinase) pathways lead to the formation of the **pharmacologically active nucleoside analog triphosphate GS-461203**.

GS-331007 is the primary circulating metabolite in humans. This was confirmed in a mass balance study with SOF, GS-566500, GS-331007 accounting for ~4%, ~7%, and >90% of drug-related material systemic exposure by AUC, respectively. No new metabolites were identified in humans.

3.2.2.4.5. Pharmacokinetics of metabolites

See above.

3.2.2.4.6. Consequences of genetic polymorphism

Not explored.

3.2.2.5. Excretion

3.2.2.5.1. Routes and mechanisms of excretion

See above.

3.2.2.5.2. Mass balance studies

Results of P7977-0312 are described above.

3.2.2.5.3. Renal clearance

As detailed above.

3.2.2.6. Intra- and inter-individual variability of pharmacokinetics

A **population PK analysis** was provided in this Application. A statistically significant, positive correlation was observed between **patient status i.e. healthy or HCV-infected**, and SOF CL/F and KA. The effect was described with a linear function with a slope population estimate of −0.165 (RSE=16.4%). The effect, however, was modest and the resulting decrease in the IIV term associated with SOF absorption rate was 14.2%. The inclusion of the patient status effect on the oral clearance resulted in the reduction of the IIV by 12.9%. No other demographic or formulation characteristics were found to have any clinically relevant effects on SOF PK. A report on the **population PK of GS-331007** is provided in this Application. A statistically significant, positive correlation was observed between Clcr and GS-331007 oral clearance. The

effect was centered at the mean ClCr 116.0 mL/min and described with a linear function with a slope population estimate of 0.336 (RSE = 8.1%). The effect, however, was modest and the resulting decrease in the IIV term associated with GS-331007 oral clearance was 15.7%. The inclusion of the HCV genotype effect on the oral clearance as a discrete variable resulted in the reduction of the IIV by 67.1%. In summary, Clcr and HCV genotype only, were identified as significant covariates of GS-331007 CL/F.

3.2.3. Pharmacokinetics in the target population

In Study P7851-1102 multiple ascending doses of GS-9851 in fasted treatment-naive CHC genotype 1 subjects showed modest plasma accumulation for the metabolite, GS-331007 (21%), but not GS-9851. Steady-state conditions for GS-331007 were achieved after 3 days of dosing. In agreement with the findings suggesting reduced intestinal solubility or saturable/reduced absorption in the single-dose study in healthy subjects (P7851-1101), less than dose-proportional increases in AUC and C_{max} relative to a 100-mg reference dose were generally observed as the dose increased, and the percentage of dose recovered in the urine decreased as the dose increased, despite similar CLr values. Study P7977-0221 evaluated PK of single and multiple ascending doses of SOF (100, 200, 400 mg for 28 days; 100-mg tablet formulation) in treatment-naive subjects with genotype 1 HCV. SOF was absorbed quickly following single and multiple oral doses, with the C_{max} occurring within 1 hr (median T_{max}) of dosing. SOF exhibited time-independent, **near linear PK across evaluated doses**. Renal clearance of GS-331007 unchanged over increasing SOF doses. No unexpected or significant accumulation (≤21%) of SOF or GS-331007 was observed at the 400-mg dose (accumulation ratios approached 1). Similar to SOF, GS-566500 and GS-331007 demonstrated near dose-proportional increases in exposure over increasing SOF doses, which were comparable to the findings in single-dose studies in healthy subjects described above (Studies P7977-0111 and P7977-0613). Across a range of Phase 1 and 2 studies, P2938-0212 (NUCLEAR), P7977-0221, P7977-0422 (PROTON), P7977-0724 (ATOMIC), P7977-0523 (ELECTRON), and P2938-0721 (QUANTUM), the PK of SOF and its metabolites after multiple dose administration of SOF (100−400mg) were evaluated in HCV-infected subjects under a variety of treatment regimens (monotherapy or +RBV±PEG). GS-331007 plasma concentrations evaluated in all 6 studies; SOF plasma concentrations evaluated in Studies P7977-0221 and P2938-0212 (NUCLEAR) only.

Table 4: Steady-State GS-331007 and SOF PK parameters after OD administration in HCV-infected (population PK analysis from Phase III) or healthy subjects (population PK analysis from Phase 1 studies).

mean (%CV) PK parameter	HCV_infected (pop'n PK)	Healthy subjects (pop'n PK)
	SOF 400mg (N=986)	SOF 400mg (N=284)
GS-331007 AUC_{tau} (ng•h/mL)	7200 (30.5)	11,900 (32.0)
GS-331007 C_{max} (ng/mL)	582 (37.1)	1140 (27.9)
SOF AUC_{tau} (ng•h/mL)	860 (36.3)	634 (35.9)

The final PK model for SOF best described the plasma concentration data with a 1-compartment PK model with a first-order absorption rate constant and absorption lag time, with interindividual variability terms on CL/F, KA, and V/F, and including the effect of HCV infection status on CL/F and KA. Despite the extensive model building process, population PK estimates of SOF C_{max} were underestimated by approximately 40% compared with intensive sampling studies; of note, AUC was well predicted by population PK analyses. Data from Phase 1 and 2 studies have shown little evidence of a relationship between SOF C_{max} and safety or efficacy parameters given the low and transient exposure of SOF. As such, the primary parameter for interpretation of data from population PK analyses for SOF was AUC_{tau}. The typical values of SOF CL/F and Vc/F were estimated to be 652 L/h, and 127 L, respectively. SOF was absorbed with a KA of 0.96 h-1 and a lag time of 0.1 hr. Covariate analyses indicated relevant effects of HCV infection status (i.e.healthy subjects vs. HCV-infected) on the CL/F and KA of SOF. All other covariates tested e.g. age, gender, race, BMI, cirrhosis were not considered relevant covariates

for population PK of SOF. The Phase 3 population PK dataset included all subjects with evaluable PK parameters. The final population PK model for GS-331007 best described the plasma concentration data with a 2-compartment mammillary PK model with a first-order absorption rate constant (KA), a zero order absorption component and absorption lag time, with interindividual variability terms on CL/F, KA, Vc/F, and included the effect of Clcr and HCV infection status (healthy subjects vs HCV-infected subpopulations) on CL/F. The typical values of GS-331007 CL/F and Vc/F were estimated to be 39.5 L/h, and 218 L, respectively, while the volume of the peripheral compartment (Vp/F) was estimated to be 594 L. GS-331007 was absorbed with a typical KA of 0.05 h-1, a zero order absorption duration of 4.4 hrs, and a lag time of 0.28 hrs. Primary parameters for interpretation of data from population PK analyses were AUC_{tau} and C_{max} for GS-331007 Based on population PK modelling, HCV infection status (healthy subjects vs. HCV-infected subpopulations) and baseline Clcr (using Cockroft-Gault equation) were identified as significant covariates for CL/F of GS-331007. All other covariates tested including age, gender, race, BMI, and cirrhosis were not considered relevant covariates for the population PK of GS-331007. Mean GS-331007 exposures (AUC_{tau} and C_{max}) observed in HCV-infected subjects were lower (39% and 49%, respectively) than in healthy subjects; mean SOF AUC_{tau} was higher (36%) in HCV-infected vs. healthy subjects. These results are expected due to the population PK findings, identifying HCV as a significant covariate for GS-331007 and SOF CL/F. Population PK-derived mean GS-331007 and SOF exposures comparable across different HCV genotypes.

3.2.4. Pharmacokinetics in other special populations

The assessment of the potential effects of intrinsic factors on the PK of GS-331007 and SOF included Clcr, age, gender, BMI, race, cirrhosis. Baseline Clcr was identified as the only significant intrinsic covariate affecting CL/F of GS-331007, but SOF CL/F (not subject to renal excretion).

3.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

3.2.4.1.1. Effect of Cirrhosis

In the population PK analyses, the percentage of compensated cirrhotic subjects (CPT Classification A) ranged from 15-34% across studies (mean: 20%). Cirrhosis did not have an effect on GS-331007 or SOF exposures as shown in Table 5, and was not a relevant covariate. These results are consistent with the findings of the hepatic impairment study (P2938-0515).

Table 5: Mean (%CV) GS-331007 and SOF exposures in Cirrhotic and Noncirrhotic subjects following administration of SOF in HCV-Infected subjects.

Race	CrCL (mL/min)	GS-331007 AUC_{tau} (ng•h/mL)	GS-331007 C_{max} (ng/mL)	SOF AUC_{tau} (ng•h/mL)
Noncirrhotic (N=784)	114(28.0)	7210(30.4)	581(36.9)	871(34.9)
cirrhotic (N=202)	117(28.3)	7150(31.0)	582(38.0)	816(41.4)

3.2.4.1.2. Effect of hepatic impairment

In Study P2938-0515, the multiple-dose PK of GS-331007 and SOF were evaluated in HCV-infected subjects with moderate (CPT B) and severe hepatic impairment (CPT C) after administration of SOF 400 mg (2 × 200-mg tablet formulation) for 7 days. SOF mean plasma exposure parameters (AUC_{tau} and C_{max}) were similar in subjects with moderate or severe hepatic impairment and modestly higher (GLSM ratio AUC_{tau}: 126–143% higher; Cmax: 72–85% higher) than those achieved in subjects with normal hepatic function. Renal clearance remained a minor pathway for SOF elimination and accounted for ~1.2% of CL/F in subjects with normal hepatic impairment. In subjects with hepatic impairment, the CLr of SOF was modestly higher and accounted for ~3.2% of CL/F. GS-331007 plasma exposure was similar in subjects with hepatic impairment and historical control subjects with normal hepatic function (Study P2938-0212

[NUCLEAR]). Inexplicably, the GS-331007 C_{tau} estimate was the highest (~46% higher) in subjects with moderate hepatic impairment and lowest in subjects with normal hepatic function. A higher C_{tau} in moderate hepatic impairment was not deemed clinically relevant. The CLr of GS-331007 was similar in hepatic impairment groups but modestly lower than that observed in the normal hepatic function group. The % of SOF dose recovered in urine as GS-331007 decreased with worsening hepatic function. Based on the results from the moderate & severe hepatic impairment groups, subjects with mild hepatic impairment (CPT A) were not evaluated. HCV RNA decline in HCV-infected subjects with varying degrees of hepatic impairment was assessed after 7 days of SOF dosing. Of note, SOF provided potent antiviral activity in subjects with hepatic impairment as evidenced by >3.5 log_{10} HCV RNA decline. A greater mean decrease and faster decline in HCV RNA were observed in control subjects vs. moderate/severe hepatically impaired. These differences with short-term SOF monotherapy were not considered clinically meaningful. Based on PK and PD results, no dose adjustment of SOF is recommended in hepatic impairment. In the Phase 3 programme, compensated cirrhotic subjects (CPT A; N = 202 [20% of study population]) and noncirrhotic subjects had comparable mean GS-331007 exposure (AUC_{tau}: 7150 vs. 7210 ng·h/mL; C_{max}: 582 vs 581 ng/mL, respectively) and SOF AUC_{tau} (816 vs. 871 ng·h/mL, respectively). Cirrhosis was not identified as a relevant covariate based on population PK.

3.2.4.2. Pharmacokinetics in subjects with impaired renal function

In Study P7977-0915, plasma exposures of SOF and GS-331007 were moderately higher in subjects with mild and moderate renal impairment vs. subjects with normal renal function i.e. SOF AUC_{inf} was 61% and 107% higher in mild and moderate renal impairment, while the GS-331007 AUC_{inf} was 55% and 88% higher, respectively. An increase in GS-331007 exposure with decrease in renal function was as expected (Study P7977-0312). For SOF, however, the increase in exposure was unlikely a result of decrease in CLr as renal excretion of SOF is a minor elimination pathway (i.e. 1.4-3.3% of CL/F; Studies P7977-0312 and P7977-0915). These results were consistent with those of population-based analyses in HCV-infected subjects that identified Clcr as the statistically significant determinant of CL/F of GS-331007 and not SOF. Similar or higher SOF and GS-331007 exposures than those associated with both the range in renal function in Phase 3 studies and for subjects with mild to moderate renal impairment were observed in other clinical studies including DDI, thorough QT, and special population studies with no safety signals. Safety margins calculated relative to exposure from results of toxicology studies are 5.4 -11.6 for SOF and 1.6 -3.5 for GS-331007 in subjects with mild & moderate renal impairment; therefore, SOF dose adjustment is not warranted in mild-moderate renal impairment. However, markedly higher GS-331007 exposures were observed in severe renal impairment or ESRD. Relative to normal renal function, SOF AUC_{inf} was 171% higher, while GS-331007 AUC_{inf} was 451% higher, respectively. In subjects with ESRD, SOF and GS-331007 AUC_{inf} was 28% and 1280% higher when SOF was dosed 1 hr before haemodialysis vs. 60% and 2070% higher when SOF was dosed 1 hr after haemodialysis.

3.2.4.3. Pharmacokinetics according to age

In the population PK analyses, median (Q1, Q3) age was 53 yrs (46, 58) with a range of 19 to 75 yrs and 634 subjects aged ≥50yrs; 62 subjects were aged ≥65yrs. Small differences in mean GS-331007 AUC_{tau} and C_{max} between subjects <50 and ≥50yrs of age were observed; however, this is explained by Clcr differences between the 2 groups. SOF exposure was comparable across age categories. In summary, age is not a relevant covariate for SOF based on population PK analyses.

3.2.4.4. Pharmacokinetics related to genetic factors

3.2.4.4.1. Gender

In population PK analyses, 36% of subjects were female. Slight differences in mean GS-331007 AUC_{tau} and C_{max} across gender were observed explained by Clcr differences. SOF exposure was

comparable across gender and gender was not a relevant covariate for SOF based on population PK analyses.

3.2.4.4.2. Race

In population PK, the % of White, Black/African American, Asian, American Indian/Alaska Native/Pacific Islander/other was 85%, 8.2%, 4.0%, 2.8%, respectively. Race did not have an effect on GS-331007 exposures in HCV-infected subjects and was not a relevant covariate based on population PK analyses. For SOF, Black/African American or Asian subjects had 13-19% higher mean AUC vs. other races. This increase in SOF AUC is unlikely to be clinically meaningful.

3.2.4.5. Pharmacokinetics in other special population / according to other population characteristic

3.2.4.5.1. Effect of body mass index

In population PK analyses, median BMI was 27.7 (24.7, 31.5) kg/m^2. The slight difference in mean GS-331007 AUC_{tau} and C_{max} across BMI quartiles, is explained by Clcr differences. SOF exposure was comparable across BMI quartiles. BMI was not a relevant covariate for GS-331007 (Clcr in the model) or SOF, based on population PK analyses.

3.2.5. Pharmacokinetic interactions

3.2.5.1. Pharmacokinetic interactions demonstrated in human studies

In agreement with the *in vitro* data, coadministration of a high dose of the potent Pgroup and BCRP inhibitor CsA increased SOF AUC and C_{max} by 353% and 154%, respectively (Study P7977-1819). Increase in SOF exposure following high dose CsA 600mg may not be clinically significant due to its very low and transient exposure relative to total drug-related material (i.e. SOF). Based upon the drug-related material calculation, SOF AUC increased from ~3% (SOF alone) to ~10% (SOF with CsA) of drug-related material AUC. With respect to systemic exposure, safety margins for SOF (GS-566500 & GS-331007) were 1.9-16.0-fold after co-administration with CsA compared with exposures obtained in toxicology studies. Further data on the SDOF-CsA interaction in the posttransplant setting is being evaluated (Study GS-US-334-0126). Study GS-US-334-0131 revealed a <2-fold increase in SOF exposure with a less potent Pgroup inhibitor, DRV/r. Drugs that are potent Pgroup inducers in the intestine (rifampin, St John's Wort) and other known inducers i.e. carbamazepine and phenytoin may significantly **decrease** SOF plasma concentration leading to reduced therapeutic effect and should not be used. Coadministration of SOF with drugs that inhibit Pgroup and/or BCRP may increase SOF plasma concentration without increasing GS-331007 plasma concentration and hence, SOF may be coadministered with Pgroup and/or BCRP inhibitors. SOF and GS-331007 are not inhibitors of Pgroup and BCRP and are not expected to increase exposures of drugs that are substrates of these transporters. Coadministration of SOF with the CYP and Pgroup inducer EFV show small decreases in SOF and GS-331007 C_{max} (19% and 23%, respectively) but not AUC. Coadministration of tacrolimus (Study P7977-1819), methadone (Study P7977-0814), RAL or RPV (Study GS-US-334-01311) resulted in either no or minimal changes in SOF and GS-331007 exposures. Coadministration of SOF 400 mg with AZT, 3TC, ATV is permitted in the ongoing HCV/HIV-coinfection study (Study P7977-1910). HCV inhibitors GS-5816, LDV, tegobuvir, GS-9451, GS-9669, BMS790052 (daclatasvir) and CYP-inhibitors (RTV and ketoconazole) did not markedly affect the formation of GS-461203 (<30% change, *in vitro*). In addition to the above, an ongoing Phase 1 study (GS-US-334-0146) is evaluating the effect of SOF on PK of the hormonal contraceptive, norgestimate/ethinyl estradiol. Results are not yet available.

3.2.5.2. Clinical implications of in vitro findings

None, aside from the potential for D-D interactions with potent PgP inducers.

3.3. Evaluator's overall conclusions on pharmacokinetics

The application includes a comprehensive PK programme. Overall, SOF exhibits a very favorable Absorption, Distribution, Metabolism, Elimination (ADME) profile. These data support the oral dosing ± food of SOF OD. The only real cautions are in ESRD where the drug should be avoided as SOF dose would have to be reduced at least 2-4 fold to provide lower GS-331007 exposures. These sorts of dose reduction would risk inadequate levels of the active moiety, GS-461203. While hepatic impairment does impact on SOF and metabolite PK, these changes do not appear to impact PD and no dose adjustments are required. In terms of likely D-D interactions, there is relatively little potential for this; this bodes well for SOF co-administration with CYP-inhibitors/inducers. The issue of CYP-inhibiton has been particularly problematic in HIV-HCV coinfected subjects because of ARV-BOC/TPV interactions via CYP. However, SOF is susceptible to Pgroup and/or BCRP transporter-based drug interactions, but its main metabolite, GS-331007, is not; taken together, avoidance of co-administration with the very potent inducers of Pgroup, is prudent.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 6 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 6: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on HCV genotype 1	**P2938-0212 (NUCLEAR) P7977-0221**	*
	Effect on HCV 1, genotype 2 and 3	**P7977-0422 (PROTON)**	*
	Effect on HCV, genotype 2 and 3	**P7977-0523 (ELECTRON)**	*
	Effect on HCV genotypes 1, 4, 5, or 6	**P7977-0724 (ATOMIC):**	*
	Effect on all HCV genotypes 1-6	**P2938-0721 (QUANTUM)**	*
Secondary Pharmacology	Effect on {@ PD parameter C}		
Gender other genetic and Age-Related Differences in PD Response	Effect of gender		
	Effect of @ {genetic characteristic}		
	Effect of age		
PD Interactions	@ {Drug A}		
Pop'n PD and PK-PD analyses	Target population		*

* Indicates the primary aim of the study; § Subjects who would be eligible to receive the drug if approved for the proposed indication; ‡ And adolescents if applicable.

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

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans. Definitions of importance in regards to virologic failure:

- **breakthrough** (HCV RNA ≥15 IU/mL on treatment after previously having HCV RNA <15 IU/mL on treatment, confirmed with 2 consecutive values /last available measurement)
- **rebound** (>1 log10 IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values/ last available m'ment)
- **non-response** (HCV RNA persistently ≥15 IU/mL through 24 wks [for genotype 1groups] of treatment) or 12 wks (for genotype 2 or 3 group)

- **relapse** (HCV RNA ≥15 IU/mL during the posttreatment period having achieved HCV RNA <15 IU/mL at EOT, confirmed with 2 consecutive values/last available m'ment).

A number of factors increase **likelihood of success** (i.e. SVR) with SOC for mono-infected HCV treatment-naïve subjects including favourable IL28B status, lower BMI, lack of insulin resistance (i.e. using the homeostasis model assessment of insulin resistance (HOMA IR) score), HCV GT-2 or 3, non-cirrhotic, lower HCV viral load (<400,000–500,000 IU/mL) and RBV dose as part of the treatment of RBV-containing regimens. These covariates are included in the analyses of the Phase 2 & 3 studies of SVR. Liver steatosis is also a known risk factor for lower SVR for GT- 3.[19]

4.2.1. Mechanism of action

SOF is a novel HCV NS5B-directed inhibitor displaying potent inhibition of HCV RNA replication *in vitro*. In human hepatocytes, SOF is converted to the active uridine triphosphate form (GS-461203) which directly inhibit NS5B polymerase activity with IC_{50} values of 0.7-2.6 μM. SOF is active against HCV GT- replicons 1a, 1b, 2a, 3a, 4a HCV, with EC_{50} values of 0.040-0.11 μM. Potent activity is also observed against chimeric GT- 1b replicons encoding NS5B from GT-2b, 5a, and 6a (EC_{50} 0.014-0.015 μM). In addition, SOF was active against GT- 1a and 2a HCV cell culture infectious virus (EC_{50} = 0.03 (GT-1a); 0.02 μM (GT 2a). SOF displays high specificity for HCV; no significant activity against HIV-1, human rhinovirus types 10 & 14, respiratory syncytial virus (RSV), influenza A up to the highest concentration tested (100 μM). The diastereoisomeric mixture GS-9851 showed limited inhibition of hepatitis B virus (HBV) (18% at 100μm). Anti-HCV activity of 2-drug combinations of SOF with the anti-HCV compounds ledipasvir (GS-5885), GS-9190, GS-9669, or GS-9451 (Gilead developmental DAAs), TPV, BOC, PEG were found to be additive in replicon assay systems; minor synergy observed with RBV. No antagonism observed. ***In vitro* resistance** selections in replicon cells were performed to determine which NS5B mutations might likely confer resistance to SOF. **S282T was the primary mutation selected in all replicon GT-s tested and site-directed mutagenesis confirmed that S282T conferred reduced susceptibility to SOF**. S282T mutation did not confer cross-resistance to other antiviral classes and appeared to increase RBV sensitivity *in vitro*. HCV replicons expressing S282T showed reduced replication capacity (RC) *in vitro*. Conversely, SOF remained active against replicons harbouring mutations that conferred resistance to HCV protease inhibitors, nonnucleoside inhibitors, NS5A inhibitors, nucleoside inhibitors (NIs; NS5B L159F, L320F), as well as RBV-associated mutants F415Y and T390I. Integrated Phase 2 Virology Analyses from P7977-0221, P7977-0422 [PROTON], P7977-0724 [ATOMIC], P7977-0523 [ELECTRON], P2938-0721 [QUANTUM]). NS5B population sequencing was attempted at baseline for all subjects from the 5 Phase 2 studies including 671 subjects that received SOF. Population sequencing revealed no S282T at baseline in 702 of 711 samples. As SOF was administered with RBV in most regimens, baseline samples were also assessed for RBV mutations: T390I & F415Y. Of 662 successfully sequenced subjects, 20 had detectable T390I or F415Y at baseline present as a full mutant or mixture. The resistance analysis population (RAP) i.e. 76 of 671 subjects (75 sequenced) included all subjects not achieving SVR24 due to virologic failure, discontinued drug, HCV RNA >1000 IU/mL. S282T mutation (mutant detection sensitivity 1%) detected S282T in 1 of 75 (GT 2b, SOF monotherapy). Postbaseline sequences, revealed 3 of 74 with detectable T390I or F415Y, all present at baseline with no enrichment through SOF exposure. Six NS5B substitutions occurred in 2 subjects either as full mutations or mixtures at time of viral failure. Phenotypic analyses showed no change in SOF sensitivity. Overall, S282T mutant replicons from multiple GT display decreased RC, occur rarely and reverse quickly; these factors likely contribute to the **lack of virologic breakthrough** observed in the Phase 2 studies.

[19] Hwang, SJ, Lee SD. (2011) Hepatic steatosis and hepatitis C: Still unhappy bedfellows? *J Gastroenterol Hepatol.* 26 Suppl 1:96-101.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

The primary PD effect of SOF in its triphosphylated form active is inhibition of HCV replication in the liver. The measurable outcome of this direct inhibiton is a very rapid reduction in plasma HCV RNA levels. More details on the speed of this effect and the PK/PD relationship are detailed below.

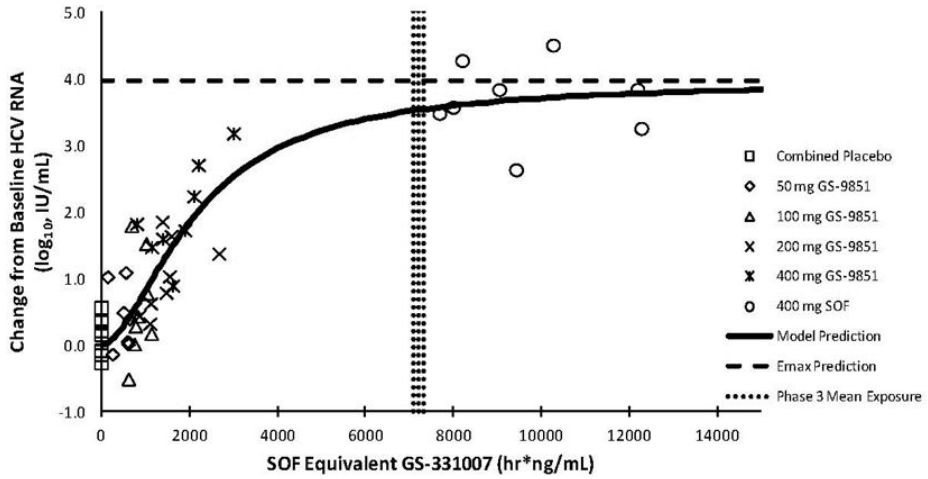
4.2.2.2. Secondary pharmacodynamic effects

No concerning secondary PD effects revealed in the programme. Study P7977 0613 in healthy subjects, demonstrated a lack of effect of SOF on prolongation of the QTcF interval consistent with the ICH E14 definition of a negative "thorough QT/QTc study." Moreover, the Phase 2 & 3 programme evaluated ECG changes as part of safety monitoring with no safety signal revealed. Mean exposure of GS-331007 (AUC_{tau} and C_{max}) and SOF (AUC_{tau}) at the supratherapeutic dose (1200mg) was 3.8-, 3.6-, and 2.9-fold higher, respectively, than the mean exposure (population PK exposures) achieved in the Phase 3 studies, indicating adequate QTc safety margins for GS-331007 and SOF if overdose or a DDI should occur. Safety profiles of SOF+RBV and SOF+PEG+RBV aligned with the expected safety profile of RBV and PEG+RBV, respectively. Consistent with the haemolytic effects of RBV, decreased Hb was the most frequently reported lab abnormality and **not convincingly enhanced by SOF**. Overall, PK/PD analyses of the GS-331007 and SOF exposure-safety relationships revealed no relevant trends in exposure-safety parameters across all GS-331007 (AUC_{tau} and C_{max}) and SOF (AUC_{tau}) quartiles. The non-clinical data indicates a low likelihood for cytotoxicity in humans. In summary, there was low potential for mitochondrial toxicity, as not significant effects on mitochondrial deoxyribonucleic acide levels or mitochondrial biogenesis in SOF- treated cells. In addition, there was no measureable inhibition of human DNA, RNA or mitochondrial polymerases by the active triphosphate form.

4.2.3. Time course of pharmacodynamic effects

An exposure response relationship identified for GS-331007 AUC_{tau} best described with a sigmoid E_{max} model. In Figure 2, the vertical dotted line is the Phase 3 mean (90% CI) exposure of GS-331007 from Phase 3 population PK analyses, the horizontal dashed line is the model estimate of E_{max} and solid line the best fit model (sigmoidal) predicted exposure-response curve. At the mean Phase 3 GS-331007 exposure, the model predicted % of maximum viral load reduction (% of E_{max}) was ~90%. GS-331007 exposures in Phase 3 studies reside in the plateau range of this relationship indicating near maximal antiviral activity. In the SOF+PEG+RBV combination therapy paradigm (Study P7977-0221), exposure-virologic response (GS-331007 AUC_{tau} -HCV RNA reduction) after 3 days of treatment, are in good agreement with the model predictions.

Figure 1: Relationship between GS-331007 AUC_{tau} (from SOF) and change from baseline HCV RNA during SOF or GS-9851 monotherapy after 3 days of treatment.



In addition, SOF exposure-response relationships provided comparable predicted exposure-response of E_{max} (80% (SOF only); 95% of E_{max} (SOF+PEG+RBV)). To explore for differences in early viral load reduction potency across GT-s, mean HCV RNA decreases in treatment-naive subjects with GT- 2 or 3 after 2 days of SOF 400 mg+PEG+RBV was compared with 3 days of SOF in GT- 1 (Table 7). These data indicate comparable early HCV RNA reduction across treatment-naive subjects with GT- 1 (85.4%), -2 (85.0%), or -3 (81.5%).

Table 7: Observed HCV RNA reduction (Log10 IU/mL and % of Emax) in treatment-naive subjects with GT- 1, 2, and 3 HCV infection after treatment with SOF 400mg+PEG+RBV.

				HCV RNA Reduction	
Study	Days of Treatment	N	HCV Genotype	Observed Mean (%CV) Decrease From Baseline (Log_{10} IU/mL)	Mean Response as % of Reference[a]
P7977-0221	3	15	Genotype 1	3.64 (15.3)	85.4
P7977-0523 Groups 2,3,4,6	2	11	Genotype 2	3.62 (9.26)	85.0
P7977-0523 Groups 2,3,4,6	2	29	Genotype 3	3.47 (15.0)	81.5

a Parameter estimates for maximum viral load reduction following treatment with SOF 400 mg +PEG+RBV ($E_{max} + E_0$ = 3.40 $\log_{10}$ IU/mL + 0.860 = 4.26) was used as reference; observed mean response within genotypes was expressed as percent of reference.

Note: Parameters are presented to 3 significant digits.

4.2.4. Relationship between drug concentration and pharmacodynamic effects

SOF dose/exposure (GS-331007 $AUC_{tau)}$ response evaluated in order to select the best dose for efficacy (SVR12) in Phase 3. The Phase 2 dose-finding studies are tabulated. In brief, these revealed an exposure-response relationship supporting the SOF 400mg dose. PK/PD analyses of GS-331007 and SOF exposure-efficacy from Phase 3 studies were performed in CHC GT- 2 or 3 HCV infection (Rx.SOF+RBV) and CHC GT- 1, 4, 5 or 6 HCV (Rx. SOF+PEG+RBV). The PK/PD dataset included all subjects in the full analysis set (FAS) (n=982) with population PK-based GS-331007 AUC_{tau} estimates (n=977). In general, univariate logistic regression analysis of GS-331007 AUC_{tau} and SVR12 across studies indicated a statistically significant ($p < 0.05$) PK/PD relationship. However, closer interrogation of these data revealed a statistically significant ($p < 0.05$) PK/PD relationship in GT- 3 but not GT- 2 treatment-experienced patients. Moreover, due to lower SVR12 in **treatment-experienced** GT- 3 HCV-infected subjects, HCV RNA reductions at the earliest measured time point (Wk 1) were examined to rule out early kinetic differences; these showed equivalent HCV RNA reduction i.e 4.5 and 4.3log_{10}IU/mL for GT- 2 and -3 respectively and in agreement with the on-treatment PK/PD analysis conducted to support Phase 3 dose selection irrespective of treatment-experience status. Together, these data

suggest on-treatment antiviral potency was optimal at 400 mg but that HCV GT- (i.e. GT-3) and treatment duration drive SVR12.

Figure 2: Observed HCV RNA reduction (Log_{10} IU/mL and % of E_{max}) across treatment-naive subjects with GT- 1, 2, and 3 HCV infection after treatment with SOF 400mg +PEG+RBV % who achieved SVR12 across studies by population quartiles of GS-331007 AUC_{tau} (PK/PD Analysis Set).

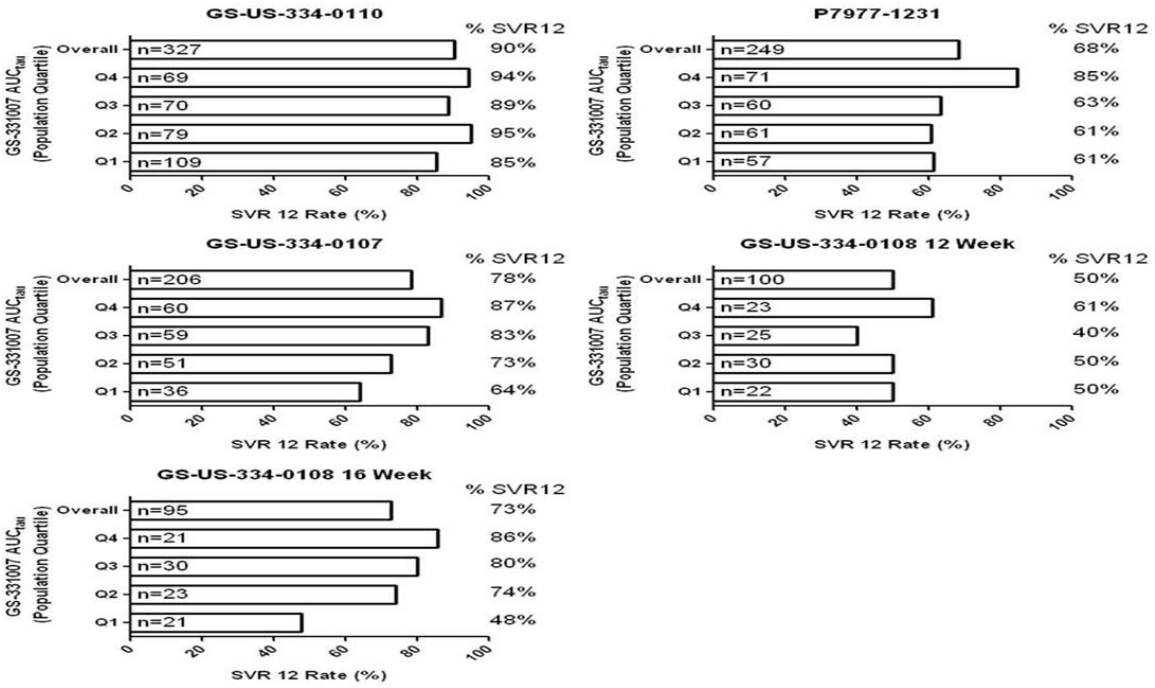
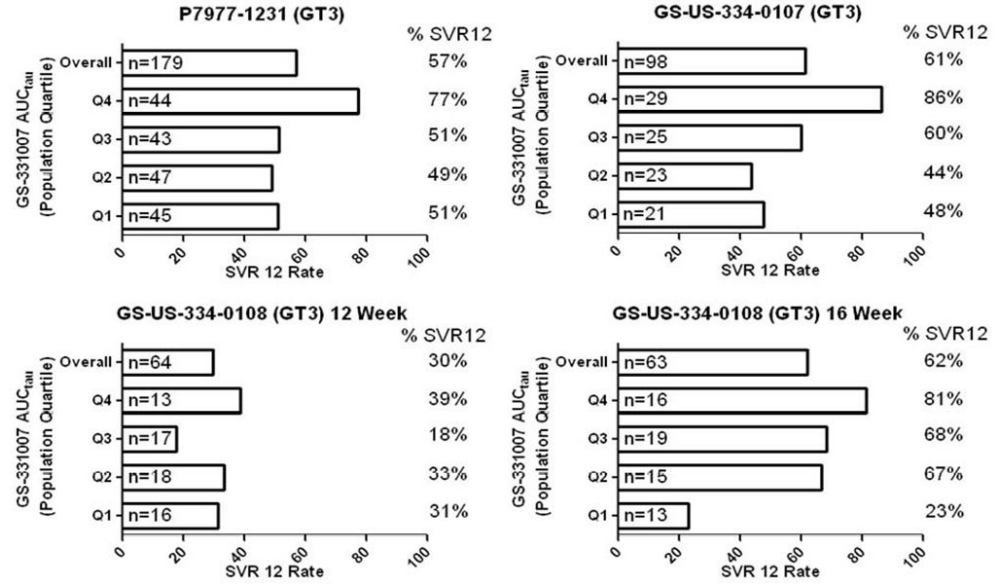


Figure 3: Percentage that achieved SVR12 after cessation of study drug across population quartiles of GS-331007 AUC_{tau} in GT- 3 HCV infection (PK/PD analysis set).



4.2.5. Genetic, gender and age related differences in pharmacodynamic response

None revealed, with the caveat that there is a paucity of data in patients older than 65 yrs of age.

4.2.6. Pharmacodynamic interactions

None revealed of concern. Lower SVR rate with GT-3 not fully explained. However, hepatic steatosis, a known important predictor of GT- 3 treatment response, was not formally assessed at enrolment.

4.3. Evaluator's overall conclusions on pharmacodynamics

A comprensive ongoing SOF PD programme is being conducted. The rationale for the 400mg dose is justified based on the slightly lower rates of virologic failure (relapse) than with lower doses especially as the drug appears to have a wide safety margin. The drug is very potent, with rapid virological suppression and no apparent cross-reactivity with other HCV antivirals in the event of viral resistance.

Phase 2 Studies in Subjects with GT-2 or -3: In P7977-0422, SOF+PEG+RBV 12 weeks resulted in SVR24 rate of 92.0%. Study P7977-0523 (ELECTRON) demonstrated antiviral potency and 100% SVR12 in treatment-naïve subjects with GT- 2 or 3, regardless of the presence/absence of PEG. **SOF monotherapy** was **less** efficacious, resulting in SVR12 of only 60.0% of treatment-naive GT- 2 or -3; thus, indicating RBV should be included. In P7977-0523, SOF+RBV had SVR12 of 68.0% in treatment-experienced GT- 2 or 3 HCV-infected subjects, a population with limited treatment options. These data supported the initiation of the Phase 3 Studies P7977-1231, GS-US-334-0107, and GS-US-334-0108 with SOF+RBV.

Phase 2 Studies in Subjects with GT-1, -4, -5, or -6: In P7977-0422, 12 wks of SOF+PEG+RBV in treatment-naive subjects with GT- 1 resulted in SVR24 rate of 91.5%. Study P7977-0523 confirmed 12 wks of SOF+RBV could effectively treat treatment-naïve GT- 1, with SVR12 rate of 84.0% (n=25, so numbers were small). Study P2938-0721 (QUANTUM) assessed 12 and 24 wks of SOF+RBV treatment. In this study, **12 weeks of SOF+RBV** was **as effective as 24 weeks** of SOF+RBV in achieving SVR12 (56.0% and 52.0%, respectively) in GT- 1 (n = 38), 2 (n = 5), or 3 (n = 7), but note the very small numbers for GT -2 and -3. In Study P7977-0724 (ATOMIC), 12 wks of SOF+PEG+RBV in treatment-naives with GT- 1, -4, or -6 resulted in SVR12 rate of 90.4%. This very high SVR rate, along with added bonuses of a shorter treatment regimen i.e. only 12 wks of PEG provided further support for the Phase 3 Study GS-US-334-0110 with SOF+PEG+RBV.

5. Dosage selection for the pivotal studies

Based on the lower rates of virologic failure in SOF 200 and 400 mg groups versus 100 mg in Study P7977-0221, 200 and 400 mg were subsequently evaluated further in combination with PEG+RBV in Study P7977-0422 (PROTON). In PROTON, on-treatment failures occurred in SOF 200 mg + PEG + RBV group (n = 3) but not in SOF 400 mg + PEG + RBV group during the second 12 week phase (PEG+RBV). These data suggest that SOF 400 mg may provide more pronounced viral suppression and the 400 mg dose once daily was selected for Phase III. The SOF 400 mg tablets containing SOF Form II (planned for commercial use) is the formulation used in GS-US-334-0110 (NEUTRINO) and GS-US-334-0108 (FUSION).

6. Clinical efficacy

6.1. Pivotal efficacy studies

Four pivotal Phase 3 studies: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION) and GS-US-334-0110 (NEUTRINO) are presented in this Application. Three of these studies assessed SOF+RBV in GT- 2 or 3 HCV-infected subjects (Studies P7977-1231, GS-

US-334-0107, GS-US-334-0108), and Study GS-US-334-0110 assessed SOF+PEG+RBV in treatment-naive GT- 1, 4, 5, or 6 HCV-infected subjects.

6.1.1. Study P7977-1231 (FISSION) A Phase 3, Multicentre, Randomised, Active-Controlled Study to Investigate the Safety and Efficacy of PSI-7977 and Ribavirin for 12 Wks Compared to Pegylated Interferon and Ribavirin for 24 Wks in Treatment-Naïve Patients with Chronic Genotype 2 or 3 HCV Infection

6.1.1.1. Study design, objectives, locations and dates

Sites: 90, USA incl. 1 in Puerto Rico (n=61); Australia (n=14), New Zealand (n=6), Canada (n=5), Sweden (n=2), Italy (n=1), the Netherlands (n=1); first subject screened: 19Dec11;15Jan13 (Last subject observation for this interim).

Protocol amendments: 4, most significant was Amendment 1, which removed the 3rd arm (SOF+PEG+RBV) prior to any enrolment.

Design: Multicentre, open-label Randomised, Study to Investigate the Safety and Efficacy of PSI-7977 in Combination with PEG and RBV for 12 wks vs. PEG and RBV for 24 Wks in Treatment-Naïve Patients with Chronic GT- 2 or 3 HCV Infection.

6.1.1.2. Inclusion and exclusion criteria

6.1.1.2.1. Key inclusion

1. Willing and able to provide written informed consent; 2. Male or female, age ≥18 years; 3. confirmation of chronic HCV infection 4. chronic GT- 2 or 3 HCV; 5. HCV RNA $\geq 10^4$ IU/mL; 6. Cirrhosis determination, CPT A in 10% - protocol defined; 6. HCV treatment-naïve; 7. BMI ≥18 kg/m2; 8. Avoidance of pregnancy including partner.

6.1.1.2.2. Key exclusion

1. Prior treatment for HCV with interferon or RBV; 2. Prior exposure to a DAA targeting the HCV NS5B polymerase; 3. Pregnant or nursing female or male with pregnant female partner; 4. Chronic liver disease of a non-HCV etiology; 5. HBV or HIV; 6. Contraindications for PEG or RBV; 7. labs outside protocol-defined limits i.e. a) ALT or AST ≥10 × ULN b) Hb <12 g/dL for male, <11 g/dL for females c) ANC <1,500/µL f) Platelets <90,000/µL g) Albumin <3 g/dL i) Direct bilirubin ≥2.0 x ULN j) CLcr <60 mL/min, as calculated by the CKD-EPI.

6.1.1.3. Study treatments

Randomised in a 1:1 ratio stratified by HCV genotype (Subjects with GT- 2 or 3 HCV infection were enrolled in approx. 1:3 ratio), screening HCV RNA levels (<6 $\log_{10}$ IU/mL or ≥6 $\log_{10}$ IU/mL), and cirrhosis. Treatment groups:

- SOF+RBV: SOF 400 mg + RBV 1000 mg or 1200 mg (based on body wt) daily for 12 wks
- PEG+RBV: PEG 180 µg wkly + RBV 800 mg daily for 24 wks.

6.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Serum HCV RNA Roche Taqman HCV Test Vn 2.0 for use with the High Pure System
- Screening, Day 1 (baseline) and at Wks 1, 2, 3, 4, 8, 12/EOT during treatment and at posttreatment Wks 4, 8, 12, 16, 20, 24. For the PEG+RBV group, HCV RNA assessed at Wks 16, 20, 24/EOT
- PK: Plasma concentrations of SOF and its metabolites collected at Wks 1, 4, 8, and 12/EOT. RBV concentrations at Wks 1, 4, 8, 12/EOT for the SOF+RBV group. Storage plasma: Wks 1, 4, 8, 12, 24/EOT in PEG+RBV group

- Safety was assessed by monitoring AEs and concomitant medications, clinical lab analyses, physical examination, vital sign measurements, ECGs
- QoL surveys SF-36 Health Survey on Day 1, Wk 12/EOT, posttreatment Wks 12 and 24 (SOF+RBV group) and Day 1, Wks 12 and 24/EOT, and posttreatment Wk 12 (PEG+RBV group).

Primary objective to determine the efficacy of SOF+RBV administered for 12 wks compared with PEG+RBV for 24 wks in treatment-naive subjects with GT- 2 or 3 as **assessed by the rate of SVR12**.

Other efficacy outcomes included: safety and tolerability; SVR24 of PSI-7977/RBV administered for 12 wks; change in HCV-RNA; ALT normalisation; QoL, SVR12 and SVR48; virologic failure and resistant variants.

6.1.1.5. Randomisation and blinding methods

Initial design was that subjects would be assigned to treatment groups using a centralised randomisation system in equal ratios to the study arms, but the study design changed after Amendment 1 and became **Open-label.**

6.1.1.6. Analysis populations

ITT population: all randomised subjects with documented evidence of receiving ≥1 dose of study drug. This will be the primary population for efficacy analyses. For all analyses based on the ITT Population, subjects analysed in the treatment group to which they are randomised, regardless of what treatment is received.

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

PK analysis set: all subjects enrolled and received ≥1 dose of study drug and for whom concentration data of study drug [GS-7977 and metabolite(s),] are available.

6.1.1.7. Sample size

N=500. A sample size of 250 per arm will provide ≥90% power at the 2.5% significance level (using one-sided 97.5% CI to assess non-inferiority), assuming the SVR24 rate of 75% in the control arm and 78% of SVR24 rate in each of PSI-7977 arms; 250 per arm will provide ≥90% power to detect a difference between the group SVR24 rate of 12% using a two-sided test at significance level of 0.05, assuming the SVR24 rate of 75% in the control arm.

6.1.1.8. Statistical methods

The primary statistical framework will be to demonstrate non-inferiority and superiority of SVR24 response of Arm A (PSI-7977+PEG/RBV) as compared to Arm B (PEG/RBV). As such, the null and alternative hypotheses to be tested are as follows:

Hypothesis for non-inferiority	Hypothesis for superiority
H0: $P_A - P_B <= -10\%$	H0: $P_A - P_B = 0$
H1: $P_A - P_B > -10\%$	H1: $P_A - P_B > 0$

The SVR24 for active treatment A is PA, and PB is the SVR24 for PEG/RBV. A non-inferiority margin of 10% of SVR24 is considered appropriate. Non-inferiority is demonstrated (or null hypothesis will be rejected) when the upper 95% CI for the difference in SVR24 is great than -10%. If non inferiority is established (the non-inferiority null hypothesis is rejected), the p-

value associated with the test of superiority will be calculated. The superiority will be demonstrated if the two-sided p-value is <0.05.

Safety: Clinical and laboratory AEs coded using the MedDRA. System Organ Class (SOrgC), High-Level Group Term, High-Level Term, Preferred Term, Lower-Level Term will be attached to the clinical database. Events summarised on the basis of date of onset for the event. A TEAE is defined as any new/worsening AE that begins on/after the date of first dose of study drug up to the date of last dose **plus** 30 days. Summaries (nos. and % of subjects) of TEAEs (by SOrgC and preferred term) will be provided.

6.1.1.9. Participant flow

Planned: 500 subjects

Analysed:

- Randomised analysis set: 527 subjects (263 SOF+RBV; 264 PEG+RBV)
- Safety analysis set: 499 subjects (256 SOF+RBV; 243 PEG+RBV)
- Full analysis set (FAS): 496 subjects (253 SOF+RBV; 243 PEG+RBV)
- Per protocol analysis set: 477 subjects (246 SOF+RBV; 231 PEG+RBV).

6.1.1.10. Major protocol violations/deviations

A total of 666 subjects screened; 527 subjects (SOF+RBV 49.9%; PEG+RBV 50.1%) randomised. During the 7-day period between randomisation and initiation of study drug, 28 discontinued and never received study drugs (SOF+RBV 7 subjects; PEG+RBV 21 subjects). Hence, 499 subjects were randomised, received treatment and were included in the SAS (SOF+RBV 256 subjects; PEG+RBV 243 subjects).

Major deviations: 3 randomised GT- 1 subjects (SOF+RBV group) excluded from the FAS (n = 496). Most subjects in the SAS (63.3%) were from the US; 12.2% from Australia, 11.8% from New Zealand, 7.8% from Canada, 4.8% from the EU. Overall, randomisation across treatment groups balanced by region and randomisation strata (HCV GT-, cirrhosis status, HCV RNA level).

6.1.1.11. Baseline data

Demographics and baseline disease characteristics of the safety analysis set were generally balanced across treatment groups by HCV GT- 2 and GT- 3.

Demographics: Mean age 48 yrs (range: 19-77 yrs); 65.5% male; 87.2% White and non-Hispanic or Latino (85.6%). Asian and black/African American subjects comprised 5.8% and 3.4% of subjects, respectively. Mean BMI 28.0 kg/m^2, 70.3% had BMI <30 kg/m^2.

HCV-related: 71.9% GT- 3 HCV infection, 20.2% had cirrhosis; 57.1% had HCV RNA ≥6 log10 IU/mL; 43.1% had IL28B GT- CC allele.

6.1.1.12. Results for the primary efficacy outcome

Of the 499 subjects in the SAS, 434 (87.0%) completed study treatment as planned (SOF+RBV 95.7%, 245 subjects; PEG+RBV 77.8%, 189 subjects).

- SVR12 rate in SOF+RBV group was 67.2% (95% CI: 61.0% to 72.9%), i.e. noninferior to SVR12 rate of 66.7% (95% CI: 60.4% to 72.6%) in the PEG+RBV group. The strata-adjusted difference (95% CI) in proportions was 0.3% (-7.5% to 8.0%). The lower bound of the 2-sided 95% CI for the difference between groups was greater than the prespecified noninferiority margin of -15%
- 29.6% of the SOF-RBV group had virologic failure; most (74 /75) due to virologic relapse, predominantly occurring by the posttreatment Wk 4 visit

- 26.3% of PEG+RBV group had virologic failure; most events (46 of 64) due to virologic relapse, predominantly occurring at posttreatment Wk 4 or 8
- higher proportion in PEG+RBV group (7.4%) had on-treatment virologic failure vs. the SOF+RBV group (0.4%)
- GT- 2 had higher SVR12 in the SOF+RBV group than PEG+RBV group (97.1% vs 77.6%, respectively); strata-adjusted difference in proportions was 19.1% (95% CI: 7.4% to 30.7%)
- For all other subgroups, the 95% CI for the difference in proportions between treatment groups crossed 0
- Subjects with GT- 3 had similar SVR12 rates in SOF+RBV and PEG+RBV groups (55.7% vs 62.5% respectively); the strata-adjusted difference in proportions was -6.9% (95% CI: -16.6% to 2.9%); 8) Differences in study treatment completion rate driven predominantly by lower rates of discontinuations due to AEs (1.2%) and virologic failure (0.4%) in SOF+RBV group vs. PEG+RBV group (10.7% and 7.0%, respectively).

In summary: The study met the predefined primary efficacy endpoint, demonstrating overall SVR12 rate (67.2%) with SOF+RBV for 12wks was noninferior to SVR12 rate (66.7%) with PEG+RBV for 24wks (strata-adjusted difference in proportions: 0.3; 95% CI for difference -7.5% to 8.0%). Moreover, SOF+RBV for 12 wks vs. 24 wks of PEG+RBV, resulted in higher response rates in GT- 2 HCV and similar response rates in GT- 3 HCV.

Table 8: P7977-1231 primary efficacy outcome.

			SOF+RBV vs PEG+RBV
	SOF+RBV (N=253)	PEG+RBV (N=243)	Prop Diff (95% CI)[a]
SVR12	170/253 (67.2%)	162/243 (66.7%)	0.3% (-7.5% to 8.0%)
Overall Virologic Failure	75/253 (29.6%)	64/243 (26.3%)	3.3% (-4.6% to 11.2%)
Relapse[b]	74/249 (29.7%)	46/217 (21.2%)	
On-Treatment Virologic Failure	1/253 (0.4%)	18/243 (7.4%)	
Other[c]	8/253 (3.2%)	17/243 (7.0%)	

6.1.1.13. Results for other efficacy outcomes

1. **Viral kinetics**: HCV RNA suppression more rapid with SOF+RBV vs. PEG+RBV. By Wk 2, 92.0% of SOF+RBV grp and 31.5% of PEG+RBV group had HCV RNA <LLOQ. The differences between groups diminished over time, but proportion with HCV RNA <LLOQ in the SOF+RBV group was numerically higher than the PEG+RBV group for all on-treatment comparisons. Median time to first HCV RNA <LLOQ, 2.0 wks and 3.0 wks in SOF+RBV and PEG+RBV groups respectively.
2. **ALT normalisation**: greater at each on-treatment time point in the SOF+RBV group vs.PEG+RBV group.
3. **Resistance:** The RAP included 79 subjects who received SOF+RBV and did not achieve SVR12. Full NS5B sequence data obtained from 75 and partial NS5B sequence data from 4 subjects. No SOF-associated mutation in NS5B detected by deep/population sequencing; 29 other NS5B substitutions observed in >2 subjects, none associated with phenotypic changes to SOF or RBV.

6.1.2. Study GS-US-334-0107 (POSITRON) a Phase 3, multicenter, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of GS-7977 + ribavirin for 12 Wks in subjects with chronic genotype 2 or 3 HCV infection who are interferon intolerant, interferon ineligible or unwilling to take interferon

6.1.2.1. Study design, objectives, locations and dates

Sites: 54 sites; US (n=43 incl. 1 in Puerto Rico), Canada (n=5), Australia (n=4), New Zealand (n=2); first subject screened: 07Mar12; 14Nov12 (Last subject observation for this interim).

Protocol amendments: One, clarification of primary endpoint.

Design: Phase 3, mulitcentre, double-blind, randomised, study evaluating the antiviral efficacy, safety, tolerability of SOF+RBV vs. placebo for GT- 2 or 3 CHC.

6.1.2.2. Inclusion and exclusion criteria

6.1.2.2.1. Key inclusion

- Willing and able to provide written informed consent; 2. Male or female, age ≥18 years; 3. chronic HCV; 4. GT- 2 or 3 HCV; 5. HCV RNA ≥104 IU/mL; 6. IFN unwilling, ineligible of intolerant: Subject completed ≤12 wks (ending ≥3 mths prior to screen) with IFN & discontinued due to development or significant worsening of a nos. of conditions listed in protocol; 7. BMI ≥18 kg/m^2; 8. lab parameters: a) ALT ≤10 × the ULN b) AST ≤10 × ULN c) Hb ≥12 g/dL (M), ≥11 g/dL (F) d) ANC ≥1,500/µL e) Platelets ≥90,000/µL f) INR ≤1.5 x ULN g) Albumin ≥3 g/dL h) bilirubin ≤1.5 x ULN i) CLcr ≥60 mL/min, (Cockcroft-Gault); j) HbA1C ≤10%; 9) avoid pregnancy including partner pregnancy.

6.1.2.2.2. Key exclusion

- Prior treatment with DAA targeting the HCV NS5B polymerase; 2. Pregnant/nursing female; male with pregnant partner; 3. Chronic liver disease of a non-HCV aetiology; 5. HBV or HIV; 6. Contraindication to RBV.

6.1.2.3. Study treatments

SOF 400 mg/day, OD + RBV orally 1000 or 1200 mg/day in divided dose BID (1000mg for body wt <75 kg; 1200 mg for body wt ≥75 kg) or matched placebos.

6.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- serum HCV RNA screening, and thereafter BLINDED – during treatment at Wks 1, 2, 4, 6, 8, 10, 12/EOT; posttreatment Wks 4, 12, 24. Assay=COBAS Taqman HCV Test, Version 2.0
- PK samples (SOF, metabolites and RBV) Day 1 (baseline) and at Wks 1, 2, 4, 6, 8, 10, 12/EOT
- Safety assessed by documenting AEs, concomitant medications, clinical lab analyses, physical exam, vital signs, ECGs at prespecified intervals throughout the study
- QoL survey (SF-36).

The **primary objective** was to determine the efficacy of treatment with SOF+RBV vs. matched placebos as measured by the proportion of subjects with SVR12.

Other efficacy outcomes included: viral kinetics**;** proportions with SVR4 and SVR24; resistance; health-related quality of life**.** All subjects to complete screening, on-treatment, posttreatment assessments incl. a 4-wk Posttreatment visit regardless of treatment duration. Subjects with HCV RNA <LLOQ at EOT and 4-wk Posttreatment to complete 12-wk and 24-wk Posttreatment visits unless viral relapse occurs. End of study occurs at the 24-wk Post-Treatment visit.

6.1.2.5. Randomisation and blinding methods

A total of 240 randomised subjects with ~180 in Arm 1 (GS-7977+RBV) and ~60 in Arm 2 (GS-7977 placebo+RBV placebo). Interactive Web Response System for subject randomisation & study drug assignment. Randomisation stratified by presence/absence of cirrhosis. Matching placebos provided. HCV RNA results blinded except at Screening. Following the 4-Wk Posttreatment Visit, subjects may be eligible for the Open Label Study (GSUS-334-0109).

6.1.2.6. Analysis populations

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

6.1.2.7. Sample size

N=240.

6.1.2.8. Statistical methods

This is a randomised, double-blind, placebo-controlled study examining safety, tolerability and antiviral efficacy of GS-7977+RBV vs. GS-7977+RBV placebos in subjects with chronic GT- 2 or 3 HCV who are IFN-intolerant, -ineligible, - unwilling to take IFN. A total of 240 subjects to be randomised in 3:1 ratio to one of two arms: **Arm 1** (n=180): GS-7977 400mg OD+RBV BID; **Arm 2** (n=60): GS-7977 placebo 400mg OD+RBV placebo BID. Randomisation stratified by cirrhosis status (~20% **may** have cirrhosis).

Safety: Clinical and lab AEs coded using the MedDRA. Events summarised on basis of date of onset. TEAE = new/worsening AE that begins on/or after the date of first dose of study drug up to the date of last dose of study drug **plus** 30 days. Summaries (nos.; % of subjects) of TEAE (by SOrgC & preferred term) to be provided.

6.1.2.9. Participant flow

Planned: 240 (180 SOF+RBV; 60 placebo) Analysed: 278 (207 SOF+RBV; 71 placebo).

6.1.2.10. Major protocol violations/deviations

Of 280 randomised subjects, 278 were included in the SAS and FAS (207 SOF+RBV group; 71 placebo group); 2 subjects were erroneously randomised to SOF+RBV, but did not receive study drug. Of the 278 in the SAS, 3.2% discontinued study drug (SOF+RBV 2.9%; placebo 4.2%). Reasons were: AE (SOF+RBV 1.9%; placebo 4.2%); LTFUP (SOF+RBV 1.0%).

6.1.2.11. Baseline data

Demographics and baseline data of the SAS balanced between the 2 groups.

Demographics: mean age 52 yrs (range 21-75 yrs); 54% male; 91.4% White, 89.2% non-Hispanic/Latino; 66.5% BMI <30 kg/m^2.

HCV related: 51.4% GT- 2; 48.6% GT- 3; mean (SD) HCV RNA 6.3 (0.77) $\log_{10}$ IU/mL; 69.8% HCV RNA ≥6 $\log_{10}$ IU/mL; 81.3% HCV treatment-naive; 45.3% IL28B CC allele; subjects unwilling, interferon, ineligible or intolerant of IFN were respectively, 47.5%, 43.5%, 9.0%. 57.2% had ALT >1.5 × ULN; 16% cirrhotic. Demographics generally well balanced across GT- 2 and GT- 3 subjects.

6.1.2.12. Results for the primary efficacy outcome

Adherence: SOF+RBV (87.4%); placebo 90.1%.

- 77.8% (CI: 71.5% to 83.2%) vs. 0% (CI: 0.0% to 5.1%)of SOF+RBV vs. placebo groups respectively achieved SV12 ($p < 0.001$)
- 42 (20.3%) subjects relapsed in the SOF+RBV group, with most relapses (32 of 42) occurring by the posttreatment Wk 4 visit. No subjects in the SOF+RBV group had on-treatment virologic failure
- None of the 71 placebo group subjects achieved SVR4 or SVR12
- Subgroup analyses demonstrated GT- 2 had higher SVR12 than GT- 3 (92.7% vs 61.2% respectively) and non-cirrhotics vs. cirrhotics had SVR12 rate of 80.7% vs 61.3% respectively. Difference in SVR12 rate in cirrhotics was attributable to differences only in GT- 3 subjects as GT- 2 cirrhotic subjects and non-cirrhotic subjects had similarly high SVR12 rates i.e. 94.1% and 92.4%, respectively.

Table 9: Primary efficacy results for GS-US-334-0107.

			SOF+RBV vs Placebo
	SOF+RBV (N=207)	Placebo (N=71)	Proportion Difference Adjusted for Stratum (95% CI)
SVR12	161/207 (77.8%)	0/71	77.3% (71.0% to 83.6%)
Overall Virologic Failure	42/207 (20.3%)	69/71 (97.2%)	-76.9% (-83.1% to -68.4%)
Relapse	42/205 (20.5%)	0/0	
On-Treatment Virologic Failure	0/207	69/71 (97.2%)	
Other[a]	4/207 (1.9%)	2/71 (2.8%)	

a Other = Subject who did not achieve SVR12 and did not meet virologic failure criteria.

6.1.2.13. Results for other efficacy outcomes

- **Viral kinetics**: rapid HCV RNA suppression in SOF+RBV group, with ~4 log10 IU/mL mean decrease after 1 wk. By Wk 4, 99.0% of subjects had HCV RNA <LLOQ
- **ALT normalisation**: observed in most SOF+RBV subjects during treatment, coincident with HCV RNA decreases. In the placebo group, most had ALT >ULN for the duration of treatment
- **Resistance**: 40 of 41 subjects not achieving SVR12, successfully sequenced, No SOF- or RBV-associated mutations detected; five other NS5B substitutions in >2 subjects -no change in phenotypic sensitivity.

6.1.3. Study GS-US-334-0108 (FUSION) a Phase 3, multicentre, randomised, double-blind study to investigate the efficacy and safety of GS-7977 + ribavirin for 12 or 16 Wks in treatment experienced subjects with chronic Genotype 2 or 3 HCV infection

6.1.3.1. Study design, objectives, locations and dates

Sites: 57 sites: US (n=43 incl. 1 in Puerto Rico), Canada (n=12), New Zealand (n=2). First subject screened: 04Jun12; 11Feb13 (Last subject observation for this **interim**).

Protocol amendments: Amendment 1, 08May12 - placebo arm replaced by a 16wk treatment arm; in the 12wk treatment arm, added placebo drugs for 4 wks; sample size increased to 200.

Design: Phase 3, Multicentre, Randomised, Double-Blind Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 or 16 wks for CHC GT- 2 or 3.

6.1.3.2. Inclusion and exclusion criteria

6.1.3.2.1. Key inclusion

- Willing and able to provide written informed consent; 2. Male or female, age ≥18 yrs; 3. confirmed chronic HCV 4. GT- 2 or 3 HCV; 5. HCV RNA ≥104 IU/mL; 6. Presence/absence of cirrhosis documented; 7. had failed prior treatment with an interferon-based regimen; 8. BMI ≥18 kg/m2; 9. Labs at screening: a) ALT ≤10 × the ULN b) AST ≤10 ×ULN c) Hb ≥12 g/dL(M), ≥11 g/dL(F) d) Platelets ≥50,000/μL e) INR ≤1.5 x ULN f) Albumin ≥3g/dL g) bilirubin ≤1.5 x ULN h) CLcr ≥60 mL/min (Cockcroft-Gault equation); i) HBA1C ≤10%; 10. avoid pregnancy including partner pregnancy.

6.1.3.2.2. Key exclusion

- Prior exposure to a DAA targeting the HCV NS5B polymerase; 2. Pregnant/nursing female or male with pregnant partner; 3. Chronic liver disease of non-HCV etiology; 5. HBV or HIV; 6. Contraindications for RBV.

6.1.3.3. Study treatments

- SOF+RBV 12Wk group: SOF 400mg OD+RBV total daily dose 1000 or 1200mg in a divided daily dose for 12 wks; followed by SOF placebo OD + RBV placebo in a divided daily dose for 4 wks

- SOF+RBV 16Wk group: SOF 400mg OD+RBV total daily dose 1000 or 1200mg in a divided daily dose for 16 wks.

6.1.3.4. Efficacy variables and outcomes

The main efficacy variables were:

- serum HCV RNA at screening, and then Blinded, Day 1, Wks 1, 2, 4, 6, 8, 10, 12, 16 during treatment, and at posttreatment Wks 4, 8, 12, 20, 24. Assay=COBAS TaqMan HCV Test v2.0
- Bloods for PK: Day 1 predose, at Wks 1, 2, 4, 6, 8, 10, 12, 16 during treatment
- Safety assessed by monitoring AEs and concomitant medications, clinical lab analyses, physical exam, vital signs, ECGs
- QoL surveys.

The primary efficacy outcome was SVR12 rate (HCV RNA <LLOQ 12 wks after cessation therapy) with either 12 or 16 wks of SOF+RBV in the FAS population. Other efficacy outcomes: safety including any AE leading to permanent discontinuation of study drugs; proportion with: SVR4 and SVR24; viral breakthrough; and relapse; viral kinetic parameters and resistance; ALT normalisation; PK.

6.1.3.5. Randomisation and blinding methods

Randomisation stratified by presence or absence of cirrhosis and HCV GT- (2 or 3); ~30% of randomised subjects could have cirrhosis.

6.1.3.6. Analysis populations

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

6.1.3.7. Sample size

N= 200.

6.1.3.8. Statistical methods

The 2 primary statistical hypotheses were that SVR12 rates in both treatment groups were >25%. The 2-sided 95% exact CI using the Clopper-Pearson method was provided for the SVR12 rate in each of the 2 treatment groups. If the tests in the primary analysis were statistically significant at the 0.025 significance level, the secondary analysis comparing the SVR12 rates between the 2 treatment groups was performed using a Cochran-Mantel-Haenszel test stratified by the randomisation stratification factors. The 2-sided 95% CI of the difference in SVR12 rates between the 2 treatment groups (SOF+RBV 12Wk – SOF+RBV 16Wk) was constructed based on stratum-adjusted Mantel Haenszel proportions. Point estimates and 2-sided 95% exact CIs for SVR12 rates were constructed for each demographic and baseline characteristic subgroup using the same methods described above. Forest plots graphically presented estimates and 95% CIs of the between-treatment group differences in SVR12 rates for each subgroup. Safety: as described before.

6.1.3.9. Major protocol violations/deviations

One of 202 randomised, excluded from the SAS & FAS due to study drug non-receipt; 6 subjects in the SAS excluded from FAS because of GT- 1. Of 201 randomised & treated subjects, 1 subject prematurely discontinued (during placebo in the SOF+RBV 12 Wk group) due to an AE.

6.1.3.10. Baseline data

Demographics were generally balanced between the 2 treatment groups.

Demographics: mean age 54 yrs (range: 24-70 yrs); 69.7% male; 86,6% White and90.5% non-Hispanic/Latino; mean (SD) BMI 28.5 (4.68) kg/m^2.

HCV-related: generally balanced between groups, 63.2% GT- 3; 33.8% GT- 2; HCV RNA 6.5 (0.65) $\log_{10}$ IU/mL; 72.6% HCV RNA ≥ 6 $\log_{10}$ IU/mL. prior IFN-treatment failure: 75.1% relapse/breakthrough; 24.9% nonresponse; 69.7% non-CC (CT or TT) IL28B alleles, 30.3% IL28B CC allele; 34.0% cirrhotic; 59.2% ALT >1.5 × ULN.

6.1.3.11. Results for the primary efficacy outcome

- 50.0% of the SOF+RBV 12 Wk group and 72.6% of the SOF+RBV 16 Wk group achieved SVR12. SVR12 rates in both groups were each statistically significantly higher (p <0.001) compared to the null rate of 25%
- SOF+RBV for 16 wks resulted in **higher SVR12** rates compared 12 wks treatment, the difference in the % of subjects achieving SVR12 (SOF+RBV 12 Wk group − SOF+RBV 16 Wk group) was −23.4% (95% CI: −35.4% to −11.4%) and statistically significant (p <0.001);
- No subject in either treatment group had on-treatment virologic failure
- **Relapse**: 47.0% of SOF+RBV 12 Wk group, relapsed; 43/47 of these did so within 4 wks of stopping active treatment, and 4 did so between posttreatment Wk 4 and 12. Similarly, in the SOF+RBV 16 Wk group, 27.4% relapsed; 22/26 subjects did so by posttreatment Wk 4, and 4 between posttreatment Wk 4 and 12
- Subgroup analysis indicated **differences in SVR12** rates between these groups, were consistent with those observed in the overall population, consistently favouring 16 Wk group. But, GT- 2 had similar SVR12 rates in the 12 Wk and 16 Wk groups (86.1% and 93.8%, respectively), whereas GT- 3 had higher SVR12 with 16 wks of treatment (61.9% vs. 29.7%)
- Within each treatment group, analyses of SVR12 by subgroup revealed generally similar SVR12 rates for the age, ethnicity, BMI, IL28B GT-, response to prior HCV treatment subps. In both SOF+RBV 12Wk and SOF+RBV 16Wk groups, there was higher SVR12 in GT- 2 vs. GT- 3, and higher SVR12 rates observed in females. In the SOF+RBV 12 Wk group, higher SVR12 observed in noncirrhotics (60.9%) than cirrhotics (30.6%); this difference was less pronounced in the SOF+RBV 16 Wk group (76.2% vs. 65.6%).

Table 10: Primary efficacy results for GS-US-334-0108.

	SOF+RBV 12 Weeks + Placebo 4 Weeks (N=100)	SOF+RBV 16 Weeks (N=95)	SOF+RBV 12 Weeks + Placebo 4 Weeks vs. SOF+RBV 16 Weeks
			Prop Diff (95% CI)
SVR12	50/100 (50.0%)	69/95 (72.6%)	−23.4% (−35.4% to −11.4%)
Overall Virologic Failure	47/100 (47.0%)	26/95 (27.4%)	
Relapse[a]	47/100 (47.0%)	26/95 (27.4%)	
On-Treatment Virologic Failure	0/100	0/95	
Other[b]	3/100 (3.0%)	0/95	

a The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
b Other = Subject who did not achieve SVR12 and did not meet virologic failure criteria.

6.1.3.12. Results for other efficacy outcomes

- **Viral kinetics**: rapid HCV RNA suppression observed in both treatment groups; similar mean HCV RNA decreases after 1 wk of treatment i.e. ~4.4 log10 IU/mL (SOF+RBV 12Wk group); ~4.5 log10 IU/mL (SOF+RBV 16Wk group). By Wk 4, ~97.0% (both groups) had HCV RNA <LLOQ, with higher numbers at subsequent assessments
- **ALT normalisation**: observed in the majority coincident with HCV RNA decreases
- **Resistance**: 77/77 subjects (66 GT-3 subjects, 7 GT-2 subjects, 4 GT-1 subjects) in the RAP had NS5B sequencing. No S282T by deep/population sequencing; 11 NS5B substitutions observed in >2 subjects, no loss of sensitivity.

6.1.4. Study GS-US-334-0110 (NEUTRINO) Phase 3, multicenter, open label study to investigate the efficacy and safety of GS-7977 with pegylated interferon Alfa 2a and ribavirin for 12 Wks in treatment-naïve subjects with chronic Genotype 1, 4, 5, or 6 HCV infection

6.1.4.1. Study design, objectives, locations and dates

Sites: USA (n=55); first subject screened: 18Jun12; 25Jan13 (Last subject observation for interim)

Protocol amendments: none.

Design: Phase 3, multicentre, **open-label**, **non-randomised,** study evaluating the safety, tolerability and antiviral efficacy of GS-7977 with PEG and RBV in treatment naïve subjects with chronic GT- 1, 4, 5 or 6 HCV infection.

6.1.4.2. Inclusion and exclusion criteria

6.1.4.2.1. Key inclusion

- Willing and able to provide written informed consent; 2. Male or female, age ≥18 yrs; 3. chronic HCV n 4. GT- 1, 4, 5, or 6; 5. HCV RNA ≥10^4 IU/mL; 6. Presence/absence of cirrhosis confirmed; 7. HCV treatment-naïve; 8. BMI ≥18 kg/m^2; 9. labs: a) ALT ≤10 × ULN b) AST ≤10 × ULN c) Hb ≥12 g/dL(M), ≥11 g/dL(F) d) WBC count ≥2,500/µL e) ANC ≥1,500/µL f) Platelets ≥90,000/µL g) INR ≤1.5 x ULN h) Albumin ≥3 g/dL i) bilirubin ≤1.5 x ULN j) CLcr ≥60 mL/min (Cockcroft-Gault; 10. avoid pregnancy including partner pregnancy.

6.1.4.2.2. Key exclusion

- Prior treatment for HCV with interferon or RBV; 2. Prior exposure to a DAA targeting the HCV NS5B polymerase; 3. Pregnant/nursing female or male with pregnant partner; 4. Chronic liver disease of a non-HCV etiology; 5. HBV or HIV; 6. Contraindications for PEG or RBV.

6.1.4.3. Study treatments

SOF 400 mg/day, OD (1 × 400mg tablet); **PEG** SC 180 µg/wk, once wkly; **RBV** orally 1000 or 1200 mg/day in divided dose BID (1000mg for body wt <75 kg; 1200 mg for body wt ≥75 kg)

6.1.4.4. Efficacy variables and outcomes

The main efficacy variables were:

- serum HCV RNA screening, Day 1, Wks 1, 2, 4, 6, 8, 10, 12 during treatment, and at post treatment Wks 4, 12, and 24
- PK: Day 1 predose, at Wks 1, 2, 4, 6, 8, 10,12 during treatment
- Safety assessed by monitoring AEs and concomitant medications, clinical lab analyses, physical exam, vital signs, ECGs at prespecified intervals throughout the study
- QoL surveys (SF-36, CLDQ-HCV, FACIT-F, WPAI: Hepatitis C) to assess effects on health-related QoL on Day 1 predose, at Wk 12 during treatment, and Wks 4, 12, and 24 post treatment.

The **primary efficacy outcome** was SVR12 rate (HCV RNA <LLOQ 12 wks after cessation of therapy) in the FAS population.

Other efficacy outcomes included: safety including any AE leading to permanent discontinuation of study drugs; proportion with SVR4 and SVR24; viral breakthrough; and relapse; HCV RNA change from Baseline; ALT normalisation; viral kinetic parameters; SOF and metabolite PK.

6.1.4.5. Analysis populations

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

6.1.4.6. Sample size

N=300.

6.1.4.7. Statistical methods

SAS software (SAS Institute, USA) used. The study hypothesises that SOF+PEG+RBV for 12 wks will achieve an SVR12 rate >60%. The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 wks after cessation of therapy) in the FAS population.

Hypothesis for superiority: H0: SVR12 rate = 60%; H1: SVR12 rate ≠ 60%. The hypothesis will be tested using two-sided one-sample binomial test to determine if a 60% rate can be ruled out at the 0.05 significance level. The basis for this 60% SVR null rate is derived from: 1) A **historical SVR rate** of ~65% calculated from the TPV (ADVANCE study) and BOC (SPRINT2 study) data after adjusting for the expected proportion of cirrhotics (~20%) in this study; and 2) a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment. The weighted average of the TPV and BOC data is ~70% in non-cirrhotics, and 44% in cirrhotics. The SVR rate for the historical control (i.e. patient population of 80% non-cirrhotics & 20% cirrhotics) is then calculated to be ~65% (i.e. 0.8 ×70% + 0.2 ×44%). As noted above, 60% null SVR rate obtained after allowing for a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter treatment duration.

Safety: as described before.

6.1.4.8. Major protocol violations/deviations

Of 328 enrolled, 327 received study drug and were included in the FAS and SAS. One subject enrolled but never returned for the Day 1 visit. Of those treated: 7 (2.1%) discontinued study treatment. The reasons were AE (1.5%), protocol violation (0.3%), withdrawal by subject (0.3%).

6.1.4.9. Baseline data

Demographics: mean age 52 yrs (range: 19–70 yrs), 4.3% >65 yrs old; 63.9% male; 78.6% White; 16.5% Black; 85.9%, non-Hispanic ethnicity; mean BMI 29.1 kg/m^2 (range: 17.8–56.1).

HCV-related: mean (SD) HCV RNA 6.4 (0.67) $\log_{10}$ IU/mL; 78.3% HCV RNA ≥6 $\log^{10}$ IU/mL. 68.8%, GT- 1a; 70.9% non-CC (CT or TT) IL28B GT-, 29.1%, IL28B CC allele; 16.7% cirrhotic; mean (SD) ALT 83 (61.1) U/L; 50.8% ALT >1.5 × ULN. Demographics for GT- 1a and 1b differed i.e. IL28B CC allele more common in GT- 1a (32.0%) vs. GT- 1b (19.7%); GT- 1b had a higher proportion of Black subjects; cirrhotics, and were older.

6.1.4.10. Results for the primary efficacy outcome

Adherence: SOF 97.2%, PEG 95.0%, RBV 91.1%; ≥95% adherence rate for SOF (93.3%); PEG (77.1%); RBV (67.3%) reflecting dose modification permitted for PEG & RBV toxicity. Overall, 76.8% had ≥80% adherence to each study drug.

- SVR12 rate significantly higher (90.2%, 95% CI: 86.5–93.2%, p <0.001) vs. historical SVR12 rate of 60%. No on-treatment virologic failure. Of the 7 prematurely discontinuing 1 LTFUP, 1 discontinued Day 16 prior to HCV RNA <LLOQ, 3 relapsed, 2 achieved SVR12 after 54 and 66 days of treatment, respectively. In total, 8.6% relapsed; 22 of these 28 relapsers within 4 wks of stopping treatment
- Pre-specified subgroup analyses demonstrated all subgroups had SVR12 of ≥80% and these did not differ greatly by GT-: 91.6% for GT- 1a, 81.8% for GT- 1b, 96.4% for GT- 4. The 1 GT-5 subject and 6 GT- 6 subjects achieved SVR12. Subjects with IL28B CC had higher SVR12 rate than non-CC - 97.9%, 95% CI: 92.6–99.7% vs. 87.1%, 95% CI: 82.1–91.1%, respectively.

Higher response rates in noncirrhotics vs. cirrhotics (92.3%, 95% CI: 88.5–95.2% vs. 79.6%, 95% CI: 66.5–89.4% respectively). In all other subgroups SVR12 rate differences were <10%. SVR12 rates between Black vs. non-Black subjects similar (87.0%, 95% CI: 75.1–94.6% & 90.8%, 95% CI: 86.8–94.0%, respectively).

Table 11: GS-US-334-0110: Virologic Outcome (FAS)

	SOF+PEG+RBV (N = 327)
SVR12	295/327 (90.2%)
Overall Virologic Failure	28/327 (8.6%)
Relapse[a]	28/326 (8.6%)
Study Drug Completer	25/320 (7.8%)
Study Drug Noncompleter	3/6 (50.0%)
On-Treatment Virologic Failure[b]	0/327
Other[c]	4/327 (1.2%)

6.1.4.11. Results for other efficacy outcomes

Viral kinetics: mean 4.7 $\log_{10}$ IU/mL HCV RNA decrease after 1 wk of, and maintained. By Wk 4, all but 4 subjects (98.8%, 321 of 325) had HCV <LLQ.

ALT normalisation: 79% had ALT >ULN at baseline, most normalised during treatment, coincident with HCV RNA decline.

Resistance: 28 subjects (8.6%) relapsed by the posttreatment Wk 12 visit, 22 of the 28 (6.7%) who relapsed did so within 4 wks of stopping treatment. No subjects had on-treatment virologic failure. All were sequenced; S282T, was not detected; one NS5B substitution observed in >2 subjects, not associated with a change in susceptibility to SOF, PEG, or RBV.

6.2. Other efficacy studies

6.2.1. Study P7977-2025: An open-label study to explore the clinical efficacy of PSI-7977 with ribavirin administered pre-transplant in preventing Hepatitis C Virus (HCV) recurrence post-transplant

Definitions (EASL-EORTC clinical practice guidelines):

- Model for End-Stage Liver Disease (MELD) uses patient's values for bilirubin, creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival.
- Milan criteria: In transplantation medicine, the Milan criteria are applied as a basis for selecting patients with cirrhosis and hepatocellular carcinoma for liver transplantation (LTx) stating that a patient is selected for transplantation when he or she has: one lesion smaller than 5 cm, up to 3 lesions smaller than 3 cm, no extrahepatic manifestations and no vascular invasion.

Objectives: To determine if SOF+RBV (≤24 wks) to HCV-infected subjects with HCC (Milan criteria) prior to undergoing liver transplantation could prevent posttransplant reinfection defined as HCV RNA <LLOQ at 12 wks posttransplant.

Secondary objectives: determine if SOF+RBV pre LTx elicits a sustained viral response (HCV RNA <LLOQ) 12 wks after discontinuation of therapy (SVR12); safety/tolerability of SOF+RBV prior to LTx; HCV RNA viral kinetics; explore presence/absence of HCV RNA in liver explants and correlate PK/PD; explore dynamics of noncorrected-for-tumor MELD core during study; SOF PK.

Sites: US (n=14); New Zealand (n=1), Spain (n=1); 1st subject screened 27 March 2012; expected completion 12 Feb 2015.

6.2.1.1. Methodology

Open-label single sequence, Phase 2, study of SOF+RBV; 2 phases: Pre-transplant; posttransplant after received LTx.

Main inclusions: males/female ≥18 yrs old; BMI ≥18 kg/m^2, CHC any GT; meet Milan criteria for LTx 2o to HCV-related cirrhosis with MELD score of <22 and HCC-weighted MELD score of ≥22 and a CPT score ≤7.

Treatment: Pre-Tx: 24 wks SOF 400mg OD + RBV (1000mg/day if wt <75 kg; 1200mg/day for wt ≥75 kg, BID). Treatment discontinued within 24 hrs prior to LTx if this occurred before 24-Wks treatment completed. Planned posttransplant immunosuppressants: Prednisone, tacrolimus, mycophenolate mofetil during the first 12 Wks posttransplant.

Number of subjects: planned: 40 subjects (≤60 subjects if ≥25 subjects underwent liver transplantation prior to 12 wks of treatment).

Analysed: Data cut for interim in January 2013. 61 subjects (safety and efficacy in pretransplant treatment phase); 15 subjects with HCV RNA <LLOQ at time of liver transplantation received ≥12 Wks of treatment for posttransplant virologic response (pTVR; primary analysis of primary efficacy endpoint); 25 subjects received any duration of treatment with HCV RNA <LLOQ at the time of liver transplantation for pTVR (secondary analysis of primary endpoint).

Treatments: SOF orally OD as 400 mg (2 × 200-mg tablets); **RBV** BID in a divided total daily dose of 1000 or 1200 mg (1000mg if wt <75 kg; 1200mg if wt ≥75 kg).

Data collection and analysis: ensure meet inclusion and exclusion, screening bloods to include; HCV genotyping. Study visits occurred in the pretransplant treatment phase at screening, baseline, and Wks 1, 2, 3, 4, 8, 12, 16, 20, 24 and every 4 wks posttreatment (pretransplant). All subjects receiving ≥1 dose study drug followed in posttreatment follow-up visits every 4 Wks until liver transplantation. Study visits in the posttransplant follow-up phase were at Wks 1, 2, 4, 8, 12, 24, 48. HCV RNA collected at all study visits. PK samples at Wks 1, 4, 8, 12, Wk 24 (EOT). Serum stored each visit for resistance analysis.

Analyses: as described across the Phase 3 programme for HCV efficacy endpoints; safety.

Relapses after stopping drug before LTx: enter retreatment substudy.

Efficacy: Serum HCV RNA (Roche COBAS Taqman HCV Test v2.0 LLOQ 25 IU/mL); viral resistance testing.

Safety: Safety assessments - AEs, safety lab tests incl. pregnancy tests, ECG, HCV RNA, physical exam, vital signs.

6.2.1.2. Results of interim analysis (Jan 2013)

Subject disposition and demographics: 63/92 screened/enrolled; 61/62 in SAS. 18 subjects (29.5%) were on study treatment (pretransplant), 14 subjects (23.0%) completed 24 Wks of study treatment and continued into the posttreatment follow-up (4 subsequently transplanted), 24 subjects (39.3%)transplanted while on study treatment, 5 subjects (8.2%) had prematurely discontinued study drug (AE (n=1); non-responders (n=2); responder breakthrough (n=2); At the time of data cut, 57 subjects (93.4%) on study; 4 subjects (6.6%) prematurely discontinued (1 due to death, 1 nonresponse, 1 efficacy failure [transplanted with an HCV-+ve liver], 1 due to progressive disease and no longer for transplant.

Demographics: mean age(SD) 59(5.5) yrs; 80.3% male; 90.2% White (19.7% Hispanic ethnicity); BMI Mean(SD)28.6(5.65)Kg/m^2; 75.% prior HCV treatment; HCV Log_{10} RNA=6.14; 39.3%, 34.3%, 3,3%, 9.8%, 11.5%, 1% GT-s 1a, 1b, 2, 2B, 3A, 4 respectively; ALT mean 81(39.1) IU/L; IL-28B CT=65%, CC=21.7%, TT=13.3%.

Efficacy results: See also Table 12.

- rapid HCV RNA i.e.3.87 log10 IU/mL mean decrease after 1 wk;
- HCV RNA <LLOQ in 93.1% of subjects by Wk;
- apart from 5 subjects with on-treatment virologic failures; all others had HCV RNA <LLOQ for the duration of treatment or until liver transplantation;
- ~90% transplanted went into liver transplantation with HCV RNA <LLOQ;
- 8 of 12 subjects completing 24 wks of treatment and had a Wk 4 posttreatment follow-up visit **relapsed in the pre-transplant phase**.

Table 12: Interim efficacy results P7977-2025.

Number of Subjects Transplanted	28
Number of Subjects with ≥ 12 Weeks of Treatment and Received a Liver Transplantation[a]	17
< LLOQ at Last HCV RNA Measurement Prior to Liver Transplantation	
Yes	15/17 (88.2%)
No	2/17 (11.8%)
Number of Subjects with Any Treatment Duration and Received a Liver Transplantation[b]	28
< LLOQ at Last HCV RNA Measurement Prior to Liver Transplantation	
Yes	26/28 (92.9%)
No	2/28 (7.1%)

a The denominator includes all subjects who received a liver transplantation and had ≥ 12 weeks of study treatment for the primary efficacy analysis set.

b The denominator includes all subjects who received a liver transplantation and had ≥ 1 dose of study treatment for the secondary efficacy analysis set.

Post-transplant: 1) Of the 25 with HCV RNA <LLOQ at liver transplantation, 1 subject died post-transplant (acute graft non-fn), 6 had recurrent HCV post-transplant and **18 continue to be followed in the post-transplant follow-up phase with HCV <LLOQ**. For the 6 subjects with recurrent HCV post-transplant, treatment durations were 4, 5, 13, 15, 17, 20 wks; **2)** Of these 6 subjects, virologic relapse occurred **within 4 Wks of liver transplant in 1 GT- 1a multiply-prior treated subject (n=1); GT- 1b (n=5)**; **3)** 8 of 13 subjects (61.5%) with HCV RNA <LLOQ and **any** treatment duration achieved the primary endpoint, SVR12 post-transplant.

Safety Results: generally well tolerated; **AE**: 85.2% experienced ≥1 AE, most frequently fatigue (36.1%), anaemia (23.0%), headache (21.3%); most AEs Gde 1 or 2; 9.8% had a Gde 3 AE; anaemia was the only Gde 3 or 4 AE that occurred in >1 subject. One subject had a Gde 4 AE of malignant hepatic neoplasm (significant and rapid progression of the HCC tumor) and tumor thrombosis; **SAE/death (N=2)**: pneumonitis (n=1) 38 days after last dose of study drug not TE; liver graft failure (n=1) not TE. 13 SAE in 8 subjects, only 1 (anaemia, reported 87 days after first dose study drug) considered TE; **TEAEs**: 46 subjects (75.4%) had AEs considered related to study drug (fatigue, anaemia, and headache were observed in >15% of subjects); **Labs:** 4.9% had a Gde 4 lab abnormality, lymphocytopaenia (n=1), AST 4 Wks after last dose study drug) (n=1); 36.1% had ≥1 Gde 3 lab abnormality. Gde 3 lab abnormalities occurring in ≥2 subjects: hyperglycaemia, 7 subjects; hypoglycaemia, 2 subjects, decreased Hb (8 subjects), increased bilirubin and decreased lymphocytes (4 subjects each); decreased platelets, increased PT (2 subjects each). All other Gde 3 lab abnormalities occurred in 1 subject each. 31.1% had Gde 2 lab; 27.9% Gde 1 lab abnormalities. **Safety profile consistent with known side-effects of RBV**. **Other:** Median ALT values decreased for the duration of treatment, returning to baseline levels by the 4 Wk post-treatment follow-up visit. MELD scores (8-9) constant during & post study. **Vital signs and ECG**: no notable changes in ECGs, physical exams, or vital signs. None reported as an AE.

6.2.1.3. Evaluator's comments

Appropriate pilot design aimed at improving LTx outcome by prevention of HCV in the graft using SOF+RBV pre-transplant, **interim data only**. The strategy did appear to work in so much

as 61.5%% of LTx recipients who had HCV<LLOQ at transplant, had an SVR12 post-transplant; HCV RNA suppression was as rapid in this HCC cohort as described in prior studies; study drugs well tolerated considering how ill the cohort are, no unexpected AE in this group.

6.2.2. Study GS-US-334-0123 (PHOTON-1): A Phase 3, open-label study to investigate the efficacy and safety of GS-7977 plus ribavirin in chronic genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) co-infected subjects

Objectives: SVR12 using SOF+RBV for 12 Wks; safety (including HIV related) and tolerability;

Secondary objectives: SVR4 and SVR24 rates; viral/resistance kinetics; **exploratory**: genetic markers for outcome; QoL.

Sites: US (N=33); Puerto Rico (n=1); 1st subject screened 20Jul12.

Methodology: Phase 3, open-label, multicentre study investigating efficacy/safety of SOF+RBV in subjects with CHC 1, 2, or 3-HIV-1. This interim synoptic CSR focuses on methodology and preliminary safety and efficacy results pertaining to the treatment-naive subjects **with GT- 2 or 3** HCV infection enrolled by 28Sep12 (Gp 1). All data for Gp 1 subjects collected up to the data cut-off date (24Jan13) were included in this interim.

Key inclusion criteria (Gp 1): males/non-pregnant females; ≥18 yrs; BMI ≥18 kg/m^2; CHC GT-2 or 3; confirmed HIV-1; on (stable ARV regimen >8 wks, CD4+ >200 cells/uL, HIV-RNA <50 cp/mL) **or** off ARVS - CD4+ >500 cells/uL.

Treatments: SOF 400mg OD+ wt-based RBV dose given BID for 12 wks; 24 wks post treatment FU.

Data collection and analysis: Screening to assess subject eligibility. Enrollment targets were as follows: ~10% untreated for HIV-1; ~20% cirrhotic. On-treatment study visits, Day 1 and at Wks 1, 2, 4, 6, 8, 10, 12. Post-treatment follow-up visits 4 wks following last dose study drug. Subjects with HCV RNA <LLOQ at post-treatment Wk 4 returned at post-treatment Wks 12 and 24, unless confirmed virologic relapse occurred. HCV RNA and viral resistance during & post-treatment; **Analyses:** efficacy/safety as previously described; **Efficacy:** Serum HCV RNA (Roche COBAS Taqman HCV Test v2.0 LLOQ of 25 IU/mL); viral resistance testing; **Safety:** AEs, safety labs (including HIV-1 RNA and CD4 T-cells), ECG, vital signs. If >20% enrolled on any specific ARV regimen experienced on-treatment virologic failure, an evaluation of the safety of continuing enrolment of subjects on this specific ARV treatment was to occur.

6.2.2.1. Study participants planned

~55 HCV-treatment-naives GT- 2 or 3 HCV-HIV-1 coinfected.

Analysed: 18 February 2013, **n=31 subjects**.

6.2.2.2. Results of interim analysis

Subject disposition and demographics: 87.1% completed treatment; 12.9% premature discon (AE, investigator decision, LTFUP, consent withdrawal). **Demographics:** mean age 46 yrs (range: 24-66 yrs); 77.4% male; 83.9% White; BMI mean(range) 27.7 (20.2-43.5)Kg/m^2; HCV-RNA $\log_{10}$ ≥6 in 74.2%; GT- 3 (61.3%); 90.3% non-cirrhotic; IL-28B CC=38.7%; 61.3% ALT >1.5 × ULN (mean: 89 U/L); 74.2% IFN eligible. **HIV:** 61.3% had CD4+ ≥500 cells/uL; mean CD4+ 601 cells/uL; 87.1% on ARVS (TDF/FTC backbone + either NNRTI (n = 13), boosted PI (n = 9), or II (n=5).

Efficacy results: See also Table 13.

Table 13: Interim efficacy results in GS-US-334-0123.

	Group 1: Genotype 2 or 3 Treatment-Naive SOF+RBV 12 Weeks (N=31)
SVR4 [95% CI]	21/31 (67.7%) [48.6% to 83.3%]
Overall Virologic Failure	7/31 (22.6%)
Relapse[a]	6/30 (20.0%)
On-Treatment Virologic Failure[b]	1/31 (3.2%)
Other[c]	3/31 (9.7%)

6.2.2.3. In summary

- SVR**4** in **67.7%** (95% CI 48.6-83.3%); **32.3% did not achieve SVR4**, 7 of whom had virologic failure and 3 not assessible (1 LTFUP, 1 died, 1 withdrew consent)
- SVR**4** in 9 of the 12 (75.0%) GT- 2 and 12 of 19 subjects (63.2%) GT- 3
- **higher virologic relapse** in 6 of the 7 **GT-3**; all had an IL28B non-CC GT.

Safety results: generally well tolerated.

Drug exposure: Mean exposure to 11.6 wks; all 31 subjects received ≥6 wks of study drug; 6 subjects had RBV dose reduction . Of note, 5 of 6 subjects with RBV dose reductions did achieve SVR4; **AE:** 74.2% had AEs, most frequently reported: fatigue (38.7%), insomnia (22.6%); nausea, irritability, URTI, headache (each reported in 16.1%). Most AEs Gde 1 or 2. Two subjects (6.5%) had at least 1 Gde 3 AE and 2 subjects (6.5%) had ≥1 Gde 4 AE; fatigue was the only Gde 3 or 4 AE in >1 subject (2 subjects; Gde 3); **SAE/death**: All of the Gde 4 AEs were also SAEs; 3 subjects (9.7%) experienced ≥1 SAE, none drug-related. One subject (who discontinued) experienced 8 SAEs (assoc. with staphylococcal septic shock), all on the same day (Day 68) but had SVR4 after ~10 wks of treatment. The 3rd subject with an SAE was **the only death**, the subject committed suicide 9 days after last dose of study drug; **Lab results:** Most Gde 1 or 2. No Gde 4 labs reported. 6.5% had Gde 3 labs (ALT; glucose, 1 each). Most AE consistent with known RBV side-effects. **Other:** Median ALT values decreased for duration of treatment and post-treatment Wk 4; **CD4+ T-cells and HIV RNA:** total lymphocytes & T-cells declined during treatment i.e. Median $1.81 \times 10^3/\mu L \rightarrow 1.38 \times 10^3/\mu L$ and 530 cells/uL → 410 cells/uL by Wk 12. Return to baseline by wk 4 post-treatment; CD4% stable. HIV viral rebound in 1 (on Truvada+RAL) at wk 12, poor adherer; **vital signs/ECG**: no notable changes.

6.2.2.4. Evaluator's comments

Appropriate pilot and safest to start with GT- 2 and 3 as these have the highest treatment response rates in mono-infected patients. These data also build on D-D interaction data (ref ARVs) and tolerability as well as HCV virological response in the coinfected. The strategy was well tolerated with early encouraging results **for SVR4**, No discernible negative impact on HIV, no clinical sequelae from the predictable declines in CD4+ T-cells (RBV-related).

6.2.3. Study 11-I-0258: A randomised controlled study to assess safety, tolerability, and efficacy of GS-7977 in combination with full or low dose RBV in HCV Genotype 1, monoinfected treatment naive participants[20]

Objectives: safety, tolerability, efficacy of SOF+ full **or** low dose RBV for 24 wks in CHC GT- 1 treatment naïve participants.

Secondary objectives: assess role of RBV in combination with SOF; viral kinetics (substudy); SVR; predictors of response incl. levels of interferon-stimulated genes (ISG) expression in PBMCs/other host genetic factors; ALT normalisation.

[20] Osinusi A, et al. High Efficacy of GS-7977 in Combination with Low or Full dose Ribavirin for 24 weeks in Difficult to Treat HCV Infected Genotype 1 Patients. 63rd Annual Meeting of the American Association for the Study of Liver Diseases, Boston MA, 9-12 Nov 2012.

Sites: US (n=1); Study Start Date: 12Sep11; Interim report 20Dec12.

6.2.3.1. Design and methodology

Open label, phase 1/2a study of HCV GT- 1, treatment naïve patients enrolled in 2 parts, 10 patients with early-moderate stage fibrosis (HAI fibrosis of 0 to 2) enrolled in **Part 1** and received SOF and weight based ribavirin (WBR); **Part 2**=50 patients with all stages of fibrosis randomised to SOF + either WBR **or** low dose ribavirin (LDR). **24 wks treatment.**

Key inclusion: CHC GT- 1 HCV; treatment naïve; ≥18 of age; max 20% in Part 2 with compensated cirrhosis.

6.2.3.2. Treatments

Data collection and analysis:

Planned:

- **Part 1.** 10 subjects receiving 24 Wks SOF + wt based RBV (1000-1200 mg/daily)
- **Part 2.** 1:1 randomisation of 50 subjects receiving either 24 Wks SOF + wt based RBV or 24 Wks SOF with low dose RBV (600mg daily).

Analysed: As above, 10 subjects on Part 1, 50 subjects on Part 2**.**

Analysis: stopping criteria not met, so part 2 commenced enrollment of 50 subjects with all stages of fibrosis (incl. compensated cirrhosis). Treatment discontinued for non-adherence to protocol requirements, safety signals or failure to experience >4 log drop in HCV RNA at Wk 4, detectable HCV RNA at Wk 12 or viral breakthrough. Treatment failures were offered current SOC Rx.

Statistical methods: primary analysis was ITT; A sub analysis involving patients who received ≥8 Wks of study drug was also performed (PP analysis); **Efficacy:** efficacy endpoints comparing the proportion of subjects with HCV RNA <LLOQ, between the treatment groups made after the last subject completes each of several specified study visits, up to Wk 24. The proportion of participants with HCV RNA <LLOQ over time will be presented by treatment group in tabular form. Additionally, HCV RNA data will be reviewed by baseline GT-. Exploratory analyses to assess demographic, baseline characteristics and antiviral activity. predictive factors of antiviral activities may be examined using regression analysis; **PK and PK-PD:** HCV viral kinetics, PK and PD using SOF and GS-331007 levels; **Safety:** all participants receiving ≥1 dose of investigational product.

6.2.3.3. Criteria for evaluation

Efficacy: proportion with HCV RNA <LOD, between treatment groups; **PK:** HCV kinetics and PK/PD between GS-7977 in combination with low or full dose RBV; **Safety:** standard methods, graded via DAIDS Toxicity Scale.

6.2.3.4. Key findings of the interim

See Tables 14 and 15.

SVR12 achieved in 9/10 (90%) of patients in part 1; 17 (68%) and 12 (48%) of patients in part 2 receiving full dose or low dose RBV respectively;

Safety: safe and well tolerated. No deaths or discontinuations due to AE; most frequent AE: headache, anaemia, fatigue, mild to moderate. **SAE:** n=1 (not related) cholelithiasis.

Table 14: Baseline demographic and clinical characteristics in 11-I-0258.

Characteristic	Randomized Part 2 GS-7977 + WBR (Part 2) N=25	Randomized Part 2 GS-7977 + LDR (Part 2) N=25	Part 1 GS-7977 + WBR (Part 1) N=10
Median age (IQR)	54(51,56)	55 (48,59)	54 (50,57)
Body mass index – median (IQR)	28 (25,31)	30 (27,37)	26 (26,34)
Male sex – no (%)	19 (76%)	14 (56%)	4 (40%)
Race or ethnicity[+]– no (%)			
White	5 (20%)	2 (8%)	1 (10%)
Black	18 (72%)	23 (92%)	9 (90%)
Other	2 (8%)		0
IL28B genotype			
CC	4 (16%)	4 (16%)	3 (33%)
CT/TT	21 (84%)	21 (84%)	6 (67%)
IFNL3 genotype			
TT	4 (16%)	2 (8%)	3 (33%)
TG/GG	21 (84%)	23 (92%)	6 (67%)
HCV genotype 1 subtype – no (%)			
1a	20 (80%)	16 (64%)	6 (60%)
1b	5 (20%)	9 (36%)	4 (4%)
HAI Fibrosis – no (%)			
0 -2	19 (76%)	18 (72%)	9 (90%)
3 - 4	6 (24%)	7 (28%)	1 (10%)
Baseline HCV RNA – $\log_{10}$IU/ml	6.2(5.4,6.4)	6.1 (5.5,6.3)	6.8 (6, 7.1)
HCV RNA > 800,000 IU/ml – no (%)	16 (64%)	14 (56%)	7 (70%)

WBR: Weight based ribavirin, LDR: Low dose ribavirin
Continuous variables are shown as median (IQR), Categorical variables are expressed as frequencies (%),
Race was self-reported. Body mass index is the weight in kilograms divided by the height in meters.

Table 15: 11-I-0258 - Subjects with HCV RNA levels below the limit of detection (ITT analysis).

Treatment Week	GS-7977 + WBR (Part 2) N=25	GS-7977 + LDR (Part 2) N=25	GS-7977 + WBR (Part 1) N=10
During the 24 week treatment period – no (% [95% CI])			
4	24 96 (80 – 100)	24 96 (80 – 100)	8 80 (44 -97)
8	24 96 (80 – 100)	22 88 (69 – 97)	9 90 (55 - 100)
12	24 96 (80 – 100)	22 88 (69 – 97)	9 90 (55 - 100)
24	24 96 (80 – 100)	22 88 (69 – 97)	9 90 (55 - 100)
During the post treatment period – no (% [95% CI])			
2	21 84 (64 – 95)	15 60 (39 – 79)	9 90 (55 - 100)
4	18 72 (51 – 88)	14 56 (35 – 76)	9 90 (55 - 100)
8	17 68 (46 – 85)	13 52 (31 – 72)	9 90 (55 - 100)
12	17 68 (46 – 85)	12 48 (29 – 69)	9 90 (55-100)

6.2.3.5. Evaluator's comments

Interim data in an appropriately conducted pilot study, lower dose of RBV associated with higher failure in regards to non-achievement of SVR12 in this PEG regimen for treatment patients with CHC GT-1.

6.3. Analyses performed across trials (pooled & meta analyses)

Efficacy data from Phase 3 studies were not pooled or grouped because of differences in the various treatments and subject populations enrolled in each study.

6.4. Evaluator's conclusions on efficacy

The proposed indication for SOF is for use **in combination with other agents for treatment of chronic hepatitis C virus infection in adults**. The sponsor has provided a comprehensive

Phase I to III development programme for SOF, a novel nucleotide pro-drug that inhibits HCV RNA replication across all genotypes *in vitro* and *in vivo*. The drug has a number of favourable attributes confirmed through the Phase I and II studies namely: rapid suppression of HCV RNA in all genotypes; high SVR (at **Week 12** post treatment) when combined with RBV±PEG; a favourable tolerability and viral resistance profile. This has meant the focus of the Phase III SOF studies has been the evaluation of **PEG free regimens**, the latter potentially of enormous benefit, as they would avoid the unpleasant, albeit manageable (for the most part) toxicities of PEG.

6.4.1. HCV GT- 2 and 3 and SOF

- For SOF+RBV, 3 studies were conducted in 3 different GT-2 and 3 HCV populations: P7977-1231 (FISSION; treatment-naive subjects); GS-US-334-0107 (POSITRON; subjects who were IFN-intolerant or -ineligible or -unwilling); and GS-US-334-0108(FUSION; treatment-experienced subjects). All studies included a subset of 15.8% to 34.0% cirrhotics.
- Phase II programme: In addition, 65 treatment naive GT- 2 or 3 HCV received SOF+PEG+RBV for up to 12 wks. SOF+RBV also evaluated in subjects with GT- 2 or 3 HCV co-infected with HIV-1 (Study GS-US-334-0123 [PHOTON-1]).

6.4.2. Efficacy of SOF+RBV regimen in subjects with GT-2 or 3 HCV infection

All the Phase III studies efficacy, each achieving their primary endpoints:

- Study P7977-1231 showed the **non-inferiority** of SOF+RBV for 12 weeks versus SOC, PEG+RBV for 24 weeks with ~67% of subjects achieving a SVR12 for both treatments
- Study GS-US-334-0107 met its primary efficacy endpoint of **superiority** for 12 weeks of SOF+RBV versus placebo, with 77.8% of subjects achieved SVR12 versus 0% in placebo group
- Study GS-US-334-0108 met its primary efficacy endpoint of **superiority** of SOF+RBV for both 12 and 16 weeks versus a historic control SVR12 rate of 25%, with 50.0% and 72.6% of subjects achieving SVR12 in the SOF+RBV 12 and 16 Week groups, respectively.

While there was no genotypic or phenotypic resistance to SOF or RBV detected in subjects not achieving SVR12 in these 3 Phase III studies, it became clear that there were treatment response differences related to whether the genotype being treated was GT-2 or 3.

6.4.2.1. GT- 2

A high level of efficacy was demonstrated with SOF+RBV for 12 weeks, that is, in **treatment naives** (Study P7977-1231), SVR12 rates were 97.1% and compare more than favourably with those with PEG+RBV (77.6%). In Study GS-US-334-0107, SVR12 rates were 92.5% in treatment naives. In prior limited treatment exposed (<3 months IFN) in Study GS-US-334-0107, SVR rates were 92.7%. For **treatment experienced** subjects with GT- 2 (Study GS-US-334-0108), SVR rates were also high with SOF+RBV for 12 and 16 wks (86.1% and 93.8%, respectively) and this SVR12 rates in the 12 Week group is only marginally lower than the SVR12 in treatment naïve subjects. Although the number of GT- 2 cirrhotics was limited (11, 17, and 19 subjects in Studies P7977-1231, GS-US-334-0107, and GS-US-334-0108, respectively), efficacy (SVR12) was high: SVR12 rates of 90.9%, 94.1%, 68.4% in Studies P7977-1231 (treatment naïve), GS-US-334-0107 (limited treatment exposed), GS-US-334-0108 (treatment experienced), respectively. In addition, a bridging analysis using Bayesian SOF logistic regression analysis was performed for treatment naive subjects with GT-2 HCV infection and showed minimal differences in SVR12 rates between 12 and 16 weeks of SOF+RBV treatment.

6.4.2.2. GT- 3

For **treatment naives** with GT- 3 HCV infection, SOF+RBV treatment for 12 weeks had a similar SVR12 rate to PEG+RBV treatment for 24 weeks (55.7% versus 62.5%) (Study P7977-1231).

For treatment experienced subjects with GT-3, the SVR12 rates in Study GS-US-334-0108 clearly demonstrated that subjects derive greater benefit from a **16 week treatment duration** (61.9%) as SVR12 with a 12 week treatment duration was only 29.7%. The SVR12 rate following 16 weeks of SOF+RBV treatment was similar to the SVR12 rates observed with 12 weeks of SOF+RBV treatment in Studies P7977-1231 and GS-US-334-0107. The results of a bridging analysis using Bayesian logistic regression indicate that for GT-3 treatment naive subjects increasing SOF+RBV treatment duration from 12 to 16 weeks may increase the SVR12 rate by 22.5%. Overall, these response rates for GT-3 HCV subjects treated with SOF+RBV are generally consistent with data published for those treated with PEG+RBV, where overall responses rates for GT-3 are lower than those with GT-2.

6.4.2.3. Other factors

Drug exposure (GS-331007 AUC_{tau}) was shown to have a significant relationship on SVR12 rates in subjects with GT-3, specifically in the SOF+RBV group in Study GS-US-334-0107 (upper quartile [PQ4] of exposure outperformed the overall mean SVR12 rate) and the SOF+RBV 16 Week group of Study GS-US-334-0108 (the lowest quartile [PQ1] of exposure underperformed the overall study mean SVR12 rate).

6.4.2.4. Cirrhosis

Results of bridging analyses indicate that for cirrhotic and non-cirrhotic GT-3 treatment naives increasing SOF+RBV treatment duration from 12 to 16 weeks may increase SVR12 rate by 42.1% and 17.3%, respectively.

6.4.2.5. HCV GT- 1, 4, 5, or 6 and SOF

The Phase III study, GS-US-334-0110 (NEUTRINO) using SOF+PEG+RBV, in **treatment naive** subjects with GT-1, 4, 5, or 6 HCV; in this study, 16.7% cirrhotic, 89.3% GT-1. In the Phase II study, P7977-2025, ~75% GT-1a or 1b HCV infection and baseline Child-Pugh Turcotte (CPT) scores of 5 or 6 (72.1%). The US National Institute of Allergy and Infectious Diseases (NIAID) sponsored Study 11-I-0258 is evaluating efficacy, safety, and tolerability of SOF+RBV (full or low dose RBV) in GT-1 treatment naïve subjects. The Janssen-sponsored Study HPC2002 and Bristol-Myers Squibb (BMS) sponsored Study AI444040 are evaluating efficacy and safety of SOF in combination with other DAA±RBV. Study P7977-2025) is using SOF-RBV pre-transplant in HCV all genotypes and HCC.

6.4.3. Efficacy of SOF+PEG+RBV regimen in Subjects with GT-1, 4, 5, or 6 HCV Infection

Study GS-US-334-0110 met its primary efficacy endpoint for superiority of SOF+PEG+RBV treatment for 12 weeks (90.2% SVR12) compared with a **predefined historic control SVR rate of 60%. The SVR rate of 89.4% for treatment naïve subjects with GT-1 HCV infection was higher than any currently available HCV treatments.** Although those with GT-1a (91.6%) had a numerically higher response than subjects with GT-1b HCV infection (81.8%), the GT-1b subjects had higher rates of several baseline characteristics typically associated with lower treatment response rates (for example, IL28B non-CC genotypes, Black race, older age) which probably contributed to this difference. Among subjects with GT-4, 5, or 6 HCV infection (note numbers are quite small), 34 achieved SVR12 (1 cirrhotic subject with GT-4 HCV infection did not achieve SVR12). A high level of efficacy was demonstrated for all subgroups for subjects, with >80% of subjects achieving SVR12 across all subgroups (including cirrhosis). An ad hoc multivariate logistic regression analysis highlighted that IL28B GT (as expected for an IFN containing regimen) and cirrhosis status were important characteristics associated with SVR12 for subjects receiving the SOF+PEG+RBV regimen. Weight based RBV dose also remained in the multivariate regression model, consistent with the results from the combined GT-2 or 3 and GT-3 multivariate regression analyses and the results of NIAID Study 11-I-0258. When the impact of exposure (GS-331007 AUC_{tau}) on SVR12 rate was evaluated by multivariate logistic regression analyses, **no statistically significant relationships were observed.**

Comprehensive analyses showed that genotypic or phenotypic resistance to SOF or RBV was not detected in any of the subjects not achieving SVR12 in this Phase III study.

6.4.4. In summary

SOF represents an important new drug in the armamentarium of DAA compounds for the treatment of CHC. Across all the most common HCV genotypes, SOF, in combination with RBV with or without PEG, has demonstrated similar or superior efficacy to currently available treatment for the most common HCV genotypes across multiple patient populations. The data derived to date suggests that while a PEG free combination of SOF+RBV for 12 weeks is highly effective for GT-2 HCV, those with GT-3 should receive SOF+RBV treatment for longer, that is, 16 weeks. Subjects with GT-1, 4, 5, or 6 show high response rates in treatment naïve patients with 12 weeks of SOF+PEG+RBV combination therapy. However, there is still a relative paucity of data for the use of SOF as part of combination therapy in treatment experienced patients with GT-1.

7. Clinical safety

7.1. Studies providing safety data

Safety data to support the proposed SOF indication for the treatment of chronic HCV from 27 clinical studies comprising 4 pivotal Phase III (3 supporting), 6 Phase II, and 13 Phase I studies. There are 2 other studies using SOF that are not Gilead sponsored shown in Table 16; safety data is included for these.

Table 16: Non Gilead sponsored studies using SOF.

Study	Design	Study Status and Data
Janssen-sponsored study HPC2002	Phase 2, multicentered, randomized, open-label study evaluating the efficacy and safety of SOF 400 mg once-daily with SMV 150 mg once daily with or without RBV 1000 or 1200 mg (divided daily dose) for 12 or 24 weeks in treatment naive subjects with genotype 1 HCV infection or subjects with genotype 1 HCV infection who had a null response with prior PEG+RBV treatment.	Ongoing study. Results of interim safety analyses for 80 subjects included.
BMS-sponsored Study AI444040	Phase 2a, randomized, open-label, 2-stage parallel-group study evaluating the efficacy and safety of SOF 400 mg once-daily with DCV 60 mg once daily with or without RBV for 24 weeks in treatment-naive subjects with genotype 1, 2, or 3 HCV infection and for 12 weeks in treatment-naive subjects with genotype 1 HCV infection or subjects with genotype 1 HCV infection who have failed therapy with telaprevir or boceprevir. Subjects received SOF 400 mg + DCV 60 mg once daily with or without RBV (1000 or 1200 mg [divided daily dose] for subjects with genotype 1 HCV infection or 800 mg daily for subjects with genotype 2 or 3 HCV infection).	Ongoing study. Results of interim safety analyses for 170 subjects across Groups A to H included.

Due to differences in treatment regimens and durations and the subject populations studied, pooling of safety data was limited to the 4 pivotal Phase III studies (primary safety population [PSP]), with data presented by treatment regimen. Next, there is safety data presented in this section from the so called, secondary safety population (SSP), with safety data from P2938-0721, P7977-0523 and NIAID 11-I-0258 studies (for SOF+RBV), P7977-0422, P7977-0724, P7977-0221 (for SOF+PEG+RBV or SOF/placebo).

7.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, safety data for SOF+PEG+RBV in subjects with GT-1, 4, 5, 6 are presented from Study GS-US-334-0110 (NEUTRINO). Safety data for SOF+RBV in GT-2 and 3 HCV infection are presented from P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), and GS-US-334-0108 (FUSION). For GT-2 and 3, the SOF+RBV 12 Week group comprises pooled data from this regimen across Studies P7977-1231, GS-US-334-0107, GS-US-334-0108. All other

treatment regimens (SOF+RBV 16 Week, placebo, PEG+RBV, SOF+PEG+RBV) were not pooled. Treatment groups for the PSP:

- Placebo SOF: 12 Weeks placebo exposure data in Study GS-US-334-0107 (POSITRON)
- SOF+RBV 12 Weeks: 12 Week exposure data - Studies P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), and GS-US-334-0108 (FUSION)
- SOF+RBV 16 Weeks: 16 Week exposure data from Study GS-US-334-0108 (FUSION)
- PEG+RBV 24 Weeks: 24 Week PEG+RBV exposure data - Study P7977-1231 (FISSION)
- SOF+PEG+RBV 12 Weeks: 12 Weeks exposure data for triple therapy (SOF+PEG+RBV) in Study GS-US-334-0110 (NEUTRINO).

The following safety data were collected:

- General adverse events (AEs) assessed by active questioning at study visits and by patient report; all AEs were graded and coded using the Medical Dictionary for Regulatory Activities; standard criteria for the definition of an SAE were applied and reporting of SAE was expedited
- AEs of particular interest, including markers of liver disease/damage and loss of synthetic function (transaminases, coagulation markers, albumin; other metabolic markers including glucose; clinical AEs: signs and symptoms/signs of decompensated liver disease, assessed clinically and through laboratory monitoring)
- Laboratory tests: routine biochemistry including liver function tests, lipase, metabolic; haematology; HCV RNA; HCV GT-/phenotype. Performed at regular timepoints as per protocol
- Vital signs, physical exam, electrocardiogram (ECG).

7.1.1.1. Classification of AEs

AEs defined as treatment emergent adverse events (TEAEs) if they were events with onset dates on/after start of treatment and **≤30 days after permanent discontinuation of study regimen** from each specified study phase, and continuing AEs diagnosed prior to start of treatment with worsening severity grade after treatment start; continuing AEs that are serious or result in any study drug discontinuation.

7.1.2. Pivotal studies that assessed safety as a primary outcome

There were 2 pivotal studies that assessed safety as a co-primary outcome.

7.1.2.1. Dose response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data, and comprise the "SSP":

- SOF+RBV: In P2938-0721, P7977-0523 and NIAID 11-I-0258 studies, 135 subjects randomised to receive SOF+RBV for 12 Weeks; 85 to receive 24 Weeks SOF+RBV. In Study P2938-0721 (QUANTUM), 50 subjects received ≥1 dose of SOF+RBV. Median durations of exposure to SOF+RBV were 12.1 and 24.1 Weeks for the 12 and 24 Week groups, respectively
- SOF+PEG+RBV: In the P7977-0422 and P7977-0724 studies, 176 subjects randomised to receive 12 Weeks of SOF+PEG+RBV and 280 subjects randomised to receive 24 Weeks of SOF+PEG+RBV for ≥12 Weeks. Subjects in P7977-0221 received 28 days of SOF+PEG+RBV. In Study P7977-0422 (PROTON), subjects received 12 Weeks of SOF or placebo plus PEG+RBV for 12 or 24 through 48 Weeks depending on GT and response; 121 GT-1 HCV infected subjects and 25 GT-2 or 3 HCV infected subjects received ≥1 dose study drug and

were included in the SAS. **Median duration of exposure to SOF or placebo was 12 Weeks** in all treatment groups.

7.1.2.2. Other studies evaluable for safety only

None; all Phase I and Phase II studies assessed safety as a co-primary or secondary endpoint.

7.2. Pivotal studies that assessed safety as a primary outcome

GS-US-334-0107 (POSITRON) and GS-US-334-0108 (FUSION) assessed safety as co-primary outcomes. These data are presented below in detail as part of the PSP.

7.3. Patient exposure

The patient exposure and disposition in the primary safety analysis set is shown in Tables 17 and 18.

Table 17: Duration of Exposure to Study Regimen in PSP.

	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Duration of Exposure to Study Regimen (Weeks)					
Mean (SD)	11.8 (1.60)	12.0 (1.32)	16.1 (0.18)	21.3 (5.82)	11.9 (1.09)
Median	12.1	12.1	16.1	24.0	12.1
Q1, Q3	12.0, 12.1	12.0, 12.1	16.0, 16.1	23.3, 24.1	12.0, 12.1
Min, Max	1.1, 12.9	0.1, 16.1	15.6, 16.6	1.1, 25.3	2.1, 12.7
Cumulative N (%) of Subjects Exposed Through:					
Baseline [Day 1]	71 (100.0%)	566 (100.0%)	98 (100.0%)	243 (100.0%)	327 (100.0%)
Week 1 [Day 7]	71 (100.0%)	563 (99.5%)	98 (100.0%)	243 (100.0%)	327 (100.0%)
Week 2 [Day 14]	70 (98.6%)	562 (99.3%)	98 (100.0%)	239 (98.4%)	327 (100.0%)
Week 4 [Day 28]	70 (98.6%)	560 (98.9%)	98 (100.0%)	236 (97.1%)	324 (99.1%)
Week 6 [Day 42]	69 (97.2%)	558 (98.6%)	98 (100.0%)	231 (95.1%)	323 (98.8%)
Week 8 [Day 56]	69 (97.2%)	555 (98.1%)	98 (100.0%)	228 (93.8%)	321 (98.2%)
Week 10 [Day 70]	68 (95.8%)	553 (97.7%)	98 (100.0%)	225 (92.6%)	320 (97.9%)
Week 12 [Day 84]	65 (91.5%)	511 (90.3%)	98 (100.0%)	221 (90.9%)	300 (91.7%)
Week 16 [Day 112]		2 (0.4%)[a]	87 (88.8%)	202 (83.1%)	
Week 20 [Day 140]				196 (80.7%)	
Week 24 [Day 168]				158 (65.0%)	

Note: Weeks on Study Regimen = (last dose date of study regimen - first dose date of study regimen +1) divided by 7.
Note: The last dose date of active treatment is used in GS-US-334-0108.
a Two subjects (0380-1519, 0380-1549) in GS-US-334-0108 SOF+RBV 12 Week+Placebo 4 Weeks group erroneously continued RBV treatment through Week 16.

Table 18: Subject Disposition in the PSP.

	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
Subjects Randomized	71	575	99	264	328
Subjects Randomized but Never Treated	0	9	1	21	1
Subjects in Safety Analysis Set	71	566	98	243	327
Subjects in Full Analysis Set	71	560	95	243	327
Study Treatment Status					
Completed Study Treatment	68 (95.8%)	548 (96.8%)	98 (100.0%)	189 (77.8%)	320 (97.9%)
Discontinued Study Treatment	3 (4.2%)	18 (3.2%)	0	54 (22.2%)	7 (2.1%)
Reason for Premature Discontinuation of Study Treatment					
Adverse Event	3 (4.2%)	8 (1.4%)	0	26 (10.7%)	5 (1.5%)
Virologic Failure	0	1 (0.2%)	0	17 (7.0%)	0
Lost to Follow-Up	0	4 (0.7%)	0	5 (2.1%)	0
Other	0	3 (0.5%)	0	4 (1.6%)	0
Consent Withdrawn	0	1 (0.2%)	0	2 (0.8%)	1 (0.3%)
Death	0	1 (0.2%)	0	0	0
Protocol Violation	0	0	0	0	1 (0.3%)

7.4. Adverse events

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

7.4.1.1. Pivotal studies

Table 19 shows an overall summary of Adverse Events in the PSP.

Table 19: Overall summary of adverse events in the PSP.

	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any					
Any AE	55 (77.5%)	496 (87.6%)	86 (87.8%)	233 (95.9%)	310 (94.8%)
Grade 3 or 4 AE	1 (1.4%)	41 (7.2%)	4 (4.1%)	45 (18.5%)	48 (14.7%)
Grade 2 and Higher AE	21 (29.6%)	238 (42.0%)	41 (41.8%)	167 (68.7%)	194 (59.3%)
Treatment-Related AE	40 (56.3%)	408 (72.1%)	75 (76.5%)	228 (93.8%)	304 (93.0%)
Grade 3 or 4 Treatment-Related AE	0	15 (2.7%)	2 (2.0%)	39 (16.0%)	42 (12.8%)
Grade 2 and Higher Treatment-Related AE	12 (16.9%)	161 (28.4%)	22 (22.4%)	149 (61.3%)	175 (53.5%)
Any SAE	2 (2.8%)	22 (3.9%)	3 (3.1%)	3 (1.2%)	4 (1.2%)
Treatment-Related SAE	0	2 (0.4%)	0	0	2 (0.6%)
Adverse Event Leading to Permanent Discontinuation from Any of the Study Drugs	3 (4.2%)	9 (1.6%)	0	29 (11.9%)	8 (2.4%)
Adverse Event Leading to Permanent Discontinuation from SOF/SOF Placebo	3 (4.2%)	8 (1.4%)	0	N/A	5 (1.5%)
Adverse Event Leading to Modification or Interruption of Study Drug	0	63 (11.1%)	7 (7.1%)	65 (26.7%)	109 (33.3%)
Death	0	1 (0.2%)	0	0	0

Note: Data included to last dose date of study regimen (or active treatment in GS-US-334-0108) + 30 days.
Note: Percentages were calculated based on the number of subjects in the safety analysis set.

PSP: Table 19 provides a summary of overall rates of AE incl. relatedness; a summary of AEs reported in ≥10% subjects in any group in the PSP is provided in Table 20. The most frequently reported AEs in the **SOF+RBV 12 Wk** and **SOF+RBV 16 Wk** groups were: **Fatigue** (SOF+RBV 12 Wk: 40.5%; SOF+RBV 16 Wk: 46.9%); **Headache** (SOF+RBV 12 Wk: 23.3%; SOF+RBV 16 Wk: 32.7%); **Insomnia** (SOF+RBV 12 Wk: 16.1%; SOF+RBV 16 Wk: 28.6%); **Nausea** (SOF+RBV 12 Wk: 20.1%; SOF+RBV 16 Wk: 20.4%). For most of the AEs occurring ≥10% of subjects (**Table**

20), similar % of SOF+RBV 12 Wk and SOF+RBV 16 Wk subjects experienced these AEs. A higher incidence of cough was reported in the SOF+RBV 16 Wk group vs. SOF+RBV 12 Wk group (13.3%, vs. 6.9%, respectively). Notably higher % of subjects in SOF+RBV 12 Wk or SOF+RBV 16 Wk groups experienced AEs of fatigue, insomnia, anaemia, dyspnoea, irritability, cough, arthralgia, myalgia, depression vs. placebo. **With the exception of arthralgia**, all are previously observed with RBV. In general, and as expected with the known side-effect profile of PEG, overall incidence of AEs was highest in the PEG+RBV group vs. placebo, SOF+RBV 12 Wk, SOF+RBV 16 Wk groups. Most of the common AEs reported for the PEG+RBV group were also reported, but for a smaller proportion of subjects in the SOF+RBV 12 Wk and SOF+RBV 16 Wk groups, suggesting the contribution of RBV to this AE profile. These AEs included headache, nausea, rash, pruritus, decreased appetite, irritability, diarrhea, myalgia, dizziness, influenza-like illness (ILI), arthralgia, chills, depression, pyrexia, pain, neutropaenia; and **all reported previously with PEG+RBV**. The incidence of fatigue, headache, and nausea was highest in the PEG-containing groups (PEG+RBV or SOF+PEG+RBV), which was consistent with the expected safety profile of PEG+RBV. The incidence of these AEs in the placebo group (18–24%,) as well as the comparable incidence of rash, pruritus, decreased appetite, dizziness, diarrhoea between the placebo, SOF+RBV 12 Wk, and SOF+RBV 16 Wk groups, are suggestive of a relatively high background rate of these AEs in HCV-infected subjects. As expected with RBV, anaemia was more commonly observed in the SOF+RBV groups than in the placebo group. Although anaemia was higher in the SOF+RBV 12 Wk than the SOF+RBV 16 Wk group (10.2%, and 4.1%, 4 subjects, respectively), the rates of Gde 2−4 anaemia AEs were similar in i.e. 4.8% and 3.1% respectively. Furthermore, mean reduction in Hb at EOT was similar in both treatment groups (−2.1 g/dL and −2.0 g/dL). Incidence of anaemia AEs in SOF+RBV groups was comparable to the PEG+RBV group (11.5%) where the bone marrow suppressive effects of PEG offset the lower dose of RBV used. Anaemia was primarily managed via RBV dose reduction. **SOF+PEG+RBV:** The 3 most common AEs in this group were: fatigue (58.7%), headache (36.1%), nausea (34.3%). These common AEs were consistent with the expected safety profile of PEG+RBV. The **rate of anaemia across all 5 treatment groups was highest in the SOF+PEG+RBV group**. This was as expected given the wt-based RBV dosing (i.e. higher doses) **and** PEG-related bone marrow effects. In SOF+RBV groups there was wt-based (i.e. higher) RBV dose but **without PEG**; the PEG+RBV group used fixed, lower RBV dose i.e. 800mg/day with PEG. Anaemia was managed primarily with no action/RBV dose reductions.

Table 20: AE in ≥10% of subjects in any group by preferred term in the PSP.

	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
Preferred Term	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any AE	55 (77.5%)	496 (87.6%)	86 (87.8%)	233 (95.9%)	310 (94.8%)
Fatigue	17 (23.9%)	229 (40.5%)	46 (46.9%)	134 (55.1%)	192 (58.7%)
Headache	14 (19.7%)	132 (23.3%)	32 (32.7%)	108 (44.4%)	118 (36.1%)
Nausea	13 (18.3%)	114 (20.1%)	20 (20.4%)	70 (28.8%)	112 (34.3%)
Insomnia	3 (4.2%)	91 (16.1%)	28 (28.6%)	70 (28.8%)	81 (24.8%)
Rash	6 (8.5%)	48 (8.5%)	12 (12.2%)	43 (17.7%)	59 (18.0%)
Pruritus	6 (8.5%)	53 (9.4%)	7 (7.1%)	42 (17.3%)	54 (16.5%)
Decreased Appetite	7 (9.9%)	33 (5.8%)	5 (5.1%)	44 (18.1%)	58 (17.7%)
Irritability	1 (1.4%)	58 (10.2%)	11 (11.2%)	40 (16.5%)	42 (12.8%)
Diarrhoea	4 (5.6%)	57 (10.1%)	6 (6.1%)	42 (17.3%)	38 (11.6%)
Dizziness	5 (7.0%)	52 (9.2%)	5 (5.1%)	33 (13.6%)	41 (12.5%)
Arthralgia	1 (1.4%)	42 (7.4%)	9 (9.2%)	35 (14.4%)	47 (14.4%)
Anaemia	0	58 (10.2%)	4 (4.1%)	28 (11.5%)	68 (20.8%)
Myalgia	0	35 (6.2%)	9 (9.2%)	40 (16.5%)	45 (13.8%)
Influenza Like Illness	2 (2.8%)	16 (2.8%)	3 (3.1%)	44 (18.1%)	51 (15.6%)
Cough	2 (2.8%)	39 (6.9%)	13 (13.3%)	21 (8.6%)	34 (10.4%)
Chills	1 (1.4%)	16 (2.8%)	0	43 (17.7%)	54 (16.5%)
Vomiting	5 (7.0%)	33 (5.8%)	4 (4.1%)	23 (9.5%)	39 (11.9%)
Pyrexia	0	19 (3.4%)	3 (3.1%)	33 (13.6%)	58 (17.7%)
Depression	1 (1.4%)	34 (6.0%)	6 (6.1%)	34 (14.0%)	31 (9.5%)
Dyspnoea	1 (1.4%)	45 (8.0%)	5 (5.1%)	20 (8.2%)	39 (11.9%)
Pain	2 (2.8%)	17 (3.0%)	5 (5.1%)	30 (12.3%)	33 (10.1%)
Neutropenia	0	0	0	30 (12.3%)	54 (16.5%)

Severity of AE: PSP. Across all treatment groups the ≥81% were Gde 1 (mild) or 2 (moderate). See Table 21 for a listing of the higher gde AEs. **SOF+RBV:** One Gde 5 AE (fatal from illicit drug overdose) reported in the SOF+RBV 12 Wk group – see under deaths. No Gde 4 AEs reported in subjects in the SOF+RBV 12 Wk group. Only 1 subject in the SOF+RBV 16 Wk group had a Gde 4 AE (opiate overdose). The incidence of Gde 3 AEs was low in the SOF+RBV 12 Wk group (7.1%) and SOF+RBV 16 Wk group (3.1%). Gde 3 AEs reported by ≥3 subjects in the SOF+RBV 12 Wk group were fatigue (0.7%), anaemia, malignant hepatic neoplasm, pyrexia (each 0.5%). Gde 3 AEs were reported rarely (≤1 subject) in the SOF+RBV 16 Wk group. Incidence of Gde 3 TRAEs was low in the SOF+RBV 12 Wk group (2.7%) and SOF+RBV 16 Wk group (2.0%). Fatigue (0.7%), anaemia (0.5%), headache (0.4%) were the only TRAE Gde 3 AEs in ≥2 subjects in SOF+RBV 12 Wk group. Incidence of Gde ≥2 AEs comparable for 12 and 16 wks i.e ~42% each. General Disorders and Administration Site Conditions was the SOrgC with most TR Gde ≥2 AEs for SOF+RBV 12 Wk group (10.1%) and SOF+RBV 16 Wk group (8.2%). 1.6% PEG+RBV had Gde 4 AEs (neutropaenia, thrombocytopaenia, atrioventricular block, pneumothorax), of which 2

events were reported as SAEs. Gde 3 AEs were reported at a higher incidence in PEG+RBV groups (16.9%) vs. SOF+RBV 12 Wk, SOF+RBV 16 Wk, placebo groups (0.0-7.1%). In the PEG+RBV group, approximately one-third of Gde 3 or 4 AEs were reported in the Blood and Lymphatic System Disorders SOrgC, with neutropaenia of Gde 3 or 4 AE with the highest incidence (3.3%). The incidence of Gde 3+ AEs was lowest in the SOF+RBV 12 Wk, SOF+RBV 16 Wk, and placebo groups (1.4–7.2%) vs. PEG+RBV-containing groups (PEG+RBV, 18.5% or SOF+PEG+RBV, 14.7%). A similar trend was observed for Gde ≥2 AEs with the lowest incidence in the SOF+RBV 12 Wk (42.0%), SOF+RBV 16 Wk (41.8%), and placebo (29.6%,) groups vs. PEG+RBV-containing groups (PEG+RBV, 68.7% and SOF+PEG+RBV, 59.3%). **Graded AEs of depression were reported at a lower incidence in the SOF+RBV 12 Wk and 16 Wk groups (7.2% and 6.1%, respectively) vs. PEG+RBV group (17.3%). Fewer subjects required treatment for depression in the SOF+RBV 12 and 16 Wk groups (2.5%, and 2.0%, respectively) compared to PEG+RBV group (11.5%,). SOF+PEG+RBV group:** No Gde 4 AEs reported in SOF+PEG+RBV group; 14.7% had a Gde 3 AE, most commonly: neutropenia (7.0%), anaemia (2.1%), fatigue & headache (each 1.5%). Most commonly reported TRAE ≥Gde 3: neutropaenia (7.0%), anaemia (2.1%), fatigue (1.5%); ≥Gde 2 AEs reported by 59.3%; ≥10% with TR Gde 2 AEs in the following SOrgCs: Blood & Lymphatic (24.2%), General and Administration Site Conditions (19.6%), nervous System (13.1%), and Gastrointestinal (GI) (10.7%). Incidence of ≥Gde 2 TRAEs lower for SOF+PEG+RBV vs. PEG+RBV for General Disorders & Administration Site Conditions (19.6% vs. 30.0%), Psychiatric Disorders (9.2% vs. 19.3%), Skin and Subcutaneous Tissue Disorders (5.2% vs. 12.8%). These differences suggest that the longer treatment duration of 24 wks of PEG+RBV in **P7977-1231** may have contributed to higher incidence of AEs vs. 12-wk duration SOF+PEG+RBV in **GS-US-334-0110**. Gded AEs of depression (depression & depressed mood) were reported at a **higher incidence in the PEG+RBV group versus SOF+PEG+RBV group (17.3% and 9.8%, respectively)**. Only 1 subject from each group experienced a Gde 3 AE of depression, but there was a higher incidence of Gde 2 depression with PEG+RBV compared to SOF+PEG+RBV (7.4% and 1.8%). More of the PEG+RBV group vs. SOF+PEG+RBV group required treatment for depression (11.5% and 5.5% respectively).

Table 21: Gde 3 and higher AE reported in ≥3 subjects in any group in the PSP.

Adverse Events by Preferred Term and Highest Grade	Placebo 12 Weeks GS-US-334-0107 (N = 71)	SOF+RBV 12 Weeks P7977-1231 GS-US-334-0107 GS-US-334-0108 (N = 566)	SOF+RBV 16 Weeks GS-US-334-0108 (N = 98)	PEG+RBV 24 Weeks P7977-1231 (N = 243)	SOF+PEG+RBV 12 Weeks GS-US-334-0110 (N = 327)
Number (%) of Subjects Experiencing Any Grade 3 and Higher AE	1 (1.4%)	41 (7.2%)	4 (4.1%)	45 (18.5%)	48 (14.7%)
Highest Grade					
Grade 3 (Severe)	0	40 (7.1%)	3 (3.1%)	41 (16.9%)	48 (14.7%)
Grade 4 (Life-Threatening)	1 (1.4%)	0	1 (1.0%)	4 (1.6%)	0
Grade 5 (Fatal)	0	1 (0.2%)	0	0	0
Neutropenia	0	0	0	8 (3.3%)	23 (7.0%)
Grade 3 (Severe)	0	0	0	7 (2.9%)	23 (7.0%)
Grade 4 (Life-Threatening)	0	0	0	1 (0.4%)	0
Fatigue	0	4 (0.7%)	1 (1.0%)	5 (2.1%)	5 (1.5%)
Grade 3 (Severe)	0	4 (0.7%)	1 (1.0%)	5 (2.1%)	5 (1.5%)
Anaemia	0	3 (0.5%)	0	2 (0.8%)	7 (2.1%)
Grade 3 (Severe)	0	3 (0.5%)	0	2 (0.8%)	7 (2.1%)
Headache	0	2 (0.4%)	0	2 (0.8%)	5 (1.5%)
Grade 3 (Severe)	0	2 (0.4%)	0	2 (0.8%)	5 (1.5%)
Adverse Events by Preferred Term and Highest Grade	**Placebo 12 Weeks GS-US-334-0107 (N = 71)**	**SOF+RBV 12 Weeks P7977-1231 GS-US-334-0107 GS-US-334-0108 (N = 566)**	**SOF+RBV 16 Weeks GS-US-334-0108 (N = 98)**	**PEG+RBV 24 Weeks P7977-1231 (N = 243)**	**SOF+PEG+RBV 12 Weeks GS-US-334-0110 (N = 327)**
Thrombocytopenia	0	1 (0.2%)	0	5 (2.1%)	1 (0.3%)
Grade 3 (Severe)	0	1 (0.2%)	0	4 (1.6%)	1 (0.3%)
Grade 4 (Life-Threatening)	0	0	0	1 (0.4%)	0
Insomnia	0	0	1 (1.0%)	3 (1.2%)	0
Grade 3 (Severe)	0	0	1 (1.0%)	3 (1.2%)	0
Hepatic Neoplasm Malignant	0	3 (0.5%)	0	0	0
Grade 3 (Severe)	0	3 (0.5%)	0	0	0
Pyrexia	0	3 (0.5%)	0	0	0
Grade 3 (Severe)	0	3 (0.5%)	0	0	0

Note: Adverse events were mapped according to MedDRA, Version 15.0.
Note: Subjects were counted once at the most severe grade for treatment group, and AE preferred term.
Note: Data included to last dose date of study regimen (or active treatment in GS-US-334-0108) plus 30 days.

7.4.1.2. Other studies

Secondary safety population. SOF+RBV: The safety profile of SOF+RBV in Studies P7977-0523 and P2938-0721 was similar to that observed in the studies of SOF+RBV in the PSP and consistent with AEs previously observed with RBV. In P7977-0523, there was a general trend towards fewer AEs during the time when subjects were not receiving PEG. The most commonly reported AEs (>15%) in all PEG-containing groups were: headache, fatigue, rash, myalgia, nausea, pruritus, as expected for the safety profile of PEG+RBV. In Study P7977-0523, the most commonly reported AE (>15%) in all SOF+RBV groups was headache. In Study P2938-0721, the most commonly reported AEs (>15%) in all SOF+RBV groups were fatigue, nausea, diarrhoea, headache, insomnia. Overall, in Study P2938-0721, proportion with AEs was similar between the 2 SOF+RBV groups with no apparent effect of duration of exposure (12 vs. 24 wks) on incidence of AEs. The 3 most commonly reported AEs occurring overall in all subjects in Study 11-I-0258 were: headache (26.6%), anaemia (26.6%), fatigue (23.3%). Anaemia was reported at a 2-fold higher incidence in the SOF + weight-based RBV groups (32 and 40%) vs. the SOF + low-dose RBV group (16%). This observation was consistent with expected safety profile of RBV.
SOF+PEG+RBV: Safety profile of SOF+PEG+RBV in P7977-0422 and P7977-0724 similar to that in Study GS-US-334-0110 of the PSP and as expected with PEG+RBV. The 3 most commonly reported AEs in the SOF+PEG+RBV and placebo+PEG+RBV treatment groups: were fatigue, nausea, headache. In Study P7977-0422, AEs reported by >30% subjects in the placebo+PEG+RBV group included chills, insomnia, pain, also reported with similar incidence in at least 1 SOF+PEG+RBV group. No additional AEs to those frequently reported with PEG+RBV

identified. In Study P7977-0422, no apparent dose response (SOF 200mg or 400mg) associated with incidence of AEs.

Secondary safety population AE severity: SOF+RBV: Most AEs either Gde 1 or 2 in all groups in P7977-0523 (≥70% of subjects for the SOF+PEG+RBV groups, ≥96% of subjects for the SOF+RBV groups) and P2938-0721 (≥92% subjects). In Studies P7977-0523 and P2938-0721, no Gde 4 AEs reported in SOF-containing groups. **SOF+PEG+RBV:** Most AEs were Gde 1 of 2 in all groups in Studies P7977-0422 (≥78% of subjects) and P7977-0724 (≥80% of subjects). In Study P7977-0422, Gde 3/4 AEs reported for 10.4-21.3% of subjects in SOF+PEG+RBV groups, similar to the reported incidence for placebo+PEG+RBV group (11.5%); similar incidence Gde 3/4 AEs reported by all groups receiving SOF+PEG+RBV in P7977-0724 (Gps A,B,C1,C2;13.3−17.6%). Neutropaenia was the most common Gde 3/4 AE reported in SOF+PEG+RBV groups (6.3−10.6%) and placebo+PEG+RBV group (7.7%) (P7977-0422). Neutropaenia was also the most common Gde 3/4 AE in all SOF+PEG+RBV groups in P7977-0724 (3.8−8.0%). No apparent dose-response associated with Gde 3/4 AEs between SOF 200mg+PEG+RBV and SOF 400mg+PEG+RBV in Study P7977-0422. In Study P7977-0724, all Gde 3/4 AEs of neutropaenia (bar 2) considered related to PEG+RBV. Besides neutropaenia, increased transaminases in Study P7977-0422 and fatigue, hepatic enzymes increased, and anaemia in Study P7977-0724 were the only other Gde 3 or 4 AEs reported in ≥2 subjects in any treatment group.

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

Given the open-label design of Studies GS-US-334-0110 and P7977-1231, the investigator evaluation of relationship to therapy could be subject **to bias** and should be interpreted with some caution. Nevertheless, a summary of TRAEs is provided for the PSP and SSP.

7.4.2.1. Pivotal studies

See Table 22 below. **SOF+RBV:** The 4 most commonly reported TRAEs in SOF+RBV 12 Wk or 16 Wk groups were: Fatigue (36.6-39.8%)**;** headache (18.4%-25.5%)**;** insomnia (13.6%-24.5%)**;** nausea (17.0%-17.3%). Most TRAEs occurring in ≥10% of subjects occurred equivalently with 12 and 16 weeks of exposure, the one exception to this was cough, in which 11.2% vs. 4.2% in the 16 vs. 12 week groups respectively had cough. But, this was unlikely due to longer treatment duration because only 2 cough events began on or after Day 84 in the SOF+RBV 16 Wk group. TRAEs of fatigue, insomnia, anaemia, irritability, arthralgia, myalgia, cough, diarrhaea, dyspnoea were higher than the placebo group. With the exception of arthralgia all described in the RBV product label. In general, overall incidences of TRAEs were highest in the PEG+RBV group vs. placebo, SOF+RBV 12 Wk, SOF+RBV 16 Wk groups. Most of the commonly reported AEs for the PEG+RBV group (ie, those in ≥10% of subjects) were reported at a lower incidence rate in the SOF+RBV 12 Wk and SOF+RBV 16 Wk groups. These AEs included fatigue, headache, nausea, rash, pruritus, decreased appetite, irritability, myalgia, ILI, arthralgia, chills, diarrhoea, pyrexia, neutropenia, depression, pain; all of which were reported previously with PEG+RBV treatment. **SOF+PEG+RBV:** In Study GS-US-334-0110, the 3 most commonly reported TRAEs: were fatigue (56.3%), nausea (31.2%), and headache (30.9%). These AEs are consistent with the expected safety profile of PEG+RBV. All AEs of neutropaenia and anaemia in the SOF+PEG+RBV and PEG+RBV groups were considered TR; consistent with the expected safety profile of PEG+RBV.

Table 22: AE related to study drug reported for ≥10% of subjects in any Gp in the PSP.

Adverse Events by Preferred Term	Placebo 12 Weeks GS-US-334-0107 (N = 71)	SOF+RBV 12 Weeks P7977-1231 GS-US-334-0107 GS-US-334-0108 (N = 566)	SOF+RBV 16 Weeks GS-US-334-0108 (N = 98)	PEG+RBV 24 Weeks P7977-1231 (N = 243)	SOF+PEG+RBV 12 Weeks GS-US-334-0110 (N = 327)
Number (%) of Subjects Experiencing Any Treatment-Related AE	40 (56.3%)	408 (72.1%)	75 (76.5%)	228 (93.8%)	304 (93.0%)
Fatigue	12 (16.9%)	207 (36.6%)	39 (39.8%)	131 (53.9%)	184 (56.3%)
Headache	12 (16.9%)	104 (18.4%)	25 (25.5%)	102 (42.0%)	101 (30.9%)
Nausea	10 (14.1%)	96 (17.0%)	17 (17.3%)	65 (26.7%)	102 (31.2%)
Insomnia	3 (4.2%)	77 (13.6%)	24 (24.5%)	65 (26.7%)	73 (22.3%)
Rash	5 (7.0%)	40 (7.1%)	11 (11.2%)	39 (16.0%)	56 (17.1%)
Pruritus	6 (8.5%)	42 (7.4%)	7 (7.1%)	40 (16.5%)	50 (15.3%)
Decreased Appetite	6 (8.5%)	30 (5.3%)	2 (2.0%)	40 (16.5%)	55 (16.8%)
Anaemia	0	57 (10.1%)	4 (4.1%)	28 (11.5%)	68 (20.8%)
Irritability	1 (1.4%)	46 (8.1%)	7 (7.1%)	39 (16.0%)	41 (12.5%)
Dizziness	5 (7.0%)	41 (7.2%)	4 (4.1%)	29 (11.9%)	30 (9.2%)
Myalgia	0	26 (4.6%)	7 (7.1%)	36 (14.8%)	42 (12.8%)
Arthralgia	0	27 (4.8%)	7 (7.1%)	31 (12.8%)	43 (13.1%)
Influenza Like Illness	2 (2.8%)	11 (1.9%)	0	44 (18.1%)	49 (15.0%)

Adverse Events by Preferred Term	Placebo 12 Weeks GS-US-334-0107 (N = 71)	SOF+RBV 12 Weeks P7977-1231 GS-US-334-0107 GS-US-334-0108 (N = 566)	SOF+RBV 16 Weeks GS-US-334-0108 (N = 98)	PEG+RBV 24 Weeks P7977-1231 (N = 243)	SOF+PEG+RBV 12 Weeks GS-US-334-0110 (N = 327)
Chills	1 (1.4%)	9 (1.6%)	0	39 (16.0%)	52 (15.9%)
Cough	1 (1.4%)	24 (4.2%)	11 (11.2%)	15 (6.2%)	29 (8.9%)
Dyspnoea	1 (1.4%)	39 (6.9%)	5 (5.1%)	18 (7.4%)	36 (11.0%)
Diarrhoea	1 (1.4%)	35 (6.2%)	3 (3.1%)	32 (13.2%)	25 (7.6%)
Pyrexia	0	4 (0.7%)	1 (1.0%)	30 (12.3%)	55 (16.8%)
Neutropenia	0	0	0	30 (12.3%)	54 (16.5%)
Depression	1 (1.4%)	21 (3.7%)	2 (2.0%)	32 (13.2%)	27 (8.3%)
Vomiting	2 (2.8%)	18 (3.2%)	3 (3.1%)	17 (7.0%)	34 (10.4%)
Pain	0	12 (2.1%)	2 (2.0%)	28 (11.5%)	32 (9.8%)

Note: Adverse events are mapped according to MedDRA Version 15.0.

Note: Subjects are counted once for each system organ class (SOC), and once for each AE preferred term (PT).

Note: AEs are related to treatment if "Related to any of the Study Drugs" = 'Yes' on the AE CRF.

Note: Data included to last dose date of study regimen (or active treatment in GS-US-334-0108) + 30 days.

7.4.2.2. Other studies

Secondary safety population: **SOF+RBV**: in Studies P7977-0523 and P2938-0721 the safety profile was similar to that observed in the SOF+RBV studies in the PSP, and consistent with AEs previously observed with RBV. In Study P7977-0523, all subjects in SOF+PEG+RBV groups had ≥1 AE considered related to study drug. Most commonly reported TEAEs (>15%) in all SOF+PEG+RBV groups: headache, fatigue, insomnia, rash, myalgia, nausea - consistent with expected safety profile of PEG+RBV. In Study P7977-0523, most commonly reported TRAE (>10%) in all SOF+RBV groups was headache. In Study P2938-0721, the most commonly reported TRAEs (>15%) in all SOF+RBV groups: fatigue, nausea, insomnia. Generally in Study P2938-0721, incidence of AEs similar between the 2 SOF+RBV groups, with no apparent effect of duration of exposure (12 vs. 24 wks) on incidence of TRAEs. In 11-I-0258, the 3 most commonly reported TRAEs were headache (26.7%), fatigue (23.3%), nausea (16.7%) -incidence did not differ across treatment groups.

SOF+PEG+RBV: In Studies P7977-0422 and P7977-0724, TRAEs were generally consistent with Study GS-US-334-0110 and the expected safety profile of PEG+RBV, most commonly reported TRAE (>25%) in all the SOF+PEG+RBV and placebo+PEG+RBV groups in Studies P7977-0422 and P7977-0724 were fatigue, nausea, headache. In P7977-0724, fatigue was themost common TRAE in ≥48%. Other TRAEs reported by ≥25% subjects in all treatment groups were: headache

and nausea. In Study P7977-0422, other related AEs reported by >30% subjects in the placebo+PEG+RBV group included chills, insomnia, pain - also reported at similar incidence in other SOF+PEG+RBV groups. In general, the common (>15%) TRAEs were as expected with the known safety profile of PEG+RBV, and no additional AEs to the PEG+RBV profile were identified. In Study P7977-0422, there was no apparent dose-response between SOF 200mg and 400mg with regards to TRAE.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal studies

Deaths in the PSP: SOF+RBV: One death in the SOF+RBV 12 Wk group due to cocaine and heroin intoxication on Study Day 1. Three non-treatment-emergent (during study follow-up period but >30 days after last dose study drug) deaths: one death (PEG+RBV group) died due to a brain neoplasm; one death (SOF+RBV group) died of cardiogenic shock secondary to aortic stenosis; one death (SOF+RBV group) from metastatic lung cancer. None considered study drug related. **SOF+PEG+RBV:** No deaths occurred in subjects receiving SOF+PEG+RBV in Study GS-US-334-0110. **Other serious adverse events in PSP:** ≤4% in all treatment groups experienced an SAE. **SOF+RBV:** SAEs comparable between the SOF+RBV 12 Wk group (3.9%) and SOF+RBV 16 Wk group (3.1%). Malignant hepatic neoplasm (0.5%) and pyrexia and cellulitis (each 0.4%) were the only SAEs reported in ≥2 subjects in the SOF+RBV 12 Wk group. No other individual SAEs in the SOF+RBV 12 Wk groups were reported in more than 1 subject and no apparent clustering of SAEs observed within SOrgCs that had ≥5 subjects reporting SAEs. TR SAEs reported in 2 subjects (0.4%) in SOF+RBV 12 Wk group: **anaemia on Day 20** in 1 subject; peripheral oedema and eczema on post-treatment Day 28 in another. Few subjects experienced SAEs in the placebo group (2.8%) and PEG+RBV group (1.2%). No subjects in these groups experienced a TR SAE. Although rates of SAEs were higher in SOF+RBV 12 Wk and 16 Wk groups (3.9% and 3.1% respectively) than other groups, the small difference was not considered to be clinically meaningful when these SAEs were reviewed. **SOF+PEG+RBV:** 8 SAEs reported in 4 subjects (1.2%) in the SOF+PEG+RBV group. No trends in SAE type observed; no individual SAE reported in >1 subject. Four SAEs in 2 subjects (0.6%) assessed as related to any study drug: anaemia and cryoglobulinaemia on post-treatment Day 13 in one subject; leukopaenia and pyrexia on Day 53 in another subject.

7.4.3.2. Other studies

Deaths in secondary safety population: SOF+RBV: No deaths; SOF+PEG+RBV: No deaths.

SAE in SSP: SOF+RBV; 7% subjects had an SAE in **P7977-0523 and P2938-0721**; incidence similar to that observed in the SOF+RBV Phase 3 studies of the PSP. In Study **P7977-0523**, 3 SAEs were reported in 3 subjects: 2 subjects who received SOF+RBV for 12 wks (furuncle and urethral injury) and 1 who received SOF+RBV for 8 wks (angina pectoris). In Study **P2938-0721**, 2 SAEs (chest pain and bronchitis) were reported in 2 subjects who received SOF+RBV for 24 wks. Both SAEs considered unrelated. One SOF + low-dose RBV subject in **Study 11-I-0258** experienced SAE of cholelithiasis considered not related and resolved with cholecystectomy. **SOF+PEG+RBV:** 7% subjects reported SAE in the SOF+PEG+RBV groups for Studies **P7977-0422 and P7977-0724**, incidences similar to Study GS-US-334-0110. In **Study P7977-0422**, 7 SAEs were reported in 5 GT- 1 in SOF+PEG+RBV and placebo+PEG+RBV groups. Except for 1 SAE (lymphangitis) considered unrelated, the remaining 6 SAEs (retinal vein occlusion, acute myocardial infarction, depression and suicide ideation, chest pain, and electrocardiogram [ECG] ST segment elevation) **were considered related to PEG and/or RBV, but not SOF or placebo**. In Study **P7977-0724**, 13 SAEs reported in 12 subjects across all treatment groups. Four subjects experienced SAEs (anaemia, pyelonephritis, autoimmune hepatitis, pancytopenia) considered related to PEG+RBV but not related to SOF.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal studies

These are shown in Table 23.

Table 23: AE leading to permanent discontinuation from any study drug in ≥2 subjects in PSP.

	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any AE Leading to Permanent Discontinuation from Any of the Study Drugs	3 (4.2%)	9 (1.6%)	0	29 (11.9%)	8 (2.4%)
Fatigue	0	0	0	6 (2.5%)	0
Anaemia	0	1 (0.2%)	0	4 (1.6%)	2 (0.6%)
Alanine Aminotransferase Increased	1 (1.4%)	0	0	2 (0.8%)	0
Depression	0	1 (0.2%)	0	4 (1.6%)	0
Insomnia	0	1 (0.2%)	0	3 (1.2%)	0
Nausea	0	0	0	3 (1.2%)	0
Neutropenia	0	0	0	2 (0.8%)	1 (0.3%)
Anxiety	0	1 (0.2%)	0	2 (0.8%)	0
Haemoglobin Decreased	0	0	0	2 (0.8%)	0
Irritability	0	0	0	2 (0.8%)	0
Loss of Consciousness	0	0	0	2 (0.8%)	0
Pain	0	0	0	2 (0.8%)	0
Platelet Count Decreased	0	0	0	2 (0.8%)	0

7.4.4.2. Other studies

Secondary safety population: SOF+RBV: In Studies P7977-0523 and P2938-0721, 1 subject across the SOF-containing groups in each study discontinued due to an AE. In Study P7977-0523, all enrolled and randomised subjects completed treatment. One subject with an AE of depression considered related to PEG, discontinued PEG on Day 29 but completed treatment with SOF+RBV. In Study P2938-0721, 1 SOF+RBV 12 Wk subject had an AE (decreased appetite considered related) that led to discontinuation on Day 33. In Study P7977-0523, AEs leading to dose interruption or modification of study drug reported at a higher incidence across SOF+PEG+RBV groups (20.0–44.4%) vs. SOF+RBV groups (0.0–30.0%), most commonly reported AEs (≥2 subjects) leading to dose interruption or modification: haemolytic anaemia, anaemia, neutropaenia in the SOF+PEG+RBV groups and haemolytic anaemia & anaemia in the SOF+RBV groups; these AEs align with known profiles for PEG+RBV and RBV, respectively. In Study P2938-0721, AEs leading to dose interruptions or modification of SOF and/or RBV were reported with similar incidence for the 12-wk (24.0%) and 24-wk (28.8%) SOF+RBV groups; most commonly reported AEs (≥2 subjects) leading to dose interruption or modification in the SOF+RBV groups were insomnia (n=5), fatigue (n=4), anaemia (n= 3), Hb decreased (n=2), pruritus (n=2); all consistent with RBV's known profile. **SOF+PEG+RBV:** In Studies P7977-0422 and P7977-0724, most commonly reported AEs leading to discontinuation or dose modification of PEG or RBV similar to those AEs observed in Study GS-US-334-0110 in the PSP and consistent the PEG+RBV safety profile. The incidence of discontinuation due to AEs in Study P7977-0422 was comparable across SOF+PEG+RBV groups (4.2–6.4%) and placebo+PEG+RBV group (11.5%) and similar to the SOF+PEG+RBV 12-wk groups in Study P7977-0724 (Gps A, C1, C2 [4.0–5.8%]). In P7977-0724, the incidence of dose modifications due to anaemia were 2-fold higher in Groups B and C2 (20.0 and 22.7%, respectively) vs. Groups A and C1 (9.6 and 10.7%, respectively), likely consequent to longer-treatment duration with RBV (≤24 wks) in Gps B & C2.

7.5. Laboratory tests

PSP for SOF+RBV: In SOF+RBV 12 Wk and 16 Wk groups, **hyperglycaemia** was the most commonly reported Gde 3 or 4 lab abnormality (2.5% and 5.1% respectively) but 5.6% of placebo subjects reported the same. The incidence of Gde 3 or 4 **coagulation abnormalities** was very low (≤ 1.0%). In the PEG+RBV group, the most commonly reported Gde 3 or 4 lab abnormality was elevated ALT (3.7%). One subject (0.4%) reported a Gde 3 elevated PT. Incidence of Gde 3 elevations of ALT & AST highest in the placebo group (8.5% and 12.7% respectively), likely due to uncontrolled HCV. **SSP**: in Studies P7977-0523 and P2938-0721, incidence of Gde 3/4 chemistry abnormalities were low, each abnormality occurred in ≤ 2 subjects. **PSP SOF+PEG+RBV:** Most common Gde 3/4 was elevated AST (3.1%). In the SSP, (Study P7977-0724), elevated AST was the most commonly reported Gde 3/4 lab abnormality across treatment groups (in 8 subjects). See also Table 24.

Table 24: Summary of Gde 3 or 4 coagulation and chemistry lab abnormalities in the PSP.

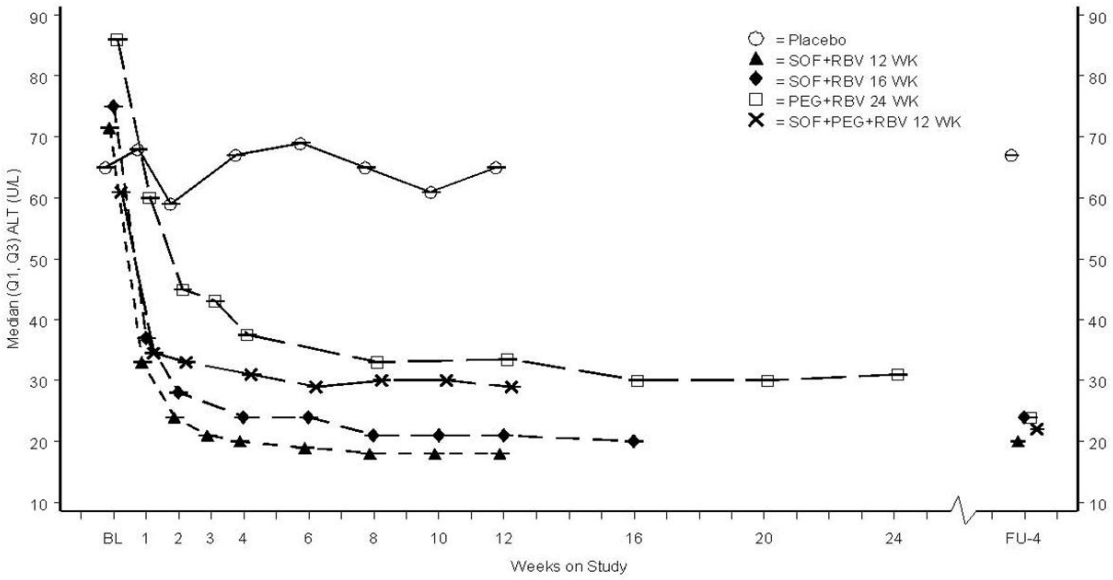
	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
		P7977-1231 GS-US-334-0107			
	GS-US-334-0107	GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
Parameter	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Coagulation					
APTT	69	549	98	235	317
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
INR	69	551	98	235	317
Grade 3	0	0	0	0	0
Grade 4	0	0	1 (1.0%)	0	0
PT	69	551	98	235	317
Grade 3	0	2 (0.4%)	0	1 (0.4%)	0
Grade 4	0	0	0	0	0
Chemistry					
ALT	71	563	98	242	327
Grade 3	6 (8.5%)	1 (0.2%)	2 (2.0%)	9 (3.7%)	7 (2.1%)
Grade 4	0	0	0	0	0
AST	71	563	98	242	327
Grade 3	9 (12.7%)	0	0	3 (1.2%)	9 (2.8%)
Grade 4	1 (1.4%)	0	0	1 (0.4%)	1 (0.3%)
Albumin	71	563	98	242	327
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Alkaline Phosphatase	71	563	98	242	327
Grade 3	0	0	0	1 (0.4%)	0
Grade 4	0	0	0	0	0
Creatine Kinase	N/A	254	N/A	242	327
Grade 3		3 (1.2%)		0	2 (0.6%)
Grade 4		2 (0.8%)		1 (0.4%)	0
Creatinine	71	563	98	242	327
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Direct Bilirubin	6	172	39	29	62
Grade 3	0	0	0	1 (3.4%)	1 (1.6%)
Grade 4	0	0	0	0	0
Lipase	71	562	98	242	327
Grade 3	1 (1.4%)	7 (1.2%)	0	3 (1.2%)	0
Grade 4	0	2 (0.4%)	0	2 (0.8%)	1 (0.3%)
Serum Glucose (Hyperglycemia)	71	563	98	242	327
Grade 3	4 (5.6%)	13 (2.3%)	5 (5.1%)	4 (1.7%)	7 (2.1%)
Grade 4	0	1 (0.2%)	0	0	0
Serum Glucose (Hypoglycemia)	71	563	98	242	327
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Serum Potassium (Hyperkalemia)	71	563	98	242	327
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Serum Potassium (Hypokalemia)	71	563	98	242	327
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Serum Sodium (Hypernatremia)	71	563	98	242	327
Grade 3	0	0	0	0	0
Grade 4	0	0	0	1 (0.4%)	0
Serum Sodium (Hyponatremia)	71	563	98	242	327
Grade 3	0	0	0	0	1 (0.3%)
Grade 4	0	1 (0.2%)	0	0	0

7.5.1. Liver function

7.5.1.1. Pivotal studies

Figure 5 summarises the declines in ALT correspondent with rapid HCV suppression.

Figure 5: Median ALT values by treatment and visit for the PSP.



Placebo (n=):	71	69	69		70	69	69	67	62			67
SOF+RBV 12 WK (n=):	566	558	553	243	558	305	554	302	526			479
SOF+RBV 16 WK (n=):	98	97	95		97	96	98	95	98	93		90
PEG+RBV 24 WK (n=):	243	237	236	235	234		227		220	201	194	159	199
SOF+PEG+RBV 12 WK (n=):	327	324	324		319	318	321	315	307				278

Note: Baseline value is the last available value on or prior to first dose date of study regimen.
Note: Data included to last dose date of study regimen (or active treatment in FUSION) + 30 days.
Note: Offsets have been applied to different treatment groups.

7.5.1.2. Other studies

SSP. SOF+RBV: In Studies P7977-0523 and P2938-0721, no Gde 3 or 4 ALT lab abnormalities reported. In Studies P7977-0523 and P2938-0721, all treatment groups had a rapid decrease from baseline in median ALT levels by Wk 2, coincident with HCV RNA suppression.
SOF+PEG+RBV: In Studies P7977-0422 and P7977-0724, all groups had a decrease serum ALT coincident with HCV RNA suppression. Gde 3/4 ALT occurred in <4%. In the first 12 wks of treatment (SOF/placebo-treatment period), all SOF+PEG+RBV groups had similar decreases from baseline in mean (SD) serum ALT (range: −14 to −25 IU/L), these were comparable to placebo+PEG+RBV group (−44 IU/L). In Study P7977-0724, 4 subjects had Gde 3/4 ALT. Only 1 subject experienced Gde 4 ALT in the setting of an SAE of autoimmune hepatitis. All treatment groups experienced a rapid decrease from baseline in median ALT levels by Wk 1 (median −20 to −25 U/L), coincident with HCV RNA suppression.

Table 25: Summary of subjects with liver-related abnormalities.

		Criterion 1: AST/ALT> 3 × ULN and Total Bilirubin > 2 × ULN	Criterion 2: ALT > 5 × ULN	Criterion 3: Total Bilirubin > 2 × ULN
Primary Safety Population	Placebo (N = 71)	0/71	9/71 (12.7%)	0/71
	SOF+RBV[a] (N = 664)	1/659 (0.2%)	1/659 (0.2%)	35/659 (5.3%)
	PEG+RBV (N = 243)	0/242	15/242 (6.2%)	3/242 (1.2%)
	SOF+PEG+RBV (N = 327)	0/327	9/327 (2.8%)	3/327 (0.9%)
Secondary Safety Population	P7977-0523 (N = 120)	0/120	1/120 (0.8%)	2/120 (1.7%)
	P2938-0721 (N = 50)	0/50	0/50	1/50 (2.0%)
	P7977-0221 (N = 63)	0/63	2/63 (3.2%)	0/63
	P7977-0422 (N = 146)	0/146	0/146	4/146 (2.7%)
	P7977-0724 (N = 332)[b]	2/332 (0.6%)	6/332 (1.8%)	7/332 (2.1%)
Special HCV Population	GS-US-334-0123 (N = 31)	0/31	1/31 (3.2%)	1/31 (3.2%)
	P7977-2025 (N = 61)	0/61	0/61	7/61 (11.5%)

a 12 and 16 week groups combined

b Subject 1004-7085 experienced Criteria 1–3 concurrently and Subject 1019-7006 experienced Criteria 1and 3 concurrently

7.5.2. Kidney function

SOF is primarily excreted in urine as GS-331007 and renal function impairment affects the levels of this metabolite in humans. Hence, in the Phase 3 studies comprising the PSP, patients with Clcr <60 mL/min (Studies GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110) or eGFR ≥60 mL/min/1.73m^2 (Study P7977-1231) were excluded.

7.5.2.1. Pivotal studies

Primary safety population: 11 subjects (in total) had Clcr <60 mL/min. In SOF+RBV 12 Wk group, 5 subjects had Clcr <60 mL/min at baseline. None of these had any AEs in the renal and Urinary Disorders SOrgC. One placebo subject in Study GS-US-334-0107 and 1 PEG+RBV subject in Study P7977-1231 had Clcr <60 mL/min at baseline. None of these subjects had any AEs in the Renal and Urinary Disorders SOrgC. In the SOF+PEG+RBV group, 4 subjects had Clcr <60 mL/min at baseline: None of these subjects had any AEs in the Renal and Urinary Disorders SOrgC. See also Table 24.

7.5.2.2. Other studies

See above.

7.5.3. Haematology

Pancytopaenia has been reported in studies assessing direct-acting antivirals+PEG+RBV and is a documented AR in the PEG and RBV labelling. An analysis of pancytopaenia was performed for all Gilead-sponsored Phase 2 and 3 studies. Pancytopaenia was not reported in the PSP but there was pancytopaenia event in the SSP. This subject in P7977-0724 (ATOMIC) received treatment with 24 wks of SOF+PEG+RBV. The subject discontinued study drugs due to anaemia on Day 78 (Hb 8.6 g/dL on Day 74, Hb Day 112.0 g/dL), on Day 9 posttreatment, she was hospitalised with Hb 8.1 g/dL, platelets 102 × 10^3/uL, WBC 2.8 x 10^3/uL, PMN 1.3 × 10^3/uL. At posttreatment Day 30, Hb and WBCs were improved at 10.9 g/dL and 4.1 × 10^3/uL, respectively, but platelets remained low at 89 × 10^3/uL. The investigator assessed the event as not SOF but possibly PEG+RBV related.

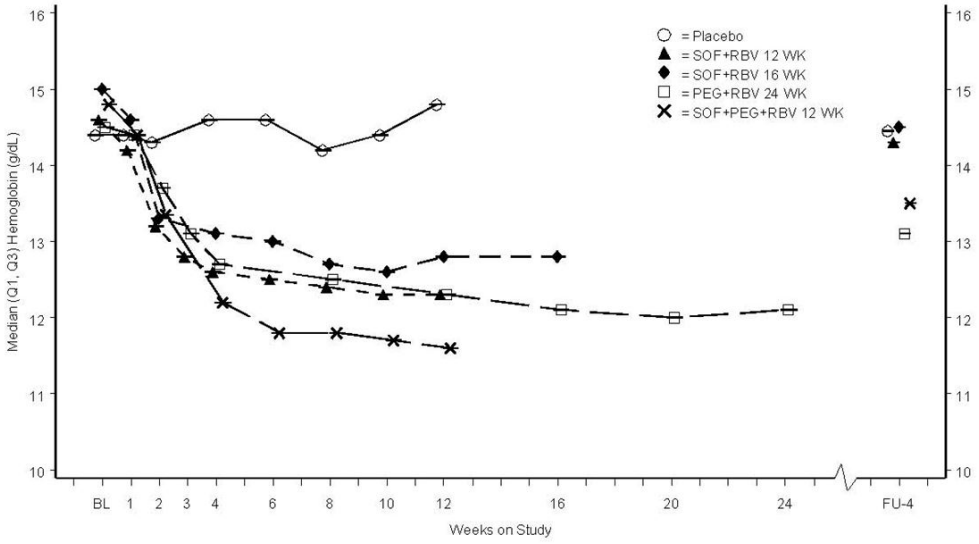
Table 26: Summary of Gde 3/4 haematology lab abnormalities in the PSP.

	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
Parameter	**(N = 71)**	**(N = 566)**	**(N = 98)**	**(N = 243)**	**(N = 327)**
Hemoglobin	71	563	98	242	327
Grade 3	0	51 (9.1%)	11 (11.2%)	24 (9.9%)	88 (26.9%)
Grade 4	0	0	0	0	1 (0.3%)
Lymphocytes	71	563	98	242	327
Grade 3	0	5 (0.9%)	0	15 (6.2%)	17 (5.2%)
Grade 4	0	2 (0.4%)	0	12 (5.0%)	0
Neutrophils	71	563	98	242	327
Grade 3	1 (1.4%)	0	0	30 (12.4%)	49 (15.0%)
Grade 4	0	1 (0.2%)	0	6 (2.5%)	17 (5.2%)
Platelets	71	563	98	242	327
Grade 3	2 (2.8%)	2 (0.4%)	0	18 (7.4%)	1 (0.3%)
Grade 4	0	0	0	0	0
WBC	71	563	98	242	327
Grade 3	0	0	0	10 (4.1%)	18 (5.5%)
Grade 4	0	1 (0.2%)	0	1 (0.4%)	0

7.5.3.1. Pivotal studies

Haemoglobin changes in the PSP: SOF+RBV: Anaemia is the most common cause of RBV dose reduction and decreased Hb was the most commonly reported Gde 3 hematology lab abnormality with SOF+RBV 12 Wk (9.1%) and 16 Wk groups(11.2%). There were no Gde 4 events of decreased Hb. Similar % (5.1-8.5%) of these subjects had at least 1 post-baseline Hb value <10 g/dL. In the SOF+RBV 12 Wk and 16 Wk groups, median Hb levels decreased notably until Wk 4, with comparable median changes from baseline at Wk 4 of −1.8 and −1.7 g/dL, respectively, the levels in both groups then remained stable for the remainder of treatment with maximal median changes from baseline of −2.1 g/dL in each group through Wk 12. Median Hb values returned to near-baseline values at the post-treatment Wk 4 visit in both SOF+RBV groups. In the absence of RBV in placebo group, no Gde 3 decreased Hb were seen. In the PEG+RBV group, no Gde 4 decreased Hb reported; 9.9% had Gde 3 decreases; 14.5% had at least 1 post-baseline Hb value <10 g/dL. Median Hb levels decreased notably through Wk 4 in PEG+RBV group, median change from baseline of −1.5 g/dL at Wk 4 and again remained stable, max median decline of −2.1 g/dL through Wk 12; values were returning to baseline values at post-treatment Wk 4 visit. Although the PEG+RBV regimen used a lower RBV dose (800 mg) compared with the wt-based RBV in the SOF+RBV groups (1000-1200 mg), the incidence of subjects with at least 1 post-baseline Hb value <10 g/dL was still higher in the PEG+RBV group (14.5%) vs. SOF+RBV 12 Wk (8.5%) and SOF+RBV 16 Wk (5.1%) groups. **SOF+PEG+RBV group:** Gde 3 decreased Hb occurred in 26.9%. Overall, 22.6% had at least 1 post-baseline Hb value <10 g/dL; 2.4%, had a post-baseline Hb<8.5 g/dL. Median Hb levels decreased notably through Wk 4 in this group, with median change from baseline of −2.6 g/dL at Wk 4, the levels then remained stable low for the remainder of treatment with a max median change from baseline of −3.0 g/dL through Wk 12; values were returning to baseline at post-treatment Wk 4 visit. Compared with PEG+RBV, the SOF+PEG+RBV group had a higher incidence of Gde 3 or 4 decreased Hb abnormalities, higher number of subjects with at least 1 post-baseline Hb value <10 g/dL, and a greater change from baseline in median Hb levels at on-treatment visits, likely accounted for by the higher dose of RBV used (wt based dosing) in the triple combination. See also Figure 6 below for a graphical depiction of Hb decline.

Figure 6: Median Hb values by treatment and visit in the PSP.

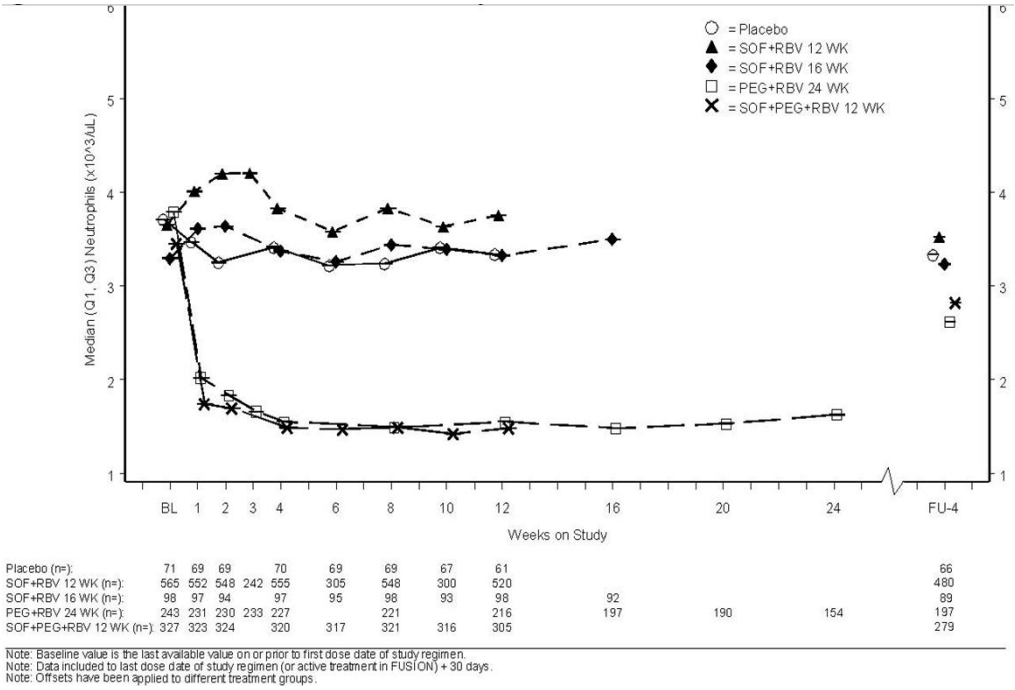


Placebo (n=):	71	69	69		70	69	69	67	61				66
SOF+RBV 12 WK (n=):	566	554	550	244	555	305	552	300	524				482
SOF+RBV 16 WK (n=):	98	97	94		97	95	98	93	98	92			89
PEG+RBV 24 WK (n=):	243	239	237	235	231		227		217	199	194	159	198
SOF+PEG+RBV 12 WK (n=):	327	323	324		320	317	321	316	305				279

Note: Baseline value is the last available value on or prior to first dose date of study regimen.
Note: Data included to last dose date of study regimen (or active treatment in FUSION) + 30 days.
Note: Offsets have been applied to different treatment groups.

Neutrophil (PMN) changes in the PSP: SOF+RBV Overall, 3.0% of SOF+RBV 12 Wk and 16 Wk groups had any gde of decreased PMN. One subject in the SOF+RBV 12 Wk group had Gde 4 decrease in PMNs. Paradoxically, there were transient increases from baseline at Wks 1 and 2 in median PMN counts observed in the SOF+RBV 12 Wk group (+0.35 and 0.54 × 10^3/µL) and SOF+RBV 16 Wk group (+ 0.18 and 0.43 × 10^3/µL). These increases normalised by Wk 4. While these changes in the first 4 weeks are noth though clinically meaningful, a puted explanation is an immunomodulatory response related to HCV clearance. The PEG+RBV group had the highest incidence of graded PMN abnormalities and the greatest decrease in median PMN levels compared with the SOF+RBV 12 Wk and SOF+RBV 16 Wk groups, changes consistent with bone marrow effects of PEG+RBV. In the PEG+RBV group, 14.9% had a Gde 3 or 4 decreased PMNs. Median PMNs decreased rapidly by Wk 1, median change from baseline of −1.75 × 10^3/µL, remained stable for the duration of treatment, returning to baseline at post-treatment Wk 4. **SOF+PEG+RBV**. In the SOF+PEG+RBV group, 15.0% and 5.2% reported Gde 3 and 4 decreased PMNs, respectively. Median PMNs decreased rapidly by Wk 1 with a median change from baseline of −1.61 × 103 /µL, then stabilised, returning to near-baseline at post-treatment Wk 4. Incidence of Gde 3/4 decreased PMNs was slightly higher in SOF +PEG +RBV group vs. PEG+RBV group (20.2% and 14.9%, respectively). A possible explanation is the lower baseline PMNs (possibly because of more Black subjects, who tend to have lower PMN) in the 2 treatment groups: the SOF+PEG+RBV group had overall lower baseline PMN counts vs. PEG+RBV group and the median change from baseline was similar for SOF+PEG+RBV and PEG+RBV groups. See also Figure 7 below for a graphical depiction of the decline in PMN.

Figure 7: Median PMN Values by Treatment and Visit in the Primary SAS.



Platelet changes in the primary safety population. SOF+RBV: No Gde 4 reductions in platelets; 0.4% in the SOF+RBV 12 Week group had a Grade 3 lab abnormality for platelets counts. Overall there was a low incidence of graded platelet abnormalities (~5%). In SOF+RBV 12 Week and SOF+RBV 16 Week groups, median platelet values **increased** from baseline over the first 4 wks of treatment with median changes from baseline of 34 and 28 × 10^3/µl, respectively, at Wk 4, then stabilising, before returning to near-baseline values at the post-treatment Week 4 visit. 2.8% of placebo group had Grade 3 reductions in platelet. In the PEG+RBV group, 7.4% had Gde 3 platelet counts; median platelets decreased rapidly over the first week of treatment (-40 × 10^3/µl); PEG+RBV group had a higher incidence of graded platelet count abnormalities i.e. 56.2%. (56.2%) In comparing the SOF+RBV, PEG+RBV, and placebo groups, the "reactive thrombocytosis" was a feature of only SOF-RBV regimens. **SOF+PEG+RBV**: No Gde 4 platelet events; 0.3% had a Gde 3 reduction in platelets counts. Median platelet values decreased rapidly over the first wk of treatment (−42 × 10^3/µl) at Week stabilised and returned to near-baseline values at FU-4. The incidence of Gde 3 thrombocytopaenia and any graded platelet abnormality was lower in the SOF+PEG+RBV group vs. PEG+RBVgroup, possibly accounted for because of the difference RBV doses used and also what appeared to be a SOF effect on increasing platelets.

7.5.3.2. Other studies

Haemoglobin in SSP: SOF+RBV: in Studies P7977-0523 and P2938-0721, there was no Gde 4 decreased Hb. Median Hb levels declined rapidly over the first 4 wks of treatment and remained decreased in the presence of RBV, an expected effects of RBV. In Study P7977-0523, Gde 3 decreased Hb was similar in SOF+PEG+RBV groups (10.0−45.5%) and SOF+RBV groups (4.0−30.0%). In all groups that received PEG+RBV or RBV, median Hb levels decreased rapidly over the first 4 wks of treatment (change from baseline: −2.2 to −3.2 g/dL and −1.8 to −3.1 g/dL, respectively), then remained constant or decreased more slowly before recovering towards baseline by post-treatment Wk 4. In the **SOF monotherapy** group, 1 subject only reported Gde 1 decreased Hb and there were no changes that were seen when SOF was partnered with RBV or PEG-RBV.

SOF+PEG+RBV: In Studies P7977-0422 and P7977-0724, no Gde 4 decreased Hb reported. In Study P7977-0422, during the first 12 wks (SOF/placebo-treatment period), Gde 3 decreased

Hb was reported at a similar incidence across SOF+PEG+RBV groups (16.7−29.9%) and placebo+PEG+RBV group (15.4%). There was no dose response observed with SOF groups on Hb. In Study P7977-0724, Gde 3 decreased Hb was reported equally across treatment groups. In Study P7977-0724, the study treatment (SOF 400mg +PEG+RBV) was the same for all treatment groups up to Wk 12. An important aspect of this study design was that it allowed for evaluation & comparison of the effects of SOF+PEG+RBV (Gp B), SOF monotherapy (Gp C1), and SOF+RBV (Gp C2) on lab parameters during Wks 13 to 24. Median Hb values decreased rapidly over the first 4 wks in all groups (i.e. −2.6 to −3.2 g/dL) when all subjects received SOF 400 mg+PEG+RBV, importantly, median Hb levels **returned to median baseline levels** in Gp C1 when subjects received SOF monotherapy. In Gp C2, in the absence of PEG, but with SOF+RBV present, there was partial recovery of Hb. However, with SOF+PEG+RBV, Hb did not recover until subjects were off treatment.

PMNS in the SSP. SOF+RBV: in P7977-0523 and P2938-0721, no Gde 3/4 decreased PMNs in SOF+RBV group or SOF-monotherapy group. In Study P7977-0523, Gde 3/4 decreased PMNs occurred in 30.0−45.5%) across SOF+PEG+RBV groups. In Studies P7977-0523 and P2938-0721, median PMNs counts remained stable in SOF+RBV groups and SOF-monotherapy group, in contrast, in SOF+PEG+RBV (P7977-0523), median PMN decreased rapidly over week 1 (change:−1.30 to −1.90 $\times 10^3/\mu L$). After completing PEG, median PMN counts increased, regardless of whether SOF+RBV treatment was completed or continued.

SOF+PEG+RBV: In Studies P7977-0422 and P7977-0724, all treatment groups had PMN decreases, PMN counts recovered once PEG or PEG+RBV ceased. In Study P7977-0422, during the first 12 wks (SOF/placebo-treatment), Gde 3 or 4 decreased PMNs were reported at comparable incidences across the SOF+PEG+RBV groups (25.0-31.9%) and placebo+.

PEG+RBV (19.2%) group; no dose response observed with SOF groups. In Study **P7977-0724**, Gde 3/4 decreased PMNs reported at comparable incidences across all groups on SOF+PEG+RBV (13.3-25.0%), although the incidence of decreased PMNs was lowest in Gp C1 (SOF+PEG+RBV 12 wks+SOF 12 wks, 13.3%). In the first wk of treatment, PMN decline was rapid in all groups (-1.6 to -1.8 x $10^3/\mu L$), remained decreased when all subjects received SOF 400mg+PEG+RBV. In Gps C1 and C2, median PMN counts increased rapidly and returned to near-baseline values during Wks 12 and 16 in **the absence of PEG**. In contrast, in the presence of continued PEG, median PMN counts in Gp B remained decreased through Wk 24 and started to approach baseline values 4 wks after study treatment finished.

Platelets in the SSP. SOF+RBV: In Studies P7977-0523 and P2938-0721, no Gde 3 or 4 platelet declines in SOF+RBV or SOF. In Study P7977-0523, there were no changes in median platelet counts in the SOF-monotherapy group; no Gde 3 or 4 platelet abnormalities in SOF+PEG+RBV groups in Study P7977-0523. But, median platelets decreased starting from Day 2 in SOF+PEG+RBV groups, reaching maximal decrease between Wks 2 to 4. Platelet counts remained decreased while subjects were receiving SOF+PEG+RBV, recovered in the absence of PEG and even while SOF+RBV continued. Change from baseline in median platelets for SOF+PEG+RBV groups (Gps 2-4 and 6) at Wk 4 was -18 to -67 $\times 10^3/\mu L$.

SOF+PEG+RBV: In Studies P7977-0422 and P7977-0724, no Gde 4 and few Gde 3 decreased platelets. In both studies, median platelet levels decreased over the first few wks of treatment and remained decreased in the presence of PEG, but recovered after stopping PEG or during FU. In Study P7977-0422, 2 subjects (SOF 200 mg+PEG+RBV) experienced Gde 3 decreased platelets. Across treatment groups, there were decreases from baseline in the median platelet levels starting Day 3, remaining decreased until EOT; overall decline over the treatment course was −50 to −64 $\times 10^3/\mu L$. In Study P7977-0724, 4 subjects had Gde 3 decreased platelets. For Gps A and B, platelet levels remained decreased until EOT; the change from baseline was −47 $\times 10^3/\mu L$ for both groups. For Gps C1 and C2, platelets began to recover after Wk 12 when PEG stopped.

7.5.4. Genotypic and/or phenotypic SOF resistance

7.5.4.1. Pivotal studies

Integrated Phase 3 virology analyses: Baseline NS5B population sequences obtained for 1292 of 1305 subjects who received either a SOF-containing regimen (991 subjects), placebo, or PEG+RBV in the Phase 3 studies. No S282T detected by population sequencing; 19 subjects had detectable RBV-associated substitutions T390I or F415Y. A statistical analysis was performed for subjects in each Phase 3 study and the combined GT- 2 and 3 studies (P7977-1231, GS-US-334-0107, GS-US-334-0108). After adjusting for multiple comparisons, no statistically significant correlations found between presence of any baseline variant and treatment outcome. **Virologic failure or non-completers:** Of 991 treated with SOF+RBV±PEG, 225 of 226 in the RAP were sequenced with **no S282T detection**. There were 63 NS5B substitutions observed in >2 subjects across the 4 Phase 3 studies. Phenotypic analysis demonstrated no reduction in susceptibility to SOF or RBV with these substitutions.

7.5.4.2. Other studies

See above, this was a pooled resistance analysis.

7.5.5. Electrocardiograph

7.5.5.1. Pivotal studies

There was no ECG signal of concern in the Phase 2 and Phase 3 programme for SOF.

7.5.5.2. Other studies

As above.

7.5.6. Vital signs

7.5.6.1. Pivotal studies

No notable trend or change in vital signs.

7.5.6.2. Other studies

No notable trend or change in vital signs.

7.5.7. Safety profile associate with PEG and RBV

7.5.7.1. Pivotal studies

Safety profile associated with PEG+RBV: Both PEG and RBV have been used to treat HCV infection for many yrs and the safety profiles are well known. For the most part these comprise constitutional upset i.e. flu-like symptoms occurring from the outset, then a swathe of AEs that occur later during prolonged treatment i.e. GI upset, haematological toxicities, neuropsychiatric and cognitive reactions, and metabolic abnormalities (e.g. wt loss). For RBV, anaemia is consequent to the accumulation of RBV in red cells resulting in haemolysis. Other known RBV AEs are fatigue, insomnia, dyspnoea, cough, irritability.

Primary safety population: In comparing the PEG+RBV-containing groups, the incidence of expected PEG+RBV AEs was reported at a similar rate in subjects in the SOF+PEG+RBV or PEG+RBV groups. Neutropaenia, leukopaenia, injection site reaction, injection site erythema were only reported by subjects in the PEG+RBV or SOF+PEG+RBV groups. In comparing the PEG-containing regimens (±SOF) with the SOF-containing regimens (without PEG), 2-fold or greater reporting frequencies for rash, pruritus, anaemia, decreased appetite, arthralgia, myalgia, ILI, pyrexia, chills, vomiting, neutropaenia, alopecia, leukopaenia in the PEG-containing regimens. When SOF+PEG+RBV was compared with the PEG+RBV regimens, anaemia was the only AE that was reported at an approximately 2-fold greater incidence in the SOF+PEG+RBV group. This difference was expected given the combination of weight-based RBV dosing (1000−1200mg a day) in the SOF+PEG+RBV regimen compared with the fixed, lower dose of

RBV (800mg a day) in the PEG+RBV regimen. Dry skin reported at ~3-fold greater incidence with PEG+RBV vs. SOF +PEG+RBV. In comparing RBV-containing regimens with placebo regimen, ~2-fold higher frequency for fatigue, insomnia, unspecified pain, anaemia, irritability, arthralgia, myalgia, dyspnoea, cough, depression. All of these events, except cough, were reported at a higher incidence with PEG+RBV-containing regimens. It is noteworthy that 10% of placebo group reported fatigue, headache, nausea, rash, pruritus, decreased appetite, dizziness, vomiting, abdominal pain, anxiety, suggesting a high background rate, perhaps attributable, in part, to untreated HCV.

7.5.7.2. Other studies

In general, AEs reported by >15% subjects in Studies P7977-0422 and P7977-0724 were consistent with the expected PEG+RBV safety profile i.e. fatigue, asthenia, pyrexia, headache, myalgia, rigors, arthralgia, nausea, insomnia, irritably/anxiety/nervousness, depression, alopecia, anorexia, injection site reaction.

7.6. Post-marketing experience

Sofosbuvir has not been marketed in any country at the time of this marketing application.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Liver toxicity

None.

7.7.2. Haematological toxicity

None.

7.7.3. Serious skin reactions

None revealed in the Phase 1, 2 and 3 studies to date.

7.7.4. Cardiovascular safety

None.

7.7.5. Unwanted immunological events

None.

7.8. Other safety issues

None.

7.8.1. Safety in special populations

Age: In a population PK analysis of SOF and GS-331007, age was not a relevant covariate. In the SOF+RBV groups of the PSP, anaemia was the only AE reported 2-fold higher incidence in subjects aged ≥50 yrs vs. <50 yrs, and subjects aged ≥65 yrs vs. <65 yrs. In the SOF+RBV 12 Wk group, anaemia was reported at a ≥2-fold frequency in those aged ≥50 yrs vs. <50 yrs (13.3% and 5.5%, respectively) and subjects aged ≥65 yrs vs. <65 yrs (18.5%, vs 9.8%). In the PEG+RBV group, anaemia was reported at up to 2-fold or higher frequency in subjects aged ≥50 yrs vs. < 50 yrs (14.4%, and 8.5%, respectively), and subjects aged ≥65 yrs vs. <65 yrs (45.5%, vs. 9.9%). Gde 3 decreased Hb was reported at a higher incidence in subjects aged ≥65 yrs vs. <65 yrs in the SOF+RBV 12 Wk (18.5% and 8.6%, respectively) and SOF+RBV 16 Wk groups (60.0% and 8.6%, respectively). In the PEG+RBV group, Gde 3 decreased Hb was reported at a higher incidence in subjects aged ≥50 yrs vs. <50 yrs (12.8%, and 6.8%, respectively) and subjects aged ≥65 yrs compared with <65 yrs (27.3%, and 9.1%, respectively). This suggested that older

subjects could be more susceptible to RBV-induced anaemia (i.e. with significant declines in Hb, i.e. Gde 3+) and effects on anaemia were not necessarily (although they could be) a SOF effect. In general, being older (≥50 and ≥65 yrs) was associated with a higher incidence of AEs leading to modification or interruption of study drug. **SOF+PEG+RBV**: In the SOF+PEG+RBV group of the PSP, anaemia was the only AE reported at a 2-fold higher incidence older subjects i.e. 25.3% in ≥50 yrs vs. 11.8% in <50 yrs and 35.0% in ≥65 yrs vs. 19.9% in <65 yrs. A similar trend was observed for the PEG+RBV group for both age subgroups analyses.

Hb findings of course aligned with the AE of "anaemia" and incidence of Gde 3 decreased Hb in SOF+PEG+RBV group was higher in older age subgroups (aged ≥50 vs <50 yrs [30.9% and 19.1%, respectively] and aged ≥65 yrs vs <65 yrs [40.0% and 26.1%). A similar trend was observed for the PEG+RBV group, suggesting that older subjects could be more susceptible to PEG- and RBV-induced decreases in Hb effects. In general in the SOF+PEG+RBV group, higher age was associated with a higher incidence of AEs leading to modification or interruption of study drug.

Gender: In a population PK analysis of SOF and GS-331007, gender was not a relevant covariate, indicating no gender effect on GS-331007 and SOF PK. In the SOF+RBV 12 Wk group, the incidence of overall AEs was slightly higher for females vs. males (92.7% vs 84.8%), though the incidence of Gde 3 or 4 AEs was similar. In the SOF+RBV 16 Wk group, incidence of overall AEs slightly higher for females, though higher Gde (≥3) were the same. Anaemia was reported at a 2-fold or higher incidence in females in the SOF+RBV 12 Wk group (19.0% and 5.3%, respectively) and SOF+RBV 16 Wk group (12.9%, and 0%, respectively). Overall, this difference is likely due to the lower baseline Hb of women. The other possibility is that female subjects may have had higher overall exposures to RBV from the weight-based RBV dosing in Phase 3 studies. The incidences of graded Hb laboratory abnormalities were similar for the SOF+RBV 12 Wk and SOF+RBV 16 Wk groups. Females had a higher incidence of AEs leading to dose modification or interruption of study drug vs. males in the SOF+RBV 12 Wk group (22.0% vs. 5.0%) and SOF+RBV 16 Wk group (19.4% vs. 1.5%). In the PEG+RBV group, female subjects had higher incidence of dose modifications or interruptions vs. males (33.3% and 23.1%, respectively). **SOF+PEG+RBV**: anaemia was the only AE reported at a 2-fold higher incidence in female subjects compared with male subjects i.e. (32.2% and 14.4%, respectively).

Reasons for this are discussed above. No other differences indicative of a SOF-containing regimen treatment effect for any other AEs or Gde 3/4 AEs. Anaemia was 2-fold or higher in female subjects compared with male subjects. As for the SOF+RBV regimens, females had a higher incidence of AEs leading to modification or interruption of study drug compared with male subjects in the SOF+PEG+RBV group (46.6% and 25.8%, respectively).

Race: In a population PK analysis of SOF and GS-331007, race was not a relevant covariate. Overall, there were very few Black subjects enrolled in Studies P7977-1231, GS-US-334-0107 and GS-US-334-0108, consistent with the epidemiology of GT- 2 and 3. In the SOF+PEG+RBV group, there was no overall differences indicative of a SOF-containing regimen treatment effect for any AE, or any Gde 3 or 4 AE. Importantly, neutropaenia was reported at a similar incidence in Black compared with nonBlack subjects (18.5% and 16.1%, respectively).

Cirrhosis: *Decompensated cirrhosis* was an exclusion for the Phase 3 clinical studies. Study GS-US-334-0108 allowed ≤30% cirrhotics and P7977-1231, GS-US-334-0107, GS-US-334-0110) allowed ≤20%. Study P7977-2025, SOF+RBV pretransplant, enrolled primarily cirrhotic subjects. In addition, the SOF Compassionate Use Program has provided access to SOF (+RBV±PEG) to HCV patients (n=31) after liver transplantation. **Primary Safety Population** Cirrhosis did not have an effect on GS-331007 or SOF exposures in HCV-infected (CPT A) and was not a relevant covariate based on population PK analyses. These results are consistent with the findings of the hepatic impairment Phase 1 study in HCV-infected subjects with CPT B and C. **SOF+RBV:** In the SOF+RBV 12 Wk and 16 Wk groups overall no differences in AEs, or any Gde 3 or 4 AE, in cirrhotics. There was also no apparent difference in AEs leading to dose modification

or interruptions. In the SOF+RBV groups, aside from the differences observed in incidence of mostly Gde 1 increased bilirubin, there were no other differences suggestive of a SOF-containing regimen treatment effect. **SOF+PEG+RBV**: anaemia and neutropaenia were reported at a higher incidence in cirrhotics. No other differences indicative of a SOF-containing regimen treatment effect apparent for any other AEs or Gde 3/4 AEs. Of the AEs reported in ≥10%, anaemia and neutropaenia were higher in cirrhotics vs. non i.e. 31.5% vs.18.7%; neutropaenia:22.2% vs.15.4%. These findings are consistent with higher incidence of AEs leading to modification or interruption of study drug in cirrhotics vs. non-cirrhotics i.e. 44.4% vs. 31.1%. Similarly, although the overall incidence of graded decreases in Hb and PMNs were similar between cirrhotics and noncirrhotics, Gde 3/4 values were slightly higher. In the SOF+PEG+RBV group, the only difference in graded lab abnormalities was total bilirubin (35.2% vs. 14.7%) and these were mostly Gde 1 and not considered clinically meaningful. **Secondary Safety Population:** only P2938-0721 allowed cirrhotics to enrol but as only 5 did so, nos. are too small for a separate analysis.

HCV/HIV-1 coinfection: Numbers of those enrolled (N=31) in PHOTON-1 are still too small for analysis.

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

None specifically, but refer to the detailed discussions elsewhere in this report.

7.9. Evaluator's overall conclusions on clinical safety

This Clinical Safety summary for the Phase I-III data for SOF is comprehensive and detailed especially in regards to exploring whether SOF compounds the toxicities of either PEG or RBV. In all, 2885 subjects have been treated in 27 studies in which, 2443 subjects have received ≥1 dose of a SOF containing regimen. At the proposed therapeutic oral dose of 400 mg once daily, 1732 HCV infected subjects have been exposed, in combination with PEG+RBV or RBV, for durations of 12 weeks (n = 1088), 16 weeks (n = 98), 24 weeks (n = 421). In terms of the enrolment into the pivotal studies, males and females constituted 63.4% and 36.6%, respectively. The lack of an upper age limit for enrolment allowed older adults to enrol, but despite this only 5.1% were ≥65 years of age. In addition, while subjects of Black race were reasonably well represented (16.5% in Study GS-US-334-0110), this was not the case in GT-2 and 3 studies, but as expected based on known epidemiology of these genotypes. Baseline characteristics were also pretty representative in regards to non-CC (CT or TT) IL28B allele in 61.8%, high baseline HCV RNA ≥ 6 $\log_{10}$ IU/mL (67.5%), and elevated ALT >1.5 ULN (55.8%). Moreover, cirrhotics could and did enrol, ranging from 16.7 to 32.7% of enrolment. Overall, SOF combined with RBV±PEG appears well tolerated. Specifically, for the treatment of GT-2 and 3 when compared to PEG+RBV for 24 weeks, SOF+RBV for 12 weeks was characterised by:

- **Fewer AEs leading to treatment discontinuation** (1.4% versus 0%. versus 10.7%, of SOF+RBV 12 Week group, SOF+RBV 16 Week group, PEG+RBV group, respectively)
- **Lower severity of AEs** (≥Grade 2 and higher AEs were reported in 42.0%, 41.8% and 68.7% of SOF+RBV 12 Week, SOF+RBV 16 Week groups, PEG+RBV group, respectively)
- **Grade 3 or 4 AEs lower incidence** (7.2%, 4.1%, 18.5% in the SOF+RBV 12 Week and SOF+RBV 16 Week group, PEG+RBV group, respectively)
- Reduced rates of treatment emergent depression and depression requiring treatment (7.2%, 6.1%, 17.3% in the SOF+RBV12 Week group, SOF+RBV16 Week group, PEG+RBV group). However, Grade 3 and 4 decreases in haemoglobin were seen in ~10%.

The current SOC for CHC GT- 1 HCV infection is a RBV-PEG+HCV PI. There are many problems associated with these regimens not least the long treatment duration, toxicities and drug-drug

interactions. GS-US-334-0110 provides definitive data, in a single arm study (with historical controls) of the benefits of 12 weeks of SOF+RBV+PEG- GT- 1 treatment naïves.

In summary, **triple therapy** for 12 weeks resulted in:

- **Higher rates of treatment completion**: triple therapy versus PEG+RBV for 24 weeks (Study P7977-1231) 97.9% versus 77.8%, respectively
- **Fewer AEs that led to study drugs discontinuation**: 1.5% versus 10.7% in the triple for 12 weeks versus dual therapy for 24 weeks, respectively
- **Lower severity of AEs**: Grade 2+ and Grade 3 or 4 AEs both lower with triple therapy for 12 weeks versus dual therapy for 24 weeks, 59.3% versus 68.7% and 14.7% versus 18.5%
- **Laboratory abnormalities consistent with PEG+RBV**: Consistent with the expected bone marrow suppressive effects of PEG and the haemolytic effects of RBV, reductions in haemoglobin and polymorphonuclear leukocytes (= neutrophil; PMN) count were the most frequently reported Grade 3 or 4 lab abnormalities by subjects receiving the SOF+PEG+RBV and PEG+RBV regimens. But, importantly, the numbers of subjects in both groups, with very low haemoglobin <8.5 g/dL was small but similar (2.4 and 1.7%, respectively); nevertheless, there were more subjects in receipt of triple therapy for 12 weeks with moderate reduction, that is, haemoglobin <10 g/dL than in the PEG-RBV group (22.6% versus 14.5%, respectively). A possible explanation for this is the lower RBV doses used in the PEG-RBV group, whereas weight based (and therefore higher) dosing with RBV (1000-1200 mg/day) was given as part of triple therapy. The alternate explanation is that SOF does indeed make a contribution, albeit small, to haemoglobin reduction. Overall, and taken together with the efficacy findings, SOF in combination with RBV±IFN appears safe and well tolerated without any signature toxicity of its own and without convincingly amplifying the known toxicity profiles of either PEG or RBV.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of oral SOF 400 mg once daily in the proposed usage "in combination with other agents for treatment of CHC virus infection in adults" are:

- **Shortened duration of treatment (that is, 12 weeks), with superior SVR12 rates** compared to historical SVR rates of SOC regimens (SVR rate ~60%) when combined with RBV+PEG for **treatment-naïve CHC Genotype 1**
- Shortened duration of RBV+PEG regimens, translates into reduced toxicity, not of the acute toxicities such as influenza like illness (with PEG) and the haematological AEs (PEG+RBV) which still occur, but of the later onset toxicities including depression and depression requiring specific treatment. These toxicities can impact on the ability of patients to tolerate full treatment which in turn impacts negatively on SVR rate
- **High SVR12 rates using PEG free regimens** (SOF+RBV over relatively short treatment periods = **12 weeks for GT-2 and 16 weeks for GT-3) for treatment naïve, limited prior treatment (<3 months IFN) and treatment experienced (had failed prior treatment with an IFN based regimen)** CHC subjects with genotypes 2 and 3
- The drug fills a potential niche for patients with CHC **GT-2 or 3, who cannot take/tolerate IFN** for whatever reason
- **Low risk for drug-drug interactions**

- Potential for **partnering with other DAA,** such that CHC treatment regimens could be both PEG and RBV free
- **Safe and well tolerated** at the proposed therapeutic dose.

8.2. First round assessment of risks

The risks of SOF in the proposed usage are:

- The **paucity of data** on the efficacy and safety of the drug when used in combination with PEG+RBV for the treatment of HCV GT-4, 5, 6. In fact there were only 35 people with these genotypes represented in the NEUTRINO study. While 34 of these 35 achieved SVR12, nonetheless this is still a very small cohort and may well not be representative. The paucity of data for GT-4, 5, 6 is potentially problematic
- There are very few subjects of Asian ethnicity enrolled in the Phase III programme for SOF; in total, 117 subjects of Asian ethnicity enrolled (6740 person days). The very small representation of Asian subjects coupled with the small numbers of subjects with HCV GT-4 and 6 enrolled in trials of SOF is potentially problematic for the Australian setting because Australia has a large and expanding Asian population and HCV infection in migrants may reflect the GT-4 and 6 that predominate in their country of origin
- There are very few Indigenous subjects enrolled across the programme
- There are no data in subjects coinfected with hepatitis B (Hepatitis B Surface Antigen +ve) or in regards to D-D interactions with drugs used for the treatment of hepatitis B such as entecavir. The evaluator acknowledges that there **are** data on co-administration of SOF and antiretroviral drugs, that is, tenofovir and emtricitabine, used for HBV and HIV
- There are hardly any data on patients with HIV-HCV co-infection who are not on antiretrovirals (87.1% of the 31 enrolled in PHOTON were on antiretrovirals), and hence the impact of SOF as part of combination therapy for CHC, on HIV viraemia and immunological markers such as CD4+ T cell count **is as yet, unknown**. Enrolment of antiretroviral naïve HIV-HCV subjects (with high CD4+ T cells) into PHOTON should be encouraged
- While the sponsor goes to some lengths to demonstrate the inclusiveness of the SOF access programme in regards to "no upper age limit" in Phase III, there is still a paucity of data in older patients, with just over 60 patients ≥65 year old enrolled. As older patients are more likely to have many concurrent co-morbidities such as **impaired renal function, subclinical cardiovascular disease and diabetes mellitus**, it is important that the Sponsor highlights this. Moreover, analysis of the AEs in this group showed higher rates, that is, **a two-fold or greater incidence of Grade 3 haemoglobin abnormalities** in both SOF+RBV and triple therapy treatment groups. In summary, elderly patients are more vulnerable to the known side effects of SOF+RBV±PEG. Moreover, their ability to withstand the predicted decline in haemoglobin with RBV-SOF or SOF+PEG+RBV, is probably less, in so much as these sorts of declines may unmask subclinical cardiovascular disease (CVD) (as an example). Moreover, while SOF is deemed safe without the need for dose modification in mild moderate renal impairment, these data are derived from **single dose exposure** in a very small numbers of subjects. The Phase III programme did not add much in terms of the safety of multi dosing of SOF in those with moderate renal impairment, as an entry criteria for all Phase III studies, was a creatinine clearance >60 mL/min (calculated by Cockcroft-Gault or Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equations)
- There is **no pivotal study data** provided on SOF in **treatment experienced patients with GT-1 CHC**, the only real data is provided in the small group of patients with HCC pre transplant

- The only combination data for SOF presented in this submission is when partnered with RBV±PEG, hence the broad request for approval of SOF "in combination with **other agents** for treatment of hepatitis C virus infection in adults" **is not supported by the data** provided in this submission. While there are currently other ongoing studies of SOF in combination with other DAA, these studies are still enrolling and no data is available yet
- The 2 year oral gavage carcinogenicity studies with SOF in mice and rats are awaited, expected in December 2013, hence there is **no long term pre-clinical carcinogencity** data provided in this Application
- While the drug appears safe in standard fertility and embryofoetal developmental toxicity studies, there is a paucity of data in pregnant women; overall, it is unclear how the B2 category is assigned
- There is no data provided on the **potential interactions (or not) with other illicit substances, or opiate replacement therapy** other than methadone
- There is no data on the use of SOF in **acute** hepatitis C infection
- The paediatric development programme is ongoing and as identified in the AU-RMP version 0.1, there is **no data in those <18 years of age**
- The **supratherapeutic dose** trialled was 1200 mg **as a single dose** only in healthy volunteers
- There is no specific information given on the potential drug interaction between a representative **OCP and SOF**, these data should be forthcoming, but are not presented in this submission. These data are important as pregnancy should be avoided when using RBV. The results of this drug-drug interaction study should be provided as soon as possible;
- There is no specific drug-drug interaction data on drugs that are **moderate inducers of PgP**
- There is no drug-drug interaction data on **other immunosuppressants** that might be used post liver transplantation, for example, mycophenolate. The evaluator acknowledges the drug-drug interaction data for tacrolimus and cyclosporine.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of SOF, given the proposed usage, is **favourable**, with the caveat that the evaluator thinks the approval should be given with a number of **important provisos** as listed below.

9. First round recommendation regarding authorisation

The evaluator recommends authorisation but the indication needs to be narrowed. The sponsor requests approval "in combination with other agents for treatment of chronic hepatitis C virus infection in adults". The evaluator thinks this is **too broad an indication** and should be narrowed to define more clearly **which agents** SOF can be combined with; as per the data provided in this submission, the only drugs are RBV±PEG. Giving a broad approval in the absence of data could potentially allow use of SOF with HCV protease inhibitors (as an example). Next, the evaluator thinks the term **"chronic hepatitis C"** needs to be clearly defined. Not all forms of chronic hepatitis C can be treated with SOF, in so much as there is **no pivotal study** presented in this submission that supports the use of SOF in **CHC GT-1 treatment experienced patients.** In addition, there is a paucity of data for SOF for treatment of HCV GT- 4, 5 and 6.

10. Clinical questions

10.1. Pharmacokinetics

None.

10.2. Pharmacodynamics

None.

10.3. Efficacy

1. What is the plan for the use of this drug in treatment-experienced patients with Genotype 1?
2. In further studies of the SOF in genotype 3, how do you plan to better assess hepatic steatosis, a major predictor of therapy response;
3. What are your plans to gather more data in the subjects of Asian ethnicity i.e. will you enrol studies in Asia, which would also include more genotype 4 and 6 patients?

10.4. Safety

4. Do you have any data on the safety of multiple doses of SOF in CHC patients with moderately impaired renal function?

11. Second round evaluation of clinical data

11.1. Contents of the clinical dossier

11.1.1. Scope of the clinical dossier

The submission was presented in CTD format and contained the following: Module 1 (3 vols), Module 3 (1 vol), Module 4 non-clinical (8 vols), Module 5 (3 vols). The submission contained the following clinical information:

- Module 5
  - 3 clinical pharmacology studies: 1 that provided PK data and 2 that provided further albeit interim efficacy data in the target population i.e. VALENCE and PHOTON-1 – the latter was reviewed as part of the first round submission, second interim analysis data is provided for this second round submission
  - Module 5.3.3.4 Extrinsic Factor PK Study Reports (n=1).
    - GS-US-334-0146: A Phase 1, Open Label, Drug Interaction Study Evaluating the Effect of Sofosbuvir or GS-5885 on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol
  - Module 5.3.5.1 pivotal efficacy/safety studies (n=3, 1 completely new to this application; 2 provide further data for studies reviewed in the first round application).
    - GS-US-334-0133 (VALENCE): A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Weeks in Treatment Naïve and Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection

- GS-US-334-0123 (PHOTON-1): A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 HCV and HIV Co-infected Subjects. Second interim analysis
- GS-US-334-0110 (NEUTRINO): A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of GS-7977 with PEGinterferon Alfa 2a and Ribavirin for 12 Wks in Treatment-Naïve Subjects with Chronic Genotype 1, 4, 5, or 6 HCV Infection – list of adverse events.

- Module 1
  - Application letter, response to questions from First round evaluation, draft Australian PI and CMI and labelling, Gilead Sciences Product Monograph dated 12-Dec-2013, information relating to pharmacovigilance; RMP vs. 0.2 for the EU with Applicant's response to Day 120 List of Questions October 2013 is supplied. Summary document of ribavarin therapeutic equivalents (US FDA).

11.1.2. Paediatric data

The submission did not include paediatric data.

11.1.3. Good clinical practice

All studies conducted as per ICH-GCP, considerations for the ethical treatment of human subjects in place when the studies were performed; informed consent obtained from all trial participants.

11.2. Pharmacokinetics

11.2.1. Studies providing pharmacokinetic data

One PK interaction was presented i.e. GS-US-334-0146: A Phase 1, Open Label, Drug Interaction Study Evaluating the Effect of SOF or Ledipasvir (LDV) on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol. The details of this study are found in SECTION 19.0.

11.2.2. Summary of pharmacokinetics

These are detailed in the first round evaluation September 2013.

11.2.2.1. Pharmacokinetic interactions demonstrated in human studies

SOF with OC containing norgestimate/ethinyl estradiol can be co-administered safely.

11.2.3. Evaluator's overall conclusions on pharmacokinetics

As per the first round evaluation. SOF administered with combined OCP is safe and does not impact on efficacy of the latter.

11.3. Pharmacodynamics

No new data.

11.4. Dosage selection for the pivotal studies

As per first round evaluation.

11.5. Clinical efficacy

11.5.1. Pivotal efficacy studies

Further **interim** data is provided for two pivotal Phase 3 studies: GS-US-334-0133 (VALENCE) and GS-US-334-0123(PHOTON-1).

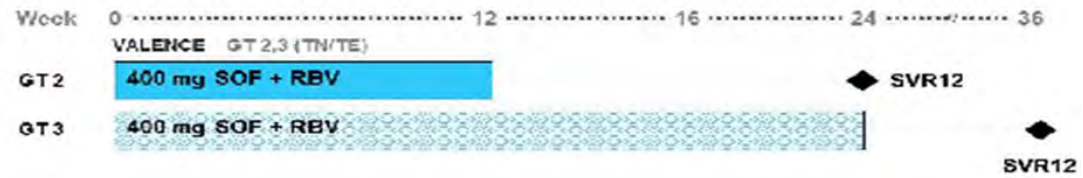
11.5.1.1. GS-US-334-0133 (VALENCE) - A Phase 3, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of GS-7977 + ribavirin for 12 Weeks in treatment naïve and treatment experienced subjects with chronic Genotype 2 or 3 HCV Infection

11.5.1.1.1. Study design, objectives, locations and dates

Study design: GS-US-334-0133 is an ongoing Phase 3, randomised, double-blind, placebo-controlled study examining safety, tolerability, antiviral efficacy of SOF and RBV vs. SOF placebo and RBV placebo in treatment-naive or treatment-experienced subjects with CHC genotype 2 or 3. Initially, eligible subjects were randomised in a 4:1 ratio to receive either SOF 400 mg QD + RBV total daily dose 1000 or 1200 mg administered in a divided daily dose for 12 wks or SOF placebo administered QD + RBV placebo BID for 12 wks. During the treatment phase of the study, changes were made to the protocol based on emerging clinical data from Study GS-US-334-0108 (FUSION) (see first round review) suggesting that in genotype 3 HCV longer treatment duration might be beneficial. Accordingly, the protocol was amended extending treatment to 24 wks in genotype 3 for those who had not yet completed the study. The original and modified study designs are shown in Figure 8.

Figure 8: Original and modified study design for GS-US-334-0133.

Figure 2. GS-US-334-0133: Amended Study Design



GT = genotype; PBO = placebo; RBV = ribavirin; SOF = sofosbuvir; TE = treatment experienced; TN = treatment naive

SOF+RBV treatment and follow-up visits as originally planned. For subjects with genotype 3 HCV infection in the SOF+RBV group, the treatment duration depended on their study status at the time of the implementation of the 24-week dosing regimen in the study. The genotype 3 HCV-infected subjects who had already completed 12 weeks of treatment with SOF+RBV or who had prematurely discontinued treatment continued to complete the follow-up visits as originally planned (n = 11). Subjects with genotype 3 HCV infection who had not completed treatment with SOF+RBV had their treatment duration extended to a total of 24 weeks (n = 250). Subjects initially randomised to receive placebo were discontinued from the study and offered treatment with SOF+RBV under a separate protocol (Study GS-US-334-0109).

11.5.1.1.2. Objectives

Primary objectives:

- To determine the efficacy of SOF+RBV measured by the proportion of subjects with SVR12

- To assess the safety and tolerability of SOF+RBV.

Secondary objectives of this study were as follows:

- Proportion of subjects who attain SVR4 and SVR24 weeks
- To determine efficacy of treatment with SOF+RBV based on prior treatment history
- To evaluate HCV kinetics
- emergence of viral resistance to SOF during treatment and after treatment discontinuation
- QOL.

Location: EU, n=77 sites[21]

Study start date: 19 September 2012 (First Subject Screened); **Study end date:** 02 October 2013 (Last Subject Observation for this **Interim Report** which included all electronic case report form data collected up to 26 September 2013 and all laboratory data collected up to 04 October 2013).

11.5.1.1.3. Inclusion and exclusion criteria

Key inclusion: 1. Willing and able to provide written informed consent; 2. Male or female, age ≥18 yrs; 3. confirmed chronic HCV; 4. GT- 2 or 3 HCV; 5. HCV RNA $\geq 10^4$ IU/mL; 6. Presence/absence of cirrhosis documented; 7. **Treatment naïve or treatment experienced i.e. either IFN intolerant or a treatment failure**; 8. BMI ≥18 kg/m^2.

Note that in the synopsis provided the **exclusion criteria were not provided, but I assume that it would be in alignment with the other Phase 3 studies i.e.** 1. Prior exposure to a DAA targeting the HCV NS5B polymerase**;** 2. Pregnant/nursing female or male with pregnant partner**;** 3. Chronic liver disease of non-HCV aetiology**;** 5. HBV or HIV**;** 6. Contraindications for RBV**.**

11.5.1.1.4. Study treatments

Oral SOF 400 mg/day (1 × 400-mg tablet) QD; matching SOF placebo QD.

Oral RBV at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets in a divided daily dose i.e. BID); matching RBV placebo given BID.

11.5.1.1.5. Efficacy variables and outcomes

Main efficacy variables:

- Serum HCV RNA (using COBAS TaqMan HCV Test vs. 2.0 for use with the High Pure System assay (limit of quantitation 25 IU/mL) at Day 1 (baseline), Week 1, 2, 4, 6, 8, 10, and 12 visits; and at the **post-treatment** Week 4, 12, and 24 visits for all subjects
- Serum HCV RNA at the Week 16, 20, and 24 visits for subjects receiving 24 weeks of treatment.

Primary efficacy outcome = proportion with SVR12 defined as HCV RNA <lower limit of quantitation (LLOQ) (i.e. <25 IU/mL) at 12 weeks after study drug cessation.

Other efficacy outcomes included:

- proportion with SVR4 i.e. HCV RNA < LLOQ (ie, <25IU/mL) at 4 wks after study drug cessation

21 ClinicalTrials.gov NCT01682720: "GS-7977 and Ribavirin in Treatment Naive and Treatment Experienced Subjects With Chronic Genotype 2 or 3 HCV Infection".

- Viral failure = HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values or last available on-treatment m'ment with no subsequent follow up values [i.e. breakthrough]; > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values or last available on-treatment m'ment with no subsequent follow up values [i.e. rebound]; or HCV RNA persistently ≥ LLOQ through 8 wks of treatment [i.e. non-response])
- Viral relapse (i.e. HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at EOT, confirmed with 2 consecutive values or last available posttreatment measurement)
- Safety assessments included AEs and concomitant medications, clinical lab results (including ALT normalisation), vital signs and physical examinations
- Viral kinetics and viral resistance
- QoL.

11.5.1.1.6. Randomisation and blinding methods

Not detailed in the interim analysis synopsis provided.

11.5.1.1.7. Analysis populations

The full analysis set (FAS) included subjects with genotype 2 or 3 HCV infection randomised into the study and received ≥1 dose of SOF. The safety analysis set (SAS) included subjects who were randomised into the study and received ≥1 dose of study drug.

11.5.1.1.8. Sample size

No details of sample size or power calculations provided in this synopsis.

11.5.1.1.9. Statistical methods

Demographic and baseline characteristics summarised by treatment group and overall using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], min and max). Disposition was summarised by treatment groups and overall. The point estimate for the SVR4 and SVR12 rates and their 2-sided 95% exact CIs were constructed for each treatment group using the Clopper-Pearson method. Virologic failure was summarised as on-treatment virologic failure or relapse. Subjects not achieving SVR12 and not meeting virologic failure criteria were categorised as "other." The denominator for relapse was the number of subjects who had HCV RNA <LLOQ at their last observed on-treatment HCV RNA m'ment; otherwise, the denominator was the number of subjects in the FAS. The point estimates for the SVR12 rate and 2-sided 95% exact CI were provided for each treatment group within each subgroup analysed (age, sex, ethnicity, +/- cirrhosis, prior treatment, prior treatment experience and IFN classification, IL28B genotype, baseline HCV RNA, baseline ALT, baseline BMI. The 2-sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rate within each treatment group and subgroup. Subjects with missing SVR12 values at the time of this interim considered as failures. For the efficacy analysis, subjects were analysed in 3 treatment groups:

- SOF+RBV 12 Week genotype 2 group (N = 73)
- SOF+RBV 12 Week genotype 3 group (N = 11)
- SOF+RBV 24 Week genotype 3 group: (N = 250).

Standard methodologies were used for coding and analysing AEs.

11.5.1.1.10. Participant flow

In all, 419 treatment-naive and treatment-experienced subjects with CHC genotype 2 or 3 were randomised and received ≥1 dose study drug/placebo. At the time of the interim report, all had

completed treatment or prematurely discontinued. The majority prematurely discontinuing, were in the placebo group, in which all subjects not yet completed treatment or prematurely discontinued treatment (79 subjects, 92.9%) were terminated by the sponsor and offered treatment in GS-US-334-0109). Treatment discontinuation due to AEs, were low in all groups (0.7%).

Table 27: GS-US-334-0133: subject disposition.

	GT 2/3 Placebo (N=85)	GT2 SOF+RBV 12 wks (N=73)	GT3 SOF+RBV 12 wks (N=11)	GT3 SOF+RBV 24 wks (N=250)	Total (N=419)
Subjects in Safety Analysis Set	85	73	11	250	419
Subjects in Full Analysis Set	0	73	11	250	334
Study Treatment Status					
Completed Study Treatment	4 (4.7%)	73 (100.0%)	8 (72.7%)	246 (98.4%)	331 (79.0%)
Discontinued Study Treatment	81 (95.3%)	0	3 (27.3%)	4 (1.6%)	88 (21.0%)
Reason for Premature Discontinuation of Study Treatment					
Terminated by Sponsor	79 (92.9%)	0	0	0	79 (18.9%)
Subject Withdrew Consent	0	0	2 (18.2%)	2 (0.8%)	4 (1.0%)
Adverse Event	1 (1.2%)	0	1 (9.1%)	1 (0.4%)	3 (0.7%)
Lost to Follow-Up	1 (1.2%)	0	0	1 (0.4%)	2 (0.5%)

GT = genotype
Note: Percentages were calculated based on the number of subjects in the safety analysis set
Note: Safety analysis set includes subjects who were randomized and received at least 1 dose of study drug.
Note: Full analysis set includes subjects with genotype 2 or 3 HCV infection who were randomized and received at least 1 dose of SOF.

11.5.1.1.1. Major protocol violations/deviations

Information not provided in the synopsis; Table 27 provides details on premature termination.

11.5.1.1.2. Baseline data

General demographics: Median age 51 yrs (range: 19 to 74); 40.3% females; 93.8% White, and not of Hispanic or Latino ethnicity (83.3%). Mean BMI 25.8 kg/m^2 (range: 16.8 to 44.1).

HCV demographics: 78.3% genotype 3 HCV; mean baseline HCV RNA 6.4 $\log_{10}$ IU/mL; 32.5% with IL28B CC allele; 66.8% with baseline ALT values >1.5x ULN; 21.0% cirrhotic. Of the treatment-naive subjects, 87.9% IFN eligible. Of the treatment-experienced subjects, 13 (5.3%) IFN intolerant, 73 (29.8%) had prior nonresponse, and 159 (64.9%) had prior relapse/breakthrough.

Table 28: GS-US-334-0133: Baseline Demographics (Safety Analysis Set).

	GT 2/3 Placebo (N=85)	GT2 SOF+RBV 12 wks (N=73)	GT3 SOF+RBV 12 wks (N=11)	GT3 SOF+RBV 24 wks (N=250)	Total (N=419)
Age at Baseline (Years)					
Median	51	60	44	50	51
Min, Max	19, 72	28, 74	30, 59	19, 69	19, 74
Sex					
Male	49 (57.6%)	40 (54.8%)	6 (54.5%)	155 (62.0%)	250 (59.7%)
Female	36 (42.4%)	33 (45.2%)	5 (45.5%)	95 (38.0%)	169 (40.3%)
Race					
Black or African American	1 (1.2%)	5 (6.8%)	0	0	6 (1.4%)
White	81 (95.3%)	65 (89.0%)	11 (100.0%)	236 (94.4%)	393 (93.8%)
Asian	3 (3.5%)	1 (1.4%)	0	9 (3.6%)	13 (3.1%)
Not Permitted	0	2 (2.7%)	0	5 (2.0%)	7 (1.7%)
Ethnicity					
Hispanic or Latino	10 (11.8%)	6 (8.2%)	1 (9.1%)	36 (14.4%)	53 (12.6%)
Not Hispanic or Latino	71 (83.5%)	65 (89.0%)	10 (90.9%)	203 (81.2%)	349 (83.3%)
Not Permitted	4 (4.7%)	2 (2.7%)	0	11 (4.4%)	17 (4.1%)
Baseline Body Mass Index (kg/m^2)					
Median	25.3	25.5	23.4	24.9	25.1
Min, Max	18.3, 40.0	19.9, 35.0	19.6, 44.1	16.8, 41.1	16.8, 44.1
Baseline Body Mass Index Category					
$< 30\ kg/m^2$	66 (77.6%)	61 (83.6%)	7 (63.6%)	220 (88.0%)	354 (84.5%)
$\geq 30\ kg/m^2$	19 (22.4%)	12 (16.4%)	4 (36.4%)	30 (12.0%)	65 (15.5%)
HCV Genotype					
Genotype 2	18 (21.2%)	73 (100.0%)	0	0	91 (21.7%)
Genotype 3	67 (78.8%)	0	11 (100.0%)	250 (100.0%)	328 (78.3%)
Cirrhosis					
No	67 (78.8%)	63 (86.3%)	9 (81.8%)	192 (76.8%)	331 (79.0%)
Yes	18 (21.2%)	10 (13.7%)	2 (18.2%)	58 (23.2%)	88 (21.0%)
Prior HCV Treatment Experience					
Experienced	50 (58.8%)	41 (56.2%)	9 (81.8%)	145 (58.0%)	245 (58.5%)
Naive	35 (41.2%)	32 (43.8%)	2 (18.2%)	105 (42.0%)	174 (41.5%)
Prior HCV Treatment Experience And Interferon Classification					
Experienced	50 (58.8%)	41 (56.2%)	9 (81.8%)	145 (58.0%)	245 (58.5%)
IFN Intolerant	0	3 (7.3%)	0	10 (6.9%)	13 (5.3%)
Non-Response	18 (36.0%)	10 (24.4%)	4 (44.4%)	41 (28.3%)	73 (29.8%)
Relapse/Breakthrough	32 (64.0%)	28 (68.3%)	5 (55.6%)	94 (64.8%)	159 (64.9%)
Naive	35 (41.2%)	32 (43.8%)	2 (18.2%)	105 (42.0%)	174 (41.5%)
IFN-eligible	30 (85.7%)	27 (84.4%)	2 (100.0%)	94 (89.5%)	153 (87.9%)
IFN-ineligible	5 (14.3%)	5 (15.6%)	0	11 (10.5%)	21 (12.1%)
IL28B					
CC	22 (25.9%)	24 (32.9%)	4 (36.4%)	86 (34.4%)	136 (32.5%)
CT	49 (57.6%)	41 (56.2%)	4 (36.4%)	131 (52.4%)	225 (53.7%)
TT	14 (16.5%)	8 (11.0%)	3 (27.3%)	33 (13.2%)	58 (13.8%)
Baseline HCV RNA (log_{10} IU/mL)					
Median	6.7	6.7	6.2	6.5	6.6
Min, Max	4.6, 7.4	4.6, 7.6	5.1, 7.2	3.5, 7.6	3.5, 7.6
Baseline ALT Category					
≤ 1.5 x ULN	32 (37.6%)	39 (53.4%)	4 (36.4%)	64 (25.6%)	139 (33.2%)
> 1.5 x ULN	53 (62.4%)	34 (46.6%)	7 (63.6%)	186 (74.4%)	280 (66.8%)

GT = genotype
Note: Percentages in prior treatment response and IFN eligibility rows are out of experienced and naive subjects respectively.
Note: Baseline value is the last available value on or prior to first dose of study regimen.

11.5.1.1.1. Results for the primary efficacy outcome

Key findings (See Tables 29 and 30):

- SVR12 rate of 93.2% for CHC genotype 2, SOF+RBV 12 – these results are consistent with prior studies in genotype 2 with 12 weeks of SOF+RBV. No subjects in this group had on-treatment virologic failure. All 5 subjects (6.8%) not achieving SVR12 experienced virologic relapse at the posttreatment Wk 4 visit i.e. early. No genotype 2 HCV-infected subjects relapsed between SVR4 and SVR12
- SVR12 rates were very low i.e. 27.3% in the SOF+RBV 12 Week genotype 3 group but numbers of patients in this go were very small i.e. n=11; 6 subjects (54.5%) experienced virologic relapse and 2 subjects (18.2%) withdrew consent during treatment with their last HCV RNA <LLOQ
- 84.0% of genotype 3 CHC SOF+RBV for 24 weeks achieved an SVR12. The rate of relapse was lower in the SOF+RBV 24 Week genotype 3 group (13.7%) vs. other Phase 3 studies (i.e. FUSION) with SOF+RBV for 12 or 16 weeks in subjects with genotype 3 HCV infection (range 37.8–68.9%). One subject in the SOF+RBV 24 Week genotype 3 group had on-treatment

virologic failure. This subject rapidly suppressed HCV RNA by Wk 2, but had HCV RNA 1,290,000 IU/mL at Wk 24. Preliminary PK results for this subject show undetectable plasma levels of the primary metabolite for SOF, GS-331007, at the Wk 12 visit and all subsequent visits, indicating non-adherence to SOF. The lack of any decline in haemoglobin also suggested RBV nonadherence. In the SOF+RBV 24 Week genotype 3 group, 8 of those achieving SVR4 did not achieve SVR12: 5 due to relapse and 3 due to missing data. The relapse rate between SVR4 and SVR12 was comparable to the relapse rates seen in the SOF+RBV registrational Phase 3 studies.

Table 29: GS-US-334-0133: Proportion of subjects with SVR4 and SVR12 (Full Analysis Set).

	GT2 SOF+RBV 12 wks (N=73)	GT3 SOF+RBV 12 wks (N=11)	GT3 SOF+RBV 24 wks (N=250)
Number of Subjects Who Were < LLOQ at Their Last Observed On-Treatment HCV RNA Value	73	11	249
SVR4	68/73 (93.2%)	5/11 (45.5%)	218/250 (87.2%)
95% CI	84.7% to 97.7%	16.7% to 76.6%	82.4% to 91.1%
SVR12	68/73 (93.2%)	3/11 (27.3%)	210/250 (84.0%)
95% CI	84.7% to 97.7%	6.0% to 61.0%	78.9% to 88.3%

Note: The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

Table 30: GS-US-334-0133: Virologic outcomes (full analysis Set).

	GT2 SOF+RBV 12 wks (N=73)	GT3 SOF+RBV 12 wks (N=11)	GT3 SOF+RBV 24 wks (N=250)
SVR12	68/73 (93.2%)	3/11 (27.3%)	210/250 (84.0%)
Overall Virologic Failure	5/73 (6.8%)	6/11 (54.5%)	35/250 (14.0%)
Relapse	5/73 (6.8%)	6/11 (54.5%)	34/249 (13.7%)
Study Drug Completer	5/73 (6.8%)	5/8 (62.5%)	33/245 (13.5%)
Study Drug Non-Completer	0/0	1/3 (33.3%)	1/4 (25.0%)
On-Treatment Virologic Failure	0/73	0/11	1/250 (0.4%)
Other	0/73	2/11 (18.2%)	5/250 (2.0%)

GT = genotype

11.5.1.1.2. Results for other efficacy outcomes

Key findings:

1. In the SOF+RBV 12 Week genotype 2 group, high rates of SVR12 achieved in all subgroups; these data are consistent with that observed in genotype 2 HCV infection described in the first round review;
2. In the SOF+RBV 12 Week genotype 3 group (n=11), response rates in subgroups were generally low, consistent with the overall SVR12 rate in this small group of subjects;
3. In the SOF+RBV 24 Week **genotype 3 group**:
   a. 93.3% treatment-naive vs. 77.2% treatment-experienced subjects achieved SVR12
   b. Females had higher SVR rates than males
   c. Higher SVR in those with low baseline HCV RNA (<106 IU/mL) vs. ≥ 106 IU/mL. When comparing these data to those with 12 or 16 weeks of SOF+RBV in treatment-naive and treatment-experienced genotype 3 subjects (55.7% in P7977-1231 (FISSION) and 61.9% in GS-US-334-0108 (FUSION)), **SVR12 rates were higher following 24 weeks of treatment**

d. In treatment-naive subjects treated for 24 weeks, SVR12 rates 92.3% in cirrhotics and 93.5% in the non-cirrhotics

e. In treatment experienced cirrhotics, SVR12 rates were 60% vs. 85.0% in treatment-experienced non-cirrhotics.

Table 31: GS-US-334-0133: SVR by Selected subgroups (full analysis Set).

	GT2 SOF+RBV 12 wks (N=73)	GT3 SOF+RBV 12 wks (N=11)	GT3 SOF+RBV 24 wks (N=250)
Overall	68/73 (93.2%)	3/11 (27.3%)	210/250 (84.0%)
95% CI	84.7% to 97.7%	6.0% to 61.0%	78.9% to 88.3%
Sex			
Male	37/40 (92.5%)	1/6 (16.7%)	122/155 (78.7%)
95% CI	79.6% to 98.4%	0.4% to 64.1%	71.4% to 84.9%
Female	31/33 (93.9%)	2/5 (40.0%)	88/95 (92.6%)
95% CI	79.8% to 99.3%	5.3% to 85.3%	85.4% to 97.0%
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	13/16 (81.3%)	2/4 (50.0%)	69/72 (95.8%)
95% CI	54.4% to 96.0%	6.8% to 93.2%	88.3% to 99.1%
≥ 6 $\log_{10}$ IU/mL	55/57 (96.5%)	1/7 (14.3%)	141/178 (79.2%)
95% CI	87.9% to 99.6%	0.4% to 57.9%	72.5% to 84.9%
IL28B			
CC	24/24 (100.0%)	2/4 (50.0%)	75/86 (87.2%)
95% CI	85.8% to 100.0%	6.8% to 93.2%	78.3% to 93.4%
Non-CC	44/49 (89.8%)	1/7 (14.3%)	135/164 (82.3%)
95% CI	77.8% to 96.6%	0.4% to 57.9%	75.6% to 87.8%
Prior HCV Treatment Experience			
Naive	31/32 (96.9%)	0/2	98/105 (93.3%)
95% CI	83.8% to 99.9%	0.0% to 84.2%	86.7% to 97.3%
Experienced	37/41 (90.2%)	3/9 (33.3%)	112/145 (77.2%)
95% CI	76.9% to 97.3%	7.5% to 70.1%	69.5% to 83.8%
Prior HCV Treatment Experience and Cirrhosis Status			
Naive, Non-Cirrhotic	29/30 (96.7%)	0/2	86/92 (93.5%)
95% CI	82.8% to 99.9%	0.0% to 84.2%	86.3% to 97.6%
Naive, Cirrhotic	2/2 (100.0%)	0/0	12/13 (92.3%)
95% CI	15.8% to 100.0%		64.0% to 99.8%
Experienced, Non-Cirrhotic	30/33 (90.9%)	3/7 (42.9%)	85/100 (85.0%)
95% CI	75.7% to 98.1%	9.9% to 81.6%	76.5% to 91.4%
Experienced, Cirrhotic	7/8 (87.5%)	0/2	27/45 (60.0%)
95% CI	47.3% to 99.7%	0.0% to 84.2%	44.3% to 74.3%
Treatment Experience Classification			
IFN Intolerant	3/3 (100.0%)	0/0	10/10 (100.0%)
95% CI	29.2% to 100.0%		69.2% to 100.0%
Non-Response	9/10 (90.0%)	2/4 (50.0%)	30/41 (73.2%)
95% CI	55.5% to 99.7%	6.8% to 93.2%	57.1% to 85.8%
Relapse/Breakthrough	25/28 (89.3%)	1/5 (20.0%)	72/94 (76.6%)
95% CI	71.8% to 97.7%	0.5% to 71.6%	66.7% to 84.7%

GT = genotype
Note: The exact 95% CI for the proportion within treatment group and subgroup is based on the Clopper-Pearson method.

11.5.1.2. Study GS-US-334-0123 (PHOTON-1) – A Phase 3, open-label study to investigate the efficacy and safety of GS-7977 plus ribavirin in chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) co-infected subjects

11.5.1.2.1. Study design, objectives, locations and dates

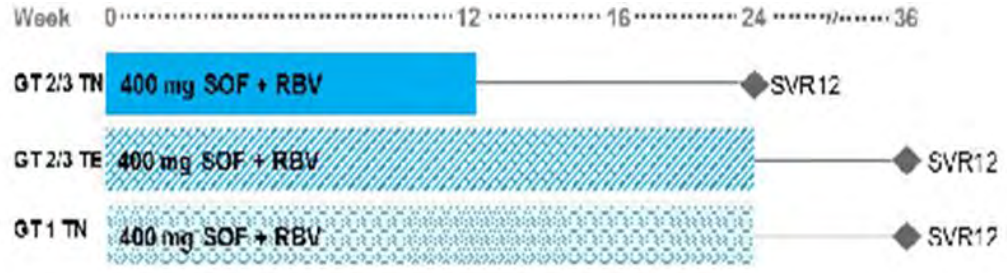
Design: A Phase 3, **Open-label** Study to Investigate the Efficacy and Safety of GS-7977 plus RBV in Chronic Genotype 1, 2 and 3 HCV and HIV Co-infected Subjects. The study population included treatment naive subjects (including IFN ineligible) and treatment experienced subjects who have failed prior therapy with PEG/RBV. Equal enrollment of genotype 2 and 3 as well as treatment naive and treatment experienced subjects will be targeted. Approximately 20% of the subjects enrolled will have evidence of compensated cirrhosis at screening.

Protocol amendments: Original: 06 June 2012; Amendment 1: 07 August 2012; Amendment 2: 20 September 2012.

Main changes: to increase sample size, expand nos of sites and extend treatment duration as follows 12 weeks for Genotype 2 and 3 HCV treatment naïve subjects and 24 weeks for Genotype 1.

HCV treatment naïve and Genotype 2/3 HCV treatment experienced subjects are shown in Figure 9. Atazanavir (ATV) is an allowable ARV Medication.

Figure 9: Study design on GS-US-334-0123 (PHOTON-1).



GT = genotype; TE = treatment experienced; TN = treatment naive

Objectives: SVR12 using SOF+RBV for 12 Wks for genotypes 1, 2, 3 – treatment naïve and experienced patients were only allowed for genotypes 2 and 3; safety (including HIV related i.e. HIV viral load changes and immunological markers i.e. Cd4+ T-cell counts) and tolerability; **Secondary objectives:** SVR4 and SVR24 rates; viral/resistance kinetics; **exploratory**: genetic markers for outcome; QoL; PK.

Sites: US (N=26); Puerto Rico (n=1);

Dates: All safety and efficacy data collected up to 30 September 2013 were included in this interim analysis.

11.5.1.2.2. Inclusion and exclusion criteria

Inclusion criteria: Age ≥ 18 years with chronic HCV and HIV-1 co-infection; HCV RNA ≥ 1 x 10^4 IU/mL at Screening; HCV Genotype 1 (**treatment naïve only**), 2 or 3; HIV-1 infection confirmed with a positive ELISA and Western-blot at Screening (if necessary); Adequate medical records to be categorised based on IFN eligibility or prior treatment with PEG/RBV into one of the following categories: Treatment Naïve - IFN- eligible; Treatment Naïve - IFN-ineligible; Treatment Experienced - IFN Intolerant (Genotype 2/3 only); Treatment Experienced - Non-Response (Genotype 2/3 only); Treatment Experienced; Relapse/Breakthrough (Genotype 2/3 only); Ability to determine the presence/absence of compensated cirrhosis -up to 20% of study subjects may be cirrhotic; HIV ARV criteria of one of the following: ARV untreated for ≥8 weeks preceding the Screening visit with a CD4+ T-cell count >500 cells/mm^3 [up to 10% of study subjects may be ARV untreated], **or** on a stable, protocol-approved, ARV for >8 weeks prior to Screening with a CD4 T-cell count >200 cells/mm^3 and undetectable plasma HIV-1 RNA level by local assay for ≥ 8 weeks preceding the Screening visit. HIV-1 viral load results should be measured within 1 year of the Screening visit. Screening HIV RNA must be < 50 cp/mL as measured by the COBAS AMPLIPREP/COBAS TaqMan 2.0 HCV RNA assay; HIV antiretroviral medications allowed in this study include the following and should be administered per the prescribing information in the package insert: emtricitabine/tenofovir (Truvada) plus: atazanavir/ritonavir; or darunavir/ritonavir; or efavirenz; or raltegravir; or rilpivirine; BMI ≥ 18 kg/m^2;Subjects must have the following laboratory parameters at Screening: ALT ≤ 10 × ULN; AST ≤ 10 × ULN; Haemoglobin ≥ 12 g/dL for male, ≥ 11 g/dL for female subjects; INR ≤1.5 x ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR; Albumin ≥ 3 g/dL; Direct bilirubin ≤ 1.5 × ULN (for subjects receiving an atazanavir/ritonavir (boosted) regimen, a direct bilirubin > 1.5 x ULN will be allowed if <25% of the total bilirubin; HbA1c ≤ 10%; creatinine clearance (CLcr) ≥ 60 mL/min as determined by Cockroft-Gault; Agree to use two forms of highly effective contraception for the duration of the study and for 6 months (7 months for males) after the last dose of study medication. Females of childbearing potential must have a negative pregnancy test at Screening and Baseline.

Exclusion criteria: Non-genotype 1/2/3 or mixed genotype at Screening; **Genotype 1 subjects who have received prior HCV treatment;** Poor control with ARV therapy requiring a modification of therapy within 1 month of GS-7977 dosing; Prior exposure to a direct-acting

antiviral targeting the HCV NS5B polymerase. Subjects participating in the Drug Interaction (part A) of P7977-1910 protocol are an exception to this criterion**;** Evidence or history of hepatic decompensation; Haematologic or biochemical parameters at screening outside the protocol-specified requirements; Screening ECG with clinically significant abnormalities as determined by the investigator; Chronic hepatitis B virus (HBV) infection; Hepatocellular carcinoma or other malignancy (with exception;of certain resolved skin cancers); Chronic use of systemic immunosuppressive agents or immunomodulatory agents; Active or recent history (≤ 1 year) of drug or alcohol abuse; A new AIDS-defining condition diagnosed within 30 days prior to screening; Active, serious infection (other than HIV-1 or HCV) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Baseline History or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study, or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.

11.5.1.2.3. Study treatments

SOF 400mg OD+ wt-based RBV dose given BID for 12 or 24 weeks wks; 24 wks post treatment FU.

11.5.1.3. Efficacy variables and outcomes

Efficacy was evaluated by measuring serum HCV RNA at Day 1 (baseline), at the Week 1, 2, 4, 6, 8, 10, and 12 visits; and at the posttreatment Week 4, 12, and 24 visits for all subjects. In addition, efficacy was evaluated by measuring serum HCV RNA at the Week 16, 20, and 24 visits for subjects receiving 24 weeks of SOF+RBV treatment (SOF+RBV 24 Week TE GT2/3 and SOF+RBV 24 Week GT 1 groups). The COBAS TaqMan HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study, with a LLOQ of < 25 IU/mL.

Primary efficacy outcome = proportion with SVR12 defined as HCV RNA < LLOQ at 12 weeks after study drug cessation.

Other efficacy outcomes included:

- proportion with SVR4 i.e. HCV RNA < LLOQ (i.e. 25IU/mL) at 4 wks after study drug cessation
- Viral failure – as defined before
- Viral relapse (i.e. HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at EOT, confirmed with 2 consecutive values or last available posttreatment m'ment)
- Safety assessments included AEs and concomitant medications, clinical laboratory results
- (including ALT normalisation), vital signs and physical examinations
- HCV viral kinetics and viral resistance; changes in HIV viral load and CD4+ T-cells; QoL.

11.5.1.3.1. Randomisation and blinding methods

Open label, non-randomised study. An Interactive Web Response System was employed to manage enrollment and study drug assignment.

11.5.1.3.2. Analysis populations

FAS and SAS as defined previously.

11.5.1.3.3. Sample size

Planned n=230 i.e. 115 treatment-naïve (TN) and treatment-experienced (TE) subjects CHC genotype 2 or 3 (1:1 ratio for HCV treatment experience and 1:1 ratio for HCV genotype) and 115 treatment-naive subjects with CHC genotype 1 infection.

- SOF+RBV 12 Week TN GT2/3 group: TN with genotype 2 or 3 received SOF 400 mg administered QD + RBV total daily dose 1000 or 1200 mg as a divided daily dose for 12 weeks (Gp 1);
- SOF+RBV 24 Week TE GT2/3 group: TE with genotype 2 or 3 received SOF 400 mg administered once daily + RBV total daily dose of 1000 or 1200 mg as a divided daily dose for 24 weeks (Gp 2);
- SOF+RBV 24 Week TN GT 1 group: TN with CHC Genotype 1 received SOF 400 mg administered QD + RBV total daily dose of 1000 or 1200 mg administered in a divided daily dose for 24 weeks (Gp 3).

11.5.1.3.4. Statistical methods

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

11.5.1.3.5. Participant flow

See Table 32.

Table 32: GS-US-334-0123: Subject Disposition (Enrolled Subjects).

	Group 1 SOF+RBV 12 Weeks GT 2/3 TN	Group 2 SOF+RBV 24 Weeks GT 2/3 TE	Group 3 SOF+RBV 24 Weeks GT 1 TN	Groups 2 and 3 SOF+RBV 24 Weeks All Subjects	Overall
Subjects in Safety Analysis Set	68	41	114	155	223
Subjects in Full Analysis Set	68	28	114	142	210
Study Treatment Status					
On Study Treatment	0	0	0	0	0
Completed Study Treatment	62 (91.2%)	40 (97.6%)	103 (90.4%)	143 (92.3%)	205 (91.9%)
Discontinued Study Treatment	6 (8.8%)	1 (2.4%)	11 (9.6%)	12 (7.7%)	18 (8.1%)
Reason for Premature Discontinuation of Study Treatment					
Adverse Event	3 (4.4%)	1 (2.4%)	3 (2.6%)	4 (2.6%)	7 (3.1%)
Protocol Violation	0	0	4 (3.5%)	4 (2.6%)	4 (1.8%)
Subject Withdrew Consent	1 (1.5%)	0	2 (1.8%)	2 (1.3%)	3 (1.3%)
Investigator Decision	1 (1.5%)	0	1 (0.9%)	1 (0.6%)	2 (0.9%)
Efficacy Failure	0	0	1 (0.9%)	1 (0.6%)	1 (0.4%)
Lost to Follow-Up	1 (1.5%)	0	0	0	1 (0.4%)

GT= genotype; TE = treatment experienced; TN = treatment naive
Note: Percentages were calculated based on the number of subjects in the safety analysis set.

11.5.1.3.6. Baseline data

As per Table 33, median age 51 yrs (range, 24 to 71 yrs), 83% male, 68.6% White, and non-Hispanic/Latino (75.8%). Black or African American patients with HCV infection have a higher percentage of genotype 1, which is reflected in the higher proportion of black or African American subjects in the SOF+RBV 24 Week GT 1 group (32.5%). Mean baseline BMI 27.3 kg/m^2, 77.1% had BMI <30 kg/m^2. The majority i.e. 77.6% had a baseline HCV RNA ≥6 log_{10} IU/mL, and 9.9% were cirrhotic. The majority of subjects had an IL28B non-CC genotype (66.2%). Baseline mean CD4+ T-cell count 625 cells/mm^3; **95.1% on ARV treatment at enrolment**. In the SOF+RBV 12 Week TN GT2/3 and SOF+RBV 24 Week TN GT 1 groups, the majority of subjects were interferon eligible (72.1% and 74.6%, respectively).

Table 33: GS-US-334-0123: Demographics and baseline characteristics (SAS).

	Group 1 SOF+RBV 12 Weeks GT 2/3 TN (N = 68)	Group 2 SOF+RBV 24 Weeks GT 2/3 TE (N = 41)	Group 3 SOF+RBV 24 Weeks GT 1 TN (N = 114)	Groups 2 and 3 SOF+RBV 24 Weeks All Subjects (N = 155)	Overall (N = 223)
Age at Baseline (Years)					
Median	50	54	49	51	51
Min, Max	24, 71	34, 68	25, 70	25, 70	24, 71
Sex					
Male	55 (80.9%)	37 (90.2%)	93 (81.6%)	130 (83.9%)	185 (83.0%)
Female	13 (19.1%)	4 (9.8%)	21 (18.4%)	25 (16.1%)	38 (17.0%)
Race					
Black or African American	8 (11.8%)	7 (17.1%)	37 (32.5%)	44 (28.4%)	52 (23.3%)
White	52 (76.5%)	32 (78.0%)	69 (60.5%)	101 (65.2%)	153 (68.6%)
Asian	1 (1.5%)	1 (2.4%)	1 (0.9%)	2 (1.3%)	3 (1.3%)
American Indian/ Alaska Native/ First Nations	0	1 (2.4%)	0	1 (0.6%)	1 (0.4%)
Hawaiian or Other Pacific Islander	1 (1.5%)	0	1 (0.9%)	1 (0.6%)	2 (0.9%)
Other	6 (8.8%)	0	6 (5.3%)	6 (3.9%)	12 (5.4%)
Ethnicity					
Hispanic or Latino	19 (27.9%)	10 (24.4%)	25 (21.9%)	35 (22.6%)	54 (24.2%)
Not Hispanic or Latino	49 (72.1%)	31 (75.6%)	89 (78.1%)	120 (77.4%)	169 (75.8%)
Baseline BMI (kg/m^2)					
Median	27.3	26.0	26.2	26.2	26.4
Min, Max	19.8, 43.5	18.8, 39.7	18.5, 46.2	18.5, 46.2	18.5, 46.2
Baseline BMI					
< 30 kg/m^2	53 (77.9%)	31 (75.6%)	88 (77.2%)	119 (76.8%)	172 (77.1%)
≥ 30 kg/m^2	15 (22.1%)	10 (24.4%)	26 (22.8%)	36 (23.2%)	51 (22.9%)
HCV Genotype					
1	0	0	114 (110.0%)	114 (73.5%)	114 (51.1%)
2	26 (38.2%)	24 (58.5%)	0	24 (15.5%)	50 (22.4%)
3	42 (61.8%)	17 (41.5%)	0	17 (11.0%)	59 (26.5%)
Cirrhosis					
No	61 (89.7%)	31 (75.6%)	109 (95.6%)	140 (90.3%)	201 (90.1%)
Yes	7 (10.3%)	10 (24.4%)	5 (4.4%)	15 (9.7%)	22 (9.9%)
IL28B Genotype					
CC	25 (36.8%)	20 (48.8%)	30 (26.5%)	50 (32.5%)	75 (33.8%)
CT	37 (54.4%)	17 (41.5%)	57 (50.4%)	74 (48.1%)	111 (50.0%)
TT	6 (8.8%)	4 (9.8%)	26 (23.0%)	30 (19.5%)	36 (16.2%)
Missing	0	0	1 (0.9%)	1 (0.6%)	1 (0.4%)
Baseline HCV RNA (log_{10} IU/mL)					
Median	6.4	6.6	6.7	6.7	6.6
Min, Max	5.0, 7.4	4.5, 7.5	1.4, 7.7	1.4, 7.7	1.4, 7.7
Baseline HCV RNA					
< 6 log_{10} IU/mL	21 (30.9%)	7 (17.1%)	22 (19.3%)	29 (18.7%)	50 (22.4%)
≥ 6 log_{10} IU/mL	47 (69.1%)	34 (82.9%)	92 (80.7%)	126 (81.3%)	173 (77.6%)
Interferon Classification					
Eligible	49 (72.1%)	NA	85 (74.6%)	NA	NA
Ineligible	19 (27.9%)	NA	29 (25.4%)	NA	NA
On ARV Treatment at Enrollment					
No	7 (10.3%)	2 (4.9%)	2 (1.8%)	4 (2.6%)	11 (4.9%)
Yes	61 (89.7%)	39 (95.1%)	112 (98.2%)	151 (97.4%)	212 (95.1%)
Tenofovir/Emtricitabine PLUS					
Efavirenz	20 (32.8%)	16 (41.0%)	42 (37.5%)	58 (38.4%)	78 (36.8%)
Atazanavir/ritonavir	7 (11.5%)	8 (20.5%)	24 (21.4%)	32 (21.2%)	39 (18.4%)
Darunavir/ritonavir	17 (27.9%)	2 (5.1%)	15 (13.4%)	17 (11.3%)	34 (16.0%)
Raltegravir	8 (13.1%)	7 (17.9%)	21 (18.8%)	28 (18.5%)	36 (17.0%)
Other	9 (14.8%)	6 (15.4%)	10 (8.9%)	16 (10.6%)	25 (11.8%)

GT= genotype; TE = treatment experienced; TN = treatment naive; NA = not applicable
Note: Baseline value was the last available value on or prior to first dose of study regimen.
Note: Three treatment-experienced subjects enrolled as HCV genotype 2b using the LiPA 2.0 assay were considered HCV genotype 1a using NS5B sequencing were included as HCV genotype 2 for this analysis.

11.5.1.3.7. Results for the primary efficacy outcome

The results of a second interim analysis were provided for this round 2 application, with preliminary SVR12 efficacy data available for 210 subjects.

Key findings (Tables 34-35):

1. For subjects in the **SOF+RBV 12 Week TN GT2/3 group**, the SVR12 rate was 75.0% i.e. consistent with that in **GS-US-334-0107 [POSITRON] which was conducted in HIV -ve patients.** In total, 17 subjects did not achieve SVR12 - 13 had virologic failure, 4 were not assessable for SVR12 (2 subjects LTFUP, 1 subject died, 1 subject withdrew consent before posttreatment Wk 12).

a. Among the 26 **treatment-naive genotype 2** HCV-infected subjects, the SVR12 rate was 88.5% with no subjects who relapsed; 1 subject had on-treatment virologic failure likely due to study drug nonadherence

b. Among the 42 **treatment-naive genotype 3** HCV-infected subjects, the SVR12 rate was 66.7% with no on-treatment virologic failures; 12 subjects relapsed. Two of the 12 subjects who relapsed achieved SVR4, but did not achieve SVR12

2. For subjects in the **SOF+RBV 24 Week TE GT2/3 group**, the SVR12 rate was 92.9%, and higher than rates seen in **GS-US-334-0108 (FUSION)** (assessing 12 and 16 wks of treatment). Among the 15 treatment-experienced genotype 2 HCV-infected subjects, the SVR12 was 93.3%. One subject did not achieve SVR12; this subject achieved SVR4, but did not achieve SVR12 and was noted to have genotype 2b HCV infection assessed by LiPA 2.0 assay, but genotype 1a HCV infection per NS5B sequencing. Among the 13 treatment-experienced genotype 3 HCV-infected subjects, the SVR12 rate was 92.3%. One subject did not achieve SVR12 due to virologic relapse at the post-treatment Wk 4 visit.

3. For subjects in the **SOF+RBV 24 Wk GT 1 group**, SVR12 was 76.3%. One subject with genotype 1 HCV infection had on-treatment virologic failure – likely not adherent to RBV and SOF. Twenty-seven subjects (23.7%) did not achieve SVR12, of whom 26 had virologic failure and 1 was not assessable for SVR12 (subject withdrew consent. Twenty-two subjects relapsed before or at posttreatment Week 4; 5 subjects achieved SVR4, but did not achieve SVR12.

Table 34: GS-US-334-0123: Proportion of subjects with SVR 4 and SVR12 (FAS).

	Group 1	Group 2	Group 3
	SOF+RBV 12 Weeks GT2/3 TN (N = 68)	SOF+RBV 24 Weeks GT 2/3 TE (N = 28)	SOF+RBV 24 Weeks GT1 TN (N = 114)
SVR4	53/68 (77.9%)	27/28 (96.4%)	92/114 (80.7%)
95% CI	66.2% to 87.1%	81.7% to 99.9%	72.3% to 87.5%
SVR12	51/68 (75.0%)	26/28 (92.9%)	87/114 (76.3%)
95% CI	63.0% to 84.7%	76.5% to 99.1%	67.4% to 83.8%

GT= genotype; TE = treatment experienced; TN = treatment naive
Note: The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

Table 35: GS-US-334-0123: Virologic Outcomes (FAS).

	Group 1	Group 2	Group 3:
	SOF+RBV 12 Weeks GT2/3 TN (N = 68)	SOF+RBV 24 Weeks GT 2/3 TE (N = 28)	SOF+RBV 24 Weeks GT1 TN (N = 114)
SVR12	51/68 (75.0%)	26/28 (92.9%)	87/114 (76.3%)
Overall Virologic Failure	13/68 (19.1%)	2/28 (7.1%)	26/114 (22.8%)
Relapse	12/67 (17.9%)	2/28 (7.1%)	25/113 (22.1%)
Study Drug Completer	11/61 (18.0%)	1/27 (3.7%)	19/103 (18.4%)
Study Drug Non-Completer	1/6 (16.7%)	1/1 (100.0%)	6/10 (60.0%)
On-Treatment Virologic Failure	1/68 (1.5%)	0/28	1/114 (0.9%)
Other	4/68 (5.9%)	0/28	1/114 (0.9%)

GT= genotype; TE = treatment experienced; TN = treatment naive

11.5.1.3.8. Results for other efficacy outcomes

Key findings from subgroup analysis:

1. For the **SOF+RBV 12 Week TN GT2/3 group**, similar SVR12 rates achieved in most subgroups. Subjects with genotype 2 had a higher SVR12 vs. those with genotype 3 i.e. 88.5% vs. 66.7% respectively. SVR12 similar in subjects +/- cirrhosis i.e.71.4% and 75.4%, respectively. Numbers are very small (Table 36) – 5/7 cirrhotics achieved SVR12.

2. For the **SOF+RBV 24 Week TE GT2/3 group**, high SVR12 rates (≥ 80%) were achieved in all subgroups. Subjects with genotype 2 HCV infection had an SVR12 rate similar to subjects with genotype 3 HCV infection (93.3% and 92.3%, respectively). Subjects without cirrhosis had a higher SVR12 rate than subjects with cirrhosis (95.2% vs. 85.7%). Six of the 7 cirrhotics achieved SVR12. The 2 cirrhotics with genotype 2 HCV infection both achieved SVR12. The other 5 cirrhotic subjects had genotype 3 HCV infection, 4 achieved SVR12 (80.0%).
3. For the **SOF+RBV 24 Week GT 1 group**, similar SVR12 rates were achieved in most subgroups. Subjects without cirrhosis had a higher SVR12 rate than subjects with cirrhosis (77.1% vs. 60.0%). Subjects with genotype 1a HCV infection had higher SVR12 rate (82.2%) vs. genotype 1b (54.2%).
4. Overall, subjects with genotype 2, both treatment-naive and treatment-experienced, had similar SVR12 rates whether treated for 12 wks and 24 wks (88.5% and 93.3%, respectively). Treatment experienced subjects with genotype 3 treated with SOF+RBV for 24 weeks had a higher SVR12 vs. treatment naive genotype 3 treated with SOF+RBV for 12 weeks (92.3% vs. 66.7%). No notable differences in SVR12 observed for subjects who were interferon eligible and ineligible in the SOF+RBV 12 Week TN GT2/3 and SOF+RBV 24 Week TN GT 1 groups. **The SVR12 rates for cirrhotic subjects were lower than for noncirrhotic subjects across all treatment groups**.

Table 36: PHOTON-1: SVR12 by HCV Genotype (2/3), prior treatment history, cirrhosis status (FAS).

	HCV Genotype 2		HCV Genotype 3	
	SOF+RBV 12 Weeks TN (N = 26)	SOF+RBV 24 Weeks TE (N = 15)	SOF+RBV 12 Weeks TN (N = 42)	SOF+RBV 24 Weeks TE (N =13)
Overall	23/26 (88.5%)	14/15 (93.3%)	28/42 (66.7%)	12/13 (92.3%)
No cirrhosis	22/25 (88.0%)	12/13 (92.3%)	24/36 (66.7%)	8/8 (100%)
Cirrhosis	1/1 (100%)	2/2 (100%)	4/6 (66.7%)	4/5 (80.0%)

TE = treatment experienced; TN = treatment naive

Table 37: GS-US-334-0123: SVR12 by selected subgroups (FAS).

	Group 1 SOF+RBV 12 Weeks GT2/3 TN (N = 68)	Group 2 SOF+RBV 24 Weeks GT 2/3 TE (N = 28)	Group 3: SOF+RBV 24 Weeks GT1 TN (N = 114)
Overall	51/68 (75.0%)	26/28 (92.9%)	87/114 (76.3%)
95% CI	63.0% to 84.7%	76.5% to 99.1%	67.4% to 83.8%
Sex			
Male	42/55 (76.4%)	22/24 (91.7%)	69/93 (74.2%)
95% CI	63.0% to 86.8%	73.0% to 99.0%	64.1% to 82.7%
Female	9/13 (69.2%)	4/4 (100.0%)	18/21 (85.7%)
95% CI	38.6% to 90.9%	39.8% to 100.0%	63.7% to 97.0%
Cirrhosis			
No	46/61 (75.4%)	20/21 (95.2%)	84/109 (77.1%)
95% CI	62.7% to 85.5%	76.2% to 99.9%	68.0% to 84.6%
Yes	5/7 (71.4%)	6/7 (85.7%)	3/5 (60.0%)
95% CI	29.0% to 96.3%	42.1% to 99.6%	14.7% to 94.7%
HCV Genotype			
Genotype 1a	NA	NA	74/90 (82.2%)
95% CI	NA	NA	72.7% to 89.5%
Genotype 1b	NA	NA	13/24 (54.2%)
95% CI	NA	NA	32.8% to 74.4%
Genotype 2	23/26 (88.5%)	14/15 (93.3%)	NA
95% CI	69.8% to 97.6%	68.1% to 99.8%	NA
Genotype 3	28/42 (66.7%)	12/13 (92.3%)	NA
95% CI	50.5% to 80.4%	64.0% to 99.8%	NA
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	16/21 (76.2%)	4/4 (100.0%)	17/22 (77.3%)
95% CI	52.8% to 91.8%	39.8% to 100.0%	54.6% to 92.2%
≥ 6 $\log_{10}$ IU/mL	35/47 (74.5%)	22/24 (91.7%)	70/92 (76.1%)
95% CI	59.7% to 86.1%	73.0% to 99.0%	66.1% to 84.4%
IL28B Genotype			
CC	17/25 (68.0%)	11/12 (91.7%)	24/30 (80.0%)
95% CI	46.5% to 85.1%	61.5% to 99.8%	61.4% to 92.3%
Non-CC	34/43 (79.1%)	15/16 (93.8%)	62/83 (74.7%)
95% CI	64.0% to 90.0%	69.8% to 99.8%	64.0% to 83.6%
Prior Experience Classification			
INF-Intolerant	NA	4/5 (80.0%)	NA
95% CI	NA	28.4% to 99.5%	NA
Non-response	NA	6/6 (100.0%)	NA
95% CI	NA	54.1% to 100.0%	NA
Relapse/breakthrough	NA	16/17 (94.1%)	NA
95% CI	NA	71.3% to 99.9%	NA

GT= genotype; TE = treatment experienced; TN = treatment naive; ARV = antiretroviral; NA = not applicable
Note: The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

11.5.2. Evaluator's conclusions on clinical efficacy for SOFOSBUVIR for use in combination with other agents for the treatment of CHC virus infection in adults

- This section should be read in conjunction with the first round review. The additional data provided from the interim analyses of VALENCE and PHOTON-1 confirm the findings of the pivotal registration studies and provide robust data in the HIV-HCV setting i.e. high SVR12 rates for **genotype 2 CHC** (treatment-naïve and experienced) in the HCV mono-infected **and** HIV-HCV co-infected setting. SVR12 responses with 12 weeks of SOF+RBV were high in mono and co-infected patients i.e. there did not appear to be significant additional SVR12 gain by extending SOF+RBV treatment to 24 weeks even in the HIV-HCV co-infected patients. Moreover, even Genotype 2 patients with cirrhosis (note smallish numbers) – most of whom were treatment-experienced - achieved high rates of SVR12. The numbers of cirrhotics with genotype 2 who are HIV-HCV co-infected is so small (n=3), it is not possible to comment
- When it comes to Genotype 3, there is a **clear benefit** in the HCV mono and HIV-HCV co-infection setting to extending the treatment of **genotype 3** to 24 weeks of SOF+RBV. SVR12 rates were low (27.3%) in the small number of HCV mono-infected subjects with genotype 3 infection who received SOF+RBV for 12 weeks, and these results are consistent with the results from the Phase 3 program. Extending treatment duration to 24 weeks in genotype 3 HCV-infected subjects substantially improved the SVR12 response rate i.e. to 84.0% - and

this represents an upward shift in the SVR12 achieved even with 16 weeks of treatment i.e. in GS-US-334-0108 (FUSION)), GT- 3 SVR12 was 61.9% vs. 29.7% respectively with 16 vs. 12 weeks of SOF+RBV treatment

- The second interim results of PHOTON-1 do not add any further information regarding the efficacy in regards to SVR12 in patients not on antiretroviral therapy as so few people enrolled in the study were ARV naive. This means the SVR12 rate data cannot be directly extrapolated to HIV-HCV co-infected patient who are ARV naïve undergoing treatment with SOF+RBV
- There is no data in HIV-HCV co-infected **treatment-experienced** patients with genotype 1 as PHOTON-1 limited the enrollment of genotype 1 treatment-naïve patients. However, 76.3% treatment-naive subjects achieved SVR12 following SOF+RBV treatment for 24 weeks and these rates are similar or higher than those achieved with current standard of care i.e. a protease inhibitor + PEG+RBV for 24 to 48 weeks (79%, telaprevir and 63-66%, boceprevir). Importantly, these studies included similar percentages of subject with cirrhosis as PHOTON-1. There appeared to be discrepant treatment responses between genotype 1a infection (82.2%) and genotype 1b (54.2%) - however the small numbers of patients with genotype 1b should be taken into consideration so as to avoid overcalling these data. Further specific data on the impact of Genotype 1 subtype should be gathered for all DAA development programmes. See below for the safety summary of extending treatment for 24 weeks for Genotype 3.

11.6. Clinical safety

11.6.1. Studies providing evaluable safety data

Reference the first round evaluation as safety methodology was identical.

11.6.2. Pivotal studies that assessed safety as a primary outcome

Studies GS-US-334-0133 (VALENCE) and GS-US-334-0123 (PHOTON-1) were pivotal studies that assessed safety as a co-primary outcome.

11.6.3. Patient exposure

GS-US-334-0133 (VALENCE): Following protocol Amendment 2, subjects with genotype 2 HCV infection continued to receive 12 weeks of SOF+RBV treatment as planned. Subjects with genotype 3 HCV infection who had completed 12 weeks of treatment or prematurely discontinued treatment continued with follow-up visits in their assigned group (SOF+RBV 12 Week), while those who had not completed had their treatment extended to 24 weeks (SOF+RBV 24 Week). Treatment was discontinued for Placebo group subjects. These subjects completed early-termination and 4-week follow-up visits and became eligible for screening for an open-label retreatment study (GS-US-334-0109). Eighty-five Placebo group subjects were treated with SOF placebo once daily + RBV placebo BID for a median exposure of 8.0 weeks; GS-US-334-0123 (PHOTON-1): Maximum duration of exposure for patients in group 2 (n=114 with TN genotype 1) and group 3 (n=41 with genotype 2/3) was 24 weeks of SOF+RBV (n=155 subjects). Sixty-eight subjects in group 1 (genotype 2/3), received a maximum of 12 weeks of SOF+RBV.

11.6.4. Adverse events

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

GS-US-334-0133 (VALENCE): Clinical Adverse Events. Table 38 summarises overall safety data. As shown, most subjects in each of the treatment groups experienced ≥1 AE, with incidence of AEs higher in the active treatment groups (85.7-91.2%) compared to placebo (71.8%). Grade 3 or 4 AEs and SAEs occurred with similar frequency across all treatment groups. There were low rates of AEs leading to treatment discontinuation and no deaths occurred in this study. The AEs

and rates of AEs reported for subjects who received SOF+RBV for 12 or 24 weeks in this study were similar to those observed in subjects who received SOF+RBV for 12 or 16 weeks in Phase 3 studies. Extending treatment duration from 12 to 24 weeks did not substantially alter the safety profile of SOF+RBV.

Table 38: GS-US-334-0133: brief summary of AE (SAS).

Number (%) of Subjects Experiencing	GT 2/3 Placebo (N = 85)	GT 2/3 SOF+RBV 12 Weeks (N = 84)	GT 3 SOF+RBV 24 Weeks (N = 250)
Any AE	61 (71.8%)	72 (85.7%)	228 (91.2%)
Grade 3 or 4 AE	4 (4.7%)	3 (3.6%)	17 (6.8%)
SAE	2 (2.4%)	0	10 (4.0%)
AE Leading to Discontinuation	1 (1.2%)	1 (1.2%)	1 (0.4%)
Death	0	0	0

Table 39 presents the most frequently reported AEs with these occurring more commonly with active treatment vs. placebo, exceptions to this were AEs of headache, fatigue, nasopharyngitis reported with similar frequencies in placebo and active treatment groups. The incidence of pruritus, asthenia, insomnia, dry skin, dyspnoea, and cough were similar in the SOF+RBV 12 Week and SOF+RBV 24 Week treatment groups. Diarrhoea and irritability were ~twice as frequent in the SOF+RBV 24 week treatment group compared to the SOF+RBV 12 Week treatment group. Nausea was more common with SOF+RBV for 12 weeks (31.0%) vs. placebo (10.6%) vs.SOF+RBV 24 weeks (12.8%).

Table 39: GS-US-334-0133: AE reported in ≥10% of subjects in any treatment Gp (SAS).

Preferred Term	GT 2/3 Placebo (N = 85)	GT 2/3 SOF+RBV 12 Weeks (N = 84)	GT 3 SOF+RBV 24 Weeks (N = 250)
Number (%) of Subjects who Experienced Any Treatment-Emergent AE	61 (71.8%)	72 (85.7%)	228 (91.2%)
Headache	23 (27.1%)	24 (28.6%)	74 (29.6%)
Fatigue	16 (18.8%)	19 (22.6%)	75 (30.0%)
Pruritus	8 (9.4%)	20 (23.8%)	67 (26.8%)
Asthenia	5 (5.9%)	21 (25.0%)	53 (21.2%)
Nausea	9 (10.6%)	26 (31.0%)	32 (12.8%)
Insomnia	2 (2.4%)	9 (10.7%)	41 (16.4%)
Nasopharyngitis	9 (10.6%)	4 (4.8%)	36 (14.4%)
Dry Skin	5 (5.9%)	7 (8.3%)	31 (12.4%)
Dyspnoea	1 (1.2%)	12 (14.3%)	27 (10.8%)
Cough	4 (4.7%)	8 (9.5%)	26 (10.4%)
Diarrhoea	4 (4.7%)	4 (4.8%)	30 (12.0%)
Irritability	3 (3.5%)	4 (4.8%)	26 (10.4%)

Most AEs were Gde 1 or Gde 2 in severity. Anaemia and fatigue were the only Gde 3 events occurring in >1 subject in the active treatment groups i.e. in 1.3% and 0.9% subjects, respectively. One Gde 4 AE (also an SAE) was reported: a suicide attempt by a subject in the SOF+RBV 24 Week group on Day 144 of treatment. This subject attempted suicide by taking 40 mg of lorazepam). His prior psychiatric history was significant for a history of polysubstance abuse. Two subjects (2.4%) in the Placebo group, no subjects in the SOF+RBV 12 Week group, and 10 subjects (4.0%) in the SOF+RBV 24 Week group had at least 1 SAE. No SAE was reported by more than 1 subject in any treatment group. Across treatment groups, 0.72% discontinued study drug due to AEs.

11.6.4.1.1. Laboratory abnormalities

Most Gde 1 or Gde 2 in severity. Gde 3 laboratory abnormalities were more common with SOF+RBV treatment for 12 or 24 wks (19.0% and 17.2%, respectively) vs. placebo (8.2%). The most frequent Gde 3 laboratory abnormality was decreased haemoglobin (defined as 7.0 to <9.0 g/dL or ≥4.5 g/dL decrease from baseline), which occurred in 1.2% in the Placebo group, 8.3% in the SOF+RBV 12 Week group, and 11.2% in the SOF+RBV 24 Week group. Despite the slightly

higher rate of Grade 3 haemoglobin reduction in the SOF+RBV 24 Week group vs. SOF+RBV 12 Week group, mean haemoglobin change from baseline at EOT was equivalent i.e. -2.1 g/dL for the SOF+RBV 24 Week group and -2.3 g/dL for the SOF+RBV 12 Week group.

Extending SOF+RBV treatment from 12 to 24 weeks did not increase graded laboratory abnormalities (Table 40). Gde 4 laboratory abnormalities occurred in 0.9% receiving SOF+RBV. One subject experienced a Gde 4 ALT elevation and concomitant Gde 3 AST elevation at the posttreatment Week 4 visit in the setting of virologic relapse. Two subjects (0.8%) in the SOF+RBV 24 Week group experienced Gde 4 lipase elevations, one at Week 6 and one at Week 16 of treatment. Both subjects had elevated lipase values at baseline, and the Gde 4 elevations was asymptomatic; with both subjects contrinuing uninterrupted treatment per protocol.

Table 40: GS-US-334-0133: Gde 3 & 4 lab abnormalities in >1 subject in any treatment Gp (SAS).

Laboratory Parameter	GT 2/3 Placebo (N = 85)	GT 2/3 SOF+RBV 12 Weeks (N = 84)	GT 3 SOF+RBV 24 Weeks (N = 250)
Maximum Post-Baseline Toxicity Grade	85	84	250
Grade 3	7 (8.2%)	16 (19.0%)	43 (17.2%)
Grade 4	2 (2.4%)	1 (1.2%)	2 (0.8%)
Hematology			
Hemoglobin	85	84	250
Grade 3	1 (1.2%)	7 (8.3%)	28 (11.2%)
Lymphocytes	85	84	250
Grade 3	0	1 (1.2%)	5 (2.0%)
Neutrophils	85	84	250
Grade 3	1 (1.2%)	1 (1.2%)	0
Platelets	84	84	250
Grade 3	0	0	3 (1.2%)
Chemistry			
ALT	85	84	250
Grade 3	2 (2.4%)	0	3 (1.2%)
Grade 4	2 (2.4%)	1 (1.2%)	0
AST	85	84	250
Grade 3	4 (4.7%)	1 (1.2%)	0
Lipase	85	84	250
Grade 3	1 (1.2%)	3 (3.6%)	3 (1.2%)
Grade 4	0	0	2 (0.8%)
Serum Glucose (Hyperglycemia)	85	84	250
Grade 3	3 (3.5%)	1 (1.2%)	2 (0.8%)
Total Bilirubin (Hyperbilirubinemia)	85	84	250
Grade 3	0	5 (6.0%)	7 (2.8%)

GS-US-334-0123 (PHOTON-1): Most subjects in all treatment groups experienced ≥1 AE, with the incidence of AEs being higher in subjects receiving 24 wks of treatment (92.3%) vs. those receiving 12 wks (83.8%). The most frequently reported AEs were fatigue, insomnia, nausea. Gde 3 or 4 AEs and SAEs occurred with similar frequency across all treatment groups, with the lowest incidence in the SOF+RBV 24 Week TE GT2/3 group (7.3%). Low rates of AEs leading to treatment discontinuation occurred in all treatment groups (2.4% to 4.4%). One subject had an SAE (death) of completed suicide; Subject 3317-8735 (SOF+RBV 12 Week TN GT2/3 group) committed suicide 9 days after the last dose of study drug; the SAE was considered not related to study drug, or ARV treatment.

Table 41: GS-US-334-0123: Brief Summary of Adverse Events (SAS).

Number (%) of Subjects Experiencing	Group 1 SOF+RBV 12 Weeks GT 2/3 TN (N = 68)	Group 2 SOF+RBV 24 Weeks GT 2/3 TE (N = 41)	Group 3 SOF+RBV 24 Weeks GT 1 TN (N = 114)	Groups 2 and 3 SOF+RBV 24 Weeks (N = 155)
Any AE	57 (83.8%)	37 (90.2%)	106 (93.0%)	143 (92.3%)
Grade 3 or 4 AE	7 (10.3%)	3 (7.3%)	15 (13.2%)	18 (11.6%)
SAE	5 (7.4%)	1 (2.4%)	8 (7.0%)	9 (5.8%)
AE Leading to Discontinuation	3 (4.4%)	1 (2.4%)	3 (2.6%)	4 (2.6%)
Death	1 (1.5%)	0	0	0

GT= genotype; TE = treatment experienced; TN = treatment naive

Table 42 below presents the most commonly reported AEs.

Table 42: GS-US-334-0123: AEs reported in ≥10% of subjects in any treatment Gp (SAS).

Preferred Term	Group 1 SOF+RBV 12 Weeks GT 2/3 TN (N = 68)	Group 2 SOF+RBV 24 Weeks GT 2/3 TE (N = 41)	Group 3 SOF+RBV 24 Weeks GT 1 TN (N = 114)	Groups 2 and 3 SOF+RBV 24 Weeks (N = 155)
Number (%) of Subjects Experiencing Any AE	57 (83.8%)	37 (90.2%)	106 (93.0%)	143 (92.3%)
Fatigue	24 (35.3%)	19 (46.3%)	41 (36.0%)	60 (38.7%)
Insomnia	14 (20.6%)	8 (19.5%)	15 (13.2%)	23 (14.8%)
Nausea	12 (17.6%)	6 (14.6%)	18 (15.8%)	24 (15.5%)
Headache	9 (13.2%)	5 (12.2%)	16 (14.0%)	21 (13.5%)
Upper Respiratory Tract Infection	8 (11.8%)	5 (12.2%)	13 (11.4%)	18 (11.6%)
Diarrhoea	6 (8.8%)	5 (12.2%)	12 (10.5%)	17 (11.0%)
Irritability	7 (10.3%)	2 (4.9%)	14 (12.3%)	16 (10.3%)
Anaemia	6 (8.8%)	3 (7.3%)	13 (11.4%)	16 (10.3%)
Cough	4 (5.9%)	4 (9.8%)	14 (12.3%)	18 (11.6%)
Dizziness	1 (1.5%)	5 (12.2%)	7 (6.1%)	12 (7.7%)

GT= genotype; TE = treatment experienced; TN = treatment naive

Overall, the most frequently reported AEs were fatigue (37.7%, 84 subjects), insomnia (16.6%, 37 subjects), nausea (16.1%, 36 subjects). The frequency of most commonly occurring AEs was similar between the 12- and 24-week arms with the exception of cough and dizziness, which were more common with the 24 wk treatment group. The incidence of these frequently reported AEs is comparable to the registrational Phase 3 studies with 12 or 16 weeks of SOF+RBV, including cough and dizziness. There was no increase SAEs, or AEs leading to discontinuation in those subjects receiving 24 wks vs. 12 wks of SOF+RBV. Most AEs were Gde 1 or 2 in severity. Among all groups, 11.2% had at least 1 Gde 3 or 4 AE. Gde 3 or 4 AEs reported in >1 subject in any treatment group included fatigue (3 subjects) and acute renal failure (3 subjects) in the setting of concurrent illness. Each event of acute renal failure (ARF) was associated with an SAE: 1 subject had an episode of staphylococcal pneumonia and sepsis in the setting of IVDU, 1 subject had salmonella gastroenteritis, 1 subject was hospitalized for diabetic ketoacidosis. In addition, Gde 3 or 4 AEs of chest pain, hyperbilirubinemia, intentional overdose, and depression occurred in 2 subjects each. Fourteen subjects (6.3%) experienced at least 1 SAE, 1 of which was considered related to RBV by the investigator (gastroenteritis salmonella). The only SAEs reported in >1 subject in any treatment group were ARF (3 subjects), cellulitis, pneumonia, and intentional overdose (2 subjects each); 3.1% discontinued treatment with SOF+RBV due to AEs. There was no individual AE that led to treatment discontinuation in >1 subject.

11.6.4.1.2. Clinical lab evaluations

Table 43 summarises Gde 3 or 4 lab abnormalities occurring in >1 subject in any treatment group. A total of 41 subjects (18.4%) had a Gde 3 or 4 laboratory abnormality. No Gde 3 or 4 haematological laboratory abnormalities were observed. Elevated total bilirubin was the most frequent Gde 3 (20 subjects, 9.0%) and Gde 4 (12 subjects, 5.4%) laboratory abnormality. These elevations occurred almost exclusively (30 of 32 subjects, 93.8%) in subjects receiving ATV as part of the ARV regimen and were consistent with RBV-induced haemolysis in the setting of UGT1A1 inhibition by ATV. Increased hyperbilirubinemia has been reported with PEG and RBV treatment in HCV/HIV co-infected subjects receiving ATV. None of the elevations in total bilirubin were associated with elevations in direct bilirubin or transaminitis, and the majority of subjects with Gde 3 (14 of 20 subjects, 70.0%) and all subjects with Gde 4 elevations in total bilirubin had baseline graded elevations in total bilirubin. Of the 30 subjects receiving ATV who had Gde 3 or 4 elevations in total bilirubin, 4 discontinued treatment with ATV and started treatment with a new ARV; 1 subject interrupted treatment with ATV for 5 days and started treatment with an additional ARV; 25 subjects continued treatment with ATV. Consistent with RBV-induced haemolysis, total bilirubin elevations peaked at Week 1 or 2 with subsequent decreases observed thereafter. All subjects had improvement in total bilirubin to near baseline

by the post-treatment Week 12 visit. Among subjects not taking ATV, Gde 3 or 4 elevated total bilirubin was observed in 2 subjects (1.5%) which is similar to the rate (2.0%) observed with HCV-monoinfected subjects receiving SOF+RBV in registrational Phase 3 studies included in the Primary Safety Population (see first round review). While there was an increase in Gde 3 or 4 total bilirubin elevations in the SOF+RBV 24 Week TE GT2/3 and SOF+RBV 24 Week TN GT 1 groups vs. SOF+RBV 12 Week TN GT2/3 group, this difference was likely due to the increased number of subjects in the SOF+RBV 24 Week TE GT2/3 and SOF+RBV 24 Week TN GT 1 groups who were receiving ATV-containing regimens (33 subjects, 21.3%) compared with the SOF+RBV 12 Week TN GT2/3 group (8 subjects, 11.8%). Gde 3 lipase elevations were the only other Gde 3 or 4 lab abnormality to occur in >1 subject, occurring in 3 subjects in the SOF+RBV 24 Week TN GT 1 group. Two of the subjects had asymptomatic elevations of lipase (one subject at Week 12 and one at Week 20). The third subject had Gde 1 or 2 lipase elevations at each on-treatment study visit; the subject had Gde 3 lipase elevation (348 U/L) at Week 8 with an associated investigator-reported AE of pancreatitis considered related to study drug. The AE was **asymptomatic** and the subject completed scheduled dosing without interruption; lipase values returned to normal range at post-treatment Week 4.

Table 43: GS-US-334-0123: Gde 3 or 4 Lab Abnormalities in >1 Subject in Any Treatment Gp (SAS).

Laboratory Parameter	Group 1 SOF+RBV 12 Weeks GT 2/3 TN (N = 68)	Group 2 SOF+RBV 24 Weeks GT 2/3 TE (N = 41)	Group 3 SOF+RBV 24 Weeks GT 1 TN (N = 114)	Groups 2 and 3 SOF+RBV 24 Weeks (N = 155)
Maximum Postdose Toxicity Grade				
Grade 3	7 (10.3%)	5 (12.2%)	15 (13.2%)	20 (12.9%)
Grade 4	1 (1.5%)	2 (4.9%)	11 (9.6%)	13 (8.4%)
Lipase				
Grade 3	0	0	3 (2.6%)	3 (1.9%)
Grade 4	0	0	0	0
Total Bilirubin (Hyperbilirubinemia)				
Grade 3	3 (4.4%)	4 (9.8%)	13 (11.4%)	17 (11.0%)
Grade 4	1 (1.5%)	2 (4.9%)	9 (7.9%)	11 (7.1%)

GT= genotype; TE = treatment experienced; TN = treatment naive
Note: Toxicity grade must increase at least 1 toxicity grade from baseline value (missing was considered grade 0) to be included.
Note: Subjects counted once at maximum toxicity grade (hyper [+] and hypo [-] when applicable) for each laboratory test.
Note: Data included to last dose date of study regimen + 30 days.

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

Common Treatment-emergent AEs in Study GS-US-334-0133 are detailed in Table 39 and also overall in Study GS-US-334-0123 in Table 44.

Table 44: GS-US-334-0123 AE brief summaries (SAS).

	SOF+RBV 12 weeks	SOF+RBV 24 weeks			
	GT2/3 TN (N=68)	GT2/3 TE (N=41)	GT1 TN (N=114)	Total of SOF+RBV 24 weeks (N=155)	Grand Total (N=223)
Number (%) of Subjects Experiencing Any					
Treatment-Emergent Adverse Event	57 (83.8%)	37 (90.2%)	106 (93.0%)	143 (92.3%)	200 (89.7%)
Grade 3 or 4 Treatment-Emergent Adverse Event	7 (10.3%)	3 (7.3%)	15 (13.2%)	18 (11.6%)	25 (11.2%)
Grade 2, 3, or 4 Treatment-Emergent Adverse Event	32 (47.1%)	18 (43.9%)	65 (57.0%)	83 (53.5%)	115 (51.6%)
Treatment-Emergent Treatment-Related Adverse Event	41 (60.3%)	31 (75.6%)	72 (63.2%)	103 (66.5%)	144 (64.6%)
Grade 3 or 4 Treatment-Emergent Treatment-Related Adverse Event	2 (2.9%)	2 (4.9%)	7 (6.1%)	9 (5.8%)	11 (4.9%)
Grade 2, 3, or 4 Treatment-Emergent Treatment-Related Adverse Event	18 (26.5%)	11 (26.8%)	33 (28.9%)	44 (28.4%)	62 (27.8%)
Treatment-Emergent Serious Adverse Event	5 (7.4%)	1 (2.4%)	8 (7.0%)	9 (5.8%)	14 (6.3%)
Treatment-Emergent Treatment-Related Serious Adverse Event	0	0	1 (0.9%)	1 (0.6%)	1 (0.4%)
Adverse Event Leading to Permanent Discontinuation from Any of the Study Drugs	3 (4.4%)	1 (2.4%)	3 (2.6%)	4 (2.6%)	7 (3.1%)
Adverse Event Leading to Permanent Discontinuation from SOF	3 (4.4%)	1 (2.4%)	3 (2.6%)	4 (2.6%)	7 (3.1%)
Adverse Event Leading to Modification or Interruption of Study Drug	6 (8.8%)	4 (9.8%)	16 (14.0%)	20 (12.9%)	26 (11.7%)
Treatment-Emergent Death	1 (1.5%)	0	0	0	1 (0.4%)

Note: SOF = Sofosbuvir , RBV= Ribavirin, GT = Genotype, TN = Treatment-naive, TE = Treatment-experienced
Note: Data included to last dose date of study regimen + 30 days.
Note: Percentages were calculated based on the number of subjects in the safety analysis set.

11.6.4.3. Deaths and other serious adverse events

One subject in PHOTON-1 died of completed suicide; Subject [information redacted] (SOF+RBV 12 Week TN GT2/3 group) committed suicide 9 days after last dose of study drug; the SAE was considered not related to study procedures, study drug, or ARV treatment. No deaths in VALENCE. In VALENCE, fourteen subjects (6.3%) experienced ≥1 SAE, 1 of which was considered related to RBV by the investigator (salmonella gastroenteritis). The only SAEs reported in >1 subject in any treatment group were acute renal failure (3 subjects), cellulitis, pneumonia, intentional overdose (2 subjects each). SAEs in PHOTON-1 are detailed above.

11.6.4.4. Discontinuation due to adverse events

These are summarised in Tables 38 and 41.

11.6.5. Post-marketing experience

Non-data provided; SOF is very recently approved in the US, Canada and EU.

11.6.6. Safety issues with the potential for major regulatory impact

None revealed. Other safety issues

11.6.6.1. Safety in special populations

PHOTON-1 enrolled HIV-CV co-infected patients.

HIV Viral load: 2 subjects (0.9%) on ARVs had HIV-1 virologic rebound during SOF+RBV treatment. Subject [information redacted] (SOF+RBV 12 Week TN GT2/3 group) was receiving ARV treatment with Truvada and raltegravir. HIV-1 RNA was detected at Week 12 and likely related to poor adherence. Subject [information redacted] (SOF+RBV 24 Week GT 1 group) was receiving ARV treatment with Truvada and ATV/r. HIV-1 RNA was <20 copies/mL at baseline, ranged between <20 and 75 copies/mL during SOF+RBV treatment, and was 491 copies/mL and 32 copies/mL at the post-treatment Week 4 and 12 visits, respectively. This subject had poor adherence. Of the 11 subjects not on ARV treatment upon enrollment, 8 had detectable HIV-1 RNA at baseline. No change in HIV RNA during HCV treatment; the remaining 3 subjects maintained control of HIV-1 RNA to <100 copies/mL for the duration of the study.

CD4 T-Lymphocytes: As previously described with RBV-containing therapy, median CD4 T-cell counts gradually decreased during SOF+RBV treatment in all treatment groups (range, -73 to 87 cells/uL at EOT. There were no clinically significant sequelae of these decreases reported. Despite the decrease in total CD4 T-cell count, the median CD4+ percent remained relatively stable i.e. ranging between 30.6-36.7%.

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

None revealed in the one D-D interaction study provided in this second round Application.

11.6.6.3. Carcinogenicity study – pre-clinical data

Two carcinogenicity studies were presented:

1. **Gilead Ref. No. TX-334-2001:** To evaluate the carcinogenicity of PSI-7977, Sprague Dawley rats were administered daily oral doses of PSI-7977 at 75, 250, or 750 mg/kg for up to 23 months. There was no evidence of a carcinogenic effect that could be attributed to PSI-7977 and administration of PSI-7977 did not affect the survivability of the animals. The few treatment-related non-neoplastic effects were attributed in part to the vehicle, a PEG:Tween combination, and/or a mild irritative effect of the PSI-7977 test article when introduced into the nasal turbinate cavities secondary to gavage
2. **Gilead Ref. No. TX-334-2002**: **24 month ORAL GLP** carcinogenicity study of PSI-7977**.** To evaluate the carcinogenicity of PSI-7977, groups of 120 mice (60/sex), were administered daily oral doses of vehicle, water, or PSI-7977 for ~97 weeks and then euthanised for necropsy. Dosages of PSI-7977 administered to male mice were 20, 60, or 200 mg/kg/day, and to females were 60, 200, and 600 mg/kg/day.PSI-7977 did not affect survivability or induce neoplastic or non-neoplastic changes at any dose level. No evidence of carcinogenic potential observed.

11.6.7. Evaluator's overall conclusions on clinical safety

No new safety concerns were revealed through these submitted interim analyses. In the HCV monoinfected patients, overall treatment with SOF+RBV was generally well tolerated in this study with no deaths, few permanent study drug discontinuations due to AEs, few SAEs, and few Gde 3/4 AEs or lab abnormalities. Treatment duration (12 or 24 wks) did not appear to affect the safety profile of the regimen, in particular in regards to haematological toxicity. Treatment with SOF+RBV for 12 or 24 wks was generally well tolerated in this study of HCV/HIV-co-infected subjects, with a safety profile generally consistent with the expected safety profile of RBV and similar to that observed in previous studies with regimens that included RBV for up to 24 weeks. Low rates of treatment discontinuation due to AEs were observed in both 12- and 24-week treatment regimens, and commonly occurring and Gde 3 or higher AEs were reported with similar frequency to that in the mono-infected population. Subjects taking ATV as part of their ARV regimen had higher rates of Grade 3 or 4 hyperbilirubinaemia due to RBV-associated haemolysis in the setting of ATV-mediated UGT1A1 inhibition that necessitated a change in ARV regimen in 11% of subjects. For most subjects taking ATV, however, the bilirubin increases had no clinical consequences – in other words it was cosmetic. There is still a paucity of safety data in HIV-HCV coinfected patients NOT on ARVS receiving SOF+RBV for any length of time, as more than 95% of patients enrolled in PHOTON-1 were on ARVS. There is no efficacy and safety data for co-infected patients who are treatment-experienced with CHC genotype 1.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of all the responses to clinical questions, the benefits of SOF in the proposed usage are:

- Proven efficacy for GT-1, 2, 3 and 4. Data from ongoing studies (Table 45) will inform further in regards to the following genotypes:

Table 45: Summary of planned SOF studies for Asia, Russia and Egypt.

Country (N)	Genotype	Regimen	Duration of Treatment	Population
Japan (134)	GT2	SOF+RBV	12 weeks	TN and TE
Egypt (100)	GT4	SOF+RBV	12, 24 weeks	TN and TE
US Egyptians (60)	GT4	SOF+RBV	12, 24 weeks	TN and TE
Russia (120)	GT 1,3	SOF+RBV	16, 24 weeks	TN
Korea (80)	GT2	SOF + RBV	12 weeks	TN and TE
Taiwan (80)	GT2	SOF+RBV	12 wks	TN and TE
Hong Kong (30)	GT1,6	SOF+RBV	12,16,24 wks	TN
India (120)	GT1,3	SOF+RBV	16, 24 wks	TN
Vietnam (40)	GT1,6	SOF+RBV	12,16,24 wks	TN
China (220)	GT1,6 GT3 GT2	SOF+RBV SOF+RBV SOF+RBV	12,16,24 wks 16,24 wks 12 wks	TN TN TN and TE

- Improved SVR12 rates with longer exposure to SOF+RBV, that is, 24 weeks for GT-3 without a significant toxicity cost of extending treatment duration; moreover the specific effects of hepatitis steatosis on treatment response is being explored in GS-US-334-0153
- Clear efficacy in the setting of HIV-HCV co-infection for treatment naïve patients with GT-1 and treatment naïve or experienced with GT-2 and 3
- Very well tolerated drug. The AE profile might be better still if partnered with other drug(s) other than RBV, current ongoing studies with ledipasvir, daclatasvir[22] and telaprevir.[23]

12.2. Second round assessment of risks

After consideration of responses to clinical questions, the risks of SOF in the proposed usage are:

- No specific data in treatment experienced patients with GT-1: HCV mono-infected or HIV-HCV co-infected patients. Modelling data is provided in the sponsor's response dated 2 January 2014. The reviewer notes that US FDA and European Medicines Agency (EMA) have used language in the Sovaldi PI to enable treatment of GT-1 treatment experienced patients based on this approach. However, the evaluator notes there are now ongoing studies in treatment experienced patients with GT-1
- No specific data on treatment responses to GT-4 in HIV-HCV co-infected patients
- Minimal efficacy and safety data in HIV-HCV co-infected subjects not on antiretrovirals and with uncontrolled HIV viraemia. It is not known whether uncontrolled HIV viraemia might blunt efficacy as measured by rates of SVR12. Moreover, there might be clinical

[22] ClinicalTrials.gov NCT02032875: "Phase III Daclatasvir, Sofosbuvir, and Ribavirin in Cirrhotic Subjects and Subjects Post-liver Transplant (ALLY 1)".
[23] ClinicalTrials.gov NCT01994486: "Open-Label Safety Study of Telaprevir and Sofosbuvir in Chronic Hepatitis C Genotype 1 (STEADFAST)".

consequences of the reduced absolute CD4+ T cell count when SOF+RBV are used, when this is coupled with ongoing HIV viral replication

- Minimal to no data for CHC GT-5 and 6
- In regards to the paucity of data in those with moderate severe renal impairment exposed to multi-dosing, the evaluator notes a study that is now recruiting in this patient population and will inform further.[24]
- No drug-drug interaction data for illicit substances. This is a group of patients who are highly likely to use illicit substances. The evaluator does not classify methadone as an 'illicit substance'. The evaluator thinks this issue of illicit substance use is a particularly problematical in HIV-HCV co-infection where rates of illicit substance use are particularly in high and middle income countries. Is SOF safe when taken concurrently with methamphetamine, ketamine, ecstasy and sildenafil?
- The evaluator noted that the RBV tablets used in the SOF clinical trials was Ribasphere which is not registered in Australia. The sponsor was asked to clarify the source of PEG and RBV used in the clinical trials. Moreover, in Australia, there is no currently standalone RBV available on the market and the marketed RBV products in Australia (Rebetol capsule and Copegus tablets) are co-packaged with pegylated or nonpegylated interferons and are indicated for use in combination with pegylated or nonpegylated interferons. In response to these issues, the sponsor provided the following a summary document of RBV therapeutic equivalents (US FDA). On review of this, the evaluator is satisfied that the generic RBV used in the registration studies of SOF, that is, Ribasphere is equivalent to Copegus. The sponsor also explained that it has partnered with a company, to register standalone RBV in Australia.

12.3. Second round assessment of benefit-risk balance

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

13. Second round recommendation regarding authorisation

Following the review of further data presented and sponsor's response to clinical questions arising from first round review, and in light of ongoing studies (in GT-4, 5 and 6) which will provide further data on the efficacy of SOF as part of combination therapy for treatment of CHC, the evaluator recommends that SOF be authorised as follows:

> *Sovaldi is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. The drug has proven efficacy as part of combination therapy for genotypes 1, 2, 3 and 4.*

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