

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Vosevi 400 mg/100 mg/100 mg film-coated tablets

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 lactose 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 “GSP” on one side and “3” on the other side.

4. CLINICAL PARTICULARS

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 trials 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. The safety and efficacy of Vosevi has not been assessed in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] < 30 mL/min/1.73 m²) or end stage renal disease (ESRD) requiring haemodialysis (see section 4.4 and 5.2).

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. rifampicin, rifabutin, St. John's wort [*Hypericum perforatum*], carbamazepine, phenobarbital and phenytoin) (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 (see section 4.5).

4.4 Special warnings and precautions for use

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when sofosbuvir used in combination with another DAA, is used with concomitant amiodarone with or without other medicinal products that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus DAAs. Cases are potentially life threatening, therefore 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 are closely monitored when initiating Vosevi. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring 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 receiving Vosevi in combination with amiodarone with or without other medicinal products that lower heart rate should also 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.

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 or moderate CYP inducers (e.g. oxcarbazepine, rifapentine, modafinil or efavirenz) 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.

Excipients

Vosevi contains lactose. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

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 or strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) 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 or moderate CYP inducers (e.g. oxcarbazepine, rifapentine, modafinil or efavirenz) 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.

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					
<i>Antacids</i>					
e.g. Aluminium or magnesium hydroxide; calcium carbonate (Increase in gastric pH decreases velpatasvir solubility)	Interaction not studied. <i>Expected:</i> ↔ Sofosbuvir ↓ Velpatasvir ↔ Voxilaprevir				It is recommended to separate antacid and Vosevi administration by 4 hours.
<i>H₂-receptor antagonists</i>					
Famotidine (40 mg single dose) + sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg single dose) ^c Famotidine dosed simultaneously with Vosevi Cimetidine ^d Nizatidine ^d Ranitidine ^d (Increase in gastric pH decreases velpatasvir solubility)	<i>Observed:</i> 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}	
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)	<i>Observed:</i> Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔		
	Voxilaprevir	↔	↔		
<i>Proton pump inhibitors</i>					
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)	<i>Observed:</i> 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)	<i>Observed:</i> Sofosbuvir	↔	↔		
	Velpatasvir	↓ 0.49 (0.43, 0.55)	↓ 0.49 (0.43, 0.55)		
	Voxilaprevir	↔	↔		
ANTIARRHYTHMICS					
Amiodarone	Interaction not studied. Effect on amiodarone, voxilaprevir, velpatasvir, and sofosbuvir concentrations unknown.				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).

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}	
Digoxin	Interaction only studied with velpatasvir. <i>Expected:</i> ↔ 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 <i>Expected:</i> ↔ Velpatasvir <i>Observed:</i> 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 <i>Expected:</i> ↔ Sofosbuvir ↔ Velpatasvir ↔ Voxilaprevir <i>Observed:</i> Dabigatran				Vosevi is contraindicated with dabigatran etexilate (see section 4.3).
		↑ 2.87 (2.61, 3.15)	↑ 2.61 (2.41, 2.82)		
Edoxaban (Inhibition of OATP1B1)	Interaction not studied. <i>Expected:</i> ↑ 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 (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir ↓ Voxilaprevir				Vosevi is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ 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}	
ANTIFUNGALS					
Ketoconazole (Inhibition of P-gp and CYP3A)	Interaction only studied with velpatasvir <i>Expected:</i> ↔ 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. <i>Expected:</i> ↔ Ketoconazole <i>Observed:</i> Velpatasvir				
		↑ 1.29 (1.02, 1.64)	↑ 1.71 (1.35, 2.18)		
Voriconazole (Inhibition of CYP3A)	Interaction only studied with voxilaprevir. <i>Expected:</i> ↔ Sofosbuvir ↑ Velpatasvir				No dose adjustment of Vosevi or voriconazole is required.
Voriconazole (200 mg twice daily) + voxilaprevir (100 mg single dose) ^f	<i>Observed:</i> Voxilaprevir	↔	↑ 1.84 (1.66, 2.03)		
ANTIMYCOBACTERIALS					
Rifampicin (single dose) (Inhibition of OATP1B)	Interaction only studied with velpatasvir and voxilaprevir. <i>Expected:</i> ↔ Rifampicin ↔ Sofosbuvir				Vosevi is contraindicated with rifampicin (see section 4.3).
Rifampicin (600 mg single dose) + velpatasvir (100 mg single dose) ^f	<i>Observed:</i> 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. <i>Expected:</i> ↔ Rifampicin				
Rifampicin (600 mg once daily) + sofosbuvir (400 mg single dose) ^f	<i>Observed:</i> 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 Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir ↓ Voxilaprevir				Vosevi is contraindicated with rifabutin (see section 4.3). 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 <i>Expected:</i> ↓ Voxilaprevir				Co-administration of Vosevi with efavirenz/emtricitabine/tenofovir disoproxil fumarate is not recommended (see section 4.4).
	<i>Observed:</i> 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)	
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	<i>Observed:</i> Rilpivirine	↔	↔	↔	No dose adjustment of Vosevi or emtricitabine/rilpivirine/tenofovir alafenamide is required.
	Sofosbuvir	↔	↔		
	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}	
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. <i>Expected:</i> ↔ Atazanavir ↔ Ritonavir <i>Observed:</i>				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.
	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) ^k + sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg once daily) + voxilaprevir (100 mg once daily) ^f (Inhibition of OATP1B, P-gp, and CYP3A)	<i>Observed:</i> 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)	
Lopinavir (Inhibition of OATP1B)	Interaction not studied. <i>Expected:</i> ↔ Lopinavir ↔ Sofosbuvir ↔ Velpatasvir ↑ Voxilaprevir				Co-administration of Vosevi with lopinavir-containing regimens is not recommended.

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}	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily) ^l + emtricitabine/tenofovir disoproxil fumarate (200/300 mg once daily) ^k + sofosbuvir/velpatasvir (400/100 mg once daily) ^{f, h}	Interaction only studied with sofosbuvir/velpatasvir <i>Expected:</i> ↔ Voxilaprevir				No dose adjustment of Vosevi, raltegravir or emtricitabine/tenofovir disoproxil fumarate is required.
	<i>Observed:</i> Raltegravir	↔	↔	↓ 0.79 (0.42, 1.48)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (150/150/200/10 mg once daily) ^m + sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg once daily) + voxilaprevir (100 mg once daily) ^f (Inhibition of OATP1B, P-gp/BCRP and CYP3A)	<i>Observed:</i> 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 <i>Expected:</i> ↔ Voxilaprevir				No dose adjustment of Vosevi or dolutegravir is required.
	<i>Observed:</i> Dolutegravir	↔	↔	↔	
	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 Vosevi
	Active	C _{max}	AUC	C _{min}	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir ↓ Voxilaprevir				Vosevi is contraindicated with St. John's wort (see section 4.3).
HMG-CoA REDUCTASE INHIBITORS					
Rosuvastatin	Effect on sofosbuvir, velpatasvir and voxilaprevir not studied. <i>Expected:</i> ↔ 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)	<i>Observed:</i> Rosuvastatin	↑ 18.9 (16.2, 22.0)	↑ 7.4 (6.7, 8.2)		
Pravastatin	Effect on sofosbuvir, velpatasvir and voxilaprevir not studied. <i>Expected:</i> ↔ 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)	<i>Observed:</i> Pravastatin	↑ 1.89 (1.53, 2.34)	↑ 2.16 (1.79, 2.60)		
Other statins (Inhibition of OATP1B)	Effect on atorvastatin, fluvastatin, lovastatin, pitavastatin and simvastatin not studied.				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. Co-administration with Vosevi is not recommended.

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}	
NARCOTIC ANALGESICS					
Methadone	Interaction only studied with sofosbuvir <i>Expected:</i> ↔ 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	<i>Observed:</i>				
	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)	<i>Observed:</i>				Co-administration of Vosevi with ciclosporin is not recommended (see section 4.4).
	Ciclosporin	↔	↔		
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. <i>Expected:</i> ↔ Velpatasvir ↔ Voxilaprevir				No dose adjustment of Vosevi or tacrolimus is required.
Tacrolimus (5 mg single dose) ^e + sofosbuvir (400 mg single dose) ^f	<i>Observed:</i>				
	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}	
ORAL CONTRACEPTIVES					
Norgestimate/ethinyl estradiol (norgestimate 0.180 mg/0.215 mg/0.25 mg /ethinyl estradiol 0.025 mg) + sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg once daily) + voxilaprevir (100 mg once daily) ^f	<i>Observed:</i> 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. <i>Expected:</i> ↔ 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.

k. Administered as emtricitabine, tenofovir disoproxil fumarate fixed-dose combination.

l. Lack of pharmacokinetics interaction bounds 50-200%.

m. 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

The safety assessment of Vosevi was based on data from Phase 2 and 3 clinical trials in which 1543 patients received sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir/velpatasvir + voxilaprevir for 8 or 12 weeks.

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.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); or uncommon ($\geq 1/1000$ to $< 1/100$).

Table 3: Adverse drug reactions identified with Vosevi

Frequency	Adverse drug reaction
<i>Nervous system disorders:</i>	
Very common	headache
<i>Gastrointestinal disorders:</i>	
Very common	diarrhoea, nausea
Common	abdominal pain, decreased appetite, vomiting
<i>Skin and subcutaneous disorders</i>	
Uncommon	rash
<i>Musculoskeletal and connective tissue disorders:</i>	
Common	myalgia
Uncommon	muscle spasm
<i>Laboratory investigations:</i>	
Common	total bilirubin increased

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir used in combination with another direct-acting antiviral, is used with concomitant amiodarone and/or other medicinal products that lower heart rate (see sections 4.4 and 4.5).

Laboratory abnormalities

Total bilirubin

In the Phase 3 trials 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.

Reporting of suspected adverse reactions

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

4.9 Overdose

The highest documented 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: Direct-acting antiviral, ATC code: not yet assigned

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 subjects 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

Patient disposition	Studies with DAA-experienced Patients		Studies with DAA-naïve Patients	
	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)
<i>Race</i>				
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)
<i>Genotype</i>				
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 \geq 800,000 IU/mL	74% (306)	75% (249)	69% (648)	69% (151)
Compensated cirrhosis	41% (172)	46% (153)	18% (174)	100% (219)
<i>Site</i>				
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 trial. 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)
<i>Outcome for patients without SVR</i>									
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 trial. 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
<i>Outcome for patients without SVR</i>		
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 trial.

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)
<i>Outcome for patients without SVR</i>		
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: BMI \geq 30 kg/m², Q80K/L/R RAVs, IL28B non-CC, HCV RNA \geq 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 trial.

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)
<i>Outcome for patients without SVR</i>		
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)
<i>Outcome for patients without SVR</i>		
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.

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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with sofosbuvir/velpatasvir/voxilaprevir 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, 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 AUC₀₋₂₄ and C_{max} for sofosbuvir (n = 1038) were 1665 ng•hr/mL and 678 ng/mL, respectively; mean steady-state AUC₀₋₂₄ and C_{max} for GS-331007 (n = 1593) were 12834 ng•hr/mL and 744 ng/mL, respectively. Sofosbuvir and GS-331007 AUC₀₋₂₄ 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 AUC₀₋₂₄ and C_{max} for velpatasvir (n = 1595) were 4041 ng•hr/mL and 311 ng/mL, respectively. Relative to healthy subjects (n = 137), velpatasvir AUC₀₋₂₄ 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 AUC₀₋₂₄ and C_{max} for voxilaprevir (n = 1591) were 2577 ng•hr/mL and 192 ng/mL, respectively. Relative to healthy subjects (n = 63), voxilaprevir AUC₀₋₂₄ 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 [¹⁴C]-sofosbuvir in healthy subjects, the blood to plasma ratio of [¹⁴C]-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 [¹⁴C]-velpatasvir in healthy subjects, the blood to plasma ratio of [¹⁴C]-radioactivity ranged between 0.5 and 0.7.

Voxilaprevir is approximately > 99% bound to human plasma proteins. After a single 100 mg dose of [¹⁴C]-voxilaprevir in healthy subjects, the blood to plasma ratio of [¹⁴C]-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 [¹⁴C]-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 [¹⁴C]-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 [¹⁴C]-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 [¹⁴C]-sofosbuvir, mean total recovery of the [¹⁴C]-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 [¹⁴C]-velpatasvir, mean total recovery of the [¹⁴C]-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 [¹⁴C]-voxilaprevir, mean total recovery of the [¹⁴C]-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

The pharmacokinetics of sofosbuvir was studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73 m²), moderate (eGFR ≥ 30 and < 50 mL/min/1.73 m²), severe renal impairment (eGFR < 30 mL/min/1.73 m²) and patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73 m²), the sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88% and 451% higher, respectively. In patients with ESRD, sofosbuvir AUC_{0-inf} was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when dosed 1 hour after haemodialysis, respectively. The AUC_{0-inf} of GS-331007 in patients with ESRD administered with sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. 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 (see section 4.2).

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). Relative to subjects with normal renal function, velpatasvir AUC_{inf} was 50% higher in subjects with severe renal impairment (see section 4.2).

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). Relative to subjects with normal renal function, voxilaprevir AUC_{inf} was 71% higher in subjects with severe renal impairment (see section 4.2).

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 AUC₀₋₂₄ was 126% and 143% higher in patients with moderate and severe hepatic impairment, while the GS-331007 AUC₀₋₂₄ 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 study at exposures up to 67-times higher than human exposure. A carcinogenicity study in rats is ongoing.

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

Colloidal anhydrous silica
Copovidone
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

Film-coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
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. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1223/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD month YYYY

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Obligation to conduct post-authorisation measures

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

Description	Due date
<u>Non-interventional post-authorisation safety study (PASS):</u> In order to evaluate the recurrence of hepatocellular carcinoma associated with Vosevi, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q2 2021

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Vosevi 400 mg/100 mg/100 mg film-coated tablets
sofosbuvir/velpatasvir/voxilaprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1223/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vosevi [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Vosevi 400 mg/100 mg/100 mg film-coated tablets sofosbuvir/velpatasvir/voxilaprevir

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

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

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

What is in this leaflet

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

1. What Vosevi is and what it is used for

Vosevi is a medicine that contains the active substances sofosbuvir, velpatasvir and voxilaprevir in a single tablet. It is given to adults of 18 years and older treat a chronic (long-term) viral infection of the liver called hepatitis C.

The active substances in this medicine work together by blocking three different proteins that the hepatitis C virus needs to grow and reproduce itself, causing the infection to be eliminated from the body.

2. What you need to know before you take Vosevi

Do not take Vosevi

- **If you are allergic** to sofosbuvir, velpatasvir, voxilaprevir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

→If this applies to you, **do not take Vosevi and tell your doctor immediately.**

- **If you are currently taking any of the following medicines:**

- **rifampicin** and **rifabutin** (antibiotics used to treat infections, including tuberculosis);
- **St. John's wort** (*Hypericum perforatum* – a herbal medicine used to treat depression);
- **carbamazepine**, **phenobarbital** and **phenytoin** (medicines used to treat epilepsy and prevent seizures).
- **rosuvastatin** (a medicine used to treat high blood cholesterol or decrease the risk of certain cardiovascular events);
- **dabigatran** (a medicine used to prevent blood clots);
- **ethinylestradiol** containing medicines, including many contraceptives.

Warnings and precautions

Talk to your doctor if you:

- **have liver problems** other than from hepatitis C, for instance
 - **if you have** a current or previous infection with the **hepatitis B** virus, since your doctor may want to monitor you more closely;
 - **if you have had a liver transplant**
- **are taking treatment for human immunodeficiency virus (HIV) infection**, since your doctor may want to monitor you more closely.

Talk to your doctor or pharmacist before taking Vosevi if:

- you currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats (your doctor may consider alternative treatments if you have taken this medicine).

Tell your doctor immediately if you are taking any medicines for heart problems and during treatment you experience:

- shortness of breath
- light-headedness
- palpitations
- fainting

Blood tests

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

- Your doctor can decide if you should take Vosevi and for how long;
- Your doctor can confirm that your treatment has worked and you are free of the hepatitis C virus.

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age. The use of Vosevi in children and adolescents has not yet been studied.

Other medicines and Vosevi

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

If you are not sure talk to your doctor or pharmacist.

Some medicines mustnot be taken with Vosevi. Taking Vosevi with any of these may stop your medicines from working properly, or make any side effects worse:

- **rifampicin** and **rifabutin** (antibiotics used to treat infections, including tuberculosis);
- **St. John's wort** (*Hypericum perforatum* – a herbal medicine used to treat depression);
- **carbamazepine, phenobarbital** and **phenytoin** (medicines used to treat epilepsy and prevent seizures).
- **rosuvastatin** (a medicine used to treat high blood cholesterol or decrease the risk of certain cardiovascular events);
- **dabigatran** (a medicine used to prevent blood clots);
- **ethinylestradiol** containing medicines, including many contraceptives.

Tell your doctor or pharmacist if you are taking any of the medicines below:

- **amiodarone**, used to treat irregular heartbeats;
- **rifapentine** (an antibiotic used to treat infections, including tuberculosis);
- **oxcarbazepine** (medicine used to treat epilepsy and prevent seizures);
- **tenofovir disoproxil fumarate**, or any medicine containing tenofovir disoproxil fumarate, used to treat HIV infection;
- **atazanavir, efavirenz** or **lopinavir**, used to treat HIV infection;

- **digoxin**, used to treat heart conditions;
- **modafinil**, used to treat sleep disorders;
- **pravastatin**, or **other statins**, used to treat high cholesterol;
- **ciclosporin**, used to suppress the immune system;

Taking Vosevi with any of these may stop your medicines from working properly, or make any side effects worse. Your doctor may need to give you a different medicine or adjust the dose of medicine you are taking. This change could be to Vosevi or another medicine you are taking.

- **Get advice from a doctor or pharmacist** if you take medicines used to treat **stomach ulcers, heartburn or acid reflux** as they can decrease the amount of velpatasvir in your blood. These medicines include:
 - antacids (such as aluminium/magnesium hydroxide or calcium carbonate). These should be taken at least 4 hours before or 4 hours after Vosevi;
 - proton pump inhibitors (such as omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole). If you need high doses of these medicines your doctor may give you a different medicine instead or adjust the dose of the medicine you are taking;
 - H₂-receptor antagonists (such as famotidine, cimetidine, nizatidine or ranitidine). If you need high doses of these medicines your doctor may give you a different medicine instead or adjust the dose of the medicine you are taking.

These medicines can decrease the amount of Vosevi in your blood. If you are taking one of these medicines your doctor will either give you a different medicine for stomach ulcers, heartburn or acid reflux, or recommend how and when you take that medicine.

- **Get advice from a doctor or pharmacist** if you take **warfarin or other similar medicines** called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

Pregnancy, breast-feeding and fertility

If you are pregnant, think you may be pregnant, are breast-feeding your baby, or are planning to have a baby ask your doctor for advice before taking this medicine.

Pregnancy

Vosevi is not recommended during pregnancy. The effects of Vosevi during pregnancy are not known.

Breast-feeding

Do not breast-feed during treatment with Vosevi. Some of the active substances of Vosevi may pass into human breast milk.

Driving and using machines

Vosevi should not affect your ability to drive or use any tools or machinery.

Vosevi contains lactose

- **Tell your doctor if you are lactose intolerant or intolerant to other sugars.** Vosevi contains lactose monohydrate. If you are lactose intolerant, or if you have been told that you have an intolerance to other sugars, talk to your doctor before taking this medicine.

3. How to take Vosevi

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

Recommended dose

The recommended dose is **one tablet once a day for 8 or 12 weeks.**

Swallow the tablet whole with food. Do not chew, crush or split the tablet as it has a very bitter taste.

Kidney problems

Tell your doctor if you **have kidney problems** or if you are on **kidney dialysis**, since Vosevi has not been fully tested in patients with severe kidney problems.

Liver problems

Vosevi should not be used if you have moderate or severe liver problems.

If you are taking an antacid, take it at least 4 hours before or at least 4 hours after Vosevi.

If you are sick (vomit) after taking Vosevi it may affect the amount of Vosevi in your blood. This may make Vosevi work less well.

- If you are sick (vomit) **less than 4 hours after** taking Vosevi, take another tablet.
- If you are sick (vomit) **more than 4 hours after** taking Vosevi, you do not need to take another tablet until your next scheduled tablet.

If you take more Vosevi than you should

If you accidentally take more than the recommended dose of Vosevi you may be at increased risk of side effects with this medicine (*see section 4 Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Vosevi

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

If you do miss a dose, work out how long it is since you last took your Vosevi:

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

Do not stop taking Vosevi

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

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

4. Possible side effects

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

Very common side effects

(may affect more than 1 in 10 people)

- headache
- diarrhoea
- feeling sick (nausea)

Common side effects

(may affect up to 1 in 10 people)

- stomach pain
- decreased appetite
- being sick (vomiting)

- muscle pain (myalgia)
- abnormality in a laboratory test of liver function (total bilirubin)

Uncommon side effects

(may affect up to 1 in 100 people)

- muscle spasms
- rash

Reporting of side effects

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

5. How to store Vosevi

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

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

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

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

6. Contents of the pack and other information

What Vosevi contains

- **The active substances are** sofosbuvir, velpatasvir and voxilaprevir. Each film-coated tablet contains 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir.

- **The other ingredients are**

Tablet core:

Colloidal anhydrous silica, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose

Film-coating:

Iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172), macrogol, polyvinyl alcohol, talc, titanium dioxide (E171)

What Vosevi looks like and contents of the pack

The film-coated tablets are beige, capsule-shaped tablets debossed with “GSI” on one side and “3” on the other side. The tablet is 20 mm long and 10 mm wide.

The tablets are packed in plastic bottles with child resistant caps. Each bottle contains a silica gel desiccant (drying agent) that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack size is available:

- outer cartons containing 1 bottle of 28 film-coated tablets

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Manufacturer

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