21 November 2013
EMA/CHMP/688774/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sovaldi

International non-proprietary name: sofosbuvir

Procedure No. EMEA/H/C/002798/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3TC	lamivudine
[^{xx}C]-	radiolabeled carbon xx
AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration-time curve
BCS	biopharmaceutics classification system
BMI	body mass index
BMS	Bristol-Myers Squibb
CatA	cathepsin A
CES	carboxyl esterase 1
CHC	chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent oral clearance after administration of the dose
C_{max}	maximum observed concentration
CsA	cyclosporine (cyclosporin A)
CYP	cytochrome P450 enzyme(s)
DAA	direct-acting antiviral
DDI	drug-drug interaction
DRV	Darunavir
DSC	differential scanning calorimetry
EC	European Commission
EC_{xx}	concentration of a compound inhibiting virus replication by xx%
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eRVR	extended rapid virologic response
ESRD	end-stage renal disease
EU	European Union
FTC	Emtricitabine
GC	gas chromatography
GD	gestation day
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVS	gravimetric vapour sorption
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	high density polyethylene

HIV, HIV-1	human immunodeficiency virus, type 1
HPLC	high performance liquid chromatography
IC_{xx}	concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICP	inductively coupled plasma
IL28B	Interleukin 28B gene
IR	infra-red
IWRS	interactive web response system
LDV	ledipasvir (GS-5885)
LLOQ	lower limit of quantitation
LOD	lower limit of detection
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
N or n	number of subjects in a population (N) or subset (n)
NIAID	National Institute of Allergy and Infectious Diseases
NMR	nuclear magnetic resonance
NMT	not more than
NOAEL	no observed adverse effect level
NOR	normal operating range
NS (3/4A/5A/5B)	nonstructural protein (3/4A/5A/5B)
NtA	Notice to Applicants
PD	pharmacodynamic(s)
PEG	pegylated interferon (peginterferon)
Pgp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
pTVR	posttransplant virologic response 12 weeks after liver transplant
q.d.	quaque die (daily)
QbD	Quality by Design
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarisation and repolarisation to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
/r	boosted with ritonavir
RAL	raltegravir
RAP	resistance analysis population
RBV	ribavirin
RH	relative humidity
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event

SmPC	summary of product characteristics
SOF	sofosbuvir (GS-7977; formerly PSI-7977)
SVR, SVRxx	sustained virologic response, sustained virologic response at “xx” weeks following completion of all treatment
TDF	tenofovir disoproxil fumarate
TND	target not detected
TTC	threshold of toxicological concern
ULN	upper limit of the normal range
US	United States
UV	ultra-violet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 19 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sovaldi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 September 2012.

The applicant applied for the following indication: Sovaldi is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that sofosbuvir was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0294/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP is not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance sofosbuvir contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 January 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: United States (US)

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill, County Cork
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bengt Ljungberg Co-Rapporteur: Alar Irs

- The application was received by the EMA on 19 April 2013.
- Accelerated Assessment procedure was agreed-upon by CHMP on 26 March 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2013 (Annex 2). In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 19 September 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2013 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 15 November 2013 (Annex 6).
- During the meeting on 21 November 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sovaldi.

2. Scientific discussion

2.1. Introduction

Sofosbuvir (SOF) is a novel nucleotide prodrug. In human hepatocytes, SOF is converted to an active uridine triphosphate form (GS 461203), which acts as an inhibitor of the hepatitis C virus (HCV) non-structural (NS) 5B ribonucleic acid (RNA) polymerase. The proposed indication for SOF is for use in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Hepatitis C virus and its treatment

Hepatitis C virus (HCV) infection is a major European public health challenge, with a prevalence of 0.4-3.5% in different EU member states. It is the most common single cause of liver transplantation in the Union. However, in the absence of effective antiviral therapy, recurrence of HCV infection in the graft is near universal. Post-transplant recurrence is often aggressive, and for this reason, patients that undergo liver transplantation due to hepatitis C have a worse prognosis than patients that do so for other indications.

HCV is divided into six major genotypes and numerous subtypes, which are based on phylogenetic relationship. Genotype 1 is the most common genotype in Europe, comprising approximately 70 % of infections. Genotype 3 is second most common, followed by genotype 2. Genotype 4 is predominant in Egypt, the nation in the world with the highest documented HCV prevalence. Genotypes 5 and -6 are uncommon in Europe and the US, but are more common in South Africa and South-East Asia, respectively (Simmonds et al, Hepatology 2005). HCV genotype does not clearly impact the rate of disease progression. Treatment response, however, differs between genotypes.

The goal of antiviral therapy against HCV is to reach sustained virological response (SVR), which is traditionally defined as the absence of quantifiable virus in plasma at least 24 weeks after the end of therapy. However, most relapses occur within 4 weeks of treatment discontinuation, and a 98-99% concordance has been shown between absence of quantifiable virus 12 weeks after therapy, and SVR24 (Florian et al, AASLD 2011). Therefore the absence of measurable virus 12 weeks post end of treatment (SVR12) is presently accepted by European and US regulators as the primary endpoint in clinical trials. Though occasional late relapses occur, in general the durability of SVR has been amply demonstrated (see e.g., Ng and Saab, Clin Gastroenterol Hepatol 2011).

Presently licensed treatment options for HCV all include peginterferon (PEG) and ribavirin (RBV). For the treatment of genotype 1 infection, the addition of either one of the NS 3/4A protease inhibitors telaprevir or boceprevir, approved in 2011, is presently considered standard-of-care. In the registrational studies for these drugs, such triple therapy yielded SVR in the order of 65-80% of patients with 24-48 weeks of therapy. However, response rates are considerably lower, e.g., in patients with prior nonresponse to interferon-based therapy and/or with cirrhosis. For genotypes other than -1 there are no direct-acting antivirals (DAA) presently approved. Bi-therapy with PEG and RBV is indicated for 16-48 weeks depending on circumstances. Whereas such therapy may cure up to 80% of unselected patients, response

rates in patients with a history of prior treatment failure are lower, and advanced liver disease negatively impacts the probability of SVR.

Interferon-based therapies are associated with a plethora of potentially serious side effects that are important in limiting real life effectiveness. These include a risk of hepatic decompensation and septicaemia in patients with advanced liver disease, as well as bone marrow suppression. Also, there are psychiatric side effects such as depression, which considerably limits eligibility to treatment in the target population (see e.g., Bini et al, Am J Gastroenterol 2005). Of particular relevance for patients with very advanced liver disease, interferons are contraindicated in patients with hepatic decompensation; furthermore, according to the product information for PEG alfa-2a and -2b, the baseline platelet count should exceed 90,000 and 100,000/µl, respectively.

Consequently, there is a clear unmet medical need for simplified HCV-treatment regimens. New treatment options are especially crucial in patient populations where treatment with PEG is not possible or has limited efficacy, including those who have failed prior therapy or have advanced liver disease.

Hepatitis C subpopulations

CHMP guidance for drug development for hepatitis C categorises patients with hepatitis C according to three different aspects. The first distinction is virological, and is determined by viral genotype. The second distinction applies to treatment experience. The third distinction relates to clinical parameters. Patients will belong to one or another subpopulation in each of these respects, which makes the potential number of subpopulations very large.

Viral genotypes

As stated above, HCV is divided into six phylogenetically defined genotypes. Each genotype is divided into subtypes. Both of the peginterferons were registered based on trials including all genotypes. The representation of patients with genotypes 4-6 in the pivotal trials was very low. The addition of RBV generally increases PEG efficacy but RBV has no clinically relevant antiviral activity of its own. In studies of PEG+RBV, higher response rates were noted in genotypes 2 and 3 compared to 1, whereas responses to PEG+RBV in genotype 4-6 appear to be somewhere in-between.

Since PEG+RBV therapy has a very considerable side effects profile, there has been a strong impetus to shorten treatment duration and lowering doses, if possible without unduly reducing SVR rates. The NV15942 study (Hadziyannis et al, Ann Intern Med 2004) indicated that this was possible while retaining activity against genotypes 2 and 3. On this basis emerged the paradigm of 48 weeks of PEG+RBV therapy for genotypes 1 and 4, and 24 weeks of therapy for genotypes 2 and 3. With these treatment paradigms, roughly 40-50% of treatment-eligible genotype 1 patients are cured, versus 70-85% of treatment-eligible genotype 2/3 patients. The labelled indications for the peginterferons encompass all genotypes and all hepatitis C subpopulations except those with decompensated liver disease/hepatic impairment. The latter is due to the specific side effects profile of these agents, which makes treatment of such patients risky, as described above.

These differences also prompted the notion that genotypes 1 and -2/3 ought to be investigated in separate trials. Responses of genotypes 2 and 3 to PEG+RBV have been considered similar.

However, responses are somewhat higher for genotype 2, as exemplified by the ACCELERATE study, in which SVR rates with 24 weeks of therapy was 75% for genotype 2 and 66% for genotype 3 (Shiffman et al, N Engl J Med 2007).

Present CHMP draft guidance anticipates that the efficacy of an antiviral should be shown in sufficiently powered studies specifically against genotypes 1, -2 and -3, with SVR as an endpoint. Whether this is done under the same trial protocol with appropriate stratification and genotype representation, or in different trials, is in practice a matter of convenience, contingent on factors such as whether the treatment regimen and comparator regimen are the same for each genotype. For the less common genotypes, it is recognised that a fully powered, independent efficacy demonstration with SVR as an endpoint may not be feasible. Therefore, a totality of evidence approach is anticipated, where in vitro data, on-treatment virological responses as well as any SVR data available, should be shown to be sufficiently similar to available data in the more common genotypes, to allow for inferences based on bridging. A drug will be recommended for use against the spectrum of genotypes for which a positive benefit-risk balance has thus been substantiated.

Treatment experience

The second distinction pertains to treatment-naïve versus treatment-experienced. In this context, it should be noted that the latter term, if not further specified, tends to refer to experience of PEG+RBV (or some other use of interferon in the absence of a DAA). Indeed, no patients in the SOF Phase 3 trials were allowed to have experience of any other hepatitis C drugs apart from interferons and RBV – that is, no prior exposure to DAAs. Of note, a Bristol-Myers-Squibb [BMS]-sponsored study (study AI444040) has included a study arm dedicated exclusively to patients with experience of failure on therapy with boceprevir- or telaprevir-based triple therapy. Importantly, there is no cross-resistance between these agents and SOF.

Insofar as the term “treatment-experienced” refers to patients that have been treated with PEG+RBV but have not been treated with a DAA, this population is in no way analogous to a “treatment-experienced” human immunodeficiency virus (HIV) population. Whereas the virus of the latter have been subjected to selection pressure for antiviral resistance, and in many cases harbour virus with reduced susceptibility to one or more antivirals, PEG+RBV does not select for viral resistance (this being essentially an immune therapy). Consequently, it has been demonstrated that interferon responsiveness on retreatment with PEG+RBV is roughly similar to a first course (Liu et al, Clin Infect Dis 2012). Therefore, such a population is to be understood as functionally represented in a treatment-naïve population, since about 50% of a treatment naïve genotype 1 population and 20-30% of a treatment- naïve genotype 2/3 population would be “treatment-experienced” without having been cured, if they had already been exposed to PEG+RBV. As available evidence indicates that, apart from the natural progression of the disease over time, nothing else would have changed, the lower response rates seen in PEG+RBV treatment-experienced population compared to a treatment naïve population is a consequence of selecting the most difficult-to-treat part of a treatment-naïve population and subjecting it to particular study. This circumstance allows for the bridging of data from the one population to the other.

Regarding patients that have experience of non-curative treatment with a DAA there are a few notes to be made. First, while presently there are plenty of PEG+RBV-experienced patients,

there are at this time relatively few patients that have failed on DAA therapy. However, while the former will decrease in number, the latter will increase. Second, when considering retreatment, it must be evaluated whether the patient, subsequent to prior drug exposure, may harbour virus cross-resistant to any of the components in the new therapy. Third, if a patient has previously failed on a regimen that induces SVR in most patients, he/she is demonstrably difficult to cure from a "constitutional" perspective (presuming that lack of adherence was not the cause of failure). Such patients may require more potent and longer treatment regimens for cure than most others.

These observations must be taken into account when evaluating trial protocols or making treatment decisions for such patients. Agents that are not cross-resistant to the agent the patient has been treated with retain their full activity in these patients, and should preferentially be used when treating such patients. Furthermore, the retreatment regimen must be more intense in terms of potency and/or duration of therapy than the prior failing regimen. Therefore, for such patients, an individualised approach to the selection of therapy, analogous to that used in patients with HIV, is anticipated.

Clinically defined subpopulations

The last set of distinctions made in the CHMP guidance pertains to clinically defined (adult) subpopulations, where patients may have any genotype, and may or may not have treatment experience. Apart from the general population of patients with chronic hepatitis C, the guidelines mention HIV/HCV co-infected patients, patients with decompensated liver disease, patients in the pre-transplant setting, and patients with recurrent HCV post-transplant. Though not discussed in CHMP guidelines, patients with acute HCV might be said to constitute a further such population.

For all of these subpopulations, dedicated studies may be required to define the magnitude of benefits and of risks, which might differ from that in the "general population". The approach toward such clinically defined subpopulations in terms of the formulation of the labelled indication (SmPC section 4.1) at approval, has historically been such, that if a general positive benefit-risk can be inferred on the basis of available data (usually consisting of efficacy and safety data from a "general population" with chronic hepatitis C and compensated liver disease, as well as drug-drug interaction (DDI) studies and special populations PK studies), the uncertainties concerning the more precise elements of the calculus and limitations of available data have been reflected in the product information, section 4.2, 4.4 and 5.1, as relevant. Examples include the use of Incivo and Victrelis in the pre-and post-transplant setting, as well as the use of these drugs in HCV co-infection. The only case where the use of an agent in such a subpopulation has been explicitly contraindicated is in the case of decompensated liver disease, due to specific safety concerns with interferons accounted for above.

<u>On the evolution of the hepatitis C treatment paradigm</u>

Combination of pegylated interferon (PEG-IFN) plus ribavirin (RBV) was considered the standard of care for HCV genotype 1 (GT1) infection until 2011, when the first DAAs (boceprevir and telaprevir) were approved. For the other HCV genotypes, the PEG-IFN plus ribavirin treatment regimen remains the standard of care.

Telaprevir and boceprevir were granted an indication in GT1-infected patients, in combination with peginterferon alfa and ribavirin. At the time of the approval of these medicines in Europe, there were no large studies on-going with different combinations e.g. interferon-free regimens. Moreover, it had indeed only very recently been demonstrated for products in development that SVR could be reached without an interferon. Thus, the only drugs for which combination therapy could be relevant for these DAAs, were PEG+RBV, both of which were needed for reasonable efficacy.

Presently, an entirely different landscape is emerging in the treatment of chronic hepatitis C. DAAs of four distinct classes (NS3/4A protease inhibitors, NS5A inhibitors, non-nucleoside and nucleos(t)ide inhibitors of the NS5B polymerase) are now in advanced stages of development. Developmental drugs of all of these classes have been studied in various combinations (including with and without PEG-IFN and ribavirin), with agents of each class having shown efficacy contributions when combined with the others.

In this respect, the evolving treatment landscape for CHC now bears similarity to that in HIV, where the beneficial antiviral effect of combining agents that lack evidence of cross resistance is well established. Also, it is anticipated that regimen selection for patients with experience of failure on regimens containing DAA will be individualised based on an understanding of resistance and cross-resistance, like in the HIV field. In summary, the evolving field of hepatitis C therapeutics is similar to that of antiretroviral therapy in the following aspects:

- Combination therapy is anticipated in all cases
- Agents with different mechanisms of action or lack of cross-resistance consistently show additive antiviral effects
- Failure of antiviral therapy is in many cases associated with selection of drug-resistant viral variants which may impact future therapeutic option. Furthermore, in hepatitis C, there are naturally occurring viral polymorphisms that impact the activity of some agents.
- Consequently, individual viral drug susceptibility will need to be taken into account when selecting an appropriate combination regimen

Antiretrovirals used against HIV are generally approved for use “in combination with other agents”, with the particular information needed for rational regimen selection provided in relevant sections of the SmPC. The emerging treatment landscape indicates that the same approach would be appropriate for hepatitis C medicines in the light of the numerous combinations of medicinal products in this field.

Thus, the CHMP considers that there is sufficient evidence to indicate the HCV medicines for use “in combination with other medicinal products”. The particular information for each compound, which is needed for rational regimen selection, should be provided in the relevant sections of the SmPC (i.e. mainly 4.2, 4.5, 5.1) as appropriate.

2.2. Quality aspects

2.2.1. Introduction

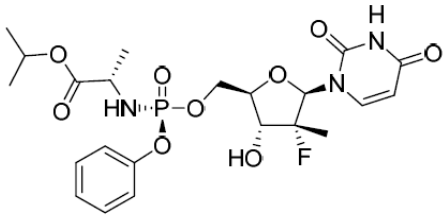
The finished product is presented as a film-coated tablet containing 400 mg of Sofosbuvir as active substance.

Other ingredients are mannitol (E421), microcrystalline cellulose (E460(i)), croscarmellose sodium, colloidal anhydrous silica (E551), magnesium stearate (E470b), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), and iron oxide yellow (E172).

The product is available in high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure, silica gel desiccant and polyester coil.

2.2.2. Active Substance

The chemical name of Sofosbuvir is (*S*)-isopropyl-2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate and has the following structure:



The structure of Sofosbuvir was unambiguously confirmed by ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR, UV spectroscopy, IR spectroscopy, mass spectrometry, elemental analysis and single crystal X-ray crystallography.

Sofosbuvir is a white to off-white non-hygroscopic crystalline solid, slightly soluble in water (pH 1.2-7.7), freely soluble in ethanol and acetone, soluble in 2-propanol, and insoluble in heptane.

Sofosbuvir is chiral and possesses 6 stereogenic centres which are well controlled by the synthetic process and the specifications of raw materials. The absolute and relative configuration of these chiral centres was established by single crystal X-ray crystallography. Eight polymorphic forms of Sofosbuvir have been observed and the manufacturing process consistently produces Sofosbuvir as the most thermodynamically stable polymorphic form, containing a small amount of a metastable form which were determined to be pharmaceutically equivalent as per ICH Q6A (decision tree #4). Other polymorphic forms are excluded by the manufacturing process and their absence is confirmed by DSC.

The active substance is a chemical substance not previously authorised as a medicinal product in the European Union. Furthermore, it is not a salt, complex, derivative or isomer, (nor mixture of isomers), of a previously authorised substance. Sofosbuvir thus meets the definition of a New Active Substance according to the Notice to Applicants (NtA), Vol 2A, Chapter 1,

Annex 3 and a Marketing Authorisation Application in accordance with Article 8(3) of Directive 2001/83/EC pertaining to a New Active Substance is justified.

Manufacture

Sofosbuvir is synthesized in four synthetic steps using three well-defined starting materials with acceptable specifications. GMP manufacturing for Sofosbuvir occurs at multiple manufacturers.

The applicant's original proposal for starting material definition was rejected by the CHMP. The applicant agreed to re-define as requested, with the caveat that implementation of GMP for one step would take until March 2014. The re-defined starting materials are considered appropriate to ensure the continued quality of the active substance throughout the product lifecycle. Adherence to GMP and the associated controls of manufacturing steps will help to prevent a drift in the impurity pattern of the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set based on the manufacturing experience to date. It is recommended that the applicant considers tightening the impurity limits when sufficient commercial scale experience has been gained to fully assess the capability of the manufacturing process.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), clarity of solution, assay (HPLC), impurities (HPLC), residual solvents and volatile organic impurities (GC), metals (ICP), particle size (Ph. Eur.), and polymorphic form (DSC – Ph. Eur.). Rationale for the absence of tests for water content (non-hygroscopic) and microbiological testing (low water content and water activity, isolation from organic solvent) was considered justified. Residue on ignition testing is not suitable as the active substance contains phosphorous: this test is replaced with a combination of clarity of solution test and ICP for elemental impurities. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on 33 batches of the active substance ranging from laboratory through pilot to commercial scale, and used for development, stability, toxicology, clinical studies, and validation were provided. Assessment focussed primarily on later pilot commercial scale batches used for development, stability and validation. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on 8 pilot scale batches of active substance from the proposed manufacturers, as well as the applicant itself, in a container closure system representative of that intended for the market, for up to 12 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were

provided. Photostability testing following ICH guideline Q1B was performed on 1 batch. Stressed studies were carried out on a single batch between -20 and 50 ^{o}C for up to 4 weeks. Forced degradation was carried out under acidic (0.1 M HCl), alkaline (10 mM Na_2CO_3) and oxidative (3% H_2O_2) conditions and at 105 ^{o}C.

The parameters tested were appearance, assay, impurity content, water content, and polymorphic form. The analytical methods used were the same as for release, except for water content, measured by GVS, and were stability indicating.

Sofosbuvir was shown to be stable under long-term, accelerated and stressed conditions and is not sensitive to light. Forced degradation revealed that the active substance may degrade *via* oxidation or hydrolysis in solution, but remains stable in the solid state even up to 105 ^{o}C after 1 week.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

The applicant commits to the continuation of all on-going stability studies under long term conditions up to the 60 month time point. In addition, stability studies will be carried out on the first 3 commercial batches of Sofosbuvir. Furthermore, at least 1 commercial batch from each proposed manufacturer per year will be placed on a long-term stability study.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of formulation development was to develop an immediate-release oral dosage form of Sofosbuvir with acceptable chemical and physical stability as well as reliable release and bioavailability. The active substance is a crystalline solid, routinely manufactured as the most thermodynamically stable polymorphic form containing small quantities of an equivalent polymorphic form. It exhibits pH-independent solubility across a pH range from 1.2-7.7. Sofosbuvir is highly soluble but has low apparent intestinal permeability (BCS class III). Particle size was found to be critical for dissolution rate, so the active substance is sieved or screen milled and particle size is controlled by specification.

The most thermodynamically stable polymorph is the third form used in product development. Initially, a 1:1 mixture of diastereomers (at the phosphorous centre) was used in clinical development since the active substance is a pro-drug and the diastereomeric centre is removed by metabolism. The phosphoester bond is cleaved *in vivo* and the resultant primary alcohol converted to the active triphosphate analogue. Phase II studies were carried out with a metastable polymorphic form of the diastereopure active substance. The thermodynamically most stable form was used in phase III studies following a pharmacokinetic study, and was the chosen commercial form.

Excipients were originally chosen for compatibility with the metastable form described above. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except for the film-coating, Opadry II yellow which is manufactured by an established supplier and tested according to established methods. There are no novel excipients

used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The film-coating was intended to to mask the taste of the active ingredient and provide the product with a unique trade dress. The formulation used during phase III clinical studies is the same as that proposed for marketing. Rapid and complete dissolution was demonstrated in both simulated fed and fasted gastric fluid. Dissolution profiles are similar between the clinically relevant polymorphic forms with >80% active substance dissolved within 20 minutes in each case.

Pharmaceutical development of the finished product contains QbD elements. The critical quality attributes identified were appearance, strength, uniformity of dosage units, dissolution and degradant and water content. The tableting process was evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. Critical process steps and process parameters of the manufacturing process steps, (dry granulation, compression and film-coating), that could have an influence on the finished product quality attributes were examined experimentally. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes, as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified. However, although design spaces were identified for some unit operations, these have not been formally applied for. The applicant will operate within normal operating ranges and any movement outside the approved limits will be subject to post-authorisation variation applications.

The primary packaging is a high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure, a silica gel desiccant and polyester coil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

Magnesium stearate used in the manufacture of Sofosbuvir tablets is obtained exclusively from vegetable sources. No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process is carried out by two manufacturers and consists of 4 main steps: (i) Sofosbuvir is blended, milled, and then dry-granulated with intra-granular excipients (mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate); (ii) the granules are blended with extra-granular excipients (microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate) and compressed to form the tablet cores; (iii) the tablet cores are film-coated; (iv) the finished product is packaged. The manufacturing process is considered to be standard for the production of film-coated tablets. Therefore, formal validation of the process in the production facilities has not yet been completed but will be carried out prior to release of Sovaldi film-coated tablets to the market. A process validation scheme has been presented which is considered acceptable.

Powder-blending, tableting, and film-coating were all shown to be critical to producing a finished product of sufficient quality. Operating parameters with normal operating ranges

(NORs) and in-process controls were defined and robustness studies carried out. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner on commercial scale.

Product specification

The finished product release specification includes tests for appearance (visual description), identification (HPLC and UV), water content (Ph. Eur.), assay (HPLC), degradants (HPLC) uniformity of dosage unit (Ph. Eur), dissolution (Ph. Eur.), and microbiological limits (Ph. Eur.). Batch analysis results from 16 pilot and commercial scale batches covering both proposed manufacturers confirm consistency and uniformity of manufacture and indicate that the process is capable and under control. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set based on the manufacturing experience to date. It is recommended that the applicant considers tightening the limits for a number of specified degradation products when sufficient commercial scale experience has gained to fully assess the capability of the manufacturing process.

Stability of the product

Stability data of 3 commercial scale batches of finished product from each proposed manufacturer stored under long term conditions for up to 12 months at 25ºC / 60% RH, for up to 12 months under intermediate conditions at 30ºC / 75% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The same batch was tested in an open-dish study, stored outside of the primary packaging under long-term or intermediate conditions for 45 days. Stress testing was also carried out on this batch, which was stored in the primary packaging for 45 days at 5 or 50 ^{o}C, or at 25 ^{o}C in 80% humidity.

Samples were tested for appearance, strength, degradation products, dissolution, and water content at each time point. Additionally, microbiological testing is performed on an annual basis. The analytical procedures used are stability indicating.

Sovaldi film-coated tablets met with the proposed specification limits after storage under long-term, intermediate and accelerated conditions. The tablets were shown not to be light-sensitive. No degradation products were observed throughout the stressed studies. A slight increase in water content was noted during the open dish study, but the level remained within specifications and had no impact on the quality of tablets.

Stability studies under long-term and intermediate conditions will be continued until the 60 month time-point. In addition, the applicant commits to instigating stability studies under long-term and accelerated conditions on the first 3 commercial batches, as well as on 1 commercial batch per year thereafter.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of MAHs to take due account of technical and scientific progress, the CHMP notes that the applicant has agreed with the Committee's recommendation to re-define the starting materials, implement GMP for step C by end of March 2014, and update the dossier *via* standard post-approval variation procedures.

In addition, the CHMP recommends the following points for investigation:

- Review the limits for impurities when sufficient commercial scale experience has been gained to fully assess the capability of the active substance manufacturing process. If necessary, specification of the active substance should be tightened via appropriate regulatory procedure.
- Review the limits for specified degradation products when sufficient commercial scale experience has been gained to fully assess the capability of the finished product manufacturing process and its long term stability. If necessary, specification of the finished product should be tightened via appropriate regulatory procedure.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non clinical package was provided, including a single-dose oral toxicity study in rats; repeat-dose oral toxicity studies in mice (up to 3 months), rats (up to 6 months) and dogs (up to 9 months), genotoxicity tests both in vitro and in vivo; and a full developmental and reproductive toxicity program. Two-year oral carcinogenicity studies in mice and rats have also been provided during the procedure.

All of the definitive safety pharmacology, toxicology, and toxicokinetic studies were conducted in accordance with Good Laboratory Practice (GLP). Pilot, exploratory, and mechanistic studies

were either conducted in full compliance with GLP procedures or were conducted using appropriate protocols and documentation to assure data integrity.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Sofosbuvir is a prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is phosphorylated intracellularly to the active triphosphate form (GS-461203). The nucleoside triphosphate is a non-obligate chain-terminating analogue of UTP that competes for incorporation at the HCV NS5B polymerase active site. Viral RNA synthesis is inhibited secondary to incorporation of the phosphorylated metabolite into nascent viral RNA by the HCV RNA-dependent RNA polymerase. In biochemical assays direct inhibition of NS5B polymerase was shown and characterised by IC_{50} values ranging from 0.7 to 2.6 µM.

Secondary pharmacodynamic studies

Sofosbuvir (S-diastereomer at phosphorus) and the diastereomeric mixture GS-9851 (isomeric mixture at phosphorus containing the S-diastereomer sofosbuvir and the R-diastereomer GS-491241) appeared to have a low potential for mitochondrial toxicity in cell-based assays as determined by measuring mitochondrial DNA (mtDNA) depletion or selective cytochrome c oxidase protein depletion. The triphosphate metabolite had no significant inhibitory activity on human DNA polymerases α, β and γ or RNA polymerase II as reflected in IC_{50}>200 µM.

In studies to determine potential for off target activity of GS-9851 no inhibition or induction greater that 50% at 10 µM was recorded in a panel of 171 receptors, enzymes and ion channels, including cytochrome P450 (CYP) enzymes. These test systems used various cell types, platelets and tissue systems and incubation times ranging from 10 min to hours. In an additional specific study to examine the effects of the major, inactive, metabolite GS-331007 (the nucleoside derivative) on a panel of receptors, enzymes, and ion channels, GS-331007 did not show > 50% inhibition or induction of any target at 10 µM.

Sofosbuvir and GS-9851 had no activity (EC_{50}>100 µM) against other viruses such as HIV-1 and hepatitis B virus (HBV). At 100 µM GS-9851 showed an 18% inhibition of HBV.

Safety pharmacology programme

Single oral doses of GS-9851 up to 1,000 mg/kg in rat and dog had no major effects on parameters monitored to determine potential for interference with the central nervous, respiratory and cardiovascular systems. In vitro, no significant inhibition of hERG current by GS-9851, GS-566500, GS-606965 and GS-331007 was reported at the highest concentrations used (100-300 µM).

Pharmacodynamic drug interactions

The potential for pharmacodynamic (PD) drug interactions is discussed in the Clinical section of the report.

2.3.3. Pharmacokinetics

PK parameters of sofosbuvir were determined in mouse, rat, dog and monkey. The oral bioavailability following administration to portal vein cannulated dogs was determined as approximately 10% while in pentagastrin-treated dogs bioavailability was reported as 18.7%. The hepatic extraction ratio was estimated as 74%. In vitro sofosbuvir was found to have a partially saturable efflux and low forward permeability as assessed in Caco-2 cell monolayers. Studies in vitro on CYP inhibition/induction, protein binding and transporters are available and assessed in the clinical PK section.

The stability of sofosbuvir and GS-9851 was investigated in vitro. The compounds were found to be stable in simulated gastric and intestinal fluids. GS-9851 was degraded rapidly in blood of mouse and rat, but was stable in non-rodent blood. Additional studies showed that sofosbuvir and GS-9851 were unstable in mouse and rat plasma due to esterase activity. Sofosbuvir, its diastereomer and the isomeric mixture GS-9851 were stable in human plasma.

Protein binding was low both for sofosbuvir and its major metabolite GS-331007 in dog and human. Due to instability protein binding for sofosbuvir could not be determined in mouse, rat and rabbit plasma, but protein binding of GS-331007 was minimal in mouse, rat and rabbit.

Tissue distribution was studied using whole body quantitative autoradiography and data indicated a similar pattern of distribution in albino and pigmented animals with levels generally higher in tissues of albino animals at 1 hour post dose, but lower than in pigmented animals at 24 hours. After single oral doses of 20 mg/kg in partially pigmented rats highest levels of radiolabel were generally determined at 4 to 6 hours post dose. Tissues with highest radioactivity included liver, alimentary canal, renal cortex, lymph node, spleen, thymus, bone marrow and lung. Levels in brain were low, but quantifiable up to 24 hours. There was no specific association of radioactive material with melanin. Studies in pregnant rats showed that sofosbuvir crossed the placenta. Foetal blood and brain sofosbuvir derived radioactivity was higher than in dams, but foetal liver and kidney had lower levels than corresponding organs in dams. Sofosbuvir-derived radioactivity was also quantifiable in milk from day 2 postpartum rats, but nursing pups did not appear to be extensively exposed to drug-derived radioactivity. Milk to plasma ratios were 0.1 at 1 hour and 0.8 at 24 hours.

In vitro studies in human liver microsomes showed that sofosbuvir was an efficient substrate for Cathepsin A (Cat A) and carboxyl esterase 1 (CES1). There were no indications of metabolism via urdine diphosphate glucuronosyltransferases (UGTs) or flavin-containing monooxygenase (FMO). Sofosbuvir was cleaved by CatA and CES1 and subsequent activation steps included amino acid removal by histidine triad nucleotide-binding protein 1 (HINT1) and phosphorylation by uridine monophosphate-cytidine monophosphate (UMP-CMP) kinase and nucleoside diphosphate (NDP) kinase. In vitro data indicated that Cat A preferentially hydrolysed sofosbuvir (the S-diastereomer) while CES1 did not exhibit stereoselectivity. This would be consistent with studies using GS-9851 showing a less efficient metabolism to the triphosphate in the hepatically-derived cell line containing the Clone A replicon and shown to exhibit low CES 1 activity, but high Cat A activity compared with primary human hepatocytes. Following incubation of hepatocytes from rat, dog, monkey and human GS-9851 was converted to the triphosphate GS-461203 in all species, most efficiently in human. Sofosbuvir was also readily converted to the triphosphate in dog liver after oral doses and was the dominant

metabolite at all time points assessed with a long half-life of approx. 18 hours. The active metabolite GS-461203 could not be detected in monkey. Further while GS-461203 was detected in rat liver, it could not be measured in liver from mouse.

Isomeric conversion was not evident in rat, dog and human plasma and human urine.

After single oral doses in mouse and rat GS-9851 was not detected in plasma, but the nucleoside metabolite GS-331007 could be determined in plasma and liver. Overall no marked differences in PK between male and female animals were evident and no accumulation appeared to take place after repeated doses.

In male mice given a single oral dose of 20 mg/kg of sofosbuvir, two metabolites GS-331007 and GS-566500, were found in plasma, accounting for 86.5% and 13.5%, respectively, of total plasma radioactivity. These two metabolites were also detected in urine with GS-331007, accounting for 55.2% of radioactivity in 0-168 hours. In mouse faeces, only GS-331007 was observed and amounted to 14.1% of total radioactivity in 0-168 hours.

In male rats given a single oral dose of 20 mg/kg of sofosbuvir, the major metabolite in plasma was GS-331007 (M1) accounting for 84.2% of area under the concentration-time curve (AUC) of total plasma radioactivity. GS-566500 (M2) was observed in plasma at levels of 10.6%. In urine GS-331007 and GS-566500 were major components. In another study using female rats plasma M1 was 53.9% and M2 was present at 14.2%. In rat liver three metabolites, M1 (4.8%, GS-331007), M2 (0.9%, GS-566500) and M3 (GS-606965) were observed, the latter a minor component. The parent compound was not detected in plasma, urine or faeces. The major pathway in rat was hydrolysis of GS-7977 to GS-331007 and minor pathways were hydrolysis of GS-7977 to GS-566500 and GS-606965.

In dog following a single oral dose of 20 mg/kg of sofosbuvir three metabolites in plasma were identified, GS-331007, GS-566500 and M4 (proposed glucuronidation product of GS-606965), accounting for 93.4%, 1.6% and 0.5%, respectively of total plasma AUC. Parent compound amounted to 4.5%. In dog (and mouse) the majority of a radioactive dose was recovered in urine within 8 to 12 hours.

GS-331007 and GS-566500 were detected in all species with GS-331007 being the major drug-related material in all species and all matrices. In plasma, urine and faeces of all species administered sofosbuvir the primary metabolite detected was GS-331007 accounting for >80% of total exposure. In rat liver and plasma GS-566500 was also detected. The metabolite profile was overall comparable between non-pregnant, pregnant and postpartum rats and in milk of postpartum rats with GS-331007 and 2 sulfate conjugates of GS-331007 being the major metabolites.

The major species used in toxicology studies, rat and dog, appear to have been adequately characterised pharmacokinetically. Less data is available for the rabbit, the second species used in studies on reproduction toxicity, but it has been ascertained that GS-331007 is formed in this species. The data indicate species differences in the disposition of sofosbuvir that could partly relate both to rate of hydrolysis in primary matrices as well as to the formation of the active triphosphate metabolite. Thus, sofosbuvir can be detected in human plasma, but not in species (rat) used in general toxicology studies, micronucleus study (mouse) and reproduction toxicity studies (rat) also indicating that, in contrast to the major metabolite (M1) that is formed in all

species, the potential toxicity of sofosbuvir may not have been fully investigated. In addition, the extent of exposure to the active triphosphate is unclear and it is noted that while this could be detected in rat liver, levels could not be determined in mouse liver, likely at least partly due to technical particulars. Formation of the triphosphate was shown in hepatocytes from human, dog, monkey and rat. The triphosphate was also detected in dog and rat liver, but in monkey and mouse, liver levels were below the limit of detection. This variability is likely explained by factors related partly to technical difficulties. The assessment of liver metabolite levels is part of an exploratory analysis in explanted liver tissues taken from HCV-infected subjects undergoing liver transplantation after up to 48 weeks of SOF/RBV as part of the ongoing study P7977-2025 (see below).

2.3.4. Toxicology

In the non-clinical testing program, sofosbuvir was administered orally to CD-1 mice, Sprague-Dawley rats, and Beagle dogs for general toxicity evaluation. The oral route of administration was chosen because this is the route of administration in patients. The diastereomeric mixture GS-9851 was used in early nonclinical and clinical studies, but the single diastereomer sofosbuvir (SOF) was chosen for development and registration. Pivotal toxicology studies were conducted with SOF, and carried out in accordance with GLP. The non-clinical toxicological package is considered to comply with current ICH guidelines. However, it should be noted that it was not possible to determine exposure to sofosbuvir in rodents likely due to high esterase activity and that the level of exposure to the active moiety, the triphosphate, which is mainly present intracellularly, is generally not known in the toxicology studies. Exposure margins are therefore primarily calculated using the major metabolite GS-331007. The only dose-related substance with a systemic exposure of >10% of total radioactivity was GS-331007 also indicating that only this metabolite would require qualification in non-clinical studies.

Single dose toxicity

Single dose toxicity study was performed with GS-9851/PSI-7851 (the diastereomeric mixture) in rats. No mortality, clinical signs, body weight changes, macroscopic pathology, or organ weight changes for liver and kidney up to a highest dose of 1,800 mg/kg (maximum observed concentration [C_{max}] 15(M)/15(F) µg/ml and AUC_{last} 205(M)/176(F) µg·h/ml for GS-331007).

Repeat dose toxicity

Sofosbuvir was generally well tolerated for up to 3 months in the mouse, 6 months in the rat, and 9 months in the Beagle dog. Target organs for toxicity were the heart, liver, gastrointestinal tract, and haematopoietic cells. Preterminal mortalities occurred in rats at high dose levels (27-fold clinical exposure as based on AUC), and in a single dog dosed at 500 mg/kg/day for 6 months (24-fold clinical exposure as based on AUC).

Preterminal mortalities

In the 14-day dose range finding study in mice, one male dosed at 1500 mg/kg/day was found dead on day 10. The cause of death was not determined. In the 3-month mouse study, preterminal mortality occurred at all dose levels (≥100 mg/kg/day), and also in controls. There was no clear dose response, and in several cases the cause of death was due to gavage error and aspiration. Cause of death could not be determined in all cases; however, histopathological

examination was not carried out on toxicokinetic (TK) animals. No target organs for toxicity were identified and the only effects related to dosing with sofosbuvir were lower food consumption and decreased body weight and body weight gain at the high dose level. Taken together, these data do not substantiate a clear causative link between sofosbuvir treatment and preterminal mortality in mice.

In the 7-day rat study, 2,000 mg/kg/day resulted in early mortalities probably due to myocardial degeneration (see under *Heart*). In the 9-month dog study, one male dosed at 500 mg/kg/day was preterminally sacrificed on Day 172. According to the applicant, the clinical and post-mortem findings in this dog were typical of idiopathic haemorrhagic gastroenteritis, a spontaneous disease of unknown aetiology. However, in view of the fact that haemorrhage in the stomach or intestine was observed in two high dose dogs in the 7-day and 1-month studies, respectively, it seems more likely that the haemorrhagic enteritis in the preterminally killed dog in the 9-month study was in fact due to treatment with sofosbuvir.

Heart

In the 7-day rat study, 2,000 mg/kg/day resulted in early mortalities probably due to myocardial degeneration. This finding was also present in 2/3 surviving females dosed at 2,000 mg/kg/day, as evaluated after a 14-day recovery period. The margin to the no observed adverse effect level (NOAEL) for myocardial degeneration and associated mortality in the 7-day rat study is small (3-fold based on AUC). However, cardiac toxicity/mortality occurred only at the highest dose level (2,000 mg/kg/day) and no doses between 250 and 2000 mg/kg/day were tested. In longer duration studies (up to 6 months), no cardiac toxicity or mortalities occurred at 9-fold exposure levels to clinical AUC. Taken together, the nonclinical data indicate that cardiac toxicity was observed only in the early dose-range finding rat study at high systemic exposure achieved at a lethal dose level and was not observed in any other toxicity studies, including the carcinogenicity studies.

Vacuolar degeneration of the myocardial muscle fibres was observed in the preterminally killed dog in the 9-month study. The study pathologist speculated that this finding may have been a response to hypotension, tachycardia, and hypovolaemia secondary to haemorrhagic enteritis. This explanation seems plausible, although a direct effect on the myocardium cannot be completely excluded. No histopathological myocardial changes were observed in other dogs, in any of the conducted studies.

QT prolongation was present in males dosed at 1,500 mg/kg/day in the 7-day study, but did not occur in the longer term dog studies. The systemic exposure (C_{max}) to GS-331007 at 1,500 mg/kg/day was 90-fold higher than the clinical exposure in patients treated at 400 mg and likely exposure to sofosbuvir was also significant although not directly determined in this study. Taken together, these animal data do not indicate that sofosbuvir is likely to produce QT prolongation in patients treated at the recommended dose of 400 mg.

Gastrointestinal tract

Diarrhoea and other clinical signs related to effects on the gastrointestinal (GI) tract occurred in all repeated-dose toxicity studies in rats, from 7 days up to 6 months. Some of these effects also occurred, to a lesser degree, in control animals, suggesting that the vehicle may have contributed. There were no histopathological changes in the GI tract of rats. In some studies,

the GI effects were associated with decreased body weight/body weight gain and decreased food consumption.

Clinical exposure margins to the GI effects in rats are small or non-existent. The applicant argues that the GI effects resolved in many rats with continued dosing, had no effect on the general welfare of the animals, and were not associated with any histopathological findings. Due to these circumstances, and also because of the vehicle contributory effect, the applicant proposed a NOAEL at the high dose (500 mg/kg/day) for both the 1- and 3-month studies. However, the treatment-related GI effects were more pronounced in the 1- and 3-month studies as compared with the 6-month study and thus it is considered that the originally (in the study reports) proposed NOAEL at 20 mg/kg/day in the 1-month study, and <20 mg/kg/day in the 3-month study, shall remain. It is agreed that the vehicle may have contributed to a certain degree, and thus it is unclear whether these effects are relevant to the clinical situation. Since the GI effects in rats were not associated with any histopathological changes, and furthermore were fully reversible upon cessation of dosing, they are not considered to be of major concern for human safety despite the small exposure margins.

Diarrhoea and emesis were also present in all dog repeated-dose toxicity studies, from 7 days up to 9 months. In some studies, these GI effects were associated with decreased body weight/body weight gain and decreased food consumption. The lowest NOAEL for GI effects in the dog was 20 mg/kg/day in the 3-month study, corresponding to a 2-fold exposure margin based on AUC. Increased mucus secretion in the stomach was observed in dogs treated at 1,500 mg/kg/day in the 7-day study, possibly indicating local irritancy. Haemorrhage was present in the lamina propria of the colon in one high dose recovery dog in the 7-day study, and also in the lamina propria of the stomach pylorus region in a dog treated at 500 mg/kg/day in the 3-month study. Furthermore, haemorrhage was observed in the lamina propria of the jejunum in the preterminally killed high dose dog in the 9-month study. The lowest NOAEL for haemorrhage in the GI tract was 100 mg/kg/day in the 6-month Phase of the 9-month study, corresponding to a 10-fold exposure margin based on AUC. Thus, there is an acceptable margin to these more severe GI effects in dogs. Similar to the situation in rats, all GI effects in dogs were reversible upon cessation of dosing.

Liver

Increased liver weights were observed at ≥100 mg/kg/day in the 1-month rat study, at ≥30 mg/kg/day in the 7-day dog study, and at 500 and ≥100 mg/kg/day in the 1-month and 3-month dog studies, respectively. At the high dose level (1,500 mg/kg/day) in the 7-day dog study, this organ weight increase correlated with hepatocellular hypertrophy. There was an increase in CYP2A1 activity in rats at the high dose level (500 mg/kg/day) in the 1-month study. Although liver samples for CYP analysis were taken in the 1-month dog study, they were not analysed. The increased liver weights in both rats and dogs, as well as the hepatocellular hypertrophy in dogs, are most likely related to the induction of drug-metabolising enzymes, which is an adaptive and non-adverse effect.

Histopathological liver findings at 1,500 mg/kg/day in the 7-day dog study included hepatocyte apoptosis, microvesiculation, decreased intracellular glycogen, and Kupffer cell pigmentation. These findings were associated with increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkalin phosphatase (ALP) and bilirubin. Except for the decreased

glycogen, the margin to the NOAEL for these effects is 13-fold based on AUC. Decreased glycogen was present in all dose groups, but not associated with increased liver enzymes or any other liver effects at the mid and low dose levels and is thus not considered to be an adverse effect. All histopathological liver findings and associated clinical chemistry changes in the 7-day dog study were reversible after the 14-day recovery period. No histopathological liver findings were present in the longer term dog studies at doses up to 500 mg/kg/day, corresponding to a 24-fold exposure margin (GS-331007) as based on AUC in the 9-month study.

Haematopoietic cells

Effects on erythropoiesis were present in the 7-day rat study (3-fold margin to NOAEL as based on AUC) and in all dog studies, from 7 days up to 9 months. The lowest exposure margin to NOAEL in dogs for these effects was 5-fold, as based on AUC (dog 1-month study). Haematology analysis showed decreased red blood cell count and lower haemoglobin and/or haematocrit concentrations. The decreased erythron mass was reflected in bone marrow changes such as lower percentage of erythroid precursors and depression of erythropoiesis. Both the peripheral and bone marrow changes were reversible. In the 6-month Phase of the 9-month dog study, there were bone marrow alterations at the high dose (500 mg/kg/day), which were not present at the end of the 9-month study.

Exposure margins were low, but according to the applicant, sofosbuvir has not been associated with haematologic side effects in the clinic when administered as monotherapy. However, such effects have been observed in Phase 2 and 3 clinical trials, when sofosbuvir has been coadministered with RBV with or without PEG. Both these substances are known to cause haematologic toxicity.

Other noteworthy findings

Lymphocyte depletion/necrosis and thymus atrophy occurred in rats and dogs treated at high dose levels and are considered to reflect generalised stress. Adrenal cortical hypertrophy at 1500 mg/kg/day in the 7-day dog study is also considered to be related to stress. These findings were reversible upon cessation of dosing.

Activated partial thromboplastin time (APTT) was increased at 1,500 mg/kg/day in the 7-day dog study (not reversible after 14 days), and at ≥100 mg/kg/day in the 6-month Phase of the 9-month dog study (reversible after 1 month). The increase was slight, and there did not seem to be any correlation with the intestinal haemorrhage present in the preterminally killed high dose dog.

Transient lameness was noted in dogs ≥100 mg/kg in the 9-month study. According to the applicant, the most likely cause of lameness was incidental injury. However, no incidents of lameness were observed in vehicle-treated control dogs. It should be noted that limping/lameness was present in single male dogs at 100 mg/kg/day in the 1- and 3-months studies. Even so, it is agreed that no causal relationship has been established.

A few other findings (e.g. organ weight changes, alterations in urine parameters etc) with potential or uncertain relationship to treatment with sofosbuvir were either of small magnitude or inconsistent between studies, and thus their relevance to the human clinical situation is questionable.

Genotoxicity

The diastereomeric mixture of SOF (GS-9851/PSI-7851) was shown to be negative in vitro in the *Salmonella typhimurium* reverse mutation assay and in a mammalian chromosome aberration test performed in primary human lymphocytes. An in vivo chromosome aberration assay in mouse was also negative. A sufficiently high exposure of the two metabolites GS-566500 (AUC_{last} 194(M)/134(F) µg·h/ml) and GS-331007 (AUC_{last} 133(M)/115(F) µg·h/ml) was achieved, while exposure to SOF (GS-9851) was low (AUC_{last} 0.7(M)/3.6(F) µg·h/ml). The results suggest that SOF does not have any genotoxic potential.

Carcinogenicity

There was no evidence of a carcinogenic effect after 2-year daily oral gavage administration of SOF to rats or mice. At the highest doses tested, exposures to the metabolite GS-331007 were 7/30 (male/female) and 13/17 (male/ female) times higher in mice and rats, respectively, as compared to the clinical exposure at 400 mg sofosbuvir (AUC_{tau} 7.20 µg.h/ml).

Reproduction Toxicity

Daily oral doses of SOF at up to 500 mg/kg for 28 days (males) or 14 days (females) prior to cohabitation, during cohabitation, and through scheduled termination (males) or Day 7 of gestation (females) did not adversely affect mating, fertility, or embryo survival at any dose level. SOF did not affect reproductive organ weight or produce macroscopic findings or histopathologic findings in reproductive organs in either sex in the performed repeat dose toxicity studies. SOF is therefore not expected to have any effect on fertility.

Embryo-foetal studies were performed with SOF in rats and rabbits. In rats SOF did not affect intrauterine growth and survival (mean numbers and/or litter proportions of viable foetuses, postimplantation loss and foetal body weights). No effects were seen on external, visceral, and skeletal foetal morphology at dose levels up to 500 mg/kg/day. Maternal and foetal NOAEL was therefore considered to be 500 mg/kg. At this dose, the maternal AUC_{0-24} for GS-331007 on gestation day (GD) 18 was 72 µg·h/ml and at GD6 34 µg·h/ml. When compared to the mean AUC at the recommended clinical dose (400 mg), the margin of exposure for GS-331007 at the NOAEL in this study is 10. Pregnant rabbits tolerated daily oral doses of SOF up to 300 mg/kg during the period of major organogenesis without any adverse effects of any sort on either the dams or developing foetuses. The NOAEL for developmental toxicity is considered to be 300 mg/kg/day, which produced a systemic exposure of 8.66 and 200 µg·h/ml for SOF and its metabolite GS-331007, respectively, corresponding to exposure margins for SOF and GS-331007 of 10 and 28, respectively, when compared to the mean AUC at the recommended clinical dose (400 mg).

In the *prenatal and postnatal development study* performed in rats no adverse SOF-related effects were noted in F0 females at any dosage level during gestation and lactation and F1 postnatal survival, body weights, developmental landmarks, startle response, motor activity, learning and memory and reproductive performance were unaffected. Intrauterine growth and survival of F2 foetuses were also unaffected. No SOF-related external malformations or developmental variations were noted in F2 foetuses. Animals were not exposed to significant levels of SOF while exposure to the metabolite GS-331007 were 12 times the expected maximum clinical exposure in F0 dams after exposure to 500 mg/kg/day at lactation day (LD)

10 (AUC_{0-24} 83 µg·h/ml) and ~6 times at GD6 (AUC_{0-24} 40 µg·h/ml). F1 Pups were found to be exposed to significant but ~50 times lower levels of the metabolite GS-331007 (AUC_{0-24} 1.5 µg·h/ml in the 500 mg/kg/day group) on postnatal day (PND) 10, but not to be exposed to GS-566500.

According to the relevant Guideline "The dose range tested by the applicant should have covered a dose resulting in minimal maternal toxicity such as e.g. decreased body weight or food consumption." Since no effects were seen on body weight or food consumption in the studies performed it is concluded that the dose range used in the studies was not high enough to fully explore the potential of sofosbuvir to induce reproductive and developmental toxicity. In addition, due to the high plasma esterase activity in rats and absence of sofosbuvir in plasma it is concluded that the studies on embryo foetal toxicity in rabbits, where plasma levels higher than that expected in the clinical situation were detected, is the only study where possible effects of sofosbuvir *per se* have been investigated. The active triphosphate GS-461203 was detected in rat liver samples despite the lack of detectable SOF plasma levels, indicating that prodrug exposure was achieved in rats. However, it is not possible to compare the tissue levels of the active triphosphate obtained with that in humans and it is therefore not possible to fully estimate exposure margins achieved for either sofosbuvir or its metabolites relative to the exposure in humans at the recommended clinical dose.

No toxicity studies in *juvenile animals* were conducted with SOF which is considered to be acceptable since sofosbuvir will initially be registered for adults only.

Local Tolerance

SOF is predicted to be a non-corrosive/ non-severe eye irritant based on results from an in vitro Bovine Corneal Opacity and Permeability Assay and is classified as a "non-irritant" in a dermal irritation study in rabbits. In addition results from a Local lymph node assay indicate that SOF is not a skin sensitizer.

Other toxicity studies

Impurities

Phenol, GS-566500, GS-606965 and GS-331007 are metabolites of SOF and are considered to be qualified at the proposed levels in drug product (0.5 % at shelf life). The proposed specification levels of 0.5 % (at shelf life), equal to ~0.04 mg/kg/day (2 mg/day/50 kg), for GS-607699 and GS-607670 in drug product and the process impurities GS-491241, GS-615014 and GS-617190 present in the drug substance, are also considered to be acceptable from a toxicological point of view.

Sofosbuvir and the process intermediates generated during manufacture were evaluated in silico for potential genotoxicity using two predictive toxicity software programs, DEREK for Windows (Lhasa Ltd) and FDA Model Applier (Leadscope). Upstream intermediates from the synthesis of the starting materials were also examined by DEREK.

The genetic toxicity suite of the Leadscope Model Applier software resulted in positive genotoxicicty predictions for sofosbuvir and some of the process intermediates. The large majority of these structural features in the alerting intermediates were also found in the positive prediction for sofosbuvir. However, since all structural feature hits identified by

Leadscope for process intermediates either map to the same features identified by Leadscope for sofosbuvir or were concluded to be entirely implausible when evaluated using well-founded chemical principles, Leadscope Model Applier software was concluded not to provide a reliable prediction of genetic toxicity for sofosbuvir process intermediates. This was further supported by the DEREK Evaluation of Sofosbuvir, process intermediates and precursors to the starting materials which did not reveal any structural alerts except for the precursor GS-606978.

The only compound identified from in silico screening that may be a potential genotoxic impurity was therefore concluded to be the chloride GS-606978. Purging studies and batch analysis demonstrate that GS-606978 is effectively purged and decomposed during the sofosbuvir production process. Spikes of up to 50,000 ppm purged to less than 0.50 ppm when carried through the representative process. These results thus demonstrate that even if GS-606978 were present in starting material at the limit for an unspecified impurity (not more than [NMT] 0.15%), it would be purged well below the threshold of toxicological concern (TTC) limit of 1.5 µg/day or 3.75 ppm for a 400 mg daily dose of sofosbuvir.

Bridging toxicity studies

14-day bridging toxicity studies comparing the isomeric mixture (PSI-7851) with the single isomer SOF (PSI-7977) have also been performed in rat and dog. No differences were detected and the toxicity and systemic exposure profiles were concluded to be similar for PSI-7851 and PSI-7977 in both studies. In the study in rat one male given PSI-7851 had minimal myofibre degeneration located at the apex of the heart. Because this finding was graded as minimal and can be a manifestation of cardiomyopathy that occurs spontaneously in rats, the finding may be incidental and unrelated to PSI-7851. This conclusion is further supported by historical control data for the incidence of cardiomyopathy within the same rat strain from the contract laboratory. The percentage of male control animals within a study that had cardiomyopathy ranged from 0% to 33% while in the 14-day bridging rat study with GS-9851 and SOF, the single incidence of cardiomyopathy in the GS-9851 group occurred at 10%, that is within the historical control of the laboratory.

Phototoxicity

No phototoxicity study has been performed with sofosbuvir. This is acceptable since sofosbuvir was shown not to absorb light within the range of 290 to 700 nm and since no accumulation in dermal or ocular tissues has been detected.

2.3.5. Ecotoxicity / environmental risk assessment

SOF is a pro-drug and the active substance is the triphosphate GS-461203. Neither the pro-drug SOF nor the active moiety GS-461203 enter the environment at >10% of the administered dose. Therefore neither SOF nor GS-461203 is considered to be environmentally relevant or present a potential environmental risk from their use in patients. The focus of the environmental risk assessment of SOF is instead GS-331007, the only drug residue detected in total excreta at >10% of the applied radioactive dose (GS-331007 accounted for 79.6%).

The mean partition coefficient was 0.398, 0.286 and 0.0593, at pH 4, 7 and 9, respectively, (log K_{ow} -0.417, -0.576 and -1.28, respectively) and GS-331007 is therefore not a persistent, bioaccumulative and toxic (PBT)-substance.

A refined market penetration of 3.5% (the highest relevant nationwide estimated prevalence) was used to calculate a refined $PEC_{surface\ water}$ value. The refined $PEC_{surface\ water}$ of 7.0 µg/L is significantly higher than the action limit of 0.01 µg/L ($PEC_{surface\ water}$ based on the default F_{pen} is 2.0 µg/L and is thus also higher than the action limit). A Phase IIA assessment has therefore been performed and since a partition to sediment was indicated (> 10% AR shifted after 14 days) a further assessment with a sediment dweller in Phase II B has also been performed. Since results indicate that GS-331007 does not adsorb to soils or activated sludges, aquatic toxicity has been the focus of Phase IIA analysis.

None of the ratios between the predicted environmental concentrations and predicted no effect levels for the Sewage treatment plant-, Surface water- or Groundwater-compartment were above 1 and no further studies are therefore required. In the Phase IIB analysis on sediment dweller the risk quotient was also found to be below 1.

The ultimate degradation of GS-331007, based on $^{14}CO_2$ generated during the test, was between 10 – 20% after 100 days at 20°C (with DT_{50} values of 60 and 66 days for the total system dissipation in silt loam and sand sediments, respectively). A single significant transformation product was observed in surface water. This was identified as an oxidation product of GS-331007 (a carboxylic acid). Since this transformation product was not seen to degrade in the test system it is potentially persistent.

Based on the data presented it is concluded that the environmentally relevant residue of sofosbuvir, GS-331007, is not expected to pose a risk to the environment.

However, considering the high HCV prevalence in some regions, and huge differences in effectiveness in collection systems of unused drugs, Sofosbuvir might be also relevant for ERA. The issue is addressed by including a precautionary statement in the Package Leaflet clearly warning against inappropriate disposal of unused medicines and directing patients to information sources able to provide details of local collection systems.

Table 1. Summary of main study results

Substance (INN/Invented Name): 2'-Deoxy-2'-fluoro-2'-C-methyluridine (GS-331007, environmentally relevant pharmaceutical residue of **Sofosbuvir**			
CAS-number (if available): 863329-66-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	- 1.28 (pH = 4) -0.417 (pH = 7) -0.576 (pH = 9)	Potential PBT: No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-1.28…-0.417	not B
	BCF	*not assessed*	-
Persistence	DT50 or ready biodegradability	*$DT_{50,water}$: 51-56 days (dissipation)*	P
Toxicity	NOEC or CMR	*NOEC = 26 000 µg/L*	*not T result has no relevance as not B*
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, Default:	2.0	µg/L	> 0.01 threshold:

Phase II refinement based on sales projections at local scale	0.025				Yes
Other concerns (e.g. chemical class)	-	-			No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 and OCSPP 835.1110	Soil: K_{oc}=17.1, 18.0, 31.2 L/kg Sludge: K_d =12.8, 32.9 L/kg			-
Ready Biodegradability Test	OECD 301	*not provided*			OECD 308 test performed
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =51-56 days (dissipation) $DT_{50, sediment}$ = *not applicable* $DT_{50, whole system}$ = 51-56 d (dissipation) $DT_{50, whole system}$ = > 100 d (degradation) % shifting to sediment => 10 % from day 3			One significant transformation product formed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	≥94 61	mg/ L	0-72 h, growth rate 0-72 h, inhibition
Daphnia sp. Reproduction Test/*Daphnia magna*	OECD 211	NOEC	26	mg/ L	21 day, reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	≥10	mg/ L	-
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	≥ 1,000	mg/ L	as EC_{10}
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	-	L/kg	%lipids: -
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	-		-
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	-	mg/ kg	-
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	-	mg/ kg	-
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	-	mg/ kg	-
Collembola, Reproduction Test	ISO 11267	NOEC	-	mg/ kg	-
Sediment dwelling organism /	OECD 218	NOEC	20	mg/ kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

Sofosbuvir is a prodrug that is hydrolysed to an intermediate subsequently phosphorylated intracellularly to an active triphosphate form with activity against the HCV NS5B RNA polymerase. No significant inhibition of host polymerases by the active metabolite was evident.

Sofosbuvir also had no remarkable effects on parameters monitored to investigate mitochondrial toxicity in cell-based assays. Screening for secondary activity was conducted using the isomeric mixture and the metabolite GS-331007 at concentrations of 10 µM. From the non-clinical point of view the data has overall provided adequate characterisation of the primary pharmacology of sofosbuvir and its major metabolites.

PK and toxicokinetic data with sofosbuvir seem overall sufficient. The assessment of sofosbuvir potential toxicity, general as well as reproductive, may, however, be compromised by species differences such that there are uncertainties as to the extent of exposure to both sofosbuvir and the active triphosphate metabolite. The parent drug sofosbuvir is, in contrast to in humans, not detectable in rodent plasma, likely due to high esterase activity.

Sofosbuvir seemed overall well tolerated in general toxicity studies of up to 9 months in rat and dog. In toxicity studies at high doses noted effects were noted in the gastrointestinal tract, liver and the haematological system. Reproductive toxicity was studied in rat and rabbit and while no relevant potential for adverse reproductive effects was evident, the high dose likely was suboptimal in these studies.

Studies in vitro and in vivo for genotoxic potential were negative and consistent with a low mutagenic potential of sofosbuvir. Long-term carcinogenicity studies in mouse and rat showed no carcinogenic potential for sofosbuvir. The only compound identified from in silico screening of process intermediates and precursors that may be a potential genotoxic impurity was concluded to be the chloride GS-606978, which was shown to be purged well below the TTC limit of 1.5 µg/day even if present in the starting material at the limit for an unspecified impurity (NMT 0.15%).

2.3.7. Conclusion on the non-clinical aspects

The review of non-clinical data available for sofosbuvir has provided adequate characterisation of primary pharmacological and toxicological properties of the compound and overall indicates no major issues for concern.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant claimed that clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

This Marketing Authorisation Application includes 22 clinical studies pertaining to the Clinical Pharmacology development of SOF (see table 2).

Table 2. Overview of sofosbuvir clinical studies

Clinical Study/ Type of Study	SOF/GS-9851				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose (mg)	n	
Comparative BA/BE Studies in Healthy Subjects					
GS-US-334-0131 Cohort 5 Phase 1	SOF 400-mg tablet	DC1203 B1	400	16	Not applicable
P7977-0111 Phase 1	SOF 100-mg tablet	9J074-P2	200	24	Not applicable
	GS-9851 100-mg tablet	9J075-P1	200		
P7977-1318 Phase 1	SOF 200-mg tablet	11D034-P1	400	40	Not applicable
	SOF 400-mg tablet	11D050-P1			
PK and Initial Tolerability Studies in Healthy Subjects					
Mass Balance Study					
P7977-0312 Phase 1	SOF 400-mg capsule containing [^{12}C]-SOF and [^{14}C]-SOF	40409002 20100414	400	7	Not applicable
Single-Dose Study					
P7851-1101 Phase 1	GS-9851 300-mg bulk powder	38508001A	25 50 100 200 400 800	42	Placebo capsule
PK and Initial Tolerability Study in HCV-Infected Subjects					
Multiple-Dose Study in Subjects with Genotype 1 HCV Infection					
P7851-1102 Phase 1	GS-9851 25-mg capsule	9D040-P1	50 100	40	Placebo capsule
	GS-9851 100-mg capsule	9F056-P1	200 400		
Intrinsic Factor PK Studies					
Renal-Impairment Study					
P7977-0915 Phase 1	SOF 200-mg tablet	0G069-P2	400	30	Not applicable
Hepatic-Impairment Study					

Clinical Study/ Type of Study	SOF/GS-9851				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose (mg)	n	
P2938-0515 Phase 1	SOF 200-mg tablet	0G069-P2 11D034-P1 0L116-P1 0F056-P1	400 300	25	Not applicable
Extrinsic Factor PK Studies					
Drug-Interaction Study Between SOF and ARVs in Healthy Subjects					
GS-US-334-0131 Cohorts 1-4 Phase 1	SOF 400-mg tablet	11J111-P1	400	72	ATR (1 × 600 mg EFV/200 mg FTC/300 mg TDF tablet) DRV/r: DRV (2 × 400-mg tablet) + RTV (1 × 100-mg tablet) RAL (1 × 400-mg tablet) RPV (1 × 25-mg tablet)
Drug-Interaction Study Between SOF and Methadone					
P7977-0814 Phase 1	SOF 200-mg tablet	0G069-P1	400	15	Methadone (30–130 mg liquid or tablet formulation)
Drug-Interaction Study Between SOF and CsA or Tacrolimus in Healthy Subjects					
P7977-1819 Phase 1	SOF 200-mg tablet	11G086-P1	400	40	CsA (Neoral® [6 × 100-mg capsules]) Tacrolimus (Prograf® [1 × 5-mg capsule])
Drug-Interaction Study Between SOF and ARVs in HCV/HIV Coinfected Subjects					
P7977-1910 Phase 1 (Part A)	SOF 200-mg tablet (Used in all subjects in Cohorts 1 and 3, and 2 subjects in Cohort 2)	11G086-P1	400	34	EFV (1 × 600-mg tablet) FTC (1 × 200-mg tablet) TDF (1 × 300-mg tablet) ZDV (1 × 300-mg tablet) 3TC (1 × 150-mg tablet)
	SOF 400-mg tablet (Used in all subjects in Cohorts 4 and 5, and 2 subjects in Cohort 2)	DC1203B1 DC1204B1			RTV (1 × 100-mg tablet) DRV (1 × 800-mg tablet) RAL (1 × 400-mg tablet) ATV (1 × 400-mg tablet)
PK/PD and PD Studies in Healthy Subjects (QT/QTc Interval Study)					

Clinical Study/ Type of Study	SOF/GS-9851				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose (mg)	n	
P7977-0613 Phase 1	SOF 200-mg tablet	0G069-P2	400 1200	60	SOF placebo tablet Moxifloxacin (Avelox® [1 × 400-mg tablet]) Moxifloxacin placebo tablet
PK/PD and PD Studies in HCV-Infected Subjects					
Multiple-Dose and Combination Study in Subjects with Genotype 1 HCV Infection					
P2938-0212 NUCLEAR Phase 1	SOF 200-mg tablet	0G069-P1 0F056-P1	400 100 200 300	80	SOF placebo tablet
Sofosbuvir in Combination with PEG+RBV Study in Treatment-Naive Subjects with Genotype 1 HCV Infection					
P7977-0221 Phase 2a	SOF 100-mg tablet	9J074-P1	100 200 400	63	SOF placebo tablet Pegasys (180 µg/week subcutaneous injection) Copegus (RBV; 1000–1200 mg/day)
Clinical Studies Pertinent to the Claimed Indication					
P7977-0422 PROTON Phase 2b	SOF 100-mg tablet	0A004-P1 0B019-P1	200 400	146	SOF placebo tablet Pegasys (180 µg/week subcutaneous injection) Copegus (RBV; 1000–1200 mg/day)
P7977-0532 ELECTRON Phase 2a	SOF 200-mg tablet	0G069-P1 1A005-P1 11D034-P1 11J110-P1	400	120	SOF placebo tablet Pegasys (180 µg/week subcutaneous injection) Copegus (RBV; 1000–1200 mg/day)
P7977-0724 ATOMIC Phase 2b	SOF 200-mg tablet	0G069-P1 1A005-P1	400	332	Pegasys (180 µg/week subcutaneous injection) Copegus (RBV; 1000–1200 mg/day)
P2938-0721 QUANTUM Phase 2	SOF 200-mg tablet	11D034-P1	400	239	SOF placebo tablet RBV (Ribasphere; 1000–1200 mg/day)

Clinical Study/ Type of Study	SOF/GS-9851				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose (mg)	n	
GS-US-334-0107 POSITRON Phase 3	SOF 400-mg tablet	11K121-P1	400	278	RBV (Ribasphere; 1000–1200 mg/day) SOF placebo tablet RBV placebo tablet
P7977-1231 FISSION Phase 3	SOF 200-mg tablet	11G086-P1 11J110-P1	400	499	Pegasys (180 µg/week subcutaneous injection) RBV (Ribasphere; 800–1200 mg/day)
GS-US-334-0108 FUSION Phase 3	SOF 400-mg tablet	DC1203B2 DC1204B2	400	201	RBV (Ribasphere; 1000–1200 mg/day) SOF placebo tablet RBV placebo tablet
GS-US-334-0110 NEUTRINO Phase 3	SOF 400-mg tablet	DC1203B2	400	327	Pegasys (180 µg/week subcutaneous injection) RBV (Ribasphere; 1000–1200 mg/day)

[^{12}C]- = radiolabeled carbon 12; [^{14}C]- = radiolabeled carbon 14; 3TC = lamivudine; API = active pharmaceutical ingredient; ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated (Atripla®); ATV = atazanavir; BA = bioavailability; BE = bioequivalence; DRV = darunavir; EFV = efavirenz; FTC = emtricitabine; QT = electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarisation and repolarisation to occur; QTc = QT interval corrected for heart rate; /r = boosted with ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SOF = sofosbuvir; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Note: Only SOF and coadministered drugs relevant to this application are presented in this table.

2.4.2. Pharmacokinetics

In clinical studies the exposure to sofosbuvir and two of its metabolites, GS-566500 and GS-331007, has been determined using validated bioanalytical methods. Interconversion between sofosbuvir and its diastereomer GS-491241 has not been seen, neither in vitro nor in vivo in preclinical species. The active metabolite GS-461203 has not been measured in vivo. Efficacy, in terms of rapid viral response, has been shown to correlate with exposure to sofosbuvir as well as GS-331007.

Absorption

SOF is administered once daily as a 400 mg tablet. Following a single dose, the PK profile of sofosbuvir show rapid turnover with a t_{max} of 0.5 h and a short half-life of approximately 0.5 h. The bioavailability of drug related material is moderate to high, at least 50%, although the absolute value is unknown. The commercial formulation is bioequivalent to the formulations used in pivotal efficacy and safety studies.

In vitro studies show that SOF is subject to marked efflux, probably mediated by P-glycoprotein (Pgp) and/or breast cancer resistance protein (BCRP). Co-administration of a single dose of 600

mg Cyclosporin A (CsA) increased the exposure to sofosbuvir 4.5 fold providing further evidence of sofosbuvir being a sensitive substrate to efflux transporters.

Exposure to SOF and GS-566500 is increased by approximately 80% and 60%, respectively, when taken with a high fat meal. The rate of absorption slows down. The exposure in terms of AUC to GS-331007 is not affected by a high fat meal although C_{max} is 25% lower. The difference between SOF and GS-331007 with respect to food effect has not been explained. In pivotal clinical trials the recommendation has been to take SOF without regard to food. However, since SOF was taken together with RBV, which has to be taken with food, administration was in effect made in combination with a meal. Therefore the SmPC recommends that SOF is taken with food.

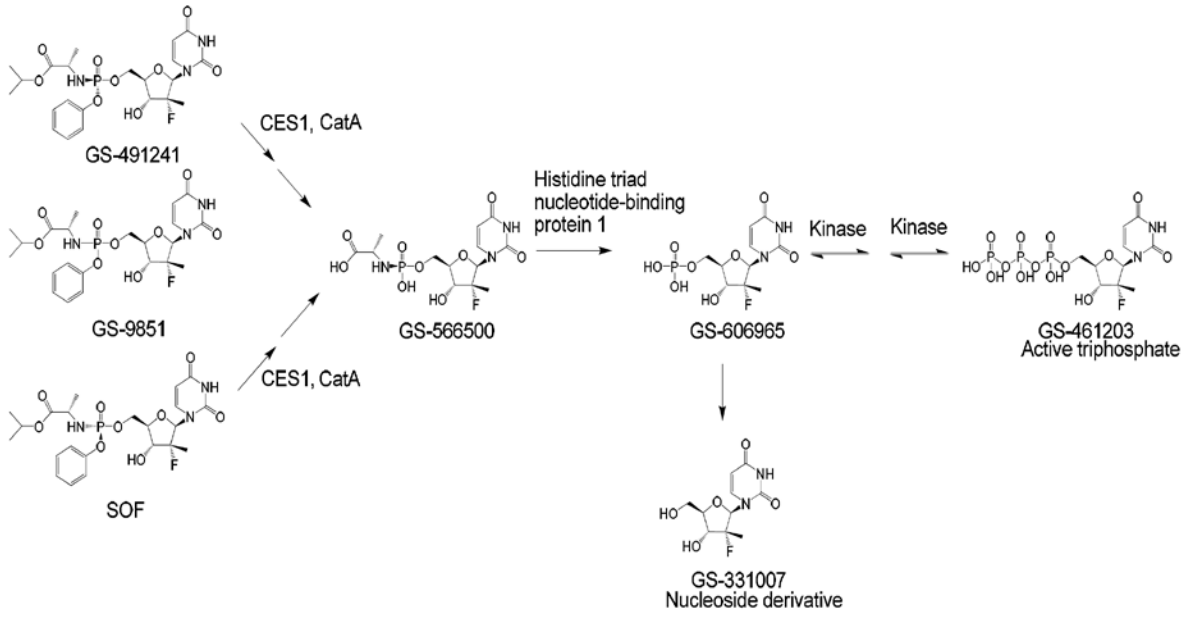
Distribution

Plasma protein binding of SOF (the fraction unbound is 18%) seems to be independent of concentration and no effect of renal impairment was seen on degree of binding. GS-331007 is minimally bound to plasma proteins.

Elimination

Sofosbuvir is subject to extensive first-pass metabolism in the intestine and in the liver. The active metabolite GS-461203 is formed through a chain of metabolic steps (Figure 1).

Figure 1. Intracellular metabolism pathway of GS-9851, GS-491241 and SOF (GS-7977)



In vitro, SOF is rapidly hydrolysed by CatA and CES1 to form GS-566500 which is further metabolised to eventually form the active triphosphate nucleoside analogue GS-461203. Involvement of CYP enzymes in the metabolism of sofosbuvir cannot currently be ruled out. Sofosbuvir is subject to very little renal elimination (fractional excretion [fe]=3.5%). Renal excretion has a greater importance in the elimination of GS-566500 and GS-331007. Active

secretion has a major role in the renal elimination; approximately half of the renal clearance of GS-331007 is due to active secretion. The transporters involved are unknown.

The intermediate metabolite GS-566500 peaks at 1 h and has a half-life of 2 h. The major metabolite GS-331007 peaks at 2 h and has a half-life of 26 h.

Most of a radioactively labelled SOF dose was excreted in urine (76%), predominantly as GS-331007 (78%) and to minor extent as SOF (<5%) and GS-566500 (<5%). In plasma, GS-331007 constituted the majority (90%) of measured radioactivity.

Pharmacokinetics of metabolites

Apart from SOF, the PK of GS-331007 and GS-566500 has been measured and partly characterised. The PK of the pharmacologically active metabolite GS-461203 has not been characterised. It is not clear which of the available entities (SOF, GS-566500 or GS-331007) is most predictive of efficacy and/or safety.

Pharmacokinetics in the target population

Population PK analyses of GS-331007 and SOF were performed using all available intensive and sparse PK samples collected in Phase 1, 2, and 3 studies in healthy and HCV-infected subjects. In the sofosbuvir Population PK model, apparent oral clearance after administration of the dose (CL/F) was approximately 30% *lower* in patients compared to healthy volunteers. In the GS-331007 Population PK model, the different HCV genotypes were associated with 50% to 60% *higher* CL/F as compared to healthy volunteers. The differing effect of patient status has not been explained. The population PK models can currently only be used for description of the observed data and not for predictions.

Dose proportionality and time dependencies

A between study comparison indicated that near dose linearity was observed for SOF and GS-331007. However, the 90% confidence interval (CI) for the power model (AUC_{inf} or C_{max} vs dose) mean slope did not contain 1 neither for sofosbuvir, nor for GS-331007. There was no evidence of marked time dependency.

Special populations

Renal impairment

Severe renal impairment led to a more than 7-fold increase in exposure to GS-331007 while mild and moderate renal impairment increased GS-331007 exposure less than 2-fold. Exposure to SOF and GS-566500 was increased approximately 3-fold in subjects with severe renal impairment. Safety margins calculated from results of toxicology studies are 5.4 to 11.6 for SOF and 1.6 to 3.5 for GS-331007 in subjects with mild and moderate renal impairment. The haemodialysis extraction ratio for GS-331007 was approximately 50%. Treatment of patients with severe renal impairment/end-stage renal disease (ESRD) is not recommended.

Hepatic impairment

Exposure to SOF and GS-566500 increased approximately 2-fold in patients with moderate (median Child-Pugh score of 8) and severe (median Child-Pugh score of 10) hepatic impairment. The exposure to GS-331007 was essentially unchanged. Of note, the viral

response was numerically lower in patients with hepatic impairment compared to historical controls.

Other intrinsic factors

Influence of gender, race, weight and age was evaluated using a Population PK approach. No apparent effects were observed. There is a lack of clinical experience treating patients older than 65 years of age. No data are available on the exposure in children or adolescents.

Pharmacokinetic interaction studies

Several in vitro DDI studies are inconclusive due to inadequate exposure to SOF. Further studies are being conducted to provide information about potential enzyme/transporter inhibition by SOF and results will be provided post-authorisation.

Renal secretion is involved in the elimination of GS-566500 and GS-331007. The transporter(s) involved are unknown. It is also unknown whether hepatic transporters are involved in the taking up of the polar SOF and its metabolites into the hepatocytes. This will be further investigated post-authorisation.

Induction of CYP3A4 and CYP2B6 was seen in vitro. An in vivo DDI study with oral contraceptives co-administered with sofosbuvir for 7 days did not show any sign of reduced exposure. The study is considered to be too short to fully exclude a minor induction. However, a clinically relevant effect is not expected based on the observed data.

DDI studies have been performed in healthy volunteers and patients to evaluate effect of SOF on the PK of antiretroviral agents (ARVs), methadone, CsA and tacrolimus. Further, the effect of these medications on the PK of SOF and its metabolites has been evaluated. Generally, SOF had no or limited effect on the PK of co-administrated ARVs; only for raltegravir AUC was decreased by 27%. Methadone exposure was unaffected by SOF as were exposures to CyA and tacrolimus, although C_{max} for tacrolimus was decreased by almost 30%.

Potential interactions with telaprevir or boceprevir have not been studied. Therefore, concomitant use is not recommended.

A 600 mg single dose of CyA had a large effect on SOF exposure with a 4.5-fold increase. However, the exposure to GS-331007 was not statistically different. Tacrolimus did not affect exposure to SOF or its metabolites. Darunavir/ritonavir (800/100 mg daily [q.d.]) increased exposure to SOF (34% increase) and to GS-566500 (80% increase), but not exposure to GS-331007.

In vitro data indicate Pgp involvement in the absorption. Inducible enzymes may be involved in the elimination. The effect of strong Pgp inducers on SOF exposure has not been studied in vivo. Due to the risk of under-exposure, a warning has been included in the SmPC and concomitant use of strong Pgp inducers is not recommended.

PK/PD relationship

The following curve describes the relationship between GS-331007 AUC_{tau} and change from baseline HCV-RNA during sofosbuvir or GS-9851 monotherapy after 3 days of treatment in subjects with genotype 1 infection.

Figure 2. Relationship between GS-331007 AUC_{tau} (from sofosbuvir) and change from baseline HCV- RNA during sofosbuvir or GS-9851 monotherapy after 3 days of treatment

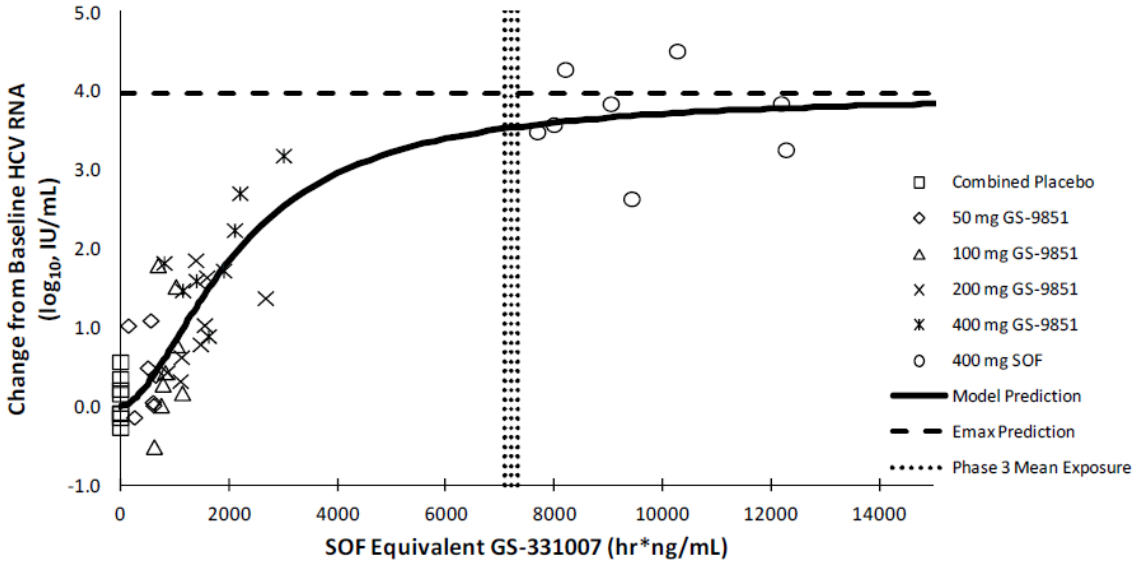


Table 3. Observed HCV-RNA reduction (log10 IU/ml and % of Emax) across treatment-naïve subjects with genotype 1, 2 and 3 HCV-infection after treatment with sofosbuvir 400 mg + PEG + RBV

Study	Days of Treatment	N	HCV Genotype	HCV RNA Reduction	
				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.

High potency in terms of a rapid viral load decline, lack of on-treatment virological breakthrough, and lack of selection of evidently clinically relevant resistance, indicate that the dose selected for sofosbuvir gives adequate response.

2.4.3. Pharmacodynamics

Mechanism of action

In human hepatocytes, SOF is converted to an active triphosphate metabolite (GS 461203). GS-461203 is a non-obligate chain-terminating analog of uridine triphosphate (UTP) that

inhibits viral RNA synthesis following its incorporation into nascent viral RNA by the HCV NS5B RNA-dependent RNA polymerase.

Primary pharmacology

In vitro activity

GS 461203 has been shown to directly inhibit NS5B polymerase activity in a biochemical assay, at concentrations that resulted in 50% inhibition (IC_{50} values) ranging from 0.7 to 2.6 µM.

SOF demonstrated in vitro activity against stable full-length HCV replicons as follows:

Table 4. In vitro activity of SOF against stable replicon cell lines

Genotype	SOF EC_{50} in nM[a]
1a H77	40
1b Con-1	110
2a JFH-1	50
2b[b]	15
3a S52	50
4a ED43	40
5a[b]	15
6a[b]	14

a EC_{50} values are the average of at least 2 independent experiments.
b Stable chimeric genotype 1b replicons carried NS5B coding sequences from genotypes 2b, 5a, or 6a consensus sequences.

Thus, estimated EC_{50} was lowest against genotypes 2b, 5a and 6a, whereas the highest value was for genotype 1b.

No significant differences were observed in SOF EC_{50} or EC_{95} values in the presence and absence of human serum or human serum albumin.

Baseline viral polymorphisms

The applicant states that no baseline viral polymorphisms have been shown to impact the activity of SOF. However, as further discussed below, activity against genotype 1b may be lower than against genotype 1a, which may be clinically apparent when only SOF+RBV bitherapy is given. In this context, it is noted that the L159F variant was found in 9.4% of genotype 1b samples at baseline by population sequencing, and very rarely in genotype 1a. The relapse rate among patients with L159F at baseline in the Phase 2/3 program was 2/14. Thus, data are not indicative of any impact on response.

In vitro and in vivo selection of resistance

In vitro resistance selection experiments in replicon cells identified S282T as the primary resistance mutation in all genotypes (1–6) tested. Site-directed mutagenesis confirmed that S282T confers reduced susceptibility to SOF; however, the S282T mutation does not confer cross-resistance to other classes of antiviral inhibitors.

Resistance analyses were attempted on plasma HCV isolates from all subjects with HCV-RNA >1,000 IU/ml at the virologic failure time point or early discontinuation time point for those who had a plasma sample available. Among all SOF-treated subjects in the Phase 2 and 3 studies, a total of 302 of 1,662 subjects qualified to be part of the resistance analysis population (RAP) with NS5B sequences available from 300 of 302 subjects in the RAP (deep sequencing from 294 with >1,000 × coverage at NS5B 282 position in 272 of 294 subjects; population sequencing from 6 subjects). The S282T substitution was detected in one subject who received SOF monotherapy, not in any of the remaining 299 subjects in the RAP with sequence data.

There were other NS5B substitutions observed in samples from >2 subjects. These include, e.g., the L159F variant, which has also been shown to be selected by the investigational nucleotide analogue mericitabine, and which was enriched in two patients with on-treatment viral breakthrough in the pre-transplant setting, and the V321A variant. However, none of these substitutions were associated with a phenotypic change in SOF or RBV susceptibility, and their clinical relevance is unknown.

Phenotypic data were successfully generated from these subjects in the RAP. No reduction in susceptibility to SOF or RBV was observed in HCV variants from 174 subjects. The sample from the 1 genotype 2b subject with S282T detected displayed a reduced susceptibility to SOF and a decreased replication capacity. S282T was no longer detectable at post-treatment Week 12 by deep sequencing with an assay cut-off of 1%, further indicative of the impaired replicative fitness of this variant. Of note, this patient, having first received monotherapy, was subsequently retreated with SOF+RBV for 12 weeks and achieved an SVR.

A phylogenetic analysis was performed on NS5B sequences from subjects in 5 treatment groups of the four Phase 3 studies who either achieved SVR12 or failed to achieve SVR12. For genotype 2 or 3 responders and non-responders were intermingled within each genotype/subtype without any apparent clustering in any of the treatment groups. Thus, this analysis was not indicative of an unidentified viral factor determining whether SVR was reached or not reached in these patients.

Activity against the less common genotypes (4-6)

Although it is recognised that SOF has not been investigated against chimeric replicons or other viral expression vectors representing all described subgenotypes of HCV, available data are indicative of the pangenotypic activity of SOF. This includes both biochemical and cell-based assay IC_{50} and EC_{50} in the same range for all tested genotypes (1-4 and 1-6, respectively), as well as experiments on the selection of resistance, in which the S282T mutation is selected regardless of genotype. These preclinical findings are supported by the outcome of the clinical investigations.

Similar, potent early on-treatment responses were seen in patients with genotypes 4-6 treated with SOF+PEG+RBV, compared to those seen in patients with genotypes 1-3. Further, to the extent that data are available, high SVR rates have been shown for patients with these genotypes.

Secondary pharmacology

Thorough QT study

Study P7977-0613, evaluating single dose therapeutic (400 mg) and supratherapeutic (1,200 mg) doses of SOF on the QTc interval in healthy subjects demonstrated a lack of effect of SOF on prolongation of the QTcF interval (primary PD endpoint) that was consistent with the ICH E14 definition of a negative thorough QT/QTc study.

2.4.4. Discussion on clinical pharmacology

Viral response has been shown to correlate both with sofosbuvir and GS-331007. However, as GS-331007 constitutes the major part of circulating and recovered radioactivity the applicant has based the interpretation of study results mainly on the exposure to GS-3310007. There is a concern that the exposure to GS-331007 cannot be considered a suitable surrogate marker for efficacy in all situations, e.g. in presence of drug-drug interactions and organ dysfunction which affect GS-331007 and sofosbuvir differently. A mechanistic understanding of the interrelation of SOF, GS-566500 and GS-331007 is lacking. This will be further investigated by the applicant post-authorisation as an additional pharmacovigilance activity.

In pivotal clinical trials the recommendation has been to take SOF without regard to food. However, when combined with RBV, administration is in effect made in combination with a meal. This means that sofosbuvir was in fact taken with food in pivotal efficacy and safety trials. There are contradictory effects of a high fat meal on the PK of sofosbuvir, GS-566500 and GS-331007 and the mechanism is not completely understood. Given the lack of mechanistic understanding, a clinically relevant effect cannot presently be excluded. Thus, the SmPC recommends to take SOF with food, in line with what has been de facto done in the pivotal trials.

Although an in vitro signal of CYP3A4/CYP2B6 enzyme induction was established, this was not seen in vivo in a 7-day DDI study with oral contraceptives. Even though the study was somewhat short, it is unlikely that a clinically relevant induction effect would be the case, since after 7 days there were no signs of any decrease in exposure to norgestromine, norgestrel or ethinyl oestradiol.

Safe use of SOF in patients with severe renal impairment or ESRD has not been established and no dosing recommendation is available. Normalising the exposure of GS-331007 in patients with severe renal impairment would require 5- to 10-fold lower dose of SOF. This may lead to suboptimal treatment. Therefore, to facilitate the use of SOF in these patients, further clinical safety and efficacy data in this population is needed and will be obtained from a study performed by the applicant as an additional pharmacovigilance activity (study GS-US-334-0154).

2.4.5. Conclusions on clinical pharmacology

The PK of SOF, GS-566500 and GS-331007 has been characterised in healthy volunteers and patients with HCV. The applicant has agreed to further investigate the clinical pharmacology of SOF as additional pharmacovigilance activities.

2.5. Clinical efficacy

Dose-response studies and main clinical studies

The clinical studies submitted to support the efficacy claims for SOF in the present dossier include the following:

Table 5. Clinical studies to support efficacy for SOF

Study Number	Treatment Regimens[a]	Subject Population		
		Genotype	Prior HCV Treatment	Cirrhosis Status
Phase 2 Studies				
P7977-0221	SOF 100, 200, or 400 mg or placebo once daily +PEG+RBV for 28 days followed by PEG+RBV for 44 weeks	1	Treatment-naïve	No subjects had cirrhosis.
P7977-0422 (PROTON)	SOF 200 or 400 mg or placebo once daily +PEG+RBV for 12 weeks followed by PEG+RBV for 0 to 36 weeks	1, 2, or 3	Treatment-naïve	No subjects had cirrhosis.
P7977-0523 (ELECTRON)	SOF+RBV for 12 weeks with and without PEG (0, 4, 8, or 12 weeks); SOF for 12 weeks; or SOF+PEG+RBV for 8 weeks	1, 2, or 3	Treatment-naïve and treatment-experienced	No subjects had cirrhosis.
P7977-0724 (ATOMIC)	SOF+PEG+RBV for 12 or 24 weeks followed by SOF or SOF+RBV for 12 additional weeks in a subset of subjects who received SOF+PEG+RBV for 12 weeks	1, 4, 5, 6, or indeterminate	Treatment-naïve	No subjects had cirrhosis.
P2938-0721 (QUANTUM)	SOF+RBV for 12 or 24 weeks	1, 2, 3, 4, 5, 6	Treatment-naïve	Up to 10% of subjects may have had cirrhosis.
Non-Gilead-Sponsored Phase 2 Studies				
11-I-0258 (NIAID-Sponsored	SOF+RBV 1000 or 1200 mg/ daily (divided dose) or 600 mg once daily up to 24 weeks	1	Treatment-naïve	Up to 20% of subjects may have had cirrhosis.
Phase 3 Studies				
P7977-1231 (FISSION)	SOF+RBV for 12 weeks or PEG+RBV 800 mg/day (2 divided doses) for 24 weeks	2, 3	Treatment-naïve	Up to 20% of subjects may have had cirrhosis.
GS-US-334-0107 (POSITRON)	SOF+RBV or placebo for 12 weeks	2, 3	IFN intolerant, IFN ineligible, or unwilling to take IFN	Up to 20% of subjects may have had cirrhosis.
GS-US-334-0108 (FUSION)	SOF+RBV for 12 or 16 weeks	2, 3	Treatment-experienced	Up to 30% of subjects may have had cirrhosis.
GS-US-334-0110 (NEUTRINO)	SOF+PEG+RBV for 12 weeks	1, 4, 5, 6	Treatment-naïve	Up to 20% of subjects may have had cirrhosis.
P7977-2025	SOF+RBV up to 24 weeks	Any genotype	Treatment-naïve and treatment-experienced	Subjects met the Milan criteria and were expected to undergoing liver transplant for HCC.

GS-US-334-0123 (PHOTON-1)	SOF+RBV for 12 weeks	2 or 3	Treatment-naïve subjects who were coinfected with HIV	Up to 20% of subjects may have had cirrhosis.

NIAID = National Institute of Allergy and Infectious Diseases
Note: Only treatment regimens and subject populations in the Phase 2 and 3 studies that are included to the submission are included.
Note: Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg/day (for subjects who weighed < 75 kg, the dose of RBV was 1000 mg/day in 2 divided doses and for subjects who weighed ≥ 75 kg, the RBV dose was 1200 mg/day in 2 divided doses), and the dose of PEG was 180 µg weekly.

Also, data from three other studies were submitted during the procedure. These are:

- study GS-US-334-0133 (VALENCE), investigating treatment with SOF+RBV for 12-24 weeks in treatment-naïve and treatment-experienced subjects with genotype 2 or 3 HCV-infection
- study GS-US-334-0151 (LONESTAR 2), investigating treatment with SOF+PEG+RBV for 12 weeks in treatment-experienced subjects with genotype 2 or 3 HCV-infection who failed prior interferon-based therapy
- the retreatment protocol for patients in the QUANTUM trial

2.5.1. Dose response studies

The initial dose ranging of SOF was a 3-day monotherapy study in patients with genotype 1, using GS-9851, a 1:1 racemic mixture of SOF and a 6-8 fold lower potency diastereomer. After three days of dosing, with doses ranging from 50-400 mg q.d., the 400 mg dose showed the greatest decline in HCV-RNA: -1.952 $\log_{10}$ IU/ml.

Further dose-ranging was done with SOF. In the P7977-0221 study, performed in non-cirrhotic, treatment-naïve subjects with genotype 1 infection, doses of 100 mg, 200 mg and 400 mg were given for 28 days in combination with PEG+RBV, followed by 44 weeks of PEG+RBV. SVR24 rates were 9/16 (56.3%), 15/18 (83.3%) and 12/15 (80%) in the respective arms. As SVR rates were lowest, and breakthrough (post SOF discontinuation) and relapse rates were highest in the SOF 100 mg+PEG+RBV group, SOF 200 mg+PEG+RBV and 400 mg+PEG+RBV were the therapeutic doses carried forward to be evaluated in Study P7977-0422 (PROTON) over a longer treatment duration.

In the PROTON study, 122 treatment-naïve, non-cirrhotic subjects with HCV genotype 1, stratified for Interleukin (IL) 28B status (C/C or any T allele) and baseline HCV-RNA levels (<800,000 IU/ml or ≥800,000 IU/ml) were randomised to receive SOF 200 mg once daily, 400 mg once daily or matching placebo, together with PEG+RBV for 12 weeks. HCV-infected subjects who achieved an eRVR (HCV-RNA < lower limit of detection [LOD] at Weeks 4 through 12 inclusive) received an additional 12 weeks of PEG+RBV. Genotype 1 HCV-infected subjects who did not achieve an eRVR received an additional 36 weeks of PEG+RBV.

SVR12 and SVR24 rates were approximately 90% in both SOF dosing groups (43/48 with 200 mg; 43/47 with 400 mg). Virologic breakthroughs during treatment with PEG+RBV following treatment with SOF+PEG+RBV, however, were more common in the SOF 200 mg+PEG+RBV

group compared with the SOF 400 mg+PEG+RBV group (3 subjects versus 0), suggesting that the SOF 400 mg dose may provide greater suppression of viral activity. There was no apparent difference in tolerability between 200 mg and 400 mg q.d. On this basis, the dose of 400 mg q.d was selected.

The dose of RBV selected is weight-based, 1,000 or 1,200 mg/ day, in accordance with the RBV (Copegus) product information for genotype 1. The 11-I-0258 study used a lower dose, 600 mg/day, in combination with SOF in genotype 1, as a comparison to this standard, which yielded lower SVR rates (see below).

Regimen selection for Phase 3

Genotype 1

As stated above, in the PROTON study 12 weeks of SOF 400 mg q.d.+PEG+RBV in treatment-naïve subjects with genotype 1 HCV-infection resulted in an SVR24 rate of 91.5% (43/47).

Study P7977-0523 (ELECTRON) indicated that 12 weeks of SOF+RBV could effectively treat treatment-naïve genotype 1 HCV-infected subjects, with an SVR12 rate of 84.0% (21/25); however the response rate among prior null responders (to interferon-based therapy) was a mere 10% (1/10).

In Study P7977-0724 (ATOMIC), 12 weeks of SOF+PEG+RBV in treatment-naïve subjects with genotype 1, 4, or 6 HCV-infection resulted in an SVR12 rate of 90.4% (47/52). This high SVR rate, along with the simplicity of the 12-week PEG-containing regimen, supported initiation of the Phase 3 Study GS US-334-0110 (NEUTRINO) with SOF+PEG+RBV.

Study P2938-0721 (QUANTUM) assessed 12 and 24 weeks of SOF+RBV treatment. In this study, 12 weeks of SOF+RBV was as effective as 24 weeks of SOF+RBV in achieving SVR12 - 53% (10/19) and 47.0% (9/19), respectively in subjects with genotype 1 HCV-infection.

The interferon-free combination of SOF+RBV was further studied in a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored trial in genotype 1, which is discussed below, but was not investigated in any pivotal Phase 3 trial, presumably based on data from the ELECTRON and QUANTUM studies. It appears that the addition of another drug to SOF+RBV would be required to optimise the regimen in genotype 1.

Genotypes 2 and 3

In the PROTON study there was an arm with genotype 2/3 patients, all of whom received 12 weeks of SOF 400 mg q.d.+PEG+RBV (800 mg q.d.). This resulted in an SVR12 rate of 92.0% (23/25).

The ELECTRON study showed SVR12 of 100% in treatment-naive subjects with genotype 2 or 3 HCV-infection, regardless of the presence or absence of PEG in the regimen (total N=50). Treatment with SOF monotherapy was less efficacious, resulting in 60.0% (6/10) of treatment-naïve genotype 2 or 3 HCV-infected subjects achieving SVR12; thus, indicating that RBV should be included in the regimen. In the ELECTRON study, SOF+RBV provided a relatively high virologic response rate of 68.0% (17/25) SVR12 in treatment-experienced genotype 2 or 3 HCV-infected subjects, a population with limited treatment options.

These data supported initiation of the Phase 3 studies P7977-1231 (FISSION), GS US 334-0107 (POSITRON), and GS US 334 0108 (FUSION) with SOF+RBV.

2.5.2. Main studies

Genotypes 1, 4, 5 and 6

The company has conducted one Phase 3 study of SOF+PEG+RBV in treatment-naïve patients with genotype 1 infection (GS-US-334-0107, NEUTRINO). This study also included a few patients with the (in Europe, and particularly the US) less common genotype 4. Furthermore, it had some individuals with genotype 5 and -6 infection. These are very uncommon in the regions where the study was performed, and have been subject to little systematic study in previous HCV trials.

Other, supportive, studies of relevance for the use of SOF in genotype 1 include the NIAID-sponsored study termed 11-I-0258 (SPARE), the QUANTUM retreatment protocol, and GS-US-334-0123 (PHOTON-1) in HCV/HIV-coinfected patients, which are all further discussed below.

Furthermore, it is worth noting that different treatment regimens including sofosbuvir are being investigated in a Janssen-Cilag-sponsored study termed HPC2002, for prior null responders to PEG+RBV, in combination with investigational NS3/4A inhibitor simeprevir, and a BMS-sponsored study, AI444040, in combination with investigational NS5A inhibitor daclatasvir.

GS-US-334-0110 (NEUTRINO) - Treatment-naïve subjects in subjects with genotype 1, 4-6

Methods

NEUTRINO was a Phase 3, multicentre, single arm, open label study to investigate the efficacy and safety of sofosbuvir with PEG alfa-2a and RBV for 12 Weeks in treatment-naïve subjects with chronic genotype 1, 4, 5, or 6 HCV-infection.

Study Participants

Subjects enrolled in this study had chronic genotype 1, 4, 5 or 6 HCV-infection and were naïve to HCV antiviral treatment. Furthermore, patients needed to have compensated liver disease and platelets >90,000/µl (in accordance with the prescribing information for PEG alfa-2a), and were not allowed to have HBV or HIV co-infection.

Treatments

- SOF was administered orally 400 mg/day, once daily (1 × 400-mg tablet)
- PEG was administered subcutaneously 180 µg/week, once weekly (180 µg, subcutaneous)
- RBV was administered orally 1,000 or 1,200 mg/day (5 or 6 × 200-mg tablets in a divided daily dose: 1,000 mg for subjects weighing < 75 kg and 1,200 mg for subjects weighing ≥75 kg)

Treatment duration was 12 weeks.

Objectives

The primary efficacy objective of NEUTRINO was to determine the efficacy of treatment with SOF+PEG+RBV, as measured by the proportion of subjects with SVR12.

Outcomes/endpoints

The primary efficacy endpoint was SVR12.

Secondary efficacy endpoints were as follows:

- SVR4 and SVR24
- absolute values and change from baseline in HCV-RNA during treatment and after treatment discontinuation
- emergence of viral resistance to SOF during treatment and after treatment discontinuation

Sample size

The planned sample size was 300 subjects. A sample size of 300 subjects provided 90% power to detect a 9% improvement in SVR12 rate from 60% to 69% using a 2-sided one-sample binomial test at a significance level of 0.05.

Randomisation

This study was not randomised.

Blinding (masking)

This was an open label, single arm study.

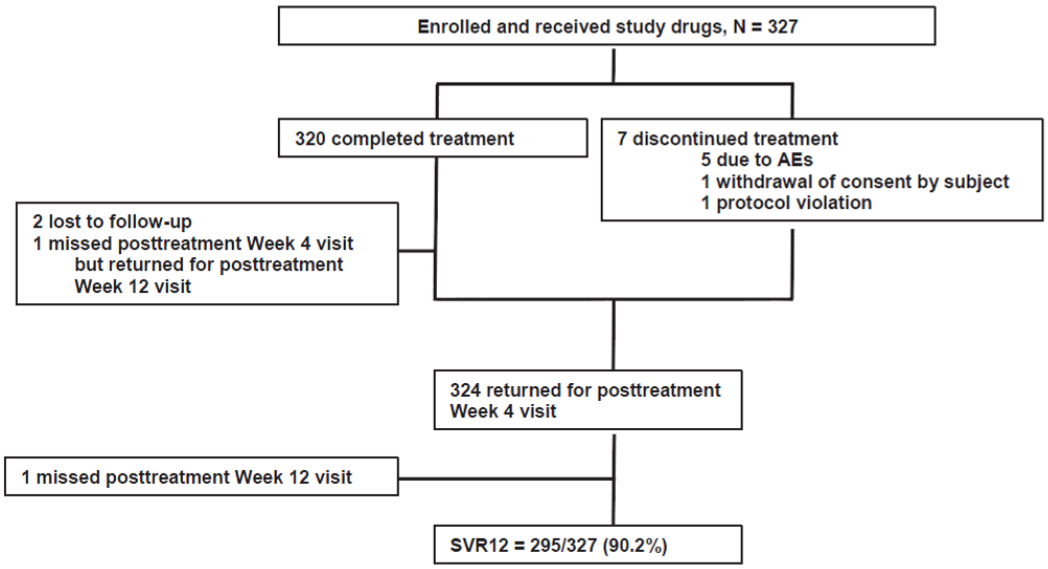
Statistical methods

The primary efficacy analysis assessed whether subjects who were administered SOF+PEG+RBV for 12 weeks achieved an SVR12 rate higher than 60%. The 95% CI on the SVR12 rates was constructed based on Clopper-Pearson exact method. The p-value associated with the test of superiority was demonstrated if the 2-sided one-sample exact test p-value was less than the 0.05 significance level.

The basis for this 60% SVR null rate was derived from: 1) an historical SVR rate of approximately 65% calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the targeted proportion of subjects with cirrhosis (approximately 20%) in this study; and 2) a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment.

Results

Participant flow



Recruitment

The study started on 18 June 2012 (first subject screened) and the last subject observation was on 16 April 2013.

Conduct of the study

The protocol was not amended during the course of the study.

A total of 80 important protocol deviations occurred in 66 subjects during the study. Of the 66 subjects, 55 had a single important deviation, 8 subjects had 2 deviations, and 3 subjects had 3 deviations. The majority of important protocol deviations (48 of 80) were for subjects not managed according to protocol-specified assessments or procedures. Of these 48 deviations, 29 deviations were for study visits completed outside of the protocol-specified visit window.

A total of 16 subjects violated at least 1 eligibility criterion. Half of the entry criteria violations (8 subjects) were due to subjects not having a liver biopsy when their Fibrotest and APRI scores were indeterminate. All of the violations due to not having a liver biopsy were identified after treatment commenced; these subjects were not discontinued from the study.

According to the applicant none of the important protocol deviations affected the overall quality or interpretation of the study data.

Baseline data

The median age of participants was 54 years; 64% were male; 79% were white, 16.5% being

black or African-American. Table 6 summarises baseline disease characteristics:

Table 6. GS-US-334-0110: baseline disease characteristics (safety analysis set)

Disease Characteristics	SOF+PEG+RBV (N = 327)
HCV Genotype	
Genotype 1a/1b	1 (0.3%)
Genotype 1a	225 (68.8%)
Genotype 1b	66 (20.2%)
Genotype 4	28 (8.6%)
Genotype 5	1 (0.3%)
Genotype 6	6 (1.8%)
Cirrhosis[a]	
No	270/324 (83.3%)
Yes	54/324 (16.7%)
Missing	3
IL28B	
CC	95 (29.1%)
CT	181 (55.4%)
TT	51 (15.6%)

Cross-study comparisons in hepatitis C therapeutics, where response rates for most regimens are heavily dependent on baseline characteristics, should be approached with great care. Still, to contextualise, the table below compares some prognostically important baseline characteristics for the NEUTRINO study, with the ADVANCE study (pivotal treatment-naïve study for telaprevir in combination with PEG+RBV) and SPRINT-2 (pivotal treatment-naïve study for boceprevir in combination with PEG+RBV):

Table 7. Important baseline characteristics – cross-study comparison

	NEUTRINO	ADVANCE	SPRINT-2
Median age	**54**	49	50
Black or African American	**16.5%**	9%	14%
Cirrhosis	**16.7%**	6%	5%
Median baseline HCV-RNA	**6.6 $\log_{10}$ IU/ml**	6.4 $\log_{10}$ IU/ml	6.5 $\log_{10}$ IU/ml*
IL28B non C/C genotype	**71%**	72%**	72%**

* geometric mean, ** based on post hoc pharmacogenetics substudy including only a subset of patients

Numbers analysed

- Safety Analysis Set: 327 subjects
- Full Analysis Set: 327 subjects

Outcomes and estimation

Efficacy outcomes were as follows:

Table 8. GS-US-334-0110: Percentages of subjects with SVR12 by HCV genotype and presence of cirrhosis (full analysis set)

	Number of Subjects with SVR12 n, %
	GS-334-0110 (NEUTRINO)
	Treatment Naive
	SOF+PEG+RBV 12 Weeks
	(N = 327)
Overall SVR12	296/327 (90.5%)
No Cirrhosis	253/273 (92.7%)
Cirrhosis	43/54 (79.6%)
Genotype 1 (1a, 1b, 1a/1b)	262/292 (89.7%)
Genotype 1a	206/225 (91.6%)
Genotype 1b	55/66 (83.3%)
Genotypes 4, 5, or 6	34/35 (97.1%)

The difference in response rates between genotype 1a and 1b were approximately 10%, with higher rates in genotype 1a. Data from the PHOTON-1 and QUANTUM retreatment studies discussed below are indicative that this may represent a real difference in the antiviral activity of SOF against these subgenotypes.

Of particular note, there were no on treatment virological failures, all virological failure being relapses (28 of 326 [8.6%] patients with EOT response).

Concerning the less common genotypes, 96.4% (27 of 28) for those with HCV genotype 4, the single subject with genotype 5, and all 6 subjects with genotype 6 HCV-infection achieved SVR12.

Genotypes 2 and 3

Based on historical precedent and Phase 2 data indicative of roughly similar efficacy in genotypes 2 and -3, these genotypes were studied in the same Phase 3 trials (P7977-1231 [FISSION]; GS-US-334-0107 [POSITRON]; GS-US-334-0108 [FUSION], where the efficacy of the interferon-free combination SOF+RBV was investigated. As these studies indicated that the efficacy is higher in genotype 2 and the required treatment duration longer in genotype 3, the outcomes of these studies are discussed below per genotype rather than per study.

Furthermore, during the approval procedure, the applicant submitted supplemental data for study GS-US-334-0133 (VALENCE). These serve to further illuminate the optimal use of SOF+RBV in genotype 2/3 subpopulations, and are discussed in the following insofar as they provide guidance on the optimal use of SOF+RBV in terms of treatment duration.

P7977-1231 (FISSION): Treatment-naïve subjects infected with genotype 2/3

Methods

FISSION was a Phase 3, multicentre, randomised, open-label, active-controlled study to investigate the safety and efficacy of sofosbuvir and RBV for 12 weeks compared to PEG and RBV for 24 weeks (present standard-of-care) in treatment-naïve patients with chronic genotype 2 or 3 HCV-infection.

Study Participants

Eligible subjects had chronic genotype 2 or 3 HCV-infection, were naïve to HCV antiviral treatment, were either non-cirrhotic or had compensated cirrhosis. Albumin was required to be ≥32 g/L. In cirrhotics, baseline platelet count needed to be >75,000/µl. Patients with HIV- or HBV-coinfection were excluded.

Subjects with genotype 2 or 3 HCV-infection were enrolled in an approximately 1:3 ratio.

Treatments

Eligible subjects were randomised to one of following treatment groups:

- SOF+RBV**:** SOF 400 mg + RBV 1,000 mg or 1,200 mg (based on baseline body weight below or above 75 kg) daily for 12 weeks
- PEG+RBV**:** PEG 180 µg weekly + RBV 800 mg daily for 24 weeks

Objectives

The primary efficacy objective of FISSION was to determine the efficacy of sofosbuvir in combination with RBV administered for 12 weeks compared with standard-of-care (PEG+RBV administered for 24 weeks) in treatment-naïve subjects with genotype 2 or 3 HCV-infection as measured by the proportion of subjects with SVR12

Outcomes/endpoints

The primary efficacy endpoint was SVR12.

Secondary efficacy endpoints were as follows:

- SVR24
- change in circulating HCV-RNA in subjects over 12 or 24 weeks of dosing
- proportion of subjects with HCV-RNA below the lower limit of quantitation (LLOQ) and LOD at various time points throughout the study
- proportion of subjects whose ALT normalised during therapy
- virologic failure rate
- HCV drug resistance substitutions at baseline, during, and after therapy with SOF

Sample size

The planned sample size of 500 subjects (250 in each treatment group) was estimated to provide >95% power to establish noninferiority of SOF+RBV treatment relative to PEG+RBV treatment in the proportion of subjects with SVR12. For the sample size calculation, it was assumed that both the SOF+RBV and PEG+RBV groups had a response rate of 75%. The noninferiority margin was chosen 15%.

A sample size of 250 per group would provide 93% power to detect a 12% difference in SVR12 rates between the treatment groups (SOF+RBV and PEG+RBV group) using a 2-sided chi-squared test and a significance level of 0.05 (assuming an SVR12 rate of 75% in the PEG+RBV group).

Randomisation

An interactive web response system (IWRS) randomly assigned subjects to receive SOF+RBV or PEG+RBV. Eligible subjects were allocated in a 1:1 ratio to SOF+RBV or PEG+RBV.

The randomisation scheme was stratified by genotype (2 or 3), screening HCV-RNA level (<6 $\log_{10}$ IU/ml or ≥6 $\log_{10}$ IU/ml), and cirrhosis (presence or absence). Subjects with mixed genotype 2/3 virus were to be randomised within the genotype 2 stratum.

Blinding (masking)

This study was open label.

Statistical methods

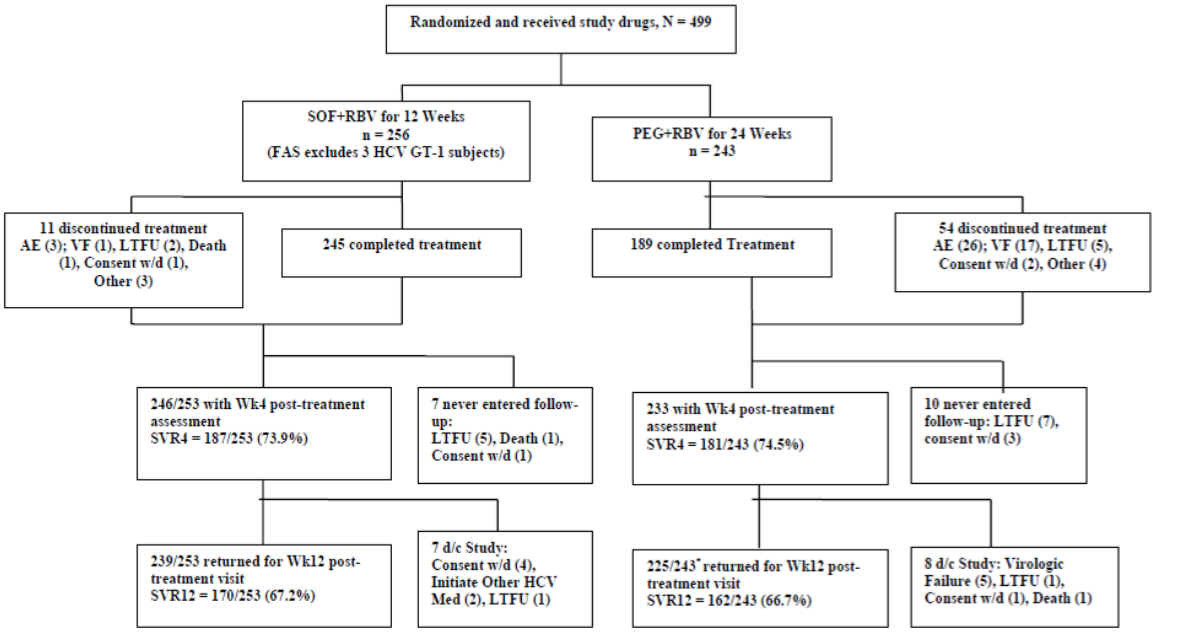
Using a closed testing procedure, the noninferiority of SOF+RBV relative to PEG+RBV for SVR12 (primary efficacy endpoint) was tested first. Noninferiority was demonstrated if the lower bound of the 2-sided 95% CI on the difference in SVR12 rates (SOF+RBV group minus PEG+RBV group) was >–15%. For the assessment of non-inferiority the estimate and 95% CI on the difference between groups in SVR12 rates was constructed based on stratum-adjusted Mantel-Haenszel (MH) proportions.

If noninferiority was established, then the superiority of SOF+RBV relative to PEG+RBV was tested using a Cochran-Mantel-Haenszel (CMH) test statistic for stratified proportions. Superiority was demonstrated if the 2-sided p-value associated with the test of superiority was <0.05.

The proportion of subjects (and 95% exact CIs calculated with the Clopper-Pearson method) with HCV-RNA below LLOQ and with ALT normalisation were presented by treatment group and visit. Estimates and 95% CIs on the difference between treatment groups at each visit for these secondary efficacy endpoints were constructed based on stratum-adjusted MH proportions. The median time to first HCV-RNA measurement <LLOQ and <LLOQ target not detected (TND) was assessed by the Kaplan-Meier method. Summary statistics were presented for HCV-RNA and change from baseline in HCV-RNA by visit through Week 12.

Results

Participant flow



Note: d/c = discontinued; LTFU = lost-to-follow-up; VF = viral failure; w/d = withdrawn; WK = week; Subjects in the PEG+RBV group could enroll into the Open Label Retreatment Study after the 8 week follow-up visit if they demonstrated confirmed virologic failure.

Recruitment

The study started on 19 December 2011 (first subject screened) and the last subject observation was on 8 April 2013.

Conduct of the study

The original study protocol (12 July 2011) was amended 4 times (Amendment 1, dated 14 September 2011; Amendment 1, Version 2, dated 16 September 2011; Amendment 2, dated 26 October 2011; Amendment 2.1, dated 07 February 2012; Amendment 3, dated 07 February 2012; Amendment 4, dated 18 June 2012). These changes were not of a nature to affect the integrity of the study.

A total of 137 important protocol deviations occurred in 112 subjects during the study. Of the 112 subjects, 92 had a single important deviation, 16 had 2 deviations, 3 had 3 deviations, and 1 had 4 deviations. The majority of important protocol deviations (99 of 137) were for subjects

not managed according to protocol assessments or procedures. Of these 99 deviations, 48 deviations were for study visits not completed. 34 deviations were for post-treatment Week 12 (SVR12) study visits completed outside the protocol-specified visit window. 17 deviations were for study assessments that were not completed during visits, including collection of HCV-RNA sequencing samples and conducting pregnancy tests. Relevant protocol deviations were proportionally distributed between treatment arms and study centres.

A total of 14 subjects violated 1 eligibility criterion. The majority of entry criteria violations were due to indeterminate liver cirrhosis assessments for subjects at the Day 1 visit date. All of the violations were identified after treatment commenced. Subjects did not have any other HCV-defining condition and were not discontinued from the study. Additionally, 24 subjects received prohibited concomitant medications within the 28 day period prior to first dose of study medication and/or while on treatment.

According to the applicant none of these important protocol deviations affected the overall quality or interpretation of the study data.

Baseline data

The mean age was 50 years (range of 19 to 77 years). Most subjects (65.5%) were male, most were white (87.2%), non-Hispanic or Latino (85.6%), with Asian and black/African American subjects comprising 5.8% and 3.4% of subjects, respectively. The mean baseline body mass index (BMI) was 28.0 kg/m^2, and most subjects (70.3%) had BMI <30 kg/m^2 at baseline.

Genotype 3 was the most prevalent HCV genotype (359/499 subjects [71.9%]). Overall, 137 subjects (27.5%) had genotype 2 HCV-infection. Treatment groups were balanced with respect to the proportion of subjects with genotype 2 HCV-infection or genotype 3 HCV-infection.

Three subjects (all in the SOF+RBV group) had genotype 1 HCV-infection as assessed by population sequencing, i.e. the screening genotype assessment by Lipa assay was inaccurate. No subject had mixed genotype 2/3 HCV-infection, and most subjects (79.8%) did not have cirrhosis at baseline.

Treatment groups also were balanced with respect to the prevalence of IL28B genotype CC allele (SOF+RBV 42.5%, 108 subjects; PEG+RBV 43.8%, 106 subjects). In the SOF+RBV group, 121 subjects (47.6%) had the IL28B genotype CT allele and 25 subjects (9.8%) had the IL28B genotype TT. In the PEG+RBV group, 98 subjects (40.5%) had the IL28B genotype CT allele and 38 subjects (15.7%) had the IL28B genotype TT allele.

Overall, 214 subjects (42.9%) had baseline HCV-RNA <6 log_{10} IU/ml (SOF+RBV 42.2%, 108 subjects, PEG+RBV 43.6%, 106 subjects), and 285 subjects (57.1%) had baseline HCV-RNA ≥6 log_{10} IU/ml (SOF+RBV 57.8%, 148 subjects, PEG+RBV 56.4%, 137 subjects). The mean baseline HCV-RNA was 6.0 log_{10} IU/ml.

Numbers 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)

Outcomes and estimation

The SVR12 rate in the SOF+RBV group was 66.8% (171/256; 95% CI: 60.7% to 72.5%), which was noninferior to the SVR12 rate in of 66.7% (162/243; 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 (ie, SOF+RBV – PEG+RBV) was greater than the pre-specified noninferiority margin of -15%.

See below for a discussion of FISSION, POSITRON and FUSION by genotype.

GS-US-334-0107 (POSITRON): Subjects who were interferon-intolerant, interferon-ineligible, or unwilling to take interferon

Methods

POSITRON was a Phase 3, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of sofosbuvir + RBV for 12 weeks in subjects with chronic genotype 2 or 3 HCV-infection who are interferon-intolerant, interferon-ineligible or unwilling to take interferon

Study Participants

For inclusion, patients were required to have chronic genotype 2 or 3 HCV-infection. Patients were also to be interferon-intolerant, interferon-ineligible, or unwilling to take interferon. Patients had to have platelets >25,000/µl, albumin >30 g/L and no history of clinical hepatic decompensation events. HIV- or HBV-coinfection were exclusion criteria.

Interferon unwilling was defined as subject having medical records documenting his/her decision to decline treatment with an interferon-based regimen ≥ 3 months prior to signing the informed consent.

Interferon ineligible was defined as subject being considered ineligible by the investigator for treatment with interferon due to at least one of several protocol-specified comorbidities that was deemed at risk for worsening with interferon treatment.

Interferon intolerant was defined as subject having completed ≤12 weeks of treatment (ending ≥3 months prior to screening) with interferon and discontinued treatment due to development or significant worsening of at least one of several protocol-specified conditions.

Treatments

Eligible subjects were randomised to one of the following two groups:

- SOF 400 mg administered once daily + RBV total daily dose of 1,000 to 1,200 mg (weight-based) administered in a divided daily dose
- SOF placebo administered once daily + RBV placebo administered in a divided daily dose

The treatment duration was 12 weeks.

Objectives

The primary efficacy objective of POSITRON was to determine the efficacy of treatment with sofosbuvir+RBV compared to treatment with placebo, as measured by the proportion of subjects with SVR12.

Outcomes/endpoints

The primary efficacy endpoint was SVR12.

The secondary efficacy endpoints were as following:

- SVR4 and SVR24
- kinetics of HCV-RNA during treatment and after treatment discontinuation
- emergence of viral resistance to SOF during treatment and after treatment discontinuation

Sample size

A sample size of 180 subjects in the active group and 60 subjects in the placebo group provided 99% power to detect a 40% difference between group SVR12 rates using a 2-sided continuity-corrected chi-square test at a significance level of 0.05.

Randomisation

An interactive web response system (IWRS) randomly assigned subjects to receive SOF+RBV or placebo. Eligible subjects were allocated in a 3:1 ratio to SOF+RBV or placebo.

The randomisation scheme was stratified by the presence or absence of cirrhosis at screening.

Blinding (masking)

This was a double-blind placebo-controlled study. SOF and RBV placebo tablets were identical in appearance, shape, and size, and packaged identically, as the SOF 400-mg tablets and RBV 200 mg tablets, respectively.

Investigators and the sponsor were blinded to HCV-RNA results except at screening. Following the post-treatment Week 4 visit and after completion of al case report forms (CRFs), subjects were informed if they were eligible for the open-label study (GS-US-334-0109).

Statistical methods

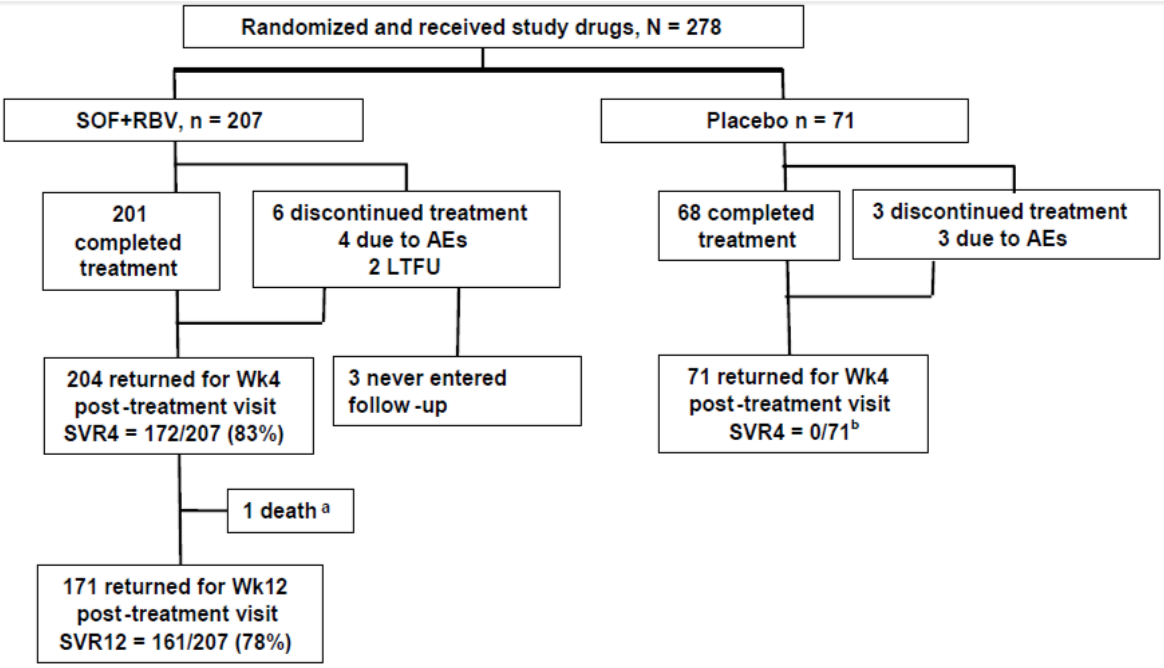
The primary efficacy analysis assessed whether in the full analysis set (subjects with chronic genotype 2 or 3 HCV-infection who were randomised and received at least 1 dose of study drug) the proportion of subjects with SVR12 who received SOF+RBV was superior to the proportion of subjects with SVR12 who received placebo. The SVR12 rates between the SOF+RBV and placebo groups were compared using a CMH test stratified by the absence or presence of cirrhosis. Superiority was demonstrated if the 2-sided CMH p-value associated with the test of superiority was <0.05.

The difference in SVR12 rates between groups and associated 95% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions. Subgroup analyses were performed to assess

the relationship between the primary efficacy endpoint and baseline demographic and disease characteristics. Point estimates and 95% exact CIs of the SVR12 rates for each treatment group, and of the difference (SOF+RBV – placebo) in SVR12 rates were displayed for each subgroup. Forest plots graphically provided the estimates and 95% CIs of the treatment differences in SVR12 rates for each subgroup.

Results

Participant flow



AEs = adverse events; LTFU = lost to follow-up; SVR12 = sustained virologic response at 12 weeks following completion of all treatment; SVR4 = sustained virologic response at 4 weeks following completion of all treatment; Wk = week

a Death due to metastatic lung cancer.

b Subjects in the placebo group who completed the 12-week treatment period with HCV RNA < LLOQ at the posttreatment Week 4 visit were offered treatment with SOF+RBV in a 12 week open-label study (GS-US-334-0109)

Recruitment

The study started on 07 March 2012 (first subject screened) and the last subject observation was on 4 February 2012.

Conduct of the study

The original protocol (dated 20 January 2012) was amended once (Amendment 1, dated 29 February 2012). These changes were not of a nature to affect the integrity of the study.

A total of 6 subjects had at least 1 eligibility criterion violation. All violations were discovered after treatment commenced and the subjects were allowed to remain in the study.

There was 1 invalid administration of study drugs. The site dispensed the incorrect SOF placebo bottle to a subject at the Week 4 visit; the subject was randomised to receive SOF placebo, therefore the subject received study drug per the protocol.

According to the applicant none of these important protocol deviations affected the overall quality or interpretation of the study data.

Baseline data

The majority of subjects in the safety analysis set were male (54%), white (91.4%), non-Hispanic/Latinos (89.2%), with a mean age of 54 years (range: 21 to 75 years). Approximately two-thirds (66.5%) of subjects had a BMI <30 kg/m^2.

Baseline disease characteristics were generally balanced between the 2 groups. The study population had similar proportions of genotype 2 and 3 HCV-infected subjects (51.4% and 48.6%, respectively) with 43.5%, 9.0%, and 47.5% classified as interferon-ineligible, interferon-intolerant and interferon-unwilling, respectively. The overall mean baseline HCV-RNA value for subjects was 6.3 $\log_{10}$ IU/ml and a majority (69.8%) had a baseline HCV-RNA ≥ 6 $\log_{10}$ IU/ml. The majority of subjects had no prior HCV treatment (81.3%) and 8.3% of subjects had failed > 12 weeks prior treatment with an interferon-based regimen. Almost half of the subjects had the IL28B CC allele (45.3%). More than half of subjects had baseline ALT >1.5 × ULN [upper limit of the normal range] (57.2%) compared with baseline ALT ≤ 1.5 × ULN (42.8%). Approximately 16% of subjects had cirrhosis.

Demographics were generally balanced across genotype 2 and genotype 3 subjects.

Numbers analysed

278 subjects (207 SOF+RBV subjects and 71 placebo subjects)

Outcomes and estimation

Overall, a statistically significant proportion of subjects in the SOF+RBV group achieved SVR12 (161/207 [77.8%]; CI: 71.5% to 83.2%) compared with placebo, for which the SVR rate was, as expected, 0% (0/71; CI: 0.0% to 5.1%) (p<0.001).

See below for a discussion of FISSION, POSITRON and FUSION by genotype.

GS-US-334-0108 (FUSION): Treatment-experienced subjects

Methods

FUSION was a Phase 3, multicentre, randomised, double blind study to investigate the efficacy and safety of sofosbuvir + RBV for 12 or 16 Weeks in subjects with chronic genotype 2 or 3 HCV-infection who had failed prior treatment with an interferon-based regimen.

Study Participants

Eligible subjects had chronic genotype 2 or 3 HCV-infection and had failed prior treatment with an interferon-based regimen. Patients had to have platelets >50,000/µl and albumin ≥30 g/L, and have no history of clinical hepatic decompensation. Also, patients could not have

HIV- or HBV-coinfection.

Treatments

Eligible subjects were randomised to one of the following two treatment groups:

- SOF+RBV 12 Week group: SOF 400 mg administered once daily + RBV total daily dose of 1,000 or 1,200 mg (weight-based) administered in a divided daily dose for 12 weeks; followed by SOF placebo administered once daily + RBV placebo administered in a divided daily dose for 4 weeks
- SOF+RBV 16 Week group: SOF 400 mg administered once daily + RBV total daily dose of 1,000 or 1,200 mg (weight-based) administered in a divided daily dose for 16 weeks

Objectives

The primary efficacy objective of FUSION was to determine the efficacy of treatment with SOF+RBV in each treatment group as measured by the proportion of subjects with SVR12

Outcomes/endpoints

The primary efficacy endpoint was SVR12.

The secondary efficacy endpoints of this study were as follows:

- SVR4 and SVR24
- kinetics of HCV-RNA during treatment and after treatment discontinuation
- emergence of viral resistance to SOF during treatment and after treatment discontinuation

Sample size

A sample size of 100 subjects in each group provided over 97% power to detect at least a 20% improvement in the SVR12 rate from the assumed null rate of 25% using a 2-sided, exact, 1-sample, binomial test at a significance level of 0.025. In addition, this sample size also provided 82% power to detect a difference of 20% in SVR12 rates (50% vs 70%) between the 12- and 16-week treatment groups.

Randomisation

An interactive web response system (IWRS) randomised subjects in a 1:1 ratio to either the SOB+RBV 12-week group or the SOF+RBV 16-week group.

Randomisation was stratified by the presence or absence of cirrhosis and HCV genotype (2 or 3) at screening.

Blinding (masking)

This was a randomised, double-blind study. Sofosbuvir was provided as a 400-mg tablet.

SOF placebo and RBV placebo tablets were identical in appearance, shape, and size, asn packaged identically as the SOF 400 mg tablets and RBV 200 mg tablets, respectively.

Investigators and the sponsor (except for employees responsible for selection of virologic samples for sequencing and analyses) were blinded to HCV-RNA results except at screening.

Statistical methods

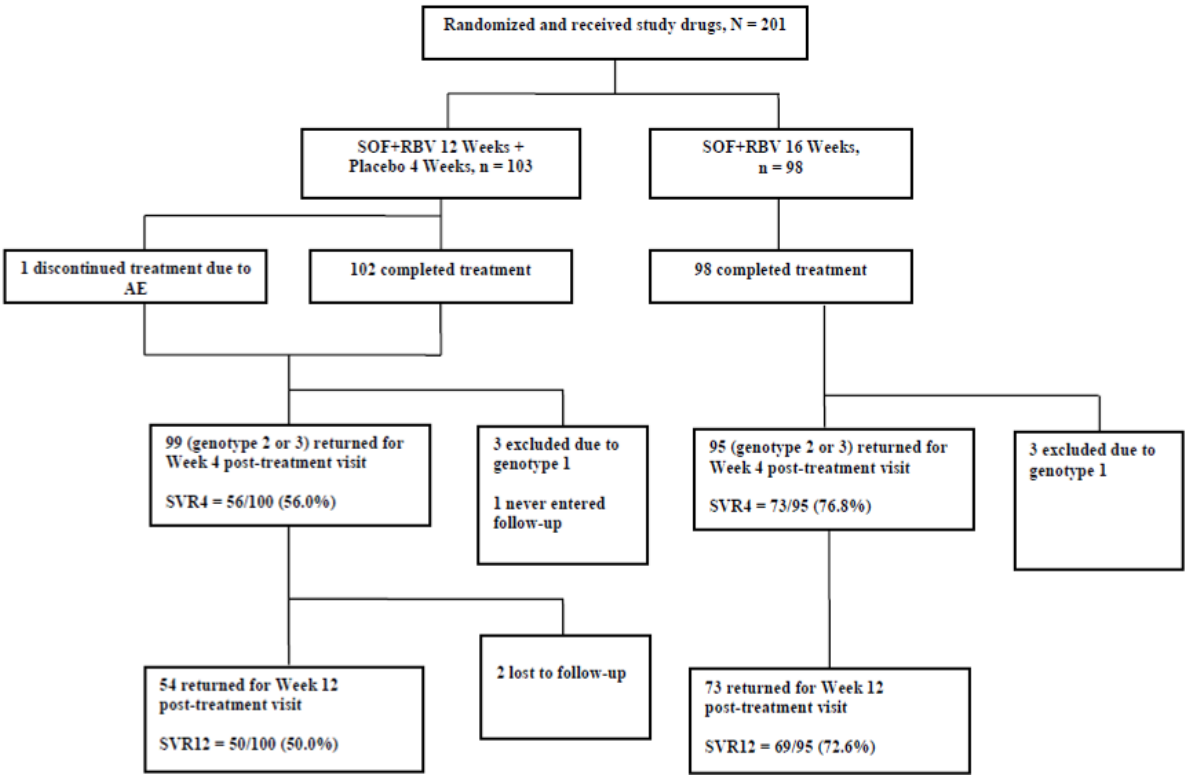
The primary efficacy endpoint was the proportion of subjects with SVR12 in the full analysis set (all subjects with genotype 2 or 3 HCV-infection who were randomised and received at least 1 dose of study drug).

The 2 primary statistical hypotheses of the study were that the SVR12 rates in both treatment groups were higher than 25%. The 2-sided, exact, 1-sample binomial test was used to test the statistical hypotheses. 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 CMH test stratified by the randomisation stratification factors (ie, presence or absence of cirrhosis; genotype 2 or 3). The 2-sided 95% CI of the difference in SVR12 rates between the 2 treatment groups (SOF+RBV 12 Week group − SOF+RBV 16 Week group) was constructed based on stratum-adjusted Mantel-Haenszel proportions. Point estimates and 2-sided 95% exact CIs for the 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.

Results

Participant flow



Recruitment

The study started on 04 June 2012 (first subject screened) and the last subject observation was on 08 May 2013.

Conduct of the study

The original clinical study protocol (dated 29 March 2012) was amended once (Protocol Amendment 1, dated 07 May 2012), before any subject entered screening.

Two administrative letters were issued (dated 16 May 2012 and 28 August 2012).

A total of 36 important protocol deviations occurred in 29 subjects during the study. Of the 29 subjects, 22 subjects had a single important deviation and 7 subjects had 2 important deviations. The majority of important protocol deviations (22 of 36) were for subjects not managed according to protocol-specified assessments or procedures. Of these 22 deviations, 13 deviations were for study visits not completed. Relevant protocol deviations were proportionally distributed between treatment groups and study centres.

A total of 6 subjects violated 1 eligibility criteria. The majority of entry criteria violations (3 subjects) were due to subjects not having liver imaging completed within 6 months of Day 1

(baseline). All of the violations were identified after treatment commenced; these subjects did not have any other HCV-defining condition and were not discontinued from the study.

A total of 3 subjects had invalid study drugs administered. All were in the SOF + RBV 12-week group and erroneously received RBV monotherapy from week 12 to week 16 (2 subjects) or day 96 (one subject).

According to the applicant none of these important protocol deviations affected the overall quality or interpretation of the study data.

Baseline data

The majority of subjects in the safety analysis set were male (69.7%), white (86.6%), and non-Hispanic/Latino (90.5%), with a mean age of 56 years (ranging from 24 to 70 years). The overall mean baseline BMI value for subjects was 28.5 kg/m^2.

The majority of subjects (63.2%) in the safety analysis set had genotype 3 HCV-infection, 33.8% had genotype 2 HCV-infection, and 3.0% had genotype 1 HCV-infection. The overall mean baseline HCV-RNA value for subjects was 6.5 $\log_{10}$ IU/ml, and most subjects (72.6%) had baseline HCV-RNA ≥6 $\log_{10}$ IU/ml. The type of prior treatment failure with interferon-based regimen(s) was relapse/breakthrough in 75.1% of subjects and nonresponse in 24.9% of subjects. The majority of subjects (69.7%) had non-CC (CT or TT) IL28B alleles. Overall, 34.0% of subjects had cirrhosis. The mean baseline ALT value was 91 U/L, and most subjects (59.2%) had baseline ALT values >1.5 × ULN. Overall, the mean baseline estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation was 115.1 ml/min.

Demographics and baseline characteristics were generally balanced between the two treatment groups and also across subjects with genotype 2 and genotype 3 HCV-infection.

Numbers analysed

- Randomised analysis set: 202 subjects (103 subjects in the SOF+RBV 12 Week group and 99 subjects in the SOF+RBV 16 Week group)
- Safety analysis set: 201 subjects (103 subjects in the SOF+RBV 12 Week group and 98 subjects in the SOF+RBV 16 Week group)
- Full analysis set: 195 subjects (100 subjects in the SOF+RBV 12 Week group and 95 subjects in the SOF+RBV 16 Week group)

Outcomes and estimation

A total of 49.5% of subjects (51 of 103) in the SOF+RBV 12-week group and 71.4% of subjects (70 of 98) in the SOF+RBV 16-week group achieved SVR12. The SVR12 rates in the SOF+RBV 12-Week group and in the SOF+RBV 16-Week group were each statistically significantly higher ($p<0.001$) compared to the null rate of 25%. The difference in the percentage of subjects who achieved SVR12 between the 2 treatment groups was -22% (95% CI: -35% to -9%) in favour of the SOF+RBV 16-week group. This difference was statistically significant ($p<0.001$).

See below for a discussion of FISSION, POSITRON and FUSION by genotype.

Results of the Phase 3 studies in genotypes 2/3

The outcomes for the active treatment arms across trials are summarised in table 9 below.

Of note, among patients treated with SOF+RBV, all cases of virological failure but one were relapses. The single patient with on treatment virological breakthrough had plasma PK parameters compatible with non-compliance.

Table 9. P7977-1231, GS-US-334-0107, and GS-US-334-0108: percentages of subjects with SVR12 by HCV genotype and presence of cirrhosis (full analysis set)

	Number of subjects with SVR12 n, %				
	P7977-1231 (FISSION)		GS-US-334-0107 (POSITRON)[a]	GS-US-334-0108 (FUSION)	
	Treatment-naïve		Interferon-ineligible, intolerant, unwilling	Treatment-experienced	
	SOF+RBV 12 Weeks	PEG+RBV 24 Weeks	SOF+RBV 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks
	N = 256	N = 243	N = 207	N = 103	N = 98
Overall SVR12	171/256 (66.7%)	162/243 (66.7%)	161/207 (77.8%)	51/103 (49.5%)	70/98 (71.4%)
No Cirrhosis	148/206 (71.8%)	143/193 (74.1%)	142/176 (80.7%)	40/67 (59.7%)	49/66 (74.2%)
Cirrhosis	23/50 (46.0%)	19/50 (38.0%)	19/31 (61.3%)	11/36 (30.6%)	21/32 (65.6%)
Genotype 2	69/73 (94.5%)	52/67 (77.6%)	101/109 (92.7%)	32/39 (82.1%)	31/35 (88.6%)
No Cirrhosis	59/61 (96.7%)	44/54 (81.5%)	85/92 (92.4%)	26/29 (89.6%)	24/26 (92.3%)
Cirrhosis	10/12 (83.3%)	8/13 (61.5%)	16/17 (94.1%)	6/10 (60.0%)	7/9 (77.8%)
Genotype 3	102/183 (55.7%)	110/176 (62.5%)	60/98 (61.2%)	19/64 (29.7%)	39/63 (61.9%)
No Cirrhosis	89/145 (61.4%)	99/139 (71.2%)	57/84 (67.9%)	14/38 (36.8%)	25/40 (62.5%)
Cirrhosis	13/38 (34.2%)	11/37 (29.7%)	3/14 (21.4%)	5/26 (19.2%)	14/23 (60.9%)

a None of the subjects in the placebo group in Study GS-US-334-0107 achieved SVR12.

Analysis of genotype 2 response

Overall responses in genotype 2 with SOF+RBV 12 weeks were 95% in a treatment-naïve population and 93% in the interferon-ineligible/intolerant/unwilling population. This is

statistically significantly higher than the 78% reached in the PEG+RBV control arm. Among treatment-experienced patients, the response rate was 82% with 12 weeks of therapy and 89% with 16 weeks. There was no significant impact of age or sex. In treatment-naïve or interferon-ineligible/intolerant/unwilling, the small number of cirrhotics seemed to do as well as those without cirrhosis (whereas this was not the case in the FISSION PEG+RBV control arm).

In the treatment-experienced population, baseline viraemia categories and IL28B genotype did not have any clear impact on responses. Responses in cirrhotics were lower than in non-cirrhotics, with 6/10 and 7/9 patients achieving SVR in the 12 and 16 week arm, respectively.

Emerging data from study GS-US-334-0133 (VALENCE), where patients with genotype 2 were treated with SOF+PEG for 12 weeks showed high responses in treatment-experienced patients: 37/41 patients (90.2%) achieved SVR. This included 9/10 patients with prior non-response (as opposed to relapse) and 7/8 patients with cirrhosis.

Analysis of genotype 3 response

Overall, response rates in treatment-naïve patients with genotype 3 given 12 weeks of SOF+RBV bitherapy were 56-61%. Cirrhosis was a strong predictor of response, with approximately halved rates of SVR in the 12-week arms of the trials, as well as in the PEG+RBV control arm of the FISSION study. Notably, there was no difference in SVR rates in cirrhotics and non-cirrhotics among treatment-experienced patients treated for 16 weeks in the FUSION study. In the treatment-experienced population, response with 12 weeks of treatment was 30%, and with 16 weeks of treatment was 62% - that is, similar to what was seen in a treatment-naïve population.

Emerging results from the VALENCE study, where after a protocol amendment all patients with genotype 3 were given 24 weeks of therapy, were submitted during the application procedure. Outcomes were as follows:

Table 10. GS-US-334-0133 (VALENCE): SVR by Cirrhotic Status and Prior Treatment Experience (Full Analysis Set)

	GS-US-334-0133 (VALENCE)	
	Genotype 3	
	SOF+RBV 12 Weeks (N = 11)	**SOF+RBV 24 Weeks (N = 245)**
Overall SVR12	3/11 (27.3%)	210/250 (84.0%)
95% CI	6.0% to 61.0%	78.9% to 88.3%
Cirrhosis		
No	3/9 (33.3%)	171/192 (89.1%)
95% CI	7.5% to 70.1%	83.8% to 93.1%
Yes	0/2	39/58 (67.2%)
95% CI	0.0% to 84.2%	53.7% to 79.0%
Prior Treatment Experience Status		
Experienced	3/9 (33.3%)	112/145 (77.2%)
95% CI	7.5% to 70.1%	69.5% to 83.8%

Naïve	0/2	98/105 (93.3%)
95% CI	0.0% to 84.2%	86.7% to 97.3%
Prior Treatment Experience and Cirrhosis Status		
Naïve , noncirrhotic	0/2	86/92 (93.5%)
95% CI	0.0% to 84.2%	86.3% to 97.6%
Naïve, cirrhotic	0/0	12/13 (92.3%)
95% CI		64.0% to 99.8%
Experienced, noncirrhotic	3/7 (42.9%)	85/100 (85.0%)
95% CI	9.9% to 81.6%	76.5% to 91.4%
Experienced, cirrhotic	0/2	27/45 (60.0%)
95% CI	0.0% to 84.2%	44.3% to 74.3%

These data demonstrate that increasing treatment duration with SOF+RBV bitherapy to 24 weeks in genotype 3 is associated with a considerable increase in SVR rates, with 90% SVR rates seen in treatment-naïve patients, including a similar rate in a small subset of cirrhotics. In the treatment-experienced population, enriched for poor interferon responders, cirrhotics still had relatively low SVR rates (60%).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11. Summary of Efficacy for trial NEUTRINO

Title: NEUTRINO		
Study identifier	GS-US-334-0110	
Design	Phase 3, multicentre, open-label, single arm study to investigate the efficacy and safety of SOF in combination with PEG alfa-2a and RBV for 12 weeks in treatment-naïve subjects with chronic genotype 1, 4, 5 or 6 HCV-infection	
	Duration of main Phase:	12 weeks treatment + 24 weeks follow-up
Hypothesis	Single arm descriptive study	
Treatments groups	Study group	SOF + RBV + PEG for 12 weeks N = 327
Endpoints and definitions	Primary endpoint	SVR12

	Secondary endpoints	• SVR4 and SVR24 • absolute values and change from baseline in HCV-RNA during treatment and after treatment discontinuation • emergence of viral resistance to SOF during treatment and after treatment discontinuation
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Analysis Set	
Descriptive statistics and estimate variability	Treatment group	SOF + RBV + PEG for 12 weeks
	Number of subjects	327
	% of subjects with SVR12	90.5
	95% CI	86.8-93.5
	Relapse rate (%)	8.6
	Virologic failure rate (%)	8.6

Table 12. Summary of Efficacy for trial FISSION

Title: FISSION		
Study identifier	P7977-1231	
Design	Multicentre, randomised, open-label, active-controlled study to investigate the safety and efficacy of SOF and RBV for 12 weeks compared to PEG and RBV for 24 weeks in treatment-naïve patients with chronic genotype 2 or 3 HCV-infection	
	Duration of main Phase:	12 or 24 weeks treatment + 24 weeks follow-up
Hypothesis	Non-inferiority	
Treatments groups	Study group	SOF + RBV for 12 weeks N = 263
	Comparator group	PEG + RBV for 24 weeks N = 264

Endpoints and definitions	Primary endpoint	SVR12
	Secondary endpoint	• SVR24 • change in circulating HCV-RNA in subjects over 12 or 24 weeks of dosing • proportion of subjects with HCV-RNA below the lower limit of quantitation (LLOQ) and LOD at various time points throughout the study • proportion of subjects whose ALT normalised during therapy • virologic failure rate • HCV drug resistance substitutions at baseline, during, and after therapy with SOF

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set		
Descriptive statistics and estimate variability	Treatment group	SOF + RBV	PEG + RBV
	Number of subjects	256	243
	% of subjects with SVR12	66.8	66.7
	95% CI	60.7-72.5	60.4-72.6
	Relapse rate (%)	30.1	21.2
	Virologic failure rate (%)	29.6	26.3

Effect estimate per comparison	Primary endpoint	Comparison groups	Proportion of differences
		%	0.3
		95% CI	-7.5 to 8.0

Table 13. Summary of Efficacy for trial POSITRON

Title: POSITRON	
Study identifier	GS-US-334-0107

Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of SOF + RBV for 12 weeks in subjects with chronic genotype 2 or 3 HCV-infection who are interferon-intolerant, interferon-ineligible or unwilling to take interferon	
	Duration of main Phase:	12 weeks treatment + 24 weeks follow-up
Hypothesis	Superiority	
Treatments groups	Study group	SOF + RBV for 12 weeks N = 207
	Comparator group	Placebo for 12 weeks N = 71
Endpoints and definitions	Primary endpoint	SVR12
	Secondary endpoints	• SVR4 and SVR24 • kinetics of HCV-RNA during treatment and after treatment discontinuation • emergence of viral resistance to SOF during treatment and after treatment discontinuation

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set		
Descriptive statistics and estimate variability	Treatment group	SOF + RBV	Placebo
	Number of subjects	207	71
	% of subjects with SVR12	77.8	0
	95% CI	71.5-83.2	0.0-5.1
	Relapse rate (%)	20.5	0
	Virologic failure rate (%)	20.3	97.2

Table 14. Summary of Efficacy for trial FUSION

Title: FUSION	
Study identifier	GS-US-334-0108

Design	Phase 3, multicentre, randomised, double-blind study to investigate the efficacy and safety of SOF + RBV for 12 or 16 weeks in treatment-experienced subjects with chronic genotype 2 or 3 HCV-infection		
	Duration of main Phase:	12 weeks treatment + 24 weeks follow-up	
Hypothesis	Non-inferiority		
Treatments groups	Study group	SOF + RBV for 12 weeks and placebo for 4 weeks N = 103	
	Comparator group	SOF + RBV for 16 weeks N = 98	
Endpoints and definitions	Primary endpoint	SVR12	
	Secondary endpoint	• SVR4 and SVR24 • kinetics of HCV-RNA during treatment and after treatment discontinuation • emergence of viral resistance to SOF during treatment and after treatment discontinuation	
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set		
Descriptive statistics and estimate variability	Treatment group	SOF + RBV for 12 weeks	SOF + RBV for 16 weeks
	Number of subjects	103	98
	% of subjects with SVR12	49.5	71.4
	95% CI	39.5,59.5	61.4,80.1
	Relapse rate (%)	46.6	28.5
	Virologic failure rate (%)	46.6	28.5

Effect estimate per comparison	Primary endpoint	Comparison groups	Proportion of differences
		%	-22
		95% CI	-35 to -9

Clinical studies in special populations

Efficacy of sofosbuvir in liver transplantation (Study P7977-2025)

For Study P7977-2025, the primary efficacy endpoint was proportion of subjects with pTVR (post-transplant virologic response; defined as HCV-RNA <LLOQ at Week 12 after transplant). An interim analysis was conducted on 61 subjects (genotypes 1 through 4) who received at least 1 dose of study drug and were included in the safety analysis set.

This is a predominantly white, male cohort with a mean age of 59, 75% of whom have experience of prior therapy. Approximately 70% have genotype 1 infection, the remaining 30% being mostly genotype 2 and -3. Seventeen (28%) patients had Child-Pugh B status at baseline.

A total of 93.1% (54 of 58) of subjects had HCV-RNA <LLOQ by Week 4 of SOF+RBV treatment. With the exception of 5 subjects who had on-treatment virologic failures, all subjects had HCV-RNA <LLOQ for the duration of treatment or until the time of liver transplantation, whichever occurred first.

To date, 44 subjects underwent liver transplantation following up to 48 weeks of treatment with SOF/RBV. Of these, 41 had HCV-RNA <LLOQ at the time of transplantation. Of these 41 subjects, 37 have reached 12 weeks post-transplant, and 23 of these (62.2%) have achieved pTVR. No relapse has hitherto been observed after week 12, with 21/23 patients achieving pTVR having reached week 24 post-transplant, and 5/23 patients having reached week 48. Of the 14 patients who had HCV-RNA <LLOQ at the time of transplantation but did not reach pTVR, 10 had recurrence of HCV, 3 died immediately post-transplant (4-14 days) and 1 patient withdrew consent with HCV-RNA <LLOQ.

Among the 5 patients with virological failure (pre-transplant), an enrichment of the L159V viral variant was seen in two. As this variant was not the dominant quasispecies at the time of measurement, and does not clearly confer phenotypic resistance to SOF, it is unclear whether this was the cause of virological failure.

Of note, 11/15 patients discontinuing therapy at 24 weeks (in the absence of transplantation) according to the original protocol relapsed; thus, patients are being treated for 48 weeks according to a protocol amendment. Seven patients retreated after relapse have been reported, all of whom have shown durable virological suppression.

Time with plasma HCV-RNA <LLOQ TND at the time of transplant was a stronger predictor of graft protection against reinfection than was time <LLOQ (which includes also time when HCV-RNA was detected below the level of quantification) or time on treatment.

Child-Pugh classification at baseline did not impact the likelihood of graft protection. Patients with genotype 1 had lower levels of graft protection than those with genotype non-1, but the sample size is presently too small to determine whether viral genotype is an independent predictor of graft protection.

Efficacy of sofosbuvir in HCV/HIV co-infection: GS-US-334-0123 (PHOTON-1)

This is an ongoing open-label, multicentre study to investigate the efficacy and safety of SOF+RBV in subjects with chronic genotype 1, 2, or 3 HCV-infection and HIV-1 coinfection,

including patients with compensated cirrhosis. Treatment-naïve patients with genotypes 2 and 3 were treated for 12 weeks. Treatment-experienced patients with genotypes 2 and 3 received 24 weeks of therapy, as did treatment-naïve patients with genotype 1. Most patients in the study were receiving antiretroviral therapy.

Among patients with genotype 1 treated with SOF+RBV, 87/114 (76.3%) of patients with genotype 1 achieved SVR12 (including 3/5 cirrhotics). A large difference in response between genotype 1a and 1b is notable – 82.2% (74/90) of patients with genotype 1a reached SVR versus 54.2% (13/24) of patients with genotype 1b.

Treatment-naïve and treatment-experienced patients with genotype 2, treated for 12 and 24 weeks respectively, reached SVR12 rates of 88.5% (23/26) and 93.3% (14/15), respectively.

Treatment-naïve and treatment-experienced patients with genotype 3, treated for 12 and 24 weeks respectively, reached SVR12 rates of 66.7% (28/42) and 92.3% (12/13) respectively.

Supportive studies

Efficacy of a PEG-free bitherapy regimen

The efficacy of an interferon-free bitherapy regimen with SOF+RBV was investigated in HCV/HIV-coinfected subjects (PHOTON-1; see above), an NIAID-sponsored trial (study 11-I-0258) as well as in the retreatment protocol of the QUANTUM study:

Study 11-I-0258 (SPARE)

This NIAID-sponsored study, which included a total of 60 patients, demonstrated that SOF in combination with weight-based RBV (1,000 or 1,200 mg/day), without PEG, resulted in an SVR12 rate of 68.0% in genotype 1 HCV-infected subjects with a high proportion of traditionally negative predictors for treatment outcome. This study also demonstrated that SOF in combination with a reduced dose of RBV (600 mg/day) resulted in a lower SVR12 rate (48.0%) compared with SOF in combination with weight-based RBV.

The QUANTUM retreatment protocol

The QUANTUM study was originally designed to evaluate monotherapy with the nucleotide RNA polymerase inhibitor GS-0938 300 mg and combinations of GS-0938 300 mg and SOF 400 mg with or without RBV. Due to a hepatotoxicity signal related to GS-0938, all subjects who were randomised to a regimen containing GS-0938 or to placebo were required to discontinue all treatment prior to the planned end of therapy. Subjects in some of the treatment arms had been exposed to sofosbuvir for a varying duration; others had been exposed to GS-0938, with or without RBV, or to placebo.

Among 105 patients with genotype 1 subsequently treated for 24 weeks with SOF + RBV 57/80 (71.3%) of genotype 1a patients reached SVR, compared to 12/25 (48%) of genotype 1b patients. Furthermore, among 71 patients that had had prior exposure to sofosbuvir (2-8 weeks), and thus potential preselection of less sensitive variants, the response rate was 48/71 (67.6%), which is similar to that seen in patients without previous exposure to SOF. There was no impact of duration of SOF exposure on the likelihood of response on retreatment.

Other studies

Sofosbuvir in combination with other DAAs

Different treatment regimens including sofosbuvir are being investigated in a Janssen-Cilag-sponsored study termed HPC2002, for prior null responders to PEG+RBV, in combination with investigational NS3/4A inhibitor simeprevir, and a BMS-sponsored study, AI444040, in combination with investigational NS5A inhibitor daclatasvir.

Results from these studies[1,2] indicate that SVR rates close to 100% can be reached when a further potent DAA is combined with SOF, even in patients with a history of treatment failure on boceprevir- or telaprevir-based triple therapy (study AI444040).

2.5.3. Discussion on clinical efficacy

The particular characteristics of SOF among DAAs against hepatitis C

SOF is a novel nucleotide HCV NS5B polymerase inhibitor. Available data support pangenotypic activity. The functional barrier to resistance is very high, as evidenced by the fact that viral breakthrough on therapy is rare, and has hitherto not clearly been shown to be caused by the selection of resistant variants. Furthermore, in patients relapsing after combination therapy with SOF, no phenotypic resistance to SOF has been detected. Available data, though scarce, indicate that durable viral resuppression may be reached on retreatment.

These characteristics make SOF unique as a new backbone for hepatitis C therapy.

In clinical trials of various sizes in the most common HCV genotype, genotype 1, increased efficacy has been indicated when SOF+/- RBV is combined with a NS3/4A inhibitor, an NS5A inhibitor, a non-nucleoside NS5B inhibitor or an interferon.

Design and conduct of clinical studies

Dose and regimen selection for Phase 3

The dose of SOF was selected on the basis of dose-ranging trials against a background of PEG+RBV, as has generally been the practice for drugs presently in development in Phase 3 in interferon-free regimens. Data support that the selected dose is maximally or near-maximally effective.

The dose of supportive RBV (1,000/1,200 mg depending on whether body weight is below or above 75 kg) is similar to that recommended according to labeling for the use against genotype 1 virus in combination with an interferon. Apart from a small study where this dose was more

[1] IM Jacobson, RM Ghalib, M Rodriguez-Torres, et al.SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: the COSMOS study. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. AbstractLB-3.

[2] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Sustained virologic response with daclatasvir plus sofosbuvir ± ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or boceprevir (BOC) (Abstract 1417). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, the Netherlands.

effective than a low dose (600 mg), no systematic dose ranging of RBV in the present context has been performed.

Regimen selection for the pivotal trials was based on the outcomes of the Phase 2 program, primarily the ATOMIC and ELECTRON trials.

Design of the pivotal clinical studies

For genotype 1, the NEUTRINO study was uncontrolled, and thus not conducted according to CHMP guidelines. However, the subjects' baseline characteristics were comparable or indeed less favourable than in the pivotal trials for telaprevir and boceprevir (ADVANCE and SPRINT-2) in a similar population.

As is well-known, interferons have a complicated side effects profile which makes them unsuitable for a considerable proportion of patients with HCV, and they are contraindicated in patients with decompensated liver disease. Drug development is presently focused on interferon-free regimens. Thus, the reason for this small study program with SOF in combination with PEG+RBV is the general recognition that the era of interferon-based HCV treatment is at its end. There is no regulatory impetus to demand further studies of SOF in combination with interferon.

In accordance with historical precedent as well as regulatory advice, and supported by Phase 2 results, patients with genotype 3 virus infection were studied in the same trials as genotype 2. Results, however, indicate a clear difference in responses with 12 weeks of treatment (see below).

Efficacy data and additional analyses

The scope of the efficacy demonstration

The Phase 3 program for SOF contains one uncontrolled study of SOF+PEG+RBV for 12 weeks in treatment-naïve patients with genotype 1-infection and compensated liver disease (NEUTRINO); one randomised controlled non-inferiority study comparing 12 weeks of SOF+RBV with 24 weeks of PEG+RBV (present standard-of-care) in treatment-naïve patients with genotype 2 or -3 infection and compensated liver disease (FISSION); one randomised placebo-controlled study of SOF+RBV for 12 weeks in patients with genotype 2 or -3 infection deemed ineligible, intolerant or unwilling to take an interferon (POSITRON); and one randomised controlled comparison of SOF+RBV for 12 or 16 weeks in treatment-experienced patients with genotype -2 or -3 infection and compensated liver disease (FUSION). Furthermore, data from the VALENCE study, performed in treatment naïve and -experienced patients with genotypes 2 and 3, and from the PHOTON-1 study, performed in HIV/HCV-coinfected patients with genotypes 1-3, contribute to the definition of appropriate treatment regimens.

Important supportive studies on the use of SOF in interferon-free regimens include: the NIAID-sponsored 11-I-0258 study in which SOF+RBV, the latter at standard or low dose, was given for 24 weeks to treatment-naïve patients with genotype 1 infection, and the PHOTON-1 study, which demonstrates that HIV co-infection does not seem to greatly impact response to sofosbuvir-based interferon-free therapy.

The dossier also contains interim results from the P7977-2025 study. This is a single arm study of SOF+RBV where patients with various genotypes and treatment experience, that have

hepatocellular carcinoma (HCC) and are waiting for transplantation, are treated with SOF+RBV until transplantation or for 24 weeks, whichever occurs first. The primary outcome measure is prevention of graft reinfection.

Efficacy against genotype 1

In the NEUTRINO study, results with 12 weeks of SOF+PEG+RBV were approximately 90% SVR in the full population, and about 80% in patients with compensated cirrhosis. These results are indicative of a near-maximally efficacious regimen in treatment naïve non-cirrhotic patients with genotype 1. Available evidence from other regimens indicates that cirrhotics in general may benefit from a longer duration of therapy than non-cirrhotics. Though the SVR rate in cirrhotics is greater than was seen in ADVANCE or SPRINT-2, it remains possible that adding one or more months of therapy might create a further increment in responses, as therapy was generally almost surprisingly well tolerated. Also, while it is recognised that potential PEG-RBV "non-responders" comprise approximately half of a typical treatment-naïve genotype 1 population, it is possible that patients with very low response to PEG ("null responders") may benefit from longer treatment duration; such patients have not been identified and systematically studied with this regimen.

Due to the number of patients with an urgent unmet need of therapy, who do not tolerate interferon, it is anticipated that there will be a considerable use in genotype 1 of SOF in interferon-free combinations subsequent to an approval. Studies of SOF in combination with the investigational NS5A inhibitor ledipasvir (LDV, GS-5885), for the treatment of genotype 1 infection are ongoing, but results are not yet available. The application dossier, however, contains a few studies of importance for the potential use of SOF without an interferon in genotype 1 infection. The QUANTUM and 11-I-0258 studies indicated that 24 weeks of SOF+RBV bitherapy may yield SVR rates in the range of 50-70%, which would make this an inoptimised, but by no means inefficient regimen; in fact, point estimates are higher than generally seen with PEG+RBV in the treatment of genotype 1 for 48 weeks. This conclusion is corroborated by findings from the PHOTON-1 study, the first larger study of an interferon-free regimen in patients with HCV/HIV-coinfection. With an SVR rate of 76% in 114 patients with HIV-HCV-coinfection, its outcomes are indicative that coinfected patients may respond similarly well as monoinfected patients to such regimens.

A finding of interest in the PHOTON-1 study is a considerably higher response rate in genotype 1a compared to -1b. The QUANTUM retreatment study revealed a similar finding. A smaller difference in response rates in favour of genotype 1a was seen in NEUTRINO, where PEG was included in the regimen. The virological reason for this difference is unclear; hypotheses include a 2.75-fold higher EC_{50} in genotype 1b versus -1a in the replicon system, as well as a higher frequency of the L159F polymorphism in genotype 1b, which is selected by SOF drug pressure and therefore might impact response. However, given the small difference in EC_{50} between genotypes, and the fact that the L159F polymorphism at baseline apparently did not impact response, the reason for this finding remains unclear.

Finally, it is worth noting that treatment regimens including sofosbuvir in combination with other investigational DAAs are currently being investigated in clinical trials. As discussed above, results to date indicate that SVR rates close to 100% can be reached when a further potent DAA is combined with SOF, even in patients with a history of treatment failure on boceprevir-

or telaprevir-based triple therapy (BMS-sponsored study AI444040). There is little doubt that these studies are representative of the treatment paradigm that is likely to guide clinical use of SOF, as other DAAs are approved.

Efficacy against genotype 2

Overall, responses in genotype 2 with SOF+RBV 12 weeks were 95% in a treatment-naïve population and 93% in the interferon-ineligible/intolerant/unwilling population. This is statistically significantly higher than the 78% reached in the PEG+RBV control arm. Among treatment-experienced patients in the FUSION study, the response rate was 82% with 12 weeks of therapy and 89% with 16 weeks. Thus, SOF+RBV for 12 weeks is an optimised or near-optimised regimen.

Responses in the small subgroup of patients that are treatment-experienced and cirrhotic may be somewhat lower; in this context, the likely possibility of successful retreatment with a longer duration in case of failure is noted.

Efficacy against genotype 3

Results from the pivotal studies conducted in genotype 2 and 3 indicate a clear difference in responses between the two genotypes with 12 weeks of treatment, with treatment failure in genotype 3, as generally the case with SOF-based therapy, almost exclusively being relapses. The company has conducted a phylogenetic analysis that does not show any clustering of relatedness of virus from patients failing therapy. This, together with similar in vitro activity and early on-treatment response to SOF for genotypes 2 and -3, indicates that host factors such as innate immunity to the different HCV genotypes, may account for the outcome difference.

During the scope of the application procedure, emerging data from the VALENCE study has demonstrated that increasing treatment duration to 24 weeks for patients with genotype 3 can substantially increase response rates, approaching those seen in the treatment of genotype 2 with 12 weeks. An alternative in selected patients that tolerate interferon, would be to add PEG to the regimen and treat for 12 weeks in accordance with the regimen used in the NEUTRINO study. Such an extrapolation, based on the higher efficacy of PEG+RBV against genotype 3 compared to genotype 1, and the similar efficacy of SOF against both genotypes, is supported by data from several small studies.

Efficacy against genotypes 4, 5 and 6

These genotypes are relatively rare in Europe and the US, although the proportion of genotype 4 infection in some European centres is reported to be around 10%. These genotypes have traditionally been treated according to the genotype 1 paradigm for PEG+RBV – that is, for 48 weeks – although it is recognised that these genotypes may in fact be somewhat easier to cure with PEG+RBV than is genotype 1. Historically, small numbers of patients with such genotypes have been included in some predominantly genotype 1 trials of PEG+RBV. The same was done within the SOF+PEG+RBV genotype 1 development program (ATOMIC and NEUTRINO studies). However, the database for all these genotypes is small, and particularly so for genotypes -5 and -6. CHMP guidelines on drug development in hepatitis C recognise that sparse clinical data may be available for such genotypes, and recommend a totality of evidence approach in order to demonstrate efficacy in such genotypes, including indications of similar in vitro susceptibility

and on treatment viral responses as in genotypes that are more extensively studied. As for safety, this is not expected to differ depending on viral genotype.

In vitro susceptibility to SOF is not different for genotypes 4-6 compared to 1-3, with EC_{50} values that are lower than in genotype 1b. No resistance pathways specific to these genotypes have been demonstrated on in vitro selection. No baseline viral polymorphisms that are conserved in these genotypes have hitherto been shown or suspected to impact SOF activity. High on-treatment potency is seen for all genotypes. Outcomes in the few patients treated are similar to those seen in genotype 1. Efficacy conclusions are thus considered robust across the spectrum of genotypes.

Impact of dose reductions PEG and RBV on efficacy

There was no apparent impact on efficacy in the patients that reduced the doses of co-treating agents PEG or RBV due to adverse effects.

Treatment in the pre-transplant setting

In the absence of an on-treatment virological response (unmeasurable plasma HCV-RNA at the time of transplantation) or an SVR, graft reinfection with HCV is near-universal. Post-transplant recurrence is often aggressive, and for this reason the prognosis after liver transplantation due to HCV is worse than the prognosis when this is due to other causes. Furthermore, the effectiveness of PEG-based therapy is low, with a risk of severe complications such as serious bacterial infections and hepatic decompensation. Interferons are contraindicated in decompensated liver disease. This highlights the importance of the P7977-2025 study. In an interim analysis, it has been shown that, in accordance with previous results for interferon therapy, an on-treatment response to SOF+RBV therapy is capable of preventing graft reinfection. Interim safety data in this study are reassuring.

Given the very considerable benefits of preventing graft reinfection, and the emerging safety profile of SOF, the benefit-risk balance is positive for this indication. Also, although in the P7977-2025 study SOF was given for 24 weeks, the company proposes that SOF therapy be continued until transplantation in patients on the waiting list. This is based on a high observed relapse rate when discontinuing at week 24, in case there has been no transplantation. It is recognised that the safety database of SOF covers 24 weeks of therapy. However, given the anticipated benefits of on-treatment viral response, and the uncertainty of when a graft from an unrelated donor will be available, this is considered reasonable. An ongoing study in patients with very advanced liver disease where treatment is given for 48 weeks is anticipated to further elucidate the safety and efficacy of SOF in the relevant population, and with treatment durations beyond six months.

Efficacy on retreatment after non-curative exposure

While conclusive retreatment studies of patients experiencing virological failure on SOF-based therapy have not been performed, several available pieces of evidence are indicative that SOF likely retains its efficacy and contribution to a retreatment regimen, also after non-curative exposure:

First, selection of phenotypic resistance in case of virological failure has not been demonstrated. Of note, the signature mutation S282T has now twice been reported to emerge;

once in the ELECTRON study, as discussed in this application, and recently at the AASLD meeting, on relapse after 8 weeks of therapy with SOF+ investigational NS5A inhibitor ledipasvir. In neither case was the emergence of this mutation associated with viral breakthrough, which is indicative that it does not convey full resistance to SOF (the EC_{50} fold-change is roughly 10). Also, both of these patients have been reported to have been successfully retreated with intensified SOF-based regimens. In one of these cases, S282T was still detectable at baseline when retreatment commenced.

Second, virological suppression was prompt and similar to the first round of therapy when patients experiencing relapse in the P7977-2025 study were retreated.

Third, when patients that had discontinued therapy in the QUANTUM trial due to hepatotoxicity concerns for GS-0938, were retreated with SOF+RBV, SVR rates were similar in patients with up to 8 weeks of prior exposure to SOF and in those that had not been exposed to SOF in the study. Furthermore, there was no relation between prior time on SOF and the probability of SVR.

Summary of clinical outcomes

A summary of clinical outcomes across the range of studies in the respective genotypes is provided in the table below.

Table 15. Summary of clinical outcomes according to genotype and cirrhosis

Genotype 1

Patient Population (Study number/name)	*Regimen/Duration*	*Subgroup*	*SVR12 % (n)*
Treatment-naïve (NEUTRINO)	SOF+PEG+RBV 12 weeks	Overall	90% (262/292)
		No cirrhosis	93% (253/273)
		Cirrhosis	80% (43/54)
Treatment-naïve and co-infected with HIV (PHOTON-1)	SOF+RBV 24 weeks	Overall	76% (87/114)
		No cirrhosis	77% (84/109)
		Cirrhosis	60% (3/5)
Treatment-naïve (QUANTUM and 11-1-0258[b])	SOF+RBV 24 weeks	Overall	65% (104/159)
		No cirrhosis	68% (100/148)
		Cirrhosis	36% (4/11)

Genotype 2

Patient Population (Study number/name)	*Regimen/Duration*	*Subgroup*	*SVR12 % (n)*
Treatment-naïve (FISSION)	SOF+RBV 12 weeks	Overall	97% (69/73)
		No cirrhosis	98% (59/61)
		Cirrhosis	91% (10/12)
Interferon intolerant, ineligible or unwilling (POSITRON)	SOF+RBV 12 weeks	Overall	93% (101/109)
		No cirrhosis	92% (85/92)
		Cirrhosis	94% (16/17)
Treatment-experienced (FUSION)	SOF+RBV 12 weeks	Overall	86% (32/39)
		No cirrhosis	96% (26/29)
		Cirrhosis	60% (6/10)
Treatment-naïve (VALENCE)	SOF+RBV 12 weeks	Overall	97% (31/32)
		No cirrhosis	97% (29/30)
		Cirrhosis	100% (2/2)

Treatment-experienced (VALENCE)	SOF+RBV 12 weeks	Overall	90% (37/41)
		No cirrhosis	91% (30/33)
		Cirrhosis	88% (7/8)
Treatment-experienced (FUSION)	SOF+RBV 16 weeks	Overall	94% (31/35)
		No cirrhosis	100% (24/26)
		Cirrhosis	78% (7/9)
Treatment-naïve co-infected with HIV (PHOTON-1)	SOF+RBV 12 weeks	Overall	89% (23/26)
		No cirrhosis	88% (22/25)
		Cirrhosis	100% (1/1)
Treatment-experienced co-infected with HIV (PHOTON-1)	SOF+RBV 24 weeks	Overall[a]	93% (14/15)
		Non-cirrhotic[a]	92% (12/13)
		Cirrhotic[a]	100% (2/2)
Treatment-naïve (ELECTRON and PROTON)	SOF+PEG+RBV 12 weeks	Overall[c]	96% (25/26)
Treatment-experienced (LONESTAR-2)	SOF+PEG+RBV 12 weeks	Overall	96% (22/23)
		No cirrhosis	100% (9/9)
		Cirrhosis	93% (13/14)

Genotype 3

Patient Population (Study number/name)	*Regimen/Duration*	*Subgroup*	*SVR12 % (n)*
Treatment-naïve (FISSION)	SOF+RBV 12 weeks	Overall	56% (102/183)
		No cirrhosis	61% (89/145)
		Cirrhosis	34% (13/38)
Interferon intolerant, ineligible or unwilling (POSITRON)	SOF+RBV 12 weeks	Overall	61% (60/98)
		No cirrhosis	68% (57/84)
		Cirrhosis	21% (3/14)
Treatment-experienced (FUSION)	SOF+RBV 12 weeks	Overall	30% (19/64)
		No cirrhosis	37% (14/38)
		Cirrhosis	19% (5/26)
Treatment-experienced (FUSION)	SOF+RBV 16 weeks	Overall	62% (39/63)
		No cirrhosis	63% (25/40)
		Cirrhosis	61% (14/23)
Treatment-naïve (VALENCE)	SOF+RBV 24 weeks	Overall	93% (98/105)
		No cirrhosis	94% (86/92)
		Cirrhosis	92% (12/13)
Treatment-experienced (VALENCE)	SOF+RBV 24 weeks	Overall	77% (112/145)
		No cirrhosis	85% (85/100)
		Cirrhosis	60% (27/45)
Treatment-naïve co-infected with HIV (PHOTON-1)	SOF+RBV 12 weeks	Overall	67% (28/42)
		No cirrhosis	67% (24/36)
		Cirrhosis	67% (4/6)
Treatment-experienced co-infected with HIV (PHOTON-1)	SOF+RBV 24 weeks	Overall[a]	92% (12/13)
		Non-cirrhotic[a]	100% (8/8)
		Cirrhotic[a]	80% (4/5)
Treatment-naïve (ELECTRON and PROTON)	SOF+PEG+RBV 12 weeks	Overall[c]	97% (38/39)
Treatment-experienced (LONESTAR-2)	SOF+PEG+RBV 12 weeks	Overall	83% (20/24)
		No cirrhosis	83% (10/12)
		Cirrhosis	83% (10/12)

Genotypes 4, 5 and 6

Patient Population (Study number/name)	*Regimen/Duration*	*Subgroup*	*SVR12 % (n)*
Treatment-naïve (NEUTRINO)	SOF+PEG+RBV 12 weeks	Overall	97% (34/35)
		No cirrhosis	100% (33/33)
		Cirrhosis	50% (1/2)

2.5.4. Conclusions on the clinical efficacy

Due to its pangenotypic antiviral activity and its very high barrier to resistance SOF represents an important addition to the therapeutic armamentarium for the treatment of HCV-infection. Available data are considered to support the efficacy of sofosbuvir across all relevant patient strata, and therefore the proposed indication for the treatment of HCV in adults in combination with other medicinal products. Further, the potential to use SOF therapy to prevent graft infection (and/or obtain SVR) in patients on the liver transplant list, marks an important therapeutic improvement. Finally, available data are indicative that SOF may retain its efficacy on retreatment after non-curative exposure.

2.6. Clinical safety

The Primary Safety Population included safety data from 4 Gilead Sciences-sponsored pivotal Phase 3 studies. The Secondary Safety Population included individual (not pooled) data from 5 Phase 2 studies and 1 Phase 1/2a NIAID-sponsored study. The Special HCV Population included individual (not pooled) data from 2 Gilead Sciences-sponsored studies in Special HCV populations: Study P7977-2025 (hepatic impairment) and Study GS-US-334-0123 (HIV/HCV-coinfection).

Patient exposure

Table 16. Estimated exposures to SOF 400 mg in Phase 2 and 3 studies for HCV-infected subjects included in this application

Study Number	Regimen	Weeks of SOF	N
< 12 Weeks			
P7977-0221	SOF+PEG+RBV	4	15
P7977-0523 (ELECTRON)	SOF+PEG+RBV	8	10
			25
12 Weeks			
P7977-0523 (ELECTRON)	Multiple	12	110
P2938-0721 (QUANTUM)	SOF+RBV	12	25
GS-US-334-0107 (POSITRON)	SOF+RBV	12	207

Study Number	Regimen	Weeks of SOF	N
P7977-1231 (FISSION)	SOF+RBV	12	256
GS-US-334-0108 (FUSION)	SOF+RBV	12	103
GS-US-334-0123 (PHOTON-1)	SOF+RBV	12	31
		SOF+RBV 12 Week Subtotal	**622**
P7977-0422 (PROTON)	SOF+PEG+RBV	24	72
P7977-0724 (ATOMIC)	SOF+PEG+RBV	12	57[a]
GS-US-334-0110 (NEUTRINO)	SOF+PEG+RBV	12	327
		SOF+PEG+RBV 12 Week Subtotal	**456**
16 Weeks			
GS-US-334-0108 (FUSION)	SOF+RBV	16	**98**
24 Weeks			
P2938-0721 (QUANTUM)	SOF+RBV	24	25
P7977-0724 (ATOMIC)	SOF+PEG+RBV (24 weeks) SOF+PEG+RBV (12 weeks) + SOF+RBV(12 weeks) SOF+PEG+RBV(12 weeks) + SOF (12 weeks)	24	275
P7977-2025 (Pre-transplant)	SOF+RBV	24	61
NIAID-Sponsored Study 11-I-0258	SOF+RBV	24	60
			421
Total			**1732**

a This total includes 52 subjects from Group A (12 weeks SOF+PEG+RBV) and also 5 subjects from Group C (SOF+PEG+RBV 12 weeks+SOF±RBV 12 weeks) who discontinued study drug treatment (n=5) before they were re-randomized to Group C1 or C2 at Week 12.

The size of the safety database is sufficient for an evaluation, and in accordance with ICH guidance. Of particular note, there are 421 patients treated in 24-week SOF arms (not including those participating in the cross-company collaborations). Data are thus considered sufficient to evaluate the safety of sofosbuvir for at least 24 weeks.

Adverse events

Adverse events in the primary safety population (safety analysis set) are summarised in tables 17 and 18 below.

Table 17. Overall summary of adverse events in the primary safety population (safety analysis set)

	GS-US-334-0107	**P7977-1231 GS-US-334-0107 GS-US-334-0108**	**GS-US-334-0108**	**P7977-1231**	**GS-US-334-0110**
	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+ RBV 12 Weeks
	(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%)
Grade 3 and Higher 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%)
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 Treatment Regimen	3 (4.2%)	8 (1.4%)	0	26 (10.7%)	5 (1.5%)
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) plus 30 days.
Note: Percentages were calculated based on the number of subjects in the safety analysis set.

Table 18. Adverse events in at least 10% of subjects in any treatment group by preferred term in the primary safety population (safety analysis set)

	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
Preferred Term	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any treatment-emergent adverse event (TEAE)	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%)

	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
Preferred Term	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
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%)

Note: Adverse events were mapped according to Medical Dictionary for Regulatory Activities (MedDRA), Version 15.0.
Note: Subjects were counted once for each system organ class, and once for each AE preferred term .
Note: Data included to last dose date of study regimen (or active treatment in GS-US-334-0108) plus 30 days.

Of note anaemia, dyspnoea, pharyngitis, rash, nausea, insomnia, and anorexia constitute the known side effects profile of RBV, whereas fatigue, decreased appetite, myalgia, pyrexia, influenza-like illness, depression and neutropenia are characteristic of PEG, and are more common in PEG-containing regimens, with or without SOF.

Serious adverse event / deaths / other significant events

One death occurred among the 566 subjects in the SOF+RBV 12-week groups. Subject 1276-310535 in Study P7977-1231 (FISSION) died due to cocaine and heroin intoxication (preferred term of “toxicity to various agents”) on Study Day 1.

No deaths occurred in the secondary Safety Population.

Serious adverse events (SAEs) across studies were infrequent (≤4% subjects in any group of the primary safety population). SAEs in the primary safety population were distributed as follows:

SOF+RBV

The incidence of SAEs was comparable between the SOF+RBV 12-week (3.9%, 22 subjects) and SOF+RBV 16-week groups (3.1%, 3 subjects).

Malignant hepatic neoplasm (0.5%, 3 subjects), pyrexia, and cellulitis (each 0.4%, 2 subjects) were the only SAEs reported in ≥2 subjects in the SOF+RBV 12-week group. The reporting of hepatic neoplasm was not unexpected given that HCC is a complication of cirrhosis. Of the 3 subjects with SAEs of malignant hepatic neoplasm, 2 subjects had cirrhosis at screening; the third subject was noted to have a cirrhotic liver configuration during evaluations for the SAE. No other individual SAE in the SOF+RBV 12-week groups was reported in more than 1 subject and there was no apparent clustering of SAEs observed within specific system organ classes that had ≥5 subjects reporting SAEs. There was no apparent trend in the types of events reported or onset time observed.

For the SOF+RBV 16 Week group, no individual SAE was reported by more than 1 subject.

Two subjects (0.4%) in the SOF+RBV 12-week group experienced 3 treatment-related SAEs: 1 subject with anaemia on Day 20, and 1 subject with peripheral oedema and eczema on post-treatment Day 28.

Few subjects experienced SAEs in the placebo (2.8%, 2 subjects) and PEG+RBV (1.2%, 3 subjects) groups. No subjects in these groups experienced a treatment-related SAE.

SOF+PEG+RBV

Eight SAEs were reported in 4 subjects (1.2%) in the SOF+PEG+RBV group. No trends in SAE type or onset time were observed, and no individual SAE was reported in more than 1 subject in the SOF+PEG+RBV group.

Four SAEs in 2 subjects (0.6%) were assessed as related to any of the 3 study drugs: anaemia and cryoglobulinaemia in 1 subject, and leukopenia and pyrexia in the other subject.

Laboratory findings

Table 19. Summary of grade 3 or 4 haematology laboratory abnormalities in the primary safety population (safety analysis set)

	GS-US-334-0107	P7977-1231 GS-US-334-0107 GS-US-334-0108	GS-US-334-0108	P7977-1231	GS-US-334-0110
	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
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%)

Parameter	GS-US-334-0107 Placebo (N = 71)	P7977-1231 GS-US-334-0107 GS-US-334-0108 SOF+RBV 12 Weeks (N = 566)	GS-US-334-0108 SOF+RBV 16 Weeks (N = 98)	P7977-1231 PEG+RBV 24 Weeks (N = 243)	GS-US-334-0110 SOF+PEG+RBV 12 Weeks (N = 327)
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
White blood cell	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

Note: Subject safety managed using Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, September 2011.
Note: Toxicity grade must increase at least 1 toxicity grade from baseline value (missing is 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 (or active treatment in GS-US-334-0108) plus 30 days.

When reviewing these data, it should be noted that the dose of RBV was 800 mg when used in combination with PEG in the control arm of the FISSION (P7977-1231) trial, but was 1,000/1,200 mg depending on body weight when used with SOF+PEG in the NEUTRINO (GS-US-334-0110) trial, as well as in all the SOF+RBV interferon-free arms. Taking the known difference in haematological side effect of these two RBV doses (which are in accordance with the Copegus [RBV] product information for the respective genotypes) and the known effects of co-administering PEG and RBV, these data are not indicative of an effect of SOF per se on haematological parameters. Extending therapy with SOF+RBV to 24 weeks did not substantially impact the haematological safety profile.

Table 20. Summary of grade 3 or 4 coagulation and chemistry laboratory abnormalities in the primary safety population (safety analysis set)

Parameter	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)
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

Parameter	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)
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

Parameter	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)
Total Bilirubin (Hyperbilirubinemia)	71	563	98	242	327
Grade 3	0	13 (2.3%)	2 (2.0%)	2 (0.8%)	0
Grade 4	0	0	0	0	0

Note: Subject safety managed using GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, September 2011.
Note: Toxicity grade must increase at least one toxicity grade from baseline value (missing is 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 (or active treatment in GS-US-334-0108) + 30 days.
Note: Direct bilirubin was measured only if total bilirubin was greater than the upper limit of normal.

SOF per se was not associated with grade 3/4 elevations of any of these blood chemistry parameters. The increase in bilirubin is secondary to RBV-related haemolysis.

Safety in special populations

Hepatic impairment

In patients with compensated cirrhosis treated with SOF+PEG+RBV a higher frequency of anaemia and neutropenia was seen, compared to patients with less advanced liver disease. This is in line with previous findings with interferon-RBV combination therapy. In study P7977-2025, the side effect profile of RBV was apparent, as in other studies, but overall the SOF+RBV regimen appeared well tolerated, with reported adverse events within the spectrum of the expected given the underlying disease condition. No SOF-specific toxicity issues have emerged in this population with very advanced liver disease. An ongoing study in patients with portal hypertension, with and without decompensated liver disease, who are treated with SOF+RBV for 48 weeks, is expected to further clarify the safety profile of this regimen in this population. A PK/PD study in patients with hepatic impairment was not indicative of a need for dose adjustment.

Renal impairment

In patients with advanced renal impairment or ESRD, there is a substantial accumulation of GS-331007, with considerably less impact on sofosbuvir. There are no clinical outcome data in this population. The company is planning a dedicated, dose comparative study in this population.

HCV/HIV coinfection

Regarding HCV/HIV-coinfection, no specific side effects profile emerged in coinfected patients.

Discontinuation due to adverse events

Discontinuation rates due to adverse events with SOF-based therapy were very low.

Across studies of genotype 2 and 3, discontinuation rates of SOF+RBV therapy were 0-4.3% in different arms, which was similar to the placebo arm of the POSITRON study (4.2%).

The very low discontinuation rate due to side effects in the NEUTRINO study (1.5%) is somewhat surprising, given the background regimen of PEG+RBV. Previous experiences of PEG+RBV-based therapies have shown discontinuation rates in a range between 5% up to and >10%. In comparison, in the PEG+RBV arm of FISSION 10.7% of subjects experienced an adverse event leading to permanent discontinuation of treatment regimen. The low discontinuation rate in NEUTRINO may be due to the psychological benefit of the anticipation of a short (12 weeks rather than up to 48 weeks) and effective regimen. However, the possibility that this is due to the selection of patients cannot be excluded in this uncontrolled trial.

2.6.1. Discussion on clinical safety

The total safety database for this marketing authorisation application contains over 1,700 patients that have been exposed in Phase 2 and 3 trials to regimens including SOF as monotherapy, in combination with RBV or in combination with PEG+RBV, for 12-24 weeks. Importantly, this includes over 600 patients in 24-week treatment arms (see table 16, and additional data from PHOTON-1 and VALENCE studies). The Phase 3 program included approximately 260 patients with compensated cirrhosis. Inclusion criteria regarding baseline platelet counts in the interferon-free Phase 3 studies were >20-50,000/µl. Furthermore, interim data from the P7977-2025 included 61 patients on the transplant list due to HCC; 17 of these where Child-Pugh B at baseline.

The proportion of patients experiencing SAEs in the SOF arms of the Phase 3 trials were 1.2-3.9%. Adverse events leading to study drug discontinuation were experienced by 0-2.4% in different SOF-containing treatment arms. One treatment-emergent death occurred in the primary safety population; this was an overdose of heroin and cocaine on Day 1 of the relevant study.

The most common side effects reported include fatigue, headache, nausea and insomnia. In the SOF+RBV-containing arms, irritability, anaemia, cough and dyspnoea were more common that with placebo. Of note, these side effects have been associated with RBV therapy, the hallmark side effect of which is haemolytic anaemia. The side effect profile when SOF was coadministered with PEG+RBV was typical of PEG-based therapy. Discontinuations due to adverse events were lower than is usually seen with such treatment modalities. Of particular interest, in relation to the toxicology findings no clinical cardiac toxicity signal has been identified.

Patients with compensated cirrhosis are somewhat more prone to hyperbilirubinaemia secondary to RBV-associated haemolysis, and to haematological abnormalities when treated with PEG, compared to patients without cirrhosis. There is no indication that SOF adds to the severity of the side effect profile in such patients. Furthermore, no specific safety signal has

been identified in the pre-transplant population. A hepatic impairment study is not indicative of a need for dose adjustment. The appropriate dose in severe renal impairment, however, has not yet been defined.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In summary, SOF is well-tolerated when used in combination with RBV, with or without PEG. Experience of SOF monotherapy is very limited, and no SOF-specific adverse effect profile has been identified.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 0.1, the PRAC considers by consensus that the risk management system for Sofosbuvir (Sofosbuvir), in combination with other agents, in the treatment of chronic hepatitis C (CHC) in adults is acceptable.

The CHMP endorsed this advice with changes: Based on the CHMP assessment of the responses to the day 120 List of Questions the applicant was requested to include pharmacovigilance measures related to clinical pharmacology.

In response the MAH submitted an updated version of the RMP (version 1.0). The content of RMP version 1.0 is as follows:

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Important Identified Risks	None
Important Potential Risks	Drug-drug interaction with potent intestinal Pgp inducers

Missing Information	Safety in children
	Safety in pregnant or breastfeeding women
	Safety in patients with severe renal impairment or end-stage renal disease

- **Pharmacovigilance plans**

Table 21. Ongoing and planned studies in the PhV development plan

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 3				
BP-US-334-0128 – A 2-part, open-label, single-arm study to investigate pharmacokinetics, efficacy and safety of GS-7977 combined with ribavirin for 24 weeks in adolescents and children with GT-1-6 chronic HCV infection	To evaluate the PK, efficacy, and safety of SOF+RBV for 24 weeks in adolescents and children	Safety in children	Planned	Final study report February 2018
BP-US-334-0127 – A randomized, open-label, single-center, 2-period, crossover, single-dose study of adult vs. age-appropriate pediatric formulations of GS-7977 in healthy adult volunteers	To evaluate the relative bioavailability and safety of an age-appropriate pediatric SOF formulation in healthy adult volunteers	Safety of age-appropriate pediatric SOF formulation	Planned	Final study report February 2018
BP-US-334-XXXX – A Phase 1 study to evaluate the pharmacokinetic drug-drug interaction between sofosbuvir and rifampicin	To evaluate the PK and the safety of SOF when coadministered with rifampicin	Drug-drug interaction with potent Pgp inducers	Planned	Final study report Q1 2015
P7977-2025-LPK – Determination of nucleotide analog	To determine if the administration of a combination of GS-	Lack of efficacy	Started	Final Study Report Q2 2014

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
levels in liver explants from HCV infected subjects undergoing liver transplant following treatment with sofosbuvir and ribavirin	7977 and ribavirin to HCV-infected subjects with hepatocellular carcinoma (HCC) meeting the MILAN criteria prior to undergoing liver transplantation can prevent post-transplant re-infection as determined by a sustained post-transplant virological response (HCV RNA <LLoQ) at 12 weeks post-transplant.			
GS-US-334-0126 – A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin for 24 weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant	To determine the antiviral efficacy of combination therapy with GS-7977 + ribavirin (RBV) for 24 weeks in subjects with recurrent HCV post liver transplant as measured by sustained virologic response 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < lower limit of quantitation [LLoQ] 12 weeks after last dose of study drug).	Drug-drug interaction with cyclosporine	Started	January 2015
GS-US-334-0154 – A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in	To evaluate the safety, efficacy and pharmacokinetics of treatment with SOF+RBV for 24 weeks in subjects	Safety in patients with severe renal impairment or end-stage renal disease	Started	Final study report July 2017

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency	with chronic genotype 1 or 3 HCV infection and severe renal impairment			
BP-US-334-0129 – A 5-year follow-up study of pediatric patients from study BP-US-334-0128	To evaluate growth, development, and viral relapse in adolescents and children who received SOF+RBV in study BP-US-334-0128	Growth and sexual maturation Neuropsychological development Long-term safety	Planned	To be determined
AD-334-2020 – Assessment of inhibition of human hepatic microsomal cytochrome P450 activities	To evaluate the potential for cytochrome P450 inhibition	Drug-drug interaction with CYP substrates	Started	Final study report Q1 2014
AD-334-2021 – In vitro interaction studies of GS-331007 with human OAT1 transporter	To evaluate if GS-331007 is a substrate or inhibitor of OAT1	Drug-drug interactions mediate by OAT1	Started	Final study report Q1 2014
AD-334-2022 – Inhibition of UGT1A1 by sofosbuvir and GS-331007 at higher concentrations	To evaluate the potential UGT1A1 inhibition by sofosbuvir and GS-331007 at high concentrations	Drug-drug interactions with UGT1A substrates in the intestine	Started	Final study report Q1 2014
AD-334-2023 – Studies to determine if sofosbuvir at high concentrations inhibits human Pgp	To evaluate the potential to inhibit Pgp by sofosbuvir at high concentrations	Drug-drug interactions with Pgp substrates in the intestine	Started	Final study report Q1 2014
AD-334-2024 – Studies to determine if GS-331007 at high concentrations is an inhibitor of Pgp, OCT1, OCT2, MATE1, OAT3, BSEP, and MRP2	To evaluate the potential to inhibit Pgp, OCT1, MATE1, OAT3, BSEP, and MRP2 by GS-331007 at high concentrations	Drug-drug interactions with transport substrates	Started	Final study report Q2 2014
AD-334-2025 –	To evaluate if	Drug-drug	Started	Final study report

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Activation of irinotecan to SN-38 in the presence of sofosbuvir or GS-331007 in primary human hepatocytes	sofosbuvir has an effect on the activation of irinotecan to its metabolite SN-38 in hepatocytes	interactions with irinotecan		Q3 2014
Mechanistic modeling of the pharmacokinetics of sofosbuvir, GS−566500 and GS−331007 and viral response over time (short term)	To substantiate the use of GS−331007 as a valid surrogate marker of efficacy	Not applicable	Started	Final report Q2 2014

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 22. Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important potential risk(s)		
Drug-drug interaction with potent intestinal Pgp inducers	The SmPC (Sections 4.4 and 4.5) includes information that St. John's wort and rifampicin should not be used with SOF due to the potential for significant decreases in SOF plasma concentrations leading to reduced therapeutic effect of SOF.	None

Missing information		
Safety in children	The SmPC (Sections 4.2, 4.4, 4.8, and 5.2) states that the safety, efficacy, and PK of SOF in pediatric subjects have not been established and that SOF is not recommended for use in children and adolescents < 18 years of age.	None
Safety in pregnant or breastfeeding women	The SmPC (Sections 4.4 and 4.6) states that there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of SOF in pregnant women, that pregnancy should be avoided in female patients and female partners of male patients when SOF is used in combination with RBV therapy, that an effective form of contraception should be used during treatment and for a period of time after treatment as recommended in the SmPC for RBV, that it is unknown whether SOF is excreted in human milk, and that SOF should not be used during breastfeeding.	None
Safety in patients with severe renal impairment or end-stage renal disease	The SmPC (Sections 4.2, 4.4, and 5.2) states that safety of SOF has not been assessed in patients with severe renal impairment or ESRD, that the appropriate dose has not been established, that the SOF and GS-331007 AUC_{0-inf} was higher in subjects with severe renal impairment relative to subjects with normal renal function, that the SOF AUC_{0-inf} was also higher in subjects with ESRD, and that markedly higher exposure of GS 331007 was observed in subjects with ESRD.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

For the treatment of genotype 1 infection in treatment-naïve patients with compensated liver disease, SOF+PEG+RBV given for 12 weeks of therapy, yielded a 90.5% SVR rate in a single-armed study (NEUTRINO). The 95% CI for this proportion was 86.6-93.5%.

In a randomised controlled trial in treatment-naïve patients with genotype 2/3 infection and compensated liver disease, SOF+RBV treatment for 12 weeks was compared with the present standard-of-care, PEG+RBV for 24 weeks (FISSION). The SOF+RBV regimen gave an SVR rate of 66.8%, versus 66.7% for the reference regimen. The difference in proportions was 0.3% with a 95% CI of -7.5 to 8.0%. Non-inferiority was met in accordance with a pre-set margin, agreed with European regulators, of -15%.

In a further study, SOF+RBV for 12 weeks was compared with placebo, in patients with genotype 2/3 infection that were ineligible, intolerant or unwilling to take interferon-based therapy (POSITRON). In this study, the SVR rate for SOF+RBV was 77.8%. As expected, the SVR rate for placebo was 0%. The difference in response was 77.3% with a 95% CI of 71-83.6%.

Also, SOF+RBV for 12 weeks was compared with SOF+RBV for 16 weeks in patients with genotype 2/3 infection and compensated liver disease who had previously failed treatment with PEG+RBV (FUSION). In this study, the overall SVR rate was 49.5% with 12 weeks of therapy, and 71.4% with 16 weeks of therapy. The difference in proportions between the two arms was 23.4% with a 95% CI of 11.4-35.4%.

SVR rates in genotype 2 and genotype 3, studied under the same protocols and with the same regimens, differed markedly. Response rates in FISSION, POSITRON, FUSION 12 week arm and FUSION 16 week arm, for SOF+RBV were as follows: For genotype 2: 94.5%, 92,7%, 82.1% and 88.6%, respectively; for genotype 3: 55.7%, 61.2%, 29.7% and 61.9%, respectively. In the VALENCE study, where treatment of genotype 3 was extended to 24 weeks, this led to a response rate of 84% (95% CI 78.9-88.3%). Results from the PHOTON-1 study in HCV/HIV-coinfected patients indicate comparable response rates compared to monoinfected patients.

In the PHOTON-1 study of HIV/HCV co-infected patients, the combination of SOF+RBV for 24 weeks in treatment-naïve patients with genotype 1 achieved an SVR rate of 76.3% (95% CI 67.4-83.8%). This regimen is supported by three other studies showing point estimates in the range of 50-70%, and its efficacy appears higher in genotype 1a compared to genotype 1b.

The combination of SOF+RBV for 24 weeks was also studied in a single-armed study in a population of patients with hepatitis C and HCC, who were on the waiting list for liver transplantation (study P7977-2025). In an interim analysis submitted as part of the dossier, 61 patients were treated, a third of whom had Child-Pugh B at baseline. 23/37 patients that had plasma HCV-RNA <LLOQ at the time of transplantation and were followed for 12 weeks post-transplant, did not show evidence of graft infection. The proportion is 62.2%, and the

90% CI is 47.3-75.5%.

Uncertainty in the knowledge about the beneficial effects.

For genotype 1, the Phase 3 study was conducted with SOF+PEG+RBV for 12 weeks in treatment-naïve patients. It is unclear whether this duration is optimal for cirrhotics who, despite a comparably high response rate of 79.6%, might have an increased probability of SVR with a longer duration. Also, while it is recognised that the category of patients termed "treatment-experienced" to PEG+RBV are functionally contained in a treatment-naïve population (as half of these patients would not reach SVR with PEG+RBV, and there is no selection of resistance with this regimen), the representation of patients with the lowest intrinsic interferon response (null responders) was likely low in the study; such patients might also benefit from a longer treatment duration.

A regimen of SOF+RBV for 24 weeks in genotype 1 has shown SVR rates of approximately 75% in HCV/HIV-coinfected patients. Other studies show that the efficacy of this regimen appears similar in monoinfected patients, indicating that HIV-coinfection likely does not greatly impact responses to SOF-based therapy. However, the efficacy of this regimen in cirrhotics with genotype 1 is unclear as few patients have been treated. Furthermore, SVR rates were lower in genotype 1b than 1a (54.2 versus 82.2%). Such differences of varying magnitude have been seen in several studies; the reason for this has not been fully elucidated.

The precise magnitude of effect of SOF in the treatment of patients in the pre-transplant setting is not known. The sample size in the interim analysis from the P7977-2025 study underlying this indication is small. Also, while 24 weeks of therapy in case no transplantation occurs yields a high relapse rate, it is unclear what rates may be reached with 48 weeks of therapy, which is presently being investigated. Also, it may be that the benefit-risk balance in this situation can be optimised by co-treatment with SOF and another DAA.

Available, limited, evidence is indicative that SOF may retain its efficacy on retreatment after non-curative exposure; however, SVR data in patients with virological failure at the planned end of treatment are still scarce.

Risks

Unfavourable effects

SOF has mainly been studied in combination therapy, particularly with RBV +/- PEG. Apart from RBV-related anaemia, side effects with SOF+RBV bitherapy that are more common than with placebo include fatigue, insomnia, arthralgia and myalgia. No clearly SOF-specific side effects have been identified, and tolerability does not evidently differ from placebo.

Uncertainty in the knowledge about the unfavourable effects

The safety database in patients with decompensated liver disease is presently very small. There are uncertainties about what magnitude of increased exposure to SOF and its metabolites is safe, which has relevance for dosing in severe renal impairment.

Benefit-risk balance

Importance of favourable and unfavourable effects

SVR is associated with an end to progression of liver disease. The possibility of reaching SVR without interferon marks a considerable therapeutic advance, partly due to the general side effects profile of interferon, but also, importantly, since this side effects profile makes a considerable proportion of HCV patients ineligible for interferon-based therapy. This includes not only patients with very advanced liver disease (e.g. with very low platelet levels or albumin <35 g/L), in whom interferon-based therapies are associated with a considerable risk of serious bacterial infections and hepatic decompensation, and patients with decompensated cirrhosis in whom PEGs are contraindicated, but also patients with psychiatric diseases, autoimmune disorders etc.

Furthermore, again given the side effects profile of interferons, the possibility of reaching very high SVR rates (90% in NEUTRINO) with only 12 weeks of interferon-based therapy marks an important advance compared to 24-48 weeks with current standard-of-care.

In the absence of treatment, graft infection after liver transplantation is near universal and post-transplant recurrence is often aggressive. For this reason, patients that are transplanted due to HCV have a worse prognosis compared to patients transplanted due to other reasons. Consequently, a further, very considerable, benefit of SOF is the possibility of preventing graft infection after liver transplantation by reaching an on treatment virological response or SVR with SOF+RBV. While this has previously been demonstrated with interferon-based therapy, most of the relevant patients are not eligible for such treatment, for reasons given above, and in those that tolerate interferon-based therapy, these have low efficacy.

Unlike several other DAAs, SOF has pangenotypic activity and a high barrier to resistance. On treatment viral breakthrough is very uncommon with SOF combination therapy. Furthermore, no selection of clinically relevant resistance to SOF has hitherto been shown. This quality of SOF makes it a potential backbone for a number of different combination regimens. Available data, though scarce, are indicative that retreatment with SOF-based therapy (in combination with more drugs, or for a longer duration), may be effective in patients that fail a first course.

Benefit-risk balance

Taking the above-mentioned uncertainties into account, including the fact that the optimal use of SOF in some situations remains unclear, and that experience in decompensated liver disease is scarce, the demonstrated considerable benefits for the sought indication, for use “in combination with other medicinal products for the treatment of chronic hepatitis C in adults”, outweigh the demonstrated risks.

Conclusions

The overall benefit-risk balance of sofosbuvir is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Sovaldi in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on "restricted" medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that sofosbuvir is qualified as a new active substance.