SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sofosbuvir/Velpatasvir Gilead® 200 mg/50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg sofosbuvir and 50 mg velpatasvir.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, oval-shaped, film-coated tablets of dimensions 14 mm x 7 mm, debossed on one side with “GSI” and “S/V” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sofosbuvir/Velpatasvir Gilead is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 3 years of age and older (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Sofosbuvir/Velpatasvir Gilead treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Posology

The recommended dose of Sofosbuvir/Velpatasvir Gilead in adults is one 400 mg/100 mg tablet, taken orally, once daily with or without food (see section 5.2).

The recommended dose of Sofosbuvir/Velpatasvir Gilead in paediatric patients aged 3 and above is based on weight as detailed in Table 3.

A granule formulation of Sofosbuvir/Velpatasvir Gilead is available for the treatment of chronic HCV infection in paediatric patients aged 3 years and above having difficulty swallowing film-coated tablets. For patients weighing < 17 kg, please refer to the Summary of Product Characteristics for Epclusa 200 mg/50 mg or 150 mg/37.5 mg granules.

Table 1: Recommended treatment and duration for adults regardless of HCV genotypes

Adult patient population[a]	**Treatment and duration**
Patients without cirrhosis and patients with compensated cirrhosis	Sofosbuvir/Velpatasvir Gilead for 12 weeks Addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis (see section 5.1.)
Patients with decompensated cirrhosis	Sofosbuvir/Velpatasvir Gilead + ribavirin for 12 weeks

a Includes patients co-infected with human immunodeficiency virus (HIV) and patients with recurrent HCV post-liver transplant (see section 4.4.).

When used in combination with ribavirin, refer also to the Summary of Product Characteristics of the medicinal product containing ribavirin.

The following dosing is recommended for adults where ribavirin is divided in two daily doses and given with food:

Table 2: Guidance for ribavirin dosing when administered with Sofosbuvir/Velpatasvir Gilead to adults with decompensated cirrhosis

Adult patient	**Ribavirin dose**
Child-Pugh-Turcotte (CPT) Class B cirrhosis pre-transplant	1,000 mg per day for patients < 75 kg and 1,200 mg for those weighing ≥ 75 kg
CPT Class C cirrhosis pre-transplant CPT Class B or C post-transplant	Starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg) if well tolerated. If the starting dose is not well tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels

If ribavirin is used in genotype 3 infected adult patients with compensated cirrhosis (pre- or post-transplant) the recommended dose of ribavirin is 1,000/1,200 mg (1,000 mg for adult patients weighing < 75 kg and 1,200 mg for adult patients weighing ≥ 75 kg).

For ribavirin dose modifications, refer to the Summary of Product Characteristics of the medicinal product containing ribavirin.

Table 3: Recommended treatment and duration for paediatric patients aged 3 to < 18 Years regardless of HCV genotype using Sofosbuvir/Velpatasvir Gilead Tablets*

Body weight (kg)	**Dosing of Sofosbuvir/Velpatasvir Gilead tablets**	**Sofosbuvir/Velpatasvir daily dose**	**Recommended treatment regimen**

≥ 30	one 400 mg/100 mg tablet once daily or two 200 mg/50 mg tablets once daily	400 mg/100 mg per day	Sofosbuvir/Velpatasvir Gilead for 12 weeks
17 to < 30	one 200 mg/50 mg tablet once daily	200 mg/50 mg per day	

* Sofosbuvir/Velpatasvir Gilead is also available as granules for paediatric patients with chronic HCV infection aged 3 years and above. For patients weighing < 17 kg, please refer to the Summary of Product Characteristics for Epclusa 200 mg/50 mg or 150 mg/37.5 mg granules.

Patients should be instructed that if vomiting occurs within 3 hours of dosing an additional tablet of Sofosbuvir/Velpatasvir Gilead should be taken. If vomiting occurs more than 3 hours after dosing, no further dose of Sofosbuvir/Velpatasvir Gilead is needed (see section 5.1).

If a dose of Sofosbuvir/Velpatasvir Gilead is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet 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 of Sofosbuvir/Velpatasvir Gilead at the usual time. Patients should be instructed not to take a double dose of Sofosbuvir/Velpatasvir Gilead.

Adult patients who have previously failed therapy with an NS5A-containing regimen
Sofosbuvir/Velpatasvir Gilead + ribavirin for 24 weeks may be considered (see section 4.4).
Elderly
No dose adjustment is warranted for elderly patients (see section 5.2).

Renal impairment
No dose adjustment of Sofosbuvir/Velpatasvir Gilead 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. Sofosbuvir/Velpatasvir Gilead 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 Sofosbuvir/Velpatasvir Gilead is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C) (see section 5.2). Safety and efficacy of Sofosbuvir/Velpatasvir Gilead have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis (see sections 4.4, 4.8 and 5.1).

Paediatric population
The safety and efficacy of Sofosbuvir/Velpatasvir Gilead in children aged less than 3 years have not been established. No data are available.

Method of administration

For oral use.

Patients should be instructed to swallow the tablet(s) whole with or without food (see section 5.2). Due to the bitter taste, it is recommended that film-coated tablets are not chewed or crushed.

4.3 Contraindications

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

Medicinal products that are strong P-glycoprotein (P-gp) and/or strong cytochrome P450 (CYP) inducers (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort).

4.4 Special warnings and precautions for use

Sofosbuvir/Velpatasvir Gilead should not be administered concurrently with other medicinal products containing sofosbuvir.

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 Sofosbuvir/Velpatasvir Gilead 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 Sofosbuvir/Velpatasvir Gilead.

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 medicinal products. 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.

Patients who have previously failed therapy with an NS5A-containing regimen

There are no clinical data to support the efficacy of sofosbuvir/velpatasvir for the treatment of patients who have failed treatment with a regimen containing another NS5A inhibitor. However, on the basis of NS5A resistance associated variants (RAVs) typically seen in patients who have failed therapy with other NS5A inhibitor containing regimens, the *in vitro* pharmacology of velpatasvir, and the outcomes of sofosbuvir/velpatasvir treatment in NS5A-naïve patients with baseline NS5A RAVs enrolled into the ASTRAL-studies, treatment with Sofosbuvir/Velpatasvir Gilead + RBV for 24 weeks can be considered for patients who have failed therapy on an NS5A-containing regimen and who are deemed at high risk for clinical disease progression and who do not have alternative treatment options.

Renal impairment

Safety data are limited in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and ESRD requiring haemodialysis. Sofosbuvir/Velpatasvir Gilead 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 Sofosbuvir/Velpatasvir Gilead is used in combination with ribavirin refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance < 50 mL/min (see section 5.2).

Use with moderate P-gp inducers and/or moderate CYP inducers

Medicinal products that are moderate P-gp and/or moderate CYP inducers (e.g. efavirenz, modafinil, oxcarbazepine or rifapentine) may decrease sofosbuvir or velpatasvir plasma concentrations leading to reduced therapeutic effect of Sofosbuvir/Velpatasvir Gilead. Co-administration of such medicinal products with Sofosbuvir/Velpatasvir Gilead is not recommended (see section 4.5).

Use with certain HIV antiretroviral regimens

Sofosbuvir/Velpatasvir Gilead has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of Sofosbuvir/Velpatasvir Gilead and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Sofosbuvir/Velpatasvir Gilead with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered,

particularly in patients at increased risk of renal dysfunction. Patients receiving Sofosbuvir/Velpatasvir Gilead concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Summary of Product Characteristics for recommendations on renal monitoring.

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 treatment modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

CPT Class C cirrhosis

Safety and efficacy of Sofosbuvir/Velpatasvir Gilead has not been assessed in patients with CPT Class C cirrhosis (see sections 4.8 and 5.1).

Liver transplant patients

The safety and efficacy of Sofosbuvir/Velpatasvir Gilead in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. Treatment with Sofosbuvir/Velpatasvir Gilead in accordance with the recommended posology (see section 4.2) should be guided by an assessment of the potential benefits and risks for the individual patient.

Excipients

This medicinal product 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

As Sofosbuvir/Velpatasvir Gilead contains sofosbuvir and velpatasvir, any interactions that have been identified with these active substances individually may occur with Sofosbuvir/Velpatasvir Gilead.

Potential for Sofosbuvir/Velpatasvir Gilead to affect other medicinal products

Velpatasvir is an inhibitor of drug transporter P-gp, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration of Sofosbuvir/Velpatasvir Gilead with medicinal products that are substrates of these transporters may increase the exposure of such medicinal products. See Table 4 for examples of interactions with sensitive substrates of P-gp (digoxin), BCRP (rosuvastatin), and OATP (pravastatin).

Potential for other medicinal products to affect Sofosbuvir/Velpatasvir Gilead

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP. Velpatasvir is also a substrate of drug transporter OATP1B. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8 and CYP3A4 was observed. Medicinal products that are strong inducers of P-gp and/or strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. carbamazepine, phenobarbital and phenytoin, rifampicin, rifabutin and St. John's wort) may decrease plasma concentrations of sofosbuvir or velpatasvir leading to reduced therapeutic effect of sofosbuvir/velpatasvir. The use of such medicinal products with Sofosbuvir/Velpatasvir Gilead is contraindicated (see section 4.3). Medicinal products that are moderate P-gp inducers and/or moderate CYP inducers (e.g. efavirenz, modafinil, oxcarbazepine or rifapentine) may decrease sofosbuvir or velpatasvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir/Velpatasvir Gilead. Co-administration with such medicinal products is not recommended with Sofosbuvir/Velpatasvir Gilead (see section 4.4). Co-administration with medicinal products that inhibit P-gp or BCRP may increase sofosbuvir or velpatasvir plasma concentrations. Medicinal products that inhibit OATP, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir. Clinically significant medicinal product interactions with Sofosbuvir/Velpatasvir Gilead mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Sofosbuvir/Velpatasvir Gilead may be co-administered with P-gp, BCRP, OATP and CYP inhibitors.

Patients treated with vitamin K antagonists

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

Impact of DAA therapy on medicinal products metabolized by the liver

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

Interactions between Sofosbuvir/Velpatasvir Gilead and other medicinal products

Table 4 provides a listing of established or potentially clinically significant medicinal product interactions (where 90% confidence interval [CI] of the geometric least-squares mean [GLSM] ratio were within "↔", extended above "↑", or extended below "↓" the predetermined interaction boundaries). The medicinal product interactions described are based on studies conducted with either sofosbuvir/velpatasvir or velpatasvir and sofosbuvir as individual agents, or are predicted medicinal product interactions that may occur with sofosbuvir/velpatasvir. The table is not all-inclusive.

Table 4: Interactions between Sofosbuvir/Velpatasvir Gilead and other medicinal products

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ACID REDUCING AGENTS					
					Velpatasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease the concentration of velpatasvir.
Antacids					
e.g. Aluminium or magnesium hydroxide; calcium carbonate (Increase in gastric pH)	Interaction not studied. *Expected.* ↔ Sofosbuvir ↓ Velpatasvir				It is recommended to separate antacid and Sofosbuvir/Velpatasvir Gilead administration by 4 hours.
H_2-receptor antagonists					
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose)[c] Famotidine dosed simultaneously with Sofosbuvir/Velpatasvir Gilead[d] Cimetidine[e] Nizatidine[e] Ranitidine[e] (Increase in gastric pH)	Sofosbuvir	↔	↔		H_2-receptor antagonists may be administered simultaneously with or staggered from Sofosbuvir/Velpatasvir Gilead at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
	Velpatasvir	↓ 0.80 (0.70, 0.91)	↓ 0.81 (0.71, 0.91)		
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose)[c] Famotidine dosed 12 hours prior to Sofosbuvir/Velpatasvir Gilead[d] (Increase in gastric pH)	Sofosbuvir	↓ 0.77 (0.68, 0.87)	↓ 0.80 (0.73, 0.88)		
	Velpatasvir	↔	↔		

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Proton pump inhibitors					
Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fasted)[c] Omeprazole dosed simultaneously with Sofosbuvir/Velpatasvir Gilead[d] Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e] (Increase in gastric pH)	Sofosbuvir	↓ 0.66 (0.55, 0.78)	↓ 0.71 (0.60, 0.83)		Co-administration with proton pump inhibitors is not recommended. If it is considered necessary to co-administer, then Sofosbuvir/Velpatasvir Gilead should be administered with food and taken 4 hours before proton pump inhibitor at max doses comparable to omeprazole 20 mg.
	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)		
Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fed)[c] Omeprazole dosed 4 hours after Sofosbuvir/Velpatasvir Gilead[d] (Increase in gastric pH)	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
	Velpatasvir	↓ 0.67 (0.58, 0.78)	↓ 0.74 (0.63, 0.86)		
ANTIARRHYTHMICS					
Amiodarone	Effect on amiodarone, velpatasvir, 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 Sofosbuvir/Velpatasvir Gilead (see sections 4.4 and 4.8).

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Digoxin	Interaction only studied with velpatasvir. *Expected:* ↔ Sofosbuvir				Co-administration of Sofosbuvir/Velpatasvir Gilead with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Sofosbuvir/Velpatasvir Gilead.
Digoxin (0.25 mg single dose)[f]/ velpatasvir (100 mg single dose) (Inhibition of P-gp)	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
	Observed: Digoxin	↑ 1.9 (1.7, 2.1)	↑ 1.3 (1.1, 1.6)		
ANTICOAGULANTS					
Dabigatran etexilate (Inhibition of P-gp)	Interaction not studied. *Expected:* ↑ Dabigatran ↔ Sofosbuvir ↔ Velpatasvir				Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Sofosbuvir/Velpatasvir Gilead. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
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 Sofosbuvir/Velpatasvir Gilead.
ANTICONVULSANTS					
Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir/Velpatasvir Gilead is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir				Sofosbuvir/Velpatasvir Gilead is contraindicated with carbamazepine (see section 4.3).
	Observed: Sofosbuvir	↓0.52 (0.43, 0.62)	↓ 0.52 (0.46, 0.59)		
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Sofosbuvir/Velpatasvir Gilead with oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir/Velpatasvir Gilead. Co-administration is not recommended (see section 4.4).

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ANTIFUNGALS					
Ketoconazole	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Sofosbuvir/Velpatasvir Gilead or ketoconazole is required.
Ketoconazole (200 mg twice daily)/ velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs) Itraconazole[e] Voriconazole[e] Posaconazole[e] Isavuconazole[e]	Effect on ketoconazole exposure not studied. *Expected:* ↔ Ketoconazole				
	Observed: Velpatasvir	↑ 1.3 (1.0, 1.6)	↑ 1.7 (1.4, 2.2)		
ANTIMYCOBACTERIALS					
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				Sofosbuvir/Velpatasvir Gilead is contraindicated with rifampicin (see section 4.3).
	Observed: Sofosbuvir	↓ 0.23 (0.19, 0.29)	↓ 0.28 (0.24, 0.32)		
Rifampicin (600 mg once daily)/ velpatasvir (100 mg single dose) (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				
	Observed: Velpatasvir	↓ 0.29 (0.23, 0.37)	↓ 0.18 (0.15, 0.22)		
Rifabutin (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir				Sofosbuvir/Velpatasvir Gilead is contraindicated with rifabutin (see section 4.3).
	Observed: Sofosbuvir	↓ 0.64 (0.53, 0.77)	↓ 0.76 (0.63, 0.91)		

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Sofosbuvir/Velpatasvir Gilead with rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir/Velpatasvir Gilead. Co-administration is not recommended (see section 4.4).
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate	Sofosbuvir/Velpatasvir Gilead has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and C_{max}) was around 40-80% during co-treatment with Sofosbuvir/Velpatasvir Gilead and tenofovir disoproxil fumarate/emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil fumarate and Sofosbuvir/Velpatasvir Gilead concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil fumarate. Refer to the tenofovir disoproxil fumarate-containing product's Summary of Product Characteristics for recommendations on renal monitoring (see section 4.4).				
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Efavirenz	↔	↔	↔	Co-administration of Sofosbuvir/Velpatasvir Gilead with efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is expected to decrease the concentration of velpatasvir. Co-administration of Sofosbuvir/Velpatasvir Gilead with efavirenz-containing regimens is not recommended (see section 4.4).
	Sofosbuvir	↑ 1.4 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓ 0.43 (0.36, 0.52)	
Emtricitabine/ **rilpivirine**/ tenofovir disoproxil fumarate (200/ 25/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Rilpivirine	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Atazanavir	↔	↔	↑ 1.4 (1.2, 1.6)	No dose adjustment of Sofosbuvir/Velpatasvir Gilead, atazanavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔		↑ 1.3 (1.5, 1.4)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↑ 1.6 (1.4, 1.7)	↑ 2.4 (2.2, 2.6)	↑ 4.0 (3.6, 4.5)	
Darunavir boosted with ritonavir (800/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Darunavir	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead, darunavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.62 (0.54, 0.71)	↓ 0.72 (0.66, 0.80)		
	Velpatasvir	↓ 0.76 (0.65, 0.89)	↔	↔	
Lopinavir boosted with ritonavir (4x200 mg/ 50 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Lopinavir	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead, lopinavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.59 (0.49 0.71)	↓ 0.7 (0.6, 0.8)		
	Velpatasvir	↓ 0.70 (0.59, 0.83)	↔	↑ 1.6 (1.4, 1.9)	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily)[g] + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Raltegravir	↔	↔	↓ 0.79 (0.42, 1.5)	No dose adjustment of Sofosbuvir/Velpatasvir Gilead, raltegravir or emtricitabine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate (150/ 150/ 200/ 10 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Elvitegravir	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead or elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate is required.
	Cobicistat	↔	↔	↑ 2.0 (1.7, 2.5)	
	Tenofovir alafenamide	↔	↔		
	Sofosbuvir	↔	↑ 1.4 (1.2, 1.5)		
	Velpatasvir	↑ 1.3 (1.2, 1.5)	↑ 1.5 (1.4, 1.7)	↑ 1.6 (1.4, 1.8)	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150/ 150/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Elvitegravir	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead or elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate is required.
	Cobicistat	↔	↔	↑ 1.7 (1.5, 1.9)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↑ 1.4 (1.2, 1.5)	
Dolutegravir (50 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)	Dolutegravir	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead or dolutegravir is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir/Velpatasvir Gilead is contraindicated with St. John's wort (see section 4.3).

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin (40 mg single dose) + sofosbuvir / velpatasvir (400/ 100 mg once daily)[d]	*Observed:* Atorvastatin	↑ 1.7 (1.5, 1.9)	↑ 1.5 (1.5, 1.6)		No dose adjustment of Sofosbuvir/Velpatasvir Gilead or atorvastatin is required.
Rosuvastatin	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				Co-administration of Sofosbuvir/Velpatasvir Gilead with rosuvastatin increases the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin, at a dose that does not exceed 10 mg, may be administered with Sofosbuvir/Velpatasvir Gilead.
Rosuvastatin (10 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B and BCRP)	*Observed:* Rosuvastatin	↑ 2.6 (2.3, 2.9)	↑ 2.7 (2.5, 2.9)		
	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
Pravastatin	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Sofosbuvir/Velpatasvir Gilead or pravastatin is required.
Pravastatin (40 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B)	*Observed:* Pravastatin	↑ 1.3 (1.1, 1.5)	↑ 1.4 (1.2, 1.5)		
	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
Other statins	*Expected:* ↑ Statins				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with Sofosbuvir/Velpatasvir Gilead, careful monitoring for statin adverse reactions should be undertaken and a reduced dose of statins should be considered if required.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]**				**Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead**
	Active	**C_{max}**	**AUC**	**C_{min}**	
NARCOTIC ANALGESICS					
Methadone (Methadone maintenance therapy [30 to 130 mg daily])/ sofosbuvir (400 mg once daily)[d]	R-methadone	↔	↔	↔	No dose adjustment of Sofosbuvir/Velpatasvir Gilead or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with sofosbuvir *Expected:* ↔ Velpatasvir				
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose)[f]	Ciclosporin	↔	↔		No dose adjustment of Sofosbuvir/Velpatasvir Gilead or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
	Sofosbuvir	↑ 2.5 (1.9, 3.5)	↑ 4.5 (3.3, 6.3)		
Ciclosporin (600 mg single dose)[f]/ velpatasvir (100 mg single dose)[d]	Ciclosporin	↔	↓ 0.88 (0.78, 1.0)		
	Velpatasvir	↑ 1.6 (1.2, 2.0)	↑ 2.0 (1.5, 2.7)		
Tacrolimus (5 mg single dose)[f]/ sofosbuvir (400 mg single dose)[d]	Tacrolimus	↓ 0.73 (0.59, 0.90)	↑ 1.1 (0.84, 1.4)		No dose adjustment of Sofosbuvir/Velpatasvir Gilead or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
	Sofosbuvir	↓ 0.97 (0.65, 1.4)	↑ 1.1 (0.81, 1.6)		
Tacrolimus	Effect on velpatasvir exposure not studied. *Expected:* ↔ Velpatasvir				

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]				Recommendation concerning co-administration with Sofosbuvir/Velpatasvir Gilead
	Active	C_{max}	AUC	C_{min}	
ORAL CONTRACEPTIVES					
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d]	Norel-gestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	Norgestrel	↔	↑ 1.2 (0.98, 1.5)	↑ 1.2 (1.0, 1.5)	
	Ethinyl estradiol	↔	↔	↔	
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ velpatasvir (100 mg once daily)[d]	Norel-gestromin	↔	↔	↔	
	Norgestrel	↔	↔	↔	
	Ethinyl estradiol	↑ 1.4 (1.2, 1.7)	↔	↓ 0.83 (0.65, 1.1)	

a Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.
b All interaction studies conducted in healthy volunteers.
c Administered as Sofosbuvir/Velpatasvir Gilead.
d Lack of pharmacokinetics interaction bounds 70-143%.
e These are medicinal products within class where similar interactions could be predicted.
f Bioequivalence/Equivalence boundary 80-125%.
g Lack of pharmacokinetics interaction bounds 50-200%.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir, velpatasvir or Sofosbuvir/Velpatasvir Gilead in pregnant women.

Sofosbuvir

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

Velpatasvir

Animal studies have shown a possible link to reproductive toxicity (see section 5.3).

As a precautionary measure, Sofosbuvir/Velpatasvir Gilead use is not recommended during pregnancy.

Breast-feeding

It is unknown whether sofosbuvir, metabolites of sofosbuvir or velpatasvir are excreted in human milk.

Available pharmacokinetic data in animals have shown excretion of velpatasvir and metabolites of sofosbuvir in milk.

A risk to the newborns/infants cannot be excluded. Therefore, Sofosbuvir/Velpatasvir Gilead should not be used during breast-feeding.

Fertility

No human data on the effect of Sofosbuvir/Velpatasvir Gilead on fertility are available. Animal studies do not indicate harmful effects of sofosbuvir or velpatasvir on fertility.

If ribavirin is co-administered with Sofosbuvir/Velpatasvir Gilead, refer to the Summary of Product Characterisitics for ribavirin for detailed recommendations regarding pregnancy, contraception, and breast-feeding.

4.7 Effects on ability to drive and use machines

Sofosbuvir/Velpatasvir Gilead has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Sofosbuvir/Velpatasvir Gilead has been determined in pooled Phase 3 clinical studies of patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and in the postmarketing setting. No adverse drug reactions to Sofosbuvir/Velpatasvir Gilead were identified from clinical trials. In the postmarketing setting, cases of severe bradycardia and heart block have been observed when SOF-containing products are used in combination with amiodarone, and HBV reactivation has been observed in patients coinfected with HCV/HBV following treatment with DAAs (see section 4.4).

Tabulated summary of adverse reactions

Assessment of adverse reactions for Sofosbuvir/Velpatasvir Gilead is based on safety data from clinical studies and postmarketing experience. All adverse reactions are presented in Table 5. The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000) or very rare (< 1/10,000).

Table 5: Adverse drug reactions identified with Sofosbuvir/Velpatasvir Gilead

Frequency	**Adverse drug reaction**
Gastrointestinal disorders	
Very common	vomiting[a]
Skin and subcutaneous tissue disorders:	
Common	rash[b]
Uncommon	angioedema[b]

a. Adverse reaction was observed in paediatric patients aged 3 to < 6 years
b. Adverse reaction identified through post-marketing surveillance for sofosbuvir/velpatasvir-containing products

Description of selected adverse reactions

Cardiac arrhythmias
Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens 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

Paediatric population

The adverse reactions observed were consistent with those observed in clinical studies of Sofosbuvir/Velpatasvir Gilead in adults. The safety assessment of Sofosbuvir/Velpatasvir Gilead in paediatric patients aged 3 years and older is based on data from a Phase 2, open-label clinical study (study 1143) that enrolled 216 patients who were treated with sofosbuvir/velpatasvir for 12 weeks.

Other special populations

Patients with decompensated cirrhosis

The safety profile of Sofosbuvir/Velpatasvir Gilead has been evaluated in one open-label study in which patients with CPT Class B cirrhosis received Sofosbuvir/Velpatasvir Gilead for 12 weeks (n = 90), Sofosbuvir/Velpatasvir Gilead + RBV for 12 weeks (n = 87) or Sofosbuvir/Velpatasvir Gilead for 24 weeks (n = 90). The adverse events observed were consistent with expected clinical sequelae of decompensated liver disease, or the known toxicity profile of ribavirin for patients receiving Sofosbuvir/Velpatasvir Gilead in combination with ribavirin.

Among the 87 patients who were treated with Sofosbuvir/Velpatasvir Gilead + RBV for 12 weeks, decreases in haemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were experienced by 23% and 7% patients, respectively. Ribavirin was discontinued in 15% of patients treated with Sofosbuvir/Velpatasvir Gilead + RBV for 12 weeks due to adverse events.

Patients with renal impairment

The safety of Sofosbuvir/Velpatasvir Gilead has been evaluated in a 12-week non-controlled study including 59 subjects with ESRD requiring dialysis (Study 4062). In this setting, exposure of sofosbuvir metabolite GS-331007 was 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.

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 Yellow Card Scheme,
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The highest documented doses of sofosbuvir and velpatasvir were a single dose of 1,200 mg and a single dose of 500 mg, respectively. In these healthy adult volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in

frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

No specific antidote is available for overdose with Sofosbuvir/Velpatasvir Gilead. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir/Velpatasvir Gilead 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 the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Haemodialysis is unlikely to result in significant removal of velpatasvir, since velpatasvir is highly bound to plasma protein

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; Direct acting antiviral, ATC code: J05AP55

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 analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Velpatasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. *In vitro* resistance selection and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Antiviral activity

The 50% effective concentration (EC_{50}) values of sofosbuvir and velpatasvir against full-length or chimeric replicons encoding NS5B and NS5A sequences from the laboratory strains are presented in Table 6. The EC_{50} values of sofosbuvir and velpatasvir against clinical isolates are presented in Table 7.

Table 6: Activity of sofosbuvir and velpatasvir against full-length or chimeric laboratory replicons

Replicon genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]
1a	40	0.014
1b	110	0.016
2a	50	0.005-0.016[c]
2b	15[b]	0.002-0.006[c]
3a	50	0.004
4a	40	0.009
4d	NA	0.004
5a	15[b]	0.021-0.054[d]
6a	14[b]	0.006-0.009
6e	NA	0.130[d]

NA = Not available

a Mean value from multiple experiments of same laboratory replicon.

b Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing.

c Data from various strains of full length NS5A replicons or chimeric NS5A replicons carrying full-length NS5A genes that contain L31 or M31 polymorphisms.

d Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

Table 7: Activity of sofosbuvir and velpatasvir against transient replicons containing NS5A or NS5B from clinical isolates

Replicon genotype	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates	
	Number of clinical isolates	Median sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median velpatasvir EC_{50}, nM (range)
1a	67	62 (29-128)	23	0.019 (0.011-0.078)
1b	29	102 (45-170)	34	0.012 (0.005-0.500)
2a	15	29 (14-81)	8	0.011 (0.006-0.364)
2b	NA	NA	16	0.002 (0.0003-0.007)
3a	106	81 (24-181)	38	0.005 (0.002-1.871)
4a	NA	NA	5	0.002 (0.001-0.004)
4d	NA	NA	10	0.007 (0.004-0.011)
4r	NA	NA	7	0.003 (0.002-0.006)
5a	NA	NA	42	0.005 (0.001-0.019)
6a	NA	NA	26	0.007 (0.0005-0.113)
6e	NA	NA	15	0.024 (0.005-0.433)

NA = Not available

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir but reduced the anti-HCV activity of velpatasvir by 13-fold against genotype 1a HCV replicons.

Evaluation of sofosbuvir in combination with velpatasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

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 genotype 1 to 6 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, the ability of the active triphosphate of sofosbuvir (GS-461203) to inhibit recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution was reduced compared to its ability to inhibit wild-type recombinant NS5B polymerase, as indicated by a 8.5- to 24-fold increase in the 50% inhibitory concentration (IC_{50}).

In vitro selection of HCV replicons with reduced susceptibility to velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92 and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V and Y93H. Site-directed mutagenesis of known NS5A RAVs showed that substitutions conferring a > 100-fold reduction in velpatasvir susceptibility are M28G, A92K and Y93H/N/R/W in genotype 1a, A92K in genotype 1b, C92T and Y93H/N in genotype 2b, Y93H in genotype 3, and L31V and P32A/L/Q/R in genotype 6. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a > 100-fold reduction in velpatasvir susceptibility. Combinations of these variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

In clinical studies
Studies in patients without cirrhosis and patients with compensated cirrhosis
In a pooled analysis of patients without cirrhosis or with compensated cirrhosis who received Sofosbuvir/Velpatasvir Gilead for 12 weeks in three Phase 3 studies, 12 patients (2 with genotype 1 and 10 with genotype 3) qualified for resistance analysis due to virologic failure. One additional patient with genotype 3 HCV infection at baseline was reinfected with genotype 1a HCV at virologic failure and was excluded from the virological analysis. No patients with genotype 2, 4, 5, or 6 HCV infection experienced virologic failure.

Of the 2 genotype 1 virologic failure patients, one patient had virus with emergent NS5A RAV Y93N and the other patient had virus with emergent NS5A RAVs L31I/V and Y93H at virologic failure. Both patients had virus at baseline harbouring NS5A RAVs. No NS5B nucleoside inhibitor (NI) RAVs were observed at failure in the 2 patients.

Of the 10 genotype 3 virologic failure patients, Y93H was observed in all 10 patients at failure (6 had Y93H emerge post-treatment and 4 patients had Y93H at baseline and post-treatment). No NS5B NI RAVs were observed at failure in the 10 patients.

Studies in patients with decompensated cirrhosis
In one Phase 3 study in patients with decompensated cirrhosis who received Sofosbuvir/Velpatasvir Gilead + RBV for 12 weeks, 3 patients (1 with genotype 1 and 2 with genotype 3) qualified for resistance analysis due to virologic failure. No patients with genotype 2 or 4 HCV infection in the Sofosbuvir/Velpatasvir Gilead + RBV 12 weeks group experienced virologic failure.

The 1 virologic failure patient with genotype 1 HCV had no NS5A or NS5B RAVs at failure.

Of the 2 genotype 3 virologic failure patients, one had NS5A RAV Y93H emerge at failure. Another patient had virus with Y93H at baseline and virologic failure and also developed low levels (< 5%) of NS5B NI RAVs N142T and E237G at failure. Pharmacokinetic data from this patient was consistent with non-adherence to treatment.

In this study, 2 patients treated with Sofosbuvir/Velpatasvir Gilead for 12 or 24 weeks without ribavirin had emergent NS5B S282T at low levels (< 5%) along with L159F.

Effect of baseline HCV resistance-associated variants on treatment outcome

Studies in patients without cirrhosis and patients with compensated cirrhosis
Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients without cirrhosis or with compensated cirrhosis in three Phase 3 clinical studies (ASTRAL-1, ASTRAL-2 and ASTRAL-3). Of the 1,035 patients treated with sofosbuvir/velpatasvir in the three Phase 3 clinical studies, 1,023 patients were included in the analysis of NS5A RAVs; 7 patients were excluded as they neither achieved sustained virologic response (SVR12) nor had virologic failure and 5 additional patients were excluded as NS5A gene sequencing failed. In the pooled analysis of the Phase 3 studies, 380/1,023 (37%) patients' virus had baseline NS5A RAVs. Genotype 2, 4, and 6 HCV-infected patients had a higher prevalence of NS5A RAVs (70%, 63% and 52%, respectively) compared to genotype 1 (23%), genotype 3 (16%), and genotype 5 (18%) HCV-infected patients.

Baseline RAVs had no relevant impact on SVR12 rates in patients infected with genotype 1, 2, 4, 5 and 6 HCV, as summarised in Table 8. Genotype 3 infected patients with the NS5A RAV Y93H at baseline had a lower SVR12 rate than patients without Y93H after treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks, as summarised in Table 9. In the ASTRAL-3 study, the Y93H RAV was detected at baseline in 9% of patients treated with Sofosbuvir/Velpatasvir Gilead.

Table 8: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (studies ASTRAL-1, ASTRAL-2 and ASTRAL-3)

	Sofosbuvir/Velpatasvir Gilead 12 weeks			
	Genotype 1	**Genotype 3**	**Genotypes 2, 4, 5 or 6**	**Total**
With any baseline NS5A RAVs	97% (73/75)	88% (38/43)	100% (262/262)	98% (373/380)
Without baseline NS5A RAVs	100% (251/251)	97% (225/231)	100% (161/161)	99% (637/643)

Table 9: SVR12 in patients with and without baseline Y93H, 1% Cut-off (Resistance Analysis Population Set) ASTRAL 3

	Sofosbuvir/Velpatasvir Gilead 12 Weeks		
	All Subjects (n = 274)	**Cirrhotic (n = 80)**	**Non-Cirrhotic (n = 197)**
Overall	95.3% (263/274)	91.3% (73/80)	97.9% (190/194)
95% CI	92.9% to 98.0%	82.8% to 96.4%	92.8% to 98.6%
SVR with Y93H	84.0% (21/25)	50.0% (2/4)	90.5% (19/21)
95% CI	63.9% to 95.5%	6.8% to 93.2%	69.6% to 98.8%
SVR without Y93H	96.4% (242/249)	93.4% (71/76)	98.8% (171/173)
95% CI	94.3% to 98.9%	85.3% to 97.8%	95.9% to 99.9%

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 studies. SVR12 was achieved in all 77 patients who had baseline NS5B NI RAVs including N142T, L159F, E/N237G, C/M289L/I, L320F/I/V, V321A/I, and S282G+V321I.

Studies in patients with decompensated cirrhosis (CPT Class B)
Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients with decompensated cirrhosis in one Phase 3 study (ASTRAL-4). Of the 87 patients treated with Sofosbuvir/Velpatasvir Gilead + RBV, 85 patients were included in the analysis of NS5A RAVs; 2 patients were excluded as they neither achieved SVR12 nor had virologic failure. Among the patients who received treatment with Sofosbuvir/Velpatasvir Gilead + RBV for 12 weeks, 29% (25/85) of patients had baseline virus with NS5A RAVs: 29% (19/66), 75% (3/4), 15% (2/13), and 50% (1/2) for patients with genotype 1, 2, 3 and 4 HCV, respectively.

SVR12 in patients with or without baseline NS5A RAVs in the Sofosbuvir/Velpatasvir Gilead + RBV 12 week group for this study is shown in Table 10.

Table 10: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (study ASTRAL-4)

	Sofosbuvir/Velpatasvir Gilead + RBV 12 weeks			
	Genotype 1	**Genotype 3**	**Genotypes 2 or 4**	**Total**
With any baseline NS5A RAVs	100% (19/19)	50% (1/2)	100% (4/4)	96% (24/25)
Without baseline NS5A RAVs	98% (46/47)	91% (10/11)	100% (2/2)	98% (58/60)

The single genotype 3 patient who had baseline NS5A RAVs and failed to achieve SVR12 had NS5A substitution Y93H at baseline; pharmacokinetic data from this patient was consistent with non-adherence to treatment.

Three patients in the Sofosbuvir/Velpatasvir Gilead + RBV 12 week group had baseline NS5B NI RAVs (N142T and L159F) and all three patients achieved SVR12.

Paediatric population

The presence of NS5A and NS5B RAVs did not impact treatment outcome; all patients with baseline NS5A (n=29) or NS5B NI (n=6) RAVs achieved SVR following 12 weeks treatment with Sofosbuvir/Velpatasvir Gilead.

Cross-resistance

In vitro data suggests that the majority of NS5A RAVs that confer resistance to ledipasvir and daclatasvir remained susceptible to velpatasvir. Velpatasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all velpatasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and velpatasvir were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of Sofosbuvir/Velpatasvir Gilead has not been assessed in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Clinical efficacy and safety

The efficacy of Sofosbuvir/Velpatasvir Gilead was evaluated in three Phase 3 studies in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis, one Phase 3 study in patients with genotype 1 to 6 HCV infection with decompensated cirrhosis, one Phase 3 study in HCV/HIV-1 co-infected patients with genotype 1 to 6 HCV infection and one Phase 2 study in patients with HCV infection and ESRD requiring dialysis, as summarised in Table 11.

Table 11: Studies conducted with Sofosbuvir/Velpatasvir Gilead in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection

Study	**Population**	**Study arms (Number of patients treated)**
ASTRAL-1	Genotype 1, 2, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir/Velpatasvir Gilead 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir/Velpatasvir Gilead 12 weeks (134) SOF+RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir/Velpatasvir Gilead 12 weeks (277) SOF+RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, with CPT Class B decompensated cirrhosis	Sofosbuvir/Velpatasvir Gilead 12 weeks (90) Sofosbuvir/Velpatasvir Gilead + RBV 12 weeks (87) Sofosbuvir/Velpatasvir Gilead 24 weeks (90)
ASTRAL-5	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis, with HCV/HIV-1 co-infection	Sofosbuvir/Velpatasvir Gilead 12 weeks (106)
GS-US-342-4062	TN and TE with or without cirrhosis, with ESRD requiring dialysis	Sofosbuvir/Velpatasvir Gilead 12 weeks (59)

TN = treatment-naïve patients; TE = treatment-experienced patients (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor)

The ribavirin dose was weight-based (1,000 mg daily administered in two divided doses for patients < 75 kg and 1,200 mg for those ≥ 75 kg) and administered in two divided doses when used in combination with sofosbuvir in the ASTRAL-2 and ASTRAL-3 studies or in combination with Sofosbuvir/Velpatasvir Gilead in the ASTRAL-4 study. Ribavirin dose adjustments were performed according to the ribavirin prescribing information. Serum HCV RNA values were measured during the clinical studies using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL. Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate.

Clinical studies in patients without cirrhosis and patients with compensated cirrhosis
Genotype 1, 2, 4, 5 and 6 HCV-infected adults – ASTRAL-1 (study 1138)
ASTRAL-1 was a randomised, double-blind, placebo-controlled study that evaluated 12 weeks of treatment with Sofosbuvir/Velpatasvir Gilead compared with 12 weeks of placebo in patients with genotype 1, 2, 4, 5, or 6 HCV infection. Patients with genotype 1, 2, 4 or 6 HCV infection were randomised in a 5:1 ratio to treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks or placebo for 12 weeks. Patients with genotype 5 HCV infection were enrolled to the Sofosbuvir/Velpatasvir Gilead group. Randomisation was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis.

Demographics and baseline characteristics were balanced between the Sofosbuvir/Velpatasvir Gilead and placebo group. Of the 740 treated patients, the median age was 56 years (range: 18 to 82); 60% of the patients were male; 79% were White, 9% were Black; 21% had a baseline body mass index of at least 30 kg/m^2; the proportions of patients with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5% and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels of at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced.

Table 12 presents the SVR12 for the ASTRAL-1 study by HCV genotypes. No patients in the placebo group achieved SVR12.

Table 12: SVR12 in study ASTRAL-1 by HCV genotype

	Sofosbuvir/Velpatasvir Gilead 12 weeks (n = 624)							
	Total (all GTs) (n = 624)	**GT-1**			**GT-2 (n = 104)**	**GT-4 (n = 116)**	**GT-5 (n = 35)**	**GT-6 (n = 41)**
		GT-1a (n = 210)	**GT-1b (n = 118)**	**Total (n = 328)**				
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
Outcome for patients without SVR12								
On-treatment virologic failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[a]	< 1% (2/623)	< 1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Other[b]	1% (4/624)	1% (3/210)	0/118	1% (3/328)	0/104	0/116	3% (1/35)	0/41

GT = genotype
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.

Genotype 2 HCV-infected adults – ASTRAL-2 (study 1139)
ASTRAL-2 was a randomised, open-label study that evaluated 12 weeks of treatment with Sofosbuvir/Velpatasvir Gilead compared with 12 weeks of treatment with SOF+RBV in patients with genotype 2 HCV infection. Patients were randomised in a 1:1 ratio to treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks or SOF+RBV for 12 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve *versus* treatment-experienced).

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 266 treated patients, the median age was 58 years (range: 23 to 81); 59% of the patients were male; 88% were White, 7% were Black; 33% had a baseline body mass index of at least 30 kg/m^2; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels of at least 800,000 IU/mL; 14% had compensated cirrhosis and 15% were treatment-experienced.

Table 13 presents the SVR12 for the ASTRAL-2 study.

Table 13: SVR12 in study ASTRAL-2 (HCV genotype 2)

	Sofosbuvir/Velpatasvir Gilead 12 weeks (n = 134)	**SOF+RBV 12 weeks (n = 132)**
SVR12	99% (133/134)	94% (124/132)
Outcome for patients without SVR12		
On-treatment virologic failure	0/134	0/132
Relapse[a]	0/133	5% (6/132)
Other[b]	1% (1/134)	2% (2/132)

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.

Treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks demonstrated the statistical superiority ($p = 0.018$) over treatment with SOF+RBV for 12 weeks (treatment difference +5.2%; 95% confidence interval: +0.2% to +10.3%).

Genotype 3 HCV-infected adults – ASTRAL-3 (study 1140)
ASTRAL-3 was a randomised, open-label study that evaluated 12 weeks of treatment with Sofosbuvir/Velpatasvir Gilead compared with 24 weeks of treatment with SOF+RBV in patients with genotype 3 HCV infection. Patients were randomised in a 1:1 ratio to treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks or SOF+RBV for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve *versus* treatment-experienced).

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 552 treated patients, the median age was 52 years (range: 19 to 76); 62% of the patients were male; 89% were White, 9% were Asian; 1% were Black; 20% had a baseline body mass index of at least 30 kg/m^2; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels of at least 800,000 IU/mL, 30% had compensated cirrhosis and 26% were treatment-experienced.

Table 14 presents the SVR12 for the ASTRAL-3 study.

Table 14: SVR12 in study ASTRAL-3 (HCV genotype 3)

	Sofosbuvir/Velpatasvir Gilead 12 weeks (n = 277)	**SOF+RBV 24 weeks (n = 275)**
SVR12	95% (264/277)	80% (221/275)
Outcome for patients without SVR12		
On-treatment virologic failure	0/277	< 1% (1/275)
Relapse[a]	4% (11/276)	14% (38/272)
Other[b]	1% (2/277)	5% (15/275)

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.

Treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks demonstrated the statistical superiority ($p < 0.001$) compared to treatment with SOF+RBV for 24 weeks (treatment difference +14.8%; 95% confidence interval: +9.6% to +20.0%).

SVR12 for selected subgroups are presented in Table 15.

Table 15: SVR12 for selected subgroups in study ASTRAL-3 (HCV genotype 3)

	Sofosbuvir/Velpatasvir Gilead 12 weeks		**SOF+RBV 24 weeks[a]**	
SVR12	Treatment-naïve (n = 206)	Treatment-experienced (n = 71)	Treatment-naïve (n = 201)	Treatment-experienced (n = 69)
Without cirrhosis	98% (160/163)	91% (31/34)	90% (141/156)	71% (22/31)
With cirrhosis	93% (40/43)	89% (33/37)	73% (33/45)	58% (22/38)

a Five patients with missing cirrhosis status in the SOF+RBV 24 week group were excluded from this subgroup analysis.

Clinical studies in patients with decompensated cirrhosis – ASTRAL-4 (study 1137)
ASTRAL-4 was a randomised, open-label study in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and CPT Class B cirrhosis. Patients were randomised in a 1:1:1 ratio to treatment with Sofosbuvir/Velpatasvir Gilead for 12 weeks, Sofosbuvir/Velpatasvir Gilead + RBV for 12 weeks or Sofosbuvir/Velpatasvir Gilead for 24 weeks. Randomisation was stratified by HCV genotype (1, 2, 3, 4, 5, 6 and indeterminate).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated patients, the median age was 59 years (range: 40 to 73); 70% of the patients were male; 90% were White, 6% were Black; 42% had a baseline body mass index of at least 30 kg/m^2. The proportions of patients with genotype 1, 2, 3, 4 or 6 HCV were 78%, 4%, 15%, 3%, and < 1% (1 patient), respectively. No patients with genotype 5 HCV infection were enrolled. 76% of the patients had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels of at least 800,000 IU/mL, 55% were treatment-experienced; 90% and 95% of patients had CPT Class B cirrhosis and Model for End Stage Liver Disease (MELD) score ≤ 15 at baseline, respectively.

Table 16 presents the SVR12 for the ASTRAL-4 study by HCV genotype.

Table 16: SVR12 in study ASTRAL-4 by HCV genotype

	Sofosbuvir/Velpatasvir Gilead 12 weeks (n = 90)	Sofosbuvir/Velpatasvir Gilead + RBV 12 weeks (n = 87)	Sofosbuvir/Velpatasvir Gilead 24 weeks (n = 90)
Overall SVR12	83% (75/90)	94% (82/87)	86% (77/90)
Genotype 1	88% (60/68)	96% (65/68)	92% (65/71)
Genotype 1a	88% (44/50)	94% (51/54)	93% (51/55)
Genotype 1b	89% (16/18)	100% (14/14)	88% (14/16)
Genotype 3	50% (7/14)	85% (11/13)	50% (6/12)
Genotype 2, 4 and 6	100% (8/8)[a]	100% (6/6)[b]	86% (6/7)[c]

a n = 4 for genotype 2 and n = 4 for genotype 4.
b n = 4 for genotype 2 and n = 2 for genotype 4.
c n = 4 for genotype 2, n = 2 for genotype 4 and n = 1 for genotype 6.

Table 17 presents the virologic outcome for patients with genotype 1 or 3 HCV infection in the ASTRAL-4 study.

No patients with genotype 2, 4 or 6 HCV infection experienced virologic failure.

Table 17: Virologic outcome for patients with genotype 1 and 3 HCV infection in study ASTRAL-4

	Sofosbuvir/Velpatasvir Gilead 12 weeks	Sofosbuvir/Velpatasvir Gilead + RBV 12 weeks	Sofosbuvir/Velpatasvir Gilead 24 weeks
Virologic failure (relapse and on-treatment failure)			
Genotype 1[a]	7% (5/68)	1% (1/68)	4% (3/71)
Genotype 1a	6% (3/50)	2% (1/54)	4% (2/55)
Genotype 1b	11% (2/18)	0% (0/14)	6% (1/16)
Genotype 3	43% (6/14)	15% (2[b]/13)	42% (5[c]/12)
Other[d]	5% (4/82)	2% (2/81)	5% (4/83)

a No patients with genotype 1 HCV had on-treatment virologic failure.
b One patient had on-treatment virologic failure; pharmacokinetic data from this patient was consistent with non-adherence to treatment.
c One patient had on-treatment virologic failure.
d Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Changes in the parameters found in the CPT score system in patients achieving SVR12 in ASTRAL-4 (all 3 regimens) are shown in Table 18.

Table 18: Changes in CPT score parameters from baseline to week 12 and 24 post-treatment in patients achieving SVR12, ASTRAL-4

	Albumin	**Bilirubin**	**INR**	**Ascites**	**Encephalopathy**
Post-treatment Week 12 (N = 236), % (n/N)					
Decreased score (Improvement)	34.5% (79/229)	17.9% (41/229)	2.2% (5/229)	7.9% (18/229)	5.2% (12/229)
No change	60.3% (138/229)	76.4% (175/229)	96.5% (221/229)	89.1% (204/229)	91.3% (209/229)
Increased score (Worsening)	5.2% (12/229)	5.7% (13/229)	1.3% (3/229)	3.1% (7/229)	3.5% (8/229)
No assessment	7	7	7	7	7
Post-treatment Week 24 (N = 236), % (n/N)					
Decreased score (Improvement)	39.4% (84/213)	16.4% (35/213)	2.3% (5/213)	15.0% (32/213)	9.4% (20/213)
No change	54.0% (115/213)	80.8% (172/213)	94.8% (202/213)	81.2% (173/213)	88.3% (188/213)
Increased score (Worsening)	6.6% (14/213)	2.8% (6/213)	2.8% (6/213)	3.8% (8/213)	2.3% (5/213)
No assessment	23	23	23	23	23

Note: Baseline frequency of ascites was: 20% none, 77% mild/moderate, 3% severe
Baseline frequency of encephalopathy was: 38% none, 62% grade 1-2.

Clinical studies in patients with HCV/HIV-1 Co-infection – ASTRAL-5 (study 1202)
ASTRAL-5 evaluated 12 weeks of treatment with Sofosbuvir/Velpatasvir Gilead in patients with genotype 1, 2, 3, or 4 HCV infection who were co-infected with HIV-1 (HCV genotype 5 and 6 allowed, but no such patients were included). Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine administered with a ritonavir boosted protease inhibitor (atazanavir, darunavir, or lopinavir), rilpivirine, raltegravir or emtricitabine/tenofovir disoproxil fumarate /elvitegravir/cobicistat.

Of the 106 treated patients, the median age was 57 years (range: 25 to 72); 86% of the patients were male; 51% were White; 45% were Black; 22% had a baseline body mass index $\geq$ 30 kg/m^2; 19 patients (18%) had compensated cirrhosis; and 29% were treatment experienced. The overall mean CD4+ count was 598 cells/µL (range: 183−1513 cells/µL).

Table 19 presents the SVR12 for the ASTRAL-5 study by HCV genotype.

Table 19: SVR12 in study ASTRAL-5 by HCV genotype

	Sofosbuvir/Velpatasvir Gilead 12 weeks (n = 106)						
	Total (all GTs) (n = 106)	**GT-1**			**GT-2 (n = 11)**	**GT-3 (n = 12)**	**GT-4 (n = 5)**
		GT-1a (n = 66)	**GT-1b (n = 12)**	**Total (n = 78)**			
SVR12	95% (101/106)	95% (63/66)	92% (11/12)	95% (74/78)	100% (11/11)	92% (11/12)	100% (5/5)
Outcome for patients without SVR							
On-treatment virologic failure	0/106	0/66	0/12	0/78	0/11	0/12	0/5
Relapse[a]	2% (2/103)	3% (2/65)	0/11	3% (2/76)	0/11	0/11	0/5
Other[b]	3% (3/106)	2% (1/66)	8% (1/12)	3% (2/78)	0/11	8% (1/12)	0/5

GT = genotype

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.

SVR12 was achieved by 19/19 patients with cirrhosis. No patient had HIV-1 rebound during the study, and CD4+ counts were stable during treatment.

Clinical studies in patients with Renal Impairment – study 4062

Study 4062 was an open-label clinical study that evaluated 12 weeks of treatment with Sofosbuvir/Velpatasvir Gilead in 59 HCV-infected patients with ESRD requiring dialysis. The proportions of patients with genotype 1, 2, 3, 4, 6 or indeterminate HCV infection were 42%, 12%, 27%, 7%, 3%, and 9%, respectively. At baseline, 29% of patients had cirrhosis, 22% were treatment experienced, 32% had received a kidney transplant, 92% were on haemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 7.3 years (range: 0 to 40 years). The overall SVR rate was 95% (56/59); of the three patients that did not achieve SVR12, one had completed Sofosbuvir/Velpatasvir Gilead treatment and relapsed and two did not meet virologic failure criteria.

Paediatric population

The efficacy of 12 weeks of treatment with sofosbuvir/velpatasvir in HCV-infected paediatric patients aged 3 years and older was evaluated in a Phase 2, open-label clinical study in 214 patients with HCV infection.

Patients aged 12 to < 18 Years:

Sofosbuvir/velpatasvir was evaluated in 102 patients aged 12 to <18 years with genotype 1, 2, 3, 4, or 6 HCV infection. A total of 80 patients (78%) were treatment-naïve and 22 patients (22%) were treatment-experienced. The median age was 15 years (range: 12 to 17); 51% of the patients were female; 73% were White, 9% were Black, and 11% were Asian; 14% were Hispanic/Latino; mean body mass index was 22.7 kg/m^2 (range: 12.9 to 48.9 kg/m^2); mean weight was 61 kg (range 22 to 147 kg); 58% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV infection were 74%, 6%, 12%, 2%, and 6%, respectively; no patients had known cirrhosis. The majority of patients (89%) had been infected through vertical transmission.

The SVR rate was 95% overall (97/102), 93% (71/76) in patients with genotype 1 HCV infection, and 100% in patients with genotype 2 (6/6), genotype 3 (12/12), genotype 4 (2/2), and genotype 6 (6/6) HCV infection. One patient who discontinued treatment early relapsed; the other four patients who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

Patients aged 6 to < 12 Years:
Sofosbuvir/velpatasvir was evaluated in 71 patients aged 6 to <12 years with genotype 1, 2, 3, and 4 HCV infection. A total of 67 patients (94%) were treatment-naïve and 4 patients (6%) were treatment-experienced. The median age was 8 years (range: 6 to 11); 54% of the patients were female; 90% were White, 6% were Black, and 1% were Asian; 10% were Hispanic/Latino; mean body mass index was 17.4 kg/m^2 (range: 12.8 to 30.9 kg/m^2); mean weight was 30 kg (range 18 to 78 kg); 48% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; the proportions of patients with genotype 1, 2, 3, or 4 HCV infection were 76%, 3%, 15%, and 6%, respectively; no patients had known cirrhosis. The majority of patients (94%) had been infected through vertical transmission.

The SVR rate was 93% overall (66/71), 93% (50/54) in patients with genotype 1 HCV infection, 91% (10/11) in patients with genotype 3 HCV infection, and 100% in patients with genotype 2 (2/2) and genotype 4 (4/4) HCV infection. One subject had on-treatment virologic failure; the other four patients who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

Patients aged 3 to < 6 Years:
Sofosbuvir/velpatasvir was evaluated in 41 treatment-naïve subjects 3 years to < 6 years of age with genotype 1, 2, 3, and 4 HCV infection. The median age was 4 years (range: 3 to 5); 59% of the subjects were female; 78% were White and 7% were Black; 10% were Hispanic/Latino; mean body mass index was 17.0 kg/m^2 (range: 13.9 to 22.0 kg/m^2); mean weight was 19 kg (range: 13 to 35 kg); 49% had baseline HCV RNA levels ≥ 800,000 IU per mL; the proportions of subjects with genotype 1, 2, 3, or 4 HCV infection were 78%, 15%, 5%, and 2%, respectively; no subjects had known cirrhosis. The majority of subjects (98%) had been infected through vertical transmission.

The SVR rate was 83% overall (34/41), 88% (28/32) in subjects with genotype 1 HCV infection, 50% (3/6) in subjects with genotype 2 HCV infection, and 100% in subjects with genotype 3 (2/2) and genotype 4 (1/1) HCV infection. No subject experienced on-treatment virologic failure or relapse. The seven subjects who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

Elderly
Clinical studies of Sofosbuvir/Velpatasvir Gilead included 156 patients aged 65 and over (12% of total number of patients in the Phase 3 clinical studies). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Sofosbuvir/Velpatasvir Gilead in one or more subsets of the paediatric

population in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of sofosbuvir, GS-331007 and velpatasvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of Sofosbuvir/Velpatasvir Gilead, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed 3 hours post-dose. Velpatasvir median peak concentrations were observed at 3 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, mean steady-state AUC_{0-24} for sofosbuvir (n = 982), GS-331007 (n = 1,428) and velpatasvir (n = 1,425) were 1,260, 13,970 and 2,970 ng•h/mL, respectively. Steady-state C_{max} for sofosbuvir, GS-331007 and velpatasvir were 566, 868 and 259 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (n = 331), velpatasvir AUC_{0-24} and C_{max} were 37% lower and 41% lower, respectively in HCV-infected patients.

Effects of food
Relative to fasting conditions, the administration of a single dose of Sofosbuvir/Velpatasvir Gilead with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal resulted in a 34% and 21% increase in velpatasvir AUC_{0-inf}, respectively, and a 31% and 5% increase in velpatasvir C_{max}, respectively. The moderate or high fat meal increased sofosbuvir AUC_{0-inf} by 60% and 78%, respectively, but did not substantially affect the sofosbuvir C_{max}. The moderate or high fat meal did not alter GS-331007 AUC_{0-inf}, but resulted in a 25% and 37% decrease in its C_{max}, respectively. The response rates in Phase 3 studies were similar in HCV-infected patients who received Sofosbuvir/Velpatasvir Gilead with food or without food. Sofosbuvir/Velpatasvir Gilead can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins 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.

Velpatasvir is > 99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 µg/mL to 1.8 µg/mL. After a single 100 mg dose of [^{14}C]-velpatasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.52 and 0.67.

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, GS-331007 accounted for approximately > 90% of total systemic exposure.

Velpatasvir is a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-velpatasvir, the majority (> 98%) of radioactivity in plasma was parent drug. The monohydroxylated and desmethylated velpatasvir were the metabolites identified in human plasma. Unchanged velpatasvir is the major species present in faeces.

Elimination

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the [^{14}C]-radioactivity 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. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of Sofosbuvir/Velpatasvir Gilead were 0.5 and 25 hours, respectively.

Following a single 100 mg oral dose of [^{14}C]-velpatasvir, mean total recovery of the [^{14}C]-radioactivity was 95%, consisting of approximately 94% and 0.4% recovered from the faeces and urine, respectively. Unchanged velpatasvir was the major species in faeces accounting for a mean of 77% of the administered dose, followed by monohydroxylated velpatasvir (5.9%) and desmethylated velpatasvir (3.0%). These data indicate that biliary excretion of parent drug was a major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of Sofosbuvir/Velpatasvir Gilead was approximately 15 hours.

Linearity/non-linearity

Velpatasvir AUC increases in a nearly dose proportional manner over the dose range of 25 mg to 150 mg. Sofosbuvir and GS-331007 AUCs are near dose-proportional over the dose range of 200 mg to 1,200 mg.

In vitro potential for sofosbuvir/velpatasvir drug-drug interactions

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Velpatasvir is also a substrate of OATP1B. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1 and OATP1B3 and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant plasma concentration, velpatasvir is not an inhibitor of hepatic transporters bile salt export pump (BSEP), sodium taurocholate cotransporter protein (NTCP), OATP2B1, OATP1A2 or organic cation transporter (OCT) 1, renal transporters OCT2, OAT1, OAT3, multidrug resistance-associated protein 2 (MRP2) or multidrug and toxin extrusion protein (MATE) 1, or CYP or uridine glucuronosyltransferase (UGT) 1A1 enzymes.

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.

Pharmacokinetics in special populations

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

Elderly
Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 82 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, or velpatasvir.

Renal impairment
A summary of the effect of varying degrees of renal impairment (RI) on the exposures of the components of Sofosbuvir/Velpatasvir Gilead compared to subjects with normal renal function, as described in the text below, are provided in Table 20.

Table 20: Effect of Varying Degrees of Renal Impairment on Exposures (AUC) of Sofosbuvir, GS-331007, and Velpatasvir 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/1.73 m^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↑	1.8-fold↑
GS-331007	1.6-fold↑	1.9-fold↑	5.5-fold↑	≥10-fold↑	≥20-fold↑	~7-fold↑	18-fold↑
Velpatasvir	-	-	1.5-fold↑	-	-	-	1.4-fold↑

The pharmacokinetics of sofosbuvir was studied in HCV negative adult 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 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 dose.

In HCV-infected 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 velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault).

The pharmacokinetics of sofosbuvir, GS-331007, and velpatasvir were studied in HCV-infected patients with ESRD requiring dialysis treated with Sofosbuvir/Velpatasvir Gilead (n=59) for 12 weeks, and compared to patients without renal impairment in the sofosbuvir/velpatasvir Phase 2/3 studies.

Hepatic impairment
The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected adult 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 HCV-infected adult patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative adult patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to subjects with normal hepatic function velpatasvir total plasma exposure (AUC_{inf}) was similar in patients with moderate or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to velpatasvir (see section 4.2).

Body weight
In adults, body weight did not have a clinically significant effect on sofosbuvir or velpatasvir exposure according to a population pharmacokinetic analysis.

Paediatric population
Sofosbuvir, GS-331007 and velpatasvir exposures in paediatric patients aged 3 years and older receiving oral once daily doses of sofosbuvir/velpatasvir 400 mg/100 mg, 200 mg/50 mg or 150 mg/37.5 mg per day were similar to those in adults receiving once daily doses of sofosbuvir/velpatasvir 400 mg/100 mg.

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

5.3 Preclinical safety data

Sofosbuvir

Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity and exposure to the major metabolite GS-331007 was instead used to estimate exposure margins.

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. No teratogenic effects were observed in the rat and rabbit developmental toxicity studies with sofosbuvir. Sofosbuvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study.

Sofosbuvir was not a carcinogen in the 2-year mouse and rat carcinogenicity studies at GS-331007 exposures up to 15 and 9 times, respectively, higher than human exposure.

Velpatasvir

Velpatasvir 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* rat micronucleus assays.

Velpatasvir was not carcinogenic in the 6-month rasH2 transgenic mouse and 2-year rat carcinogenicity studies at exposures at least 50-times and 5-times higher than human exposure, respectively.

Velpatasvir had no adverse effects on mating and fertility. No teratogenic effects were observed in the mouse and rat developmental toxicity studies with velpatasvir at AUC exposures approximately 31- and 6-fold higher, respectively, than the human exposure at the recommended clinical dose. However, a possible teratogenic effect was indicated in rabbits where an increase in total visceral malformations was seen in exposed animals at AUC exposures up to 0.7 fold the human exposure at recommended clinical dose. The human relevance of this finding is not known. Velpatasvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 5-fold higher than the human exposure at the recommended clinical dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Copovidone (E1208)
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film-coating

Poly (vinyl alcohol) (E 1203)
Titanium dioxide (E 171)
Macrogol
Talc (E553b)
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 28 film-coated tablets with polyester coil.

Pack size of 1 bottle containing 28 film-coated tablets.

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 Ltd
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WC1V 7EE
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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 11972/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/11/2024

10 DATE OF REVISION OF THE TEXT

20/06/2025