EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
EMA/697409/2013

Summary on compassionate use for

Sofosbuvir Gilead

International non-proprietary name: SOFOSBUVIR

Procedure No. EMEA/H/K/003891/CU

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Product Information

Name of the medicinal product for Compassionate Use:	Sofosbuvir Gilead
Company:	Gilead Sciences International Ltd.
Active substance:	Sofosbuvir
International Nonproprietary Name:	Sofosbuvir
Target Population:	Sofosbuvir Gilead, when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C who are also: • actively on the waiting list for liver transplantation (documented) and require treatment to prevent graft reinfection with hepatitis C virus, or • who have undergone liver transplantation and have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease, and are at a high risk of death or decompensation within 12 months if left untreated
Pharmaceutical form:	Film-coated tablets
Strength:	400 mg
Route of administration:	Oral use
Packaging:	High density polyethylene (HDPE) bottles
Package sizes:	28 tablets, 3 x 28 tablets

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1. Background information on the procedure

1.1. Submission of the dossier

Sweden notified the European Medicines Agency (EMA) on 16 July 2013 and requested a CHMP opinion on the compassionate use for the above mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004).

The legal basis for this application refers to:

Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004)

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

Rapporteur: Bengt Ljungberg Co-Rapporteur: Alar Irs

1.2. Steps taken for the assessment of the product

- The timetable for the procedure was agreed upon by CHMP on 25 July 2013
- The dossier was received by the EMA on 30 August 2013
- The Rapporteur's preliminary Assessment Report was circulated to all CHMP members on 23 September 2013
- The Rapporteur's updated Assessment Report was circulated to all CHMP members on 15 October 2013
- The CHMP opinion was adopted on 24 October 2013

2. General conditions for the manufacturer

2.1. Manufacturers

Manufacturer of the active substance

Name: ST Pharm Co. Ltd

Address: Sihwa Industrial Complex, Jeongwang-dong, Siheung-si, Gyeonggi-do 429-450

Country: Republic of Korea

Manufacturer(s) of the finished product

Name: Patheon Inc.

Address: 2100 Syntex Court, Mississauga, Ontario

Country: Canada

Manufacturer responsible for import and batch release in the European Economic Area

Name: Gilead Sciences Limited

Address: IDA Business & technology Park, Carrigtohill, County Cork

Country: Ireland

2.2. Conditions of distribution

Medicinal product subject to restricted medical prescription.

2.3. Conditions for update of Compassionate Use to be implemented by the manufacturer

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP on 24 October 2013, related to the conditions of use, distribution and targeted population of Sofosbuvir Gilead, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4. Conditions for safety monitoring to be implemented by the manufacturer

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 28(1) and 28(2) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. The manufacturer will ensure that these pharmacovigilance obligations are fulfilled.

2.5. Conditions for safety monitoring to be implemented by the Member States.

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. The Member State(s) will ensure that these pharmacovigilance obligations are fulfilled.

3. Scientific Discussion

3.1. Introduction

There is currently no standard-of-care therapy available for patients with chronic Hepatitis C virus (HCV) infection awaiting liver transplantation or for those that have received liver transplantation. Presently licensed treatment regimens for HCV are not approved for patients with decompensated liver cirrhosis who are transplant candidates, and most of these patients cannot tolerate the side effects of peginterferon (PEG)-based therapies, which are also contraindicated in decompensated liver disease. In the absence of treatment, graft re-infection is near-universal. Furthermore, in patients receiving necessary post-transplant immunosuppressive medications complications of re-infection are common and can be both serious and severe due to the accelerated natural history of recurrent HCV infection. Although current therapies for HCV may be utilised after liver transplantation (pre-emptive therapy) or later once chronic hepatitis has been confirmed and immunosuppression is relatively low, PEG-based therapies cannot be tolerated by most post-transplant patients and are contraindicated in decompensated liver disease. Therefore, many patients with HCV infection in the pre- and post-transplant setting are in urgent medical need of therapy to prevent graft reinfection or to treat recurrent HCV infection in the graft.

This article 83 application considers the compassionate use of Sofosbuvir Gilead in combination with other agents in the pre-and post-transplant setting. The company proposes that the target populations be defined as follows:

Sofosbuvir Gilead, when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C who are also:

- Actively on the waiting list for liver transplantation (documented) and require treatment to prevent hepatitis C reinfection, or
- Who have undergone liver transplantation and who have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease with a predicted life expectancy of less than 12 months if left untreated.

For these respective populations, the company proposes the following regimens:

- *pre-transplant patients*: sofosbuvir 400 mg film-coated tablets (one tablet per day) in combination with ribavirin (1,000 to 1,200 mg/day) until the time of liver transplantation

and in

- *post-transplant patients*: sofosbuvir 400 mg film coated tablets (one tablet per day) in combination with ribavirin (1,000 to 1,200 mg/day) for 24 weeks.

3.2. Quality aspects

Introduction

Sofosbuvir (SOF) for compassionate use is formulated as film-coated tablets and packed in HDPE bottles. The excipients used are mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silica, magnesium stearate and the film-coating agent containing polyvinyl alcohol, titanium dioxide, macrogol, talc, and yellow iron oxide. In the EU, an application for marketing authorisation of a drug product containing sofosbuvir as active substance is currently under assessment via the Centralised Procedure.

Drug Substance

Sofosbuvir is (S)- isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)-propanoate with the CAS number [1190307-88-0]. The molecular formula is C22H29FN3O9P and the molecular weight 529.45.

Sofosbuvir is a white to off-white powder, slightly soluble in water and freely soluble in ethanol. Different polymorphic forms exist and the drug substance is manufactured as form II. Form II is non-hygroscopic. The drug substance has been appropriately characterised. The synthesis is described in satisfactory detail.

Control of Drug Substance

The drug substance specification covers appearance, identification, water content, assay, related substances by HPLC, related substances by GC, residual solvents, residue on ignition, differential scanning calorimetry (DSC), heavy metals and particle size. Impurities have been evaluated and found to be acceptable. Acceptable analytical results of nine batches of the active substance are included. The control of drug substance can be accepted.

Stability

The drug substance is stored in double polyethylene bags. A retest period of 18 months is proposed with the recommended storage condition of "25°C, excursions permitted 15–30°C". Stability data of one batch over 12 months at long-term conditions 25°C/60% relative humidity (RH) and accelerated stability data at 40°C/75% RH are available. Reference can also be made to the stability studies reported in the application in the Centralised Procedure, where a re-test period of 2 years has been proposed. A re-test period of 18 months can be accepted.

Drug Product

Pharmaceutical Development

The drug product is described as yellow, film-coated, capsule-shaped tablets packed in white HDPE bottles with desiccant. The excipients are commonly used in drug development.

Adventitious Agents

Neither the excipients nor the active substance are derived from human or animal origin. The magnesium stearate is obtained exclusively from vegetable sources.

Manufacture of the Product

The drug product is manufactured by a standard manufacturing process. In-process controls are made at the powder-blend, tablet, film-coating and packaging stages.

Product Specification

The specification presented is considered appropriate. The drug product specification covers appearance, identification, water content, assay, related substances, uniformity of dosage units, dissolution and microbiological examination. The analytical procedures are described and validated. One batch analysis is included and it conforms to the specification. It is noted that the application in the Centralised Procedure contains several more batch analyses conforming to specification. The impurity profile of the drug product is consistent with the impurity profile observed in the drug substance.

Stability of the Product

Stability data is presented for 200 mg and 400 mg tablets. Long-term stability results are available covering twelve months at 25°C/60% RH. The parameters covered in the stability program are appearance, water content, assay, related substances and dissolution. No trend in degradation can be seen over twelve months at long-term conditions or over six months at accelerated conditions. A shelf-life of two years is proposed when stored at 25°C, excursions permitted from 15–30°C. The proposed shelf-life can be accepted.

Overall assessment on Quality

The overall assessment has taken into consideration the purpose of compassionate use. All relevant information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results indicate satisfactory consistency and uniformity of all the important quality characteristics of the product. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. The Quality documentation can be accepted and is not expected to have a negative impact on the benefit-risk balance of the product for the purpose of compassionate use.

3.3. Non-clinical aspects

Introduction

The non-clinical information for sofosbuvir in combination with ribavirin (RBV) for compassionate use in a pre- and post-transplant setting is based on a complete set of pharmacology and toxicology studies, although carcinogenicity studies are ongoing.

Data submitted

Non-clinical data have been summarised in the Investigator's Brochure, Edition 5, dated 24 June 2013.

The pharmacology of sofosbuvir has been adequately described, characterised by activity against HCV genotype 1 to 6 replicon RNA replication, without significant cytotoxicity or mitochondrial toxicity. The active triphosphate form of sofosbuvir inhibited recombinant NS5B RNA-dependent RNA polymerase (RdRp) activity and the native HCV replicase activity, but did not inhibit human RNA polymerase II. DNA polymerases did not appear to be inhibited by sofosbuvir.

Secondary pharmacology studies did not indicate any off-target activity. However, these studies were deficient in that exposure to the major in vivo metabolite was not recorded, but likely was very low.

Safety pharmacology studies did not suggest any notable effects of sofosbuvir on the nervous, cardiovascular or respiratory systems.

Data indicate that the anti-HCV activity of sofosbuvir did not interfere with efficacy of nucleoside or nucleotide analogues used to treat HIV infection. In combination with RBV a minor synergistic interaction was reported.

Sofosbuvir is well absorbed in non-clinical species and sufficient exposure levels were achieved in species chosen for assessment of toxicology. Oral administration resulted in high exposure to its major metabolites GS-566500 and GS-331007 across species tested. The oral bioavailability of sofosbuvir was 9.07%, reflecting a fraction absorbed of 36.4% and hepatic extraction of 74%, following oral administration to portal vein cannulated dogs. Higher esterase levels in the plasma from mice and rats limited sofosbuvir exposure, but levels of its major circulating metabolites remained high in these species.

Following oral administration of radioactive compound to rats, high concentrations of label were observed in the organs of absorption and excretion and the lymphatic system. Liver-to-plasma concentration ratios were approximately 15:1 at plasma T_{max} and were ≥20:1 at 24 hours post-dose. Sofosbuvir was primarily excreted in urine as metabolites in rats and dogs, with urinary recovery accounting for 72% and 81%, respectively, of the administered radiolabeled material. Low levels of radioactivity were reported in the brain and central nervous system (CNS). Tissue distribution in pigmented and non-pigmented rats was similar.

Extensively metabolism of sofosbuvir occurs mediated by esterase activity leading to high relative exposure to the metabolites GS-566500 and GS-331007 across species. The predominant circulating metabolite in rat and dog after oral doses was GS-331007. This metabolite was also the predominant metabolite in bile in rats and in urine and faeces in both species. The intracellular activation pathway of sofosbuvir involves sequential hydrolytic steps catalysed by cathepsin A (CatA), Carboxylesterase 1 (CES1), and histidine triad nucleotide-binding protein 1 (HINT1), followed by efficient phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Incubation of hepatocytes from across species showed formation of the pharmacologically active nucleoside analogue triphosphate *in vitro.* The triphosphate $t_{1/2}$ in dog liver was 17.8 hours after oral administration.

In general the distribution, metabolism and elimination of sofosbuvir in selected animal species were consistent with those observed in humans during clinical studies. Sofosbuvir had no relevant

interactions with Cytochrome P450 (CYP) enzymes. Sofosbuvir is a substrate but not an inhibitor of P-glycoprotein (Pgp) and BCRP, and its absorption may be decreased by coadministration with inducers of the expression of these transporters.

The nonclinical toxicologic profile of sofosbuvir has been characterised in single- and repeat-dose toxicity studies up to 39 weeks in duration and genetic toxicity, developmental and reproductive toxicity, and local tolerance studies. Studies up to 3 months in the mouse, 6 months in the rat, and 9 months in the dog were conducted. The primary target organ toxicities observed at high doses were in the cardiovascular, hepatobiliary, gastrointestinal and haematopoietic (erythroid) systems. In 7-day toxicity studies with GS-9851 (a 1:1 mixture of sofosbuvir and its stereoisomer GS-491241), high doses of GS-9851 resulted in adverse liver findings in dogs, and in adverse gastrointestinal (GI) and cardiac effects in both rats and dogs at doses of 2,000 mg/kg/day and 1,500 mg/kg/day, respectively. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), the only observed effects were in high dose dogs (500 mg/kg/day) and were GI-related clinical signs (soft faeces and emesis) and a slight decrease (10%) in mean erythron mass. The no observed adverse effect level (NOAELs) were 500 mg/kg/day and 100 mg/kg/day in the 26-week rat and 39-week dog studies, respectively, at exposures for GS-331007 that were 9- and 13-fold above the clinical exposure of sofosbuvir at 400 mg, respectively (based on the mean GS-331007 AUC_{tau} of 7.20 µg● h/ml from HCV subjects at 400 mg given once daily).

Sofosbuvir was not genotoxic and did not result in developmental or reproductive toxicity. Sofosbuvir was considered a non-irritant to skin and a non-severe irritant to eyes and was negative in a delayed-type hypersensitivity study. Carcinogenicity studies in mice and rats are ongoing.

Discussion on non-clinical aspects

There are no non-clinical issues identified that are particular to the use of sofosbuvir in the pre- and post-transplant setting. The potential pharmacodynamic interactions and effects of a pre- and post-transplant liver and its functional and mutational susceptibility status on pharmacokinetics (PK) and efficacy of sofosbuvir is not considered in the non-clinical part. The non-clinical studies are sufficient in scope and extent to support duration of clinical use.

The proposed use is in combination with RBV. This has also implications for use in pregnancy and breast-feeding and appropriate warnings have been considered.

Overall conclusion on non-clinical aspects

From the non-clinical point of view there are no issues that need to be further considered when sofosbuvir is used at the proposed dose and administration route in combination with RBV in the pre- and post-transplant setting.

3.4. Clinical aspects

Introduction

Sofosbuvir is a nucleotide prodrug. The active intracellular triphosphorylated metabolite cannot be measured. Therefore, only sofosbuvir and two of its other metabolites, GS-566500 and GS-331007 have been characterised. However it is not clear which, if any, of the available entities (sofosbuvir, GS-566500 or GS-331007) is most predictive of efficacy and/or safety.

Pharmacokinetics

- Absorption

Peak sofosbuvir concentrations were generally observed approximately 0.5 to 2 hours post-dose, regardless of dose level, in HCV-infected subjects and healthy subjects. Peak plasma concentrations of the metabolite GS-331007 were generally observed between 2 to 4 hours after sofosbuvir administration. The absolute bioavailability of sofosbuvir has not been established.

After a high fat meal the exposure to sofosbuvir and GS-566500 was increased 1.8 fold and 1.6 fold. The bioequivalence criteria were met for GS-331007 which was the primary analysis in this study (P7977 1318- food-effect study).

In the pivotal phase III protocols, sofosbuvir could be taken without regard to food. For the combination with RBV, however, the recommendation is to take RBV with food. Therefore, in practice sofosbuvir was likely administered with food in the pivotal clinical studies.

- Distribution

Protein binding of GS-331007 was minimal in all evaluated species. There was a discrepancy between ex vivo (fraction unbound [fu] 18%) and in vitro (fu 38%) determination of plasma protein binding (PPB) for sofosbuvir due to unknown reasons. The main binding protein is probably albumin.

Sofosbuvir is transported by breast cancer resistance protein (BCRP) and Pgp based on in vitro data.

- Elimination and Excretion

Sofosbuvir can be hydrolysed, both by human CatA and CES1 to form GS-566500 which is further metabolised to eventually form the active triphosphate nucleoside analogue. GS-331007 is also formed by metabolism of GS-566500 but likely via a pathway that is parallel to the formation of the active triphosphate.

GS-331007 is the major radioactive component in the plasma and accounts for an average of 90% of the total drug-related exposure. Sofosbuvir and GS-566500 account for an average of 6% and 3% of the total drug-related exposure, respectively.

Following a single 400 mg oral dose of [^{14}C] sofosbuvir, mean total recovery of the radioactivity was greater than 92%, consisting of approximately 76%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. GS-331007 was the dominant radioactive component in all faecal samples (13% of the dose) and neither sofosbuvir nor GS-566500 were detected in the faeces of any subject. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The median terminal half-life of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

- Drug Interactions

Sofosbuvir is transported by BCRP and Pgp based on in vitro data. This has also been confirmed in vivo with the Pgp inhibitor cyclosporin A. Potent inducers of Pgp (ie rifampin or St. John's wort [*Hypericum perforatum*]) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect and thus should not be used in combination with sofosbuvir.

Co-administration of sofosbuvir 400 mg qd had no or modest effect on the exposure (AUC) to tenofovir, emtricitabine, efavirenz, darunavir, ritonavir, raltegravir (27% decrease) or rilpivirine.

Ritonavir-boosted darunavir (800/100 mg qd) increased exposure to sofosbuvir by 34% and to GS-566500 by 80%, but not exposure to GS-331007.

Sofosbuvir has no or limited effect on the PK of co-administered cyclosporin A, tacrolimus or methadone. No modification of the dose of these agents is required.

Cyclosporin A (600 mg) increased sofosbuvir C_{max} and AUC 2.5-fold and 4.5-fold, respectively and decreased GS-331007 C_{max} by 40% while AUC was unchanged. No modification of the dose of sofosbuvir is required.

Tacrolimus had a very limited effect on the PK of sofosbuvir, GS-566500 or GS-331007.

- Special populations

Renal impairment

The PK of sofosbuvir were studied in HCV-negative subjects with mild (estimated glomerular filtration rate [eGFR] ≥50 and <80 ml/min/1.73 m^2), moderate (eGFR ≥30 and <50 ml/min/1.73 m^2), severe renal impairment (eGFR <30 ml/min/1.73 m^2) and subjects with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR >80 ml/min/1.73 m^2), the sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir AUC_{0-inf} was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% when sofosbuvir was dosed 1 hour after haemodialysis. The AUC_{0-inf} of GS-331007 in subjects with ESRD could not be reliably determined. However, data indicate at least 10-fold and 20-fold higher exposure to GS-331007 in ESRD compared to normal subjects when sofosbuvir was administered 1 hour before or 1 hour after haemodialysis, respectively.

The proposed dosing recommendation (no change) for patients with mild to moderate renal impairment is adequate. No dose recommendation can be given in patients with severe renal impairment and subjects with ESRD.

Hepatic impairment

The PK of sofosbuvir was studied in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, sofosbuvir exposure was 1.3- and 1.4-fold higher in subjects with moderate and severe hepatic impairment, while the exposure to GS-331007 was 1.2 and 1.1-fold higher, respectively. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate or severe hepatic impairment.

Elderly

Population pharmacokinetic analysis in HCV infected subjects showed that within the age range (19 to 75 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir or GS-331007.

Clinical efficacy

Data submitted

Clinical efficacy in a general population with HCV infection

The phase III program contains four trials for which sustained virologic response 12 weeks after end of treatment (SVR12) data are available. These include one single armed study of sofosbuvir + 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 sofosbuvir + 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 sofosbuvir + 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 sofosbuvir + RBV for 12 or 16 weeks in treatment-experienced patients with genotype 2 or -3 infection and compensated liver disease (FUSION). Treatment outcomes are summarised in tables 1 and 2.

Table 1. NEUTRINO (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	252/273 (92.3%)
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%)

Table 2. FISSION (P7977-1231), POSITRON (GS-US-334-0107), and FUSION (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 Naive		**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 = 253	**N = 243**	**N = 207**	**N = 100**	**N = 95**
Overall SVR12	170/253 (67.2%)	162/243 (66.7%)	161/207 (77.8%)	50/100 (50.0%)	69/95 (72.6%)
No Cirrhosis	147/204 (72.1%)	143/193 (74.1%)	142/176 (80.7%)	39/64 (60.9%)	48/63 (76.2%)
Cirrhosis	23/49 (46.9%)	19/50 (38.0%)	19/31 (61.3%)	11/36 (30.6%)	21/32 (65.6%)
Genotype 2	68/70 (97.1%)	52/67 (77.6%)	101/109 (92.7%)	31/36 (86.1%)	30/32 (93.8%)
No Cirrhosis	58/59 (98.3%)	44/54 (81.5%)	85/92 (92.4%)	25/26 (96.2%)	23/23 (100.0%)
Cirrhosis	10/11 (90.9%)	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.

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 sofosbuvir-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 >1000 × coverage at NS5B position 282 in 272/294 subjects; population sequencing from 6 subjects). The S282T substitution, which is selected by sofosbuvir in vitro and confers reduced susceptibility to sofosbuvir, was detected in one subject who received sofosbuvir 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. However, none of these substitutions were associated with a phenotypic change in sofosbuvir or RBV susceptibility.

Clinical efficacy in the pre-transplant setting

Gilead is conducting a study (P7977-2025) in HCV-infected patients scheduled to receive an orthotopic liver transplant to investigate if treatment with sofosbuvir + RBV prior to transplant can reduce the rate of re-infection with HCV post-transplantation. In this study, patients with chronic HCV infection (all genotypes) and hepatocellular carcinoma (HCC) meeting the MILAN criteria with an anticipated time until transplantation within 1 year were included.

Subjects were receiving oral sofosbuvir 400 mg once daily and RBV 1,000 or 1,200 mg (administered as a divided dose, twice daily [BID]) for a maximum of 24 weeks, prior to a protocol amendment, and subsequently a maximum of 48 weeks, or until time of transplant, whichever comes first.

The primary objective of this study is to determine if the administration of a combination of sofosbuvir and RBV can prevent post-transplant reinfection as determined by a sustained post-transplant virological response (HCV-RNA <lower limit of quantitation [LLOQ]) at 12 weeks post-transplant.

Demographic and baseline characteristics in study P7977-2025 are summarised in table 3.

Table 3. Demographic and baseline characteristics in study P7977-2025

	SOF + RBV (N=61)
Age at Baseline (Years)	
N	61
Mean (SD)	59 (5.5)
Min, Max	46, 73
Sex	
Male	49 (80.3%)
Female	12 (19.7%)
Race	
White	55 (90.2%)
Black of African American	6 (9.8%)
Ethnicity	
Hispanic or Latino	12 (19.7%)
Not Hispanic or Latino	49 (80.3%)
Baseline Body Mass Category	
< 30 kg/m^2	43 (70.5%)
≥ 30 kg/m^2	18 (29.5%)
Prior HCV Treatment	
Yes	46 (75.4%)
No	15 (24.6%)
Baseline HCV RNA (log_{10} IU/mL)	
Mean (SD)	6.14 (0.633)
Min, Max	4.06, 7.23
Baseline HCV RNA Category (log_{10} IU/mL)	
<6	20 (32.8%)
≥ 6 and < 7	38 (62.3%)
≥ 7	3 (4.9%)
HCV Genotype	
1A	24 (39.3%)

1B	21 (34.4%)
2	2 (3.3%)
2B	6 (9.8%)
3A	7 (11.5%)
4	1 (1.6%)
IL28B Genotype	
CC	13 (21.7%)
CT	39 (65.0%)
TT	8 (13.3%)
Missing	1
Baseline ALT (IU/L)	
Mean (SD)	81 (39.1)
Min, Max	22, 202
Baseline ALT Category	
≤ 1.5 × ULN	35 (57.4%)
> 1.5 × ULN	26 (42.6%)
Baseline CPT Score	
5	26 (42.6%)
6	18 (29.5%)
7	14 (23.0%)
8	3 (4.9%)
Baseline MELD Score	
6	5 (8.2%)
7	18 (29.5%)
8	12 (19.7%)
9	9 (14.8%)
10	6 (9.8%)
11	8 (13.1%)
13	2 (3.3%)
14	1 (1.6%)

A total of 44 subjects have undergone liver transplantation at the time of the latest interim analysis. Of the 44 subjects, 41 (93.2%) had HCV-RNA <LLOQ at the time of liver transplantation and 3 had HCV-RNA ≥LLOQ at the time of liver transplantation (Table 4).

Table 4. P7977-2025: Proportion of subjects with last observed HCV-RNA prior to transplantation <LLOQ (FAS subjects who received a transplant)

	SOF + RBV
Number of Subjects with ≥12 Weeks of Treatment and Received a Liver Transplantation[a]	33
<LLOQ at Last HCV-RNA Measurement Prior to Liver Transplantation	
Yes	30/33 (90.9%)
No	3/33 (9.1%)
Number of Subjects with Any Treatment Duration and Received a Liver Transplantation[b]	44
<LLOQ at Last HCV RNA Measurement Prior to Liver Transplantation	
Yes	41/44 (93.2%)
No	3/44 (6.8%)

a. The denominator includes all subjects who received a liver transplantation and had ≥12 weeks of study treatment for the primary efficacy analysis.
b. The denominator includes all subjects who received a liver transplantation and had ≥ 1 dose of study treatment for the secondary efficacy analysis.

At the interim analysis, post-treatment virological response was as follows (Table 5).

Table 5. P7977-2025: post-transplantation virologic response by visit in subjects with HCV-RNA <LLOQ at last measurement prior to transplant

	Virologic response in evaluable subjects[a]
Week 2 post-transplant	32/40 (80%)
Week 4 post-transplant	27/39 (69%)
Week 8 post-transplant	26/38 (68%)
Week 12 post-transplant (pTVR)[b]	23/37 (62%)

[a] evaluable subjects are defined as those who have reached the specified time point at the time of the interim analysis
[b] pTVR: post-transplant virologic response (HCV-RNA <LLOOQ at 12 weeks post-procedure)

As described above, 33 patients received at least 12 weeks of therapy prior to transplant, whereas 11 received less that 12 weeks of therapy. Recurrent HCV was observed in 10 subjects, 4 of whom had received less that 12 weeks of therapy, and 6 of whom had received more than 12 weeks of therapy.

A total of 11 of 15 subjects (73.3%) who completed 24 weeks of treatment and had an observed or imputed Week 4 post-treatment follow-up HCV-RNA value relapsed during post-treatment follow-up. This prompted a protocol amendment to extend the treatment duration from 24 weeks to 48 weeks or the time of transplant.

In no subject in whom baseline resistance testing was available, was the S282T mutation (conferring resistance to sofosbuvir) detected by population sequencing. In none of the patients qualifying for resistance testing after treatment initiation (due to virological nonresponse/ breakthrough, pre-transplant relapse, or graft reinfection) was the S282T mutation detected by deep sequencing.

Clinical efficacy in the post-transplant setting

Very limited data exist on the use of sofosbuvir in the post-transplant setting. Gilead is investigating treatment with sofosbuvir plus RBV for 24 weeks in patients with recurrent HCV infection post-liver transplantation (GS-US-334-0126). This trial has completed enrolment. At the time of data submission for the present application, 31 of 40 patients had completed up to 24 weeks treatment with sofosbuvir + RBV. By Week 4 on treatment 100% of subjects had HCV-RNA <25 IU/ml. A total of 15 of 19 subjects (79%) have HCV-RNA <LLOQ four weeks after the end of treatment. Two subjects have terminated treatment early due AEs (progression of HCC and pneumonia).

Discussion on clinical efficacy

Pre-transplant

Interim data from the P7977-2025 study show that 62% (23/37) of patients with an on-treatment plasma HCV-RNA <LLOQ at the time of transplantation had post-transplant virological response (HCV-RNA <LLOQ 12 weeks post-transplantation). No relation between the time on treatment prior to transplant and the risk of graft reinfection was reported. The rate of virologic

relapse after 24 weeks of treatment in this patient population and the need for HCV-RNA to be <LLOQ at the time of transplant suggests that subjects should continue on sofosbuvir + RBV treatment until the time of transplant.

Post-transplant

There are little data on the efficacy of sofosbuvir in the post-transplant setting. However, evidence from a general population indicate that high (90%) SVR rates can be reached in genotype 1, and by bridging conclusions, likely in all genotypes, with only 12 weeks of therapy including sofosbuvir + PEG + RBV. In small studies, SVR rates around 50-60% in genotype 1 have been reported with sofosbuvir + RBV bitherapy for 12-24 weeks. The relevance of these data in the post-transplant setting, however, is unknown. In patients with genotype 2 infection, similarly high SVR rates may be reached with 12 weeks of sofosbuvir + RBV bitherapy. In genotype 3 infection, sofosbuvir + RBV bitherapy yielded approximately 60% SVR. Data indicate that higher rates are likely with 24 weeks of therapy.

In summary, these data support the proposed compassionate use of sofosbuvir + RBV for 24 weeks in the post-transplant setting. However, it is recognised that SVR rates in genotypes other than -2 may be relatively low with this bitherapy regimen. Therefore, it is anticipated that clinicians may consider the addition of a third active agent, if tolerated, in this scenario.

Overall conclusion on clinical efficacy

The use of sofosbuvir + RBV combination therapy in the pre-transplant setting offers a considerable chance of avoiding otherwise ubiquitous graft reinfection. This benefit requires viral suppression at the time of transplantation. According to available data, SVR is unlikely with 24 weeks of therapy in this population with very advanced liver disease. Therefore, the proposal to continue therapy beyond 24 weeks while waiting for a graft seems reasonable.

Given the poor tolerability and, subsequently, effectiveness, of presently licensed treatment options in the post-transplant setting, the use of sofosbuvir + RBV for 24 weeks offers a possibility to reach SVR in patients that may otherwise decompensate and die in the absence of re-transplantation. The addition of a third agent to sofosbuvir + RBV bitherapy, if tolerated, may increase SVR rates in genotypes 1 and -3.

Clinical safety

Data submitted

The total safety database for sofosbuvir contains over 1,700 patients that have been exposed in phase II and III trials to regimens including sofosbuvir as monotherapy, in combination with RBV or in combination with PEG + RBV, for 12-24 weeks. This includes over 400 patients in 24-week treatment arms. The phase III program included approximately 260 patients with compensated cirrhosis. Furthermore, interim data from the P7977-2025 study included 61 patients on the transplant list due to HCC; 17 of these where Child-Pugh B at baseline.

The proportion of patients experiencing serious adverse events (SAEs) in the sofosbuvir arms of the phase III trials were 1.2-3.9%. Adverse events (AEs) leading to study drug discontinuation were experienced by 0-2.4% in different SOF-containing treatment arms. One treatment-emergent death occurred in the phase III studies; this was an overdose of heroin and cocaine on day 1 of the relevant trial.

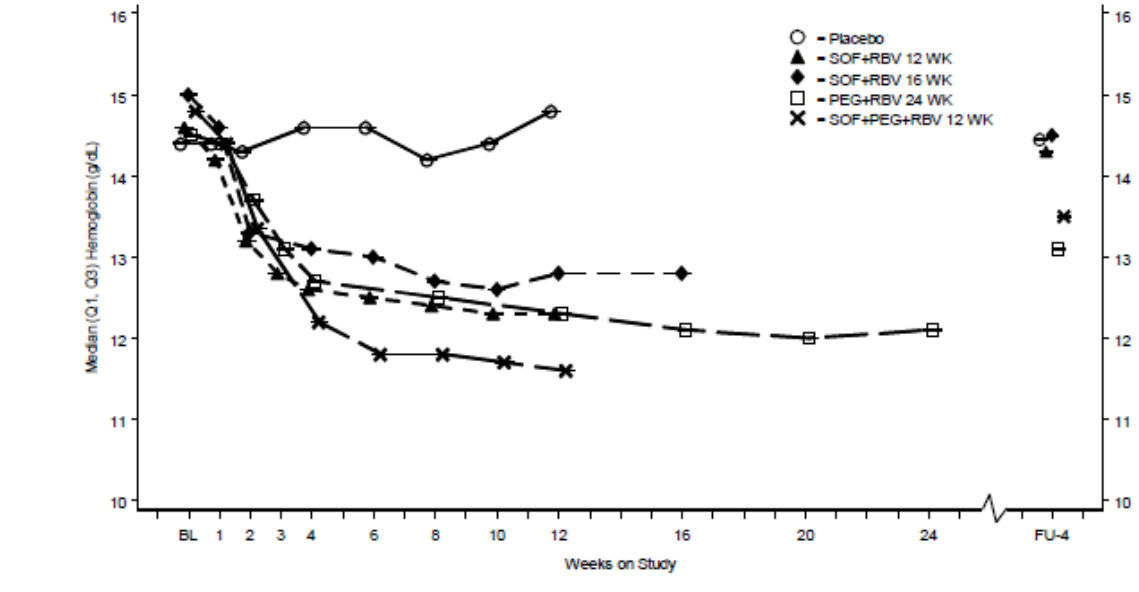
The incidence of SAEs was comparable between patients treated with sofosbuvir + RBV for 12 weeks and for 16 weeks (3.9%, 22 subjects and 3.1%, 3 subjects, respectively). Malignant

hepatic neoplasm (0.5%, 3 subjects) and pyrexia and cellulitis (each 0.4%, 2 subjects) were the only SAEs reported in ≥2 subjects in the sofosbuvir + RBV 12 Week group. No other individual SAEs in the sofosbuvir + RBV 12-week group were reported in >1 subject, and there was no apparent clustering of SAEs observed within SOCs that had >5 subjects reporting SAEs. There was no apparent trend in the types of events reported or onset time observed. For the sofosbuvir + RBV 16-week group, no individual SAE was reported by >1 subject. Treatment-related SAEs were reported in 2 subjects (0.4%) in the sofosbuvir + RBV 12-week group: anaemia on Day 20 and peripheral oedema and eczema on post-treatment Day 28, respectively.

The most common side effects reported include fatigue, headache, nausea and insomnia. In the sofosbuvir + RBV containing arms, irritability, anaemia, cough and dyspnoea were more common than with placebo. Of note, these side effects have been associated with RBV therapy, the hallmark side effect of which is haemolytic anaemia.

Figure 1 summarises the median haemoglobin values by treatment and visit in the primary safety population. In these studies, RBV was given at an 800 mg flat dose in the PEG + RBV 24 weeks group, and 1,000/1,200 mg weight based in all sofosbuvir + RBV groups.

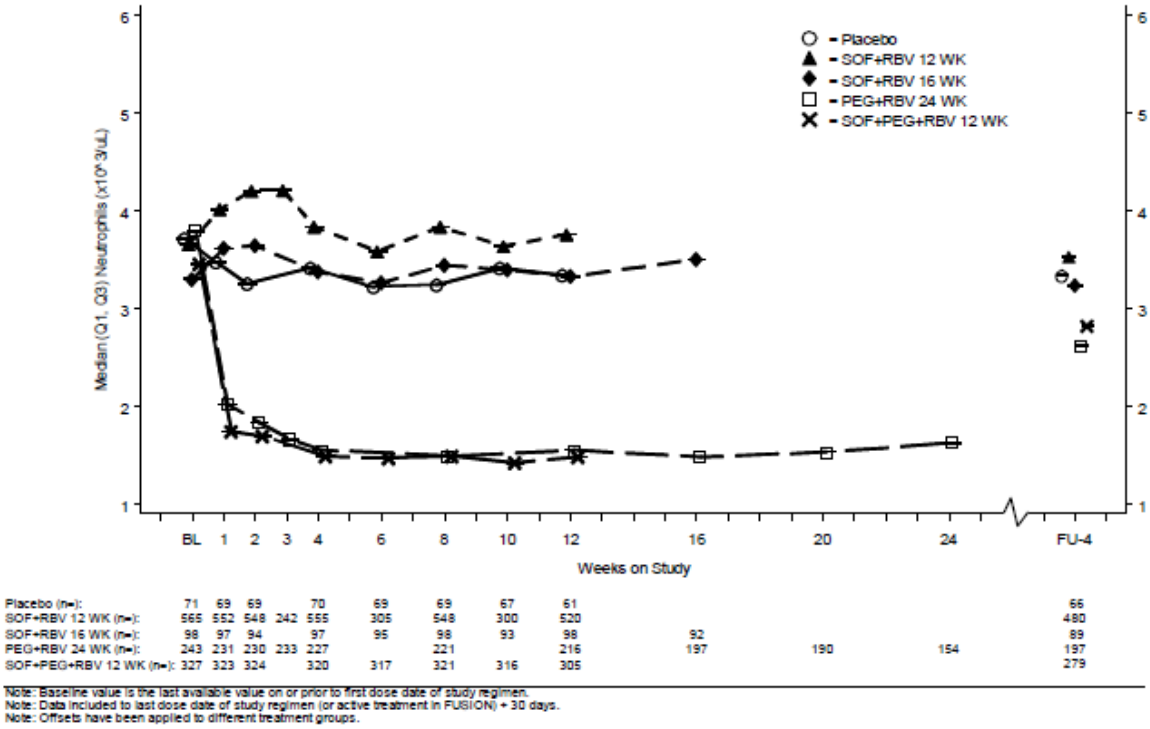
Figure 1. Median haemoglobin values by treatment and visit in the primary safety population (Safety Analysis Set)



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

The side effect profile when sofosbuvir was co-administered with PEG + RBV was typical of PEG-based therapy. It does not appear that sofosbuvir co-administration adds to the anaemia and cytopenias induced by RBV and/or PEG + RBV. Figure 2 summarises the median neutrophil values by treatment and visit in the primary safety population:

Figure 2. Median neutrophil values by treatment and visit in the primary safety population (Safety Analysis Set)



Adverse events (in ≥10% of subjects in any treatment group) and grade 3 and 4 coagulation and chemistry laboratory abnormalities (in ≥2 subjects in any treatment group) reported in in the pivotal phase III studies are summarised in tables 6 and 7 below:

Table 6. Adverse events in ≥10% of subjects in any group by preferred term in the pivotal phase 3 studies (Safety Analysis Set)

Preferred Term	GS-US-334-0107 (POSITRON)	P7977-1231 (FISSION) GS-US-334-0107 (POSITRON)	GS-US-334-0108 (FUSION)	P7977-1231 (FISSION)	GS-US-334-0110 (NEUTRINO)
	Placebo 12 Weeks	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%)
Fatigue	17 (23.9%)	229 (40.5%)	46 (46.9%)	134 (55.1%)	192 (58.7%)
Headache	14 (19.7%)	132 (23.3%)	32 (32.7%)	108 (44.4%)	118 (36.1%)
Nausea	13 (18.3%)	114 (20.1%)	20 (20.4%)	70 (28.8%)	112 (34.3%)
Insomnia	3 (4.2%)	91 (16.1%)	28 (28.6%)	70 (28.8%)	81 (24.8%)
Rash	6 (8.5%)	48 (8.5%)	12 (12.2%)	43 (17.7%)	59 (18.0%)
Pruritus	6 (8.5%)	53 (9.4%)	7 (7.1%)	42 (17.3%)	54 (16.5%)
Decreased Appetite	7 (9.9%)	33 (5.8%)	5 (5.1%)	44 (18.1%)	58 (17.7%)

Irritability	1 (1.4%)	58 (10.2%)	11 (11.2%)	40 (16.5%)	42 (12.8%)
Diarrhoea	4 (5.6%)	57 (10.1%)	6 (6.1%)	42 (17.3%)	38 (11.6%)
Dizziness	5 (7.0%)	52 (9.2%)	5 (5.1%)	33 (13.6%)	41 (12.5%)
Arthralgia	1 (1.4%)	42 (7.4%)	9 (9.2%)	35 (14.4%)	47 (14.4%)
Anaemia	0	58 (10.2%)	4 (4.1%)	28 (11.5%)	68 (20.8%)
Myalgia	0	35 (6.2%)	9 (9.2%)	40 (16.5%)	45 (13.8%)
Influenza Like Illness	2 (2.8%)	16 (2.8%)	3 (3.1%)	44 (18.1%)	51 (15.6%)
Cough	2 (2.8%)	39 (6.9%)	13 (13.3%)	21 (8.6%)	34 (10.4%)
Chills	1 (1.4%)	16 (2.8%)	0	43 (17.7%)	54 (16.5%)
Vomiting	5 (7.0%)	33 (5.8%)	4 (4.1%)	23 (9.5%)	39 (11.9%)
Pyrexia	0	19 (3.4%)	3 (3.1%)	33 (13.6%)	58 (17.7%)
Depression	1 (1.4%)	34 (6.0%)	6 (6.1%)	34 (14.0%)	31 (9.5%)
Dyspnoea	1 (1.4%)	45 (8.0%)	5 (5.1%)	20 (8.2%)	39 (11.9%)
Pain	2 (2.8%)	17 (3.0%)	5 (5.1%)	30 (12.3%)	33 (10.1%)
Neutropenia	0	0	0	30 (12.3%)	54 (16.5%)

Table 7. Summary of grade 3 and 4 coagulation and chemistry laboratory abnormalities reported in ≥2 subjects in any treatment group in the pivotal phase 3 studies (Safety Analysis Set)

	GS-US-334-0107 (POSITRON)	**P7977-1231 (FISSION) GS-US-334-0107 (POSITRON) GS-US-334-0108 (FUSION)**	**GS-US-334-0108 (FUSION)**	**P7977-1231 (FISSION)**	**GS-US-334-0110 (NEUTRINO)**
	Placebo 12 Weeks	**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)**
Coagulation					
Prothrombin Time, N	69	551	98	235	317
Grade 3	0	2 (0.4%)	0	1 (0.4%)	0
Chemistry					
Alanine Amino-transferase, N	71	563	98	242	327
Grade 3	6 (8.5%)	1 (0.2%)	2 (2.0%)	9 (3.7%)	7 (2.1%)
Asaparate Amino-transferase, N	71	563	98	242	327
Grade 3	9 (12.7%)	0	0	3 (1.2%)	9 (2.8%)
Creatine Kinase, N	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
Lipase, N	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%)

Glucose (Hyper-glycemia), N	71	563	98	242	327
Grade 3	4 (5.6%)	13 (2.3%)	5 (5.1%)	4 (1.7%)	7 (2.1%)
Total Bilirubin (Hyper-bilirubinemia), N	71	563	98	242	327
Grade 3	0	13 (2.3%)	2 (2.0%)	2 (0.8%)	0

No specific safety signal has been identified in the pre-transplant population (P7977-2025 study). A summary of reported SAEs in the interim analysis is shown in table 8.

Table 8. P7977-2025: treatment-emergent serious adverse events (Safety Analysis Set)

Preferred Term	**SOF + RBV (N=61) N(%)**
Subjects Experiencing Any Serious Adverse Event	11 (18.0%)
Hepatocellular carcinoma	2 (3.3%)
Pyrexia	2 (3.3%)
Umbilical Hernia, Obstructive	2 (3.3%)
Atrial Fibrillation	1 (1.6%)
Abdominal Pain	1 (1.6%)
Abdominal Strangulated Hernia	1 (1.6%)
Cellulitis	1 (1.6%)
Confusional State	1 (1.6%)
Hepatic Encephalopathy	1 (1.6%)
Hyponatraemia	1 (1.6%)
Intervertebral Disc Degeneration	1 (1.6%)
Nausea	1 (1.6%)
Osteoarthritis	1 (1.6%)
Peritonitis Bacterial	1 (1.6%)
Pneumonitis	1 (1.6%)
Prostate Cancer	1 (1.6%)
Renal Failure Acute	1 (1.6%)
Sepsis	1 (1.6%)
Tumor Thrombosis	1 (1.6%)
Vomiting	1 (1.6%)

Five deaths were reported during the study, none of which were attributed to the study treatment. Three graft losses were reported (2 of which resulted in death). A review of the deaths and graft losses by the study safety review committee, as well as from 3 independent experts in the field, found that all 5 patients died of complications of liver disease and transplantation and that the complications were within the realm of problems that occur with end-stage liver disease patients.

Grade 3 or 4 laboratory abnormalities occurred in 34.4% and 9.8% of subjects, respectively. Decreases in haemoglobin were attributed to RBV-dosing. No Grade 3 or 4 laboratory abnormality led to a discontinuation of study treatment.

There are little safety data specific to the use of sofosbuvir in a post-transplant setting. Concerning the impact of renal impairment, and co-administration with cyclosporin or tacrolimus, see above.

Discussion on clinical safety

The side effect profile of sofosbuvir + RBV or sofosbuvir +PEG + RBV for up to 24 weeks is not markedly different from that of RBV or PEG + RBV alone, as described in previous studies. No clear sofosbuvir-specific side effect-profile has emerged. Importantly with regards to the presently relevant treatment populations, there appear to be no additive effects to the haematological side effects profile of RBV or PEG + RBV. While the exposure to the major circulating metabolite of sofosbuvir is somewhat increased in mild to moderate renal impairment, there is no clear indication that this would compromise the safety profile of sofosbuvir, and it does not constitute an objection to the compassionate use in such patients. In patients with severe renal impairment exposure to sofosbuvir metabolite (as well as to RBV) is considerably increased. There is no validated dosing regimen and treatment decisions must be made taking this into account. There is an increased sofosbuvir exposure on co-treatment with cyclosporin. Given the general safety profile of sofosbuvir, this does not imply that co-treatment cannot be recommended; however, unless specific circumstances favour the use of cyclosporin, tacrolimus-based immunosuppressive regimens may be preferable.

Overall conclusion on clinical safety

No sofosbuvir -specific side effects profile has been identified over 24 weeks. While data are sparse for longer exposure, there is no specific concern to preclude longer exposure in compassionate use, if clinically indicated. While there is increased exposure to sofosbuvir and/or sofosbuvir -metabolites in renal impairment and on co-treatment with cyclosporin, no exposure-dependent side effects have been identified to preclude the compassionate use in such situations.

3.5. Pharmacovigilance

In order to ensure the safety monitoring of the patients, the following conditions have been adopted and are annexed to the CHMP opinion on compassionate use for Sofosbuvir Gilead as follows:

Conditions for safety monitoring to be implemented by the company

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 28(1) and 28(2) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use in accordance with Article 83(4) of Regulation (EC) No 726/2004 has been adopted.

The manufacturer will ensure that these pharmacovigilance obligations are fulfilled.

Conditions for safety monitoring to be implemented by the Member States

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. The Member State(s) will ensure that these pharmacovigilance obligations are fulfilled.

3.6. Risk-benefit assessment and recommendation

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 more or less universal. The effectiveness of PEG-based therapy in a pre-transplant setting is low, with a risk of severe complications such as serious bacterial infections and hepatic decompensation. Interferons are contraindicated in decompensated liver disease.

Post-transplant HCV recurrence is often aggressive, and for this reason the prognosis after liver transplantation due to HCV complications is worse than the prognosis when transplantation is due to other causes.

Interim data from the P7977-2025 study indicate that graft reinfection may be prevented in about two-thirds of patients that receive a graft while on sofosbuvir therapy with plasma HCV-RNA <LLOQ. No specific safety concerns have emerged in this study. Given the very considerable benefits of preventing graft reinfection, and the emerging safety profile of sofosbuvir, the benefit-risk balance is deemed positive for compassionate use in this indication, for patients that do not have the possibility to enroll in relevant clinical trials. Also, although in the P7977-2025 study sofosbuvir was given for 24 weeks (with a retreatment option for which data are not yet available) the company proposes that sofosbuvir therapy be continued until transplantation in patients on the waiting list. It is recognised that the safety database of sofosbuvir primarily covers 24 weeks of therapy. However, given the anticipated benefits of on-treatment viral response, the uncertainty of when a graft from an unrelated donor will be available, and the high probability of relapse after completing 24 weeks of therapy without receiving a graft in the P7977-2025 study, this is considered reasonable and to carry a positive benefit-risk balance.

As stated above, post-transplant recurrence of HCV may be aggressive, with a rapid progression to cirrhosis. Tolerance of therapy is a major issue in this situation. These patients, being treated with calcineurin inhibitors to prevent rejection, often have impaired renal function, and are particularly susceptible to haematological side effect of HCV therapy. Consequently, reports of the addition of boceprevir or telaprevir to PEG + RBV in this setting indicate that this is associated with a high frequency of SAEs and treatment discontinuations. Given that sofosbuvir does not contribute to haematological AEs and, as opposed to the presently approved direct acting antivirals (DAAs), does not have major drug-drug interactions with calcineurin inhibitors, sofosbuvir-based therapy is an important option for compassionate use in the post-transplant population. However, while a 24-week regimen of sofosbuvir + RBV will likely have a high efficacy in genotype 2, the likelihood of SVR in other genotypes, in a post-transplant population with aggressive recurrence, may be relatively low. Therefore, clinicians may consider the use of a suitable third agent in such a situation, if this is deemed likely tolerable.

Furthermore, the applicant proposes that the appropriate post-transplant target population include those "who have undergone liver transplantation and who have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease with a predicted life expectancy of less than 12 months if left untreated". The latter may be difficult to ascertain in practice. Provided that the patient does not have the possibility of enrolling in a clinical trial, a positive benefit/risk for the compassionate use of sofosbuvir in the post-transplant setting can be inferred if the treating physician deems the risk of death or decompensation within 12 months to

be considerable. Therefore, the CHMP proposed that the appropriate target population for the compassionate use of sofosbuvir in a pre- and post-transplant population be defined as follows:

Sofosbuvir Gilead, when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C who are also:

- **actively on the waiting list for liver transplantation (documented) and require treatment to prevent *graft* reinfection *with hepatitis C virus*, or**
- **Who have undergone liver transplantation and have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease, *and are at a high risk of death or decompensation within 12 months if left untreated***

Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for Sofosbuvir Gilead available for compassionate use (see appendix 2).