Sofosbuvir/Velpatasvir for the treatment of Hepatitis C

Application for inclusion on the WHO Model List of Essential Medicines (EML)

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General Items

Summary statement of the proposal for inclusion, change or deletion

Velpatasvir in combination with sofosbuvir is a once-daily US-FDA approved pan-genotypic regimen for the treatment of chronic hepatitis C (HCV) genotypes 1-6 in adults. [1] Velpatasvir is a NS5A inhibitor, preventing HCV viral RNA replication and virion assembly, and is administered in combination with sofosbuvir, a HCV NS5B polymerase inhibitor with established pharmacological properties, already included on the WHO Essential Medicines List (EML).

Over a number of clinical trials, sofosbuvir/velpatasvir for 12 weeks provided very high rates of sustained virological response at 12 weeks post treatment (SVR12) in treatment-naïve and experienced patients with chronic HCV genotype 1-6 infection, including those with compensated cirrhosis or human immunodeficiency virus (HIV) co-infection. High SVR12 rates have also been observed in individuals with decompensated cirrhosis. The regimen is generally well tolerated, with low rates of adverse events, and low discontinuation rates.

Considering this efficacy and safety data, sofosbuvir/ledipasvir is a valuable treatment option in adults with chronic HCV genotypes 1-6 and should supplement the current HCV regimens included in the WHO EML.

Name of the WHO technical department and focal point supporting the application (where relevant)

WHO Global Hepatitis Programme, Department of HIV/AIDS

Name of organization(s) consulted and/or supporting the application

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International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

- Velpatasvir (J05AX)

Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate)

Velpatasvir is available as a fixed-dose tablet in combination with sofosbuvir, manufactured by Gilead Sciences (trade name, *Epclusa*). Each tablet contains 100 mg of velpatasvir and 400 mg of sofosbuvir. The recommended dose of the combination is one tablet taken orally once daily with or without food.

This information is shown in Table 1. The safety and effectiveness of sofosbuvir/velpatasvir have not been established in paediatric patients and as such, no paediatric formulations are included.

Table 1 Formulations and strengths proposed for inclusion

Medicine	Formulation	Market availability
Velpatasvir	100 mg	-
Fixed-dose combinations		
Sofosbuvir + **Velpatasvir**	**Tablet:** 400 mg + 100 mg	Epclusa; Gilead Sciences

[a]No known market availability of individual formulations of velpatasvir

Whether listing is requested as an individual medicine or as representative of a pharmacological class

The listing is requested as Individuals medicines.

Treatment details, public health relevance and evidence appraisal and synthesis

Velpatasvir/sofosbuvir treatment details

Velpatasvir 100 mg in combination with sofosbuvir 400 mg should be provided as per the recommendations from international/national guidelines as detailed in the sections below.

Table 2 Product presentation and posology

Product	Presentation	Posology
Velpatasvir/sofosbuvir	Tablet containing 100 mg of velpatasvir and 400 mg of sofosbuvir	One tablet once daily (morning)

WHO Guidelines

Velpatasvir/sofosbuvir was not considered in the 2016 WHO Guidelines as it had not received stringent regulatory approval (SRA) at the time of the Guidelines Development Group meeting. [2] The guidelines state that preliminary data suggest that the regimen will provide good efficacy and safety with strong potential for a pan-genotypic regimen.

US Guidelines (AASLD/IDSA)

The 2016 AASLD/IDSA guidelines have been update to include velpatasvir/sofosbuvir as a recommended treatment for individuals across genotypes 1 to 6. [3] Treatment duration is 12 weeks for individuals either treatment-naïve or previously Peg-IFN/RBV treated regardless of the presence of compensated cirrhosis. This information is summarised in Table 3.

Additionally, velpatasvir/sofosbuvir + weight based ribavirin (WB RBV) for 12 weeks is recommended for patients with genotype 1, 2, 3 or 4 infection who have decompensated cirrhosis; treatment can be extended to 24 weeks in those RBV ineligible. For decompensated patients with previous sofosbuvir-based treatment failure, 24 weeks of sofosbuvir/velpatasvir + WB RBV is recommended. Sofosbuvir/velpatasvir is recommended for use in individuals with HIV and can be used with most antiretrovirals (ARVs). No dosage adjustments are required for patients with mild to moderate renal impairment; the regimen is not recommended for those with severe renal impairment.

Table 3 AASLD velpatasvir/sofosbuvir treatment recommendations in individuals with or without compensated cirrhosis

Patient population	Treatment	Duration
Genotype 1: Treatment-naïve or Peg-IFN/RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir	12 weeks
Genotype 1: PI+Peg-IFN/RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir	12 weeks
Genotype 2: Treatment-naïve or Peg-IFN/RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir	12 weeks
Genotype 2: SOF+RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir + WB RBV	12 weeks
Genotype 3: Treatment-naïve (no cirrhosis or compensated)	Velpatasvir/sofosbuvir	12 weeks
Genotype 3: Peg-IFN/RBV experienced, no cirrhosis	Velpatasvir/sofosbuvir	12 weeks
Genotype 3: Peg-IFN/RBV experienced, compensated cirrhosis	Velpatasvir/sofosbuvir + WB RBV	12 weeks
Genotype 3: SOF+RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir + WB RBV	12 weeks
Genotype 4: Treatment-naïve or Peg-IFN/RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir	12 weeks
Genotype 5/6: Treatment-naïve or Peg-IFN/RBV experienced (no cirrhosis or compensated)	Velpatasvir/sofosbuvir	12 weeks

Abbreviations: Peg-IFN, pegylated interferon; RBV, ribavirin; WB RBV, weight-based ribavirin; PI, hepatitis C protease inhibitor

European guidelines (EASL)

Sofosbuvir/velpatasvir is recommended by EASL for all genotypes (genotypes 1 to 6). [4] Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination for 12 weeks without RBV;

treatment-experienced genotype 3 individuals require the addition of WB RBV. The same regimens can be provided in patients co-infected with HIV.

The regimen is recommended for individuals with decompensated cirrhosis for 12 weeks with the addition of RBV. Sofosbuvir/velpatasvir is not recommended in individuals with severe renal impairment.

Summary

- Not yet included in WHO Guidelines but recommended in US and European guidelines;
- Pan-genotypic, recommended across genotypes 1-6 infection;
- Recommended for use in individuals with HIV, with few contraindications with antiretrovirals;
- Recommended in patients with genotype 1-4 infection with decompensated cirrhosis;
- Not recommended for use in individuals with severe renal impairment.

Additional requirements associated with treatment

Prior to administration of HCV treatment, active chronic HCV needs to be confirmed. In most settings, this is conducted through an initial assay to detect the hepatitis C antibody (HCVAb). If HCVAb are detected, HCV RNA should be determined by a sensitive molecular method. [4] In areas where HCV RNA assays are not available or not affordable, measurement of HCV core antigen levels provides an alternative measure to confirm infection and whether treatment has been successful. [5, 6]

If feasible, other pre-therapeutic assessments should be conducted, including liver disease severity and renal function. Contraindications to therapy should be thoroughly explored, particularly in patients co-infected with HIV on antiretroviral regimens. Given that the regimen is pan-genotypic, treatment with sofosbuvir/velpatasvir negates the need to conduct genotyping which is expensive and infeasible in resource-limited settings.

Treatment should be initiated and monitored by a physician experienced in the management of patients with chronic HCV. The safety and effectiveness of task shifting of HCV treatment to non-specialised providers are currently being explored in various settings. [7, 8, 9] Specialised treatment facilities are not required for the initiation or monitoring of treatment.

Monitoring includes assessments of treatment efficacy, of safety and side-effects, and of drug-drug interactions. Monitoring of treatment efficacy can be simplified by measuring HCV RNA (or HCV core antigen levels) at baseline and 12 or 24 weeks after the end of

therapy. In terms of safety, new regimens, including sofosbuvir/velpatasvir are generally well tolerated with low frequencies of adverse advents.

Information supporting the public health relevance

Most recent analyses of the global prevalence of HCV indicate that an estimated 115 million persons are HCVAb positive of which approximately 80 million are chronically infected. [10] The prevalence varies greatly by region and population, with the highest burden, in terms of numbers chronically infected, observed in sub-Saharan Africa and South and East Asia.

Data from the Global Burden of Disease study indicates that the number of deaths attributable to HCV has been steadily increasing over the past decades from around 330,000 in 1990 to over 700,000 deaths per year in 2013. [11] This reflects the lag time between infection and the development of complications, such as liver cirrhosis and hepatocellular carcinoma. The number of deaths is projected to increase through several more decades unless there is a rapid scale-up in accessibility to treatment. [12]

The availability of direct-acting antivirals (DAAs) for treatment against HCV provide a realistic opportunity to scale-up treatment, particularly in resource-limited settings, where public health programmes were previously unfeasible. Scale-up of screening and treatment using efficacious DAA regimens, inclusive of sofosbuvir/ledipasvir, has the potential to reduce the incidence of liver-related complications and mortality in individuals with HCV infection. [13, 14] Data suggests that an increase in screening rates combined with treatment with highly efficacious regimens will be necessary to curb the increased mortality expected over the coming years. [13] Inclusion of sofosbuvir/velpatasvir on the WHO EML will help to ensure timely access to HCV treatment worldwide, alleviating the approaching health and economic burden.

Most DAA-based regimens currently available are not equally effective across all HCV genotype, however, sofosbuvir/ledipasvir for 12 weeks is recommended across all genotypes in patients without cirrhosis or with compensated cirrhosis, including those with previous treatment failure. Given the pan-genotypic nature of sofosbuvir/velpatasvir, use of the regimen permits a reduction in the need for complex and expensive diagnostics and is facilitative of task-shifting to lower cadres of health care professionals. The use of this simplified regimen is likely to facilitate scale-up of public health programmes in resource-limited settings, where most of the infected population reside. Further, sofosbuvir/ledipasvir plus ribavirin provides a treatment option for difficult-to-treat patients with decompensated cirrhosis.

Review of benefits: summary of comparative effectiveness in a variety of clinical settings

Several Phase 2 and 3 studies have been carried out evaluating the efficacy of velpatasvir and sofosbuvir with or without ribavirin for treatment of HCV genotypes 1 to 6. These trials include ASTRAL-1, ASTRAL-2, ASTRAL-3, ASTRAL-4, ASTRAL-5, Gane et al 2016, Everson et al. 2015 and Pianko et al. 2015.

Overview of sofosbuvir/velpatasvir efficacy

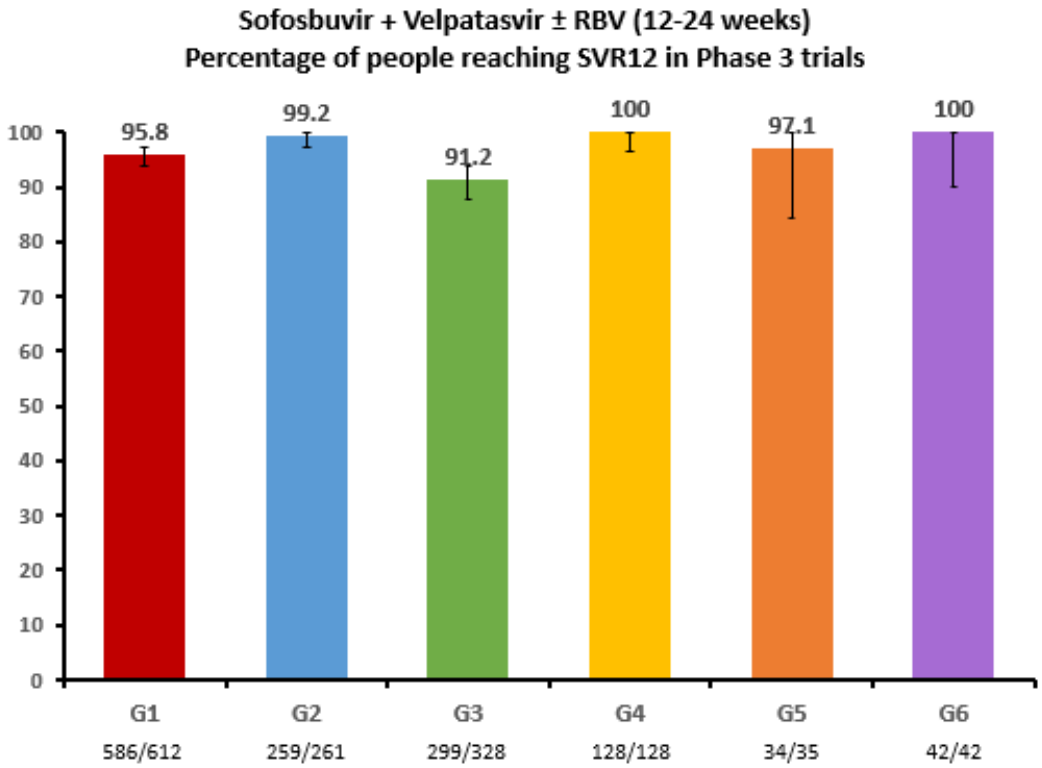
Table 4 and Figure 1 show a summary of the Phase 3 clinical trials conducted for sofosbuvir/ledipasvir. High rates of SVR12 have been observed with sofosbuvir/velpatasvir (400 mg/100 mg) for 12 weeks in treatment-naïve and treatment-experience, non-cirrhotic and cirrhotic patients, with chronic HCV genotype 1-6 infection. High efficacy has also been demonstrated in those with compensated cirrhosis and in adults with HCV/HIV co-infection.

Table 4 Summary of sofosbuvir/velpatasvir Phase 3 trials by genotype

Geno - type	Trials included	Patient Characteristics	Interventions	SVR12/Total (%)
1	ASTRAL-1, ASTRAL-4, ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV coinfected	SOF+VEL (12-24wks)	586/612 (95.8%) 95%CI: 93.8-97.1%
2	ASTRAL-1, ASTRAL-2, ASTRAL-4, ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV coinfected	SOF+VEL±RBV (12-24wks)	259/261 (99.2%) 95%CI: 97.1->99.9%
3	ASTRAL-3, ASTRAL-4, ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV coinfected	SOF+VEL±RBV (12-24wks)	299/328 (91.2%) 95%CI: 87.6-93.8%
4	ASTRAL-1, ASTRAL-4, ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV coinfected	SOF+VEL±RBV (12-24wks)	128/128 (100.0%) 95%CI: 96.5-100.0%
5	ASTRAL-1	TN & TE	SOF+VEL (12wks)	34/35 (97.1%) 95%CI: 84.2->99.9%
6	ASTRAL-1, ASTRAL-4	TN & TE, cirrhosis, decompensated cirrhosis	SOF+VEL (12wks-24wks)	42/42 (100.0%) 95%CI: 90.0-100.0%
TOTAL	All trials above	All above characteristics included	SOF+VEL±RBV (12-24wks)	1348/1406 (95.9%) 95%CI: 94.7-96.8%*

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; PR, pegylated interferon
*Not meta-analysis performed, simple addition of trial results

Figure 1 Overall proportion of patients achieving SVR when combining Phase 3 trials for each genotype. Confidence intervals are represented by error bars at 95% confidence



Genotype 1

Phase 3 trials

Table 5 Completed Phase 3 clinical trials in HCV genotype 1 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)
ASTRAL -1 (Feld et al. 2015) [15]	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN & TE	SOF+VEL 12 wks (318)	GT1a: 206/210 (98%) GT1b: 117/118 (99%)	Relapse: 2/328 (0.6%)
ASTRAL -4 (Curry et al. 2015) [16]	Multicentre, randomised ,open-label, Phase 3	TN & TE, Decompensated cirrhosis	SOF/VEL 12 wks (68)	GT1a: 44/50 (88%) GT1b: 16/18 (89%)	Relapse: GT1a: 3/50 (6%) GT1b: 2/18 (11%)
		TN & TE, Decompensated cirrhosis	SOF/VEL + RBV 12 wks (68)	GT1a: 51/54 (94%) GT1b: 14/14 (94%)	Relapse: GT1a: 1/54 (2%)

		TN & TE, Decompensated cirrhosis	SOF/VEL 24 wks (71)	GT1a: 51/55 (93%) GT1b: 14/16 (88%)	Relapse: GT1a: 2/55 (4%) GT1b: 1/16 (6%)
ASTRAL -5 (Wyles et al. 2016) [17]	Multicentre, open-label, single arm, Phase 3	HIV coinfected, TN & TE, Cirrhosis and Non	SOF/VEL 12 wks (77)	GT1a: 62/65 (95%) GT1b: 11/12 (92%)	Relapse: GT1a 2/65 (3%)
TOTAL: all Phase 3 trials	-	-	SOF/VEL 12-24 wks (612)	586/612 (95.8%)	13/612 (2.1%)

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Phase 2 trials

Table 6 Completed Phase 2 clinical trials in HCV genotype 1 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)
Gane et al 2016 [18]	Multicentre, open-label, single arm, Phase 2, Non-randomised	TN, Non Cirrhosis	SOF/VEL/GS-9857 4 wks (15)	4/15 (27%)	Relapse: 11/15 (73%)
		TN, Non Cirrhosis	SOF/VEL/GS-9857 6 wks (15)	14/15 (93%)	Relapse: 1/15 (7%)
		TN, Cirrhosis	SOF/VEL/GS-9857 6 wks (15)	13/15 (87%)	Relapse: 2/15 (13%)
		TE, Cirrhosis and Non	SOF/VEL/GS-9857 6 wks (30)	20/30 (67%)	Relapse: 10/30 (30%)
		TE, Cirrhosis	SOF/VEL/GS-9857 8 wks (17)	17/17 (100%)	0
		TE, Cirrhosis and Non	SOF/VEL/GS-9857 8 wks (28)	25/28 (89%)	Relapse: 3/28 (89%)
Everson et al. 2015 [19]	PART A Multicentre, open-label, randomised, phase 2 (GT 2, 4-6 combined)	TN, Non Cirrhotic,	SOF/VEL, 25 mg, 12 wks	26/27 (96%)	Relapse: 1/27 (4%)
			SOF/VEL, 100 mg, 12 wks	28/28 (100%)	0
	PART B Multicentre, open-label, randomised, phase 2	TN, Non Cirrhotic	SOF/VEL, 25 mg, 8 wks	26/30 (87%)	Relapse: 3/30 (10%) WC: 1/30 (3%)
			SOF/VEL, 25 mg + RBV, 8 wks	25/30 (83%)	Relapse: 5/30 (17%)

			SOF/VEL, 100 mg, 8 wks	26/29 (90%)	Relapse: 3/29 (10%)
			SOF/VEL, 100 mg + RBV, 8 wks	25/31 (81%)	Relapse: 5/31 (16%) LTFU: 1/31 (3%)
Pianko et al. 2015 [20]	Multicentre, open-label, randomised, phase 2.	Cirrhotic and Non, TE	SOF/VEL, 25mg, 12 wks	27/27 (100%)	0
			SOF/VEL, 25mg + RBV, 12 wks	28/29 (97%)	Relapse: 1/29 (3%)
			SOF/VEL, 100mg, 12 wks	27/27 (100%)	0
			SOF/VEL, 100mg + RBV, 12 wks	27/28 (96%)	Relapse: 1/28 (96%)
TOTAL: all Phase 2 trials	-	-	SOF/VEL ±RBV (4-12 wks)	358/405 (88.4%)	47/405 (11.6%)

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Genotype 1 summary

A total of 1,008 genotype 1 HCV infected patients were treated in 6 trials (3 Phase 3 and 3 Phase 2) with sofosbuvir (400 mg) and velpatasvir (100 mg or 25 mg), with and without ribavirin. Patients were both treatment-naïve and experienced; 77 (8%) patients were co-infected with HIV and 201 (20%) had decompensated cirrhosis. For treatment regimens of 12 weeks or longer the overall SVR12 rate was 96.3% (749/778). These studies have led to the recommendation of sofosbuvir/velpatasvir, regardless of treatment experience or HIV co-infection; treatment is also recommended in individuals with genotype 1 infection and decompensated cirrhosis.

Genotype 2

Phase 3 trials

Table 7 Completed Phase 3 clinical trials in HCV genotype 2 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)
ASTRAL-1 (Feld et al. 2015) [15]	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN & TE	SOF/VEL 12 wks (104)	104/104 (100%)	0
ASTRAL-2 (Foster et al. 2015) [21]	Multicentre, randomised, open-label, Phase 3	TN & TE	SOF/VEL 12 wks (134)	133/134 (99%)	0
ASTRAL -4 (Curry et al. 2015) [16]	Multicentre, randomised ,open-label, Phase 3	TN & TE, Decompensated cirrhosis	SOF/VEL 12 wks (4)	4/4 (100%)	0
		TN & TE, Decompensated cirrhosis	SOF/VEL + RBV 12 wks (4)	4/4 (100%)	0
		TN & TE, Decompensated cirrhosis	SOF/VEL 24 wks (4)	3/4 (75%)	0
ASTRAL -5 (Wyles et al. 2016) [17]	Multicentre, open-label, single arm, Phase 3	HIV coinfected, TN & TE, Cirrhosis and Non	SOF/VEL 12 wks (11)	11/11 (100)	0
TOTAL: all Phase 3 trials	-	-	SOF/VEL ±RBV 12-24wks	259/261 (99.2%)	0

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Phase 2 trials

Table 8 Completed Phase 2 clinical trials in HCV genotype 2 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF or Relapse, n(%)
Everson et al. 2015 [19]	PART B Multicentre, open-label, randomised, phase 2.	TN, Non Cirrhotic	SOF/VEL, 25 mg, 8 wks	20/26 (77%)	Relapse: 6/26 (23%)
			SOF/VEL, 25 mg, + RBV, 8 wks	22/25 (88%)	Relapse: 2/25 (8%) LTFU: 1/25 (4%)
			SOF/VEL, 100 mg, 8 wks	23/26 (88%)	Relapse: 3/26 (12%)
			SOF/VEL, 100 mg + RBV, 8 wks	23/26 (88%)	Relapse: 3/26 (12%)
TOTAL: all Phase 2 trials	-	-	SOF/VEL ±RBV (8 wks)	88/103 (85.4%)	Relapse: 14/103 (13.6%)

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.

Genotype 2 summary

A total of 364 individuals with HCV genotype 2 were treated in 5 trials (4 Phase 3 and 1 Phase 2) with sofosbuvir (400 mg) and velpatasvir (100 mg or 25 mg) with and without ribavirin. Individuals were both treatment-naïve and experienced; 11 (4.2%) were co-infected with HIV and 12 (4.6%) had decompensated cirrhosis. For treatment regimens 12 weeks of longer the overall SVR12 rate was 99.2% (259/261). These studies have led to the approval of sofosbuvir/velpatasvir in genotype 2 infected individuals.

Genotype 3

Phase 3 trials

Table 9 Completed Phase 3 clinical trials in HCV genotype 3 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)
ASTRAL-3 (Foster et al. 2015) [21]	Multicentre, randomised, open-label, Phase 3	TN & TE (GT3) (TN:206; TE:71)	SOF/VEL 12 wks (277)	264/277 (95%)	Relapse: 11/276 (4%)
ASTRAL -4 (Curry et al. 2015)	Multicentre, randomised ,open-label,	TN & TE, Decompensated cirrhosis, (GT3:14)	SOF/VEL 12 wks (14)	7/14 (50%)	Relapse: 6/14 (43%)

[16]	Phase 3	TN & TE, Decompensated cirrhosis, (GT3:13)	SOF/VEL + RBV 12 wks (13)	11/13 (85%)	Relapse: 1/13 (8%) Breakthrough: 1/13 (8%)
		TN & TE, Decompensated cirrhosis, (GT3:12)	SOF/VEL 24 wks (12)	6/12 (50%)	Relapse: 4/12 (33.3%) Breakthrough: 1/12 (8%)
ASTRAL -5 (Wyles et al. 2016) [17]	Multicentre, open-label, single arm, Phase 3	HIV coinfected, TN & TE, Cirrhosis and Non	SOF/VEL 12 wks (12)	11/12 (92%)	0
TOTAL: all Phase 3 trials	-	-	SOF/VEL ±RBV (12-24 wks)	299/328 (91.2%)	Relapse: 22/328 (6.7%) Breakthrough: 2/328 (0.6%)

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Phase 2 trials

Table 10 Completed Phase 2 clinical trials in HCV genotype 3 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF or Relapse, n(%)
Gane et al 2016 [18]	Multicentre, open-label, single arm, Phase 2, Non-randomised	TN, Cirrhosis	SOF/VEL/GS-9857 6 wks (18)	15/18 (83%)	Relapse: 2/18 (11%) LTFU: 1/18 (6%)
		TE, Cirrhosis	SOF/VEL/GS-9857 8 wks (19)	19/19 (100%)	0
		TE, Cirrhosis & Non	SOF/VEL/GS-9857 8 wks (4)	4/4 (100%)	0
Everson et al. 2015 [19]	PART A Multicentre, open-label, randomised, phase 2 (GT 2, 4-6 combined)	TN, Non Cirrhotic	SOF/VEL, 25 mg, 12 wks	25/27 (93%)	On treatment: 1/27 (4%) Relapse: 1/27 (4%)
			SOF/VEL, 100 mg, 12 wks	25/27 (93%)	Relapse: 2/27 (7%)
Pianko et al. 2015 [20]	Multicentre, open-label, randomised, phase 2.	Corrhotic, TE	SOF/VEL, 25mg, 12 wks	15/26 (58%)	Relapse: 11/26 (42%)
			SOF/VEL, 25mg + RBV, 12 wks	21/25 (84%)	Relapse: 3/25 (12%)
			SOF/VEL, 100 mg, 12 wks	23/26 (88%)	Relapse: 3/26 (12%)

			SOF/VEL, 100 mg + RBV, 12 wks	25/26 (96%)	Relapse: 1/26 (4%)
		Non-cirrhotic, TE	SOF/VEL, 25mg, 12 wks	22/26 (85%)	Relapse: 4/26 (15%)
			SOF/VEL, 25mg + RBV, 12 wks	27/28 (96%)	Relapse: 1/28 (4%)
			SOF/VEL, 100 mg, 12 wks	27/27 (100%)	0
			SOF/VEL, 100 mg + RBV, 12 wks	26/26 (100%)	0
TOTAL: all Phase 2 trials	-	-	SOF/VEL±RBV (6-12wks)	274/305 (89.8%)	On treatment: 1/305 (0.3%) Relapse: 28/305 (9.2%) LTFU: 1/305 (0.3%)

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Genotype 3 summary

A total of 592 HCV genotype 3 infected individuals were treated in 6 trials (3 Phase 3 and 3 Phase 2) with sofosbuvir (400 mg) and velpatasvir (100 mg or 25 mg) with and without ribavirin. Patients were both treatment-naïve and experienced; 12 (2%) were co-infected with HIV and 39 (7%) had decompensated cirrhosis. For treatment regimens 12 weeks or longer the overall SVR12 rate was 90.4% (535/592). These studies have led to the approval of sofosbuvir/velpatasvir for treatment of genotype 3 HCV infection.

Genotype 4

Phase 3 trials

Table 11 Completed Phase 3 clinical trials in HCV genotype 4 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)	LTFU n(%)	W/C n(%)
ASTRAL -1 (Feld et al. 2015) [15]	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN & TE	SOF/VEL 12 wks (116)	116/116 (100%)	0	0	0
ASTRAL -4 (Curry et al. 2015)	Multicentre, randomised ,open-label,	TN & TE, Decompensated cirrhosis	SOF/VEL 12 wks (4)	4/4 (100%)	0	0	0

[16]	Phase 3	TN & TE, Decompensated cirrhosis	SOF/VEL + RBV 12 wks (2)	2/2 (100%)	0	0	0
		TN & TE, Decompensated cirrhosis	SOF/VEL 24 wks (2)	2/2 (100%)	0	0	0
ASTRAL -5 (Wyles et al. 2016) [17]	Multicentre, open-label, single arm, Phase 3	HIV coinfected, TN & TE, Cirrhosis and Non	SOF/VEL 12 wks (4)	4/4 (100)	0	0	0
TOTAL: all Phase 3 trials	-	-	SOF/VEL±RBV 12-24wks	128/128 (100%)			

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Phase 2 trials

No Phase 2 trials evaluating ledipasvir in individuals with genotype 4 HCV infection were conducted.

Genotype 4 summary

A total of 128 genotype 4 HCV infected individuals were treated in 3 Phase 3 trials with sofosbuvir (400 mg) and velpatasvir (100 mg) with and without ribavirin. Patients were both treatment-naïve and experienced; 4 (3%) were co-infected with HIV and 8 (6%) had decompensated cirrhosis. For treatment regimens 12 weeks or longer the overall SVR12 rate was 100.0% (128/128). These studies have led to the approval of sofosbuvir/velpatasvir for the treatment of HCV genotype 4 infection.

Genotype 5

Phase 3 trials

Table 12 Completed Phase 3 clinical trials in HCV genotype 5 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)
ASTRAL -1 (Feld et al. 2015) [15]	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN & TE	SOF/VEL 12 wks (35)	34/35 (97%)	0
TOTAL: all Phase 3 trials	-	-	SOF/VEL 12wks	34/35 (97.1%)	

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Phase 2 trials

No Phase 2 trials evaluating ledipasvir in individuals with genotype 4 HCV infection were conducted.

Genotype 5 summary

A total of 35 genotype 5 HCV infected individuals were treated in a single Phase 3 trial with sofosbuvir (400 mg) and velpatasvir (100 mg) with and without ribavirin. Patients were both treatment-naïve and experienced. For treatment regimens 12 weeks or longer the overall SVR12 rate was 97.1% (34/35). This study has led to the approval of sofosbuvir/velpatasvir for the treatment of HCV genotype 5 infection.

Genotype 6

Phase 3 trials

Table 13 Completed Phase 3 clinical trials in HCV genotype 6 infected individuals (intent-to-treat analyses)

Study Reference	Study Design	Patient Characteristics	Intervention	SVR12, n(%)	VF n(%)
ASTRAL -1 (Feld et al. 2015) [15]	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN & TE	SOF/VEL 12 wks (41)	41/41 (100%)	0
ASTRAL -4 (Curry et al. 2015) [16]	Multicentre, randomised ,open-label, Phase 3	TN & TE: Decompensated cirrhosis	SOF/VEL 24 wks (1)	1/1 (100%)	0
TOTAL: all Phase 3 trials	-	-	SOF/VEL (12-24wks)	42/42 (100.0%)	0

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VF, virological failure; LTFU, lost to follow up; W/C, withdrawn consent.
SOF (400 mg), VEL (100 mg), unless otherwise stated.

Phase 2 trials

No Phase 2 trials evaluating ledipasvir in individuals with genotype 4 HCV infection were conducted.

Genotype 6 summary

A total of 42 individuals infected with HCV genotype 6 were treated in 2 Phase 3 trials with sofosbuvir (400 mg) and velpatasvir (100 mg). Patients were both treatment naïve and experienced; 1 (2%) had decompensated cirrhosis. For treatment regimens 12 weeks or longer the overall SVR12 rate was 100.0% (42/42). These studies have led to the approval of sofosbuvir/velpatasvir for the treatment of HCV genotype 6 infection.

Special populations

HCV-HIV coinfection

HCV-HIV coinfection is a significant concern, with over 4 million people worldwide coinfected with HIV and HCV. [22] Detectable HIV infection accelerates the progression of chronic HCV and has been associated with higher rates of all-cause, liver-related, and AIDS-related deaths. [23] Thus, concurrent treatment of HIV and HCV is necessary.

Sofosbuvir/velpatasvir was tested in coinfected patients in one key trial: ASTRAL-5, the results of which have been included above. [17] Eligible patients had HCV of any genotype (although no genotype 5 or 6 were enrolled). Patients were treatment-naïve and experienced, with and without cirrhosis, on stable antiretroviral therapy. Sofosbuvir/velpatasvir for 12 weeks was associated with an SVR12 of 95.3% (101/106); two patients experienced virological relapse.

Drug-drug interactions

Sofosbuvir/velpatasvir can be co-administered with most antiretroviral regimens, although its concomitant use with efavirenz or tipranavir/ritonavir is not recommended, and co-administration with tenofovir containing regimens requires caution. In AASLD/IDSA guidelines, co-administration of sofosbuvir/velpatasvir with efavirenz, etravirine, or nevirapine is not recommended.

Decompensated cirrhosis

The ASTRAL-4 trial evaluated the efficacy of sofosbuvir/velpatasvir plus ribavirin for 12 weeks, or sofosbuvir/velpatasvir for 12 or 24 weeks in patients with decompensated cirrhosis. [16] Patients were infected with genotypes 1, 2, 3, 4, 6; no patients had HCV genotype 5. Sofosbuvir/velpatasvir plus ribavirin for 12 weeks and sofosbuvir/velpatasvir for 12 or 24 weeks provided high rates of SVR12 at 94%, 83%, and 86%, respectively. This study led to the approval of sofosbuvir/velpatasvir for the treatment of individuals with decompensated cirrhosis.

Efficacy conclusion

Sofosbuvir/velpatasvir is approved in HCV guidelines as a first-line option for the treatment of treatment-naïve and treatment-experienced individuals with HCV genotypes 1-6, with or

without cirrhosis. Sofosbuvir/velpatasvir may be used in patients with HIV coinfection and in individuals with decompensated liver cirrhosis.

Review of harms and toxicity: summary of evidence on safety

Safety data from Phase 2 and 3 trials of sofosbuvir/velpatasvir have shown that the regimen is well tolerated and safe. A total 2267 individuals have been treated with sofosbuvir/ledipasvir based regimens in Phase 2 and 3 trials; an unknown number of individuals have been treated in real-world situations since the approval of the regimen.

Data from the Phase 2/3 studies shows few discontinuation because of adverse events and a rate of serious adverse events comparable to other regimens. Of the 13 individuals that died during studies, none were considered related to sofosbuvir/velpatasvir treatment.

The most common adverse events observed over the clinical trials were headache, fatigue, nasopharyngitis, pruritus, and nausea. These adverse events are similar to those observed with treatment with alternative DAA regimens; the overall incidence of adverse events did not significantly differ between sofosbuvir/velpatasvir and placebo. As expected, among individuals taking ribavirin, additional commonly reported adverse events included anaemia, insomnia, and diarrhoea.

Phase 3 trials

Table 14 Safety data from Phase 3 trials of sofosbuvir/velpatasvir

Study Reference	Genotypes	Total No. of Patients	D/C due to AE, n (%)	Serious AE n (%)	Deaths, n (%) (causes)
ASTRAL-1	1,2,4,5,6	624	1 (<1%)	15 (2%)	1 (<1%)
ASTRAL-4	1,2,3,4,6	267	9 (3%)	47 (18%)	9 (3%)
ASTRAL-5	1,2,3,4	106	2 (2%)	2 (2%)	0
ASTRAL-2	2	134	1 (<1%)	2 (1%)	2 (1%)
ASTRAL-3	3	277	0	6 (2%)	0
Total	1,2,3,4,5,6	1408	13 (<1%)	72 (5%)	12 (<1%)

Abbreviations: AE, adverse event; D/C, discontinuation

Overall, 12 deaths were observed from a total of 1408 individuals. None of the deaths were considered to be related to therapy. The occurrence of adverse events and deaths in ASTRAL-4 was higher than observed in other studies. ASTRAL-4 enrolled only individuals with decompensated cirrhosis and as such you would expect this higher rate; most of the deaths observed in this study were due to complications of end-stage liver disease.

Phase 2 trials

Table 15 Safety data from Phase 2 trials of sofosbuvir/velpatasvir

Study Reference	Genotypes	Total No. of Patients	D/C due to AE, n (%)	Serious AE n (%)	Deaths, n (%) (causes)
Gane et al. 2016	1,3	161	0	3 (2%)	0
Everson et al. 2015	1,2,3,4,5,6*	377	1 (<1%)	7 (2%)	1 (<1%)
Pianko et al. 2015	1,3	321	1 (<1%)	8 (3%)	0
Total	1,2,3	859	2 (<1%)	18 (2%)	1 (<1%)

*Very few patients with genotypes 4,5, and 6 included; efficacy results not available by genotype
Abbreviations: AE, adverse event; D/C, discontinuation

One individual out of 859 treated in Phase 2 trials of velpatasvir died during the study period. This individual committed suicide considered unrelated to therapy.

Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

United States pricing

The US wholesale acquisition cost (WAC) of sofosbuvir/velpatasvir is US$74,760 for a 12-week course of therapy. This is lower than the retail cost of a 12-week regimen with sofosbuvir/ledipasvir (US$94,500) and sofosbuvir (US$84,000); the only regimen with a lower list price is Merck's grazoprevir/elbasvir which is only indicated for genotypes 1 and 4 (US$54,600). It should be noted that federal and state programmes in the US procure medications at substantially discounted prices compared with the WAC.

Non-United States pricing

Pharmaceutical companies have several strategies for access in low and middle-income countries. Gilead Sciences' (the manufacturer of sofosbuvir/velpatasvir) strategy has involved signing licenses with generic manufacturers who in turn can manufacture and sell the medications for a small royalty. The medications included under the licensing agreements can be sold to a predefined list of 101 developing countries and medications include: sofosbuvir, ledipasvir/sofosbuvir, and sofosbuvir/velpatasvir. [24] The current access price of sofosbuvir/velpatasvir from Gilead Sciences is US$300/28-day supply, meaning a total cost of US$900 per 12-week treatment course in the 101 listed developing countries. The price of sofosbuvir/velpatasvir from generic manufacturers has the potential to decrease further still from this access price.

Regulatory information

Summary of regulatory status of the medicine

Velpatasvir/sofosbuvir (as Epclusa, Gilead Sciences) received US-FDA regulatory approval in June 2016 and has since received approval from EMA and Health Canada. This information is summarised in Table 16.

Table 16 Regulatory status according to stringent regulatory authorities

Product	SRA board	Approval status
Epclusa (400 mg sofosbuvir + 200 mg velpatasvir)	US-FDA	Approved (28/06/16)
	EMA	Approved (06/07/16)
	Australia	Not listed
	Japan	Not listed
	Health Canada	Approved (11/07/16)

Availability of pharmacopoeial standards

None of the drugs included in this application are included in the British, International, US, or European Pharmacopeia's.

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