Summary of Product Characteristics

1. Name of the medicinal product
HEPCINAT 400 mg film-coated tablets

2. Qualitative and quantitative composition
HEPCINAT 400 mg film-coated tablets
Each film-coated tablet contains 400 mg of sofosbuvir.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet.
HEPCINAT 400 mg film-coated tablets

Brick red coloured, capsule shaped, film coated tablets debossed with ’400’ on one side and plain on other side.

4. Clinical particulars
4.1 Therapeutic indications

HEPCINAT 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

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

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

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

HEPCINAT 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 HEPCINAT 150 mg or 200 mg granules.

HEPCINAT should be used in combination with other medicinal products. Monotherapy of HEPCINAT 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 HEPCINAT. The recommended co-administered medicinal product(s) and treatment duration for HEPCINAT 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 HEPCINAT combination therapy

Patient population*	Treatment	Duration
Adult patients with genotype 1, 4, 5 or 6 CHC	HEPCINAT + ribavirin[c] + peginterferon alfa	12 weeks[a,b]
	HEPCINAT + 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	HEPCINAT [d] + ribavirin[c, e]	12 weeks[b]
Adult patients with genotype 3 CHC	HEPCINAT + ribavirin[c] + peginterferon alfa	12 weeks[b]
	HEPCINAT + ribavirin[c]	24 weeks
Paediatric patients aged 3 years and above with genotype 3 CHC	HEPCINAT [d] + ribavirin[e]	24 weeks
Adult patients with CHC awaiting liver transplantation	HEPCINAT + 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 HEPCINAT, 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 HEPCINAT 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 HEPCINAT tablets*

Body Weight (kg)	**Dosing of** HEPCINAT **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

* HEPCINAT 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 HEPCINAT 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 HEPCINAT HEPCINAT 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 HEPCINAT 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 HEPCINAT 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 HEPCINAT 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 HEPCINAT are permanently discontinued, HEPCINAT 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 HEPCINAT 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 m^2) and end stage renal disease (ESRD) requiring haemodialysis. HEPCINAT 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 HEPCINAT 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 HEPCINAT have not been established in patients with decompensated cirrhosis.

Patients awaiting liver transplantation
The duration of administration of HEPCINAT 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
HEPCINAT 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 HEPCINAT 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 HEPCINAT plasma concentration and could result in loss of efficacy of HEPCINAT (see section 4.5).

4.4 Special warnings and precautions for use

General
HEPCINAT 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 HEPCINAT are permanently discontinued, HEPCINAT should also be discontinued (see section 4.2). Consult the Summary of Product Characteristics for co-prescribed medicinal products before starting therapy with HEPCINAT.

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 HEPCINAT 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 HEPCINAT.

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

HEPCINAT 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 HEPCINAT 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 HEPCINAT 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

HEPCINAT 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 HEPCINAT and telaprevir or boceprevir. Such co-administration is not recommended (see also section 4.5).

Pregnancy and concomitant use with ribavirin

When HEPCINAT 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 HEPCINAT. Co-administration of such medicinal products is not recommended with HEPCINAT (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 m^2) and ESRD requiring haemodialysis. HEPCINAT vcan 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 HEPCINAT 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

NNNN

4.5 Interaction with other medicinal products and other forms of interaction

Sofosbuvir is a nucleotide prodrug. After oral administration of HEPCINAT, 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 HEPCINAT and thus are contraindicated with HEPCINAT (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 HEPCINAT. Co-administration with such medicinal products is not recommended with HEPCINAT (see section 4.4). Co-administration of HEPCINAT with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus HEPCINAT 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 HEPCINAT, 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 HEPCINAT 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 HEPCINAT 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 HEPCINAT
ANALEPTICS		
Modafinil	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of HEPCINAT with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of HEPCINAT. 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 HEPCINAT (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 HEPCINAT
ANTICONVULSANTS		
Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	HEPCINAT is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine	*Sofosbuvir* ↓ 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)	HEPCINAT is contraindicated with carbamazepine (see section 4.3).

	(Induction of P-gp)	
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of HEPCINAT with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of HEPCINAT. Such co-administration is not recommended (see section 4.4).
ANTIMYCOBACTERIALS		
Rifampicin[f] (600 mg single dose)	*Sofosbuvir* ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C_{min} (NA) *GS-331007* ↔ C_{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) C_{min} (NA) (Induction of P-gp)	HEPCINAT is contraindicated with rifampicin (see section 4.3).
Rifabutin	*Sofosbuvir* ↓ C_{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C_{min} (NA) *GS 331007* ↔ 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 HEPCINAT is required when concomitantly used with rifabutin.
Rifapentine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of S HEPCINAT with rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of HEPCINAT. Such co-administration is not recommended (see section 4.4).
HERBAL SUPPLEMENTS		
St. John's wort	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	HEPCINAT is contraindicated with St. John's wort (see section 4.3).
HCV ANITIVIRAL AGENTS: HCV PROTEASE INHIBITORS		

Boceprevir (BOC) Telaprevir (TPV)	Interaction not studied. *Expected:* ↑ Sofosbuvir (TPV) ↔ Sofosbuvir (BOC) ↔ GS-331007 (TPV or BOC)	No drug-drug interaction data exists regarding the co-administration of HEPCINAT with boceprevir or telaprevir.
NARCOTIC ANALGESICS		
Methadone[f] (Methadone maintenance therapy [30 to 130 mg/daily])	*R-methadone* ↔ C_{max} 0.99 (0.85, 1.16) ↔ AUC 1.01 (0.85, 1.21) ↔ C_{min} 0.94 (0.77, 1.14) *S-methadone* ↔ C_{max} 0.95 (0.79, 1.13) ↔ AUC 0.95 (0.77, 1.17) ↔ C_{min} 0.95 (0.74, 1.22) *Sofosbuvir* ↓ C_{max} 0.95[c] (0.68, 1.33) ↑ AUC 1.30[c] (1.00, 1.69) C_{min} (NA) *GS-331007* ↓ 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.
IMMUNOSUPPRESSANTS		
Ciclosporin[e] (600 mg single dose)	*Ciclosporin* ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) C_{min} (NA) *Sofosbuvir* ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) C_{min} (NA) *GS-331007*	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.

	↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20) C_{min} (NA)	
Tacrolimus[e] (5 mg single dose)	*Tacrolimus* ↓ C_{max} 0.73 (0.59, 0.90) ↔ AUC 1.09 (0.84, 1.40) C_{min} (NA) *Sofosbuvir* ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) C_{min} (NA) *GS-331007* ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13) C_{min} (NA)	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]	*Efavirenz* ↔ C_{max} 0.95 (0.85, 1.06) ↔ AUC 0.96 (0.91, 1.03) ↔ C_{min} 0.96 (0.93, 0.98) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ 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]	*Emtricitabine* ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 0.99 (0.94, 1.05)	No dose adjustment of sofosbuvir or emtricitabine is required when sofosbuvir and emtricitabine are used concomitantly.

	↔ C_{min} 1.04 (0.98, 1.11) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	
Tenofovir disoproxil[f] (245 mg once daily)[d]	*Tenofovir* ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ 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)	*Rilpivirine* ↔ C_{max} 1.05 (0.97, 1.15) ↔ AUC 1.06 (1.02, 1.09) ↔ C_{min} 0.99 (0.94, 1.04) *Sofosbuvir* ↑ C_{max} 1.21 (0.90, 1.62) ↔ AUC 1.09 (0.94, 1.27) C_{min} (NA) *GS-331007* ↔ C_{max} 1.06 (0.99, 1.14)	No dose adjustment of sofosbuvir or rilpivirine is required when sofosbuvir and rilpivirine are used concomitantly.

	↔ AUC 1.01 (0.97, 1.04) C_{min} (NA)	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Darunavir boosted with ritonavir[f] (800/100 mg once daily)	*Darunavir* ↔ C_{max} 0.97 (0.94, 1.01) ↔ AUC 0.97 (0.94, 1.00) ↔ C_{min} 0.86 (0.78, 0.96) *Sofosbuvir* ↑ C_{max} 1.45 (1.10, 1.92) ↑ AUC 1.34 (1.12, 1.59) C_{min} (NA) *GS-331007* ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30) C_{min} (NA)	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)	*Raltegravir* ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12) *Sofosbuvir* ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{min} (NA) *GS-331007* ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08) C_{min} (NA)	No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.
ORAL CONTRACEPTIVES		
Norgestimate/ethinyl estradiol	*Norgestromin* ↔ C_{max} 1.06 (0.93, 1.22)	No dose adjustment of norgestimate/ethinyl estradiol is required when sofosbuvir and norgestimate/ethinyl estradiol are used concomitantly.

	↔ AUC 1.05 (0.92, 1.20) C_{min} (NA) *Norgestrel* ↔ C_{max} 1.18 (0.99, 1.41) ↔ AUC 1.19 (0.98, 1.44) C_{min} (NA) *Ethinyl estradiol* ↔ C_{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C_{min} (NA)	

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 HEPCINAT 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 HEPCINAT 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, HEPCINAT should not be used during breast-feeding.

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

4.7 Effects on ability to drive and use machines

HEPCINAT 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).

HEPCINAT 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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
Infections and infestations:		
Common	nasopharyngitis	
Blood and lymphatic system disorders:		
Very common	haemoglobin decreased	anaemia, neutropenia, lymphocyte count decreased, platelet count decreased
Common	anaemia	
Metabolism and nutrition disorders:		
Very common	decreased appetite[d]	decreased appetite
Common		weight decreased

Psychiatric disorders:		
Very common	insomnia	insomnia
Common	depression	depression, anxiety, agitation
Nervous system disorders:		
Very common	headache	dizziness, headache
Common	disturbance in attention	migraine, memory impairment, disturbance in attention
Eye disorders:		
Common		vision blurred
Respiratory, thoracic and mediastinal disorders:		
Very common		dyspnoea, cough
Common	dyspnoea, dyspnoea exertional, cough	dyspnoea exertional
Gastrointestinal disorders:		
Very common	nausea	diarrhoea, nausea, vomiting
Common	abdominal discomfort, constipation, dyspepsia	constipation, dry mouth, gastroesophageal reflux
Hepatobiliary disorders:		
Very common	blood bilirubin increased	blood bilirubin increased
Skin and subcutaneous tissue disorders:		
Very common		rash, pruritus
Common	alopecia, dry skin, pruritus	alopecia, dry skin
Musculoskeletal and connective tissue disorders:		
Very common		arthralgia, myalgia
Common	arthralgia, back pain, muscle spasms, myalgia	back pain, muscle spasms
General disorders and administration site conditions:		
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 HEPCINAT 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 HEPCINAT in paediatric patients aged 3 years and above are based on data from 106 patients who were treated with HEPCINAT 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 HEPCINAT have been identified. The adverse reactions observed were generally consistent with those observed in clinical studies of HEPCINAT plus ribavirin in adults (see Table 6). Decreased appetite was observed as a very common adverse

drug reaction to HEPCINAT 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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system (see details below).

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions

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 HEPCINAT. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with HEPCINAT 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 μM, 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 μM. The mean ± SD EC_{50} of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.068 ± 0.024 μM for genotype 1a (n = 67), 0.11 ± 0.029 μM for genotype 1b (n = 29), 0.035 ± 0.018 μM for genotype 2 (n = 15) and 0.085 ± 0.034 μM 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 HEPCINAT 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/m^2 (range: 18 to 56 kg/m^2); 78% had baseline HCV RNA greater than 6 log_{10} 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 $\log_{10}$ IU/mL *versus* ≥6 $\log_{10}$ 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/m^2 (range: 17 to 52 kg/m^2); 57% had baseline HCV RNA levels greater than 6 $\log_{10}$ 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/m^2 (range: 18 to 53 kg/m^2); 70% had baseline HCV RNA levels greater than 6 $\log_{10}$ 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/m^2 (range: 19 to 44 kg/m^2); 73% had baseline HCV RNA levels greater than 6 log_{10} 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/m^2 (range: 17 to 44 kg/m^2); the mean baseline HCV RNA level was 6.4 log_{10} 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/mm^3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm^3. 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 ≥10^4 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)
		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 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 AUC_{0-24} 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 AUC_{0-24} 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 [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-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 [^{14}C]-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 [^{14}C]-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
				Dosed 1 hr Before Dialysis	Dosed 1 hr After Dialysis		
Sofosbuvir	1.6-fold↑	2.1-fold↑	2.7-fold↑	1.3-fold↑	1.6-fold↑	~2-fold↑	1.9-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 m^2), moderate (eGFR ≥30 and <50 mL/min/1.73 m^2), severe renal impairment (eGFR <30 mL/min/1.73 m^2) and 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 AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} 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
NNN

Film-coating
NNN

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Plastic bottle of 1 x 28’s

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

NATCO PHARMA LIMITED
PHARMA DIVISION KOTHUR - 509228
RANGAREDDY DISTRICT
TELANGANA STATE
INDIA

8. Marketing authorisation number(s)

TZ 19 H 0234

9. Date of first authorisation/renewal of the authorisation

August 02, 2019

10. Date of revision of the text

October 12, 2023