Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for: Sofosbuvir / Velpatasvir

Proprietary Product Name: Epclusa

Sponsor: Gilead Sciences Pty Ltd

November 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au> .

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
3TC	lamivudine
Ab	antibody
ADME	absorption/distribution/metabolism/excretion
AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	Atripla
ATV	atazanavir
AUC	area under the concentration/time curve
AUC_{inf}	area under the plasma concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
BCRP	breast cancer resistance protein
BMI	body mass index
BSEP	for bile salt export pump
BVDV	Bovine viral diarrhoea virus
CI	confidence interval
CL	clearance
CL/F	apparent oral clearance after administration of the drug: CL/F = $Dose/AUC_{inf}$, where “Dose” is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug in serum, plasma, or PBMCs
CLcr	creatinine clearance

Abbreviation	Meaning
C_{max}	maximum observed concentration of drug in plasma
CNS	central nervous system
COBI	cobicistat
CPT	Child-Pugh-Turcotte
C_{tau}	observed drug concentration at the end of the dosing interval
CV	coefficient of variation
CYP	cytochrome P450
DAA	direct-acting antiviral agent
DILI	drug induced liver injury
DRV	darunavir
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EC50	concentration of a compound inhibiting virus replication by 50%
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
E_{max}	maximum effect
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed dose combination
FSH	follicle stimulating hormone
FTC	emtricitabine
GCP	Good Clinical Practice
GLP	good laboratory practice
GLSM	geometric least-squares means
GT1a	genotype 1a (HCV)

Abbreviation	Meaning
GT1b	genotype 1b (HCV)
GT4	genotype 4 (HCV)
h	hour/s
H2RA	H2-receptor antagonist
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
hERG	Human ether-a-go-go-related gene
HIV	human immunodeficiency virus
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IFNα	Interferon alpha
IL28B	interleukin 28B
IU	international units
K_a	absorption rate constant
LDV	ledipasvir
LLOQ	lower limit of quantitation
LOQ	limit of quantification
LPV	lopinavir
LS	least squares
MATE1	Multidrug and toxin extrusion protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
mL	millilitre
mRNA	messenger RNA

Abbreviation	Meaning
MRP2	multidrug resistance protein 2
ms	milliseconds
N	number
NS3	non-structural protein 3
NS4A	non-structural protein 4A
NS5A	non-structural protein 5A
NS5B	non-structural protein 5B
NTCP	sodium taurocholate co-transporting polypeptide
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PD	pharmacodynamics
Peg-IFN	pegylated interferon
P-gp	p-glycoprotein
PK	pharmacokinetics
PopPK	population PK
PPI	proton pump inhibitor
qd	once daily
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected Friderichia's formula
QTcN	QT interval corrected
r	ritonavir
RAL	raltegravir
RAV	resistance associated variants

Abbreviation	Meaning
RBV	ribavirin
RNA	ribonucleic acid
RPV	rilpivirine
RSV	Respiratory syncytial (sin-SISH-ul) virus
RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
SOF	sofosbuvir (GS-7977)
SOF	sofosbuvir/solvaldi/GS-7977/PSI-7977
SOF/VEL	sofosbuvir/velpatasvir FDC
SVR	sustained virologic response
SVR12	sustained virologic response at 12 weeks following completion of all treatment
SVR24	sustained virologic response 24 weeks post-dosing
SVR4	sustained virologic response 4 weeks post-dosing
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
T_{lag}	Lag-time (time delay between drug administration and first observed concentration above LOQ in plasma)
TN	treatment naïve
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
US	United States
Vc	volume of distribution in the central compartment
Vc/F	apparent volume of distribution in central compartment after oral dosing

Abbreviation	Meaning
VEL	velpatasvir/GS-5816
Vp	volume of distribution in the peripheral compartment
Vp/F	apparent volume of distribution in peripheral compartment after oral dosing
ZDV	zidovudine

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	13 December 2016
Date of entry onto ARTG	19 December 2016
Active ingredients:	Sofosbuvir/Velpatasvir
Product name:	Epclusa
Sponsor's name and address:	Gilead Sciences Pty Ltd Level 6/ 417 St Kilda Road Melbourne VIC 3004
Dose form:	Film coated tablet
Strength:	Sofosbuvir 400 mg/ Velpatasvir 100 mg
Container:	bottle
Pack size:	28 tablets
Approved therapeutic use:	*Epclusa (sofosbuvir/velpatasvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults.* *(see DOSAGE AND ADMINISTRATION section for the recommended regimens for different patient subgroups).*
Route of administration:	oral
Dosage:	One tablet daily with or without food
ARTG number:	266823

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd (the sponsor) to register Epclusa sofosbuvir (400 mg) and velpatasvir (100 mg) Fixed Dose Combination (FDC) oral tablet for the following indication:

> *Epclusa (sofosbuvir/velpatasvir fixed dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.*

Velpatasvir is a new chemical entity whereas sofosbuvir (SOF) has recently been registered (by Gilead Sciences Pty Ltd) both as a 400 mg monotherapy tablet (Sovaldi, sofosbuvir 400 mg tablet, ARTG 211019) and with another antiviral, ledipasvir, in a FDC tablet (Harvoni (90 mg ledipasvir and 400 mg sofosbuvir tablet ARTG 222848).

Sofosbuvir (SOF) and velpatasvir (VEL) are direct acting antiviral agents (DAA) against Hepatitis C Virus (HCV). Sofosbuvir is a nucleotide analogue non-structural protein 5B (NS5B) polymerase inhibitor.

Velpatasvir is a novel HCV NS5A inhibitor with potent antiviral activity in vitro against GT1 to 6 replicons. Velpatasvir and sofosbuvir have been formulated in a FDC tablet for once daily use. It is hoped that Epclusa will offer a well-tolerated, once daily, single dose, 12 week treatment for patients with HCV infection of any genotype, in non-cirrhotic patients and in those with compensated or decompensated cirrhosis. Gilead does not intend to develop velpatasvir for use as a single agent tablet.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 19 December 2016.

At the time the TGA considered this application a similar application had been approved in the following countries as shown in Table 1.

Table 1 Overseas regulatory status

Country	Approval date	Indication
USA Submitted 29 October 2015	29 October 2015	Epclusa is a fixed dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection (1) – Without cirrhosis or with compensated cirrhosis – With decompensated cirrhosis for use in combination with ribavirin.
European Union (Centralised Procedure) Rapporteur: Sweden Co – Rapporteur: Estonia Submitted 14 November 2015	6 July 2016	Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.
Canada Submitted 10 December 2015	11 July 2016	Epclusa (sofosbuvir/velpatasvir) is indicated: – for the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis – in combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis.

Country	Approval date	Indication
New Zealand Submitted 18 January 2016	10 November 2016	Epclusa (sofosbuvir/velpatasvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

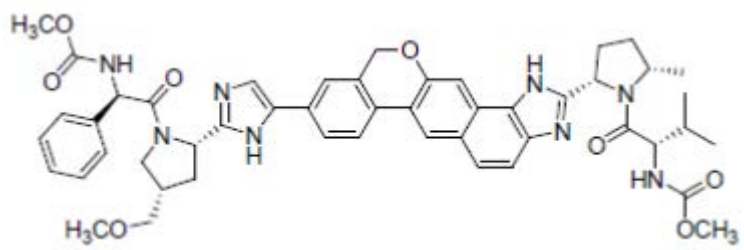
II. Quality findings

Drug substance (active ingredient)

Velpatasvir

Velpatasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both ribonucleic acid (RNA) replication and the assembly of HCV virions.

Figure 1: Structure of velpatasvir



It has six chiral centres and is produced as a single isomer. The drug substance is obtained as an amorphous powder; it is soluble at pH 1.2 (> 36 mg/mL) slightly soluble at pH 2 (3.6 mg/mL) and practically insoluble above pH 5 (< 0.01 mg/mL).

Particle size and polymorphic form are not considered critical in this case because the drug substance is fully dissolved in ethanol during manufacture.

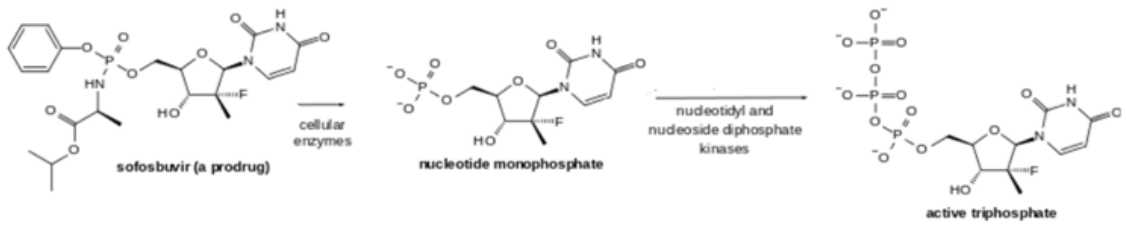
Based on its low apparent permeability and low solubility, velpatasvir is considered a Class 4 drug with respect to the Biopharmaceutics Classification System (BCS).

The proposed drug substance specification complies with TGA requirements and is considered adequate to ensure the quality and consistency of manufacture of the finished product.

Sofosbuvir

Sofosbuvir, a prodrug of it nucleotide monophosphate, is ultimately converted within the hepatocyte to the active triphosphate form, as shown below. This is an HCV NS5B directed inhibitor that has displayed potent in vitro inhibition of HCV replicon RNA replication.

Figure 2: Sofosbuvir



Sofosbuvir (anhydrous, crystal form II) is a white to off-white powder which is slightly soluble across the physiological pH range (pH 2-7.7; approximately 2 mg/mL). Sofosbuvir has six stereocenters and is chirally pure. Based on the low apparent permeability and high solubility, Sofosbuvir is a Class 3 drug with respect to the Biopharmaceutics Classification System (BCS).

Data relating to sofosbuvir is identical to that previously submitted for registration of the sofosbuvir monotherapy tablet (Submission PM-2013-01283-1-2). The previously agreed drug substance specifications comply with TGA requirements and are considered adequate to ensure the quality and consistency of manufacture of the combination tablets.

Drug Product

The proposed product is a pink, diamond shaped, film coated tablet debossed with 'GSI' on one side and '7916' on the other.

The manufacturing method of the combination tablet is a conventional dry granulation process in which the velpatasvir and sofosbuvir drug substance are blended together with the excipients in a monolayer. Inactive excipients selected are conventional for a film coated tablet.

The proposed finished product specifications have been adequately justified and comply with TGA requirements. They are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

The tablets show good stability and a shelf life of 24 months when stored below 30°C, has been established.

A fixed dose combination tablet was chosen as the dosage form for the product due to previous experience in developing sofosbuvir single-agent and combination tablets.

Drug product development began with the development of a velpatasvir single-agent formulation intended to maximise dissolution and minimise potential food and gastrointestinal pH effects.

Various strengths of velpatasvir (5 mg, 50 mg, 25 mg and 100 mg) were trialled in the Phase I and Phase II studies. The velpatasvir tablet formulations were then modified to incorporate 400 mg sofosbuvir and produce 400 mg/25 and mg 400 mg/100 mg combination tablets. On the basis of these studies, sofosbuvir/velpatasvir 400 mg/25 mg and 400 mg/100 mg tablets were manufactured and used in a relative bioavailability and food effect study.

The 400/100 mg strength was selected for use in the Phase III studies; the formulation proposed for marketing is the same as that used in the relative bioavailability study and the provided Phase III studies.

Biopharmaceutics

Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed approximately 0.5 to 1 hour post dose. Median peak plasma concentration of the active metabolite of sofosbuvir was observed approximately3 hours post dose. Median peak plasma concentration of velpatasvir was also observed approximately3 hours post dose.

Very little metabolism of velpatasvir occurs, with > 98% of a [^{14}C]-labelled 100 mg dose present in plasma as unchanged drug.

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside triphosphate analogue (as shown above) which is dephosphorylated to the inactive nucleoside metabolite. After a single 400 mg oral dose of [^{14}C]-Sofosbuvir, the nucleoside triphosphate active metabolite accounted for approximately > 90% of total systemic exposure.

Biostudy GS-US-342-0104; bioequivalence and food effect

Study GS-US-342-0104 was a two part study comparative bioavailability study. The first part examined the relative bioavailabilities of sofosbuvir, its metabolites GS-566500 and GS-331007, and velpatasvir after administration of a sofosbuvir/velpatasvir 400 mg/100 mg or 400 mg/25 mg dose either as a combination tablet or co-administration of individual sofosbuvir and velpatasvir tablets. The second part examined the relative bioavailability of sofosbuvir, GS-331007 and velpatasvir after administration of a sofosbuvir/velpatasvir 400/100 mg combination tablet either without food, with a moderate fat meal, or with a high fat meal.

Part 1

The reported pharmacokinetics (PK) parameters for the two cohorts administered sofosbuvir 400 mg/velpatasvir 100 mg are shown below (Table 2).

Table 2: Biostudy GS-US-342-0104; relative bioavailability

	GLSM		%GLSM Ratio (90% CI)
PK Parameter	SOF 400 mg + GS-5816 100 mg (Reference) (N = 26)[a]	SOF/GS-5816 (400 mg/100 mg) (Test) (N = 26)	SOF/GS-5816 (400 mg/100 mg) vs SOF 400 mg + GS-5816 100 mg
SOF			
AUC_{last} (h•ng/mL)	1585.90	1408.21	88.80 (78.09, 100.96)
AUC_{inf} (h•ng/mL)	1592.19	1425.58	89.54 (78.78, 101.76)
C_{max} (ng/mL)	1454.61	1309.21	90.00 (74.72, 108.42)
GS-566500			
AUC_{last} (h•ng/mL)	1717.90	1536.72	89.45 (79.36, 100.83)
AUC_{inf} (h•ng/mL)	1781.36	1603.08	89.99 (80.40, 100.73)
C_{max} (ng/mL)	446.61	412.05	92.26 (82.98, 102.58)
GS-331007			
AUC_{last} (h•ng/mL)	11138.53	11169.92	100.28 (95.79, 104.98)
AUC_{inf} (h•ng/mL)	11949.15	11936.70	99.90 (95.42, 104.58)
C_{max} (ng/mL)	869.41	933.71	107.40 (101.12, 114.06)
GS-5816			
AUC_{last} (h•ng/mL)	3137.58	3263.13	104.00 (75.02, 144.18)
AUC_{inf} (h•ng/mL)	3213.10	3326.48	103.53 (75.67, 141.65)
C_{max} (ng/mL)	404.57	416.57	102.97 (74.47, 142.37)

The results indicate that the 90% confidence intervals for maximum observed concentration of drug in plasma (C_{max}) and area under the concentration/time curve over the dosing interval (AUC_t) of sofosbuvir and velpatasvir are outside the interval (80.00 to 125.00%) accepted to indicate bioequivalence to the co-administered monotherapies.

Part 2

The reported PK parameters for the two cohorts administered sofosbuvir 400 mg/velpatasvir 100 mg with and without food (either high fat or moderate fat) are shown below (Table 3).

Table 3: Biostudy GS-US-342-0104 PK parameters with or without food

	GLSM			%GLSM Ratio (90% CI)	
PK Parameter	High-Calorie, High-Fat Meal (N = 30)	Moderate-Fat Meal (N = 30)	Fasted (N = 30)	High-Calorie, High-Fat Meal/Fasted	Moderate-Fat Meal/Fasted
SOF					
AUC_{last} (h•ng/mL)	2566.66	2312.04	1442.22	177.97 (157.32, 201.32)	160.31 (141.72, 181.35)
AUC_{inf} (h•ng/mL)	2589.02	2324.73	1452.76	178.21 (157.87, 201.18)	160.02 (141.75, 180.65)
C_{max} (ng/mL)	1275.69	1367.09	1434.41	88.94 (75.26, 105.10)	95.31 (80.65, 112.63)
GS-566500					
AUC_{last} (h•ng/mL)	2713.48	2297.60	1492.73	181.78 (162.65, 203.16)	153.92 (137.72, 172.02)
AUC_{inf} (h•ng/mL)	2786.88	2375.16	1568.54	177.67 (160.43, 196.78)	151.43 (136.73, 167.70)
C_{max} (ng/mL)	532.84	472.88	389.03	136.97 (123.85, 151.47)	121.55 (109.91, 134.42)
GS-331007					
AUC_{last} (h•ng/mL)	11846.01	11672.17	11993.94	98.77 (94.43, 103.30)	97.32 (93.05, 101.78)
AUC_{inf} (h•ng/mL)	13155.93	12860.93	12875.58	102.18 (97.75, 106.80)	99.89 (95.56, 104.41)
C_{max} (ng/mL)	605.38	722.65	963.39	62.84 (58.35, 67.68)	75.01 (69.65, 80.79)
GS-5816					
AUC_{last} (h•ng/mL)	4574.49	5054.54	3758.60	121.71 (99.09, 149.49)	134.48 (109.49, 165.17)
AUC_{inf} (h•ng/mL)	4637.86	5130.92	3827.71	121.17 (99.01, 148.28)	134.05 (109.53, 164.05)
C_{max} (ng/mL)	510.48	638.74	487.44	104.73 (86.61, 126.63)	131.04 (108.38, 158.44)

Administration of a single dose of the proposed product with a moderate or high fat meal increased sofosbuvir area under the concentration/time curve (AUC) by 60% and 78% respectively relative to fasting conditions but did not substantially affect C_{max}. GS-331007 AUC was not affected by food but C_{max} decreased by 25% and 37% respectively after a moderate or high fat meal. Velpatasvir AUC and C_{max} increased by 34% and 31% respectively after a moderate fat meal and 21% and 5% respectively after a high fat meal.

In Phase III trials, response rates were similar in patients who were dosed with or without food. The PI recommends the dose be taken with or without food.

Absolute bioavailability

An absolute bioavailability study has not been performed. The sponsor's justification asserts that:

- the pharmacokinetics and clinical pharmacology of sofosbuvir have been extensively characterised through in vitro, nonclinical, and clinical studies
- nonclinical and clinical studies have shown that systemic bioavailability of sofosbuvir is low due to extensive hepatic metabolism
- development of a parenteral velpatasvir formulation was difficult due to its poor solubility profile
- oral bioavailability of velpatasvir in nonclinical studies was low (approximately25 to 30%)
- an absolute bioavailability study would be difficult to conduct due to the low solubility of velpatasvir and is unnecessary as estimates of bioavailability from existing data are sufficient.

Quality summary and conclusions

Registration of the proposed product is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the pharmaceutical subcommittee of the ACPM.

III. Nonclinical findings

Introduction

This submission included the previous studies included in the application on sofosbuvir. With the exception of carcinogenicity studies, which were not complete at the time of the earlier submission, these were all previously assessed in PM-2013-01283-1-2. The carcinogenicity studies on sofosbuvir were assessed in PM-2014-00469-1. Nonclinical virology studies were provided in the clinical module. Some virology studies were submitted previously for sofosbuvir and sofosbuvir/ledipasvir. This assessment covers reports relating to velpatasvir and combination studies of velpatasvir with sofosbuvir.

Pharmacology

Primary pharmacology

Velpatasvir inhibits HCV replication by interaction with the viral NS5A protein. The function of NS5A is unknown at present but it plays a key role in the regulation of viral replication. NS5A appears to play this role regardless of HCV genotype. The mechanism of action of NS5A inhibitors is also unknown at present. Phosphorylation of NS5A is thought to be an important step in the production of new virus and interference with this process by agents such as velpatasvir may explain their effects, but this remains speculative. Inhibition of NS5A appears to be the only action of velpatasvir as it showed no activity against the HCV enzymes NS3/4A protease, NS5B polymerase or the internal ribosome entry site. Velpatasvir showed no selective activity against Bovine viral diarrhoea

virus (BVDV), Respiratory syncytial (sin-SISH-ul) virus (RSV), hepatitis B virus (HBV) or human immunodeficiency virus (HIV) HIV-1.

The antiviral actions of velpatasvir were studied in full-length and chimeric HCV replicons. Velpatasvir had antiviral activity against HCV genotypes 1 to 6 with mean concentration of a compound inhibiting virus replication by 50% (EC50) values ranging from 0.002 nM (GT2b) to 0.130 nM (GT6e). In studies on chimeric replicons carrying NS5A from clinical isolates, velpatasvir showed potent and broad antiviral activity against HCV genotypes 1 to 6 with no or minimal differences in potency against different subtypes within a genotype. Velpatasvir activity against HCV genotype 1a was reduced 13.3 fold in 40% human serum. Protein adjusted EC50 values (studies PC-282-2028 and PC-281-2029) ranged from 0.027 to 0.21 nM for genotypes 1a, 1b, 2a, 2b, 3a, 4a, and 6a, and from 0.72 to 1.7 nM for genotypes 5a and 6e.

Reductions in susceptibility to velpatasvir were infrequent and were associated with variants at known resistance associated positions in NS5A. Velpatasvir resistance associated variants (RAVs) were identified in vitro at positions 24, 28, 31, 32, 58, 92 and 93, most commonly at positions 28, 31, and 93. Substitutions conferring a > 100 fold reduction in velpatasvir susceptibility were identified in all genotypes. Combinations of these resistance associated variants (RAVs) often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

The antiviral activities of velpatasvir combined with sofosbuvir, boceprevir, simeprevir, telaprevir (non-structural protein 3 (NS3) inhibitors), daclatasvir (NS5A inhibitor), ribavirin, or interferon alpha (IFNα) were additive in vitro. There was no cross resistance between sofosbuvir and velpatasvir in vitro. Velpatasvir was active against the NS5B S282T mutant replicon which shows reduced susceptibility to sofosbuvir. Sofosbuvir was active against NS5A mutants resistant to velpatasvir. The activity of velpatasvir alone or in combination with sofosbuvir was unaffected by anti-HIV drugs, and velpatasvir had no effect on the anti-HIV activity of representative HIV drugs.

Secondary pharmacodynamics and safety pharmacology

Potential off target activity of velpatasvir was evaluated in a panel of 65 mammalian enzymes, ion channels and receptors. No significant interactions were observed at concentrations of 10 μM. Velpatasvir showed no antiviral activity against bovine viral diarrhoea virus (a related flavivirus), or the unrelated viruses respiratory syncytial virus, hepatitis B virus and human immunodeficiency virus. Velpatasvir showed no significant cytotoxicity to any of the cell lines used in the replicon assays.

Safety studies with velpatasvir examined Human ether-a-go-go-related gene (hERG) channel inhibition in vitro and cardiovascular, respiratory and central nervous system (CNS) studies in vivo. Velpatasvir had no effect of hERG currents at the highest concentration tested (6.5 μM). Single doses of velpatasvir up to 100 mg/kg had no effect on any cardiovascular parameters in dogs. Single doses of velpatasvir up to 100 mg/kg had no effect on any CNS parameters in rats. Single doses of velpatasvir up to 200 mg/kg had no effect on any respiratory parameters in rats.

Pharmacokinetics

Absorption

T_{max} values ranged from 1 hour to around 12 hours in nonclinical species. Oral bioavailability ranged from 25 to 29.7% suggesting modest absorption, and volume of distribution ranged from 1.4 to 1.6 L/kg. Systemic clearance was low in all species with values ranging from 0.25 to 0.94L/h/kg. Terminal half-life ranged from 2.36 hours in rats

to 5.5 hours in dogs. There were no consistent sex differences in absorption parameters in any species. Exposure was generally less than dose proportional at high doses in all species and this limited the animal: human exposure ratios achieved.

Distribution

Plasma protein binding by velpatasvir was high in humans and laboratory animal species at greater than 99% plasma protein bound in all species in vitro. Limited red blood cell partitioning was evident in mice and rats with blood: plasma ratios of < 0.623 and < 0.635, respectively. Tissue distribution of velpatasvir associated radioactivity was wide in mice and rats with highest concentrations appearing in liver, kidney and Harderian glands in both species. There was no penetration into testes and very limited penetration into brain in mice and rats. Fetal transfer was not seen but velpatasvir was present in milk from lactating rats.

Metabolism

Metabolites were formed and interconverted by oxidation, O-demethylation, hydrolysis, dehydrogenation and glucuronidation. Unchanged velpatasvir was by far the dominant circulating species in humans and laboratory animals. There were no major circulating metabolites in human plasma with M18 and M19 constituting 0.4 and 0.7 % plasma AUC respectively. There were no unique human metabolites. Slow metabolic turnover of velpatasvir was observed in vitro with incubation with cytochrome P450's (CYP) CYP2B6, CYP2C9 and CYP3A4. Clinical observations were reported that velpatasvir exposure can be affected by co-administration with the inhibitor ketoconazole or the inducer rifampicin.

Excretion

The major route of excretion for velpatasvir was the faecal route in humans and nonclinical species. The faecal excretion of velpatasvir consisting of both unabsorbed drug and biliary excretion products reached up to 97% in rats. In humans the urine accounted for just 0.4% of the administered dose while faecal excretion accounted for 94%.

Conclusion: considering the metabolic profiles of mice, rats, dogs and humans and the similarity in disposition of velpatasvir in humans and the nonclinical species, an adequate model for the assessment of velpatasvir toxicity has been employed in the present submission.

Pharmacokinetic drug interactions

Velpatasvir showed no significant inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2D6 or 3A4. Velpatasvir was a substrate for CYP2B6, 2C9 and 3A4 but with slow turnover. Clinical drug interactions are possible with inhibitors or inducers of these CYPs. Velpatasvir is an inhibitor of drug transporters p-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporting polypeptide (OATP) OATP1B3 and may increase intestinal absorption of co-administered drug substrates for these transporters. Velpatasvir inhibited hepatic uptake transporters OATP1B1 and OATP1B3 with half maximal inhibitory concentration (IC_{50}) values in the potential range for concentrations at the hepatic inlet and therefore has the potential to increase circulating concentrations of drug substrates of these transporters. The IC_{50} for bile salt export pump (BSEP) was in the same range as BCRP and OATP1B3 and therefore BSEP inhibition may occur at clinical concentrations. The absorption of both sofosbuvir and velpatasvir may be increased by administration of inhibitors or decreased by administration of inducers of intestinal efflux transporters. Velpatasvir was not an inhibitor of multidrug resistance protein 2(MRP2), sodium taurocholate co-transporting polypeptide (NTCP), OATP1A2, OAT1 and OAT3.

Velpatasvir showed dose-dependent inhibition of the efflux transporters OATP2B1, organic cation transporter (OCT); OCT1, OCT2 and multidrug and toxin extrusion protein 1 (MATE1) however this inhibition occurred at concentrations above the anticipated clinical exposure. Previously assessed in vitro studies with the proposed combination showed that velpatasvir did not affect the generation of the active metabolite of sofosbuvir. These studies also showed a reduction in basolateral to apical permeability (efflux ratio) consistent with the clinical increase in sofosbuvir exposure in the presence of velpatasvir.

Toxicology

Acute toxicity

No acute toxicity studies with velpatasvir or velpatasvir and sofosbuvir combined were submitted.

Repeat-dose toxicity

Repeat dose toxicity studies with velpatasvir alone were conducted in three species: mouse, rat and dog. All studies were conducted using the clinical (oral) route. Velpatasvir has low aqueous solubility. The mouse study employed a different vehicle (aqueous suspension) from that employed in the rat and dog studies (45% propylene glycol and 15% Kolliphor HS-15 in reverse osmosis water, pH 2.0 ± 0.1) which allowed higher doses to be tested in this species. The durations of the pivotal studies, the species used and the group sizes were consistent with ICH guidelines.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma $AUC_{0-24\,h}$. Human reference values are from several clinical studies. The relative exposure achieved in mice was high but exposure was limited by absorption in rats and dogs leading to modest ratios.

Table 4: Relative exposure in repeat dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Mouse (CByB6F1-Tg(HRAS)2Jic Model 1178-wild-type)	4 weeks	100	74100	25
		300	84500	29
		1500	219500	74
Rat (Sprague Dawley)	2 weeks	20	4381	2
		60	11446.5	4
		200	17130.5	6
	26 weeks	20	3500	1
		60	6705	2
		200	12200	4
Dog (Beagle)	2 weeks	5	1879	0.6
		20	10204.5	3
		100	22510	8
	39 weeks	5	1725	0.6
		20	6705	2
		100	27650	9

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Human (HCV positive patients)	steady state	[100 mg]	2967	–

= animal: human plasma $AUC_{0-24\,h}$

Major toxicities

The repeat dose toxicity of velpatasvir was low and no potentially serious organ toxicities were seen in any of the pivotal long-term toxicity studies. In the mouse study, reductions in mean white blood cell, absolute neutrophil and absolute lymphocyte counts were observed at all doses. The effects were not, however, clearly dose related or consistent across sexes. The lack of any dose response relation suggests that this effect was not related to the higher exposures achieved in mice. No comparable effects were seen in other species. Slight reductions in haemoglobin and haematocrit were seen in male Crl:CD(SD) rats in a 2 week study on impurities. Comparable effects were not seen in the pivotal repeat dose studies conducted in Hsd: Sprague Dawley rats although exposures were comparable. The effect was seen both in the presence and absence of the impurities. The effect was, however, small and unlikely to be of toxicological significance.

Combination toxicity studies

No toxicity studies on the combination of velpatasvir and sofosbuvir were submitted. The sponsor justified their absence thus: "*Based on the well-defined toxicity profiles of the single agents, the combination of SOF and VEL is not anticipated to exacerbate known toxicities or lead to new toxicities. Therefore, combination toxicity studies with SOF and VEL were not conducted*." The guideline[1] (TGA adopted) states "*Combination toxicity studies are also not generally warranted for antiviral agents for treatment of Hepatitis C*." The absence of combination studies is therefore acceptable.

Genotoxicity

Velpatasvir was evaluated for its potential to induce reverse mutations in *S. typhimurium* and *E. coli*, its mutagenic potential in vitro in primary human lymphocytes, and its mutagenic potential in vivo in a rat bone marrow micronucleus study (Option 1 in ICH S2(R1)[2]). Velpatasvir was negative in all the tests and is unlikely to pose a mutagenic or clastogenic risk to humans. A precursor molecule was positive in genotoxic tests (see impurities attachment).

Carcinogenicity

No carcinogenicity studies on velpatasvir were submitted but the sponsor indicated that long term studies on mice and rats are ongoing.

Reproductive toxicity

Reproductive toxicity was assessed in mice, rats and rabbits in good laboratory practice (GLP) compliant studies. The studies investigated potential effects on male and female fertility in rats, embryofetal toxicity (mice, rats and rabbits) and pre-/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were appropriate.

[1] ICH M3(R2) Guideline: Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. Questions & answers (2012).

[2] ICH S2(R1) Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use

Relative exposure

Table 5: Relative exposure

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Mouse (CD-1)	Embryofetal development	10	6820	2
		30	22100	7
		100	43700	15
		1000	93000	31
Rat (Sprague Dawley)	Embryofetal development	20	3830	1
		60	9300	3
		200	17100	6
Rat (Sprague Dawley)	Embryofetal development	20	3830	1
		60	9300	3
		200	17100	6
Rabbit (NZW)	Embryofetal development	100	1940	0.7
		300	2060	0.7
Rabbit (NZW)	Embryofetal development	100	5966	2
		300	11800	4
		600	9010	3
Human (HCV positive patients)	steady state	[100 mg]	2967	–

= animal: human plasma $AUC_{0-24\,h}$

The level of the relative exposure achieved in the studies was modest and variable.

Placental transfer was not evident but excretion in milk was demonstrated in lactating rats.

Velpatasvir had no effects on fertility in rats, embryofetal development in mice, rats or rabbits or on pre-postnatal development in rats.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[3] for Epclusa. This category is appropriate for velpatasvir. There are no studies on the effects of velpatasvir and

[3]Pregnancy Category B1*: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*

sofosbuvir in combination on reproduction. When Epclusa is used in combination with ribavirin, Category X[4] is applicable.

Local tolerance

Velpatasvir was classified as non-irritant to skin and showed no potential as a skin sensitizer. Velpatasvir was not a severe eye irritant in the Bovine Cornea Opacity/Permeability test (BCOP) assay but the possibility of some effect on eyes could not be ruled out.

Phototoxicity

Velpatasvir demonstrated phototoxic potential in the Balb/c 3T3 neutral red uptake assay in vitro, however no phototoxicity was observed in a multiple dose phototoxicity study in Long-Evans pigmented rats at oral doses up to 200 mg/kg/day, hence no further phototoxicity testing was warranted[5].

Impurities

The qualification of impurities was assessed and the details were provided.

Paediatric use

Velpatasvir is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to GLP.
- Primary pharmacology studies were conducted entirely in vitro using HCV replicons, including chimeric replicons carrying NS5A from clinical isolates. Velpatasvir showed the greatest potency against GT 1a but was active against all genotypes tested: GT 1a and 1b, GT 2 (8 subtypes), GT 3 (3 subtypes), GT 4 (10 subtypes), GT 5a and GT 6 (8 subtypes). It was unaffected by common anti-HIV drugs, and had no effect on the activity of common anti-HIV drugs in MT4 cells. Velpatasvir activity against HCV genotype 1a was reduced 13.3 fold in 40% human serum. Velpatasvir showed no activity against BVDV, HIV-1, RSV, or HBV.
- Genotype 1 to 6 replicon resistance selection assays identified velpatasvir resistance associated variants (RAVs) at positions 24, 28, 31, 32, 58, 92 and 93, most commonly at positions 28, 31, and 93. There was both overlapping and non-overlapping resistance amongst genotypes 1-6. The Y93H variant conferred high-level resistance (> 100 fold EC_{50} increase) in genotypes 1a, 2b and 3a.
- The majority of NS5A RAVs conferring resistance to ledipasvir and daclatasvir remained susceptible to velpatasvir. Velpatasvir showed additivity or minor synergism in combination with sofosbuvir, and minor synergism in combination with ribavirin. Sofosbuvir and ribavirin retained full activity against NS5A mutants with reduced susceptibility to velpatasvir, and velpatasvir retained full activity against NS3/4A and NS5B RAVs, including the sofosbuvir primary resistant mutant S282T in genotypes 1 to 6.

[4] Pregnancy Category X*: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.*
[5] ICH Photosafety Evaluation of Pharmaceuticals S10 (13 Nov 2013).

- Velpatasvir had no off-target actions in vitro that were considered potentially clinically significant.
- Velpatasvir did not have any notable effects on CNS, cardiovascular or respiratory function following oral administration at the highest doses tested and had no effects on hERG channels in vitro.
- Exposure was generally less than dose proportional at high doses in all species and this limited the animal: human exposure ratios achieved.
- Velpatasvir is an inhibitor of drug transporters P-gp, BCRP and OATP2B1. Based on the estimated maximal intestinal concertation, velpatasvir may increase intestinal absorption of co-administered drug substrates for these transporters. Velpatasvir inhibited hepatic uptake transporters OATP1B1 and OATP1B3 with IC_{50} values in the potential range for concentrations at the hepatic inlet and therefore has the potential to increase circulating concentrations of drug substrates of these transporters.
- No acute toxicity studies were conducted with velpatasvir. There was no evidence of acute toxicity in any repeat dose toxicity studies.
- No major toxicities were apparent in repeat dose studies at exposures up to ER_{AUC} 74 (mouse), ER_{AUC} 6 (rat), and ER_{AUC} 9 (dog). Adequate justification was provided for the lack of combination toxicity studies with sofosbuvir and velpatasvir (Epclusa), and Epclusa with ribavirin.
- The potential genotoxicity of velpatasvir was investigated in a standard battery of tests. The results were negative in all tests and velpatasvir is unlikely to pose a mutagenic or clastogenic risk to humans. No carcinogenicity studies with velpatasvir were submitted but the sponsor indicated that long-term studies on mice and rats are on-going.
- Velpatasvir had no effects on fertility, embryofetal or post-natal development in rats or on embryofetal development in mice or rabbits.
- Velpatasvir did not produce skin irritation and was not a severe eye irritant.
- Velpatasvir was positive in an in vitro phototoxicity study, but was negative in vivo in Long-Evans rats.

Conclusions and recommendation

- There are no major nonclinical deficiencies.
- Primary pharmacology studies established anti-HCV activity *in-vitro* against HCV genotypes 1 to 6.
- No clinically relevant hazards were identified in safety studies.
- Velpatasvir is an inhibitor of drug transporters P-gp, BCRP and OATP2B1. Based on the estimated maximal intestinal concentration velpatasvir may increase intestinal absorption of co-administered drug substrates for these transporters. Velpatasvir inhibited hepatic uptake transporters OATP1B1 and OATP1B3 with IC_{50} values in the potential range for concentrations at the hepatic inlet and therefore has the potential to increase circulating concentrations of drug substrates of these transporters.
- No major organ toxicities were observed with velpatasvir in repeat dose studies in any species at the exposures achievable in nonclinical species.
- Velpatasvir is unlikely to pose a genotoxic hazard. Carcinogenicity studies in rasH2 transgenic mice and rats are ongoing, and should be submitted when complete.

- There was no evidence of reproductive toxicity with velpatasvir and Australian Pregnancy category B1 is appropriate.
- There are no nonclinical objections to registration of velpatasvir.
- Based on the nonclinical data provided in this submission for velpatasvir and evaluated in the previous submission for sofosbuvir there are no nonclinical objections to the registration of Epclusa.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

It is estimated that 130 to 210 million people worldwide are infected with HCV with 2 to 4 million new infections reported annually. Approximately 80% of infections are related to IV drug use, with lesser numbers attributed to sexual transmission, blood transfusions, and tattoos. Approximately 300,000 Australians were infected with HCV in 2011. Acute infections become chronic in 70% to 90% of cases and this leads commonly to cirrhosis, chronic liver failure, hepatocellular carcinoma, liver transplantation and death. After 20 years of infection, 20 to 30% of patients will have progressed to cirrhosis, 5 to 10% will have developed end-stage liver disease, and 4 to 8% will have died of liver-related causes. HCV has six genotypes (GT) and multiple subtypes with genotypes 1 to 3 distributed worldwide. Genotypes 1a and 1b account for 60% of global HCV infections. In Australia, the most common genotypes are 1a and 1b (54% prevalence) and 3a (37% prevalence). The incidence of HCV GT4 infection is low in the US (approximately 1%), and in Europe (approximately 5% on average). However, in North Africa and the Middle East, GT4 infection has a prevalence of approximately 50% (up to 90% in Egypt), and it is spreading to Europe and the rest of the world through immigration and IV drug use.

Until recently, the standard of care treatment for chronic HCV infection for all genotypes was the combination of pegylated interferon and ribavirin (pegIFN/RBV) for 48 weeks. The response to this treatment varies according to HCV genotype and host interleukin 28B (IL28B) genotypic subtypes (CC, CT, and TT). Patients with the IL28B CC genotype are able to mount stronger immune responses to the HCV virus, and spontaneous viral clearance rates and responsiveness to antiviral therapy are enhanced. In patients with HCV GT1 infection, sustained viral response (SVR) rates following pegIFN/RBV therapy are only 45% in treatment naïve patients, and significantly lower rates are achieved in prior relapsers and non-responders. Moreover, the side effect profile of pegIFN/RBV is unfavourable with a high incidence of lethargy, fatigue, depression and anaemia. Recently approved DAA combinations such as Viekira PAK (paritaprevir, ombitasvir, and dasabuvir) and Technivie (paritaprevir and ombitasvir) achieve high SVR rates in HCV GT1 and GT4 infections without the adverse events associated with pegIFN. Harvoni (lepidasvir and sofosbuvir) is well tolerated and effective in HCV GT1 infection, and sofosbuvir with ribavirin (RBV) is effective in HCV GT2 and GT3 infections. It is also approved for use GT4 GT5, or GT6-infected patients who are not suitable for pegIFN treatment. In the EU, Harvoni with RBV for 24 weeks is approved for the treatment of GT1 and GT4 infection in patients with decompensated cirrhosis, who are either awaiting liver transplantation or during the post-transplant period. There are no approved treatments for patients with decompensated cirrhosis in the US.

Velpatasvir is a novel HCV NS5A inhibitor with potent antiviral activity in vitro against GT1 to 6 replicons. Velpatasvir and sofosbuvir have been formulated in a FDC tablet for once daily use. It is hoped that Epclusa will offer a well-tolerated, once daily, single dose, 12 week treatment for patients with HCV infection of any genotype, in non-cirrhotic patients and in those with compensated or decompensated cirrhosis.

Contents of the clinical dossier

The submission contained the following clinical information:

- Fifteen clinical pharmacology studies, including 15 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- Three population pharmacokinetic analyses.
- Three pivotal Phase III efficacy/safety studies (GS-US-342-1138, GS-US-342-1139, GS-US-342-1140)
- A pivotal Phase III special population study in patients with decompensated cirrhosis (GS-US-342-1137).
- Two Phase II dose ranging studies (P7977-0221 and P7977-0422)
- Three Phase II studies (GS-US-337-0122, GS-US-342-0102, GS-US-342-0109)
- A pooled efficacy and safety analysis of the three pivotal Phase III studies (GS-US-342-1138, GS-US-342-1139, GS-US-342-1140).

The submission included a clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All clinical studies were performed according to the principles of ICH Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Comment: Many of the PK/ pharmacodynamics (PD) studies that form part of the present submission have been previously evaluated by the TGA as part of the applications for Harvoni Ledipasvir (90 mg)/ Sofosbuvir (400 mg) Tablets (PM-2014-00469-1-2) and Sovaldi Sofosbuvir (400 mg) Tablets (PM-2013-01283-1-2). Therefore, the current PK/PD evaluation will focus on the previously unevaluated studies, in particular those that examined the proposed FDC, and the evaluator requests that the Delegate please refer to the appropriate CERs when reviewing the previously submitted data.

Table 6: The studies relating to each pharmacokinetic topic

PK topic	Subtopic	Study ID	Primary Aim of the study
PK in healthy adults	PK Single dose†	GS-US-342-0104	Relative bioavailability of FDC tablets relative to free combination and the effect of food
	Multi-dose	GS-US-281-0101	PKs of escalating single and multiple oral doses of VEL
Special Populations	Hepatic Impairment	GS-US-281-0112	Single dose PKs of VEL in subjects with normal hepatic function, moderate and severe hepatic impairment
	Renal Impairment	GS-US-281-1056	Single-dose PKs of VEL in subjects with severe renal impairment and matched healthy subjects
Mass Balance	Healthy subjects	GS-US-281-1055	Mass balance of VEL using a single dose of radiolabelled [^{14}C]VEL
PopPK	Healthy and HCV infected	15-0001 to 15-0003	Develop popPK models for VEL, SOF, and GS-331007 in healthy and HCV infected subjects
Target Population§	HCV infected	GS-US-281-0102	PKs following escalating multiple oral doses of VEL in subjects infected with HCV
Drug-drug Interactions	FDC and , ARVs	GS-US-342-1167	PKs of SOF, its metabolites and VEL upon co-administration with ATR; EFV/FTC/TDF, Complera, Tivicay, or EVG/COBI/FTC/TAF
		GS-US-342-1326	PKs of SOF, its metabolites and VEL upon co-administration with EVG/COBI/FTC/TDF, DRV + RTV + FTC/TDF, ATV + RTV + FTC/TDF, LPV/RTV + FTC/TDF or RAL + FTC/TDF
	FDC and s	GS-US-342-1709	PKs of SOF/VEL upon co-administration with a representative PPI and food
		GS-US-342-1346	PKs of SOF/VEL upon co-administration with a representative H2RA or PPI.
	VEL and OATP/BCRP/ P-gp/CYP substrates, inhibitors and inducers	GS-US-281-0115	Effect of VEL on OATP/BCRP and P-gp substrates; CYP3A/CYP2C8/P-gp inducers or inhibitors on the PKs of VEL; selective OATP1B1/1B3 inhibitors and mixed OATP/P-gp/MRP2 inhibitors on the PK of VEL; and potent selective CYP3A or CYP2C8 inhibitors on the PK of VEL
	VEL and oral contraceptive	GS-US-281-1058	Effect of VEL on the PK of a representative hormonal contraceptive medication
	VEL and PPI/H2RA	GS-US-281-0119	PKs of VEL upon co-administration with a representative PPI (omeprazole) or H2RA (famotidine)

PK topic	Subtopic	Study ID	Primary Aim of the study
	SPF and ARVs	P7977-1910	Effect of SOF on the PK parameters of ATV/r, EFV, TDF, FTC, ZDV, 3TC, DRV/r, or RAL in healthy HIV/HCV co-infected subjects

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. PPIs = proton pump inhibitors; Complera; FTC/RPV/TDF; Tivicay – DTG ARVs = antiretrovirals ATR = Atripla ATV = atazanavir; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC= emtricitabine; H2RA = H2-receptor antagonist; LPV = lopinavir; SOF/VEL = sofosbuvir/velpatasvir FDC; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide fumarate ZDV= zidovudine

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

For the full evaluation of the PK/PD please see Attachment 2.

Evaluator's conclusions on pharmacokinetics

ADME (absorption/distribution/metabolism/excretion)

- Epclusa is an oral FDC tablet, which contains 400 mg SOF and 100 mg VEL that is to be taken once daily with or without food.
- Following a single oral dose of Epclusa in fasted, healthy subjects the T_{max} values for SOF and VEL occurred at 1 hour and 3 hours, respectively.
- Plasma exposure to SOF, its metabolites GS-566500 and GS-331007, and VEL were similar but not bioequivalent following administration of either Epclusa or the free combination. The geometric least-squares means (GLSM) ratios (90% confidence intervals (Cis)) for SOF AUC_{inf}[6] and C_{max} were 89.5 (78.8, 101.8) and 90.0 (74.7, 108.4), respectively, and for VEL were 103.5 (75.7, 141.7) and 103.0 (74.5, 142.4), respectively.
- Compared to administration of sofosbuvir/velpatasvir FDC (SOF/VEL) under fasted conditions, a moderate fat or high fat meal increased SOF AUC_{inf} by 1.6 fold and 1.78 fold, respectively, whereas, there was little to no change in SOF C_{max} (≥ 11% decrease). For the VEL component, a moderate fat meal increased VEL AUC_{inf} and C_{max} by 1.34 fold and 1.31 fold, respectively and a high fat meal increased these values by 1.22 fold and 1.05 fold, respectively.
- Following single doses of 5 mg to 450 mg VEL, T_{max} ranged from 1.50 hours to 3.25 hours and VEL exhibited nonlinear PK across the entire dose range with greater than dose proportional increases in AUC and C_{max} from doses of 5 to 50 mg and less than dose proportional increases in exposure at doses from 50 to 450 mg.
- Following multiple doses, VEL exhibited nonlinear PK across the entire dose range examined with greater than dose proportional increases in AUC and C_{max} from doses of 5 to 50 mg and less than dose proportional increases in exposure at doses from 50 to 450 mg. Little to no accumulation in VEL AUC was identified, for instance following a single dose of 50 mg VEL AUC_{last}[7] was 2,971 ng.h/mL, whereas, following multiple doses 50 mg VEL AUC_{tau} was 3033 ng.h/mL.

[6] AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$

[7] AUC_{last} = area under the plasma concentration versus time curve from time zero to the last quantifiable concentration

- VEL was widely distributed to the tissues of healthy subjects as the Vz/F ranged from 521 L to 678 L. In vitro and clinical trials identified that VEL was highly bound to plasma proteins (≥ 99.5%). The whole blood-to-plasma concentration ratio for VEL through 12 hours ranged from 0.517 to 0.670, indicating that total radioactivity was excluded from erythrocytes.
- In vitro studies indicated that VEL was slowly metabolised by CYP2B6, CYP2C8 and CYP3A4 and that it was also a substrate for both P-gp and BCRP mediated transport.
- Following a single oral dose administration of [^{14}C] VEL approximately 94% of the radioactive dose was recovered in the faeces, with the major species identified being unchanged VEL, which accounted for a mean of 76.6% of the administered dose, followed by one known oxidative metabolite M18 (hydroxy-VEL-1, 5.9%) and one known dealkylated metabolite M19 (desmethyl-VEL, 3.0%).
- The activity of the VEL metabolites identified in the mass balance study is not discussed but due to the extremely low levels detected in plasma they are unlikely to be pharmacologically active.

Intra- and inter-individual variability

The inter-individual variability on VEL CL/F[8], Vc/F[9], Vp/F[10] and absorption rate constant (Ka) in fasted subjects were 50.8%, 68.9%, 50.8% and 54.2%, respectively, whereas, the intra-subject variability was 56.7%. For SOF PKs, the inter-individual variability on clearance (CL), Vc/F and Ka were 48.2%, 94.9% and 4.6%, respectively, whereas, the intra-subject variability was 119.9% and 108.8% in healthy volunteers and in patients, respectively.

Pharmacokinetics in the target population

- VEL was absorbed quickly following single and multiple oral doses, with a median T_{max} of between 1.5 hours and 3.0 hours.
- Following 100 mg VEL the C_{max} and AUC_{inf} were 372.8 ng/mL and 2727.3 ng.h/mL, respectively.
- Over the dose range of 25 mg to 150 mg VEL increases in exposure were near dose proportional, whereas, increases in VEL exposures were generally greater than dose proportional from 5 mg to 25 mg. A modest accumulation (less than 1.5 fold) was observed following 3 days of dosing.
- VEL plasma PKs were similar between subjects with genotype 1a, 1b, 2, 3, or 4 HCV.
- PPK analyses indicated that following once daily administration of SOF 400 mg and VEL 100 mg as either, a free combination, or FDC, VEL C_{max} and AUC_{inf} were approximately 1.71 fold and 1.59 fold lower in HCV infected subjects than in healthy subjects. By contrast, SOF C_{max} and AUC_{inf} were equivalent in HCV infected and healthy subjects.

Pharmacokinetics in other special populations

- VEL AUC_{inf} values in subjects with normal hepatic function, moderate or severe impairment were relatively similar and ranged from 4104.6 ng.h/mL to 5403.7 ng.h/mL, whereas, C_{max} decreased from 599.7 ng/mL to 268.4 ng/mL as impairment increased. t½ values were prolonged for subjects with moderate hepatic impairment

[8] CL/F = apparent oral clearance after administration of the drug: CL/F = Dose/AUC_{inf}, where "Dose" is the dose of the drug
[9] Vc/F,= apparent volume of distribution in central compartment after oral dosing
[10] Vp/F = apparent volume of distribution in peripheral compartment after oral dosing

(approximately 23 hours) and severe hepatic impairment (approximately 31 hours) compared to subjects with normal hepatic function (approximately 18 hours).

- VEL AUC_{inf} was approximately 1.5 fold higher in subjects with severe renal impairment compared to those with normal renal function, whereas, C_{max} was approximately 1.11 fold higher.
- Covariate analysis indicated statistically significant effects of sex, HCV infection, and decompensated cirrhosis on VEL CL/F and Vc/F and food on VEL Ka, F1 and lag time. For SOF PKs, the significant covariates on SOF CL/F and Vc/F were sex and hepatic impairment and food on SOF Ka.
- Age, race, ethnicity, creatinine clearance (CLcr), HCV genotype, IL28B genotype, (compensated) cirrhosis, body weight, body mass index (BMI), and concomitant medications were not considered relevant covariates for the population PK of either VEL or SOF.

Interaction between SOF and VEL

Co-administration of SOF (400 mg) with VEL (150 mg) had little to no effect on VEL AUC_{tau}, C_{max}, and observed drug concentration at the end of the dosing interval (C_{tau}). By contrast, SOF plasma exposures increased approximately 1.8 (C_{max}) and 2.4 fold (AUC) when co-administered with VEL. GS-566500 C_{max} and AUC increased approximately 1.6 and 1.8 fold, respectively, when SOF was co-administered with VEL. GS-331007 (the predominant circulating nucleoside metabolite of SOF) C_{max} decreased approximately 36%, but AUC was unaffected by co-administration of SOF+VEL.

Effect of antiretroviral drugs on the PKs of the FDC

- The PKs of SOF and its metabolites were within the predetermined lack of PK alteration boundaries of 70% to 143%, following co-administration of the FDC with EFV/FTC/TDF, FTC/RPV/TDF, DTG, RAL + FTC/TDF, EVG/COBI/FTC/TDF or ATV+RTV+FTC/TDF.[11]
- For the VEL component of the FDC, the PKs of VEL were not affected by the co-administration of FTC/RPV/TDF, DTG, RAL + FTC/TDF, EVG/COBI/FTC/TDF, DRV+RTV+FTC/TDF or LPV/RTV+FTC/TDF.[12]
- Co-administration with EVG/COBI/FTC/TAF increased the AUC_{tau} of SOF and GS-331007 by 37% and 48%, respectively, and GS-331007 C_{tau} increased by 58%, whereas, DRV+RTV+FTC/TDF or LPV/RTV+FTC/TDF resulted in decreased exposure to SOF (approximately 28% and approximately 29%, respectively) with no alteration in the overall exposure of GS-566500 or GS-331007.
- Co-administration with ATV+RTV+FTC/TDF resulted in an increase in VEL AUC_{tau} (approximately 142%), C_{max} (approximately 55%), and C_{tau} (approximately 301%) and EVG/COBI/FTC/TAF increased VEL C_{max}, AUC_{tau} and C_{tau} by 30%, 50% and 60%, respectively. By contrast, VEL C_{max} and AUC_{tau} were decreased by 47% and 53%, respectively, when co-administered with EFV/FTC/TDF.

Effect of FDC on the PKs of other antiretroviral drugs

- Co-administration of SOF/VEL had no effect on the PKs of EFV, RPV, DTG, EVG, FTC, EVG, DRV, ATV, LPV or RTV.

[11] ATV = atazanavir; COBI = cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV = lopinavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

[12] DRV = darunavir

- COBI C_{tau} increased by 103% and approximately 71% when the FDC was co-administered with either EVG/COBI/FTC/TAF or EVG/COBI/FTC/TDF.
- TAF C_{max} decreased by 20% when the FDC was co-administered with EVG/COBI/FTC/TAF.
- Tenofovir (TFV) AUC_{tau}, C_{max}, and C_{tau} increased by approximately 81%, 77%, and 121%, respectively, following co-administration of EFV/FTC/TDF with SOF/VEL. Similarly, TFV AUC_{tau}, C_{max}, and C_{tau} increased approximately 40%, 44%, and 84%, respectively, following co-administration of FTC/RPV/TDF. In addition, TFV AUC_{tau} (range: 39% to 40%), C_{max} (range: 36% to 55%), and C_{tau} (range: 45% to 70%) values were increased following co-administration with EVG/COBI/FTC/TDF, DRV+RTV+FTC/TDF, or RAL+FTC/TDF and an increase in TFV C_{max} (approximately 55%) and C_{tau} (approximately 39%), but no change in AUC, was observed following administration of ATV+RTV+FTC/TDF with SOF/VEL. TFV C_{max} also increased (approximately 42%) following administration of LPV/RTV+FTC/TDF with SOF/VEL, whereas, there was no change in either TFV AUC_{tau} or C_{tau} under these conditions.
- C_{tau} values for ATV and RTV increased by approximately 39% and approximately 29%, respectively, following co-administration of ATV+RTV+FTC/TDF with SOF/VEL.

Interaction between the FDC and proton pump inhibitors (PPIs)/H2RA

- Administration of SOF/VEL with food and the PPI omeprazole had no effect on the AUC of SOF or its metabolites GS-566500 and GS-331007, regardless of timing or dose of omeprazole, whereas, SOF C_{max} was 16% to 30% lower. By contrast, VEL C_{max} and AUC_{inf} decreased by 33% to 56% and 26% to 53%, respectively, following co-administration of the FDC with food and omeprazole.
- When SOF/VEL was administered under fasted conditions with omeprazole 20 mg (simultaneous or staggered by 12 hours) the AUC_{inf} values for SOF, GS-566500, and VEL, decreased by 29% to 55%, whereas there was no effect on the PKs of GS-331007.
- Administration of SOF/VEL with the H2-receptor antagonist (H2RA) famotidine 40 mg (simultaneously or staggered by 12 hours) had no effect on the AUC values for SOF, GS-566500, GS-331007 or VEL, whereas, there was a small decrease in SOF C_{max} (23%).

Effect of other drugs on VEL PKs in the absence of SOF

- Co-administration with rifampin, a strong inducer of CYP3A4/2C8 and P-gp, substantially reduced VEL AUC (approximately 82%) and C_{max} (approximately 71%).
- Co-administration with ketoconazole, a strong inhibitor of CYP3A4/2C8 and P-gp, increased VEL AUC and C_{max} by approximately 70% and 29%, respectively.
- Administration of single dose rifampin, an inhibitor of OATP, with VEL resulted in an approximate 47% and 28% increase in VEL AUC and C_{max}, respectively.
- VEL AUC and C_{max} were approximately 2 fold and 56% higher, respectively, following co-administration with cyclosporine, a strong inhibitor of OATP/P-gp/MRP2, as compared to VEL administered alone.
- Hormonal oral contraceptives do not appear to affect the PKs of VEL.
- Simultaneous administration of famotidine, had no impact on the AUC of VEL as the 90% CIs of the GLS mean ratios were between 70% and 120%, whereas, VEL C_{max} decreased modestly (approximately 14%). By contrast, staggered administration famotidine had little to no impact on the AUC_{last}, AUC_{inf}, and C_{max} of VEL.
- Simultaneous administration of the PPI, omeprazole, with VEL resulted in substantial decreases in the AUC_{inf} (approximately 53%) and C_{max} (approximately 55%) values of VEL.

Effect of VEL on the PKs of other drugs in the absence of SOF

- Pravastatin AUC and C_{max} were modestly increased by 35% and 28%, respectively, following co-administration with VEL, relative to pravastatin administration alone.
- Rosuvastatin AUC and C_{max} were approximately 2.8 fold and approximately 2.6 fold higher, respectively, following co-administration with VEL, relative to rosuvastatin administration alone.
- Digoxin AUC_{last}, AUC_{inf}, and C_{max} were 60%, 34%, and 88% higher, respectively, following co-administration with VEL, relative to digoxin administration alone.
- VEL had little to no effect on cyclosporine exposure (approximately 10% decrease) or the PKs of a hormonal oral contraceptive.

Effect of SOF on the PKs of other drugs in the absence of VEL

Co-administration of SOF (400 mg qd) with range of anti-retroviral therapies including: ATR; EFV + ZDV/3TC; ATV/r + TVD; DRV/r + TVD; and RAL + TVD[13] in healthy HIV/HCV co-infected subjects identified only modest changes in the PK parameters of the evaluated antiretrovirals (ARVs). The largest identified decrease in C_{max} (38%) was for RTV following administration of SOF with DRV/r + TVD, whereas, the largest decrease identified in AUC_{tau} (21%) was for RTV following the administration of SOF with ATV/r + TVD. Conversely, the largest increases in C_{max} values were identified following co-administration of SOF with ATR (35% increase in TFV) or ATV/r + TVD, which resulted in a 40% increase in TFV C_{max}.

Effect of other drugs on the PKs of SOF in the absence of VEL

The largest increases in exposure of SOF, GS-566500, and GS-331007 resulted following co-administration of SOF with ATV/r + TVD, DRV/r + TVD and RAL + TVD. For instance following co-administration of SOF with ATV/r + TVD, DRV/r + TVD or RAL + TVD the AUC_{tau} values for SOF were increased by 342%, 173%and 221%, respectively.

Population PK modelling

- The final population PK (PopPK) model that best described VEL plasma concentration data was a 2 compartment PK model with first order absorption, an absorption lag time, and first order elimination from the central compartment, with inter-individual variability terms on PK variables Ka, CL/F, Vc/F, and Vp/F.
- Values of VEL CL/F, Vc/F, Vp/F, Q/F, Ka, and lag-time (time delay between drug administration and first observed concentration above limit of quantification (LOQ) in plasma) (T_{lag}) for the 'typical' male HCV infected subject weighing 80 kg who was administered SOF/VEL under fasting conditions were estimated to be 46.5 L/hour, 392 L, 219 L, 10.8 L/hour, 0.78 hour-1, and 0.295 hour, respectively.
- The final population PK model that best described SOF plasma concentration data was a 1 compartment PK model with first order absorption, an absorption lag time, and first order elimination from the central compartment, with inter-individual variability terms on PK variables Ka, CL/F, and Vc/F.
- Values of SOF CL/F, Vc/F, Ka, and Tlag for the 'typical' male HCV infected subject weighing 80 kg who was administered SOF/VEL under fasting conditions were estimated to be 352.4 L/hour, 197.2 L, 1.247 hour-1, and 0.0925 hour, respectively.

[13] ATR = Atripla DRV/r = darunavir/ritonavir EFV = ZDV = zidovudine ; 3TC = lamivudine; ATV =r = TVD = DRV = RAL = raltegravir

Limitation of PK studies

- The absolute bioavailability of Epclusa was not determined.
- The effect of timing of Epclusa administration has not been examined.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 7 below shows the studies relating to each pharmacodynamic topic.

Table 7: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary aim of the study
Secondary Pharmacology	Effect on QTc[14]	GS-US-281-1054	Effects of VEL on time matched, baseline adjusted, and placebo corrected QTcF (corrected QT calculated using Fridericia's correction formula).

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

For the full evaluation of the pharmacodynamic studies please see Attachment 2.

Evaluator's conclusions on pharmacodynamics

Mechanisms of action

SOF is a novel inhibitor of the HCV NS5B RNA dependent RNA polymerase with potent broad genotypic activity in vitro, whereas, VEL is a novel HCV NS5A inhibitor that has demonstrated potent in vitro antiviral activity against genotype 1 to 6 HCV replicons.

VEL; Antiviral Response

- Administration of 3 consecutive daily doses of VEL (5 to 150 mg) resulted in rapid reductions in HCV RNA, with median reductions of ≥ 2 $\log_{10}$ international units (IU)/mL observed within 12 hours across all HCV genotypes.
- The greatest median change from baseline in HCV RNA in each treatment group was generally observed by 54 hours, and was > 2 $\log_{10}$ IU/mL and 6 of 70 subjects with varying genotypes and VEL doses had reductions in HCV RNA below the lower limit of quantitation (LLOQ).
- Antiviral activity was similar for subjects with genotype 1a and 1b HCV who received VEL 150 mg.

VEL; QTc

Therapeutic (100 mg) and supratherapeutic doses (500 mg) of VEL in healthy subjects did not prolong either QT interval corrected using Friderichia's formula (QTcF) or QTcN. In addition, no clinically significant changes from baseline in PR, QRS[15], or RR intervals or HR

[14] QT = electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
[15] QRS = electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization

were observed following administration of VEL compared with placebo and no notable U or T wave abnormalities were detected.

VEL; RAVs

- RAVs were detected pre-VEL treatment in 22 of 70 subjects.
- In genotype 1a and 3a HCV infected subjects, the pre-treatment presence of NS5A RAVs was associated with a slightly reduced decline in HCV RNA compared with subjects without NS5A RAVs at baseline.
- Following VEL treatment, NS5A RAVs emerged at more positions in the genotype 1a virus than in other genotypes.
- Long-term persistence results showed that NS5A RAVs that were present prior to treatment persisted through the 48 week follow-up period; however, NS5A RAVs that developed during treatment were more likely to disappear during the follow-up period.

VEL - Relationship between drug concentration and pharmacodynamic effect

A maximum effect (E_{max}) model predicted that exposures achieved following administration of VEL doses ≥ 5 mg would provide > 95% of maximal antiviral response in subjects with genotype 1 HCV infection. Based on this model, VEL systemic exposures for subjects with genotype 3 HCV infection were predicted to achieve at least 80% of maximal antiviral response at the ≥ 25 mg dose.

Pharmacodynamic interactions

- VEL (100 mg qd) did not affect the ability of oral contraceptives to reduce serum LH, follicle stimulating hormone (FSH) and progesterone levels.
- In the presence of pre-specified ARV regimens, 7 days treatment with SOF resulted in a rapid decline in HCV RNA level, with a mean reduction in RNA of > 4 $\log_{10}$ IU/mL over the 7 days. At Day 14 (7 days after stopping SOF dosing), the overall mean standard deviation (SD) change in HCV RNA levels from baseline was -3.08 (1.529) $\log_{10}$ IU/mL and early HCV viral kinetics appeared to be independent of HCV genotype and subtype.
- Ninety-one percent of subjects administered SOF+ pegylated interferon (Peg-IFN) + RBV achieved SVR12 and there was no on-treatment virologic failure. There were a total of 2 subjects (8.7%) who relapsed; both of these subjects relapsed within 4 weeks of stopping treatment.
- Potent and rapid suppression of HCV RNA was observed with a mean 4.88 $\log_{10}$ IU/mL decrease in HCV RNA after 1 week of treatment with SOF + Peg-IFN + RBV that was maintained for the duration of the study. By Week 4 and at each subsequent on-treatment assessment, 100% of subjects had HCV RNA < LLOQ.
- Approximately 57% of subjects had alanine aminotransferase (ALT) > upper limit of normal (ULN) at baseline and most had normalised ALT values during treatment with SOF + Peg-IFN + RBV, coincident with decreases in viral HCV RNA.

Dosage selection for the pivotal studies

The dose of sofosbuvir 400 mg given once daily with RBV, with or without pegIFN, is the approved dose for the treatment of HCV infection. Safety and efficacy have been confirmed in multiple Phase II and Phase III studies. For the NCE velpatasvir, activity against HCV was demonstrated in the Phase II study GS-US-281-0102. Doses > 25 mg achieved at least 80% of maximal antiviral response in all HCV genotypes. Favourable safety, efficacy and PK profiles have been shown for the SOF/VEL 400 mg/100 mg FDC in Phase II studies

involving 237 patients with HCV infection evaluated in Section 7(GS-US-342-0102, GS-US-337-0102 and GS-US-342-0109). In study GS-US-281-0112, systemic exposure to velpatasvir 100 mg was similar in patients with normal hepatic function and those with moderate or severe hepatic dysfunction.

Efficacy

Studies providing efficacy data

The following studies were evaluated:

Pivotal efficacy studies

- Study GS-US-342-1137 (ASTRAL-4)
- Study GS-US-342-1138 (ASTRAL-1)
- Study GS-US-342-1139 (ASTRAL-2)
- Study GS-US-342-1140 (ASTRAL-3)

Other efficacy studies

- Study GS-US-337-0122 (ELECTRON-2)
- Study GS-US-342-0102
- Study GS-US-342-0109

Analyses performed across trials

A pooled efficacy analysis of the pivotal Phase III studies GS-US-342-1138, GS-US-342-1139, GS-US-342-1140 was performed in patient groups who received SOF /VEL for 12 weeks.

For the full details of the evaluation please see Attachment 2.

Evaluator's conclusions on efficacy

In the Phase II studies, SOF + VEL regimens were compared at different doses and for different durations of treatment (8, 12 or 24 weeks). Treatment naïve and treatment experienced patients included all genotypes, and those with or without cirrhosis. The SOF + VEL regimens were given with or without RBV, and compared with LDV[16]/SOF (Harvoni) and other SOF containing regimens. High efficacy rates were observed in patient groups treated for 8 weeks, and in patients given VEL 25 mg. However, the best SVR12 rates were obtained in patients given SOF + VEL 100 mg for 12 weeks, particularly in patients with GT3 infection. The SVR12 rates were 100.0% in treatment naïve GT1 patients without cirrhosis, and 100.0% in treatment experienced patients. The SVR12 rate was 92.6% in treatment naïve, GT3 patients without cirrhosis; 100% in treatment experienced, GT3 patients without cirrhosis; and 88.5% in treatment experienced, GT3 patients with cirrhosis. All patients with genotype 2, 4, 5, or 6 were treatment naïve without cirrhosis and none had virologic failure.

The SOF/VEL combination was given for 12 weeks to a total of 1035 patients in the Phase III studies, and the SVR12 rates ranged from 95.3% to 100%. Only 35 GT5 and 41 GT6 patients were studied but the results in these patients were comparable to the overall population. In studies GS-US-342-1138, GS-US-342-1139, and GS-US-342-1140, there were no on-treatment virologic failures in patients given SOF/VEL for 12 weeks.

[16] LDV = ledipasvir

Overall, viral relapse was reported in only 13/1035 patients, in two (0.6%) patients with GT1 infection, and in 11 (4%) patients with GT3 infection. Overall, SVR4 rates were comparable to the SVR12 rates; however, full SVR24[17] data were not available for the interim analyses. Patients with decompensated cirrhosis were evaluated in GS-US-342-1137. The overall SVR12 rate in 90 patients treated with SOF/VEL for 12 weeks was 83.3% (range 50% to 100.0%) compared with 94.3% (range 84.6% to 100%) in patients treated with SOF/VEL + RBV for 12 weeks, and 85.6% (range 50% to 100%) in patients treated with SOF/VEL for 24 weeks. Patients with GT3 infection were least likely to achieve SVR12 (50%, 84.6%, and 50% in the respective treatment groups). Overall virologic failure was also common in GT3 patients treated with SOF/VEL for 12 weeks (42.9%).

Subgroups in the Phase III studies were analysed according to age, gender, race, region, baseline HCV RNA, baseline BMI, prior HCV treatment, IL28B genotype, NS5A RAVs, and cirrhosis. In patients treated with SOF/VEL for 12 weeks in studies GS-US-342-1138, GS-US-342-1139, and GS-US-342-1140, there were no meaningful differences in SVR12 and all subgroups achieved SVR12 rates > 95%. SVR12 rates were > 91% across all genotypes in patients with cirrhosis, and > 90% in patients with prior treatment experience.

Safety

For the full evaluation of the safety data please see Attachment 2.

Studies providing safety data

The following pivotal studies provided evaluable safety data:

- Study GS-US-342-1137 (ASTRAL-4)
- Study GS-US-342-1138 (ASTRAL-1)
- Study GS-US-342-1139 (ASTRAL-2)
- Study GS-US-342-1140 (ASTRAL-3)

Patient exposure

A total of 2,603 patients received at least one dose of SOF and VEL as individual agents or as the FDC tablet (Table 8). Of these, a total of 1,302 patients received the SOF/VEL FDC for a minimum of 12 weeks; 802 patients received SOF + VEL in three Phase II studies; and 499 patients received SOF/VEL in five Phase I studies. In GS-US-342-1137, a total of 267 patients with decompensated cirrhosis received SOF/VEL (SOF/VEL for 12 weeks, n = 90; SOF/VEL + RBV for 12 weeks, n = 87; or SOF/VEL for 24 weeks, n = 90).

[17] SVR4= sustained virologic response 4 weeks post-dosing; SVR12 = sustained virologic response 12 weeks post-dosing; SVR24 = sustained virologic response 24 weeks post-dosing

Table 8: SOF/VEL exposure in Phase I, Phase II, and Phase III studies

Study	Regimen	Total (N = 2603)
Phase 3 Studies	SOF/VEL FDC	
GS-US-342-1138	SOF/VEL FDC for 12 weeks	624
GS-US-342-1139	SOF/VEL FDC for 12 weeks	134
GS-US-342-1140	SOF/VEL FDC for 12 weeks	277
GS-US-342-1137	SOF/VEL FDC for ≥ 12 weeks	267
	SOF/VEL FDC for 12 weeks	90
	SOF/VEL FDC + RBV for 12 weeks	87
	SOF/VEL FDC for 24 weeks	90
	Total	**1302**
Phase 2 Studies	SOF + VEL	
GS-US-342-0102, GS-US-342-0109, GS-US-337-0122	SOF + VEL 100 mg ± RBV for 12 weeks	237
	SOF + VEL 100 mg for 12 weeks	157
	SOF + VEL 100 mg + RBV for 12 weeks	80
	SOF + VEL 25 mg ± RBV for 8 weeks	162
	SOF + VEL 100 mg ± RBV for 8 weeks	165
	SOF + VEL 25 mg ± RBV for 12 weeks	238
	Total	**802**
Phase 1 Studies	SOF/VEL/FDC	
GS-US-342-0104, GS-US-342-1167, GS-US-342-1326, GS-US-342-1346, GS-US-342-1709	SOF/VEL FDC (dosed to evaluate bioavailability, food effects, and DDIs with ARVs, PPIs, and H2RAs)	499
	Total	**499**
Total Exposure to SOF/VEL and SOF+VEL in Phase 1, 2, and 3 Clinical Studies		**2603**

SOF = sofosbuvir; VEL = velpatasvir; FDC = fixed-dose combination; DDI = drug-drug interaction; RBV = ribavirin; ARV = antiretroviral; PPI = proton pump inhibitor; H2RA = H2 receptor agonist
SOF/VEL dose was 400/100 mg FDC tablet once daily; SOF single-agent dose was 400 mg once daily; RBV dose was 1000 or 1200 mg divided daily dose (for subjects who weighed < 75 kg, the RBV dose was 1000 mg/day divided; for subjects who weighed ≥ 75 kg, the RBV dose was 1200 mg/day divided).

Safety issues with the potential for major regulatory impact

Liver toxicity

Grade 3 or 4 liver chemistry abnormalities were provided. No safety signals were detected. In the integrated Phase III study analysis, one patient (< 0.1%) in the SOF/VEL 12 week group had a Grade 3 or 4 ALT abnormality compared with eight (6.9%) in the placebo group. There was no Grade 3 or 4 total bilirubin elevations in the SOF/VEL or placebo groups. An independent adjudication committee assessed predefined criteria for drug induced liver injury (DILI). A total of 56 cases were reviewed in the Phase II and Phase III safety populations but only one case of potential DILI was identified. This was a Phase II study, female patient who received SOF + VEL 25 mg + RBV who developed unexplained increases in ALT and aspartate aminotransferase (AST). The LFT abnormalities were associated with starting anti-hypertensive therapy and they resolved when the antihypertensive therapy was stopped.

Haematological toxicity

With the exception of the well understood toxicity profile of RBV, no haematological safety signals were detected. There were no cases of pancytopenia. In the SOF/VEL group of integrated Phase III safety analysis, the only Grade 3 events were decreased lymphocytes (0.5%), neutrophils (0.4%), and platelets (0.2%). There was no Grade 3 or 4 events in the placebo group.

Serious skin reactions

No serious skin reactions were reported in the integrated Phase III study analysis. One patient in the SOF + RBV 24 week group was hospitalised due to a generalised eczematous reaction but study treatment was not interrupted.

Cardiovascular safety

No significant safety signals were detected in the Phase III program. In the integrated Phase III study analysis, one patient in the SOF/VEL 12 week group had a Grade 3 adverse event (AE) of ischaemic cardiomyopathy. The event resolved and it was considered unrelated to drug treatment. Bradycardia at the start of treatment has been observed in previous studies of sofosbuvir and other DAAs. In the integrated Phase III studies, 7.9% of patients had cardiac disease at baseline. However, similar percentages of patients using beta-blockers, calcium channel blockers, or neither treatment had cardiac AEs during treatment. Four treatment emergent electrocardiogram (ECG) abnormalities events were noted, one case each of QTc prolongation, extra-systoles, atrial fibrillation, and supraventricular tachycardia. Three events were in the SOF/VEL 12 week group and one was in the SOF + RBV 12 week group.

Evaluator's conclusions on safety

No specific safety concerns have been identified in the SOF/VEL development program. In the integrated safety analysis, the overall rates of AEs were comparable in patients given SOF/VEL for 12 weeks and in patients given placebo. The most commonly reported AEs in the SOF/VEL and placebo groups were headache (28.6% versus 28.4%), fatigue (21.0% versus 19.8%), nausea (13.0% versus 11.2%) and nasopharyngitis (11.7% versus 10.3%). Most AEs were mild to moderate in severity and the pattern of AEs was similar in all subgroups, irrespective of gender, race, age, and other factors. In the SOF/VEL group, Grade 3 AEs were reported in 3% of patients, most commonly headache and anxiety, with only 0.7% considered drug related. Only two Grade 4 AEs were reported in the SOF/VEL group and neither was considered drug related. In patients treated with SOF/VEL, serious adverse events (SAEs) were reported in 2.2% of patients. Only three deaths were reported, each occurring post treatment and were considered unrelated to drug treatment. Laboratory abnormalities were reported less frequently in the SOF/VEL group compared with placebo. Grade 3 AEs were reported in 6.5% and 10.3% of the respective groups, and Grade 4 AEs were reported in 1.0% and 1.7% of the respective groups. Five patients had Grade 4 lipase elevations in the SOF/VEL group but all were asymptomatic and transient.

AEs of special interest were identified based on historical treatment regimens including regimens containing RBV, Peg-IFN, and other DAAs. These included serious skin rash, pancytopaenia, depression and other psychiatric events, pancreatitis, rhabdomyolysis and renal failure. In addition, bradycardia has been observed with DAAs following initiation of treatment. However, with the exception of a single AE of depression, no events of special interest were observed. As would be expected, AEs occurred more commonly in the SOF + RBV compared with the SOF/VEL and placebo groups.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of SOF/VEL in the proposed usage are:

- Very high efficacy rates in non-cirrhotic patients of all HCV genotypes
- Effective in patients with compensated or decompensated cirrhosis
- Effective in all patients, irrespective of age, gender, race, BMI, and hepatic function
- Improves underlying hepatic dysfunction
- Simple, once daily treatment regimen
- Well tolerated with an adverse event profile comparable to placebo
- The safety profile of sofosbuvir is well established
- Potential use in patients before or after liver transplantation
- While a controlled clinical trial cannot be conducted, SOF/VEL will inevitably reduce the incidence of cirrhosis, hepatocellular carcinoma (HCC) and liver-related deaths in patients with chronic HCV who achieve SVR12.

First round assessment of risks

The risks of SOF/VEL in the proposed usage are:

- No specific safety signals have been identified but uncommon ADRs relating to velpatasvir may emerge
- SOF/VEL has not been studied in patients with severe renal impairment or in patients with HCV/HIV co-infection
- Unidentified drug-drug interactions may emerge
- Treatment emergent viral resistance in a very small percentage of patients.

First round assessment of benefit-risk balance

The benefit-risk balance of SOF/VEL, given the proposed usage, is favourable.

SOF/VEL given for 12 weeks provides outstanding SVR12 rates of 90 to 100% in HCV patients with or without cirrhosis, irrespective of genotype and prior treatment experience. Virologic failure (mainly relapse) is uncommon and reported mostly in patients with GT3 infection. SOF/VEL is given as a simple once daily dose and it obviates the need for potentially toxic RBV, Peg-IFN, or other DAA therapies. SOF/VEL with RBV is also extremely effective in patients with decompensated cirrhosis. In this vulnerable population, high SVR12 rates are associated with improved liver function in a significant proportion of patients. It is effective in all subgroups irrespective of age, gender, and race, including those with impaired hepatic function. SOF/VEL is well tolerated and no specific ADRs have been identified. The safety profile of sofosbuvir is well established but uncommon ADRs to velpatasvir may emerge.

First Round Recommendation Regarding Authorisation

Authorisation is recommended for the proposed indication:

"Epclusa (sofosbuvir/velpatasvir fixed dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults".

Clinical Questions and Second Round Evaluation of clinical data submitted in response to questions

For details of the clinical questions raised, sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

No change to the first round assessment.

V. Pharmacovigilance findings

Risk management plan

Gilead Sciences International Ltd has submitted EU-RMP version 0.1 (11 November 2015; DLP 26 August 2015) and ASA version 0.1 (December 2015) in support of this application. In response to the round 1 RMP evaluation, the sponsor submitted revised versions of the EU RMP (version 0.2, date 21 April 2016, DLP 26 August 2015) and the ASA (version 0.2, date July 2016), which addressed the recommendation of the RMP Evaluator.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 9.

Table 9: Proposed summary of safety concerns and risk minimisation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Severe bradycardia and heart block when used with concomitant amiodarone1	ü	ü	ü	–
Important potential risks	Drug-drug interaction with moderate and potent P-gp inducers2	ü	–	ü	–
	Drug-drug interaction with moderate and potent inducers of CYP2B6, CYP2C8, or CYP3A4	ü	–	ü	–
	Drug-drug interaction with PPIs	ü	–	ü	–
	Drug-drug interaction with TDF	ü	ü	ü	–
	Drug-drug interaction with	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	rosuvastatin				
	Drug-drug interaction with digoxin	ü	–	ü	–
Missing information	Safety in children	ü	ü	ü	–
	Safety in pregnant or breastfeeding women	ü	ü	ü	–
	Safety in patients with HCV/HIV coninfection	ü	ü	ü	–
	Safety in patients with HCV/HBV coninfection	ü	–	ü	–
	Safety in post-transplant patients	ü	–	ü	–
	Safety in HCV patients with severe renal impairment or end-stage renal disease	ü	ü	ü	–
	Development of resistance	ü	ü	ü	–

[1] = Updated from an important potential risk in response to the round 1 evaluation of the RMP
[2] = Updated to include moderate as well as potent P-gp inducers in response to the European RMP evaluation, which satisfactorily addressed the TGA recommendation to include drug interactions with anticonvulsants.

The additional pharmacovigilance activities are follow up studies to address selected important identified and potential risks and missing information, as indicated in Table 9 above. Most of these studies are already underway.

New and outstanding recommendations

No new RMP issues have been identified during the second round of evaluation.

Recommendation

The sponsor should update the wording in the PI document to reflect the addition of 'drug-drug interaction with moderate P-gp inducers' to the safety profile.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *Implement EU-RMP (version 0.2; date 21 April 2016, DLP 26 August 2015) with Australian Specific Annex (version 0.2, date July 2016) and any future updates as a condition of registration.*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There are no outstanding quality issues. The submission did not require referral to the Pharmaceutical Subcommittee.

Nonclinical

There are no nonclinical objections to the registration. Australian Pregnancy category B1 is considered appropriate. Recommendations for PI have been provided.

Clinical

The clinical dossier in this submission was comprised of 15 PK studies, 4 PD studies, 3 PopPK reports, 4 pivotal Phase III efficacy studies (ASTRAL-1, ASTRAL-2, ASTRAL-3 and ASTRAL-4) and 5 Phase II studies (0221 and 0422; 0122, 0102 and 0109). A pooled analysis of Phase III studies ASTRAL-1, ASTRAL-2 and ASTRAL-3 was also provided. Some of the PK/PD studies in this submission have been previously evaluated in relation to SOF.

This overview mainly focusses on the efficacy analysis of the 4 pivotal studies. Please refer to the Clinical Evaluation Report (CER) (Attachment 2) for additional details.

Pharmacodynamics and pharmacokinetics

SOF is a nucleotide pro-drug that undergoes intracellular metabolism to form active triphosphate (GS-461203), which can be incorporated by HCV NS5B and acts as a chain terminator.

VEL is a novel HCV NS5A inhibitor that has shown in vitro activity against genotype 1 to 6 HCV replicons. VEL lacks activity against the HCV NS3/4A protease, NS5B polymerase, or the HCV internal ribosomal entry site.

SOF (and its inactive circulating metabolite GS-331007) behaved dose proportionally over 200-1200 mg range. VEL exhibited nonlinear PK with greater than dose proportional increase in AUC and C_{max} in 5 to 50 mg dose range and less than dose proportional increase at doses from 50 to 450 mg following single or multiple dosing. SOF is extensively metabolised in liver and excreted via kidneys. VEL is mainly eliminated unchanged in faeces via the biliary route.

Table 10: Pharmacokinetics of SOF and VEL

	SOF	VEL
	Prominent first pass effect; intracellular conversion to active form (GS-461203); subsequent metabolism to GS-331007 as the main circulating metabolite to be excreted via urine.	Biliary excretion is the major route of elimination with 77% unchanged compound in faeces, but also products of slow metabolism by CYP2B6, CYP2C8, CYP3A4; urinary excretion is negligible.

	SOF	VEL
Protein binding	approximately65%	> 99.5%
T_{max} (median)	1 h	3 h
C_{max} (median)	3 h (GS-331007)	3 h
t½ (median)	0.5 h (SOF); 25 h (GS-331007)	15 h

Bioavailability

The absolute bioavailability of SOF/VEL FDC was not determined.

Interaction between SOF and VEL: Co-administration of SOF (400 mg) with VEL (150 mg) had no effect on VEL exposure (AUC or C_{max}), whereas SOF plasma exposures increased approximately 1.8 (C_{max}) and 2.4 (AUC) fold. The GS-331007 C_{max} decreased approximately 36%, but AUC was unaffected.

HCV patients

Based on population PK analyses, SOF and GS-331007 AUC0-24 and C_{max} were similar in healthy adults and HCV patients. VEL AUC0-24 and C_{max} were 37% lower and 41% lower respectively in HCV-infected patients compared to healthy adults

Food effect

A single dose of Epclusa with a moderate or high fat meal increased SOF exposure (AUC) by 60% and 78% respectively, but did not affect its C_{max}. The GS-331007 AUC was not affected, but there was 25% and 37% decrease in C_{max}. For VEL, moderate or high fat meal resulted in 34% and 21% increase in AUC respectively, and 31% and 5% increase in C_{max} respectively.

Renal impairment

Following single dose (400 mg) SOF AUC was 61%, 107% and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 AUC was 55%, 88%, and 451% higher respectively compared to HCV patients with normal renal function. The metabolite GS-331007 is removed by haemodialysis with an extraction coefficient of approximately 53%. Renal impairment does not affect exposure to VEL.

Hepatic impairment

Following multiple dosing, SOF AUC was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC was 18% and 9% higher respectively. Following a single (100 mg) dose, VEL AUC was similar in patients with moderate or severe hepatic impairment compared to subjects with normal hepatic function.

Drug-drug interactions:

SOF and VEL are substrates of drug transporters P-gp and BCRP.

SOF and GS-331007 are not inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, and OCT1. The metabolite GS-331007 is not an inhibitor of OAT1, OAT3, OCT2, and MATE1. SOF and GS-331007 are not inhibitors or inducers of CYP450 or uridine glucuronosyltransferase (UGT) UGT1A1 enzymes.

VEL is an inhibitor of P-gp, BCRP, OATP1B1, and OATP1B3. At clinically relevant levels, VEL does not inhibit hepatic transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP450 or UGT1A1 enzymes.

A range of drug-drug interaction studies (including rosuvastatin; risk of rhabdomyolysis) were performed. Please see Attachment 2 including sponsor's response to questions in round 2. Drugs that are potent inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (for example, rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to reduced therapeutic effect of Epclusa.

Co-administration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and/or velpatasvir plasma concentrations without increasing GS-331007 plasma concentration. Drugs that inhibit CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir.

Clinical Efficacy

Dose selection

The 400 mg once daily SOF is the currently approved dose of this drug. Although there was evidence of interaction with co-administered VEL, no other dose level was considered. For VEL, based on Phase I and II data, the 100 mg daily is considered a pragmatic choice from doses > 25 mg to maximise efficacy.

Pivotal efficacy studies

Four randomised clinical trials (ASTTRAL 1, 2, 3 and 4) form the pivotal evidence of efficacy of Epclusa.

ASTRAL-1 was conducted mainly in HCV genotype 1 patients but also included genotypes 2, 4, 5 and 6. ASTRAL-2 and ASTRAL-3 were conducted in HCV genotype 2 and 3 patients respectively. The population in these 3 trials consisted of patients who were treatment naïve (TN) or treatment experienced (TE) (approximately20%), with cirrhosis and compensated liver function (approximately20%) or without cirrhosis.

In ASTRAL-1, patients were stratified by HCV genotype (except GT5) and cirrhosis at randomisation. In ASTRAL-2 and ASTRAL-3, patients were stratified by cirrhosis and prior treatment experience at randomisation. The patient inclusion/exclusion criteria were similar in ASTRAL-1, ASTRAL-2, and ASTRAL-3 (except in regard to the HCV genotypes).

ASTRAL-4 was conducted in patients TN or TE patients with decompensated liver disease and included all HCV genotypes. In this trial, baseline hepatic Child-Pugh-Turcotte (CPT) class B was present in approximately90% patients. Mild to moderate ascites was present in 77.5% patients and severe ascites in 2.6% patients. At baseline, 38.2% patients had no encephalopathy and 61.8% had Grade 1-2 encephalopathy. No patients had severe encephalopathy. Approximately 55% patients were non-responders to previous therapies, mostly peg-IFN based regimens.

All four trials were in adult population and included both genders. ASTRAL-1 was randomised, double blind, placebo controlled study designed as a superiority trial, whereas ASTRAL-2 and ASTRAL-3 were randomised, active (but not optimally) controlled, open label studies designed as non-inferiority trials. Overall, baseline features were generally comparable in the treatment groups in respective trials. ASTRAL-4 was a randomised, active controlled superiority trial.

Epclusa (400/100 mg) FDC tablets were taken without regard for food. Dose modification for SOF/VEL was not permitted but RBV dose modification or discontinuation was permitted at the discretion of the investigator where relevant. The treatment groups, number of patients and duration of treatment were as shown in Table 11.

Table 11: Pivotal studies treatment groups, number of patients and duration of treatment

Trial	Population	EPCLUSA and Comparator Groups (Number of Subjects Treated)
ASTRAL-1	Genotype 1, 2, 4, 5, and 6 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (134) SOF + RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (277) SOF + RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3, 4, 5, and 6 TN and TE, with CP class B decompensated cirrhosis	EPCLUSA 12 weeks (90) EPCLUSA + RBV 12 weeks (87) EPCLUSA 24 weeks (90)

TN = treatment-naïve subjects; TE = treatment-experienced subjects (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor); SOF = sofosbuvir, RBV = ribavirin; CP = Child-Pugh.
(Table reference: FDA approved prescribing information)

The trial set-up and procedures, including efficacy and safety outcomes, were similar in the 4 trials. The primary efficacy outcome was the proportion of patients achieving SVR12. All trials are ongoing with only interim reports in this dossier. PK sub-studies were also carried out within these trials.

Results

ASTRAL-1

In ASTRAL-1, SVR12 rate in SOF/VEL group was to be compared with a hypothetical performance goal of 85% for the successful demonstration of efficacy. SVR12 was 99.0% (95%CI 97.9%, 99.6%), which was statistically superior to the pre-specified performance goal of 85% ($p < 0.001$) following 12 weeks of treatment. The SVR12 rates were comparable in all genotypic and demographic subgroups. SVR12 was achieved in 99.2% cirrhotic patients and 99.5% treatment experienced patients. No patient in the placebo group achieved SVR12. In SOF/VEL group at Weeks 4 and Week 8, 90.5% and 99.7% patients respectively had HCV RNA < lower limit of quantification (LLOQ). Mean HCV RNA levels declined rapidly by -5.12 to -4.82 $\log_{10}$ IU/mL from baseline to the end of treatment across the study genotypes.

No patient in SOF/VEL group had on-treatment virologic failure. A total of 6 out of 624 (1%) patients did not achieve SVR12. Two had virologic relapse and 4 patients did not achieve SVR12 due to other reasons. The 2 relapsed patients (GT1) had NS5A RAVs at baseline and both developed additional NS5A RAVs at relapse. There were no virologic failures in patients with GT 2, 4, 5, or 6. In the second round clinical evaluation, summary results for SVR24 were reported as shown in Table 12.

Table 12: ASTRAL-1; summary results for SVR24

	SOF/VEL 12 Weeks SVR24							
	Total (All Genotypes)		Genotype 1a		Genotype 1b		Genotype 1 Total	
	Yes (N = 610)	No (N = 0)	Yes (N = 205)	No (N = 0)	Yes (N = 115)	No (N = 0)	Yes (N = 320)	No (N = 0)
SVR12								
Yes	610	0	205	0	115	0	320	0
No	0	0	0	0	0	0	0	0
Positive Predictive Value	100%	0	100%	0	100%	0	100%	0

	Genotype 2		Genotype 4		Genotype 5		Genotype 6	
	Yes (N = 100	No (N = 0)	Yes (N = 115)	No (N = 0)	Yes (N = 34)	No (N = 0)	Yes (N = 41)	No (N = 0)
SVR12								
Yes	100	0	115	0	34	0	41	0
No	0	0	0	0	0	0	0	0
Positive Predictive Value	100%	0	100%	0	100%	0	100%	0

SVR12 response was highly predictive of SVR24.

ASTRAL-2

SVR12 rates were as follows:

- SOF/VEL for 12 weeks = 99.3% (95%CI 95.9%, 100%)
- SOF+RBV for 12 weeks = 93.9% (95%CI 88.4%, 97.3%)

Non-inferiority was demonstrated based on pre-specified -10% level. In this instance, the treatment difference between the two groups was 5.2% (95%CI 0.2%, 10.3%) indicating statistically superior (p = 0.018) result in SOF/VEL group compared with SOF+RBV group. Response in subgroups was consistent with the overall population. In both treatment groups, 90.2% and 100% patients had HCV RNA < LLOQ at Weeks 4 and 8 respectively. Mean HCV RNA levels declined rapidly by -5.32 and -5.04 $\log_{10}$ IU/mL from baseline to end of treatment in the SOF/VEL and SOF +RBV groups.

In SOF/VEL group, one patient (0.7%) failed to achieve SVR12. No patient had on-treatment virologic failure or relapse. In SOF+RBV group, eight patients (6.1%) failed to achieve SVR12, of which 6 experienced relapse. Two patients had NS5B RAVs detectable at baseline. In the second round clinical evaluation, summary results for SVR24 were reported as shown in Table 13.

Table 13: ASTRAL-2 summary results for SVR24

	SOF/VEL 12 Weeks SVR24		SOF+RBV 12 Weeks SVR24		Overall SVR24	
	Yes (N = 127)	No (N = 0)	Yes (N = 122)	No (N = 0)	Yes (N = 249)	No (N = 2)
SVR12						
Yes	127	0	122	0	249	0
No	0	0	0	2	0	2
Positive Predictive Value	100%		100%		100%	

SVR12 response was highly predictive of SVR24.

ASTRAL-3

SVR12 rates were as follows:

- SOF/VEL for 12 weeks = 95.3% (95%CI 92.1%, 97.5%)
- SOF+RBV for 24 weeks = 80.4% (95%CI 75.2%, 84.9%).

The treatment difference was 14.8% (95%CI 9.6%, 20.0%) indicative of statistical ($p < 0.001$) and clinical superiority of SOF/VEL (12 weeks) over SOF+RBV (24 weeks). Response in sub-groups was consistent with the overall population. SVR12 rates in cirrhotic patients and treatment experienced patients were 91.3% and 90.1% respectively in SOF/VEL group compared to 66.3% and 63.4% respectively in SOF+RBV (24 weeks) group. In SOF/VEL group, HCV RNA < LLOQ was reported in 91.7% and 99.6% patients at Weeks 4 and 8, respectively compared to 88.2% and 99.3% respectively in SOF+RBV (24 weeks) group. Mean HCV RNA levels declined by -5.14 and -4.79 $\log_{10}$ IU/mL from baseline to the end of treatment in SOF/VEL and SOF +RBV groups.

In SOF/VEL (12 weeks) group 13 out of 277 (4.7%) patients failed to achieve SVR12. Of these, no patient had on-treatment virologic failure, 11 patients experienced relapse and two patients were lost to follow-up. One patient had GT3 infection at baseline but GT1 infection at the point of virologic failure (new infection?). NS5A RAV Y93H mutation emerged in the 10 remaining patients.

In the SOF+RBV (24 weeks) group, 54 out of 275 (19.6%) patients failed to achieve SVR12. One patient had on-treatment virologic failure, 38 patients relapsed, and 15 patients did not achieve SVR12 for reasons other than virologic failure. Seven patients had treatment emergent NS5B RAVs.

In the second round clinical evaluation, summary results of SVR24 were reported as shown in Table 14.

Table 14: ASTRAL-3 summary results of SVR24

	SOF/VEL 12 Weeks SVR24		SOF+RBV 24 Weeks SVR24		Overall SVR24	
	Yes (N = 254)	No (N = 2)	Yes (N = 215)	No (N = 5)	Yes (N = 469)	No (N = 7)
SVR12						
Yes	254	0	215	0	469	0
No	0	2	0	5	0	7
Positive Predictive Value	100%		100%		100%	

SVR12 response was highly predictive of SVR24.

Pooled efficacy analysis (SVR12) of ASTRAL-1, ASTRAL-2 and ASTRAL-3

In the pooled efficacy analysis of ASTRAL-1, ASTRAL-2 and ASTRAL-3, a total of 1,038 patients were randomised and 1,035 received at least one dose of SOF/ VEL. The mean duration of exposure to study drug was 12 weeks.

Overall, the mean age was 53 years and majority of patients were aged < 65 years (88.1%).

Overall, by HCV genotype, the patients were GT1 (31.7%), GT2 (23.0%), GT3 (26.8%), GT4 (11.2%), GT5 (3.4%), or GT6 (4.0%).

Overall, 71.9% patients were treatment naïve, 28.1% were treatment experienced, and most were non-cirrhotic (78.6%). IL28B genotypic sub-types were CC (33.4%), CT (52.9%), or TT (13.1%).

Mean baseline HCV RNA was 6.3 $\log_{10}$ IU/mL, and 73.7% patients had HCV RNA ≥ 800,000 IU/mL. ALT > 1.5 x ULN was present in 49.8% patients. Mean estimated glomerular filtration rate (eGFR) was 109.4 mL/min.

The results for SVR12 in the pooled analysis, by genotype, for treatment with SOF/VEL for 12 weeks treatment, are shown below (Table 15). Overall, SVR12 was achieved by 98.1% patients (range 95.3% to 100.0%).

Table 15: SVR12 by genotype in the pooled efficacy analysis (ASTRAL-1, ASTRAL-2 and ASTRAL-3)

	SOF/VEL 12 Weeks						
	Genotype 1 (N = 328)	Genotype 2 (N = 238)	Genotype 3 (N = 277)	Genotype 4 (N = 116)	Genotype 5 (N = 35)	Genotype 6 (N = 41)	Total (N = 1035)
SVR12	323/328 (98.5%)	237/238 (99.6%)	264/277 (95.3%)	116/116 (100.0%)	34/35 (97.1%)	41/41 (100.0%)	1015/1035 (98.1%)
95% CI	96.5% to 99.5%	97.7% to 100.0%	92.1% to 97.5%	96.9% to 100.0%	85.1% to 99.9%	91.4% to 100.0%	97.0% to 98.8%

Overall, SVR12 was achieved in 96.4% patients with cirrhosis (range 91.3% to 100%) and 97.3% patients with prior treatment experience (range 90.1% to 100%). SVR4 rates (98.6%; range 96.8% to 100%) were similar to SVR12.

Rapid viral suppression was observed in all genotypes. At Week 4, 90.8% patients (range 89.3% to 92.7%) had HCV RNA < LLOQ.

Overall, virologic failure occurred in 1.3% of patients, mostly in those with GT3 infection. No cases of on-treatment virologic failure were reported (SOF/VEL for 12 weeks). All virologic failures were due to relapse. Viral relapse was reported in 13 out of 1,035 patients. Of these, 2 patients were GT1 and in 11 were GT3 including one GT3 patient at baseline who had GT1 infection post treatment. The NS5A RAVs Y93H and Y93N conferred high level resistance to VEL in 11 patients. No SOF NS5B resistance was observed in patients who had virologic failure.

SVR12 response by baseline NS5A RAVs was as shown in Table 16 (ASTRAL-1, ASTRAL-2 and ASTRAL-3).

Table 16: ASTRAL-1, ASTRAL-2 and ASTRAL-3; SVR12 response by baseline NS5A RAVs

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

ASTRAL-4

SVR12 rates were as follows:

- Group 1 = SOF/VEL for 12 weeks = 83.3% (95%CI 74.0%, 90.4%)
- Group 2 = SOF/VEL+RBV for 12 weeks = 94.3% (95%CI 87.1%, 98.1%)
- Group 3 = SOF/VEL for 24 weeks = 85.6% (95%CI 76.6%, 92.1%).

SVR12 rates were statistically significantly superior ($p < 0.001$) to the assumed spontaneous rate of 1% in all 3 groups. Efficacy was to be claimed if the SVR12 response rate was at least 40%. This was achieved in all 3 groups but no advantage was

demonstrated with addition of RBV to SOF/VEL or 24 weeks treatment with SOF/VEL compared to SOF/VEL for 12 weeks.

There were no notable differences between the subgroups but numbers were too small for meaningful comparisons. At Week 4, 80.5% to 91.0% patients had HCV RNA < LLOQ and all but two patients were suppressed at Week 8. Mean HCV RNA levels declined by approximately -4.5 $\log_{10}$ IU/mL from baseline to the end of treatment in all treatment groups and genotypes.

The majority of patients in this trial had GT1 (77.5%) or GT3 infection (14.6%).

In patients with HCV GT1 infection (n = 207), SVR12 was achieved by 88.2% (95%CI 78.1%, 94.8%) patients in Group 1, 95.6% (95%CI 87.6%, 99.1%) in Group 2 and 91.5% (95%CI 82.5%, 96.8%) in Group 3. There were no notable differences in SVR12 rates between patients with GT1a and GT1b infection (88.0% versus 88.9%).

In patients with GT3 infection (n = 39), SVR12 was achieved by 50% (95%CI 23.0%, 77.0%) patients in Group 1, 84.6% (95%CI 54.6%, 98.1%) in Group 2 and 50.0% (95%CI 21.1%, 78.9%) in Group 3.

There were only small numbers of patients with GT2, GT4, and GT6 infection but all achieved SVR12. One exception was a patient with HCV GT2 in Group 3 who died 39 days after receiving 28 days of treatment.

Approximately half of the patients who achieved SVR12 had improved liver function assessed by CPT and Model for End-stage Liver Disease (MELD) scores (most commonly increased serum albumin and decreased total bilirubin). Overall, CPT scores were improved in 47.2% patients and remained unchanged in 43.2% patients. Worsening occurred in 9.6% patients. Overall, MELD scores were improved in 55.5% patients and remained unchanged in 19.7% patients. Worsening occurred in 24.9% patients. A total of 84% patients with baseline MELD ≥ 15 improved and 8% worsened.

A total of 256 patients had a virologic outcome (86, 85 and 85 in Groups 1, 2 and 3 respectively). A total of 22 patients (9%) experienced virologic failure (2 on-treatment failure and 20 relapsed). Mutations at NS5A position 93 (mainly Y93H) were observed in 19/22 (86%) patients at the time of virologic failure. NS5B mutations occurred in 5 out of 22 (23%) patients at the time of virologic failure.

In Group 1, 12.2% patients relapsed but no patients had on-treatment virologic failure. In Group 2, 2.4% patients relapsed and one patient had on-treatment virologic failure. In Group 3, 8.0% patients relapsed and one patient had on-treatment virologic failure.

In GT1 patients, overall virologic failure occurred in 7.4%, 1.5%, and 4.2% patients in Groups 1, 2, and 3 respectively.

In GT3 patients, virologic failure occurred in 42.9%, 15.4%, and 41.7% patients in Groups 1, 2, and 3 respectively.

There were no virologic failures in patients with GT2, GT4, or GT6 infected patients. Virologic outcomes could not be assessed in 11 patients, 7 patients died, and a further four patients were lost to follow-up. No patients with GT5 infection were treated in this trial.

In the second round clinical evaluation, summary results of SVR24 were reported as shown in Table 17.

Table 17: ASTRAL-4 summary results of SVR24

	SOF/VEL 12 Weeks SVR24		SOF/VEL+RBV 12 Weeks SVR24		SOF/VEL 24 Weeks SVR24		Overall SVR24	
	Yes (N = 71)	No (N = 3)	Yes (N = 76)	No (N = 1)	Yes (N = 73)	No (N = 1)	Yes (N=220)	No (N = 5)
SVR12								
Yes	71	0	76	0	73	0	220	0
No	0	3	0	1	0	1	0	5
Positive Predictive Value	100%		100%		100%		100%	

SVR12 response was highly predictive of SVR24. SVR12 response by baseline NS5A RAVs was as shown in Table 18 (ASTRAL-4).

Table 18: ASTRAL-4 SVR12 response by baseline NS5A RAVs

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

Clinical Safety

A total of 2603 patients received at least one dose of SOF and VEL as individual agents or as FDC. Of these, 1302 patients received SOF/VEL FDC for a minimum of 12 weeks, 802 received SOF+VEL in Phase II studies and 499 received SOF/VEL in Phase I studies. In the Phase III studies, the cumulative total exposure to study drugs was mean 12 weeks for SOF/VEL (12 weeks), mean 11.9 weeks for placebo, mean 12.1 weeks for SOF+RBV (12 weeks) and mean 23.2 weeks for SOF+RBV (24 weeks).

In the integrated safety analysis, the most commonly reported AEs in the SOF/VEL and placebo groups were headache (28.6% versus 28.4%), fatigue (21.0% versus 19.8%), nausea (13.0% versus 11.2%) and nasopharyngitis (11.7% versus 10.3%). The pattern of AEs was similar in subgroups. In the SOF/VEL group, Grade 3 AEs were reported in 3% of patients, most commonly headache and anxiety, with 0.7% considered drug related. Two Grade 4 AEs were reported in the SOF/VEL group. In patients treated with SOF/VEL, SAEs were reported in 2.2% patients. Three deaths were reported, each occurring post treatment and considered unrelated to study treatment. AEs occurred more commonly in the SOF+RBV compared with the SOF/VEL and placebo groups.

Laboratory abnormalities were reported less frequently in the SOF/VEL group compared with placebo. Grade 3 AEs were reported in 6.5% and 10.3% of the respective groups, and Grade 4 AEs were reported in 1.0% and 1.7% of the respective groups. Five patients had Grade 4 lipase elevations in the SOF/VEL group but all were asymptomatic and transient.

In a dedicated QT study in healthy volunteers therapeutic (100 mg) and supra therapeutic doses (500 mg) of VEL did not prolong QT interval. No clinically significant changes from baseline in PR, QRS, or RR or HR were observed.

AEs of special interest included hepatotoxicity, haematological toxicity, serious skin rash, cardiovascular toxicity (bradycardia) and psychiatric events. In addition, pancreatitis, rhabdomyolysis (drug interactions), renal failure and other drug-drug interactions were of interest.

In the integrated Phase III study analysis, one patient (< 0.1%) in SOF/VEL 12 week group had a Grade 3 or 4 ALT abnormality compared with eight (6.9%) in placebo group. There was no Grade 3 or 4 total bilirubin elevations in either group. A total of 56 cases were reviewed in the Phase II and III safety populations and one case of potential drug induced liver injury was identified. This was in a female patient in a Phase II study who received SOF+VEL 25 mg + RBV and developed increase in ALT/AST. The rise was associated with anti-hypertensive therapy and resolved when antihypertensive therapy was stopped.

No unexpected haematological signals were detected. There were no cases of pancytopenia. In the SOF/VEL group of integrated Phase III safety analysis, the only Grade 3 events were decreased lymphocytes (0.5%), neutrophils (0.4%), and platelets (0.2%). There was no Grade 3 or 4 events in the placebo group.

No serious skin reactions were reported in the integrated Phase III study analysis. One patient in the SOF+RBV (24 week) group was hospitalised due to a generalised eczematous reaction but study treatment was not interrupted.

One patient in the SOF/VEL (12 week) group had a Grade 3 AE of ischaemic cardiomyopathy in the integrated Phase III study analysis. The event resolved and was considered unrelated to the study treatment. In the integrated Phase III studies, 7.9% of patients had cardiac disease at baseline. Four treatment emergent ECG abnormalities were reported, one case each of QTc prolongation, extrasystoles, atrial fibrillation, and supraventricular tachycardia. Three events were in the SOF/VEL 12 week group and one was in the SOF+RBV 12 week group.

One psychiatric event of depression was reported in the integrated Phase III study analysis. There were no cases of pancreatitis, rhabdomyolysis, myopathy, or renal failure.

Risk management plan

The EU-RMP (version 0.2; date 21 April 2016, DLP 26 August 2015) with Australian Specific Annex (version 0.2, date July 2016) and any future updates apply to this submission. ACSOM advice was not sought for this submission.

Routine pharmacovigilance is proposed. A clinical registry will reportedly be set up to monitor treatment emergent viral mutations. The sponsor was requested to include details of this registry in its Pre-ACPM response.

Delegate's considerations

The dossier for this submission represented full clinical drug development program. All TGA evaluation areas (Quality, Toxicology, Clinical, and RMP) recommend approval.

The pivotal clinical efficacy studies demonstrated very high efficacy (SVR12 > 95%) following 12 weeks of treatment with SOF/VEL (400/100 mg once daily) across all HCV genotypes in patients with compensated liver disease with or without cirrhosis and in previously treated or new patients. The SVR12 was sustained through to SVR24 indicating effective clinical cure. The response was homogenous across various demographic and prognostic subgroups. There were no on-treatment failures and virologic failure due to relapse was low (most commonly in GT3 patients). The number of participating patients (GT1 > 300, GT2 > 200, GT3 > 250, GT4 > 100) was reasonable to allow valid efficacy conclusions. The number of GT5 (n = 35) and GT6 (n = 41) was low but is consistent with the prevalence of these genotypes.

It is noted that SOF/VEL+RBV for 12 weeks was not tested in ASTRAL-1, ASTRAL-2 and ASTRAL-3 studies. This is of no concern for GT 1 and 2 patients and the reported SVR12 response rates were near 100% but may have been a more useful comparator in the

treatment of GT3 patients in ASTRAL-3. SOF/VEL+RBV (12 weeks) is proposed in patients with decompensated liver disease (all genotypes) based on the results of ASTRAL-4 trial.

No studies have yet been reported in patients with HBV or HIV co-infections and in children. Shorter duration of treatment for example 8 weeks was not examined in Phase III studies.

The adverse effects profile was acceptable based on limited safety database at present. Routine pharmacovigilance is proposed. The sponsor is asked to provide more information on the proposed clinical registry. The potential for drug-drug interactions is noted. The information in the PI is consistent with the clinical studies, including precautions about use with amiodarone (bradycardia) and rosuvastatin (rhabdomyolysis).

All four pivotal studies are ongoing and final clinical study reports should be provided to the TGA when available. Future trials are identified as ASTRAL-5 in HCV/HIV coinfection, GS-US-342-1143 in paediatric population and GS-US-334-0154 in patients with severe renal failure with HCV GT1/GT3 infection.

Overall, the risk-balance is considered supportive of approval. In particular, clinical need is noted for HCV GT3 patients and patients with decompensated liver disease. Authorisation is recommended for the pan-genotype indication:

> *"Epclusa (sofosbuvir/velpatasvir fixed dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults"*

and the dosing regimen as proposed by the sponsor.

Table 19: Recommended Treatment Regimen Regardless of HCV Genotype

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis	EPCLUSA for 12 weeks
Patients with decompensated cirrhosis	EPCLUSA + ribavirin[a] for 12 weeks

a. When administered with EPCLUSA, the recommended dose of ribavirin is based on weight: 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily with food. For ribavirin dose modifications, refer to the ribavirin product information.

Use without dose adjustment in severe hepatic impairment is also supported by data.

Proposed action

The Delegate had no reason to say, at this time, that the application for Epclusa should not be approved for registration.

Request for ACPM advice

The ACPM was requested to provide advice on the following specific issues:

1. Does the Committee support the overall adequacy of the data package to allow use of Epclusa (400/100 once daily for 12 weeks) in all HCV genotypes and the proposed dosing regimen in patients with compensated liver disease (without RBV) and decompensated liver disease (with RBV)?

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Gilead welcomes the Delegate's recommendation that the application to register Epclusa tablets should be approved for the pan-genotypic indication and the dosing regimen as proposed by Gilead:

> *"Epclusa (sofosbuvir/velpatasvir fixed dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults".*

Summary

Chronic Hepatitis C Virus (HCV) infection is a serious, progressive, and potentially life threatening disease and a major public health concern globally. Worldwide, an estimated 180 million people have HCV.[18] The prevalence of HCV in Australia is estimated to be approximately 1.3%.[19]

Recently, there has been a transformation in the treatment of HCV infection with the development of DAAs targeting viral proteins essential to viral replication. Recently approved DAA based treatment regimens are generally well tolerated and result in high SVR rates at 12 weeks following completion of all treatment across most, but not all, patient populations. Most DAA development has focused on DAAs that are active against genotype 1 HCV infection as this is the most prevalent HCV genotype in developed countries. However, in Australia genotype 3 infection accounts for approximately 30% of chronic HCV infection and these patients tend to have lower response rates (especially patients with cirrhosis) and a faster progression of liver disease than patients with other HCV genotypes.

Gilead considers that the goal of HCV drug development is to maximise SVR12 rates and provide a cure for HCV infection for all patient populations with a safe and well tolerated regimen. In support of this goal Gilead has developed Epclusa, a fixed dose combination of 2 potent DAAs, sofosbuvir (SOF) and velpatasvir. Epclusa represents the third sofosbuvir-based regimen that Gilead has developed for the treatment of HCV infection after Sovaldi and Harvoni and it is the first, 12 week, once daily, all oral pan genotypic treatment option for all HCV patients.

Importantly, Epclusa addresses an unmet medical need for patients with decompensated cirrhosis as there are no currently available treatment options for HCV infected patients with decompensated cirrhosis in Australia. The large number of patients with decompensated liver disease, the small number of patients able to obtain a liver transplant, and the limited prognosis because of the universal recurrence of infection in those who receive a liver transplant, highlight the need for efficacious and safe therapies for patients infected with all HCV genotypes with decompensated cirrhosis. Epclusa + Ribavirin (RBV) for 12 weeks will provide a safe and effective regimen for the treatment of HCV infection in all patients with decompensated disease.

Epclusa therefore represents a significant treatment advance in the rapidly evolving field of HCV treatment, and Gilead is encouraged by the Delegate highlighting the importance and clinical need of Epclusa for genotype 3 patients and patients with decompensated liver disease.

Epclusa is currently approved for the treatment of HCV infection in the USA, European Union, Switzerland, Canada and New Zealand.

[18] Ghany MG, et al Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; 49: 1335-1374.
[19] Dore GJ, et al. Epidemiology of hepatitis C virus infection in Australia. *J Clin Virol* 2003; 26: 171-184

Discussion of Delegate's comments

The Delegate's comments are presented in bold print, and are followed by Gilead's response.

ACPM advice sought by the TGA Delegate

1. ***Does the Committee support the overall adequacy of the data package to allow use of Epclusa (400/100 once daily for 12 weeks) in all HCV genotypes and the proposed dosing regimen in patients with compensated liver disease (without RBV) and decompensated liver disease (with RBV).***

Gilead considers that the goal of HCV drug development is to maximise the SVR12 rates and provide a cure for HCV infection for all patient populations with a safe and well-tolerated regimen.

The application to register Epclusa was supported by data from four international Phase III studies, GS-US-342-1138 (ASTRAL-1), GS-US-342-1139 (ASTRAL-2), GS-US-342-1140 (ASTRAL-3) and GS-US-342-1137 (ASTRAL-4). The Phase III program was designed to evaluate the efficacy and safety of treatment of Epclusa in a diverse patient population with respect to HCV genotypes and subtypes, demographic characteristics, and geographical regions. This data summarized below supports the use of Epclusa in all HCV genotypes and the proposed dosing regimen in patients with compensated liver disease (without RBV) and decompensated liver disease (with RBV).

Patients with Genotype 1 to 6 HCV

In the ASTRAL-1, ASTRAL-2 and ASTRAL-3 studies, 1,035 patients with genotype 1-6 chronic HCV infection, without cirrhosis or with compensated cirrhosis received 12 weeks of Epclusa.

Of the 1,035 patients treated with Epclusa for 12 weeks in the ASTRAL-1, ASTRAL-2 and ASTRAL-3 studies, 1,015 (98%) achieved SVR12.

The SVR12 rates achieved with Epclusa are comparable with or greater than the SVR12 rates achieved with currently available treatment options across genotype 1 to 6 HCV infections. In patients with genotype 1 HCV infection, treatment with Epclusa provided SVR12 rates greater than 95% in all patient subgroups including those with cirrhosis or with prior treatment failure.

There were no virologic failures among any of the patients with genotype 2 HCV infection who received Epclusa in ASTRAL-1 and ASTRAL-2, and in ASTRAL-2 the SVR12 rate for patients with genotype 2 HCV infection who received Epclusa for 12 weeks was statistically superior to the SVR12 rate achieved by patients who received SOF+RBV for 12 weeks.

The SVR12 rate achieved in patients with genotype 3 HCV infection who received Epclusa for 12 weeks was statistically superior to the SVR12 rate for patients who received SOF+RBV for 24 weeks.

Patients with genotype 3 HCV infection with cirrhosis have had suboptimal response rates to prior DAA based regimens; however, in the ASTRAL-3 study, the SVR12 rate among patients with cirrhosis was 91.3%. Across all subgroups, the SVR12 rates achieved with 12 weeks of Epclusa treatment were similar to those achieved with 12 weeks of the IFN-containing regimen of SOF+Peg-IFN+RBV.

There were no virologic failures among the patients with genotype 4, 5, or 6 HCV infection who received Epclusa for 12 weeks.

Patients with decompensated HCV liver disease

There are currently no available DAAs in Australia including specific dosing for treating decompensated HCV liver disease.

The ASTRAL-4 study randomized 267 patients with genotype 1 to 6 HCV infection, with decompensated cirrhosis (Child-Pugh B), to receive 12 weeks of Epclusa with or without RBV or 24 weeks of Epclusa. The primary endpoint for all studies was SVR12.

In ASTRAL-4, patients with decompensated cirrhosis receiving Epclusa with RBV for 12 weeks achieved a high SVR12 rate (94%) and a lower virologic failure rate compared to those who received Epclusa for 12 weeks or 24 weeks (83% and 86 %, respectively).

The response rates among patients with genotype 1 or 3 HCV infection who received Epclusa + RBV for 12 weeks were comparable with the highest response rates reported to date for DAA based regimens in patients with decompensated cirrhosis. A large proportion of the patients who achieved SVR12 with a 12 week regimen of Epclusa had improvements in CPT score and MELD score. A longer period of posttreatment observation than was performed in ASTRAL-4 will be necessary to determine whether the improvements in CPT score or MELD score translate to improvement in liver function and long-term outcomes.

Conclusion

The pivotal ASTRAL studies demonstrated very high efficacy (SVR12 > 95%) following 12 weeks of treatment with Epclusa across all HCV genotypes in patients with compensated liver disease with or without cirrhosis. The SVR12 was sustained through to SVR24 indicating effective clinical cure.

The clinical study results strongly support the use of Epclusa for treatment of all HCV genotypes and the proposed dosing regimen in patients with compensated liver disease (without RBV) and decompensated liver disease (with RBV). Epclusa represents a significant treatment advance in the rapidly evolving field of HCV treatment as the first all-oral, pan genotypic single tablet regimen for the treatment of adults with genotype 1 to 6 chronic HCV infection.

Summary of other issues raised by the TGA Delegate

Routine pharmacovigilance is proposed. A clinical registry will reportedly be set up to monitor treatment emergent viral mutations. The sponsor is requested to include details of this registry in its Pre-ACPM response.

Long term follow-up of NS5A resistance in patients who failed therapy with Epclusa was not available during the Phase II and Phase III clinical trials. Data on development of resistance will be collected from Study GS-US-248-0123. Study GS-US-248-0123 is a long term follow-up registry study of patients who did not achieve sustained virologic response after treatment with a Gilead oral antiviral containing regimen in a previous Gilead sponsored hepatitis C study. This study will evaluate HCV viral sequences and the persistence or evolution of treatment emergent viral mutations.

As outlined in Version 0.2 of the ASA to the EU- RMP, the final study report is due for completion in July 2020 and Gilead will provide the final study report to TGA when complete.

Review of PI: Note FDA advisory (MedWatch/SafetyAlertforDAAs) in regard to the risk of hepatitis B reactivation in association with the use of DAAs. The sponsor is requested to provide comment and proposal for inclusion of appropriate text in the Australian PI.

The FDA Drug Safety Communication notification from 4 October 2016 describes 24 reported cases of suspected HBV reactivation. Gilead's analysis of these cases is presented below.

Of the 24 suspected cases of HBV reactivation, 20 cases occurred in patients with possible chronic HBV/HCV coinfection (hepatitis B surface antigen (HBsAg) positive or HBV viremia at baseline) and 4 cases occurred in patients with identified occult or resolved HBV infection (HBsAg negative).

Of the 20 cases of HBV reactivation, 8 were cases of clinical HBV reactivation and included 2 fatal cases. The 2 fatal cases reported both occurred in HBsAg positive patients, but notably both were Japanese patients who were treated with daclatasvir and asunaprevir for HCV infection and had met criteria for initiation of HBV treatment per EASL, AASLD and APASL HBV treatment guidelines.[20] One of the patients with a fatal outcome had discontinued entecavir therapy for HBV infection, a well described risk factor for HBV reactivation, prior to initiating daclatasvir and asunaprevir. The second patient with a fatal outcome had underlying cirrhosis and active HBV viremia.

The remaining 12 cases in HBsAg positive patients describe silent reactivation (increased HBV replication with no evidence of clinical or biochemical flare). Most of these cases did not meet criteria for initiation of HBV treatment according to HBV guidelines. Fluctuations in HBV replication have been well described in patients with HBV monoinfection[21], [22], [23]{10682, 14155, 38352}, and in patients with HBV/HCV coinfection during and after IFN based treatments.[24], [25], [26], [27]

Of the 4 cases that occurred in patients with identified occult or resolved HBV infection (HBsAg negative), the most serious case occurred in a patient with an underlying history of treated Burkitt's lymphoma and non-alcoholic steatohepatitis (NASH) who eventually developed liver failure resulting in liver transplantation. A second case of reactivation occurred in a patient who was HBsAg-, HBcAb+ who had recently discontinued tenofovir disoproxil fumarate treatment a few months earlier. These 2 cases of HBV reactivation would have warranted close monitoring and/or HBV treatment according to the HBV treatment guidelines.

Based on our analysis of these events and the analysis described in the responses to questions issued by the EU Pharmacovigilance Risk Assessment Committee (PRAC), Gilead concludes that there is insufficient evidence to associate HBV reactivation with treatment of HCV infection in HBV/HCV co-infected patients. HBV reactivation can occur during the natural course of chronic HBV infection, even in HBV mono-infected patients. As such,

[20] per European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD) and Asian Pacific Association for the Study of the Liver (APASL) HBV treatment guidelines
[21] Brunetto MR, et al. Outcome of anHBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long te cohort study. *J Hepatol* 2002; 36: 263-270.
[22] Liaw YF, Chu CM. Hepatitis B virus infection. *Lancet* 2009; 373: 582-592.
[23] Chang ML, Liaw YF. Hepatitis B flares in chronic hepatitis B: pathogenesis, natural course, and management. *J Hepatol* 2014; 61: 1407-1417.
[24] Yalcin K, et al. A severe hepatitis flare in an HBV-HCV coinfected patient during combination therapy with alpha-interferon and ribavirin. *J Gastroenterol* 2003; 38: 796-800.
[25] Liu JY, et al. The influence of hepatitis B virus on antiviral treatment with interferon and ribavirin in Asian patients with hepatitis C virus/hepatitis B virus coinfection: a meta-analysis. *Virology journal* 2012; 9: 186.
[26] Yu ML, et al. Sustained hepatitis C virus clearance and increased hepatitis B surface antigen seroclearance in patients with dual chronic hepatitis C and B during posttreatment follow-up. *Hepatology* 2013; 57: 2135-2142.
[27] Vigano M, et al. The course of inactive hepatitis B in hepatitis-C-coinfected patients treated with interferon and ribavirin. *Antivir Ther* 2009

monitoring for HBV and treatment of HBV in HBV infected patients (whether mono-infected or co-infected with HCV) should be a matter for good clinical practice for physicians treating patients with viral hepatitis.

Gilead therefore proposes that the following PRECAUTION be included in the Epclusa Product Information (PI):

> Hepatitis B Virus Reactivation
>
> Cases of hepatitis B virus (HBV) reactivation have been reported during treatment with HCV direct-acting antivirals, including sofosbuvir-containing regimens. HBV screening should be performed in all patients before initiation of treatment with Epclusa. HCV/HBV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

In addition, Gilead proposes that the current text in the Epclusa Consumer Medicine Information (CMI) be modified as follows:

> Tell your doctor if you have, or have had, any of the following medical conditions:
>
> Have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely.

The updated PI and CMI are hereby provided in section 1.3 of this response.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Epclusa new fixed dose combination tablet containing 400 mg of sofosbuvir and 100 mg velpatasvir to have an overall positive benefit-risk profile. However, the ACPM preferred the amended indication:

> *Epclusa (sofosbuvir/velpatasvir fixed dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype I, 2,3,4,5 or 6) in adults.*
>
> *Epclusa (Sofosbuvir/velpatasvir) to be used alone in individuals without cirrhosis or with compensated cirrhosis*
>
> *Epclusa (Sofosbuvir/ velpatasvir) to be used in combination with ribavirin in individuals with decompensated cirrhosis*

In making this recommendation the ACPM noted:

- the potential for cross-resistance with medicines in the relevant classes
- the reduced efficacy in genotype 3 patients in ASTRAL-3 trial compared to efficacy against genotype I in ASTRAL-I trial but that the ASTRAL-4 study provided some indirect support for co- treatment with ribavirin in genotype 3 patients
- no data were provided in paediatric patients but a study is currently underway.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The inclusion with the indication of (as above) HCV genotypes.
- The inclusion in tabular format showing virologic failure outcomes observed by genotype to inform prescribers particularly as indicative of effect of adding ribavirin in genotype 3 patients.
- The inclusion of a statement in the DOSAGE and ADMINISTRATION section to the effect that addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis.
- A statement in the PRECAUTIONS section of the PI and relevant sections of the CMI on the potential for Hepatitis B virus reactivation in patients that are HCV/HBV co-infected.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the Committee support the overall adequacy of the data package to allow use of Epclusa (4001100 once daily for 12 weeks) in all HCV genotypes and the proposed dosing regimen in patients with compensated liver disease (without RBV) and decompensated liver disease (with RBV)?*

The ACPM considered the efficacy, data package to support use of Epclusa (sofosbuvir 400/ velpatasvir 100 once daily for 12 weeks) in all genotypes of HCV in patients with compensated liver disease (with and without cirrhosis) and decompensated liver disease (in combination with ribavirin). However, the committee noted the lower level of efficacy in patients diagnosed with genotype 3 HCV especially with cirrhosis (ASTRAL-3) as well as with decompensated liver disease (ASTRAL-4). One study (ASTRAL-4) provided some support for the addition of ribavirin to treatment for these patients and the ACPM recommended addition of ribavirin for all patients with decompensated liver disease and a recommendation for consideration by prescribers of ribavirin co-treatment for any patient with genotype 3.

The ACPM further advised thot it considered the product packaging (bottle presentation) may not assist patient compliance. The committee recommended consideration of a suitably marked foil pack for daily dosing.

Participation in the Notional Treatment Surveillance is recommended.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of EPCLUSA (400 mg sofosbuvir/100 mg velpatasvir) tablet (bottle), indicated for:

> *EPCLUSA (sofosbuvir/velpatasvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults.*
> *(see DOSAGE AND ADMINISTRATION section for the recommended regimens for different patient subgroups).*

Specific conditions of registration applying to these goods

The EPCLUSA containing fixed-dose combination of (400 mg sofosbuvir/100 mg velpatasvir) Risk Management Plan (RMP): Implement EU-RMP (version 0.2; date 21 April 2016, DLP 26 August 2015) with Australian Specific Annex (version 0.2, date July 2016), included with submission PM-2015-03984-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Epclusa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

Attachment 2. Extract from the Clinical Evaluation Report

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