Vosevi®
(sofosbuvir, velpatasvir, voxilaprevir)
Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Vosevi®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir.

Excipients with known effect

Each film-coated tablet contains 111 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Beige, capsule-shaped, film-coated tablet of dimensions 10 mm x 20 mm, debossed with "GSI" on one side and "3" on the other side.

4. CLINICAL PARTICULARS

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with Vosevi. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals (DAA) and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated *[see Special warnings and precautions for use (Section 4.4)]*.

4.1 Therapeutic indications

Vosevi is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Vosevi treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Posology

The recommended dose of Vosevi is one tablet, taken orally, once daily with food (see section 5.2).

The recommended durations of treatment applicable to all HCV genotypes are shown in Table 1.

Table 1: Recommended treatment durations for Vosevi for all HCV genotypes

Patient population	Treatment duration
DAA naïve patients without cirrhosis	8 weeks
DAA naïve patients with compensated cirrhosis	12 weeks 8 weeks may be considered in genotype 3 infected patients (see section 5.1)
DAA experienced patients* without cirrhosis or with compensated cirrhosis	12 weeks

DAA: direct-acting antiviral agent

* In clinical studies the DAA experienced patients had been exposed to combination regimens containing any of the following: daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, ombitasvir, paritaprevir, sofosbuvir, velpatasvir, voxilaprevir (administered with sofosbuvir and velpatasvir for less than 12 weeks)

Missed dose
If a dose of Vosevi 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 Vosevi at the usual time. Patients should be instructed not to take a double dose of Vosevi.

Patients should be instructed that if vomiting occurs within 4 hours of dosing an additional tablet of Vosevi should be taken. If vomiting occurs more than 4 hours after dosing, no further dose of Vosevi is needed (see section 5.1).

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

Renal impairment
No dose adjustment of Vosevi 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. Vosevi has not been studied in patients with ESRD requiring dialysis. Vosevi 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).

Vosevi has not been studied in patients with severe renal impairment not requiring dialysis.

Hepatic impairment
No dose adjustment of Vosevi is required for patients with mild hepatic impairment (Child-Pugh-Turcotte [CPT] Class A). Vosevi is not recommended in patients with moderate or severe hepatic impairment (CPT Class B or C) (see section 5.2).

Paediatric population
The safety and efficacy of Vosevi in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

For oral use.

Patients should be instructed to swallow the tablet whole with food (see section 5.2). Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed.

4.3 Contraindications

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

Concomitant use with medicinal products that are strong P-glycoprotein (P-gp) and/or strong cytochrome P450 (CYP) inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort) (see section 4.5).

Concomitant use with rosuvastatin or dabigatran etexilate (see section 4.5).

Concomitant use with ethinylestradiol-containing medicinal products such as combined oral contraceptives or contraceptive vaginal rings or transdermal patches (see section 4.5).

4.4 Special warnings and precautions for use

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 Vosevi 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 Vosevi.

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 co-infection

There are no data on the use of Vosevi in patients with HCV/hepatitis B virus (HBV) co-infection. Cases of HBV reactivation, some of them fatal, have been reported during or after treatment with DAAs. HBV screening should be performed in all patients before initiation of treatment. HCV/HBV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

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 ESRD requiring haemodialysis. Vosevi 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).

Hepatic impairment

No dose adjustment of Vosevi is required for patients with mild hepatic impairment (CPT Class A). Vosevi is not recommended in patients with moderate or severe hepatic impairment (CPT Class B or C) (see section 5.2).

Liver transplant patients

The safety and efficacy of Vosevi in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. Treatment with Vosevi, 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.

Use with moderate P-gp inducers 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, velpatasvir and/or voxilaprevir plasma concentrations leading to reduced therapeutic effect of Vosevi. Co-administration of such medicinal products with Vosevi is not recommended (see section 4.5).

Use with strong OATP1B inhibitors

Medicinal products that are strong OATP1B inhibitors (e.g. ciclosporin) may substantially increase voxilaprevir plasma concentrations, the safety of which has not been established. Co-administration of strong OATP1B inhibitors with Vosevi is not recommended (see section 4.5).

Use with certain HIV antiretroviral regimens

Vosevi has been shown to increase tenofovir exposure 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 Vosevi and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Vosevi 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. darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Vosevi 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 DAA treatment. Glucose levels of diabetic patients initiating DAA 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 DAA therapy is initiated.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

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 Vosevi contains sofosbuvir, velpatasvir and voxilaprevir, any interactions that have been identified with these active substances individually may occur with Vosevi.

Pharmacokinetic interactions

Potential for Vosevi to affect other medicinal products

Velpatasvir and voxilaprevir are inhibitors of drug transporters P-gp, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration of Vosevi with medicinal products that are substrates of these transporters may increase the exposure of such medicinal products. Medicinal products that are sensitive substrates of these transporters and for which elevated plasma levels are associated with serious events are contraindicated (see Table 2). Dabigatran etexilate (P-gp substrate) and rosuvastatin (OATP1B and BCRP substrate) are contraindicated (see section 4.3 and Table 2).

Potential for other medicinal products to affect Vosevi

Sofosbuvir, velpatasvir and voxilaprevir are substrates of drug transporters P-gp and BCRP. Velpatasvir and voxilaprevir are substrates of drug transporters OATP1B1 and OATP1B3. *In vitro,* slow metabolic turnover of velpatasvir primarily by CYP2B6, CYP2C8 and CYP3A4 and of voxilaprevir primarily by CYP3A4 was observed.

Medicinal products that may decrease plasma exposure of Vosevi
Medicinal products that are strong inducers of P-gp and/or strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort) may decrease plasma concentrations of sofosbuvir, velpatasvir and/or voxilaprevir leading to reduced therapeutic effect of Vosevi. The use of such medicinal products with Vosevi is contraindicated (see section 4.3 and Table 2).

Medicinal products that are moderate P-gp inducers and/or moderate CYP inducers (e.g. efavirenz, modafinil, oxcarbazepine or rifapentine) may decrease sofosbuvir, velpatasvir and/or voxilaprevir plasma concentrations leading to reduced therapeutic effect of Vosevi. Co-administration with such medicinal products is not recommended with Vosevi (see section 4.4 and Table 2).

Medicinal products that may increase plasma exposure of Vosevi
Co-administration with medicinal products that inhibit P-gp or BCRP may increase sofosbuvir, velpatasvir or voxilaprevir plasma concentrations. Medicinal products that inhibit OATP1B, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentrations of velpatasvir or voxilaprevir. The use of strong inhibitors of OATP1B (e.g. ciclosporin) with Vosevi is not recommended (see section 4.4 and Table 2). Clinically significant medicinal product interactions with Vosevi mediated by P-gp, BCRP and CYP inhibitors are not expected. Vosevi may be co-administered with P-gp, BCRP and CYP inhibitors.

Pharmacodynamic interactions

Patients treated with vitamin K antagonists

As liver function may change during treatment with Vosevi, 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 agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Patients treated with ethinylestradiol-containing medicinal products

Concomitant use with ethinylestradiol-containing medicinal products may increase the risk of alanine aminotransferase (ALT) elevations and is contraindicated (see section 4.3 and Table 2).

Interactions between Vosevi and other medicinal products

Table 2 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/voxilaprevir, its components (sofosbuvir, velpatasvir, and/or voxilaprevir), or are predicted medicinal product interactions that may occur with Vosevi. The table is not all-inclusive.

Table 2: Interactions between Vosevi 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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ACID REDUCING AGENTS					
Antacids					
e.g. Aluminium or magnesium hydroxide; calcium carbonate (Increase in gastric pH decreases velpatasvir solubility)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↓ Velpatasvir ↔ Voxilaprevir				It is recommended to separate antacid and Vosevi administration by 4 hours.
H_2-receptor antagonists					
Famotidine (40 mg single dose) + sofosbuvir/velpatasvir/ voxilaprevir (400/100/100 mg single dose)[c] Famotidine dosed simultaneously with Vosevi Cimetidine[d] Nizatidine[d]	*Observed:* Sofosbuvir	↔	↔		H_2-receptor antagonists may be administered simultaneously with or staggered from Vosevi at a dose that does not exceed doses comparable with famotidine 40 mg twice daily.
	Velpatasvir	↔	↔		
	Voxilaprevir	↔	↔		

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Ranitidine[d] (Increase in gastric pH decreases velpatasvir solubility)					
Famotidine (40 mg single dose) + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg single dose)[c] Famotidine dosed 12 hours prior to Vosevi (Increase in gastric pH decreases velpatasvir solubility)	*Observed:* Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔		
	Voxilaprevir	↔	↔		
Proton pump inhibitors					
Omeprazole (20 mg once daily) + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg single dose)[c] Omeprazole dosed 2 hours prior to Vosevi Lansoprazole[d] Rabeprazole[d] Pantoprazole[d] Esomeprazole[d] (Increase in gastric pH decreases velpatasvir solubility)	*Observed:* Sofosbuvir	↓ 0.77 (0.65, 0.91)	↓ 0.73 (0.67, 0.79)		Proton pump inhibitors may be administered with Vosevi at a dose that does not exceed doses comparable with omeprazole 20 mg.
	Velpatasvir	↓ 0.43 (0.38, 0.49)	↓ 0.46 (0.41, 0.52)		
	Voxilaprevir	↓ 0.76 (0.69, 0.85)	↔		
Omeprazole (20 mg once daily) + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg single dose)[c] Omeprazole dosed 4 hours after Vosevi (Increase in gastric pH decreases velpatasvir solubility)	*Observed:* Sofosbuvir	↔	↔		
	Velpatasvir	↓ 0.49 (0.43, 0.55)	↓ 0.49 (0.43, 0.55)		
	Voxilaprevir	↔	↔		

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ANTIARRHYTHMICS					
Amiodarone	Effect on amiodarone, voxilaprevir, 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 Vosevi (see sections 4.4 and 4.8).
Digoxin	Interaction only studied with velpatasvir. *Expected:* ↔ Sofosbuvir ↔ Voxilaprevir				Co-administration of Vosevi with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended.
Digoxin (0.25 mg single dose)[e] + velpatasvir (100 mg single dose) (Inhibition of P-gp)	Effect on velpatasvir exposure-not studied *Expected:* ↔ Velpatasvir				
	Observed: Digoxin	↑ 1.88 (1.71, 2.08)	↑ 1.34 (1.13, 1.60)		
ANTICOAGULANTS					
Dabigatran etexilate (75 mg single dose) + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg single dose) + voxilaprevir (100 mg single dose)[f] (Inhibition of P-gp)	Effect on sofosbuvir, velpatasvir and voxilaprevir concentrations not studied *Expected:* ↔ Sofosbuvir ↔ Velpatasvir ↔ Voxilaprevir				Vosevi is contraindicated with dabigatran etexilate (see section 4.3).
	Observed: Dabigatran	↑ 2.87 (2.61, 3.15)	↑ 2.61 (2.41, 2.82)		
Edoxaban (Inhibition of OATP1B1)	Interaction not studied. *Expected:* ↑ Edoxaban (active metabolite) ↔ Sofosbuvir ↔ Velpatasvir ↔ Voxilaprevir				Co-administration of Vosevi with edoxaban is not recommended. Should direct Xa inhibitor use be deemed necessary, apixaban or rivaroxaban may be considered.
Vitamin K antagonists (Liver function changes during treatment with Vosevi).	Interaction not studied.				Close monitoring of INR is recommended when Vosevi is co-administered with all vitamin K antagonists.
ANTICONVULSANTS					
Phenytoin Phenobarbital	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Vosevi is contraindicated with phenobarbital and phenytoin (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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
(Induction of P-gp and CYPs)	↓ Voxilaprevir				
Carbamazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir ↓ Voxilaprevir				Vosevi is contraindicated with carbamazepine (see section 4.3).
	Observed: Sofosbuvir	↓ 0.52 (0.43, 0.62)	↓ 0.52 (0.46, 0.59)		

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ANTIFUNGALS					
Ketoconazole (Inhibition of P-gp and CYP3A)	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir ↑ Voxilaprevir				No dose adjustment of Vosevi or ketoconazole is required.
Ketoconazole (200 mg twice daily) + velpatasvir (100 mg single dose)[f] Itraconazole[d] Posaconazole[d] Isavuconazole[d] (Inhibition of P-gp and CYP3A)	Effect on ketoconazole exposure not studied. *Expected:* ↔ Ketoconazole				
	Observed: Velpatasvir	↑ 1.29 (1.02, 1.64)	↑ 1.71 (1.35, 2.18)		
Voriconazole (Inhibition of CYP3A)	Interaction only studied with voxilaprevir. *Expected:* ↔ Sofosbuvir ↑ Velpatasvir				No dose adjustment of Vosevi or voriconazole is required.
Voriconazole (200 mg twice daily) + voxilaprevir (100 mg single dose)[f]	*Observed:* Voxilaprevir	↔	↑ 1.84 (1.66, 2.03)		
ANTIMYCOBACTERIALS					
Rifampicin (single dose) (Inhibition of OATP1B)	Interaction only studied with velpatasvir and voxilaprevir. *Expected:* ↔ Rifampicin ↔ Sofosbuvir				Vosevi is contraindicated with rifampicin (see section 4.3).
Rifampicin (600 mg single dose) + velpatasvir (100 mg single dose)[f]	*Observed:* Velpatasvir	↑ 1.28 (1.05, 1.56)	↑ 1.46 (1.17, 1.83)		
Rifampicin (600 mg single dose) + voxilaprevir (100 mg single dose)[f]	Voxilaprevir	↑ 11.10 (8.23, 14.98)	↑ 7.91 (6.20, 10.09)		
Rifampicin (multiple dose) (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				
Rifampicin (600 mg once daily) + sofosbuvir (400 mg single dose)[f]	*Observed:* Sofosbuvir	↓ 0.23 (0.19, 0.29)	↓ 0.28 (0.24, 0.32)		

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Rifampicin (600 mg once daily) + velpatasvir (100 mg single dose)[f]	Velpatasvir	↓ 0.29 (0.23, 0.37)	↓ 0.18 (0.15, 0.22)		
Rifampicin (600 mg once daily) + voxilaprevir (100 mg single dose)[f]	Voxilaprevir	↔	↓ 0.27 (0.23, 0.31)		
Rifabutin (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir ↓ Voxilaprevir				Vosevi is contraindicated with rifabutin (see section 4.3).
	Observed: Sofosbuvir	↓ 0.64 (0.53, 0.77)	↓ 0.76 (0.63, 0.91)		
Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir ↓ Voxilaprevir				Co-administration of Vosevi with rifapentine is not recommended (see section 4.4).
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate (Inhibition of P-gp)	Vosevi has been shown to increase tenofovir exposure (P-gp inhibition). There was an increase in tenofovir exposure (AUC and C_{max}) of around 40% during co-treatment with Vosevi and darunavir + ritonavir + tenofovir disoproxil fumarate/emtricitabine. Patients receiving tenofovir disoproxil fumarate and Vosevi 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)[g] + sofosbuvir/ velpatasvir (400/100 mg once daily)[f, h] (Induction of CYPs)	Interaction only studied with sofosbuvir/velpatasvir *Expected:* ↓ Voxilaprevir				Co-administration of Vosevi with efavirenz/emtricitabine/tenofovir disoproxil fumarate is not recommended (see section 4.4).
	Observed: Efavirenz	↔	↔	↔	
	Sofosbuvir	↑ 1.38 (1.14, 1.67)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓ 0.43 (0.36, 0.52)	

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Emtricitabine/**rilpivirine**/ tenofovir alafenamide (200/25/25 mg once daily)[i] + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg once daily) + voxilaprevir (100 mg once daily)[f]	*Observed:* Rilpivirine	↔	↔	↔	No dose adjustment of Vosevi or emtricitabine/rilpivirine/tenofovir alafenamide is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
	Voxilaprevir	↔	↔	↔	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300 + 100 mg single dose) + sofosbuvir/ velpatasvir/voxilaprevir (400/100/100 mg single dose)[f] (Inhibition of OATP1B, P-gp and CYP3A)	Effect on atazanavir and ritonavir exposure not studied. *Expected:* ↔ Atazanavir ↔ Ritonavir				Co-administration of Vosevi with atazanavir is expected to increase the concentration of voxilaprevir. Co-administration of Vosevi with atazanavir-containing regimens is not recommended.
	Observed: Sofosbuvir	↑ 1.29 (1.09, 1.52)	↑ 1.40 (1.25, 1.57)		
	Velpatasvir	↑ 1.29 (1.07, 1.56)	↑ 1.93 (1.58, 2.36)		
	Voxilaprevir	↑ 4.42 (3.65, 5.35)	↑ 4.31 (3.76, 4.93)		
Darunavir boosted with ritonavir (800 + 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/300 mg once daily)[j] + sofosbuvir/ velpatasvir/voxilaprevir (400/100/100 mg once daily) + voxilaprevir (100 mg once daily)[f] (Inhibition of OATP1B, P-gp, and CYP3A)	*Observed:* Darunavir	↔	↔	↓ 0.66 (0.58, 0.74)	No dose adjustment of Vosevi, darunavir (ritonavir boosted) or emtricitabine/tenofovir disoproxil fumarate is required.
	Ritonavir	↑ 1.60 (1.47, 1.75)	↑ 1.45 (1.35, 1.57)	↔	
	Sofosbuvir	↓ 0.70 (0.62, 0.78)	↔		
	Velpatasvir	↔	↔	↔	
	Voxilaprevir	↑ 1.72 (1.51, 1.97)	↑ 2.43 (2.15, 2.75)	↑ 4.00 (3.44, 4.65)	

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Lopinavir (Inhibition of OATP1B)	Interaction not studied. *Expected:* ↔ Lopinavir ↔ Sofosbuvir ↔ Velpatasvir ↑ Voxilaprevir				Co-administration of Vosevi with lopinavir-containing regimens is not recommended.
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily)[k] + emtricitabine/ tenofovir disoproxil fumarate (200/300 mg once daily)[j] + sofosbuvir/ velpatasvir (400/100 mg once daily)[f, h]	Interaction only studied with sofosbuvir/velpatasvir *Expected:* ↔ Voxilaprevir				No dose adjustment of Vosevi, raltegravir or emtricitabine/tenofovir disoproxil fumarate is required.
	Observed: Raltegravir	↔	↔	↓ 0.79 (0.42, 1.48)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide fumarate (150/150/200/10 mg once daily)[l] + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg once daily) + voxilaprevir (100 mg once daily)[f] (Inhibition of OATP1B, P-gp/BCRP and CYP3A)	*Observed:* Elvitegravir	↔	↔	↑ 1.32 (1.17, 1.49)	No dose adjustment of Vosevi or elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide fumarate is required.
	Cobicistat	↔	↑ 1.50 (1.44, 1.58)	↑ 3.50 (3.01, 4.07)	
	Tenofovir	↓ 0.79 (0.68, 0.92)	↔		
	Sofosbuvir	↑ 1.27 (1.09, 1.48)	↔		
	Velpatasvir	↔	↔	↑ 1.46 (1.30, 1.64)	
	Voxilaprevir	↑ 1.92 (1.63, 2.26)	↑ 2.71 (2.30, 3.19)	↑ 4.50 (3.68, 5.50)	
Dolutegravir (50 mg once daily) + sofosbuvir/ velpatasvir (400/100 mg once daily)[h]	Interaction only studied with sofosbuvir/velpatasvir *Expected:* ↔ Voxilaprevir				No dose adjustment of Vosevi or dolutegravir is required.
	Observed: Dolutegravir	↔	↔	↔	

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir ↓ Voxilaprevir				Vosevi is contraindicated with St. John's wort (see section 4.3).
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin	Interaction only studied with sofosbuvir/ velpatasvir. *Expected:* ↔ Voxilaprevir				Atorvastatin may be administered with Vosevi at a dose that does not exceed atorvastatin 20 mg.
Atorvastatin (40 mg single dose) + sofosbuvir/ velpatasvir (400/100 mg once daily)[f]	*Observed:* atorvastatin	↑ 1.7 (1.5, 1.9)	↑ 1.5 (1.5, 1.6)		
Rosuvastatin	Effect on sofosbuvir, velpatasvir and voxilaprevir not studied. *Expected:* ↔ Sofosbuvir ↔ Velpatasvir ↔ Voxilaprevir				Vosevi is contraindicated with rosuvastatin (see section 4.3).
Rosuvastatin (10 mg single dose) + sofosbuvir/ velpatasvir/voxilaprevir (400/100/100 mg once daily) + voxilaprevir (100 mg once daily)[f] (Inhibition of OATP1B and BCRP)	*Observed:* Rosuvastatin	↑ 18.9 (16.2, 22.0)	↑ 7.4 (6.7, 8.2)		
Pravastatin	Effect on sofosbuvir, velpatasvir and voxilaprevir not studied. *Expected:* ↔ Sofosbuvir ↔ Velpatasvir ↔ Voxilaprevir				Pravastatin may be administered with Vosevi at a dose that does not exceed pravastatin 40 mg.
Pravastatin (40 mg single dose) + sofosbuvir/ velpatasvir/voxilaprevir (400/100/100 mg once daily) + voxilaprevir (100 mg once daily)[f] (Inhibition of OATP1B)	*Observed:* Pravastatin	↑ 1.89 (1.53, 2.34)	↑ 2.16 (1.79, 2.60)		
Other statins (Inhibition of OATP1B)	Effect on fluvastatin, lovastatin, pitavastatin and simvastatin not studied.				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. Co-administration

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
					with Vosevi is not recommended.
NARCOTIC ANALGESICS					
Methadone	Interaction only studied with sofosbuvir *Expected:* ↔ Velpatasvir ↔ Voxilaprevir				No dose adjustment of Vosevi or methadone is required.
Methadone (Methadone maintenance therapy [30 to 130 mg daily]) + sofosbuvir (400 mg once daily)[f]	*Observed:* R-methadone	↔	↔	↔	
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.30 (1.00, 1.69)		
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)[f] + sofosbuvir (400 mg single dose)[e] (Inhibition of OATP1B or P-gp or BCRP)	*Observed:* Ciclosporin	↔	↔		Co-administration of Vosevi with ciclosporin is not recommended (see section 4.4).
	Sofosbuvir	↑ 2.54 (1.87, 3.45)	↑ 4.53 (3.26, 6.30)		
Ciclosporin (600 mg single dose)[e] + velpatasvir (100 mg single dose)[f]	Ciclosporin	↔	↓ 0.88 (0.78, 1.0)		
	Velpatasvir	↑ 1.56 (1.22, 2.01)	↑ 2.03 (1.51, 2.71)		
Ciclosporin (600 mg single dose)[e] + voxilaprevir (100 mg single dose)[f]	Ciclosporin	↔	↔		
	Voxilaprevir	↑ 19.0 (14.1, 25.6)	↑ 9.4 (7.4, 12.0)		
Tacrolimus	Effect on velpatasvir or voxilaprevir exposure not studied. *Expected:* ↔ Velpatasvir ↔ Voxilaprevir				No dose adjustment of Vosevi or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
Tacrolimus (5 mg single dose)[e] + sofosbuvir (400 mg single dose)[f]	*Observed:* Tacrolimus	↓ 0.73 (0.59, 0.90)	↑ 1.09 (0.84, 1.40)		
	Sofosbuvir	↓ 0.97 (0.65, 1.43)	↑ 1.13 (0.81, 1.57)		

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 Vosevi**
	Active	**C_{max}**	**AUC**	**C_{min}**	
HORMONAL CONTRACEPTIVES					
Oral norgestimate/ethinyl estradiol (norgestimate 0.180 mg/0.215 mg/0.25 m g/ethinyl estradiol 0.025 mg) + sofosbuvir/velpatasvir/ voxilaprevir (400/100/ 100 mg once daily) + voxilaprevir (100 mg once daily)[f]	*Observed:* Norelgestromin	↔	↔	↔	Vosevi is contraindicated with ethinylestradiol-containing medicinal products (see section 4.3). Alternative methods of contraception (e.g. progestin only contraception or non-hormonal methods) should be considered.
	Norgestrel	↔	↔	↔	
	Ethinyl estradiol	↔	↔	↔	
STIMULANTS					
Modafinil (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↔ Modafinil ↓ Sofosbuvir ↓ Velpatasvir ↓ Voxilaprevir				Co-administration of Vosevi with modafinil is not recommended (see section 4.4).

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. Lack of pharmacokinetics interaction lower bound 70%.
d. These are medicinal products within class where similar interactions could be predicted.
e. Bioequivalence/Equivalence boundary 80-125%.
f. Lack of pharmacokinetics interaction bounds 70-143%.
g. Administered as efavirenz, emtricitabine and tenofovir DF fixed-dose combination.
h. Administered as sofosbuvir, velpatasvir fixed-dose combination.
i. Administered as emtricitabine, rilpivirine, and tenofovir alafenamide fixed-dose combination.
j. Administered as emtricitabine, tenofovir disoproxil fumarate fixed-dose combination.
k. Lack of pharmacokinetics interaction bounds 50-200%.
l. Administered as elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fixed-dose combination.

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, voxilaprevir or Vosevi 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).

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

As a precautionary measure, Vosevi use is not recommended during pregnancy.

Breast-feeding

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

Available pharmacokinetic data in animals have shown excretion of velpatasvir and metabolites of sofosbuvir in milk. When administered to lactating rats, voxilaprevir was detected in the plasma of nursing pups.

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

Fertility

No human data on the effect of Vosevi on fertility are available. Animal studies do not indicate harmful effects of sofosbuvir, velpatasvir or voxilaprevir on fertility.

4.7 Effects on ability to drive and use machines

Vosevi has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In Phase 2 and 3 clinical studies, the proportion of patients who permanently discontinued treatment due to adverse reactions was 0.1% for patients receiving sofosbuvir/velpatasvir/voxilaprevir for 8 weeks. There were no patients receiving sofosbuvir/velpatasvir/voxilaprevir for 12 weeks who permanently discontinued treatment due to adverse reactions in the Phase 2 and 3 pivotal clinical studies.

Tabulated summary of adverse reactions

Assessment of adverse reactions for Vosevi is based on safety data from clinical studies and post-marketing experience. All adverse reactions are presented in Table 3. 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 3: Adverse reactions identified with Vosevi

Frequency	**Adverse reaction**
Nervous system disorders:	
Very common	headache
Gastrointestinal disorders:	
Very common	diarrhoea, nausea
Common	abdominal pain, decreased appetite, vomiting
Skin and subcutaneous tissue disorders:	
Common	rash
Uncommon	angioedema[a]
Musculoskeletal and connective tissue disorders:	
Common	myalgia
Uncommon	muscle spasm
Laboratory investigations:	
Common	total bilirubin increased

a. 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

Laboratory abnormalities

Total bilirubin
In the Phase 3 studies increases in total bilirubin less than or equal to 1.5 x the upper limit of normal were observed in 4% of patients without cirrhosis and 10% of patients with compensated cirrhosis, due to inhibition of OATP1B1 and OATP1B3 by voxilaprevir. Total bilirubin levels decreased after completing Vosevi treatment.

Patients with renal impairment

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.
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.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il) which redirects to the online form for reporting side effects, or by clicking on the link: https://sideeffects.health.gov.il.

You can also report any side effects directly to the registration holder via email: DrugSafety.Israel@gilead.com.

4.9 Overdose

The highest documented doses of sofosbuvir, velpatasvir and voxilaprevir were single doses of 1,200 mg, 500 mg, and 900 mg, respectively. In healthy volunteer studies with sofosbuvir and velpatasvir, 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 most common adverse reactions in patients receiving voxilaprevir 900 mg were diarrhoea (34%), nausea (17%) and headache (9%).

No specific antidote is available for overdose with Vosevi. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Vosevi 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 or voxilaprevir since velpatasvir and voxilaprevir are highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; Direct-acting antivirals, ATC code: J05AP56

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required 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. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Velpatasvir is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is required for viral replication.

Voxilaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease. Voxilaprevir acts as a noncovalent, reversible inhibitor of the NS3/4A protease.

Antiviral activity

The 50% effective concentration (EC_{50}) values of sofosbuvir, velpatasvir and voxilaprevir against full-length or chimeric replicons encoding NS5B, NS5A and NS3 protease sequences from the laboratory strains are presented in Table 4. The EC_{50} values of sofosbuvir, velpatasvir and voxilaprevir against clinical isolates are presented in Table 5.

Table 4: Activity of sofosbuvir, velpatasvir and voxilaprevir against full-length or chimeric laboratory replicons

Replicon genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]	Voxilaprevir EC_{50}, nM[a]
1a	40	0.014	3.9[e]
1b	110	0.016	3.3[e]
2a	50	0.005-0.016[c]	3.7-4.5[e]
2b	15[b]	0.002-0.006[c]	1.8-6.6[f]
3a	50	0.004	6.1[f]
4a	40	0.009	2.9[e]
4d	33	0.004	3.2[e]
5a	15[b]	0.021-0.054[d]	1.9[f]
6a	14-25[b]	0.006-0.009	3.0-4.0[e]
6e	NA	0.130[d]	0.33[f]
6n	NA	NA	2.9[f]

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.
e. Stable cell lines expressing Renilla luciferase-encoding replicons.
f. Data obtained from transiently transfected replicons.

Table 5: Activity of sofosbuvir, velpatasvir and voxilaprevir against transient replicons containing NS5A, NS5B or NS3 protease from clinical isolates

Replicon genotype	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates		Replicons containing NS3 protease from clinical isolates	
	Number of clinical isolates	Median sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median velpatasvir EC_{50}, nM (range)	Number of clinical isolates	Median voxilaprevir EC_{50}, nM (range)
1a	67	62 (29-128)	23	0.019 (0.011-0.078)	58	0.59 (0.14-19.16)
1b	29	102 (45-170)	34	0.012 (0.005-0.500)	29	0.50 (0.19-2.87)
2a	1	28	8	0.011 (0.006-0.364)	18	2.8 (1.78-6.72)
2b	14	30 (14-81)	16	0.002 (0.0003-0.007)	43	2.1 (0.92-8.3)
3a	106	81 (24-181)	38	0.005 (0.002-1.871)	32	6.3 (1.3-21.48)
4a	NA	NA	5	0.002 (0.001-0.004)	58	0.52 (0.12-1.7)
4d	NA	NA	10	0.007 (0.004-0.011)	11	0.85 (0.41-1.1)
4r	NA	NA	7	0.003 (0.002-0.006)	1	1.15 NA
5a	NA	NA	42	0.005 (0.001-0.019)	16	1.8 (0.87-5.63)
6a	NA	NA	26	0.007 (0.0005-0.113)	15	2.7 (0.23-7.35)
6e	NA	NA	15	0.024 (0.005-0.433)	12	0.2 (0.12-0.43)

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 and voxilaprevir by 13- and 6.8-fold, respectively, against genotype 1a HCV replicons.

Resistance

In cell culture
For sofosbuvir, the NS5B substitution S282T was selected in genotype 1-6 replicons and was associated with 2- to 18-fold reduced susceptibility to sofosbuvir.

For velpatasvir in genotype 1-6 replicons, resistance-associated substitutions selected in 2 or more genotypes were L31I/V and Y93H. Site directed mutagenesis of NS5A resistance associated variants (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 RAV tested in genotypes 2a, 4a or 5a conferred a > 100-fold reduction in velpatasvir susceptibility.

For voxilaprevir in genotype 1-6 replicons, resistance-associated substitutions selected in 2 or more genotypes were Q41H, A156V/T/L and D168E/H/Y. Site directed mutagenesis of known NS3 RAVs showed that substitutions conferring a > 100-fold reduction in voxilaprevir susceptibility are A156V, A156T or A156L in genotype 1a, 1b, 2a, 3a and 4. No individual RAV tested in genotypes 2b, 5a or 6a conferred a > 100-fold reduction in voxilaprevir susceptibility.

For both velpatasvir and voxilaprevir, combinations of RAVs often showed greater reductions in susceptibility than individual RAVs alone.

Cross resistance in cell culture
Voxilaprevir is active *in vitro* against most of the NS3 RAVs that confer resistance to first generation NS3/4A protease inhibitors. Additionally, velpatasvir is active *in vitro* against most of the NS5A RAVs that confer resistance to ledipasvir and daclatasvir. Sofosbuvir, velpatasvir, and voxilaprevir were fully active against substitutions associated with resistance to other classes of DAAs with different mechanisms of actions, e.g. voxilaprevir was fully active against NS5A and NS5B NI RAVs.

In clinical studies
Studies in DAA-experienced patients
Of the 263 NS5A inhibitor-experienced patients treated with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in POLARIS-1 (see Table 10), 7 of 263 (3%) patients (2 with genotype 1, 4 with genotype 3, and 1 with genotype 4) did not achieve sustained virologic response (SVR12) and qualified for resistance analysis; 6 relapsed and 1 experienced virologic breakthrough with pharmacokinetic data consistent with nonadherence. The patient with genotype 1a and virologic breakthrough developed the NS5A RAVs L31M and Y93H. One patient with genotype 4d who relapsed developed the NS5A RAV Y93H. No NS3, NS5A, or NS5B nucleoside inhibitor (NI) RAVs emerged in the other 5 patients who relapsed.

Of the 182 DAA-experienced patients treated with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in POLARIS-4 (see Table 11), 1 of 182 (1%) patients relapsed and qualified for resistance analysis. No NS3, NS5A, or NS5B NI RAVs emerged in this patient infected with genotype 1a HCV.

Studies in DAA-naïve patients
In the POLARIS-2 sofosbuvir/velpatasvir/voxilaprevir 8-week treatment group (see Table 12), a total of 21 of 501 (4%) patients (16 with genotype 1, 2 with genotype 2, 2 with genotype 4, and 1 with genotype 5) qualified for resistance analysis due to relapse. Of these 21 patients, 1 patient had virus with emergent NS5A RAVs Q30R and L31M at failure. No NS3 and NS5B NI RAVs emerged in any of these 21 patients at failure. In the sofosbuvir/velpatasvir 12-week treatment group, a total of 3 of 440 (1%) patients (2 with genotype 1, 1 with genotype 4) qualified for resistance analysis due to relapse. Of these 3 patients, 1 patient (33%) had virus with emergent NS5A RAV Y93N at failure. No NS3 and NS5B NI RAVs emerged in any of these 3 patients.

In the POLARIS-3 sofosbuvir/velpatasvir/voxilaprevir 8-week treatment group (see Table 14), 2 of 110 (2%) patients (genotype 3) qualified for resistance analysis due to relapse. No NS3, NS5A, or NS5B NI RAVs emerged in either of these patients. In the sofosbuvir/velpatasvir 12-week treatment group, 2 of 109 (2%) patients qualified for resistance analysis due to virologic failure. Both of these patients had virus with emergent NS5A RAV Y93H at failure. No NS3 or NS5B NI RAVs emerged in either of these patients.

Effect of baseline HCV resistance-associated variants on treatment outcome

Studies in DAA-experienced patients
Analyses were conducted to explore the association between pre-existing baseline NS3 and NS5A RAVs and treatment outcome for patients that had previously been treated with DAA regimens and received sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in POLARIS-1 and POLARIS-4. These are shown in Table 6.

Table 6: SVR12 in DAA-experienced patients with or without baseline NS3 or NS5A RAVs by study

	sofosbuvir/velpatasvir/voxilaprevir 12 weeks	
	POLARIS-1 (n = 260)	**POLARIS-4 (n = 179)**
No NS3 or NS5A RAVs	98% (42/43)	99% (85/86)
Any NS3 or NS5A RAV	97% (199/205)	100% (83/83)
NS3 Only	100% (9/9)	100% (39/39)
NS5A Only	97% (120/124)	100% (40/40)
NS3 and NS5A	97% (70/72)	100% (4/4)
RAVs not determined for both NS3 and NS5A[a]	100% (12/12)	100% (10/10)

a. Patients with NS3 and/or NS5A gene sequencing failure.

SVR12 was achieved in 18 of 19 (95%) patients who had baseline NS5B NI RAVs in POLARIS-1, including 2 patients who had virus with the S282T NS5B NI RAV in addition to NS5A RAVs at baseline. In POLARIS-4, a total of 14 patients had virus with NS5B NI RAVs at baseline and all achieved SVR12.

Studies in DAA-naïve patients
Analyses were conducted to explore the association between pre-existing baseline NS3 and NS5A RAVs and treatment outcome for patients that had not previously been treated with DAA regimens and received sofosbuvir/velpatasvir/voxilaprevir for 8 weeks in POLARIS-2 and POLARIS-3. These are shown in Table 7.

Table 7: SVR12 in DAA-naïve patients with or without baseline NS3 or NS5A RAVs by study

	sofosbuvir/velpatasvir/voxilaprevir 8 weeks	
	POLARIS-2 (n = 498)	**POLARIS-3 (n = 108)**
No NS3 or NS5A RAVs	98% (224/229)	98% (80/82)
Any NS3 or NS5A RAV	94% (234/250)	100% (23/23)
NS3 only	91% (100/110)	100% (2/2)
NS5A only	95% (114/120)	100% (20/20)
NS3 and NS5A	100% (20/20)	100% (1/1)
RAVs not determined for both NS3 and NS5A[a]	100% (19/19)	100% (3/3)

a. Patients with NS3 and/or NS5A gene sequencing failure.

SVR12 was achieved in all 39 patients who had baseline NS5B NI RAVs in POLARIS-2 and 2 of 3 (67%) patients in POLARIS-3. The NS5B NI RAV S282T was not detected in any patient in POLARIS-2 and POLARIS-3 studies. Among patients with genotype 1a in POLARIS-2, SVR12 was 87% (53/61) for those with Q80K/L/R RAVs and 94% (99/105) for those without Q80K/L/R RAVs.

Clinical efficacy

The efficacy of Vosevi (sofosbuvir [SOF]/velpatasvir [VEL]/voxilaprevir [VOX]) was evaluated in four Phase 3 studies, two studies in DAA-experienced patients and two studies in DAA-naïve patients with, genotype 1 to 6 HCV infection without cirrhosis or with compensated cirrhosis, as summarised in Table 8. Demographics and baseline characteristics for all studies are detailed in Table 9.

Table 8: Studies conducted with Vosevi

Study	Population	Study arms and duration (Number of patients treated)	Additional study details
POLARIS-1 (randomised double blind)	NS5A inhibitor-experienced patients, GT1-6, with or without cirrhosis	• SOF/VEL/VOX 12 weeks (N=263) • Placebo 12 weeks (N=152)	Placebo-controlled study in which patients with GT1 infection were randomised in a 1:1 ratio to SOF/VEL/VOX or placebo for 12 weeks. Patients with GT2-6 infection were enrolled into the SOF/VEL/VOX 12 week group only.
POLARIS-4 (open label)	DAA-experienced patients (who have not received an NS5A inhibitor), GT1-6, with or without cirrhosis	• SOF/VEL/VOX 12 weeks (N=182) • SOF/VEL 12 weeks (N=151)	Patients with GT1-3 infection were randomised in a 1:1 ratio to SOF/VEL/VOX or SOF/VEL for 12 weeks. Patients with GT4-6 infection were enrolled into the SOF/VEL/VOX 12 week group only.
POLARIS-2 (open label)	DAA-naïve patients, GT 1, 2, 4, 5, or 6, with or without cirrhosis GT 3 without cirrhosis	• SOF/VEL/VOX 8 weeks (N=501) • SOF/VEL 12 weeks (N=440)	Patients with GT1-4 were randomised in a 1:1 ratio to SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks. Patients with GT5-6 infection were enrolled into the SOF/VEL/VOX 8 week group only.
POLARIS-3 (open label)	DAA-naïve patients with GT 3 and cirrhosis	• SOF/VEL/VOX 8 weeks (N=110) • SOF/VEL 12 weeks (N=109)	Patients were randomised in a 1:1 ratio to SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks.

DAA: direct-acting antiviral; GT: genotype; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

Table 9: Demographics and baseline characteristics for patients enrolled into POLARIS-1, -2, -3 and -4

	Studies with DAA-experienced Patients		Studies with DAA-naïve Patients	
Patient disposition	**POLARIS-1 (n =415)**	**POLARIS-4 (n =333)**	**POLARIS-2 (n =941)**	**POLARIS-3 (n =219)**
Age (years) median (range)	59 (27-84)	58 (24-85)	55 (18-82)	56 (25-75)
Male Gender	77% (321)	77% (257)	52% (492)	72% (157)
Race				
Black/African American	14% (60)	9% (29)	10% (95)	< 1% (1)
White	81% (335)	87% (291)	80% (756)	90% (197)
Hispanic/Latino	6% (25)	8% (27)	9% (84)	8% (17)
Genotype				
Genotype 1a	53% (218)	29% (98)	36% (341)	0
Genotype 1b	18% (76)	14% (46)	13% (122)	0
Genotype 2	1% (5)	19% (64)	12% (116)	0
Genotype 3	19% (78)	32% (106)	19% (181)	100% (219)
Genotype 4	5% (22)	5.7% (19)	13% (120)	0
Genotype 5	< 1% (1)	0	2% (18)	0
Genotype 6	2% (8)	0	4% (39)	0
IL28B CC	18% (74)	19% (62)	32% (302)	42% (93)
HCV RNA ≥ 800,000 IU/mL	74% (306)	75% (249)	69% (648)	69% (151)
Compensated cirrhosis	41% (172)	46% (153)	18% (174)	100% (219)
Site				
US	57% (236)	56% (188)	59% (552)	44% (96)
Non-US	43% (179)	44% (145)	41% (389)	56% (123)

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 per 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 DAA-experienced patients

NS5A inhibitor-experienced adults (POLARIS-1)

Table 10 presents the SVR12 by HCV genotype for the POLARIS-1 study. The median time between prior DAA failure and first dose of Vosevi for patients enrolled into POLARIS-1 was 39 weeks (range: 11 to 299 weeks). No patients in the placebo group achieved SVR4.

Table 10: SVR12 in NS5A-inhibitor experienced patients by HCV genotype in study POLARIS-1*

	SOF/VEL/VOX 12 weeks (n = 263)								
	Total (all GTs)[a] (n = 263)	**GT-1**			**GT-2 (n = 5)**	**GT-3 (n = 78)**	**GT-4 (n = 22)**	**GT-5 (n = 1)**	**GT-6 (n = 6)**
		GT-1a (n = 101)	**GT-1b (n = 45)**	**Total[b] (n = 150)**					
SVR12	96% (253/263)	96% (97/101)	100% (45/45)	97% (146/150)	100% (5/5)	95% (74/78)	91% (20/22)	100% (1/1)	100% (6/6)
Outcome for patients without SVR									
On-treatment virologic failure[c]	<1% (1/263)	1% (1/101)	0/45	1% (1/150)	0/5	0/78	0/22	0/1	0/6
Relapse[d]	2% (6/261)	1% (1/100)	0/45	1% (1/149)	0/5	5% (4/78)	5% (1/21)	0/1	0/6
Other[e]	1% (3/263)	2% (2/101)	0/45	1% (2/150)	0/5	0/78	5% (1/22)	0/1	0/6

GT = genotype

* The most common prior NS5A inhibitors were ledipasvir (LDV) (51%), daclatasvir (27%), and ombitasvir (11%).

a. One patient with undetermined genotype achieved SVR12.

b. Four patients had genotype 1 subtypes other than genotype 1a or genotype 1b; all 4 patients achieved SVR12.

c. Pharmacokinetic data for the 1 patient with on-treatment virologic failure was consistent with non-adherence.

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

e. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

DAA-experienced adults who had not received an NS5A inhibitor (POLARIS-4)

Table 11 presents the SVR12 by HCV genotype and virologic outcome for the POLARIS-4 study. The median time between prior DAA failure and first dose of Vosevi or sofosbuvir/velpatasvir for patients enrolled into POLARIS-4 was 76 weeks (range: 10 to 549 weeks).

Table 11: SVR12 by HCV genotype and virologic outcome in study POLARIS-4

	SOF/VEL/VOX 12 weeks (n = 182)	**SOF/VEL 12 weeks (n = 151)**
Overall SVR12	**98% (178/182)**	**90% (136/151)**
Genotype 1	97% (76/78)	91% (60/66)
Genotype 1a	98% (53/54)	89% (39/44)
Genotype 1b	96% (23/24)	95% (21/22)
Genotype 2	100% (31/31)	97% (32/33)
Genotype 3	96% (52/54)	85% (44/52)
Genotype 4	100% (19/19)	0/0
Outcome for patients without SVR		
On-treatment virologic failure[a]	0/182	1% (1/151)
Relapse[b]	1% (1/182)	9% (14/150)
Other[c]	2% (3/182)	0/151

a. The majority (85%) of patients previously failed a regimen containing sofosbuvir.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Clinical studies in DAA-naïve patients

DAA-naïve adults with genotype 1, 2, 3, 4, 5, or 6 HCV infection (POLARIS-2)

Table 12 presents the SVR12 by HCV genotype and virologic outcome for the POLARIS-2 study.

Table 12: SVR12 by HCV genotype and virologic outcome in study POLARIS-2*

	SOF/VEL/VOX 8 weeks (n = 501)	**SOF/VEL 12 weeks (n = 440)**
Overall SVR12[a]	**95% (477/501)**	**98% (432/440)**
Genotype 1[b]	93% (217/233)	98% (228/232)
Genotype 1a	92% (155/169)	99% (170/172)
Genotype 1b	97% (61/63)	97% (57/59)
Genotype 2	97% (61/63)	100% (53/53)
Genotype 3	99% (91/92)	97% (86/89)
Genotype 4	94% (59/63)	98% (56/57)
Genotype 5	94% (17/18)	0/0
Genotype 6	100% (30/30)	100% (9/9)
Outcome for patients without SVR		
On-treatment virologic failure	0/501	0/440
Relapse[c]	4% (21/498)	1% (3/439)
Other[d]	1% (3/501)	1% (5/440)

* 23% of patients enrolled into POLARIS-2 had received prior treatment with an interferon-based regimen.
a. Two patients with undetermined genotype in the SOF/VEL/VOX group achieved SVR12.
b. Two patients had genotype 1 subtypes other than genotype 1a or genotype 1b; both patients achieved SVR12.
c. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
d. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Treatment with Vosevi for 8 weeks in POLARIS-2 did not demonstrate noninferiority to treatment with sofosbuvir/velpatasvir for 12 weeks with a prespecified margin of -5%. The difference in SVR12 was driven by a lower response rate in patients with genotype 1a infection and/or cirrhosis. In patients with genotype 1a without cirrhosis treated with Vosevi for 8 weeks, outcome was influenced by the following baseline factors: Body Mass Index (BMI) ≥ 30 kg/m^2, Q80K/L/R RAVs, IL28B non-CC, HCV RNA ≥ 800,000 IU/mL. The SVR12 was 98% among those with two or fewer factors and 81% among those with three or four factors. Table 13 presents the SVR12 by HCV genotype by cirrhosis status for the POLARIS-2 study.

Table 13: SVR12 by HCV genotype and virologic outcome in patients who received Vosevi 8 weeks without cirrhosis or with cirrhosis in study POLARIS-2

	SOF/VEL/VOX 8 weeks	
	Without Cirrhosis (411/501)	**With Cirrhosis (90/501)**
Overall SVR12[a]	**96% (395/411)**	**91% (82/90)**
Genotype 1[b]	94% (162/172)	90% (55/61)
Genotype 1a	92% (109/118)[c]	90% (46/51)
Genotype 1b	98% (52/53)	90% (9/10)
Genotype 2	96% (47/49)	100% (14/14)
Genotype 3	99% (90/91)	100% (1/1)
Genotype 4	96% (51/53)	80% (8/10)
Genotype 5	94% (16/17)	100% (1/1)
Genotype 6	100% (27/27)	100% (3/3)
Outcome for patients without SVR		
On-treatment virologic failure	0/411	0/90
Relapse[d]	3% (14/409)	8% (7/89)
Other[e]	< 1% (2/411)	1% (1/90)

a. Two patients without cirrhosis with undetermined genotype in the SOF/VEL/VOX group achieved SVR12.
b. One patient without cirrhosis had genotype 1 subtype other than genotype 1a or genotype 1b; the patient achieved SVR12.
c. SVR12 is 89% in genotype 1a patients enrolled at sites in the US and 97% in genotype 1a patients enrolled at sites outside the US
d. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
e. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

DAA-naïve adults with genotype 3 HCV infection and compensated cirrhosis (POLARIS-3)
Table 14 presents the SVR12 and virologic outcome for the POLARIS-3 study.

Table 14: SVR12 and virologic outcome in study POLARIS-3 (HCV genotype 3 with compensated cirrhosis) *

	SOF/VEL/VOX 8 weeks (n = 110)	**SOF/VEL 12 weeks (n = 109)**
SVR12	96% (106/110)	96% (105/109)
Outcome for patients without SVR		
On-treatment virologic failure	0/110	1% (1/109)
Relapse[a]	2% (2/108)	1% (1/107)
Other[b]	2% (2/110)	2% (2/109)

***** 29% of patients enrolled into POLARIS-3 had received prior treatment with an interferon-based regimen.
a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Adults previously treated with sofosbuvir/velpatasvir-containing regimens
Vosevi for 12 weeks was evaluated in patients who were previously treated with a sofosbuvir/velpatasvir-containing regimen. The median time to re-treatment was 414 days (range 198-1271). Of the 31 patients enrolled, 74% (23/31) were male, 81% (25/31) were white, 71% (22/31) had a baseline body mass index < 30 kg/m^2, 48% (15/31) had compensated cirrhosis, 58% (18/31) had previously received sofosbuvir, velpatasvir and voxilaprevir, and 42% (13/31) had previously received

sofosbuvir and velpatasvir. Most patients had genotype 1 (61% (19/31) [1a, 48% (15/31); 1b, 13% (4/31)]) or genotype 3 (26% (8/31)) HCV infection. The overall SVR12 rate was 100% (31/31).

Elderly
Clinical studies of Vosevi included 189 patients aged 65 and over (17% of total number of patients in the Phase 2 and 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.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of sofosbuvir, GS-331007, velpatasvir and voxilaprevir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C.

Sofosbuvir
Following oral administration of Vosevi, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 2 hours post-dose. Median peak plasma concentration of GS-331007 was observed 4 hours post-dose. Based on the population pharmacokinetic analysis in HCV-infected patients, mean steady-state AUC_{0-24} and C_{max} for sofosbuvir (n = 1038) were 1665 ng•hr/mL and 678 ng/mL, respectively; mean steady-state AUC_{0-24} and C_{max} for GS-331007 (n = 1593) were 12834 ng•hr/mL and 744 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection.

Velpatasvir
Velpatasvir median peak concentrations were observed at 4 hours post-dose. Based on the population pharmacokinetic analysis in HCV-infected patients mean steady-state AUC_{0-24} and C_{max} for velpatasvir (n = 1595) were 4041 ng•hr/mL and 311 ng/mL, respectively. Relative to healthy subjects (n = 137), velpatasvir AUC_{0-24} and C_{max} were 41% lower and 39% lower, respectively, in HCV-infected patients.

Voxilaprevir
Voxilaprevir median peak concentrations were observed 4 hours post-dose. Based on the population pharmacokinetic analysis in HCV-infected patients mean steady-state AUC_{0-24} and C_{max} for voxilaprevir (n = 1591) were 2577 ng•hr/mL and 192 ng/mL, respectively. Relative to healthy subjects (n = 63), voxilaprevir AUC_{0-24} and C_{max} were both 260% higher in HCV-infected patients.

Effects of food
When Vosevi or its components taken together were administered with food, sofosbuvir AUC_{0-inf} and C_{max} were 64% to 144% and 9% to 76% higher, respectively; velpatasvir AUC_{0-inf} and C_{max} were 40% to 166% and 37% to 187% higher, respectively; and voxilaprevir AUC_{0-inf} and C_{max} were 112% to 435% and 147% to 680% higher, respectively. GS-331007 AUC_{0-inf} did not change and C_{max} was 19% to 35% lower when Vosevi or its components together were administered with 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% 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 0.5 and 0.7.

Voxilaprevir is approximately > 99% bound to human plasma proteins. After a single 100 mg dose of [^{14}C]-voxilaprevir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.5 and 0.8.

Biotransformation

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analogue 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.* After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately > 90% of total systemic exposure.

Velpatasvir is primarily 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.

Voxilaprevir is primarily a substrate of CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-voxilaprevir, the majority (approximately 91%) of radioactivity in plasma was parent drug. The hydrolysed and dehydrogenated voxilaprevir were the major metabolites identified in human plasma. Unchanged voxilaprevir 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 Vosevi were 0.5 and 29 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 Vosevi was approximately 17 hours.

Following a single 100 mg oral dose of [^{14}C]-voxilaprevir, mean total recovery of the [^{14}C]-radioactivity was 94%, with all radioactivity measured in the faeces and none in the urine. Unchanged voxilaprevir was the major species in faeces accounting for a mean of 40% of the administered dose. Voxilaprevir metabolites also identified in faeces included des-[methylcyclopropylsulphonamide]-voxilaprevir (22.1%), which is formed intestinally, dehydro-voxilaprevir (7.5%), and two des-[methylcyclopropylsulphonamide]-oxy-voxilaprevir metabolites (5.4% and 3.9%). Biliary excretion of parent drug was the major route of elimination for voxilaprevir. The median terminal half-life of voxilaprevir following administration of Vosevi was approximately 33 hours.

Linearity/non-linearity

Sofosbuvir and GS-331007 AUCs are near dose-proportional over the dose range of 200 mg to 1200 mg. Velpatasvir AUC increases in a greater than proportional manner from 5 to 50 mg and in a less than proportional manner from 50 to 450 mg, indicating velpatasvir absorption is solubility

limited. Voxilaprevir (studied under fed conditions) AUC increases in a greater than dose-proportional manner over the dose range of 100 to 900 mg.

In vitro potential for sofosbuvir/velpatasvir/voxilaprevir drug-drug interactions

Sofosbuvir, velpatasvir and voxilaprevir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Voxilaprevir, and to a lesser extent velpatasvir, are also substrates of OATP1B1 and OATP1B3. *In vitro,* slow metabolic turnover of velpatasvir primarily by CYP2B6, CYP2C8, and CYP3A4 and of voxilaprevir primarily by CYP3A4 was observed.

Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, multidrug resistance-associated protein 2 (MRP2), bile salt export pump (BSEP), OATP1B1, OATP1B3 and organic cation transporter (OCT) 1 and GS-331007 is not an inhibitor of OAT1, OAT3, OCT2, and multidrug and toxin extrusion protein (MATE) 1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or uridine glucuronosyltransferase (UGT) 1A1 enzymes.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1, OATP1B3 and OATP2B1, and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentrations, velpatasvir is not an inhibitor of hepatic transporters BSEP, sodium taurocholate cotransporter protein (NTCP), OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3, MRP2 or MATE1, or CYP or UGT1A1 enzymes.

Voxilaprevir is an inhibitor of drug transporters 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 concentrations, voxilaprevir is not an inhibitor of hepatic transporters OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Pharmacokinetics in special populations

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

Elderly
Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 85 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, velpatasvir or voxilaprevir. In the 13 patients aged 75 to 84 years with available pharmacokinetic data, mean exposure to voxilaprevir was 93% higher than the mean exposure observed in patients aged 18 to 64 years.

Renal impairment
A summary of the effect of varying degrees of renal impairment (RI) on the exposures of the components of Vosevi compared to subjects with normal renal function, as described in the text below, are provided in Table 15.

Table 15: Effect of varying degrees of renal impairment on exposures (AUC) of SOF, GS-331007, velpatasvir and voxilaprevir 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/1.73 m^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↑
Voxilaprevir	-	-	1.7-fold↑	-	-	-	-

The pharmacokinetics of sofosbuvir was studied in 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 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 patients with severe renal impairment.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Voxilaprevir is not renally eliminated.
Additionally, the pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). The pharmacokinetics of voxilaprevir have not been studied in subjects with ESRD requiring dialysis (see section 4.2).

The pharmacokinetics of sofosbuvir, GS-331007, and velpatasvir were studied in HCV-infected patients with ESRD requiring dialysis treated with once daily sofosbuvir/velpatasvir 400/100 mg for 12 weeks, and compared to patients without renal impairment in the sofosbuvir/velpatasvir Phase 2/3 trials.

Although exposures of the fixed-dose combination sofosbuvir, GS-331007, velpatasvir, and voxilaprevir were not directly evaluated in HCV-infected patients with ESRD requiring dialysis after administration of Vosevi, the exposures of sofosbuvir, GS-331007, and velpatasvir are expected to be similar to those observed after administration of sofosbuvir/velpatasvir 400/100 mg in HCV-infected patients with ESRD requiring dialysis.

Hepatic impairment
The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in 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 patients with moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (CPT Class A) had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in patients with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetic analysis in HCV-infected patients indicated that cirrhosis (CPT Class A) had no clinically relevant effect on the exposure of velpatasvir.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Relative to patients with normal hepatic function, the voxilaprevir AUC_{inf} was 299% and 500% higher in patients with moderate and severe hepatic impairment, respectively. The unbound fraction of voxilaprevir was approximately 2-fold higher in severe hepatic impairment compared with moderate hepatic impairment or normal hepatic function. Population pharmacokinetic analysis in HCV-infected

patients indicated that patients with cirrhosis (CPT Class A) had 73% higher exposure of voxilaprevir than those without cirrhosis (see section 4.2).

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

Paediatric population
The pharmacokinetics of Vosevi in paediatric patients have not been established (see section 4.2).

5.3 Preclinical safety data

Sofosbuvir

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 carcinogenic in the 2-year mouse and rat carcinogenicity studies at GS-331007 exposures up to 17 and 10-times higher, respectively 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 26-week transgenic mouse and 2-year rat carcinogenicity studies at exposures up to 67- 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 23- and 4-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 0.5 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 3-fold higher than the human exposure at the recommended clinical dose.

Voxilaprevir

Voxilaprevir 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.

Carcinogenicity studies for voxilaprevir have not been conducted.

Voxilaprevir had no adverse effects on mating and fertility. No teratogenic effects were observed in the rat and rabbit developmental toxicity studies with voxilaprevir at AUC exposures approximately 141- and 4-times higher, respectively, than the human exposure at the recommended clinical dose. Voxilaprevir had no adverse effects on behavior, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 238-times higher than the human exposure at the recommended clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)
Copovidone
Lactose monohydrate
Croscarmellose sodium (E468)
Magnesium stearate
Colloidal anhydrous silica

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

No special storage conditions, recommended to store at room temperature.
Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

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 and a silica gel desiccant.

Pack size: outer carton containing 1 bottle of 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. MANUFACTURER

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

8. REGISTRATION HOLDER

Gilead Sciences Israel Ltd.
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Israel

Revised in May 2023 in accordance with MoH guidelines.

Reference: EU SmPC from May 2022.

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