Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Geometric Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK With/Without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
Cyclosporine	600 single dose	SOF	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
		VEL	100 single dose	12	velpatasvir	1.56 (1.22, 2.01)	2.03 (1.51, 2.71)	NA
		VOX	100 single dose	25	voxilaprevir	19.02 (14.12, 25.62)	9.39 (7.37, 11.96)	NA
Darunavir + ritonavir + emtricitabine/ tenofovir DF	800 + 100 + 200/300 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	sofosbuvir	0.70 (0.62, 0.78)	0.78 (0.73, 0.83)	NA
					GS-331007	1.06 (1.01, 1.10)	1.15 (1.12, 1.19)	NA
					velpatasvir	0.78 (0.73, 0.84)	0.95 (0.88, 1.02)	1.16 (1.07, 1.26)
					voxilaprevir	1.72 (1.51, 1.97)	2.43 (2.15, 2.75)	4.00 (3.44, 4.65)
Dolutegravir	50 once daily	SOF/VEL	400/100 once daily	24	sofosbuvir	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
					GS-331007	1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
					velpatasvir	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)
Efavirenz/ emtricitabine/ tenofovir DF[b]	600/200/300 once daily	SOF/VEL	400/100 once daily	14	sofosbuvir	1.38 (1.14, 1.67)	0.97 (0.83, 1.14)	NA
					GS-331007	0.86 (0.80, 0.93)	0.90 (0.85, 0.96)	1.01 (0.95, 1.07)
					velpatasvir	0.53 (0.43, 0.64)	0.47 (0.39, 0.57)	0.43 (0.36, 0.52)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[c]	150/150/200/ 10 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	sofosbuvir	1.27 (1.09, 1.48)	1.22 (1.12, 1.32)	NA
					GS-331007	1.28 (1.25, 1.32)	1.43 (1.39, 1.47)	NA
					velpatasvir	0.96 (0.89, 1.04)	1.16 (1.06, 1.27)	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)
Ketoconazole	200 twice daily	VEL	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Geometric Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK With/Without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
Methadone	30 to 130 daily	SOF	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA
Omeprazole	20 once daily 2 hours prior to VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	34	sofosbuvir	0.77 (0.65, 0.91)	0.73 (0.67, 0.79)	NA
					GS-331007	1.27 (1.20, 1.34)	0.97 (0.94, 1.01)	NA
					velpatasvir	0.43 (0.38, 0.49)	0.46 (0.41, 0.52)	NA
					voxilaprevir	0.76 (0.69, 0.85)	0.80 (0.74, 0.87)	NA
	20 once daily 4 hours after VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	34	sofosbuvir	0.94 (0.83, 1.06)	0.82 (0.77, 0.87)	NA
					GS-331007	1.19 (1.13, 1.26)	0.99 (0.97, 1.01)	NA
					velpatasvir	0.49 (0.43, 0.55)	0.49 (0.43, 0.55)	NA
					voxilaprevir	1.08 (0.96, 1.22)	0.95 (0.88, 1.03)	NA
Rifampin	600 once daily	SOF	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
		VEL	100 single dose	12	velpatasvir	0.29 (0.23, 0.37)	0.18 (0.15, 0.22)	NA
		VOX	100 single dose	24	voxilaprevir	0.91 (0.76, 1.10)	0.27 (0.23, 0.31)	NA
	600 single dose	VEL	100 single dose	12	velpatasvir	1.28 (1.05, 1.56)	1.46 (1.17, 1.83)	NA
		VOX	100 single dose	24	voxilaprevir	11.10 (8.23, 14.98)	7.91 (6.20, 10.09)	NA
Tacrolimus	5 single dose	SOF	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA
Voriconazole	200 twice daily	VOX	100 single dose	24	voxilaprevir	1.13 (0.98, 1.31)	1.84 (1.66, 2.03)	NA

NA = not available/not applicable, ND = not dosed.
a. All interaction studies conducted in healthy volunteers.
b. Administered as ATRIPLA (efavirenz, emtricitabine and tenofovir DF fixed-dose combination).
c. Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fixed-dose combination).

No effect on the pharmacokinetic parameters of sofosbuvir, GS-331007, velpatasvir, or voxilaprevir was observed with the combination of emtricitabine, rilpivirine, and tenofovir alafenamide; famotidine; gemfibrozil; or the combination of raltegravir, emtricitabine, and tenofovir DF.

Table 7 Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI[a]

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)			Geometric Mean Ratio (90% CI) of Coadministered Drug PK With/Without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)	N	C_{max}	AUC	C_{min}
Cyclosporine	600 single dose	SOF	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
		VEL	100 single dose	12	0.92 (0.82, 1.02)	0.88 (0.78, 1.00)	NA
		VOX	100 single dose	24	0.95 (0.88, 1.03)	0.94 (0.84, 1.06)	NA
Dabigatran etexilate	75 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	36	2.87 (2.61, 3.15)	2.61 (2.41, 2.82)	NA
Darunavir + ritonavir + emtricitabine/ tenofovir DF[b]	darunavir 800 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	0.89 (0.85, 0.94)	0.86 (0.81, 0.91)	0.66 (0.58, 0.74)
	ritonavir 100 once daily				1.60 (1.47, 1.75)	1.45 (1.35, 1.57)	0.80 (0.72, 0.89)
	emtricitabine 200 once daily				0.88 (0.82, 0.94)	0.99 (0.96, 1.03)	1.20 (1.15, 1.26)
	tenofovir DF 300 once daily				1.48 (1.36, 1.61)	1.39 (1.32, 1.46)	1.47 (1.38, 1.56)
Digoxin	0.25 single dose	VEL	100 once daily	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA
Efavirenz/ emtricitabine/ tenofovir DF[c]	efavirenz 600 once daily	SOF/VEL	400/100 once daily	15	0.81 (0.74, 0.89)	0.85 (0.80, 0.91)	0.90 (0.85, 0.95)
	emtricitabine 200 once daily				1.07 (0.98, 1.18)	1.07 (1.00, 1.14)	1.10 (0.97, 1.25)
	tenofovir DF 300 once daily				1.77 (1.53, 2.04)	1.81 (1.68, 1.94)	2.21 (2.00, 2.43)
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide	elvitegravir 150 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	0.79 (0.75, 0.85)	0.94 (0.88, 1.00)	1.32 (1.17, 1.49)
	cobicistat 150 once daily				1.23 (1.18, 1.28)	1.50 (1.44, 1.58)	3.50 (3.01, 4.07)
	emtricitabine 200 once daily				0.87 (0.84, 0.91)	0.96 (0.94, 0.99)	1.14 (1.09, 1.20)
	tenofovir alafenamide 10 once daily				0.79 (0.68, 0.92)	0.93 (0.85, 1.01)	NA
Emtricitabine/ rilpivirine/tenofovir alafenamide[e]	emtricitabine 200 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	30	0.88 (0.83, 0.93)	0.93 (0.90, 0.96)	1.07 (1.01, 1.14)
	rilpivirine 25 once daily				0.79 (0.74, 0.84)	0.80 (0.76, 0.85)	0.82 (0.77, 0.87)
	tenofovir alafenamide 25 once daily				1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Geometric Mean Ratio (90% CI) of Coadministered Drug PK With/Without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
Pravastatin	40 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	19	1.89 (1.53, 2.34)	2.16 (1.79, 2.60)	NA
Rosuvastatin	10 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	19	18.88 (16.23, 21.96)	7.39 (6.68 8.18)	NA
Raltegravir + emtricitabine/ tenofovir DF	emtricitabine 200 once daily	SOF/VEL	400/100 once daily	30	1.08 (1.04, 1.12)	1.05 (1.03, 1.07)	1.02 (0.97, 1.08)
	tenofovir DF 300 once daily				1.46 (1.39, 1.54)	1.40 (1.34, 1.45)	1.70 (1.61, 1.79)
	raltegravir 400 twice daily				1.03 (0.74, 1.43)	0.97 (0.73, 1.28)	0.79 (0.42, 1.48)
Tacrolimus	5 single dose	SOF	400 once daily	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA

NA = not available/not applicable
a. All interaction studies conducted in healthy volunteers
b. Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir DF.
c. Administered as ATRIPLA (efavirenz, emtricitabine and tenofovir DF fixed-dose combination).
d. Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fixed-dose combination).
e. Administered as ODEFSEY (emtricitabine, rilpivirine, and tenofovir alafenamide fixed-dose combination).

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with VOSEVI (ethinyl estradiol/norgestimate) or its components sofosbuvir/velpatasvir (dolutegravir) or sofosbuvir (methadone).

12.4 Microbiology

Mechanism of Action

Sofosbuvir is an 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 analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC_{50} value ranging from 0.36 to 3.3 µM. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Voxilaprevir is a noncovalent, reversible inhibitor of the NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature

forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical inhibition assay, voxilaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1b and 3a with K_i values of 38 and 66 pM, respectively.

Antiviral Activity

In HCV replicon assays, sofosbuvir had median EC_{50} values of 15–110 nM against full-length or chimeric laboratory isolates and clinical isolates from subtypes 1a, 1b, 2a, 2b, 3a, 4a, 4d, 5a, and 6a. Velpatasvir had median EC_{50} values of 0.002–0.13 nM against full-length or chimeric laboratory isolates and clinical isolates from subtypes 1a, 1b, 2a, 2b, 3a, 4a, 4d, 4r, 5a, 6a, and 6e. Voxilaprevir had median EC_{50} values of 0.2–6.6 nM against full-length or chimeric laboratory isolates and clinical isolates from subtypes 1a, 1b, 2a, 2b, 3a, 4a, 4d, 4r, 5a, 6a, 6e, and 6n.

Evaluation of sofosbuvir in combination with velpatasvir or voxilaprevir, as well as the combination of velpatasvir and voxilaprevir, showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the nucleotide analog NS5B polymerase inhibitor resistance substitution, S282T, in all replicon genotypes examined. An M289L substitution emerged along with the S282T substitution in genotypes 2a, 5 and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of genotype 1 to 6 conferred 2- to 18-fold reduced susceptibility to sofosbuvir.

HCV genotype 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to velpatasvir were selected in cell culture. The replicon variants developed amino acid substitutions at NS5A inhibitor resistance-associated positions 24, 28, 30, 31, 32, 58, 92, and 93. Phenotypic analysis of site-directed mutant replicons of the selected NS5A substitutions showed that single Y93H/N and the combination of L31V + Y93H/N in genotype 1a, the combination of L31V + Y93H in genotype 1b, the single substitution Y93H/S in genotype 3a, and single substitutions L31V and P32A/L/Q/R in genotype 6 conferred greater than 100-fold reduction in velpatasvir susceptibility. In the genotype 2a replicon, the single substitutions F28S and Y93H showed 91-fold and 46-fold reduced susceptibility to velpatasvir, respectively. The single substitution Y93H conferred 3-fold reduced susceptibility to velpatasvir in genotype 4a replicons. Combinations of these NS5A substitutions often showed greater reductions in susceptibility to velpatasvir than single substitutions alone.

HCV genotype 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to voxilaprevir were selected in cell culture. Amino acid substitutions were selected at NS3/4A protease inhibitor resistance-associated positions 41, 156, and 168. Site-directed mutagenesis of NS3 resistance-associated substitutions showed that

substitutions conferring a greater than 100-fold reduction in voxilaprevir susceptibility were A156L/T in genotype 1a, A156T/V in genotype 1b, A156L/V in genotype 2a, A156T/V in genotype 3a, and A156L/T/V in genotype 4. Combinations of these NS3 substitutions often showed greater reductions in susceptibility to voxilaprevir than single substitutions alone.

In Clinical Trials
Of the 263 NS5A inhibitor-experienced subjects treated with VOSEVI for 12 weeks in POLARIS-1, 7 of 263 (3%) subjects (2 with genotype 1a, 4 with genotype 3a, and 1 with genotype 4d) did not achieve SVR12 and qualified for resistance analysis; 6 relapsed and 1 experienced virologic breakthrough. All the virologic failures had cirrhosis and all had a previous DAA regimen containing sofosbuvir; 3 were previously treated with ledipasvir/sofosbuvir, 2 were previously treated with sofosbuvir/velpatasvir, and 2 were previously treated with daclatasvir and sofosbuvir. Six of the 7 virologic failures had baseline NS5A inhibitor resistance-associated substitutions at position 30 or 93. All 7 virologic failures had NS5A resistance-associated substitutions at failure using a sensitivity threshold of 1% of the viral population.

Of the 2 genotype 1a virologic failure subjects, one subject with virologic breakthrough at Week 12 had virus with the NS5A resistance-associated substitution Q30T at baseline and failure and emergent NS5A resistance-associated substitutions L31M and Y93H at breakthrough; the other subject had virus with the NS5A resistance-associated substitution Y93N at baseline and relapse and emergence of low-level K24R (1.2%) in NS5A and V36A (2%) in NS3 at relapse.

Of the 4 genotype 3a virologic failure subjects, one subject had virus with emergent NS5A resistance-associated substitution E92K. Two subjects had virus with Y93H at relapse that was enriched from baseline. The remaining subject had virus with the NS5A resistance-associated substitution A30K at baseline and relapse and emergence of low-level Q41K (2%), V55A (3%) and R155M (1%) substitutions in NS3 at relapse.

The genotype 4d subject who relapsed had virus with emergent NS5A resistance-associated substitution Y93H.

No NS5B nucleotide analog inhibitor resistance-associated substitutions emerged among the virologic failure subjects from POLARIS-1.

In POLARIS-4, of the 182 DAA-experienced subjects who had not received an NS5A inhibitor treated with VOSEVI for 12 weeks, 1 subject (genotype 1a) of 182 (1%) subjects relapsed and qualified for resistance analysis. The NS5A resistance-associated substitution M28T (7.5%) emerged in this subject at relapse. No NS3/4A protease inhibitor or nucleotide analog NS5B inhibitor substitutions were observed in this subject at relapse.

Persistence of Resistance-Associated Substitutions

No data are available on the persistence of sofosbuvir, velpatasvir or voxilaprevir resistance-associated substitutions. NS5A inhibitor resistance-associated substitutions observed with administration of other NS5A inhibitors have been found to persist for longer than 1 year in most patients. The long-term clinical impact of the emergence or persistence of virus containing sofosbuvir, velpatasvir, or voxilaprevir resistance-associated substitutions is unknown.

Effect of Baseline HCV Variants on Treatment Response

Analyses were conducted to explore the association between SVR12 rates and preexisting baseline NS3/4A protease inhibitor and NS5A inhibitor resistance-associated substitutions for subjects in POLARIS-1 and POLARIS-4. Amino acid positions considered in resistance analyses included NS3 positions 36, 41, 43, 54, 55, 56, 155, 156, and 168, and NS5A positions 24, 28, 30, 31, 58, 92, or 93. Baseline resistance-associated amino acid substitutions, which may include natural polymorphisms or prior treatment-emergent substitutions relative to subtype-specific references, were identified by next generation sequencing analysis using a sensitivity threshold of 15% of the viral population.

Overall, the presence of baseline NS3/4A protease inhibitor, NS5A inhibitor, and nucleotide analog NS5B polymerase inhibitor resistance-associated substitutions did not alter the SVR rates for DAA-experienced subjects in the POLARIS-1 and POLARIS-4 trials who received 12 weeks of VOSEVI. For subjects treated with VOSEVI for 12 weeks, SVR12 rates in subjects with or without baseline NS3 and NS5A resistance-associated substitutions in the POLARIS-1 and POLARIS-4 trials were all greater than or equal to 97%.

In POLARIS 1, which included NS5A inhibitor-experienced subjects, 79% (206/260) of subjects had baseline NS5A resistance-associated substitutions across all genotypes. The most prevalent NS5A resistance-associated substitutions were at primary resistance-associated amino acid positions 30 (97/206; 47%), 31 (58/206; 28%) and 93 (103/206; 50%). Fifty-five percent (n=113/206) of the subjects had a single NS5A resistance-associated substitution, while 2 resistance-associated substitutions were detected in 65/206 subjects (32%) and 3 or more were detected in 28/206 subjects (14%). Overall prevalence of NS3/4A protease inhibitor resistance-associated substitutions across all genotypes was 15% (37/248). The most prevalent NS3 resistance-associated substitutions were at positions 36 (5/17; 29%) and 168 (7/17; 41%) in genotype 1a and position 56 in genotype 1b (8/12; 67%). Substitutions at positions 36, 56, or 168 were detected in 1-2 subjects for each genotype 2, 3 or 4.

In POLARIS-4, which included DAA-experienced subjects who had not received an NS5A inhibitor, 32% (57/177) of subjects who received 12 weeks of VOSEVI had baseline NS5A inhibitor resistance-associated substitutions. Most of the subjects had a single NS5A resistance-associated substitution (n=40; 70%). The most prevalent NS5A resistance-associated substitution was at amino acid position 31 (n=27; 47%). Overall

prevalence of baseline NS3/4A protease inhibitor resistance-associated substitutions was 12% (21/169). The most prevalent NS3 resistance-associated substitutions were at positions 55 (5/10) and 168 (3/10) in genotype 1a, position 56 in genotype 1b (3/5) and genotype 2 (3/3), and at position 168 in genotype 4 (3/3).

SVR12 was achieved in 18 of 19 (95%) subjects who had baseline nucleotide analog NS5B polymerase inhibitor resistance-associated substitutions in POLARIS-1, including 2 subjects who had virus with the S282T nucleotide analog NS5B polymerase inhibitor resistance-associated substitution in addition to NS5A resistance-associated substitutions at baseline. In POLARIS-4, a total of 14 subjects had virus with nucleotide analog NS5B polymerase inhibitor resistance-associated substitutions at baseline and all achieved SVR12.

Cross Resistance

Cross-resistance is possible between HCV NS3/4A protease inhibitors and between HCV NS5A inhibitors by class. Sofosbuvir, velpatasvir, and voxilaprevir were each active against substitutions associated with resistance to other classes of DAAs with different mechanisms of actions (e.g., voxilaprevir was fully active against virus with NS5A resistance-associated substitutions and nucleotide analog NS5B inhibitor resistance-associated substitutions).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

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.

Sofosbuvir was not carcinogenic in a 2-year mouse study (up to 200 mg/kg/day in males and 600 mg/kg/day in females) and in a 2-year rat study (up to 750 mg/kg/day), resulting in exposures of the predominant circulating metabolite GS-331007 of approximately 4 and 17 times (in male and female mice, respectively) and 9 times (in rats) the exposure in humans at the recommended human dose (RHD).

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 a 26-week transgenic mouse study (up to 1000 mg/kg/day). A carcinogenicity study in rats is ongoing.

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.

Impairment of Fertility

Sofosbuvir: Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS-331007 was approximately 4 times the exposure in humans at the RHD.

Velpatasvir: Velpatasvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, velpatasvir exposure was approximately 4 times the exposure in humans at the RHD.

Voxilaprevir: Voxilaprevir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, voxilaprevir exposure was approximately 149 times the exposure in humans at the RHD.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy of VOSEVI was evaluated in two Phase 3 trials in DAA-experienced subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis, as summarized in Table 8.

Table 8 Trials Conducted With VOSEVI in DAA-Experienced Subjects With HCV Infection

Trial	Population	Study Arms and Comparator Groups (Number of Subjects Treated)
POLARIS-1	Genotype 1, 2, 3, 4, 5, or 6 NS5A inhibitor-experienced[a], without cirrhosis or with compensated cirrhosis	VOSEVI 12 weeks (263) Placebo 12 weeks (152)
POLARIS-4	Genotype 1, 2, 3, or 4 DAA-experienced[b] who have not received an NS5A inhibitor, without cirrhosis or with compensated cirrhosis	VOSEVI 12 weeks (182) SOF/VEL 12 weeks (151)

DAA: direct-acting antiviral; SOF: sofosbuvir; VEL: velpatasvir

a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.

b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

Serum HCV RNA values were measured during the clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL. Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in both trials. Relapse is defined as HCV RNA greater than or equal to LLOQ after end-of-treatment response among subjects who completed treatment. On-treatment virologic failure is defined as breakthrough, rebound, or non-response.

14.2 Clinical Trials in HCV DAA-Experienced Subjects

NS5A Inhibitor-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis (POLARIS-1)

POLARIS-1 was a randomized, double-blind, placebo-controlled trial that evaluated 12 weeks of treatment with VOSEVI compared with 12 weeks of placebo in DAA-experienced subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Subjects with genotype 1 HCV infection were randomized 1:1 to each group. Subjects with genotype 2, 3, 4, 5, or 6 HCV infection were enrolled to the VOSEVI group. Randomization was stratified by the presence or absence of cirrhosis.

Demographics and baseline characteristics were generally balanced across treatment groups. Of the 415 treated subjects, the median age was 59 years (range: 27 to 84); 77% of the subjects were male; 81% were White; 14% were Black; 6% were Hispanic or Latino; 33% had a baseline body mass index at least 30 kg/m^2; the majority of subjects had genotype 1 (72%) or genotype 3 (19%) HCV infection; 82% had a non-CC IL28B genotype (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; and 41% had compensated cirrhosis. In the POLARIS-1 trial, prior DAA regimens contained the following NS5A inhibitors: ledipasvir (51%), daclatasvir (27%), ombitasvir (11%), velpatasvir (7%), and elbasvir (3%).

Table 9 presents the SVR12 by HCV genotype for the POLARIS-1 trial. No subjects in the placebo group achieved SVR12.

Table 9 POLARIS-1 Trial: Virologic Outcomes by HCV Genotype in VOSEVI-Treated Subjects Without Cirrhosis or With Compensated Cirrhosis (12 Weeks After Treatment)

	VOSEVI 12 Weeks (N=263)								
	Total (all GTs)[a] (N=263)	GT-1			GT-2 (N=5)	GT-3 (N=78)	GT-4 (N=22)	GT-5 (N=1)	GT-6 (N=6)
		GT-1a (N=101)	GT-1b (N=45)	Total[b] (N=150)					
SVR12	96% (253/263)	96% (97/101)	100% (45/45)	97% (146/150)	100% (5/5)	95% (74/78)	91% (20/22)	100% (1/1)	100% (6/6)
Outcome for Subjects without SVR									
On-Treatment Virologic Failure	<1% (1/263)	1% (1/101)	0/45	1% (1/150)	0/5	0/78	0/22	0/1	0/6
Relapse[c]	2% (6/261)	1% (1/100)	0/45	1% (1/149)	0/5	5% (4/78)	5% (1/21)	0/1	0/6
Other[d]	1% (3/263)	2% (2/101)	0/45	1% (2/150)	0/5	0/78	5% (1/22)	0/1	0/6

GT: genotype
a. One subject with undetermined genotype achieved SVR12.
b. Four subjects had GT-1 subtypes other than GT-1a or GT-1b; all 4 subjects achieved SVR12.
c. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the end-of-treatment assessment.
d. Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

DAA-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis Who Had Not Received An NS5A Inhibitor (POLARIS-4)

POLARIS-4 was a randomized, open-label trial that evaluated 12 weeks of treatment with VOSEVI and 12 weeks of treatment with SOF/VEL in subjects with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed a HCV DAA-containing regimen that did not include an NS5A inhibitor. Subjects whose only DAA exposure was an NS3/4A protease inhibitor were excluded. Subjects with genotype 1, 2, or 3 HCV infection were randomized 1:1 to each group. Randomization was stratified by HCV genotype and by the presence or absence of cirrhosis. Subjects with genotype 4 HCV infection were enrolled to the VOSEVI group. No subjects with genotype 5 or 6 were enrolled.

Demographics and baseline characteristics were generally balanced across treatment groups. Of the 333 treated subjects, the median age was 58 years (range: 24 to 85); 77% of the subjects were male; 87% were White, 9% were Black; 8% were Hispanic or Latino; 35% had a baseline body mass index at least 30 kg/m^2; 81% had non-CC IL28B genotypes (CT or TT); 75% had baseline HCV RNA levels at least 800,000 IU/mL; and 46% had compensated cirrhosis. In the POLARIS-4 trial, prior DAA regimens contained sofosbuvir (85%) with the following: peginterferon alfa and ribavirin or ribavirin (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (<1%). Of the 15% of subjects without prior sofosbuvir exposure, most received investigational HCV DAAs or approved HCV NS3/4A protease inhibitors, with or without peginterferon alfa and ribavirin.

Treatment with VOSEVI for 12 weeks resulted in numerically higher SVR12 rates than treatment with sofosbuvir/velpatasvir for 12 weeks in subjects with HCV genotype 1a and 3 infection. Comparable SVR12 rates were observed in subjects with HCV genotype 1b and 2 infection treated with VOSEVI for 12 weeks or with sofosbuvir/velpatasvir for 12 weeks. No comparison data are available for HCV genotypes 4, 5, and 6. Given these data, the additional benefit of VOSEVI has not been shown over sofosbuvir/velpatasvir for these genotypes and VOSEVI is only indicated for the treatment of HCV genotypes 1a or 3 infection in adults who previously received sofosbuvir without an NS5A inhibitor.

Table 10 presents the comparative virologic outcome data for HCV genotype 1, 2, and 3 subjects with prior exposure to a sofosbuvir-containing regimen.

Table 10 POLARIS-4 Trial: Virologic Outcomes by HCV Genotype in VOSEVI-Treated Subjects* and SOF/VEL-Treated Subjects* Without Cirrhosis or With Compensated Cirrhosis (12 Weeks After Treatment)

*Subjects with prior exposure to a SOF-containing regimen	VOSEVI 12 Weeks (N=139)	SOF/VEL 12 Weeks (N=125)
Overall (Genotypes 1, 2, and 3)		
SVR12	97% (135/139)	88% (110/125)
Not achieving SVR12		
On-treatment virologic failure	0% (0/139)	1% (1/125)
Relapse[a]	1% (1/139)	10% (13/124)
Other[b]	2% (3/139)	1% (1/125)
Genotype 1		

*Subjects with prior exposure to a SOF-containing regimen	VOSEVI 12 Weeks (N=139)	SOF/VEL 12 Weeks (N=125)
SVR12	96% (52/54)	85% (34/40)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/40)
Relapse[a]	2% (1/54)	13% (5/40)
Other[b]	2% (1/54)	3% (1/40)
Genotype 1a		
SVR12	97% (35/36)	82% (23/28)
Not achieving SVR12		
On-treatment virologic failure	0% (0/36)	0% (0/28)
Relapse[a]	3% (1/36)	18% (5/28)
Other[b]	0% (0/36)	0% (0/28)
Genotype 1b		
SVR12	94% (17/18)	92% (11/12)
Not achieving SVR12		
On-treatment virologic failure	0% (0/18)	0% (0/12)
Relapse[a]	0% (0/18)	0% (0/12)
Other[b]	6% (1/18)	8% (1/12)
Genotype 2		
SVR12	100% (31/31)	97% (32/33)
Not achieving SVR12		
On-treatment virologic failure	0% (0/31)	3% (1/33)
Relapse[a]	0% (0/31)	0% (0/32)
Other[b]	0% (0/31)	0% (0/33)
Genotype 3		
SVR12	96% (52/54)	85% (44/52)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/52)
Relapse[a]	0% (0/54)	15% (8/52)
Other[b]	4% (2/54)	0% (0/52)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the end-of-treatment assessment.
b. Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

In POLARIS-4, VOSEVI was administered for 12 weeks to 18 HCV genotype 4 subjects (with or without cirrhosis) who had prior exposure to a SOF-containing regimen without an NS5A inhibitor. All subjects achieved SVR12.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each VOSEVI tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. The tablets are beige, capsule-shaped, film-coated, and debossed with "GSI" on one side and "3" on the other side. Each bottle contains 28 tablets (NDC 61958-2401-1), polyester coil, silica gel desiccant, and is closed with a child-resistant closure.

Store below 30 °C (86 ºF). Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV
Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV virus infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B infection *[see Warnings and Precautions (5.1)].*

Serious Symptomatic Bradycardia When Coadministered with Amiodarone
Advise patients to seek medical evaluation immediately for symptoms of bradycardia such as near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems *[see Warnings and Precautions (5.2), Adverse Reactions (6.2), and Drug Interactions (7.3)].*

Drug Interactions
Inform patients that VOSEVI may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products including St. John's wort *[see Warnings and Precautions (5.2, 5.3) and Drug Interactions (7)].*

Administration
Advise patients to take VOSEVI once daily on a regular dosing schedule with food. Inform patients that it is important not to miss or skip doses and to take VOSEVI for the duration that is recommended by the physician.

Manufactured and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

209195-GS-000

Patient Information
VOSEVI (voh-SEV-ee)
(sofosbuvir, velpatasvir, and voxilaprevir) tablets

What is the most important information I should know about VOSEVI?

VOSEVI can cause serious side effects, including,

Hepatitis B virus reactivation: Before starting treatment with VOSEVI, your healthcare provider will do blood tests to check for hepatitis B virus infection. If you have ever had hepatitis B virus infection, the hepatitis B virus could become active again during or after treatment of hepatitis C virus with VOSEVI. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure and death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop taking VOSEVI.

For more information about side effects, see the section "What are the possible side effects of VOSEVI?"

What is VOSEVI?

VOSEVI is a prescription medicine used to treat adults with chronic (lasting a long time) hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis who have:

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
- genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

It is not known if VOSEVI is safe and effective in children.

Do not take VOSEVI: if you also take any medicines that contain rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)

Before taking VOSEVI, tell your healthcare provider about all your medical conditions, including if you:

- have ever had hepatitis B infection
- have liver problems other than hepatitis C infection
- have severe kidney problems or you are on dialysis
- are pregnant or plan to become pregnant. It is not known if VOSEVI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VOSEVI passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take VOSEVI.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VOSEVI and other medicines may affect each other. This can cause you to have too much or not enough VOSEVI or other medicines in your body. This may affect the way VOSEVI or your other medicines work, or may cause side effects.

Keep a list of your medicines to show your healthcare provider and pharmacist.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with VOSEVI.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take VOSEVI with other medicines.

How should I take VOSEVI?

- Take VOSEVI exactly as your healthcare provider tells you. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking VOSEVI without first talking with your healthcare provider.
- Take 1 VOSEVI tablet by mouth each day on a regular schedule.
- Take VOSEVI with food.
- If you need to take an antacid medicine that contains aluminum or magnesium, take it either 4 hours before or 4 hours after you take your dose of VOSEVI.
- It is important that you do not miss or skip doses of VOSEVI during treatment.
- If you take too much VOSEVI, call your healthcare provider or go to the nearest hospital emergency

room right away.

What are the possible side effects of VOSEVI?

VOSEVI may cause serious side effects, including:

- **Hepatitis B virus (HBV) reactivation.** See "What is the most important information I should know about VOSEVI?"
- **Slow heart rate (bradycardia).** VOSEVI treatment may result in slowing of the heart rate along with other symptoms when taken with amiodarone (Cordarone®, Nexterone®, Pacerone®), a medicine used to treat certain heart problems. In some cases bradycardia has led to death or the need for a heart pacemaker when amiodarone is taken with medicines similar to VOSEVI that contain sofosbuvir. Get medical help right away if you take amiodarone with VOSEVI and get any of the following symptoms:
  - fainting or near-fainting
  - dizziness or lightheadedness
  - not feeling well
  - weakness
  - extreme tiredness
  - shortness of breath
  - chest pains
  - confusion
  - memory problems
- The most common side effects of VOSEVI include headache, tiredness, diarrhea, and nausea.
- These are not all the possible side effects of VOSEVI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VOSEVI?

- Store VOSEVI below 86 °F (30 °C).
- Keep VOSEVI in its original container.

Keep VOSEVI and all medicines out of the reach of children.

General information about the safe and effective use of VOSEVI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VOSEVI for a condition for which it was not prescribed. Do not give VOSEVI to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about VOSEVI that is written for health professionals.

What are the ingredients in VOSEVI?

Active ingredients: sofosbuvir, velpatasvir, and voxilaprevir

Inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

The tablet film-coat contains: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by:
Gilead Sciences, Inc., Foster City, CA 94404
For more information, call 1-800-445-3235 or go to www.VOSEVI.com.

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