

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 400 mg film-coated tablets
Sovaldi 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sovaldi 400 mg film-coated tablets

Each film-coated tablet contains 400 mg of sofosbuvir.

Sovaldi 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of sofosbuvir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sovaldi 400 mg film-coated tablets

Yellow, capsule-shaped, film-coated tablet of dimensions of approximately 20 mm x 9 mm, debossed on one side with “GSI” and “7977” on the other side.

Sovaldi 200 mg film-coated tablets

Yellow, oval-shaped, film-coated tablet of dimensions of approximately 15 mm x 8 mm, debossed on one side with “GSI” and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and paediatric patients aged 3 years and above (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Sovaldi treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose of Sovaldi in adults is one 400 mg tablet, taken orally, once daily with food (see section 5.2).

The recommended dose of Sovaldi in paediatric patients aged 3 years and above is based on weight (as detailed in Table 2). Sovaldi should be taken with food (see section 5.2).

Sovaldi oral granules are available for the treatment of chronic HCV-infection in paediatric patients aged 3 years and above having difficulty in swallowing film-coated tablets. Please refer to the Summary of Product Characteristics for Sovaldi 150 mg or 200 mg granules.

Sovaldi should be used in combination with other medicinal products. Monotherapy of Sovaldi is not recommended (see section 5.1). Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Sovaldi. The recommended co-administered medicinal product(s) and treatment duration for Sovaldi combination therapy are provided in Table 1.

Table 1: Recommended co-administered medicinal product(s) and treatment duration for adults and paediatric patients treated with Sovaldi combination therapy

Patient population*	Treatment	Duration
Adult patients with genotype 1, 4, 5 or 6 CHC	Sovaldi + ribavirin ^c + peginterferon alfa	12 weeks ^{a,b}
	Sovaldi + ribavirin ^c	24 weeks
	Only for use in patients ineligible or intolerant to peginterferon alfa (see section 4.4)	
Adult and paediatric patients aged 3 years and above with genotype 2 CHC	Sovaldi ^d + ribavirin ^{c,e}	12 weeks ^b
Adult patients with genotype 3 CHC	Sovaldi + ribavirin ^c + peginterferon alfa	12 weeks ^b
	Sovaldi + ribavirin ^c	24 weeks
Paediatric patients aged 3 years and above with genotype 3 CHC	Sovaldi ^d + ribavirin ^e	24 weeks
Adult patients with CHC awaiting liver transplantation	Sovaldi + ribavirin ^c	Until liver transplantation ^f

* Includes patients co-infected with human immunodeficiency virus (HIV).

- a. For previously treated patients with HCV genotype 1 infection, no data exists with the combination of Sovaldi, ribavirin and peginterferon alfa (see section 4.4).
- b. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).
- c. Adults: weight-based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg); administered orally in two divided doses with food.
- d. See Table 2 for weight-based Sovaldi dosing recommendations for paediatric patients aged 3 years and above.
- e. See Table 3 for weight-based ribavirin dosing recommendations for paediatric patients aged 3 years and above.
- f. See Special patient populations – Patients awaiting liver transplantation below.

Table 2: Dosing for paediatric patients aged 3 years and above using Sovaldi tablets*

Body Weight (kg)	Dosing of Sovaldi Tablets	Sofosbuvir Daily Dose
≥ 35	one 400 mg tablet once daily or two 200 mg tablets once daily	400 mg/day
17 to < 35	one 200 mg tablet once daily	200 mg/day

- * Sovaldi is also available as granules for use in paediatric patients with CHC aged 3 years and above (see section 5.1). Patients that weigh < 17 kg are not recommended to take tablets. Please refer to the Summary of Product Characteristics for Sovaldi 150 mg or 200 mg granules.

In paediatric patients aged 3 years and above the following ribavirin dosing is recommended where ribavirin is divided into two daily doses and given with food:

Table 3: Guidance for ribavirin dosing when administered in combination with Sovaldi to HCV-infected paediatric patients aged 3 years and above

Body weight kg (lbs)	RBV daily dose*
< 47 (< 103)	15 mg/kg/day
47-49 (103-108)	600 mg/day
50-65 (110-143)	800 mg/day
66-80 (145-176)	1000 mg/day
> 81 (178)	1200 mg/day

* The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

Concerning co-administration with other direct-acting antivirals against HCV, see section 4.4.

Dose modification in adults

Dose reduction of Sovaldi is not recommended.

If sofosbuvir is used in combination with peginterferon alfa, and a patient has a serious adverse reaction potentially related to this medicinal product, the peginterferon alfa dose should be reduced or discontinued. Refer to the peginterferon alfa Summary of Product Characteristics for additional information about how to reduce and/or discontinue the peginterferon alfa dose.

If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 4 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 4: Ribavirin dose modification guideline for co-administration with Sovaldi in adults

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Haemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Haemoglobin in patients with history of stable cardiac disease	≥2 g/dL decrease in haemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1,000 mg to 1,200 mg daily).

Dose modification in paediatric patients aged 3 years and above

Dose reduction of Sovaldi is not recommended.

If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Refer to the ribavirin prescribing information for guidance on dose modification or discontinuation.

Discontinuation of dosing

If the other medicinal products used in combination with Sovaldi are permanently discontinued, Sovaldi should also be discontinued (see section 4.4).

Vomiting and missed doses

Patients should be instructed that if vomiting occurs within 2 hours of dosing an additional dose should be taken. If vomiting occurs more than 2 hours after dosing, no further dose is needed. These recommendations are based on the absorption kinetics of sofosbuvir and GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the dose as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed not to take a double dose.

Special patient populations

Elderly

No dose adjustment is warranted for elderly patients (see section 5.2).

Renal impairment

No dose adjustment of Sovaldi is required for patients with mild or moderate renal impairment.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) and end stage renal disease (ESRD) requiring haemodialysis. Sovaldi can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.1 and 5.2).

Hepatic impairment

No dose adjustment of Sovaldi is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.2). The safety and efficacy of Sovaldi have not been established in patients with decompensated cirrhosis.

Patients awaiting liver transplantation

The duration of administration of Sovaldi in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient (see section 5.1).

Adult liver transplant recipients

Sovaldi in combination with ribavirin is recommended for 24 weeks in liver transplant recipients. In adults a starting ribavirin dose of 400 mg administered orally in two divided doses with food is recommended. If the starting dose of ribavirin is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing <75 kg and 1,200 mg for patients weighing ≥75 kg). If the starting dose of ribavirin is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels (see section 5.1).

Paediatric population aged < 3 years

The safety and efficacy of Sovaldi in children aged <3 years have not yet been established. No data are available.

Method of administration

Oral use.

Patients should be instructed to swallow the tablet(s) whole. The film-coated tablet(s) should not be chewed or crushed, due to the bitter taste of the active substance. The tablet(s) should be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Medicinal products that are strong P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort). Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of Sovaldi (see section 4.5).

4.4 Special warnings and precautions for use

General

Sovaldi is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. If the other medicinal products used in combination with Sovaldi are permanently discontinued, Sovaldi should also be discontinued (see section 4.2). Consult the Summary of Product Characteristics for co-prescribed medicinal products before starting therapy with Sovaldi.

Severe bradycardia and heart block

Life-threatening cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone. Bradycardia has generally occurred within hours to days, but cases with a longer time to onset have been observed mostly up to 2 weeks after initiating HCV treatment.

Amiodarone should only be used in patients on Sovaldi when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Sovaldi.

All patients with concurrent or recent use of amiodarone should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

HCV/HBV (hepatitis B virus) co-infection

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection

Sovaldi has not been studied in a Phase 3 study in treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection. Thus, the optimal treatment duration in this population has not been established (see also sections 4.2 and 5.1).

Consideration should be given to treating these patients, and potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).

Treatment of patients with genotype 5 or 6 HCV infection

The clinical data to support the use of Sovaldi in patients with genotype 5 and 6 HCV infection is very limited (see section 5.1).

Interferon-free therapy for genotype 1, 4, 5 and 6 HCV infection

Interferon-free regimens for patients with genotype 1, 4, 5 and 6 HCV infection with Sovaldi have not been investigated in Phase 3 studies (see section 5.1). The optimal regimen and treatment duration have not been established. Such regimens should only be used for patients that are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment.

Co-administration with other direct-acting antivirals against HCV

Sovaldi should only be co-administered with other direct-acting antiviral medicinal products if the benefit is considered to outweigh the risks based upon available data. There are no data to support the co-administration of Sovaldi and telaprevir or boceprevir. Such co-administration is not recommended (see also section 4.5).

Pregnancy and concomitant use with ribavirin

When Sovaldi is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for a period of time after the treatment as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

Use with moderate P-gp inducers

Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sovaldi. Co-administration of such medicinal products is not recommended with Sovaldi (see section 4.5).

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

Renal impairment

Safety data are limited in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) and ESRD requiring haemodialysis. Sovaldi can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 4.8, 5.1 and 5.2). When Sovaldi is used in combination with ribavirin or peginterferon alfa/ribavirin, refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance (CrCl) <50 mL/min (see also section 5.2).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Sofosbuvir is a nucleotide prodrug. After oral administration of Sovaldi, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic and intestinal metabolism. Intracellular hydrolytic prodrug cleavage catalysed by enzymes including carboxylesterase 1 and sequential phosphorylation steps catalysed by nucleotide kinases result in formation of the pharmacologically active uridine nucleoside analogue triphosphate. The predominant inactive circulating metabolite GS-331007 that accounts for greater than 90% of drug-related material systemic exposure is formed through pathways sequential and parallel to formation of active metabolite. The parent sofosbuvir accounts for approximately 4% of drug-related material systemic exposure (see section 5.2). In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not.

Medicinal products that are strong P-gp inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John’s wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sovaldi and thus are contraindicated with Sovaldi (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sovaldi. Co-administration with such medicinal products is not recommended with Sovaldi (see section 4.4). Co-administration of Sovaldi with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus Sovaldi may be co-administered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of medicinal products that are substrates of these transporters.

The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant medicinal products (see section 5.2).

Patients treated with vitamin K antagonists

As liver function may change during treatment with Sovaldi, a close monitoring of International Normalised Ratio (INR) values is recommended.

Impact of DAA therapy on drugs metabolized by the liver

The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Other interactions

Drug interaction information for Sovaldi with potential concomitant medicinal products is summarised in Table 5 below (where 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio were within “↔”, extended above “↑”, or extended below “↓” the predetermined equivalence boundaries). The table is not all-inclusive.

Table 5: Interactions between Sovaldi and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
ANALEPTICS		
Modafinil	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Sovaldi with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sovaldi. Such co-administration is not recommended.
ANTIARRHYTHMICS		
Amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown.	Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia. Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Sovaldi (see sections 4.4 and 4.8).
ANTICOAGULANTS		
Vitamin K antagonists	Interaction not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Sovaldi.
ANTICONVULSANTS		
Phenobarbital Phenytoin	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sovaldi is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine	<i>Sofosbuvir</i> ↓ C _{max} 0.52 (0.43, 0.62) ↓ AUC 0.52 (0.46, 0.59) C _{min} (NA) <i>GS-331007</i> ↔ C _{max} 1.04 (0.97, 1.11) ↔ AUC 0.99 (0.94, 1.04) C _{min} (NA) (Induction of P-gp)	Sovaldi is contraindicated with carbamazepine (see section 4.3).
Oxcarbazepine	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Sovaldi with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sovaldi. Such co-administration is not recommended (see section 4.4).
ANTIMYCOBACTERIALS		
Rifampicin ^f (600 mg single dose)	<i>Sofosbuvir</i> ↓ C _{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C _{min} (NA) <i>GS-331007</i> ↔ C _{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) C _{min} (NA) (Induction of P-gp)	Sovaldi is contraindicated with rifampicin (see section 4.3).

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}^{a,b}	Recommendation concerning co-administration with Sovaldi
Rifabutin	<i>Sofosbuvir</i> ↓ C _{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C _{min} (NA) <i>GS 331007</i> ↔ C _{max} 1.15 (1.03, 1.27) ↔ AUC 1.03 (0.95, 1.12) C _{min} (NA) (Induction of P-gp)	No dose adjustment of Sovaldi is required when concomitantly used with rifabutin.
Rifapentine	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Sovaldi with rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sovaldi. Such co-administration is not recommended (see section 4.4).
HERBAL SUPPLEMENTS		
St. John's wort	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sovaldi is contraindicated with St. John's wort (see section 4.3).
HCV ANTI VIRAL AGENTS: HCV PROTEASE INHIBITORS		
Boceprevir (BOC) Telaprevir (TPV)	Interaction not studied. <i>Expected:</i> ↑ Sofosbuvir (TPV) ↔ Sofosbuvir (BOC) ↔ GS-331007 (TPV or BOC)	No drug-drug interaction data exists regarding the co-administration of Sovaldi with boceprevir or telaprevir.
NARCOTIC ANALGESICS		
Methadone ^f (Methadone maintenance therapy [30 to 130 mg/daily])	<i>R-methadone</i> ↔ C _{max} 0.99 (0.85, 1.16) ↔ AUC 1.01 (0.85, 1.21) ↔ C _{min} 0.94 (0.77, 1.14) <i>S-methadone</i> ↔ C _{max} 0.95 (0.79, 1.13) ↔ AUC 0.95 (0.77, 1.17) ↔ C _{min} 0.95 (0.74, 1.22) <i>Sofosbuvir</i> ↓ C _{max} 0.95 ^c (0.68, 1.33) ↑ AUC 1.30 ^c (1.00, 1.69) C _{min} (NA) <i>GS-331007</i> ↓ C _{max} 0.73 ^c (0.65, 0.83) ↔ AUC 1.04 ^c (0.89, 1.22) C _{min} (NA)	No dose adjustment of sofosbuvir or methadone is required when sofosbuvir and methadone are used concomitantly.

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
IMMUNOSUPPRESSANTS		
Ciclosporin ^e (600 mg single dose)	<p><i>Ciclosporin</i> ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) C_{min} (NA)</p> <p><i>Sofosbuvir</i> ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) C_{min} (NA)</p> <p><i>GS-331007</i> ↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
Tacrolimus ^e (5 mg single dose)	<p><i>Tacrolimus</i> ↓ C_{max} 0.73 (0.59, 0.90) ↔ AUC 1.09 (0.84, 1.40) C_{min} (NA)</p> <p><i>Sofosbuvir</i> ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz ^f (600 mg once daily) ^d	<p><i>Efavirenz</i> ↔ C_{max} 0.95 (0.85, 1.06) ↔ AUC 0.96 (0.91, 1.03) ↔ C_{min} 0.96 (0.93, 0.98)</p> <p><i>Sofosbuvir</i> ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA)</p> <p><i>GS-331007</i> ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or efavirenz is required when sofosbuvir and efavirenz are used concomitantly.
Emtricitabine ^f (200 mg once daily) ^d	<p><i>Emtricitabine</i> ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 0.99 (0.94, 1.05) ↔ C_{min} 1.04 (0.98, 1.11)</p> <p><i>Sofosbuvir</i> ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA)</p> <p><i>GS-331007</i> ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or emtricitabine is required when sofosbuvir and emtricitabine are used concomitantly.

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}^{a,b}	Recommendation concerning co-administration with Sovaldi
Tenofovir disoproxil ^f (245 mg once daily) ^d	<p><i>Tenofovir</i> ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07)</p> <p><i>Sofosbuvir</i> ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA)</p> <p><i>GS-331007</i> ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or tenofovir disoproxil is required when sofosbuvir and tenofovir disoproxil are used concomitantly.
Rilpivirine ^f (25 mg once daily)	<p><i>Rilpivirine</i> ↔ C_{max} 1.05 (0.97, 1.15) ↔ AUC 1.06 (1.02, 1.09) ↔ C_{min} 0.99 (0.94, 1.04)</p> <p><i>Sofosbuvir</i> ↑ C_{max} 1.21 (0.90, 1.62) ↔ AUC 1.09 (0.94, 1.27) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 1.06 (0.99, 1.14) ↔ AUC 1.01 (0.97, 1.04) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or rilpivirine is required when sofosbuvir and rilpivirine are used concomitantly.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Darunavir boosted with ritonavir ^f (800/100 mg once daily)	<p><i>Darunavir</i> ↔ C_{max} 0.97 (0.94, 1.01) ↔ AUC 0.97 (0.94, 1.00) ↔ C_{min} 0.86 (0.78, 0.96)</p> <p><i>Sofosbuvir</i> ↑ C_{max} 1.45 (1.10, 1.92) ↑ AUC 1.34 (1.12, 1.59) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or darunavir (ritonavir boosted) is required when sofosbuvir and darunavir are used concomitantly.
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir ^f (400 mg twice daily)	<p><i>Raltegravir</i> ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12)</p> <p><i>Sofosbuvir</i> ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}^{a,b}	Recommendation concerning co-administration with Sovaldi
ORAL CONTRACEPTIVES		
Norgestimate/ethinyl estradiol	<i>Norgestromin</i> ↔ C _{max} 1.06 (0.93, 1.22) ↔ AUC 1.05 (0.92, 1.20) C _{min} (NA) <i>Norgestrel</i> ↔ C _{max} 1.18 (0.99, 1.41) ↔ AUC 1.19 (0.98, 1.44) C _{min} (NA) <i>Ethinyl estradiol</i> ↔ C _{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C _{min} (NA)	No dose adjustment of norgestimate/ethinyl estradiol is required when sofosbuvir and norgestimate/ethinyl estradiol are used concomitantly.

NA = not available/not applicable

- a. Mean ratio (90% CI) of co-administered drug pharmacokinetics with/without sofosbuvir and mean ratio of sofosbuvir and GS-331007 with/without co-administered drug. No effect = 1.00
- b. All interaction studies conducted in healthy volunteers
- c. Comparison based on historical control
- d. Administered as Atripla
- e. Bioequivalence boundary 80%-125%
- f. Equivalence boundary 70%-143%

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

When Sovaldi is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin (see section 4.4). Women of childbearing potential or their male partners must use an effective form of contraception during treatment and for a period of time after the treatment has concluded as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. No effects on foetal development have been observed in rats and rabbits at the highest doses tested. However, it has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Sovaldi during pregnancy.

However, if ribavirin is co-administered with sofosbuvir, the contraindications regarding use of ribavirin during pregnancy apply (see also the Summary of Product Characteristics for ribavirin).

Breast-feeding

It is unknown whether sofosbuvir and its metabolites are excreted in human milk.

Available pharmacokinetic data in animals have shown excretion of metabolites in milk (for details see section 5.3).

A risk to newborns/infants cannot be excluded. Therefore, Sovaldi should not be used during breast-feeding.

Fertility

No human data on the effect of Sovaldi on fertility are available. Animal studies do not indicate harmful effects on fertility.

4.7 Effects on ability to drive and use machines

Sovaldi has moderate influence on the ability to drive and use machines. Patients should be informed that fatigue and disturbance in attention, dizziness and blurred vision have been reported during treatment with sofosbuvir in combination with peginterferon alfa and ribavirin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile in adults

Assessment of adverse reactions is based on pooled data from five Phase 3 clinical studies (both controlled and uncontrolled).

Sovaldi has been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in patients receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with sofosbuvir in combination with ribavirin or in combination with peginterferon alfa and ribavirin (Table 6). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) or very rare ($< 1/10,000$).

Table 6: Adverse drug reactions identified with sofosbuvir in combination with ribavirin or peginterferon alfa and ribavirin

Frequency	SOF ^a + RBV ^b	SOF + PEG ^c + RBV
<i>Infections and infestations:</i>		
Common	nasopharyngitis	
<i>Blood and lymphatic system disorders:</i>		
Very common	haemoglobin decreased	anaemia, neutropenia, lymphocyte count decreased, platelet count decreased
Common	anaemia	
<i>Metabolism and nutrition disorders:</i>		
Very common	decreased appetite ^d	decreased appetite
Common		weight decreased
<i>Psychiatric disorders:</i>		
Very common	insomnia	insomnia
Common	depression	depression, anxiety, agitation
<i>Nervous system disorders:</i>		
Very common	headache	dizziness, headache
Common	disturbance in attention	migraine, memory impairment, disturbance in attention

<i>Eye disorders:</i>		
Common		vision blurred
<i>Respiratory, thoracic and mediastinal disorders:</i>		
Very common		dyspnoea, cough
Common	dyspnoea, dyspnoea exertional, cough	dyspnoea exertional
<i>Gastrointestinal disorders:</i>		
Very common	nausea	diarrhoea, nausea, vomiting
Common	abdominal discomfort, constipation, dyspepsia	constipation, dry mouth, gastroesophageal reflux
<i>Hepatobiliary disorders:</i>		
Very common	blood bilirubin increased	blood bilirubin increased
<i>Skin and subcutaneous tissue disorders:</i>		
Very common		rash, pruritus
Common	alopecia, dry skin, pruritus	alopecia, dry skin
<i>Musculoskeletal and connective tissue disorders:</i>		
Very common		arthralgia, myalgia
Common	arthralgia, back pain, muscle spasms, myalgia	back pain, muscle spasms
<i>General disorders and administration site conditions:</i>		
Very common	fatigue, irritability	chills, fatigue, influenza-like illness, irritability, pain, pyrexia
Common	pyrexia, asthenia	chest pain, asthenia

a. SOF = sofosbuvir; b. RBV = ribavirin; c. PEG = peginterferon alfa; d. Decreased appetite was identified as an adverse drug reaction to Sovaldi in combination with ribavirin oral solution in paediatric patients aged 3 to < 12 years

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir containing-regimes are used in combination with amiodarone and/or other medicinal products that lower heart rate (see sections 4.4 and 4.5).

Skin disorders

Frequency not known: Stevens-Johnson syndrome

Other special population(s)

HIV/HCV co-infection

The safety profile of sofosbuvir and ribavirin in HCV/HIV co-infected adult patients was similar to that observed in mono-infected HCV patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1).

Patients awaiting liver transplantation

The safety profile of sofosbuvir and ribavirin in HCV infected adult patients prior to liver transplantation was similar to that observed in patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1).

Patients with Renal Impairment

Sofosbuvir in a fixed dose combination with ledipasvir was administered for 12 weeks to 18 patients with genotype 1 CHC and severe renal impairment in an open-label study (Study 0154). The safety of sofosbuvir in a fixed dose combination with either ledipasvir or velpatasvir has been studied in 154 patients with ESRD requiring dialysis (Study 4062 and Study 4063). In this setting, exposure of sofosbuvir metabolite GS-331007 is 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

Adult liver transplant recipients

The safety profile of sofosbuvir and ribavirin in liver transplant adult recipients with chronic hepatitis C was similar to that observed in patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1). In study 0126, decreases in haemoglobin during treatment were very common with 32.5% (13/40 patients) experiencing a decline in haemoglobin to <10 g/dL, 1 of whom also had a decline to <8.5 g/dL. Eight patients (20%) received epoetin and/or a blood product. In 5 patients (12.5%), study drugs were discontinued, modified or interrupted due to adverse events.

Paediatric population

The safety and efficacy of Sovaldi in paediatric patients aged 3 years and above are based on data from 106 patients who were treated with Sovaldi and ribavirin for 12 weeks (genotype 2 patients) and for 24 weeks (genotype 3 patients) in a Phase 2, open-label clinical trial. No adverse drug reactions specific to Sovaldi have been identified. The adverse reactions observed were generally consistent with those observed in clinical studies of Sovaldi plus ribavirin in adults (see Table 6). Decreased appetite was observed as a very common adverse drug reaction to Sovaldi when given in combination with ribavirin oral solution in paediatric patients aged 3 to < 12 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1,200 mg administered to 59 healthy subjects. In that study, there were no untoward effects observed at this dose level, and adverse reactions were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are unknown.

No specific antidote is available for overdose with Sovaldi. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sovaldi consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4-hour haemodialysis session removed 18% of the administered dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct-acting antiviral; ATC code: J05AP08

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with a 50% inhibitory concentration (IC₅₀) value ranging from 0.7 to 2.6 µM. GS-461203 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity

In HCV replicon assays, the effective concentration (EC_{50}) values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a were 0.04, 0.11, 0.05, 0.05 and 0.04 μ M, respectively, and EC_{50} values of sofosbuvir against chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a were 0.014 to 0.015 μ M. The mean \pm SD EC_{50} of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was $0.068 \pm 0.024 \mu$ M for genotype 1a (n = 67), $0.11 \pm 0.029 \mu$ M for genotype 1b (n = 29), $0.035 \pm 0.018 \mu$ M for genotype 2 (n = 15) and $0.085 \pm 0.034 \mu$ M for genotype 3a (n = 106). In these assays, the *in vitro* antiviral activity of sofosbuvir against the less common genotypes 4, 5 and 6 was similar to that observed for genotypes 1, 2 and 3.

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Resistance

In cell culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In clinical studies - Adults

In a pooled analysis of 991 patients who received sofosbuvir in Phase 3 studies, 226 patients qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA >1,000 IU/mL. Post-baseline NS5B sequences were available for 225 of the 226 patients, with deep sequencing data (assay cutoff of 1%) from 221 of these patients. The sofosbuvir-associated resistance substitution S282T was not detected in any of these patients by deep sequencing or population sequencing. The S282T substitution in NS5B was detected in a single subject receiving Sovaldi monotherapy in a Phase 2 study. This subject harboured <1% HCV S282T at baseline and developed S282T (>99%) at 4 weeks post-treatment which resulted in a 13.5-fold change in sofosbuvir EC_{50} and reduced viral replication capacity. The S282T substitution reverted to wild-type over the next 8 weeks and was no longer detectable by deep sequencing at 12 weeks post-treatment.

Two NS5B substitutions, L159F and V321A, were detected in post-treatment relapse samples from multiple genotype 3 HCV infected patients in the Phase 3 clinical studies. No shift in the phenotypic susceptibility to sofosbuvir or ribavirin of subject isolates with these substitutions was detected. In addition, S282R and L320F substitutions were detected on treatment by deep sequencing in a pre-transplant subject with a partial treatment response. The clinical significance of these findings is unknown.

Effect of baseline HCV polymorphisms on treatment outcome

Adult population

Baseline NS5B sequences were obtained for 1,292 patients from Phase 3 studies by population sequencing and the S282T substitution was not detected in any subject with available baseline sequence. In an analysis evaluating the effect of baseline polymorphisms on treatment outcome, no statistically significant association was observed between the presence of any HCV NS5B variant at baseline and treatment outcome.

Paediatric population

The presence of NS5B RAVs did not impact treatment outcome; all patients with baseline NS5B nucleoside inhibitor RAVs achieved SVR following treatment with sofosbuvir.

Cross-resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were fully susceptible to other classes of anti-HCV agents. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. Sofosbuvir was fully active against substitutions associated with resistance to other direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors, NS3 protease inhibitors and NS5A inhibitors.

Clinical efficacy and safety

The efficacy of sofosbuvir was evaluated in five Phase 3 studies in a total of 1,568 adult patients with genotypes 1 to 6 chronic hepatitis C. One study was conducted in treatment-naïve patients with genotype 1, 4, 5 or 6 chronic hepatitis C in combination with peginterferon alfa 2a and ribavirin and the other four studies were conducted in patients with genotype 2 or 3 chronic hepatitis C in combination with ribavirin including one in treatment-naïve patients, one in interferon intolerant, ineligible or unwilling patients, one in patients previously treated with an interferon-based regimen, and one in all patients irrespective of prior treatment history or ability to receive treatment with interferon. Patients in these studies had compensated liver disease including cirrhosis. Sofosbuvir was administered at a dose of 400 mg once daily. The ribavirin dose was weight-based at 1,000-1,200 mg daily administered in two divided doses, and the peginterferon alfa 2a dose, where applicable, was 180 µg per week. Treatment duration was fixed in each study and was not guided by patients' HCV RNA levels (no response guided algorithm).

Plasma HCV RNA values were measured during the clinical studies using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU/mL. Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate for all studies which was defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment (SVR12).

Clinical studies in patients with genotype 1, 4, 5 and 6 chronic hepatitis C

Treatment-naïve adult patients - NEUTRINO (study 110)

NEUTRINO was an open-label, single-arm study that evaluated 12 weeks of treatment with sofosbuvir in combination with peginterferon alfa 2a and ribavirin in treatment-naïve patients with genotype 1, 4, 5 or 6 HCV infection.

Treated patients (n = 327) had a median age of 54 years (range: 19 to 70); 64% of the patients were male; 79% were White; 17% were Black; 14% were Hispanic or Latino; mean body mass index was 29 kg/m² (range: 18 to 56 kg/m²); 78% had baseline HCV RNA greater than 6 log₁₀ IU/mL; 17% had cirrhosis; 89% had HCV genotype 1 and 11% had HCV genotype 4, 5 or 6. Table 7 presents the response rates for the treatment group of sofosbuvir + peginterferon alfa + ribavirin.

Table 7: Response rates in study NEUTRINO

	SOF+PEG+RBV 12 weeks (n = 327)
Overall SVR12	91% (296/327)
Outcome for patients without SVR12	
On-treatment virologic failure	0/327
Relapse ^a	9% (28/326)
Other ^b	1% (3/327)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 8.

Table 8: SVR12 rates for selected subgroups in NEUTRINO

	SOF+PEG+RBV 12 weeks (n = 327)
Genotype	
Genotype 1	90% (262/292)
Genotype 4, 5 or 6	97% (34/35)
Cirrhosis	
No	93% (253/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-Black	91% (249/273)

SVR12 rates were similarly high in patients with baseline IL28B C/C allele [94/95 (99%)] and non-C/C (C/T or T/T) allele [202/232 (87%)].

27/28 patients with genotype 4 HCV achieved SVR12. A single subject with genotype 5 and all 6 patients with genotype 6 HCV infection in this study achieved SVR12.

Clinical studies in patients with genotype 2 and 3 chronic hepatitis C

Treatment-naïve adults - FISSION (study 1231)

FISSION was a randomised, open-label, active-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve patients with genotype 2 or 3 HCV infection. The ribavirin doses used in the sofosbuvir + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1,000-1,200 mg/day and 800 mg/day regardless of weight, respectively. Patients were randomised in a 1:1 ratio and stratified by cirrhosis (presence *versus* absence), HCV genotype (2 *versus* 3) and baseline HCV RNA level (<6 log₁₀ IU/mL *versus* ≥6 log₁₀ IU/mL). Patients with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Treated patients (n = 499) had a median age of 50 years (range: 19 to 77); 66% of the patients were male; 87% were White; 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m² (range: 17 to 52 kg/m²); 57% had baseline HCV RNA levels greater than 6 log₁₀ IU/mL; 20% had cirrhosis; 72% had HCV genotype 3. Table 9 presents the response rates for the treatment groups of sofosbuvir + ribavirin and peginterferon alfa + ribavirin.

Table 9: Response rates in study FISSION

	SOF+RBV 12 weeks (n = 256)^a	PEG+RBV 24 weeks (n = 243)
Overall SVR12	67% (171/256)	67% (162/243)
Genotype 2	95% (69/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for patients without SVR12		
On-treatment virologic failure	< 1% (1/256)	7% (18/243)
Relapse ^b	30% (76/252)	21% (46/217)
Other ^c	3% (8/256)	7% (17/243)

a. The efficacy analysis includes 3 patients with recombinant genotype 2/1 HCV infection.

b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

The difference in the overall SVR12 rates between sofosbuvir + ribavirin and peginterferon alfa + ribavirin treatment groups was 0.3% (95% confidence interval: -7.5% to 8.0%) and the study met the predefined non-inferiority criterion.

Response rates for patients with cirrhosis at baseline are presented in Table 10 by HCV genotype.

Table 10: SVR12 rates by cirrhosis and genotype in study FISSION

	Genotype 2		Genotype 3	
	SOF+RBV 12 weeks (n = 73) ^a	PEG+RBV 24 weeks (n = 67)	SOF+RBV 12 weeks (n = 183)	PEG+RBV 24 weeks (n = 176)
Cirrhosis				
No	97% (59/61)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	83% (10/12)	62% (8/13)	34% (13/38)	30% (11/37)

a. The efficacy analysis includes 3 patients with recombinant genotype 2/1 HCV infection.

Interferon intolerant, ineligible or unwilling adults - POSITRON (study 107)

POSITRON was a randomised, double-blinded, placebo-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin (n = 207) compared to placebo (n = 71) in patients who are interferon intolerant, ineligible or unwilling. Patients were randomised in 3:1 ratio and stratified by cirrhosis (presence *versus* absence).

Treated patients (n = 278) had a median age of 54 years (range: 21 to 75); 54% of the patients were male; 91% were White; 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 kg/m² (range: 18 to 53 kg/m²); 70% had baseline HCV RNA levels greater than 6 log₁₀ IU/mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of patients who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most patients had no prior HCV treatment (81.3%). Table 11 presents the response rates for the treatment groups of sofosbuvir + ribavirin and placebo.

Table 11: Response rates in study POSITRON

	SOF+RBV 12 weeks (n = 207)	Placebo 12 weeks (n = 71)
Overall SVR12	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
Outcome for patients without SVR12		
On-treatment virologic failure	0/207	97% (69/71)
Relapse ^a	20% (42/205)	0/0
Other ^b	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

The SVR12 rate in the sofosbuvir + ribavirin treatment group was statistically significant when compared to placebo (p <0.001).

Table 12 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 12: SVR12 rates for selected subgroups by genotype in POSITRON

	SOF+RBV 12 weeks	
	Genotype 2 (n = 109)	Genotype 3 (n = 98)
Cirrhosis		
No	92% (85/92)	68% (57/84)
Yes	94% (16/17)	21% (3/14)
Interferon classification		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Previously treated adults - FUSION (study 108)

FUSION was a randomised, double-blinded study that evaluated 12 or 16 weeks of treatment with sofosbuvir and ribavirin in patients who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Patients were randomised in a 1:1 ratio and stratified by cirrhosis (presence *versus* absence) and HCV genotype (2 *versus* 3).

Treated patients (n = 201) had a median age of 56 years (range: 24 to 70); 70% of the patients were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m² (range: 19 to 44 kg/m²); 73% had baseline HCV RNA levels greater than 6 log₁₀ IU/mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. Table 13 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 16 weeks.

Table 13: Response rates in study FUSION

	SOF+RBV 12 weeks (n = 103) ^a	SOF+RBV 16 weeks (n = 98) ^a
Overall SVR12	50% (51/103)	71% (70/98)
Genotype 2	82% (32/39)	89% (31/35)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for patients without SVR12		
On-treatment virologic failure	0/103	0/98
Relapse ^b	48% (49/103)	29% (28/98)
Other ^c	3% (3/103)	0/98

a. The efficacy analysis includes 6 patients with recombinant genotype 2/1 HCV infection.

b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 14 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 14: SVR12 rates for selected subgroups by genotype in study FUSION

	Genotype 2		Genotype 3	
	SOF+RBV 12 weeks (n = 39)	SOF+RBV 16 weeks (n = 35)	SOF+RBV 12 weeks (n = 64)	SOF+RBV 16 weeks (n = 63)
Cirrhosis				
No	90% (26/29)	92% (24/26)	37% (14/38)	63% (25/40)
Yes	60% (6/10)	78% (7/9)	19% (5/26)	61% (14/23)
Response to prior HCV treatment				
Relapser	86% (25/29)	89% (24/27)	31% (15/49)	65% (30/46)
Nonresponder	70% (7/10)	88% (7/8)	27% (4/15)	53% (9/17)

Treatment-naïve and previously treated adults - VALENCE (study 133)

VALENCE was a Phase 3 study that evaluated sofosbuvir in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior interferon-based treatment, including patients with compensated cirrhosis. The study was designed as a direct comparison of sofosbuvir and ribavirin *versus* placebo for 12 weeks. However, based on emerging data, the study was unblinded and all HCV genotype 2 patients continued to receive sofosbuvir and ribavirin for 12 weeks, whilst treatment for HCV genotype 3 patients was extended to 24 weeks. Eleven HCV genotype 3 patients had already completed treatment with sofosbuvir and ribavirin for 12 weeks at the time of the amendment.

Treated patients (n = 419) had a median age of 51 years (range: 19 to 74); 60% of the patients were male; median body mass index was 25 kg/m² (range: 17 to 44 kg/m²); the mean baseline HCV RNA level was 6.4 log₁₀ IU/mL; 21% had cirrhosis; 78% had HCV genotype 3; 65% were prior relapsers. Table 15 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 24 weeks.

Placebo recipients are not included in the tables since none achieved SVR12.

Table 15: Response rates in study VALENCE

	Genotype 2 SOF+RBV 12 weeks (n = 73)	Genotype 3 SOF+RBV 12 weeks (n = 11)	Genotype 3 SOF+RBV 24 weeks (n = 250)
Overall SVR12	93% (68/73)	27% (3/11)	84% (210/250)
Outcome for patients without SVR12			
On-treatment virologic failure	0% (0/73)	0% (0/11)	0.4% (1/250)
Relapse ^a	7% (5/73)	55% (6/11)	14% (34/249)
Other ^b	0% (0/73)	18% (2/11)	2% (5/250)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 16 presents the subgroup analysis by genotype for cirrhosis and exposure to prior HCV treatment.

Table 16: SVR12 rates for selected subgroups by genotype in study VALENCE

	Genotype 2 SOF+RBV 12 weeks (n = 73)	Genotype 3 SOF+RBV 24 weeks (n = 250)
Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	93% (86/92)
Cirrhotic	100% (2/2)	92% (12/13)
Treatment-experienced	90% (37/41)	77% (112/145)
Non-cirrhotic	91% (30/33)	85% (85/100)
Cirrhotic	88% (7/8)	60% (27/45)

SVR12 to SVR24 concordance

The concordance between SVR12 and SVR24 (SVR 24 weeks after the end of the treatment) following treatment with sofosbuvir in combination with ribavirin or ribavirin and pegylated interferon demonstrates a positive predictive value of 99% and a negative predictive value of 99%.

Clinical efficacy and safety in special populations***HCV/HIV co-infected adult patients - PHOTON-1 (study 123)***

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 12 or 24 weeks of treatment with sofosbuvir and ribavirin in patients with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were naïve to prior treatment. Treatment duration was 12 weeks in treatment-naïve patients with genotype 2 or 3 HCV infection, and 24 weeks in treatment-experienced patients with genotype 3 HCV infection, as well as patients with genotype 1 HCV infection. Patients received 400 mg sofosbuvir and weight-based ribavirin (1,000 mg for patients weighing <75 kg or 1,200 mg for patients weighing ≥75 kg). Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm³ or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm³. 95% of patients received antiretroviral therapy at the time of enrolment. Preliminary SVR12 data are available for 210 patients.

Table 17 presents the response rates by genotype and exposure to prior HCV treatment.

Table 17: Response rates in study PHOTON-1

	Genotype 2/3 treatment-naïve SOF+RBV 12 weeks (n = 68)	Genotype 2/3 treatment-experienced SOF+RBV 24 weeks (n = 28)	Genotype 1 treatment-naïve SOF+RBV 24 weeks (n = 114)
Overall SVR12	75% (51/68)	93% (26/28)	76% (87/114)
Outcome for patients without SVR12			
On-treatment virologic failure	1% (1/68)	0/28	1% (1/114)
Relapse ^a	18% (12/67)	7% (2/28)	22% (25/113)
Other ^b	6% (4/68)	0/28	1% (1/114)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 18 presents the subgroup analysis by genotype for cirrhosis.

Table 18: SVR12 rates for selected subgroups by genotype in study PHOTON-1

	HCV genotype 2		HCV genotype 3	
	SOF+RBV 12 weeks TN (n = 26)	SOF+RBV 24 weeks TE (n = 15)	SOF+RBV 12 weeks TN (n = 42)	SOF+RBV 24 weeks TE (n = 13)
	88% (23/26)	93% (14/15)	67% (28/42)	92% (12/13)
No cirrhosis	88% (22/25)	92% (12/13)	67% (24/36)	100% (8/8)
Cirrhosis	100% (1/1)	100% (2/2)	67% (4/6)	80% (4/5)

TN = treatment-naïve; TE = treatment-experienced.

Adult patients awaiting liver transplantation - Study 2025

Sofosbuvir was studied in HCV infected patients prior to undergoing liver transplantation in an open-label clinical study evaluating the safety and efficacy of sofosbuvir and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the study was post-transplant virologic response (pTVR, HCV RNA <LLOQ at 12 weeks post-transplant).

HCV infected patients, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria received 400 mg sofosbuvir and 1,000-1,200 mg ribavirin daily for a maximum of 24 weeks, subsequently amended to 48 weeks, or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 patients who received sofosbuvir and ribavirin; the majority of patients had HCV genotype 1, 44 patients were CPT class A and 17 patients were CPT class B. Of these 61 patients, 44 patients underwent liver transplantation following up to 48 weeks of treatment with sofosbuvir and ribavirin; 41 had HCV RNA <LLOQ at the time of transplantation. The virologic response rates of the 41 patients transplanted with HCV RNA <LLOQ is described in Table 19. Duration of viral suppression prior to transplantation was the most predictive factor for pTVR in those who were HCV RNA <LLOQ at the time of transplantation.

Table 19: Virologic response post-transplant in patients with HCV RNA <LLOQ at the time of liver transplantation

	Week 12 post-transplant (pTVR) ^b
Virologic response in evaluable patients ^a	23/37 (62%)

a. Evaluable patients 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 <LLOQ at 12 weeks post-procedure).

In patients that discontinued therapy at 24 weeks, according to protocol, the relapse rate was 11/15.

Adult liver transplant recipients - Study 0126

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 24 weeks of treatment with sofosbuvir and ribavirin in liver transplant recipients with chronic hepatitis C. Eligible patients were ≥18 years old and had undergone liver transplantation 6 to 150 months prior to screening. Patients had HCV RNA ≥10⁴ IU/mL at screening and documented evidence of chronic HCV infection pre-transplantation. The starting dose of ribavirin was 400 mg given in a divided daily dose. If patients maintained haemoglobin levels ≥12 g/dL, ribavirin dose was increased at weeks 2, 4, and up to every 4 weeks until the appropriate weight-based dose was reached (1,000 mg daily in patients <75 kg, 1,200 mg daily in patients ≥75 kg). The median ribavirin dose was 600 mg-800 mg daily at weeks 4-24.

Forty patients (33 with HCV genotype 1 infection, 6 with HCV genotype 3 infection, and 1 with HCV genotype 4 infection) were enrolled, 35 of whom had previously failed interferon-based treatment, and 16 of whom had cirrhosis. 28 out of 40 (70%) patients achieved SVR12: 22/33 (73%) with HCV genotype 1 infection, 6/6 (100%) with HCV genotype 3 infection, and 0/1 (0%) with HCV genotype 4 infection. All patients who achieved SVR12 achieved SVR24 and SVR48.

Overview of outcomes by therapeutic regimen and treatment duration, a comparison across studies

The following tables (Table 20 to Table 23) present data from Phase 2 and Phase 3 studies relevant to the dosing to help clinicians determine the best regimen for individual patients.

Table 20: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 1 HCV infection

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/N)
Treatment-naïve ^a (NEUTRINO)	SOF+PEG+RBV 12 weeks	Overall	90% (262/292)
		Genotype 1a	92% (206/225)
		Genotype 1b	83% (55/66)
		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)
		Genotype 1a	82% (74/90)
		Genotype 1b	54% (13/24)
		No cirrhosis	77% (84/109)
		Cirrhosis	60% (3/5)
Treatment-naïve (QUANTUM ^b and 11-1-0258 ^b)	SOF+RBV 24 weeks	Overall ^c	65% (104/159)
		Genotype 1a ^c	69% (84/121)
		Genotype 1b ^c	53% (20/38)
		No cirrhosis ^c	68% (100/148)
		Cirrhosis ^c	36% (4/11)

n = number of patients with SVR12 response; N = total number of patients per group.

- a. For previously treated patients with genotype 1 HCV infection, no data exists with the combination of sofosbuvir, peginterferon alfa and ribavirin. Consideration should be given to treating these patients, and potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (prior null response to peginterferon alfa and ribavirin therapy, advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).
- b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients.
- c. Summary data from both studies.

Table 21: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 2 HCV infection

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/N)
Treatment-naïve (FISSION)	SOF+RBV 12 weeks	Overall	95% (69/73)
		No cirrhosis	97% (59/61)
		Cirrhosis	83% (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	82% (32/39)
		No cirrhosis	90% (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	89% (31/35)
		No cirrhosis	92% (24/26)
		Cirrhosis	78% (7/9)

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/N)
Treatment-naïve co-infected with HIV (PHOTON-1)	SOF+RBV 12 weeks	Overall	88% (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)
		No cirrhosis ^a	92% (12/13)
		Cirrhosis ^a	100% (2/2)
Treatment-naïve (ELECTRON ^b and PROTON ^b)	SOF+PEG+RBV 12 weeks	Overall ^c	96% (25/26)
Treatment-experienced (LONESTAR-2 ^b)	SOF+PEG+RBV 12 weeks	Overall	96% (22/23)
		No cirrhosis	100% (9/9)
		Cirrhosis	93% (13/14)

n = number of patients with SVR12 response; N = total number of patients per group.

a. These data are preliminary.

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin.

c. All patients were non-cirrhotic in these two studies.

Table 22: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 3 HCV infection

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/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)
		No cirrhosis ^a	100% (8/8)
		Cirrhosis ^a	80% (4/5)
Treatment-naïve (ELECTRON ^b and PROTON ^b)	SOF+PEG+RBV 12 weeks	Overall ^c	97% (38/39)
Treatment-experienced (LONESTAR-2 ^b)	SOF+PEG+RBV 12 weeks	Overall	83% (20/24)
		No cirrhosis	83% (10/12)
		Cirrhosis	83% (10/12)

n = number of patients with SVR12 response; N = total number of patients per group.

a. These data are preliminary.

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin.

c. All patients were non-cirrhotic in these two studies.

Table 23: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 4, 5 and 6 HCV infection

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

n = number of patients with SVR12 response; N = total number of patients per group.

Patients with renal impairment

Study 0154 was an open-label clinical study that evaluated the safety and efficacy of 24 weeks of treatment with sofosbuvir in combination with ribavirin in 20 genotype 1 or 3 HCV-infected patients with severe renal impairment not requiring dialysis. Following treatment with sofosbuvir 200 mg or 400 mg in combination with ribavirin the SVR12 rate in patients with ESRD was 40% and 60%, respectively. The safety and efficacy of 12 weeks of treatment with ledipasvir/sofosbuvir in 18 genotype 1 HCV-infected patients with severe renal impairment not requiring dialysis was also studied in Study 0154. At baseline, two patients had cirrhosis and the mean eGFR was 24.9 mL/min (range: 9.0-39.6). SVR12 was achieved in 100 % (18/18) of patients treated with ledipasvir/sofosbuvir.

Study 4063 was an open-label study that evaluated a fixed dose combination of sofosbuvir and ledipasvir in 95 patients with HCV-infection and ESRD requiring dialysis. The SVR rates for the 8, 12, and 24 week ledipasvir/sofosbuvir treatment groups were 93% (42/45), 100% (31/31), and 79% (15/19), respectively. Of the seven patients who did not achieve SVR12, none experienced virologic failure or relapsed.

Study 4062 was an open-label study that evaluated a fixed dose combination of sofosbuvir and velpatasvir in 59 HCV-infected patients with ESRD requiring dialysis. The SVR rate was 95% (56/59); of the three patients that did not achieve SVR12, one had completed sofosbuvir with velpatasvir treatment and relapsed.

Paediatric population

The efficacy of sofosbuvir in HCV-infected patients aged 3 years and above was evaluated in a Phase 2, open label clinical trial that enrolled 106 patients with genotype 2 (n = 31) or genotype 3 (n = 75) chronic HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with sofosbuvir with ribavirin for 12 or 24 weeks, respectively.

Patients aged 12 to < 18 Years:

Sofosbuvir was evaluated in 52 patients 12 to < 18 years with genotype 2 (n = 13) or genotype 3 (n = 39) HCV infection. The median age was 15 years (range: 12 to 17); 40% of the patients were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 60.4 kg (range: 29.6 to 75.6 kg); 17% were treatment experienced; 65% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (69%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (100% [13/13] in genotype 2 patients and 97% [38/39]) in genotype 3 patients. No patient experienced on-treatment virologic failure or relapse; one patient with genotype 3 HCV infection achieved SVR4 but did not return for the SVR12 visit.

Patients aged 6 to < 12 Years:

Sofosbuvir was evaluated in 41 patients 6 to < 12 years of age with genotype 2 (n = 13), or genotype 3 (n = 28) HCV infection. The median age was 9 years (range: 6 to 11); 73% of the patients were female; 71% were White and 20% were Asian; 15% were Hispanic/Latino; mean weight was 33.7 kg (range: 15.1 to 80.0 kg); 98% were treatment naïve; 46% had baseline HCV RNA levels greater than or equal to 800,000 IU /mL; and no patients had known cirrhosis. The majority of patients (98%) had been infected through vertical transmission.

The SVR12 rate was 100% (100% [13/13] in genotype 2 patients and 100% [28/28] in genotype 3 patients). No patients experienced on-treatment virologic failure or relapse.

Patients aged 3 to < 6 Years:

Sofosbuvir was evaluated in 13 patients 3 to < 6 years with genotype 2 (n = 5) or genotype 3 (n = 8) HCV infection. The median age was 4 years (range: 3 to 5); 77% of the patients were female; 69% were White, 8% were Black, and 8% were Asian; 8% were Hispanic/Latino; mean weight was 16.8 kg (range: 13.0 to 19.2 kg); 100% were treatment naive; 23% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (85%) had been infected through vertical transmission.

The SVR12 rate was 92% overall (80% [4/5] in genotype 2 patients and 100% [8/8] in genotype 3 patients). No patients experienced on-treatment virologic failure or relapse; one patient with genotype 2 HCV prematurely discontinued study treatment after three days due to abnormal taste of the medication and did not return for post-treatment Week 12.

5.2 Pharmacokinetic properties

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is formed in hepatocytes and not observed in plasma. The predominant (>90%) metabolite, GS-331007, is inactive. It is formed through sequential and parallel pathways to the formation of active metabolite.

Absorption

The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration, sofosbuvir was absorbed quickly and the peak plasma concentration was observed ~0.5-2 hour post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose. Based on population pharmacokinetic analysis in patients with genotypes 1 to 6 HCV infection (n = 986), steady-state AUC₀₋₂₄ for sofosbuvir and GS-331007 was 1,010 ng•h/mL and 7,200 ng•h/mL, respectively. Relative to healthy subjects (n = 284), the sofosbuvir and GS-331007 AUC₀₋₂₄ was 57% higher and 39% lower, respectively in HCV infected patients.

Effects of food

Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold, with little effect on peak concentration. The exposure to GS-331007 was not altered in the presence of a high-fat meal.

Distribution

Sofosbuvir is not a substrate for hepatic uptake transporters, organic anion-transporting polypeptide (OATP) 1B1 or 1B3, and organic cation transporter (OCT) 1. While subject to active tubular secretion, GS-331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or 3, OCT2, MRP2, P-gp, BCRP or MATE1. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Sofosbuvir is approximately 85% bound to human plasma proteins (*ex vivo* data) and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [¹⁴C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ¹⁴C-radioactivity was approximately 0.7.

Biotransformation

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes.

After a single 400 mg oral dose of [¹⁴C]-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug-related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Elimination

Following a single 400 mg oral dose of [¹⁴C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 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. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

Linearity/non-linearity

The dose linearity of sofosbuvir and its primary metabolite, GS-331007, was evaluated in fasted healthy subjects. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 400 mg.

Pharmacokinetics in special populations

Gender and race

No clinically relevant pharmacokinetic differences due to gender or race have been identified for sofosbuvir and GS-331007.

Elderly

Population pharmacokinetic analysis in HCV infected patients showed that within the age range (19 to 75 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir and GS-331007. Clinical studies of sofosbuvir included 65 patients aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups.

Renal impairment

A summary of the effect of varying degrees of renal impairment (RI) on the exposures of sofosbuvir and GS-331007 compared to subjects with normal renal function, as described in the text below, are provided in Table 24.

Table 24: Effect of varying degrees of renal impairment on exposures (AUC) of sofosbuvir and GS-331007 compared to subjects with normal renal function

	HCV-Negative Subjects				HCV-Infected Subjects	
	Mild RI (eGFR ≥50 and <80 mL/min/ 1.73m ²)	Moderate RI (eGFR ≥30 and <50 mL/min/ 1.73m ²)	Severe RI (eGFR <30 mL/min/ 1.73m ²)	ESRD Requiring Dialysis	Severe RI (eGFR <30 mL/min/ 1.73m ²)	ESRD Requiring Dialysis
Sofosbuvir	1.6-fold↑	2.1-fold↑	2.7-fold↑	1.3-fold↑	1.6-fold↑	~2-fold↑
GS-331007	1.6-fold↑	1.9-fold↑	5.5-fold↑	≥10-fold↑	≥20-fold↑	~7-fold↑
						21-fold↑

The pharmacokinetics of sofosbuvir were studied in adult HCV negative patients with mild (eGFR ≥50 and <80 mL/min/1.73 m²), moderate (eGFR ≥30 and <50 mL/min/1.73 m²), severe renal impairment (eGFR <30 mL/min/1.73 m²) and patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir, relative to adult patients with normal renal function (eGFR >80 mL/min/1.73 m²). GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered sofosbuvir dose.

In HCV-infected adult patients with severe renal impairment treated with sofosbuvir 200 mg with ribavirin (n=10) or sofosbuvir 400 mg with ribavirin (n=10) for 24 weeks or ledipasvir/sofosbuvir 90/400 mg (n=18) for 12 weeks, the pharmacokinetics of sofosbuvir and GS-331007 were consistent with that observed in HCV negative adult patients with severe renal impairment.

The pharmacokinetics of sofosbuvir, and GS-331007 were studied in HCV-infected adult patients with ESRD requiring dialysis treated with ledipasvir/sofosbuvir (n = 94) for 8, 12, or 24 weeks or sofosbuvir/velpatasvir (n = 59) for 12 weeks, and compared to patients without renal impairment in the ledipasvir/sofosbuvir and sofosbuvir/velpatasvir Phase 2/3 trials (see section 4.4).

Hepatic impairment

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in adult HCV-infected patients with moderate and severe hepatic impairment (CPT class B and C). Relative to patients with normal hepatic function, the sofosbuvir AUC₀₋₂₄ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC₀₋₂₄ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in adult HCV-infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment (see section 4.2).

Paediatric population

Sofosbuvir and GS-331007 exposures in paediatric patients aged 3 years and above were similar to those in adults from Phase 2/3 studies following administration of sofosbuvir. The pharmacokinetics of sofosbuvir and GS-331007 have not been established in paediatric patients aged < 3 years (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

Efficacy, in terms of rapid virologic response, has been shown to correlate with exposure to sofosbuvir as well as GS 331007. However, neither of these entities has been evidenced to be a general surrogate marker for efficacy (SVR12) at the therapeutic 400 mg dose.

5.3 Preclinical safety data

In repeat dose toxicology studies in rat and dog, high doses of the 1:1 diastereomeric mixture caused adverse liver (dog) and heart (rat) effects and gastrointestinal reactions (dog). Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity; however, exposure to the

major metabolite GS-331007 at the adverse dose was 29 times (rat) and 123 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 9 times (rat) and 27 times (dog) higher than the clinical exposure.

Sofosbuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was up to 30 times (mouse) and 15 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir had no effects on embryo-foetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 9 times the expected clinical exposure. In the rat studies, exposure to sofosbuvir could not be determined but exposure margins based on the major human metabolite ranged from 8 to 28 times higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir-derived material was transferred through the placenta in pregnant rats and into the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)
Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating

Polyvinyl alcohol
Titanium dioxide
Macrogol
Talc
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

6 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sovaldi 400 mg tablets are supplied in high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure containing 28 film-coated tablets with a silica gel desiccant and polyester coil.

Sovaldi 200 mg tablets are supplied in high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure containing 28 film-coated tablets and a polyester coil.

The following pack sizes are available:

- outer cartons containing 1 bottle of 28 film-coated tablets
- and for the 400 mg tablets only; outer cartons containing 84 (3 bottles of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/894/001

EU/1/13/894/002

EU/1/13/894/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2014

Date of latest renewal: 17 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 150 mg coated granules in sachet
Sovaldi 200 mg coated granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sovaldi 150 mg coated granules in sachet

Each sachet contains 150 mg sofosbuvir.

Excipients with known effect:

Each 150 mg sachet contains 173 mg of lactose (as monohydrate).

Sovaldi 200 mg coated granules in sachet

Each sachet contains 200 mg sofosbuvir.

Excipients with known effect:

Each 200 mg sachet contains 231 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated granules in sachet.

White to off-white coated granules in sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients aged 3 years and above (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Sovaldi treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose of Sovaldi in paediatric patients aged 3 years and above is based on weight (as detailed in Table 2). Sovaldi should be taken with food (see section 5.2).

Sovaldi should be used in combination with other medicinal products. Monotherapy of Sovaldi is not recommended (see section 5.1). Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Sovaldi. The recommended co-administered medicinal product(s) and treatment duration for Sovaldi combination therapy are provided in Table 1.

Table 1: Recommended co-administered medicinal product(s) and treatment duration for adults and paediatric patients treated Sovaldi combination therapy

Patient population*	Treatment	Duration
Adult patients with genotype 1, 4, 5 or 6 CHC	Sovaldi + ribavirin ^c + peginterferon alfa	12 weeks ^{a,b}
	Sovaldi + ribavirin ^c Only for use in patients ineligible or intolerant to peginterferon alfa (see section 4.4)	24 weeks
Adult and paediatric patients aged 3 years and above with genotype 2 CHC	Sovaldi ^d + ribavirin ^{c,e}	12 weeks ^b
Adult patients with genotype 3 CHC	Sovaldi + ribavirin ^c + peginterferon alfa	12 weeks ^b
	Sovaldi + ribavirin ^c	24 weeks
Paediatric patients aged 3 years and above with genotype 3 CHC	Sovaldi ^d + ribavirin ^e	24 weeks
Adult patients with CHC awaiting liver transplantation	Sovaldi + ribavirin ^c	Until liver transplantation ^f

* Includes patients co-infected with human immunodeficiency virus (HIV).

- a. For previously treated patients with HCV genotype 1 infection, no data exists with the combination of Sovaldi, ribavirin and peginterferon alfa (see section 4.4).
- b. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).
- c. Adults: weight-based ribavirin (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg); administered orally in two divided doses with food. Paediatric Patients: for ribavirin dosing recommendations see Table 3 below.
- d. See Table 2 for weight-based Sovaldi dosing recommendations for paediatric patients aged 3 years and above.
- e. See Table 3 for weight-based ribavirin dosing recommendations for paediatric patients aged 3 years and above.
- f. See Special patient populations – Patients awaiting liver transplantation below.

Table 2: Dosing for paediatric patients aged 3 years and above using Sovaldi oral granules*

Body Weight (kg)	Dosing of Sovaldi Oral Granules	Sofosbuvir Daily Dose
≥ 35	two 200 mg sachets of granules once daily	400 mg/day
17 to < 35	one 200 mg sachet of granules once daily	200 mg/day
< 17	one 150 mg sachet of granules once daily	150 mg/day

* Sovaldi is also available as film-coated tablet for use in paediatric patients with CHC aged 3 years and above (see section 5.1). Please refer to the Summary of Product Characteristics for Sovaldi 200 mg or 400 mg tablets.

In paediatric patients aged 3 years and above the following ribavirin dosing is recommended where ribavirin is divided into two daily doses and given with food:

Table 3: Guidance for ribavirin dosing when administered in combination with Sovaldi to HCV-infected paediatric patients aged 3 years and above.

Body weight kg	Ribavirin Dose*
< 47	15 mg/kg/day
47-49	600 mg/day
50-65	800 mg/day
66-80	1000 mg/day
> 81	1200 mg/day

* The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

Concerning co-administration with other direct-acting antivirals against HCV, see section 4.4.

Dose modification in adults

Dose reduction of Sovaldi is not recommended.

If sofosbuvir is used in combination with peginterferon alfa, and a patient has a serious adverse reaction potentially related to this medicinal product, the peginterferon alfa dose should be reduced or discontinued. Refer to the peginterferon alfa Summary of Product Characteristics for additional information about how to reduce and/or discontinue the peginterferon alfa dose.

If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 4 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 4: Ribavirin dose modification guideline for co-administration with Sovaldi in adults

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Haemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Haemoglobin in patients with history of stable cardiac disease	≥2 g/dL decrease in haemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1,000 mg to 1,200 mg daily).

Dose modification in paediatric patients aged 3 years and above

Dose reduction of Sovaldi is not recommended.

If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Refer to the ribavirin prescribing information for guidance on dose modification or discontinuation.

Discontinuation of dosing

If the other medicinal products used in combination with Sovaldi are permanently discontinued, Sovaldi should also be discontinued (see section 4.4).

Vomiting and missed doses

Patients should be instructed that if vomiting occurs within 2 hours of dosing an additional dose should be taken. If vomiting occurs more than 2 hours after dosing, no further dose is needed. These recommendations are based on the absorption kinetics of sofosbuvir and GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the dose as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed not to take a double dose.

Special patient populations

Elderly

No dose adjustment is warranted for elderly patients (see section 5.2).

Renal impairment

No dose adjustment of Sovaldi is required for patients with mild or moderate renal impairment.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) and end stage renal disease (ESRD) requiring haemodialysis. Sovaldi can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.1 and 5.2).

Hepatic impairment

No dose adjustment of Sovaldi is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.2). The safety and efficacy of Sovaldi have not been established in patients with decompensated cirrhosis.

Patients awaiting liver transplantation

The duration of administration of Sovaldi in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient (see section 5.1).

Adult liver transplant recipients

Sovaldi in combination with ribavirin is recommended for 24 weeks in liver transplant recipients. In adults a starting ribavirin dose of 400 mg administered orally in two divided doses with food is recommended. If the starting dose of ribavirin is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing <75 kg and 1,200 mg for patients weighing ≥75 kg). If the starting dose of ribavirin is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels (see section 5.1).

Paediatric population aged < 3 years

The safety and efficacy of Sovaldi in children aged <3 years have not yet been established. No data are available.

Method of administration

Oral use.

Sovaldi must be taken shortly before food, shortly after food, or with food.

To help with swallowing of the Sovaldi oral granules you can use food or water as detailed below. Alternatively, Sovaldi can be swallowed without food or water.

Taking Sovaldi granules with food to aid swallowing

To administer with food to aid swallowability of the granules, patients should be instructed to sprinkle the granules on one or more spoonfuls of non-acidic soft food at or below room temperature. Patients should be instructed to take the Sovaldi granules within 30 minutes of gently mixing with food and to swallow the entire contents without chewing to avoid a bitter taste. Examples of non-acidic foods include chocolate syrup, mashed potato, and ice-cream.

Taking Sovaldi granules with water to aid swallowing

To administer with water, patients should be instructed that the granules can be taken directly into the mouth and swallowed with water.

Taking Sovaldi granules without food or water

To administer without food or water, patients should be instructed that the granules can be taken directly into the mouth and swallowed. Patients should be instructed to swallow the entire contents without chewing (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Medicinal products that are strong P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort). Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of Sovaldi (see section 4.5).

4.4 Special warnings and precautions for use

General

Sovaldi is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. If the other medicinal products used in combination with Sovaldi are permanently discontinued, Sovaldi should also be discontinued (see section 4.2). Consult the Summary of Product Characteristics for co-prescribed medicinal products before starting therapy with Sovaldi.

Severe bradycardia and heart block

Life-threatening cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone. Bradycardia has generally occurred within hours to days, but cases with a longer time to onset have been observed mostly up to 2 weeks after initiating HCV treatment.

Amiodarone should only be used in patients on Sovaldi when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Sovaldi.

All patients with concurrent or recent use of amiodarone should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

HCV/HBV (hepatitis B virus) co-infection

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection

Sovaldi has not been studied in a Phase 3 study in treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection. Thus, the optimal treatment duration in this population has not been established (see also sections 4.2 and 5.1).

Consideration should be given to treating these patients, and potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).

Treatment of patients with genotype 5 or 6 HCV infection

The clinical data to support the use of Sovaldi in patients with genotype 5 and 6 HCV infection is very limited (see section 5.1).

Interferon-free therapy for genotype 1, 4, 5 and 6 HCV infection

Interferon-free regimens for patients with genotype 1, 4, 5 and 6 HCV infection with Sovaldi have not been investigated in Phase 3 studies (see section 5.1). The optimal regimen and treatment duration have not been established. Such regimens should only be used for patients that are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment.

Co-administration with other direct-acting antivirals against HCV

Sovaldi should only be co-administered with other direct-acting antiviral medicinal products if the benefit is considered to outweigh the risks based upon available data. There are no data to support the co-administration of Sovaldi and telaprevir or boceprevir. Such co-administration is not recommended (see also section 4.5).

Pregnancy and concomitant use with ribavirin

When Sovaldi is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for a period of time after the treatment as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

Use with moderate P-gp inducers

Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sovaldi. Co-administration of such medicinal products is not recommended with Sovaldi (see section 4.5).

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

Renal impairment

Safety data are limited in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) and ESRD requiring haemodialysis. Sovaldi can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 4.8, 5.1 and 5.2). When Sovaldi is used in combination with ribavirin or peginterferon alfa/ribavirin, refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance (CrCl) <50 mL/min (see also section 5.2).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Sofosbuvir is a nucleotide prodrug. After oral administration of Sovaldi, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic and intestinal metabolism. Intracellular hydrolytic prodrug cleavage catalysed by enzymes including carboxylesterase 1 and sequential phosphorylation steps catalysed by nucleotide kinases result in formation of the pharmacologically active uridine nucleoside analogue triphosphate. The predominant inactive circulating metabolite GS-331007 that accounts for greater than 90% of drug-related material systemic exposure is formed through pathways sequential and parallel to formation of active metabolite. The parent sofosbuvir accounts for approximately 4% of drug-related material systemic exposure (see section 5.2). In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not.

Medicinal products that are strong P-gp inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sovaldi and thus are contraindicated with Sovaldi (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sovaldi. Co-administration with such medicinal products is not recommended with Sovaldi (see section 4.4). Co-administration of Sovaldi with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus Sovaldi may be co-administered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of medicinal products that are substrates of these transporters.

The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant medicinal products (see section 5.2).

Patients treated with vitamin K antagonists

As liver function may change during treatment with Sovaldi, a close monitoring of International Normalised Ratio (INR) values is recommended.

Impact of DAA therapy on drugs metabolized by the liver

The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Other interactions

Drug interaction information for Sovaldi with potential concomitant medicinal products is summarised in Table 5 below (where 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio were within “↔”, extended above “↑”, or extended below “↓” the predetermined equivalence boundaries). The table is not all-inclusive.

Table 5: Interactions between Sovaldi and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
<i>ANALEPTICS</i>		
Modafinil	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Sovaldi with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sovaldi. Such co-administration is not recommended.
<i>ANTIARRHYTHMICS</i>		
Amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown.	Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia. Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Sovaldi (see sections 4.4 and 4.8).
<i>ANTICOAGULANTS</i>		
Vitamin K antagonists	Interaction not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Sovaldi.
<i>ANTICONVULSANTS</i>		
Phenobarbital Phenytoin	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sovaldi is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine	<i>Sofosbuvir</i> ↓ C _{max} 0.52 (0.43, 0.62) ↓ AUC 0.52 (0.46, 0.59) C _{min} (NA) GS 331007 ↔ C _{max} 1.04 (0.97, 1.11) ↔ AUC 0.99 (0.94, 1.04) C _{min} (NA) (Induction of P-gp)	Sovaldi is contraindicated with carbamazepine (see section 4.3).
Oxcarbazepine	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Sovaldi with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sovaldi. Such co-administration is not recommended (see section 4.4).

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
ANTIMYCOBACTERIALS		
Rifampicin ^f (600 mg single dose)	<i>Sofosbuvir</i> ↓ C _{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C _{min} (NA) <i>GS-331007</i> ↔ C _{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) C _{min} (NA) (Induction of P-gp)	Sovaldi is contraindicated with rifampicin (see section 4.3).
Rifabutin	<i>Sofosbuvir</i> ↓ C _{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C _{min} (NA) <i>GS 331007</i> ↔ C _{max} 1.15 (1.03, 1.27) ↔ AUC 1.03 (0.95, 1.12) C _{min} (NA) (Induction of P-gp)	No dose adjustment of Sovaldi is required when concomitantly used with rifabutin.
Rifapentine	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Sovaldi with rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sovaldi. Such co-administration is not recommended (see section 4.4).
HERBAL SUPPLEMENTS		
St. John's wort	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sovaldi is contraindicated with St. John's wort (see section 4.3).
HCV ANITIVIRAL AGENTS: HCV PROTEASE INHIBITORS		
Boceprevir (BOC) Telaprevir (TPV)	Interaction not studied. <i>Expected:</i> ↑ Sofosbuvir (TPV) ↔ Sofosbuvir (BOC) ↔ GS-331007 (TPV or BOC)	No drug-drug interaction data exists regarding the co-administration of Sovaldi with boceprevir or telaprevir.

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
NARCOTIC ANALGESICS		
Methadone ^f (Methadone maintenance therapy [30 to 130 mg/daily])	<p><i>R-methadone</i> ↔ C_{max} 0.99 (0.85, 1.16) ↔ AUC 1.01 (0.85, 1.21) ↔ C_{min} 0.94 (0.77, 1.14)</p> <p><i>S-methadone</i> ↔ C_{max} 0.95 (0.79, 1.13) ↔ AUC 0.95 (0.77, 1.17) ↔ C_{min} 0.95 (0.74, 1.22)</p> <p><i>Sofosbuvir</i> ↓ C_{max} 0.95^c (0.68, 1.33) ↑ AUC 1.30^c (1.00, 1.69) C_{min} (NA)</p> <p><i>GS-331007</i> ↓ C_{max} 0.73^c (0.65, 0.83) ↔ AUC 1.04^c (0.89, 1.22) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or methadone is required when sofosbuvir and methadone are used concomitantly.
IMMUNOSUPPRESSANTS		
Ciclosporin ^e (600 mg single dose)	<p><i>Ciclosporin</i> ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) C_{min} (NA)</p> <p><i>Sofosbuvir</i> ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) C_{min} (NA)</p> <p><i>GS-331007</i> ↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
Tacrolimus ^e (5 mg single dose)	<p><i>Tacrolimus</i> ↓ C_{max} 0.73 (0.59, 0.90) ↔ AUC 1.09 (0.84, 1.40) C_{min} (NA)</p> <p><i>Sofosbuvir</i> ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz ^f (600 mg once daily) ^d	<i>Efavirenz</i> $\leftrightarrow C_{\max}$ 0.95 (0.85, 1.06) $\leftrightarrow AUC$ 0.96 (0.91, 1.03) $\leftrightarrow C_{\min}$ 0.96 (0.93, 0.98) <i>Sofosbuvir</i> $\downarrow C_{\max}$ 0.81 (0.60, 1.10) $\leftrightarrow AUC$ 0.94 (0.76, 1.16) C _{min} (NA) <i>GS-331007</i> $\downarrow C_{\max}$ 0.77 (0.70, 0.84) $\leftrightarrow AUC$ 0.84 (0.76, 0.92) C _{min} (NA)	No dose adjustment of sofosbuvir or efavirenz is required when sofosbuvir and efavirenz are used concomitantly.
Emtricitabine ^f (200 mg once daily) ^d	<i>Emtricitabine</i> $\leftrightarrow C_{\max}$ 0.97 (0.88, 1.07) $\leftrightarrow AUC$ 0.99 (0.94, 1.05) $\leftrightarrow C_{\min}$ 1.04 (0.98, 1.11) <i>Sofosbuvir</i> $\downarrow C_{\max}$ 0.81 (0.60, 1.10) $\leftrightarrow AUC$ 0.94 (0.76, 1.16) C _{min} (NA) <i>GS-331007</i> $\downarrow C_{\max}$ 0.77 (0.70, 0.84) $\leftrightarrow AUC$ 0.84 (0.76, 0.92) C _{min} (NA)	No dose adjustment of sofosbuvir or emtricitabine is required when sofosbuvir and emtricitabine are used concomitantly.
Tenofovir disoproxil ^f (245 mg once daily) ^d	<i>Tenofovir</i> $\uparrow C_{\max}$ 1.25 (1.08, 1.45) $\leftrightarrow AUC$ 0.98 (0.91, 1.05) $\leftrightarrow C_{\min}$ 0.99 (0.91, 1.07) <i>Sofosbuvir</i> $\downarrow C_{\max}$ 0.81 (0.60, 1.10) $\leftrightarrow AUC$ 0.94 (0.76, 1.16) C _{min} (NA) <i>GS-331007</i> $\downarrow C_{\max}$ 0.77 (0.70, 0.84) $\leftrightarrow AUC$ 0.84 (0.76, 0.92) C _{min} (NA)	No dose adjustment of sofosbuvir or tenofovir disoproxil is required when sofosbuvir and tenofovir disoproxil are used concomitantly.
Rilpivirine ^f (25 mg once daily)	<i>Rilpivirine</i> $\leftrightarrow C_{\max}$ 1.05 (0.97, 1.15) $\leftrightarrow AUC$ 1.06 (1.02, 1.09) $\leftrightarrow C_{\min}$ 0.99 (0.94, 1.04) <i>Sofosbuvir</i> $\uparrow C_{\max}$ 1.21 (0.90, 1.62) $\leftrightarrow AUC$ 1.09 (0.94, 1.27) C _{min} (NA) <i>GS-331007</i> $\leftrightarrow C_{\max}$ 1.06 (0.99, 1.14) $\leftrightarrow AUC$ 1.01 (0.97, 1.04) C _{min} (NA)	No dose adjustment of sofosbuvir or rilpivirine is required when sofosbuvir and rilpivirine are used concomitantly.

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C _{max} , C _{min} ^{a,b}	Recommendation concerning co-administration with Sovaldi
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Darunavir boosted with ritonavir ^f (800/100 mg once daily)	<p><i>Darunavir</i> ↔ C_{max} 0.97 (0.94, 1.01) ↔ AUC 0.97 (0.94, 1.00) ↔ C_{min} 0.86 (0.78, 0.96)</p> <p><i>Sofosbuvir</i> ↑ C_{max} 1.45 (1.10, 1.92) ↑ AUC 1.34 (1.12, 1.59) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or darunavir (ritonavir boosted) is required when sofosbuvir and darunavir are used concomitantly.
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir ^f (400 mg twice daily)	<p><i>Raltegravir</i> ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12)</p> <p><i>Sofosbuvir</i> ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{min} (NA)</p> <p><i>GS-331007</i> ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08) C_{min} (NA)</p>	No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.
ORAL CONTRACEPTIVES		
Norgestimate/ethinyl estradiol	<p><i>Norgestromin</i> ↔ C_{max} 1.06 (0.93, 1.22) ↔ AUC 1.05 (0.92, 1.20) C_{min} (NA)</p> <p><i>Norgestrel</i> ↔ C_{max} 1.18 (0.99, 1.41) ↔ AUC 1.19 (0.98, 1.44) C_{min} (NA)</p> <p><i>Ethinyl estradiol</i> ↔ C_{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C_{min} (NA)</p>	No dose adjustment of norgestimate/ethinyl estradiol is required when sofosbuvir and norgestimate/ethinyl estradiol are used concomitantly.

NA = not available/not applicable

- a. Mean ratio (90% CI) of co-administered drug pharmacokinetics with/without sofosbuvir and mean ratio of sofosbuvir and GS-331007 with/without co-administered drug. No effect = 1.00
- b. All interaction studies conducted in healthy volunteers
- c. Comparison based on historical control
- d. Administered as Atripla
- e. Bioequivalence boundary 80%-125%
- f. Equivalence boundary 70%-143%

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

When Sovaldi is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin (see section 4.4). Women of childbearing potential or their male partners must use an effective form of contraception during treatment and for a period of time after the treatment has concluded as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. No effects on foetal development have been observed in rats and rabbits at the highest doses tested. However, it has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Sovaldi during pregnancy.

However, if ribavirin is co-administered with sofosbuvir, the contraindications regarding use of ribavirin during pregnancy apply (see also the Summary of Product Characteristics for ribavirin).

Breast-feeding

It is unknown whether sofosbuvir and its metabolites are excreted in human milk.

Available pharmacokinetic data in animals have shown excretion of metabolites in milk (for details see section 5.3).

A risk to newborns/infants cannot be excluded. Therefore, Sovaldi should not be used during breast-feeding.

Fertility

No human data on the effect of Sovaldi on fertility are available. Animal studies do not indicate harmful effects on fertility.

4.7 Effects on ability to drive and use machines

Sovaldi has moderate influence on the ability to drive and use machines. Patients should be informed that fatigue and disturbance in attention, dizziness and blurred vision have been reported during treatment with sofosbuvir in combination with peginterferon alfa and ribavirin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile in adults

Assessment of adverse reactions is based on pooled data from five Phase 3 clinical studies (both controlled and uncontrolled).

Sovaldi has been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common

adverse drug reactions occurring in patients receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with sofosbuvir in combination with ribavirin or in combination with peginterferon alfa and ribavirin (Table 6). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) or very rare ($< 1/10,000$).

Table 6: Adverse drug reactions identified with sofosbuvir in combination with ribavirin or peginterferon alfa and ribavirin

Frequency	SOF ^a + RBV ^b	SOF + PEG ^c + RBV
<i>Infections and infestations:</i>		
Common	nasopharyngitis	
<i>Blood and lymphatic system disorders:</i>		
Very common	haemoglobin decreased	anaemia, neutropenia, lymphocyte count decreased, platelet count decreased
Common	anaemia	
<i>Metabolism and nutrition disorders:</i>		
Very common	decreased appetite ^d	decreased appetite
Common		weight decreased
<i>Psychiatric disorders:</i>		
Very common	insomnia	insomnia
Common	depression	depression, anxiety, agitation
<i>Nervous system disorders:</i>		
Very common	headache	dizziness, headache
Common	disturbance in attention	migraine, memory impairment, disturbance in attention
<i>Eye disorders:</i>		
Common		vision blurred
<i>Respiratory, thoracic and mediastinal disorders:</i>		
Very common		dyspnoea, cough
Common	dyspnoea, dyspnoea exertional, cough	dyspnoea exertional
<i>Gastrointestinal disorders:</i>		
Very common	nausea	diarrhoea, nausea, vomiting
Common	abdominal discomfort, constipation, dyspepsia	constipation, dry mouth, gastroesophageal reflux
<i>Hepatobiliary disorders:</i>		
Very common	blood bilirubin increased	blood bilirubin increased
<i>Skin and subcutaneous tissue disorders:</i>		
Very common		rash, pruritus
Common	alopecia, dry skin, pruritus	alopecia, dry skin
<i>Musculoskeletal and connective tissue disorders:</i>		
Very common		arthralgia, myalgia
Common	arthralgia, back pain, muscle spasms, myalgia	back pain, muscle spasms
<i>General disorders and administration site conditions:</i>		
Very common	fatigue, irritability	chills, fatigue, influenza-like illness, irritability, pain, pyrexia
Common	pyrexia, asthenia	chest pain, asthenia

a. SOF = sofosbuvir; b. RBV = ribavirin; c. PEG = peginterferon alfa; d. Decreased appetite was identified as an adverse drug reaction to Sovaldi in combination with ribavirin oral solution in paediatric patients aged 3 to < 12 years

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir containing-regimes are used in combination with amiodarone and/or other medicinal products that lower heart rate (see sections 4.4 and 4.5).

Skin disorders

Frequency not known: Stevens-Johnson syndrome

Other special population(s)

HIV/HCV co-infection

The safety profile of sofosbuvir and ribavirin in HCV/HIV co-infected adult patients was similar to that observed in mono-infected HCV patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1).

Patients awaiting liver transplantation

The safety profile of sofosbuvir and ribavirin in HCV infected adult patients prior to liver transplantation was similar to that observed in patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1).

Patients with Renal Impairment

Sofosbuvir in a fixed dose combination with ledipasvir was administered for 12 weeks to 18 patients with genotype 1 CHC and severe renal impairment in an open-label study (Study 0154). The safety of sofosbuvir in a fixed dose combination with either ledipasvir or velpatasvir has been studied in 154 patients with ESRD requiring dialysis (Study 4062 and Study 4063). In this setting, exposure of sofosbuvir metabolite GS-331007 is 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

Adult liver transplant recipients

The safety profile of sofosbuvir and ribavirin in liver transplant adult recipients with chronic hepatitis C was similar to that observed in patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1). In study 0126, decreases in haemoglobin during treatment were very common with 32.5% (13/40 patients) experiencing a decline in haemoglobin to <10 g/dL, 1 of whom also had a decline to <8.5 g/dL. Eight patients (20%) received epoetin and/or a blood product. In 5 patients (12.5%), study drugs were discontinued, modified or interrupted due to adverse events.

Paediatric population

The safety and efficacy of Sovaldi in paediatric patients aged 3 years and above are based on data from 106 patients who were treated with Sovaldi and ribavirin for 12 weeks (genotype 2 patients) and for 24 weeks (genotype 3 patients) in a Phase 2, open-label clinical trial. No adverse drug reactions specific to Sovaldi have been identified. The adverse reactions observed were generally consistent with those observed in clinical studies of Sovaldi plus ribavirin in adults (see Table 6). Decreased appetite was observed as a very common adverse drug reaction to Sovaldi when given in combination with ribavirin oral solution in paediatric patients 3 to < 12 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1,200 mg administered to 59 healthy subjects. In that study, there were no untoward effects observed at this dose level, and adverse reactions were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are unknown.

No specific antidote is available for overdose with Sovaldi. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sovaldi consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4-hour haemodialysis session removed 18% of the administered dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct-acting antiviral; ATC code: J05AP08

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with a 50% inhibitory concentration (IC_{50}) value ranging from 0.7 to 2.6 μ M. GS-461203 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity

In HCV replicon assays, the effective concentration (EC_{50}) values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a were 0.04, 0.11, 0.05, 0.05 and 0.04 μ M, respectively, and EC_{50} values of sofosbuvir against chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a were 0.014 to 0.015 μ M. The mean \pm SD EC_{50} of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was $0.068 \pm 0.024 \mu$ M for genotype 1a ($n = 67$), $0.11 \pm 0.029 \mu$ M for genotype 1b ($n = 29$), $0.035 \pm 0.018 \mu$ M for genotype 2 ($n = 15$) and $0.085 \pm 0.034 \mu$ M for genotype 3a ($n = 106$). In these assays, the *in vitro* antiviral activity of sofosbuvir against the less common genotypes 4, 5 and 6 was similar to that observed for genotypes 1, 2 and 3.

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Resistance

In cell culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In clinical studies - Adults

In a pooled analysis of 991 patients who received sofosbuvir in Phase 3 studies, 226 patients qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA >1,000 IU/mL. Post-baseline NS5B sequences were available for 225 of the 226 patients, with deep sequencing data (assay cutoff of 1%) from 221 of these patients. The sofosbuvir-associated resistance substitution S282T was not detected in any of these patients by deep sequencing or population sequencing. The S282T substitution in NS5B was detected in a single subject receiving Sovaldi monotherapy in a Phase 2 study. This subject harboured <1% HCV S282T at baseline and developed S282T (>99%) at 4 weeks post-treatment which resulted in a 13.5-fold change in sofosbuvir EC₅₀ and reduced viral replication capacity. The S282T substitution reverted to wild-type over the next 8 weeks and was no longer detectable by deep sequencing at 12 weeks post-treatment.

Two NS5B substitutions, L159F and V321A, were detected in post-treatment relapse samples from multiple genotype 3 HCV infected patients in the Phase 3 clinical studies. No shift in the phenotypic susceptibility to sofosbuvir or ribavirin of subject isolates with these substitutions was detected. In addition, S282R and L320F substitutions were detected on treatment by deep sequencing in a pre-transplant subject with a partial treatment response. The clinical significance of these findings is unknown.

Effect of baseline HCV polymorphisms on treatment outcome

Adult population

Baseline NS5B sequences were obtained for 1,292 patients from Phase 3 studies by population sequencing and the S282T substitution was not detected in any subject with available baseline sequence. In an analysis evaluating the effect of baseline polymorphisms on treatment outcome, no statistically significant association was observed between the presence of any HCV NS5B variant at baseline and treatment outcome.

Paediatric population

The presence of NS5B RAVs did not impact treatment outcome; all patients with baseline NS5B nucleoside inhibitor RAVs achieved SVR following treatment with sofosbuvir.

Cross-resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were fully susceptible to other classes of anti-HCV agents. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. Sofosbuvir was fully active against substitutions associated with resistance to other direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors, NS3 protease inhibitors and NS5A inhibitors.

Clinical efficacy and safety

The efficacy of sofosbuvir was evaluated in five Phase 3 studies in a total of 1,568 adult patients with genotypes 1 to 6 chronic hepatitis C. One study was conducted in treatment-naïve patients with genotype 1, 4, 5 or 6 chronic hepatitis C in combination with peginterferon alfa 2a and ribavirin and the other four studies were conducted in patients with genotype 2 or 3 chronic hepatitis C in combination with ribavirin including one in treatment-naïve patients, one in interferon intolerant, ineligible or unwilling patients, one in patients previously treated with an interferon-based regimen, and one in all patients irrespective of prior treatment history or ability to receive treatment with interferon. Patients in these studies had compensated liver disease including cirrhosis. Sofosbuvir was administered at a dose of 400 mg once daily. The ribavirin dose was weight-based at 1,000-1,200 mg daily administered in two divided doses, and the peginterferon alfa 2a dose, where applicable, was 180 µg per week. Treatment duration was fixed in each study and was not guided by patients' HCV RNA levels (no response guided algorithm).

Plasma HCV RNA values were measured during the clinical studies using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU/mL. Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate for all studies which was defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment (SVR12).

Clinical studies in patients with genotype 1, 4, 5 and 6 chronic hepatitis C

Treatment-naïve adult patients - NEUTRINO (study 110)

NEUTRINO was an open-label, single-arm study that evaluated 12 weeks of treatment with sofosbuvir in combination with peginterferon alfa 2a and ribavirin in treatment-naïve patients with genotype 1, 4, 5 or 6 HCV infection.

Treated patients (n = 327) had a median age of 54 years (range: 19 to 70); 64% of the patients were male; 79% were White; 17% were Black; 14% were Hispanic or Latino; mean body mass index was 29 kg/m² (range: 18 to 56 kg/m²); 78% had baseline HCV RNA greater than 6 log₁₀ IU/mL; 17% had cirrhosis; 89% had HCV genotype 1 and 11% had HCV genotype 4, 5 or 6. Table 7 presents the response rates for the treatment group of sofosbuvir + peginterferon alfa + ribavirin.

Table 7: Response rates in study NEUTRINO

	SOF+PEG+RBV 12 weeks (n = 327)
Overall SVR12	91% (296/327)
Outcome for patients without SVR12	
On-treatment virologic failure	0/327
Relapse ^a	9% (28/326)
Other ^b	1% (3/327)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 8.

Table 8: SVR12 rates for selected subgroups in NEUTRINO

	SOF+PEG+RBV 12 weeks (n = 327)
Genotype	
Genotype 1	90% (262/292)
Genotype 4, 5 or 6	97% (34/35)
Cirrhosis	
No	93% (253/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-Black	91% (249/273)

SVR12 rates were similarly high in patients with baseline IL28B C/C allele [94/95 (99%)] and non-C/C (C/T or T/T) allele [202/232 (87%)].

27/28 patients with genotype 4 HCV achieved SVR12. A single subject with genotype 5 and all 6 patients with genotype 6 HCV infection in this study achieved SVR12.

Clinical studies in patients with genotype 2 and 3 chronic hepatitis C

Treatment-naïve adults - FISSION (study 1231)

FISSION was a randomised, open-label, active-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve patients with genotype 2 or 3 HCV infection. The ribavirin doses used in the sofosbuvir + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1,000-1,200 mg/day and 800 mg/day regardless of weight, respectively. Patients were randomised in a 1:1 ratio and stratified by cirrhosis (presence *versus* absence), HCV genotype (2 *versus* 3) and baseline HCV RNA level (<6 log₁₀ IU/mL *versus* ≥6 log₁₀ IU/mL). Patients with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Treated patients (n = 499) had a median age of 50 years (range: 19 to 77); 66% of the patients were male; 87% were White; 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m² (range: 17 to 52 kg/m²); 57% had baseline HCV RNA levels greater than 6 log₁₀ IU/mL; 20% had cirrhosis; 72% had HCV genotype 3. Table 9 presents the response rates for the treatment groups of sofosbuvir + ribavirin and peginterferon alfa + ribavirin.

Table 9: Response rates in study FISSION

	SOF+RBV 12 weeks (n = 256)^a	PEG+RBV 24 weeks (n = 243)
Overall SVR12	67% (171/256)	67% (162/243)
Genotype 2	95% (69/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for patients without SVR12		
On-treatment virologic failure	< 1% (1/256)	7% (18/243)
Relapse ^b	30% (76/252)	21% (46/217)
Other ^c	3% (8/256)	7% (17/243)

a. The efficacy analysis includes 3 patients with recombinant genotype 2/1 HCV infection.

b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

The difference in the overall SVR12 rates between sofosbuvir + ribavirin and peginterferon alfa + ribavirin treatment groups was 0.3% (95% confidence interval: -7.5% to 8.0%) and the study met the predefined non-inferiority criterion.

Response rates for patients with cirrhosis at baseline are presented in Table 10 by HCV genotype.

Table 10: SVR12 rates by cirrhosis and genotype in study FISSION

	Genotype 2		Genotype 3	
	SOF+RBV 12 weeks (n = 73)^a	PEG+RBV 24 weeks (n = 67)	SOF+RBV 12 weeks (n = 183)	PEG+RBV 24 weeks (n = 176)
Cirrhosis				
No	97% (59/61)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	83% (10/12)	62% (8/13)	34% (13/38)	30% (11/37)

a. The efficacy analysis includes 3 patients with recombinant genotype 2/1 HCV infection.

Interferon intolerant, ineligible or unwilling adults - POSITRON (study 107)

POSITRON was a randomised, double-blinded, placebo-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin (n = 207) compared to placebo (n = 71) in patients who are interferon intolerant, ineligible or unwilling. Patients were randomised in 3:1 ratio and stratified by cirrhosis (presence *versus* absence).

Treated patients (n = 278) had a median age of 54 years (range: 21 to 75); 54% of the patients were male; 91% were White; 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 kg/m² (range: 18 to 53 kg/m²); 70% had baseline HCV RNA levels greater than 6 log₁₀ IU/mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of patients who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most patients had no prior HCV treatment (81.3%). Table 11 presents the response rates for the treatment groups of sofosbuvir + ribavirin and placebo.

Table 11: Response rates in study POSITRON

	SOF+RBV 12 weeks (n = 207)	Placebo 12 weeks (n = 71)
Overall SVR12	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
Outcome for patients without SVR12		
On-treatment virologic failure	0/207	97% (69/71)
Relapse ^a	20% (42/205)	0/0
Other ^b	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

The SVR12 rate in the sofosbuvir + ribavirin treatment group was statistically significant when compared to placebo (p <0.001).

Table 12 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 12: SVR12 rates for selected subgroups by genotype in POSITRON

	SOF+RBV 12 weeks	
	Genotype 2 (n = 109)	Genotype 3 (n = 98)
Cirrhosis		
No	92% (85/92)	68% (57/84)
Yes	94% (16/17)	21% (3/14)
Interferon classification		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Previously treated adults - FUSION (study 108)

FUSION was a randomised, double-blinded study that evaluated 12 or 16 weeks of treatment with sofosbuvir and ribavirin in patients who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Patients were randomised in a 1:1 ratio and stratified by cirrhosis (presence *versus* absence) and HCV genotype (2 *versus* 3).

Treated patients (n = 201) had a median age of 56 years (range: 24 to 70); 70% of the patients were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m² (range: 19 to 44 kg/m²); 73% had baseline HCV RNA levels greater than 6 log₁₀ IU/mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. Table 13 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 16 weeks.

Table 13: Response rates in study FUSION

	SOF+RBV 12 weeks (n = 103)^a	SOF+RBV 16 weeks (n = 98)^a
Overall SVR12	50% (51/103)	71% (70/98)
Genotype 2	82% (32/39)	89% (31/35)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for patients without SVR12		
On-treatment virologic failure	0/103	0/98
Relapse ^b	48% (49/103)	29% (28/98)
Other ^c	3% (3/103)	0/98

a. The efficacy analysis includes 6 patients with recombinant genotype 2/1 HCV infection.

b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 14 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 14: SVR12 rates for selected subgroups by genotype in study FUSION

	Genotype 2		Genotype 3	
	SOF+RBV 12 weeks (n = 39)	SOF+RBV 16 weeks (n = 35)	SOF+RBV 12 weeks (n = 64)	SOF+RBV 16 weeks (n = 63)
Cirrhosis				
No	90% (26/29)	92% (24/26)	37% (14/38)	63% (25/40)
Yes	60% (6/10)	78% (7/9)	19% (5/26)	61% (14/23)
Response to prior HCV treatment				
Relapser	86% (25/29)	89% (24/27)	31% (15/49)	65% (30/46)
Nonresponder	70% (7/10)	88% (7/8)	27% (4/15)	53% (9/17)

Treatment-naïve and previously treated adults - VALENCE (study 133)

VALENCE was a Phase 3 study that evaluated sofosbuvir in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior interferon-based treatment, including patients with compensated cirrhosis. The study was designed as a direct comparison of sofosbuvir and ribavirin *versus* placebo for 12 weeks. However, based on emerging data, the study was unblinded and all HCV genotype 2 patients continued to receive sofosbuvir and ribavirin for 12 weeks, whilst treatment for HCV genotype 3 patients was extended to 24 weeks. Eleven HCV genotype 3 patients had already completed treatment with sofosbuvir and ribavirin for 12 weeks at the time of the amendment.

Treated patients (n = 419) had a median age of 51 years (range: 19 to 74); 60% of the patients were male; median body mass index was 25 kg/m² (range: 17 to 44 kg/m²); the mean baseline HCV RNA level was 6.4 log₁₀ IU/mL; 21% had cirrhosis; 78% had HCV genotype 3; 65% were prior relapsers. Table 15 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 24 weeks.

Placebo recipients are not included in the tables since none achieved SVR12.

Table 15: Response rates in study VALENCE

	Genotype 2 SOF+RBV 12 weeks (n = 73)	Genotype 3 SOF+RBV 12 weeks (n = 11)	Genotype 3 SOF+RBV 24 weeks (n = 250)
Overall SVR12	93% (68/73)	27% (3/11)	84% (210/250)
Outcome for patients without SVR12			
On-treatment virologic failure	0% (0/73)	0% (0/11)	0.4% (1/250)
Relapse ^a	7% (5/73)	55% (6/11)	14% (34/249)
Other ^b	0% (0/73)	18% (2/11)	2% (5/250)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 16 presents the subgroup analysis by genotype for cirrhosis and exposure to prior HCV treatment.

Table 16: SVR12 rates for selected subgroups by genotype in study VALENCE

	Genotype 2 SOF+RBV 12 weeks (n = 73)	Genotype 3 SOF+RBV 24 weeks (n = 250)
Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	93% (86/92)
Cirrhotic	100% (2/2)	92% (12/13)
Treatment-experienced	90% (37/41)	77% (112/145)
Non-cirrhotic	91% (30/33)	85% (85/100)
Cirrhotic	88% (7/8)	60% (27/45)

SVR12 to SVR24 concordance

The concordance between SVR12 and SVR24 (SVR 24 weeks after the end of the treatment) following treatment with sofosbuvir in combination with ribavirin or ribavirin and pegylated interferon demonstrates a positive predictive value of 99% and a negative predictive value of 99%.

Clinical efficacy and safety in special populations

HCV/HIV co-infected adult patients - PHOTON-1 (study 123)

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 12 or 24 weeks of treatment with sofosbuvir and ribavirin in patients with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were naïve to prior treatment. Treatment duration was 12 weeks in treatment-naïve patients with genotype 2 or 3 HCV infection, and 24 weeks in treatment-experienced patients with genotype 3 HCV infection, as well as patients with genotype 1 HCV infection. Patients received 400 mg sofosbuvir and weight-based ribavirin (1,000 mg for patients weighing <75 kg or 1,200 mg for patients weighing ≥75 kg). Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm³ or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm³. 95% of patients received antiretroviral therapy at the time of enrolment. Preliminary SVR12 data are available for 210 patients.

Table 17 presents the response rates by genotype and exposure to prior HCV treatment.

Table 17: Response rates in study PHOTON-1

	Genotype 2/3 treatment-naïve SOF+RBV 12 weeks (n = 68)	Genotype 2/3 treatment-experienced SOF+RBV 24 weeks (n = 28)	Genotype 1 treatment-naïve SOF+RBV 24 weeks (n = 114)
Overall SVR12	75% (51/68)	93% (26/28)	76% (87/114)
Outcome for patients without SVR12			
On-treatment virologic failure	1% (1/68)	0/28	1% (1/114)
Relapse ^a	18% (12/67)	7% (2/28)	22% (25/113)
Other ^b	6% (4/68)	0/28	1% (1/114)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 18 presents the subgroup analysis by genotype for cirrhosis.

Table 18: SVR12 rates for selected subgroups by genotype in study PHOTON-1

	HCV genotype 2		HCV genotype 3	
	SOF+RBV 12 weeks TN (n = 26)	SOF+RBV 24 weeks TE (n = 15)	SOF+RBV 12 weeks TN (n = 42)	SOF+RBV 24 weeks TE (n = 13)
Overall	88% (23/26)	93% (14/15)	67% (28/42)	92% (12/13)
No cirrhosis	88% (22/25)	92% (12/13)	67% (24/36)	100% (8/8)
Cirrhosis	100% (1/1)	100% (2/2)	67% (4/6)	80% (4/5)

TN = treatment-naïve; TE = treatment-experienced.

Adult patients awaiting liver transplantation - Study 2025

Sofosbuvir was studied in HCV infected patients prior to undergoing liver transplantation in an open-label clinical study evaluating the safety and efficacy of sofosbuvir and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the study was post-transplant virologic response (pTVR, HCV RNA <LLOQ at 12 weeks post-transplant).

HCV infected patients, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria received 400 mg sofosbuvir and 1,000-1,200 mg ribavirin daily for a maximum of 24 weeks, subsequently amended to 48 weeks, or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 patients who received sofosbuvir and ribavirin; the majority of patients had HCV genotype 1, 44 patients were CPT class A and 17 patients were CPT class B. Of these 61 patients, 44 patients underwent liver transplantation following up to 48 weeks of treatment with sofosbuvir and ribavirin; 41 had HCV RNA <LLOQ at the time of transplantation. The virologic response rates of the 41 patients transplanted with HCV RNA <LLOQ is described in Table 19. Duration of viral suppression prior to transplantation was the most predictive factor for pTVR in those who were HCV RNA <LLOQ at the time of transplantation.

Table 19: Virologic response post-transplant in patients with HCV RNA <LLOQ at the time of liver transplantation

	Week 12 post-transplant (pTVR)^b
Virologic response in evaluable patients ^a	23/37 (62%)

a. Evaluable patients 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 <LLOQ at 12 weeks post-procedure).

In patients that discontinued therapy at 24 weeks, according to protocol, the relapse rate was 11/15.

Adult liver transplant recipients - Study 0126

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 24 weeks of treatment with sofosbuvir and ribavirin in liver transplant recipients with chronic hepatitis C. Eligible patients were ≥18 years old and had undergone liver transplantation 6 to 150 months prior to screening. Patients had HCV RNA ≥10⁴ IU/mL at screening and documented evidence of chronic HCV infection pre-transplantation. The starting dose of ribavirin was 400 mg given in a divided daily dose. If patients maintained haemoglobin levels ≥12 g/dL, ribavirin dose was increased at weeks 2, 4, and up to every 4 weeks until the appropriate weight-based dose was reached (1,000 mg daily in patients <75 kg, 1,200 mg daily in patients ≥75 kg). The median ribavirin dose was 600 mg-800 mg daily at weeks 4-24.

Forty patients (33 with HCV genotype 1 infection, 6 with HCV genotype 3 infection, and 1 with HCV genotype 4 infection) were enrolled, 35 of whom had previously failed interferon-based treatment, and 16 of whom had cirrhosis. 28 out of 40 (70%) patients achieved SVR12: 22/33 (73%) with HCV genotype 1 infection, 6/6 (100%) with HCV genotype 3 infection, and 0/1 (0%) with HCV genotype 4 infection. All patients who achieved SVR12 achieved SVR24 and SVR48.

Overview of outcomes by therapeutic regimen and treatment duration, a comparison across studies

The following tables (Table 20 to Table 23) present data from Phase 2 and Phase 3 studies relevant to the dosing to help clinicians determine the best regimen for individual patients.

Table 20: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 1 HCV infection

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/N)
Treatment-naïve ^a (NEUTRINO)	SOF+PEG+RBV 12 weeks	Overall	90% (262/292)
		Genotype 1a	92% (206/225)
		Genotype 1b	83% (55/66)
		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)
		Genotype 1a	82% (74/90)
		Genotype 1b	54% (13/24)
		No cirrhosis	77% (84/109)
		Cirrhosis	60% (3/5)
Treatment-naïve (QUANTUM ^b and 11-1-0258 ^b)	SOF+RBV 24 weeks	Overall ^c	65% (104/159)
		Genotype 1a ^c	69% (84/121)
		Genotype 1b ^c	53% (20/38)
		No cirrhosis ^c	68% (100/148)
		Cirrhosis ^c	36% (4/11)

n = number of patients with SVR12 response; N = total number of patients per group.

- a. For previously treated patients with genotype 1 HCV infection, no data exists with the combination of sofosbuvir, peginterferon alfa and ribavirin. Consideration should be given to treating these patients, and potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (prior null response to peginterferon alfa and ribavirin therapy, advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).
- b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients.
- c. Summary data from both studies.

Table 21: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 2 HCV infection

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/N)
Treatment-naïve (FISSION)	SOF+RBV 12 weeks	Overall	95% (69/73)
		No cirrhosis	97% (59/61)
		Cirrhosis	83% (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	82% (32/39)
		No cirrhosis	90% (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	89% (31/35)
		No cirrhosis	92% (24/26)
		Cirrhosis	78% (7/9)
Treatment-naïve co-infected with HIV (PHOTON-1)	SOF+RBV 12 weeks	Overall	88% (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)
		No cirrhosis ^a	92% (12/13)
		Cirrhosis ^a	100% (2/2)
Treatment-naïve (ELECTRON ^b and PROTON ^b)	SOF+PEG+RBV 12 weeks	Overall ^c	96% (25/26)
Treatment-experienced (LONESTAR-2 ^b)	SOF+PEG+RBV 12 weeks	Overall	96% (22/23)
		No cirrhosis	100% (9/9)
		Cirrhosis	93% (13/14)

n = number of patients with SVR12 response; N = total number of patients per group.

a. These data are preliminary.

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin.

c. All patients were non-cirrhotic in these two studies.

Table 22: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 3 HCV infection

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/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)

Patient population (Study number/name)	Regimen/Duration	Subgroup	SVR12 rate % (n/N)
		Cirrhosis	92% (12/13)
Treatment-experienced (VALENCE)	SOF+RBV 24 weeks	Overall	77% (112/145)
		No cirrhosis	85% (85/100)
		Cirrhosis	60% (27/45)
		Overall	67% (28/42)
Treatment-naïve co-infected with HIV (PHOTON-1)	SOF+RBV 12 weeks	No cirrhosis	67% (24/36)
		Cirrhosis	67% (4/6)
		Overall ^a	92% (12/13)
Treatment-experienced co-infected with HIV (PHOTON-1)	SOF+RBV 24 weeks	No cirrhosis ^a	100% (8/8)
		Cirrhosis ^a	80% (4/5)
Treatment-naïve (ELECTRON ^b and PROTON ^b)	SOF+PEG+RBV 12 weeks	Overall ^c	97% (38/39)
Treatment-experienced (LONESTAR-2 ^b)	SOF+PEG+RBV 12 weeks	Overall	83% (20/24)
		No cirrhosis	83% (10/12)
		Cirrhosis	83% (10/12)

n = number of patients with SVR12 response; N = total number of patients per group.

a. These data are preliminary.

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin.

c. All patients were non-cirrhotic in these two studies.

Table 23: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 4, 5 and 6 HCV infection

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

n = number of patients with SVR12 response; N = total number of patients per group.

Patients with renal impairment

Study 0154 was an open-label clinical study that evaluated the safety and efficacy of 24 weeks of treatment with sofosbuvir in combination with ribavirin in 20 genotype 1 or 3 HCV-infected patients with severe renal impairment not requiring dialysis. Following treatment with sofosbuvir 200 mg or 400 mg in combination with ribavirin the SVR12 rate in patients with ESRD was 40% and 60%, respectively. The safety and efficacy of 12 weeks of treatment with ledipasvir/sofosbuvir in 18 genotype 1 HCV-infected patients with severe renal impairment not requiring dialysis was also studied in Study 0154. At baseline, two patients had cirrhosis and the mean eGFR was 24.9 mL/min (range: 9.0-39.6). SVR12 was achieved in 100 % (18/18) of patients treated with ledipasvir/sofosbuvir.

Study 4063 was an open-label study that evaluated a fixed dose combination of sofosbuvir and ledipasvir in 95 patients with HCV-infection and ESRD requiring dialysis. The SVR rates for the 8, 12, and 24 week ledipasvir/sofosbuvir treatment groups were 93% (42/45), 100% (31/31), and 79% (15/19), respectively. Of the seven patients who did not achieve SVR12, none experienced virologic failure or relapsed.

Study 4062 was an open-label study that evaluated a fixed dose combination of sofosbuvir and velpatasvir in 59 HCV-infected patients with ESRD requiring dialysis. The SVR rate was 95% (56/59); of the three patients that did not achieve SVR12, one had completed sofosbuvir with velpatasvir treatment and relapsed.

Paediatric population

The efficacy of sofosbuvir in HCV-infected patients aged 3 years and above was evaluated in a Phase 2, open label clinical trial that enrolled 106 patients with genotype 2 (n = 31) or genotype 3

(n = 75) chronic HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with sofosbuvir with ribavirin for 12 or 24 weeks, respectively.

Patients aged 12 to < 18 Years:

Sofosbuvir was evaluated in 52 patients 12 to < 18 years with genotype 2 (n = 13) or genotype 3 (n = 39) HCV infection. The median age was 15 years (range: 12 to 17); 40% of the patients were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 60.4 kg (range: 29.6 to 75.6 kg); 17% were treatment experienced; 65% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (69%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (100% [13/13] in genotype 2 patients and 97% [38/39]) in genotype 3 patients. No patient experienced on-treatment virologic failure or relapse; one patient with genotype 3 HCV infection achieved SVR4 but did not return for the SVR12 visit.

Patients aged 6 to < 12 Years:

Sofosbuvir was evaluated in 41 patients 6 to < 12 years of age with genotype 2 (n = 13), or genotype 3 (n = 28) HCV infection. The median age was 9 years (range: 6 to 11); 73% of the patients were female; 71% were White and 20% were Asian; 15% were Hispanic/Latino; mean weight was 33.7 kg (range: 15.1 to 80.0 kg); 98% were treatment naive; 46% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (98%) had been infected through vertical transmission.

The SVR12 rate was 100% (100% [13/13] in genotype 2 patients and 100% [28/28] in genotype 3 patients). No patients experienced on-treatment virologic failure or relapse.

Patients aged 3 to < 6 Years:

Sofosbuvir was evaluated in 13 patients 3 to < 6 years with genotype 2 (n = 5) or genotype 3 (n = 8) HCV infection. The median age was 4 years (range: 3 to 5); 77% of the patients were female; 69% were White, 8% were Black, and 8% were Asian; 8% were Hispanic/Latino; mean weight was 16.8 kg (range: 13.0 to 19.2 kg); 100% were treatment naive; 23% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (85%) had been infected through vertical transmission.

The SVR12 rate was 92% overall (80% [4/5] in genotype 2 patients and 100% [8/8] in genotype 3 patients). No patients experienced on-treatment virologic failure or relapse; one patient with genotype 2 HCV prematurely discontinued study treatment after three days due to abnormal taste of the medication and did not return for post-treatment Week 12.

5.2 Pharmacokinetic properties

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is formed in hepatocytes and not observed in plasma. The predominant (>90%) metabolite, GS-331007, is inactive. It is formed through sequential and parallel pathways to the formation of active metabolite.

Absorption

The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration, sofosbuvir was absorbed quickly and the peak plasma concentration was observed ~0.5-2 hour post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose. Based on population pharmacokinetic analysis in patients with genotypes 1 to 6 HCV infection (n = 986), steady-state AUC₀₋₂₄ for sofosbuvir and GS-331007 was 1,010 ng•h/mL and 7,200 ng•h/mL, respectively. Relative to healthy subjects (n = 284), the sofosbuvir and GS-331007 AUC₀₋₂₄ was 57% higher and 39% lower, respectively in HCV infected patients.

Effects of food

Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold, with little effect on peak concentration. The exposure to GS-331007 was not altered in the presence of a high-fat meal.

Distribution

Sofosbuvir is not a substrate for hepatic uptake transporters, organic anion-transporting polypeptide (OATP) 1B1 or 1B3, and organic cation transporter (OCT) 1. While subject to active tubular secretion, GS-331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or 3, OCT2, MRP2, P-gp, BCRP or MATE1. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Sofosbuvir is approximately 85% bound to human plasma proteins (*ex vivo* data) and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [¹⁴C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ¹⁴C-radioactivity was approximately 0.7.

Biotransformation

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes.

After a single 400 mg oral dose of [¹⁴C]-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug-related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Elimination

Following a single 400 mg oral dose of [¹⁴C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 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. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

Linearity/non-linearity

The dose linearity of sofosbuvir and its primary metabolite, GS-331007, was evaluated in fasted healthy subjects. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 400 mg.

Pharmacokinetics in special populations

Gender and race

No clinically relevant pharmacokinetic differences due to gender or race have been identified for sofosbuvir and GS-331007.

Elderly

Population pharmacokinetic analysis in HCV infected patients showed that within the age range (19 to 75 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir and GS-331007. Clinical studies of sofosbuvir included 65 patients aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups.

Renal impairment

A summary of the effect of varying degrees of renal impairment (RI) on the exposures of sofosbuvir and GS-331007 compared to subjects with normal renal function, as described in the text below, are provided in Table 24.

Table 24: Effect of varying degrees of renal impairment on exposures (AUC) of sofosbuvir and GS-331007 compared to subjects with normal renal function

	HCV-Negative Subjects					HCV-Infected Subjects	
	Mild RI (eGFR \geq 50 and <80 mL/min/1.73 m 2)	Moderate RI (eGFR \geq 30 and <50 mL/min/1.73 m 2)	Severe RI (eGFR <30 mL/min/1.7 3m 2)	ESRD Requiring Dialysis		Severe RI (eGFR <30 mL/min/1. 73m 2)	ESRD Requiring Dialysis
				Dosed 1 hr Before Dialysis	Dosed 1 hr After Dialysis		
Sofosbuvir	1.6-fold \uparrow	2.1-fold \uparrow	2.7-fold \uparrow	1.3-fold \uparrow	1.6-fold \uparrow	\sim 2-fold \uparrow	1.9-fold \uparrow
GS-331007	1.6-fold \uparrow	1.9-fold \uparrow	5.5-fold \uparrow	\geq 10-fold \uparrow	\geq 20-fold \uparrow	\sim 7-fold \uparrow	21-fold \uparrow

The pharmacokinetics of sofosbuvir were studied in HCV negative adult patients with mild (eGFR \geq 50 and <80 mL/min/1.73 m 2), moderate (eGFR \geq 30 and <50 mL/min/1.73 m 2), severe renal impairment (eGFR <30 mL/min/1.73 m 2) and patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir, relative to adult patients with normal renal function (eGFR >80 mL/min/1.73 m 2). GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered sofosbuvir dose.

In HCV-infected adult patients with severe renal impairment treated with sofosbuvir 200 mg with ribavirin (n=10) or sofosbuvir 400 mg with ribavirin (n=10) for 24 weeks or ledipasvir/sofosbuvir 90/400 mg (n=18) for 12 weeks, the pharmacokinetics of sofosbuvir and GS-331007 were consistent with that observed in HCV negative adult patients with severe renal impairment.

The pharmacokinetics of sofosbuvir, and GS-331007 were studied in HCV-infected adult patients with ESRD requiring dialysis treated with ledipasvir/sofosbuvir (n = 94) for 8, 12, or 24 weeks or sofosbuvir/velpatasvir (n = 59) for 12 weeks, and compared to patients without renal impairment in the ledipasvir/sofosbuvir and sofosbuvir/velpatasvir Phase 2/3 trials (see section 4.4).

Hepatic impairment

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in adult HCV-infected patients with moderate and severe hepatic impairment (CPT class B and C). Relative to patients with normal hepatic function, the sofosbuvir AUC₀₋₂₄ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC₀₋₂₄ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in adult HCV-infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment (see section 4.2).

Paediatric population

Sofosbuvir and GS-331007 exposures in paediatric patients aged 3 years and above were similar to those in adults from Phase 2/3 studies following administration of sofosbuvir.

The pharmacokinetics of sofosbuvir and GS-331007 have not been established in paediatric patients aged < 3 years (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

Efficacy, in terms of rapid virologic response, has been shown to correlate with exposure to sofosbuvir as well as GS 331007. However, neither of these entities has been evidenced to be a general surrogate marker for efficacy (SVR12) at the therapeutic 400 mg dose.

5.3 Preclinical safety data

In repeat dose toxicology studies in rat and dog, high doses of the 1:1 diastereomeric mixture caused adverse liver (dog) and heart (rat) effects and gastrointestinal reactions (dog). Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity; however, exposure to the major metabolite GS-331007 at the adverse dose was 29 times (rat) and 123 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 9 times (rat) and 27 times (dog) higher than the clinical exposure.

Sofosbuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was up to 30 times (mouse) and 15 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir had no effects on embryo-foetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 9 times the expected clinical exposure. In the rat studies, exposure to sofosbuvir could not be determined but exposure margins based on the major human metabolite ranged from 8 to 28 times higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir-derived material was transferred through the placenta in pregnant rats and into the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granule Cores

Lactose monohydrate
Microcrystalline cellulose
Crocarmellose sodium
Hydroxypropyl cellulose
Colloidal anhydrous silica
Sodium stearyl fumarate

Film-coating

Hypromellose
Macrogol 400
Amino methacrylate copolymer
Talc
Stearic acid
Sodium lauryl sulfate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sovaldi oral granules, 150 mg and 200 mg, are supplied in sachets consisting of polyester/aluminium/polyethylene film in cartons. Each carton contains 28 sachets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/894/004
EU/1/13/894/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2014
Date of latest renewal: 17 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk management plan (RMP)**

The marketing authorization holder (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.
- Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with Sovaldi, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q4 2021

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE
PACKAGING**

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 400 mg film-coated tablets
sofosbuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg of sofosbuvir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets.
84 (3 bottles of 28) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/894/001 28 film-coated tablets
EU/1/13/894/002 84 (3 bottles of 28) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sovaldi 400 mg film-coated tablets [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE
PACKAGING**

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 200 mg film-coated tablets
sofosbuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of sofosbuvir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/894/003 [28 film-coated tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Sovaldi 200 mg film-coated tablets [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN{number}

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE
PACKAGING**

CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 150 mg coated granules in sachet
sofosbuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of coated granules contains 150 mg of sofosbuvir.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 sachets in carton.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carraigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/894/004 28 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sovaldi 150 mg coated granules in sachet [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNIT

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 150 mg coated granules in sachet
sofosbuvir
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER < DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

GILEAD

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE
PACKAGING**

CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 200 mg coated granules in sachet
sofosbuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of coated granules contains 200 mg sofosbuvir.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 sachets in carton.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carraigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/894/005 28 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sovaldi 200 mg coated granules in sachet [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNIT

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Sovaldi 200 mg coated granules in sachet
sofosbuvir
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER < DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

GILEAD

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Sovaldi 400 mg film-coated tablets Sovaldi 200 mg film-coated tablets sofosbuvir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sovaldi is and what it is used for
2. What you need to know before you take Sovaldi
3. How to take Sovaldi
4. Possible side effects
5. How to store Sovaldi
6. Contents of the pack and other information

If Sovaldi has been prescribed for your child, please note that all the information in this leaflet is applicable to your child (in this case please read “your child” instead of “you”).

1. What Sovaldi is and what it is used for

Sovaldi contains the active substance sofosbuvir which is given to treat hepatitis C virus infection in adults and children 3 years of age and older.

Hepatitis C is a virus that infects the liver. This medicine works by lowering the amount of hepatitis C virus in your body and removing the virus from your blood over a period of time.

Sovaldi is always taken with other medicines to treat hepatitis C. It will not work on its own. It is commonly taken with either:

- Ribavirin (children and adult patients), or
- Peginterferon alfa and ribavirin (adult patients)

It is very important that you also read the leaflets for the other medicines that you will be taking with Sovaldi. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Sovaldi

Do not take Sovaldi

- If you are allergic to sofosbuvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).
- If you are currently taking any of the following medicines:

- **Rifampicin** (antibiotic used to treat infections, including tuberculosis);
- **St. John's wort** (herbal medicine used to treat depression);
- **Carbamazepine, phenobarbital and phenytoin** (medicines used to treat epilepsy and prevent seizures).

→ If any of these conditions apply to you, tell your doctor immediately.

Warnings and precautions

Sovaldi is always taken with other medicines to treat hepatitis C (see section 1 above). Talk to your doctor or pharmacist before taking this medicine if you:

- currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats, as it may result in a life-threatening slowing of your heart beat. Your doctor may consider different treatments if you have taken this medicine. If treatment with Sovaldi is needed, you may require additional heart monitoring;
- have liver problems other than hepatitis C, e.g. if you are awaiting a liver transplantation;
- have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely;
- have diabetes. You may need closer monitoring of your blood glucose levels and/or adjustment of your diabetes medication after starting Sovaldi. Some diabetic patients have experienced low sugar levels in the blood (hypoglycaemia) after starting treatment with medicines like Sovaldi.

Tell your doctor immediately if you currently take, or have taken in the last months, any medicines for heart problems and during treatment you experience:

- slow or irregular heartbeat, or heart rhythm problems;
- shortness of breath or worsening of existing shortness of breath;
- chest-pain;
- light-headedness;
- palpitations
- near fainting or fainting

Blood tests

Your doctor will test your blood before, during and after your treatment with Sovaldi. This is so your doctor can:

- Decide what other medicines you should take with Sovaldi and for how long;
- Confirm that your treatment has worked and you are free of the hepatitis C virus.

Children and adolescents

Do not give this medicine to children under 3 years of age. The use of Sovaldi in children under 3 years of age has not yet been studied.

Other medicines and Sovaldi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Warfarin and other similar medicines called vitamin K antagonists are used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

Your liver function may change with treatment of hepatitis C and therefore may affect other medications (e.g. medicines used to suppress your immune system, etc.). Your doctor may need to closely monitor these other medicines you are taking and make adjustments after starting Sovaldi.

Talk to your doctor about taking Sovaldi if you are taking any of the following medicines:

- Oxcarbazepine (a medicine used to treat epilepsy and prevent seizures);
- Modafinil (a medicine to treat people with narcolepsy to help them stay awake);
- Rifapentine (a medicine used to treat infections, including tuberculosis);

This is because they may make Sovaldi work less well.

Tell your doctor if you take any of the following medicines:

- amiodarone, used to treat irregular heartbeats.

If you are not sure of what medicines can be taken with Sovaldi, talk to your doctor or pharmacist.

Pregnancy and contraception

Pregnancy must be avoided due to the use of Sovaldi together with ribavirin. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ribavirin can be very damaging to an unborn baby. Therefore, special precautions in sexual activity must be taken if there is any chance for pregnancy to occur.

- Sovaldi is commonly used together with ribavirin. Ribavirin can damage your unborn baby. It is therefore very important that you (or your partner) **do not become pregnant** during this therapy.
- You or your partner must use an effective birth control method **during treatment and afterwards**. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ask your doctor for an effective contraceptive method suitable for you.
- If you or your partner become pregnant during Sovaldi treatment or in the months that follow, you must **contact your doctor immediately**.

Breast-feeding

You should not breast-feed during treatment with Sovaldi. It is not known whether sofosbuvir, the active substance of Sovaldi, passes into human breast milk.

Driving and using machines

When taking Sovaldi together with other medicines for the treatment of hepatitis C infection, patients have reported tiredness, dizziness, blurred vision and reduced attention. If you feel tired, dizzy, have blurred vision or reduced attention after taking Sovaldi you should not take part in activities such as driving, riding a bike or operating machines.

Sovaldi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Sovaldi

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose

Sovaldi is to be taken as advised by your doctor. The recommended dose of Sovaldi **in adults** is **one tablet (400 mg) once a day** with food. Your doctor will tell you for how long you should take Sovaldi.

The recommended dose of Sovaldi **in children aged 3 years and above is based on weight. Take Sovaldi with food, as advised by your doctor.**

Swallow the tablet(s) whole. Do not chew, crush or split the tablet as it has a very bitter taste. Tell your doctor or pharmacist if you have problems swallowing tablets.

Sovaldi should always be taken in combination with other medicinal products for use against hepatitis C as advised by your doctor.

If you are sick (vomit) **less than 2 hours** after taking Sovaldi, take another dose. If you vomit **more than 2 hours** after taking Sovaldi you do not need to take another dose until your next regularly scheduled dose.

Kidney problems

Tell your doctor if you have kidney problems or if you are on kidney dialysis.

If you take more Sovaldi than you should

If you accidentally take more than the recommended dose you should contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Sovaldi

It is important not to miss a dose of this medicine.

If you do miss a dose:

- **and you notice within 18 hours** of the time you usually take Sovaldi, you must take the dose as soon as possible. Then take the next dose at your usual time.
- **and you notice 18 hours or more** after the time you usually take Sovaldi, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

Do not stop taking Sovaldi

Do not stop taking this medicine unless your doctor tells you to. It is very important that you complete the full course of treatment to give the medicines the best chance to treat your hepatitis C virus infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you take Sovaldi in combination with amiodarone (a medicine used for heart problems), you may get one or more of the side effects below:

- slow or irregular heartbeat or heart rhythm problems
- shortness of breath or worsening of any shortness of breath you already have

Tell your doctor or your pharmacist if you notice any of the above side effects during therapy.

When you take Sovaldi with ribavirin or both peginterferon alfa and ribavirin, you may get one or more of the side effects below:

Very common side effects

(may affect more than 1 in 10 people)

- fever, chills, flu-like symptoms
- diarrhoea, feeling sick (nausea), being sick (vomiting)
- trouble sleeping (insomnia)
- feeling tired and irritable
- headache
- rash, itchy skin
- loss of appetite, decreased appetite
- feeling dizzy
- muscle aches and pains, pain in the joints
- shortness of breath, cough

Blood tests may also show:

- low red blood cell count (anaemia); the signs may include feeling tired, headaches, shortness of breath when exercising
- low white blood cell count (neutropenia); the signs may include getting more infections than usual, including fevers and chills, or sore throat or mouth ulcers
- low blood platelet count
- changes in your liver (as shown by increased amounts of a substance called bilirubin in the blood)

Common side effects

(may affect up to 1 in 10 people)

- changes in your mood, feeling depressed, feeling anxious and feeling agitated
- blurred vision
- severe headaches (migraine), memory loss, loss of concentration
- weight loss
- shortness of breath when exercising
- stomach discomfort, constipation, dry mouth, indigestion, acid reflux
- hair loss and thinning hair
- dry skin
- back pain, muscle spasms
- chest pain, feeling weak
- getting a cold (nasopharyngitis)

Other effects that may be seen during treatment with sofosbuvir:

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- a wide-spread severe rash with peeling skin which may be accompanied by fever, flu-like symptoms, blisters in the mouth, eyes, and/or genitals (Stevens-Johnson syndrome).

→ If any of the side effects get serious tell your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly to the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sovaldi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sovaldi contains

- **The active substance is** sofosbuvir. Each film-coated tablet contains 400 mg of sofosbuvir or 200 mg of sofosbuvir.

- **The other ingredients are**

Tablet core:

Mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate.

Film-coating:

Polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow.

What Sovaldi looks like and contents of the pack

Sovaldi 400 mg film-coated tablets are yellow, capsule-shaped tablets, debossed on one side with “GSI” and “7977” on the other side. The tablet is approximately 20 mm long and 9 mm wide.

Sovaldi 200 mg film-coated tablets are yellow, oval-shaped, film-coated tablets, debossed with “GSI” on one side and “200” on the other side. The tablet is approximately 15 mm long and 8 mm wide.

Each bottle of Sovaldi 400 mg film-coated tablets contains a silica gel desiccant (drying agent) that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack sizes are available:

- outer cartons containing 1 bottle of 28 film-coated tablets for the 400 mg and 200 mg film-coated tablets
- and 84 (3 bottles of 28) film-coated tablets for the 400 mg film coated tablets only. Not all pack sizes may be marketed in your country.

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Carrigtohill

County Cork, T45 DP77

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Manufacturer

Gilead Sciences Ireland UC

IDA Business & Technology Park

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Package leaflet: Information for the user

Sovaldi 150 mg coated granules in sachet Sovaldi 200 mg coated granules in sachet sofosbuvir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sovaldi is and what it is used for
2. What you need to know before you take Sovaldi
3. How to take Sovaldi
4. Possible side effects
5. How to store Sovaldi
6. Contents of the pack and other information

If Sovaldi has been prescribed for your child, please note that all the information in this leaflet is applicable to your child (in this case please read “your child” instead of “you”).

1. What Sovaldi is and what it is used for

Sovaldi granules contain the active substance sofosbuvir which is given in a granule formulation to treat hepatitis C virus infection in **adults and children aged 3 years of age and older**.

Hepatitis C is a virus that infects the liver. This medicine works by lowering the amount of hepatitis C virus in your body and removing the virus from your blood over a period of time.

Sovaldi is always taken with other medicines to treat hepatitis C. It will not work on its own. It is commonly taken with either:

- Ribavirin (children and adult patients), or
- Peginterferon alfa and ribavirin (adult patients)

It is very important that you also read the leaflets for the other medicines that you will be taking with Sovaldi. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Sovaldi

Do not take Sovaldi

- If you are allergic to sofosbuvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).
- **If you are currently taking any of the following medicines:**
 - **Rifampicin** (antibiotic used to treat infections, including tuberculosis);

- **St. John's wort** (herbal medicine used to treat depression);
- **Carbamazepine, phenobarbital and phenytoin** (medicines used to treat epilepsy and prevent seizures).

→ If any of these conditions apply to you, tell your doctor immediately.

Warnings and precautions

Sovaldi is always taken with other medicines to treat hepatitis C (see section 1 above). Talk to your doctor or pharmacist before taking this medicine if you:

- Currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats, as it may result in a life-threatening slowing of your heart beat. Your doctor may consider different treatments if you have taken this medicine. If treatment with Sovaldi is needed, you may require additional heart monitoring;
- have liver problems other than hepatitis C, e.g. if you are awaiting a liver transplantation;
- have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely;
- have diabetes. You may need closer monitoring of your blood glucose levels and/or adjustment of your diabetes medication after starting Sovaldi. Some diabetic patients have experienced low sugar levels in the blood (hypoglycaemia) after starting treatment with medicines like Sovaldi.

Tell your doctor immediately if you currently take, or have taken in the last months, any medicines for heart problems and during treatment you experience:

- slow or irregular heartbeat, or heart rhythm problems;
- shortness of breath or worsening of existing shortness of breath;
- chest-pain;
- light-headedness;
- palpitations
- near fainting or fainting

Blood tests

Your doctor will test your blood before, during and after your treatment with Sovaldi. This is so your doctor can:

- Decide what other medicines you should take with Sovaldi and for how long;
- Confirm that your treatment has worked and you are free of the hepatitis C virus.

Children

Do not give this medicine to children under 3 years of age. The use of Sovaldi in children under 3 years of age has not yet been studied.

Other medicines and Sovaldi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Warfarin and other similar medicines called vitamin K antagonists are used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

Your liver function may change with treatment of hepatitis C and therefore may affect other medications (e.g. medicines used to suppress your immune system, etc.). Your doctor may need to closely monitor these other medicines you are taking and make adjustments after starting Sovaldi.

Talk to your doctor about taking Sovaldi if you are taking any of the following medicines:

- Oxcarbazepine (a medicine used to treat epilepsy and prevent seizures);
- Modafinil (a medicine to treat people with narcolepsy to help you stay awake).
- Rifapentine (a medicine used to treat infections, including tuberculosis);

This is because they may make Sovaldi work less well.

Tell your doctor if you take any of the following medicines:

- amiodarone, used to treat irregular heartbeats.

If you are not sure of what medicines can be taken with Sovaldi, talk to your doctor or pharmacist.

Pregnancy and contraception

Pregnancy must be avoided due to the use of Sovaldi together with ribavirin. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ribavirin can be very damaging to an unborn baby. Therefore, special precautions in sexual activity must be taken if there is any chance for pregnancy to occur.

- Sovaldi is commonly used together with ribavirin. Ribavirin can damage your unborn baby. It is therefore very important that you (or your partner) **do not become pregnant** during this therapy.
- You or your partner must use an effective birth control method **during treatment and afterwards**. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ask your doctor for an effective contraceptive method suitable for you.
- If you or your partner become pregnant during Sovaldi treatment or in the months that follow, you must **contact your doctor immediately**.

Breast-feeding

Do not breast-feed during treatment with Sovaldi. It is not known whether sofosbuvir, the active substance of Sovaldi, passes into human breast milk.

Driving and using machines

When taking Sovaldi together with other medicines for the treatment of hepatitis C infection, patients have reported tiredness, dizziness, blurred vision and reduced attention. If you feel tired, dizzy, have blurred vision or reduced attention after taking Sovaldi you should not take part in activities such as driving, riding a bike or operating machines.

Sovaldi granules contain lactose

- **If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.**

Sovaldi granules contain sodium

This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

3. How to take Sovaldi

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose

Sovaldi is to be taken as advised by your doctor. Your doctor will tell you for how long you should take Sovaldi and how many sachets you should take.

The recommended dose is the **entire contents of the sachet(s), taken once daily** shortly before food, shortly after food, or with food.

To help with swallowing of the Sovaldi oral granules you can use food or water as detailed below. Alternatively, Sovaldi can be swallowed without food or water.

Sovaldi should always be taken in combination with other medicinal products for use against hepatitis C as advised by your doctor.

Giving Sovaldi granules with food to aid swallowing:

1. Hold sachet with cut line on top
2. Shake sachet gently to settle contents
3. Tear sachet open along cut line, or use scissors to cut across line
4. Carefully pour entire contents of sachet onto one or more spoonfuls of non-acidic soft food such as, chocolate syrup, mashed potato or ice-cream at or below room temperature
5. Make sure that no granules remain in the sachet
6. Take all the granules within 30 minutes of gently mixing with food
7. Swallow combination of food and granules without chewing to avoid a bitter taste. Make sure that all the food is eaten.

Giving Sovaldi granules without food or water or with water to aid swallowing:

1. Hold sachet with cut line on top
2. Shake sachet gently to settle contents
3. Tear sachet open along cut line, or use scissors to cut across line
4. The granules can be taken directly in the mouth and swallowed without chewing to avoid a bitter taste or with or without non-acidic liquids such as water. **Do not** use fruit juices, for example apple, cranberry, grape, orange, pineapple as these are acidic and should not be used.
5. Make sure no granules remain in the sachet
6. Swallow all the granules.

If you are sick (vomit) **less than 2 hours** after taking Sovaldi, take another sachet(s). If you vomit **more than 2 hours** after taking Sovaldi, you do not need to take another dose until your next regularly scheduled dose

Kidney problems

Tell your doctor if you have kidney problems or if you are on kidney dialysis.

If you take more Sovaldi than you should

If you accidentally take more than the recommended dose you should contact your doctor or nearest emergency department immediately for advice. Keep the sachet carton with you so that you can easily describe what you have taken.

If you forget to take Sovaldi

It is important not to miss a dose of this medicine.

If you do miss a dose:

- **and you notice within 18 hours** of the time you usually take Sovaldi, you must take the dose as soon as possible. Then take the next dose at your usual time.
- **and you notice 18 hours or more** after the time you usually take Sovaldi, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

Do not stop taking Sovaldi

You should not stop taking this medicine unless your doctor tells you. It is very important that you complete the full course of treatment to give the medicines the best chance to treat your hepatitis C virus infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you take Sovaldi in combination with amiodarone (a medicine used for heart problems), you may get one or more of the side effects below:

- slow or irregular heartbeat or heart rhythm problems
 - shortness of breath or worsening of any shortness of breath you already have
- Tell your doctor or your pharmacist if you notice any of the above side effects during therapy.

When you take Sovaldi with ribavirin or both peginterferon alfa and ribavirin, you may get one or more of the side effects below:

Very common side effects

(may affect more than 1 in 10 people)

- fever, chills, flu-like symptoms
- diarrhoea, feeling sick (nausea), being sick (vomiting)
- trouble sleeping (insomnia)
- feeling tired and irritable
- headache
- rash, itchy skin
- loss of appetite, decreased appetite
- feeling dizzy
- muscle aches and pains, pain in the joints
- shortness of breath, cough

Blood tests may also show:

- low red blood cell count (anaemia); the signs may include feeling tired, headaches, shortness of breath when exercising
- low white blood cell count (neutropenia); the signs may include getting more infections than usual, including fevers and chills, or sore throat or mouth ulcers
- low blood platelet count
- changes in your liver (as shown by increased amounts of a substance called bilirubin in the blood)

Common side effects

(may affect up to 1 in 10 people)

- changes in your mood, feeling depressed, feeling anxious and feeling agitated
- blurred vision
- severe headaches (migraine), memory loss, loss of concentration
- weight loss
- shortness of breath when exercising
- stomach discomfort, constipation, dry mouth, indigestion, acid reflux
- hair loss and thinning hair
- dry skin
- back pain, muscle spasms
- chest pain, feeling weak
- getting a cold (nasopharyngitis)

Other effects that may be seen during treatment with sofosbuvir:

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- a wide-spread severe rash with peeling skin which may be accompanied by fever, flu-like symptoms, blisters in the mouth, eyes, and/or genitals (Stevens-Johnson syndrome).

→ If any of the side effects get serious tell your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly to the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sovaldi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the sachet and carton after {EXP}. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sovaldi contains

The active substance is sofosbuvir.

- **Sovaldi 150 mg coated granules in sachet** contains 150 mg sofosbuvir.
- **Sovaldi 200 mg coated granules in sachet** contains 200 mg sofosbuvir.
- **The other ingredients are** lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal anhydrous silica, sodium stearyl fumarate, hypromellose, macrogol 400, amino methacrylate copolymer, talc, stearic acid, sodium lauryl sulfate.

What Sovaldi looks like and contents of the pack

The granules are white to off-white and contained in a sachet.

The following pack size is available:

- outer carton containing 28 sachets.

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