Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for asunaprevir

Proprietary Product Name: Sunvepra

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

December 2015

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 Record (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, in that it will provide 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

Most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASV	asunaprevir (BMS-650032)
AUC	area under the plasma concentration-time curve
BD	twice daily
BMI	body mass index
BOC	boceprevir
Cavgss	steady state average concentration
CRF	case record form
cEVR	complete early virologic response
CHC	chronic hepatitis C
CI(s)	confidence interval(s)
CSR	clinical study report
DAAs	direct acting antivirals
DCV	daclatasvir (BMS-790052)
EOT	end of treatment
EOTR	end of treatment response
E-R	exposure-response
eRVR	extended rapid virologic response
EU	European Union
EVR	early virologic response
GT	genotype
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon

Abbreviation	Meaning
IFNα	interferon alfa
IFNβ	interferon beta
ITT	intent-to-treat
LLOQ (LOQ)	lower limit of quantitation
NA	Not applicable
NS3	non-structural protein 3
NS5A	non-structural protein 5A
PBO	placebo
PD	pharmacodynamic
PDR	protocol-defined response
pegIFNα/RBV	peginterferon alfa plus ribavirin
PK	pharmacokinetics
PKVC	pharmacokinetic viral kinetic analysis
PPK	population pharmacokinetics analysis
QD	once daily
QW	weekly
RAV	resistance-associated variant
RBV	ribavirin
RCI	replication complex inhibitor
RNA	ribonucleic acid
RVR	rapid virologic response
SC	subcutaneous
SMV	simeprevir
SNP	single nucleotide polymorphisms
SOF	sofosbuvir
SVR	sustained virologic response
SVR4, 12, 24, 36, 48	sustained virologic response at follow-up Week 4, 12, 24, 36, 48

Abbreviation	Meaning
TD	target detected
TND	target not detected
TVR	telaprevir
VBT	virologic breakthrough

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	21 May 2015
ARTG entry date:	25 May 2015
Active ingredient(s):	Asunaprevir
Product name(s):	Sunvepra
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd PO Box 1080, Mt Waverley VIC 3149
Dose form(s):	Soft gelatin capsules
Strength(s):	100 mg
Container(s):	Blister pack
Pack size(s):	14 or 56 capsules
Approved therapeutic use:	*Sunvepra (asunaprevir) is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) [see Clinical Trials and Dosage and Administration.]*
Route(s) of administration:	Oral (PO)
Dosage:	Sunvepra is for oral administration and may be taken with or without food. The recommended dose of Sunvepra is 100 mg twice daily. Sunvepra must be administered in combination with Daklinza or with Daklinza, peginterferon alfa, and ribavirin. Recommended regimens and treatment duration are shown in Table 8. For specific dosage instructions for Daklinza, peginterferon alfa, and ribavirin, refer to the respective product information.

Table 8: Recommended Regimens for SUNVEPRA 100 mg Twice Daily Combination Therapy

HCV Genotype	Prior Treatment	Treatment	Duration
Genotype 1b	None, or failed peginterferon alfa/ribavirin	SUNVEPRA and DAKLINZA	24 weeks
Genotype 1 or 4	None, or failed peginterferon alfa/ribavirin	SUNVEPRA, DAKLINZA, peginterferon alfa, and ribavirin	24 weeks

ARTG number (s):	222744

Product background

This AusPAR describes the application by the sponsor to register Sunvepra (asunaprevir) as a combination therapy with use only with Daklinka (daclatasvir (DCV)) ± pegIFNα (peginterferon alfa)/RBV (ribavirin).

Asunaprevir (ASV) is a new chemical entity of the class of 'direct acting antiviral' agents (DAA) against the hepatitis C virus (HCV). It acts as a direct-acting antiviral agent (DAA) selectively inhibiting the hepatitis C virus (HCV) non-structural protein 3 (NS3) protease and subsequently viral ribonucleic acid (RNA) replication with genotype (GT) 1 and 4 coverage.

Current standard-of-care for HCV GT-1 consists of a DAA as a component of a combination antiviral treatment regimen. Newer treatment options provide an improvement over the use of IFN-based therapies alone for patients with GT-1. However, there is still a need for improved efficacy in HCV GT-1 patients, particularly in patients with limited response to pegIFNα/RBV or in patients who are intolerant or ineligible for IFN based therapy, and for patients who have failed current protease inhibitor therapies.
Asunaprevir (ASV) is only recommended in combination with other agents. One of these agents is Daclatasvir (DCV) which is also a new chemical entity and the subject of a parallel submission to the TGA. Daclatasvir inhibits the hepatitis C virus (HCV) non-structural protein 5A (NS5A) replication complex.

The proposed indication is:

- *Sunvepra (asunaprevir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) in combination with:*
  - *Daklinza, an NS5A replication complex inhibitor, for patients with HCV genotype 1b infection (See CLINICAL TRIALS and DOSAGE AND ADMINISTRATION)*

Sunvepra is for oral administration and may be taken with or without food at the recommended dose of 100 mg twice daily. Sunvepra must be administered in combination with Daklinza or with Daklinza, peginterferon alfa, and ribavirin.

Dose modification of Sunvepra or Daklinza is not recommended. Treatment interruption should be avoided; however, if treatment interruption is necessary because of adverse reactions, neither Sunvepra nor Daklinza should be given as monotherapy. If resumption of therapy is considered, the risks and benefits should be carefully assessed [see PI]. For the Sunvepra/Daklinza regimen, both drugs must be restarted at the same time.

Discontinuation of therapy is recommended for patients experiencing confirmed virologic breakthrough (greater than 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir).

The TGA has adopted the following European Medicines Agency guidelines which are relevant to the submission:

- Guideline on pharmacokinetic studies in man.[1]
- Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function.[2]
- Concept paper on the need for revision of the note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function.[3]

[1] European Medicines Agency. Pharmacokinetic studies in man. 1987. Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical
[2] European Medicines Agency. Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function (CHMP/EWP/225/02); 2004. Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function.[4]
- Guideline on the investigation of drug interactions.[5]
- Guideline on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.[6]
- Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C.[7]

In addition, the following US Food and Drug Administration guidance is noted:

- Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment.[8]

Regulatory status

This is an application to register a new chemical entity in Australia.

At the time the TGA considered this application a similar application had been approved in Japan and was under consideration in several jurisdictions including Canada and Singapore.

Table 1: International regulatory status

Country	Approved indication	Status
Japan	*Improvement of viraemia in either of the following patients with chronic hepatitis C serogroup 1 (genotype 1) or chronic hepatitis C serogroup 1 (genotype 1) with compensated cirrhosis;* *(1) Patients who are ineligible or intolerant to interferon based therapy* *(2) Patients who have failed to respond to interferon-based therapy*	Approved July 2014
USA	Not applicable	Withdrawn 6 October 2014*

[3] European Medicines Agency. Concept paper on the need for revision of the Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (EMA/CHMP/203926/2012); 2012 Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

[4] European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02). 2005. Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

[5] European Medicines Agency. Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.) 2012. Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

[6] European Medicines Agency. Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (CHMP/ICH/2/04); 2005. Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

[7] European Medicines Agency. Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C (EMEA/CHMP/EWP/30039/2008). Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

[8] United States Food and Drug Administration. Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. Draft October 2013. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf

*Due to evolving HCV treatment landscape resulting in access to multiple all-oral treatment options with high cure rates and 12-week treatment duration for HCV genotype 1 patients in the U.S.A., 24 week treatment with daclatasvir (DCV)+ASV and DCV+ASV+peginterferon-alfa/ribavirin is considered not to be competitive in the U.S. Hence, BMS has decided to withdraw the ASV US NDA and focus on the DCV NDA and shorter treatment regimens in the U.S.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

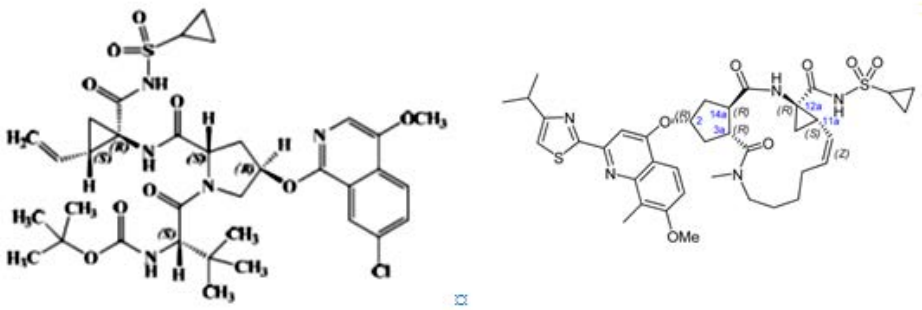
Introduction

Asunaprevir is presented in soft gelatin capsules containing 100 mg of asunaprevir, under the tradename Sunvepra. The recommended dose of asunaprevir is 100 mg twice daily, with or without food. It *must* be taken in combination with daclatasvir (an NS5A inhibitor) or with daclatasvir, peginterferon alfa, and ribavirin. Daclatasvir ('Daklinza') 30 mg and 60 mg tablets are the subject of a current parallel submission for registration in Australia.

Drug substance (active ingredient)

Asunaprevir is a new, fully synthetic, 'direct acting antiviral' agent which has some structural similarity with other registered members of the therapeutic class, particularly simeprevir (see below). It is a potent and selective inhibitor of the HCV non-structural protein 3 (NS3) protease and subsequent viral RNA replication.

Figure 1: Chemical structure of asunaprevir and simeprevir



asunaprevir	simeprevir
Sunvepra soft gelatin 100 mg capsules	*Olysio* 150 mg capsules
Bristol-Meyers Squibb *(proposed)*	Janssen-Cilag

Asunaprevir is a white to off-white powder which is 'practically insoluble' in water (<50 mg/L) over the physiological pH range (pH 1.2 to 6.8). However it has a high solubility (20 to 40% weight/weight) in organic solvents and in medium chain triglycerides, caprylic/capric glycerides and polysorbate 80, which are the principal components of the

proposed capsule fill solution. The drug substance is classified as a BCS Class II[9] compound (low solubility, high permeability) at the dose of 100 mg. It has five stereocenters and is chirally pure. Particle size and polymorphism of the drug substance are not important in this case, since the drug substance is present as a lipid solution in the proposed capsule.

The proposed drug substance specifications comply with TGA requirements and are considered adequate to ensure the quality and consistency of manufacture of the finished product.

Adequate stability data have been provided to support a retest period for the drug substance.

Drug product

The proposed asunaprevir 100 mg soft gelatin capsules contain a solution of asunaprevir dissolved at a concentration of 20% w/w in a 3:3:2 mixture of medium-chain triglycerides, medium-chain mono and diglycerides ('caprylic/capric glycerides') and polysorbate 80, with 0.1% w/w butylated hydroxytoluene (BHT) present as an antioxidant. The excipients used in the drug product are all conventional substances with well-known properties and functions.

The solution is encapsulated in opaque, white to pale yellow, oval, soft gelatin capsules (size #10), imprinted with *'BMS*' in black on one line and '*711'* in black on second line.

The product is described as a self-emulsifying drug delivery system (SEDDS) in which the liquid contents of the capsules self-emulsify immediately upon contact with the aqueous environment of the gastrointestinal tract. This forms an oil-in-water emulsion in which the drug is incorporated in the oil droplet and is presented in a solubilised state for delivery in the gastrointestinal tract. At least one registered product employs an analogous SEDDS design, including similar excipients.

The product is to be marketed with 14 or 56 capsules packed into blisters with push through paper backed aluminium foil.

Capsule specifications include a 'dissolution test', although the test is not a true dissolution test because the drug is already in solution in the product. It is really a dispersion test, which measures the rate of release of the contents from the capsule shell and the rate and extent of emulsification of the SEDDS formulation. A second tier dissolution test includes pancreatin in the dissolution medium, to ensure release from capsules in which the gelatin has formed cross-links, as this is a common phenomenon after storage of soft gelatin capsules.

The limit at release and expiry limit for individual impurities is within the applicable International Conference on Harmonisation qualification threshold. Batches of the capsules typically have very low levels of total impurities at release and after 12 months long-term storage (<0.06%). Capsules show good stability and a shelf life of 24 months, when stored below 25ºC protected from light in the original container, has been established.

Formulation development

Phase I clinical studies used a hard gelatin capsule and for Phase II trials an immediate-release film-coated tablet was developed. To improve oral bioavailability and mitigate a significant positive food effect that was observed for the Phase I and II dosage forms, a 100

[9] Biopharmaceutics Classification System (BCS): According to the BCS, drug substances are classified as follows: Class I - High Permeability, High Solubility; Class II - High Permeability, Low Solubility; Class III - Low Permeability, High Solubility; Class IV - Low Permeability, Low Solubility.

mg soft gelatin capsule formulation was developed. The bioavailability from the soft gelatin capsule in the fasted state was approximately 2 to 4 fold higher compared to the tablet formulations, which provided essentially complete mitigation of the food effect.

The composition of the capsules used in the relative bioavailability study, Phase III studies, long-term stability studies (LTSS) and commercial product are identical, with the exception of the applied printing/logo.

Biopharmaceutics

Asunaprevir peak plasma concentration (C_{max}), area under the plasma concentration versus time curve (AUC) and trough plasma concentration (Cmin) increased in an approximately dose proportional manner. Steady state was achieved after 7 days of twice-daily administration in healthy subjects. In vitro studies performed with human Caco-2 cells indicated that asunaprevir is a substrate of permeability glycoprotein (P-gp). Time to Cmax (Tmax) of asunaprevir when administered with food occurred about 1.5 h postdose relative to about 2.5 h postdose when administered under fasting conditions. In vitro studies demonstrate that asunaprevir undergoes oxidative metabolism primarily mediated by cytochrome P450 isozyme 3A4 (CYP3A).

Following single dose oral administration of radioactively labelled (^{14}C)-asunaprevir in healthy subjects, 84% of total radioactivity was recovered in faeces (primarily as metabolites) and less than 1% was recovered in the urine (primarily as metabolites). Metabolism was the major route of asunaprevir elimination. Of dose recovered in faeces, unchanged asunaprevir accounted for 7.5% of the dose. Following multiple dose administration of asunaprevir in healthy subjects, the terminal elimination half-life ranged from 17 to 23 h.

Food

Study AI447043 included a study of the effect of food on the proposed 100 mg soft gelatin capsules. Administration with a high fat meal had the following effects, compared to administration under fasting conditions:

- C_{max} was increased by approximately 34%.
- AUC_{0-t} was increased by approximately 20%
- T_{max} was reduced (median 2.5 h versus 1.5 h),

The modest (20%) increase in asunaprevir exposure, when the capsules are given with a high fat meal, is argued by the company to not be clinically relevant, and in the PI it is stated that the capsules can administered without regard for food.

Absolute bioavailability

The absolute bioavailability of asunaprevir was investigated using the commercial dose and formulation (Study AI447027), followed 3 h later (approximate T_{max}) by a 100 µg intravenous microdose of ^{14}C-asunaprevir (approximately 200 nCi). The results indicate that asunaprevir has low (approximately 9.3%) absolute oral bioavailability (90% confidence interval (CI): 7.0, 12.5).

Advisory committee considerations

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee of the TGA's Advisory Committee for Prescription Medicines (ACPM).

Quality summary and conclusions

Registration of the proposed Sunvepra (asunaprevir 100 mg) soft gelatin capsules is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved.

III. Nonclinical findings

Introduction

The overall quality of the submitted nonclinical data for asunaprevir was high. All pivotal safety studies were conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

All pharmacology studies of asunaprevir were appropriately designed and conducted in compliance with International Conference on Harmonization (ICH) guidelines.

Primary pharmacology

Asunaprevir was developed as an inhibitor of the NS3 serine protease of HCV, and subsequent viral RNA replication. The nonclinical efficacy studies submitted assessed the inhibitory activity of asunaprevirin in vitro enzyme assays and standard subgenomic cell-based HCV replicon assays. The extent of virology data for genotype 4 was significantly less than for genotypes 1a and 1b. The most prevalent HCV genotype in Australia[10] is genotype 1 with 55%, while the prevalence of genotype 4 is 3%. The prevalence of genotypes 3, 2, and others, is 33, 8 and 1%, respectively[11]. No proof of concept studies were conducted in animal models of HCV. This is not considered a major deficiency.[12]

Asunaprevir competitively inhibited the binding of substrate to NS3/4A protease complex, binding directly and reversibly to the protease with Ki 0.24 to 1.0 nM, depending upon the genotype strain employed.

In biochemical assays in vitro, asunaprevir inhibited the activity of purified NS3/4A protease enzyme complexes from HCV strains of genotypes 1b (50% inhibitory concentration (IC_{50}) 0.3 nM), 1a (IC_{50} 0.7-1.8 nM), 6a (IC_{50} 0.9 nM), 4a (IC_{50} 1.6 nM), 5a (IC_{50} 1.7 nM), and with a significantly lower potency 2a (IC_{50} 15 nM), 2b (IC_{50} 78 nM), and 3a (IC_{50} 320 nM). Except for genotype 2b, asunaprevir was more potent than telaprevir.

In cell-based HCV replicon assays, asunaprevir inhibited HCV genotype 1a (50% effective concentration (EC_{50}) 4 nM), 1b (EC_{50} 1.2 nM), and 2a (EC_{50} 230 nM), replication. Hybrid replicons encoding the NS3 protease domain representing HCV genotype 4a was inhibited with EC_{50} 1.8-7.6 nM, whereas GT-2b and GT-3a NS3 protease replicon hybrids were inhibited with EC_{50} values of 0.48 mM and 1.2 mM, respectively. The potency of asunaprevir in subgenomic GT-1b (Con1) HCV replicon assays was reduced by approximately 6.5 fold in the presence of 40% human serum.

Asunaprevir is unlikely to be active against genotype 2a, 2b and 3a at the proposed clinical dose, taking into account a clinical C_{max} of 560 nM (0.419 µg/mL).

[10] Approximately 210 000 people are estimated to be living with HCV infection in Australia (Dore et al., 2003).
[11] Dore GJ, Law M., MacDondald M., Kaldor JM. Epidemiology of hepatitis C virus infection in Australia. Journal of Clinical Virology 26 (2003) 171-/184.
[12] FDA Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013.

Asunaprevir showed additive and/or synergistic interactions with interferon alfa, daclatasvir, HCV NS5B active-site or allosteric inhibitors, and ribavirin in two or three drug combination studies using a cell-based HCV replicon system. No antagonism of antiviral activity was observed.

Treatment of HCV GT-1b replicon cells with combinations of asunaprevir and IFN alpha or RBV, and/or direct-acting antivirals targeting HCV NS5A (daclatasvir) and/or HCV NS5B (BMS-791325) displayed additive to synergistic effects (DCN 930023123, DCN 930029019).

Cytotoxicity

The 50% cytotoxic concentration (CC_{50}) values ranged from 11 to 38 mM against 6 human cell lines derived from T-cells, liver, lung, cervix, and kidney cells, providing a significant therapeutic index (2750 to 9500) when contrasting potency values generated against the HCV GT-1a (H77) replicon (EC_{50} 4 nM).

Resistance and cross-resistance

Mutations in NS3 that conferred some resistance to asunaprevir were identified from in vitro studies (treatment-emergent mutations in HCV replicon assays), as well as from literature reports of mutations conferring resistance to other NS3 polymerase inhibitors (such as telaprevir and boceprevir). Mutations in the NS3 protease domain at T40A, Q41E, V51A, R62K, D79E, T95A, I114V, R123G, R155K, D168G, I170T, N174Y, L175P, G176E (genotype 1a), Q41R, Q80R, Q86R, P89L, Y105C, D168A/G/H/V/Y, E173G, and E176G (genotype 1b), conferred some resistance to asunaprevir. These substitutions decreased the susceptibility of GT-1a replicons to asunaprevir 11 to 49 fold, and the susceptibility of GT-1b replicons 170 to 400 fold.

Cross-resistance data generated against engineered drug-resistant replicons containing key single and double point substitutions at amino acid positions reported in clinical studies can be found in Table 2. When introduced into recombinant HCV replicons, NS3 protease substitution D168V conferred a high level of resistance to GT-1a and GT-1b, whereas substitutions D168A and D168Y conferred a high level of resistance to GT-1b (see Table 2).

Table 2: Mutations in NS3 that conferred resistance to asunaprevir in HCV replicon assays

Mutation	Fold loss of activity	EC_{50} (nM)
Parent GT-1a replicon	-	0.76
Parent GT-1b replicon	-	0.86
V36A	3 (1a), 2 (1b)	2.3 (1a), 1.6 (1b)
V36L	2 (1a), 1 (1b)	1.8 (1a), 0.65 (1b)
V36M	2 (1a)	1.5 (1a),
T54A	0.4 (1a), 0.4 (1b)	0.33 (1a), 0.35 (1b)
T54S	1 (1a), 2 (1b)	0.74 (1a), 1.6 (1b)
Q80K	3 (1a), 6.5 (1b)	2.5 (1a), 5.6 (1b)

Mutation	Fold loss of activity	EC_{50} (nM)
Q80R	5 (1b)	4.0 (1b)
R155K	21 (1a)	16 (1a),
V36M+R155K	55 (1a)	42 (1a),
D168A	127 (1b)	109 (1b)
D168G	14 (1a), 16 (1b)	11 (1a), 13 (1b)
D168V	373 (1a), 280 (1b)	283 (1a), 241 (1b)
D168Y	238 (1b)	205 (1b)
Q80K+D168V	713 (1a)	542 (1a),
I170T	5 (1a)	3.6 (1a),
A156S	7 (1b)	5.9 (1b)
A156T	6 (1b)	5.4 (1b)
A156V	20 (1b)	17 (1b)
V170A	2 (1b)	1.6 (1b)

Asunaprevir exhibited no to moderate cross-resistance against HCV replicons conferring resistance to inhibitors such as boceprevir and telaprevir[13]. Against GT-1a replicons carrying NS3 protease substitutions at amino acid positions V36 (V36A/M), T54 (T54A/S), R155 (R155K), and V36-R155 (V36M- R155K) asunaprevir exhibited EC_{50} values ranging from 0.33 to 42 nM (parent GT-1a replicon EC_{50} = 0.76 nM). Against GT-1b replicons carrying NS3 protease substitutions at amino acid positions A156 (A156 to serine, threonine or valine), asunaprevir demonstrated low to moderate resistance with EC_{50} values of 5.4 to 17 nM (parent GT-1b replicon EC_{50} = 0.86 nM). These mutations are not expected to confer resistance to asunaprevir (which has a clinical C_{max} of 560 nM), therefore asunaprevir could be efficacious against boceprevir and telaprevir resistant HCV strains.

The potency of an NS5A inhibitor against GT-1a replicons with NS3 substitutions R155K, V36M+R155K, D168G and I170T (EC_{50}s ranging from 3.1 to 4.4 pM) was unchanged compared to the potency against the parent GT-1a replicon (EC_{50}: 4.8 pM), confirming the value of using multi-therapy with drugs with different mechanisms of action in order to contain the development of resistant virus strains.

Treatment of HCV GT-1b replicon cells with combinations of asunaprevir and interferon alpha (IFNα) or ribavirin, and/or drugs targeting NS5A (daclastavir) and/or NS5B (BMS-791325) displayed additive to synergistic effects, and did not display antagonistic effects. Treatment of HCV GT-1a replicons and HCV GT-1a replicons carrying the NS3 substitution

[13] Susser, S, B. *et al.* (2009) Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus–infected patients. *Hepatology.* **50:** 1709-1718.

R155K with a combination of asunaprevir, daclatasvir and interferon-alfa also suppressed HCV RNA replication.

This further confirmed that drugs targeting multiple viral targets are of potential value against emerging resistant virus. It is noted that asunaprevir is not indicated as monotherapy due to the propensity for resistance. Cross-resistance with daclatasvir, peginterferon alfa and ribavirin is not expected due to their differing mechanisms of action.

Secondary pharmacodynamics

In in vitro assays, asunaprevir had no antiviral activity against HIV, human rhinovirus or human coronavirus strains at concentrations significantly greater than would be expected clinically. Therefore, asunaprevir is not expected to have an effect on HIV, HRV or HcoV infection.

Asunaprevir exerted minimal to no activity against the closely related viral serine protease, GBV-B NS3 protease (IC_{50} 21 μM), a panel of 10 human serine and cysteine proteases, and 37 mammalian receptors, ion channels and transporters. No off-target activities are predicted during clinical use.

Safety pharmacology

A series of in vitro and in vivo safety pharmacology studies assessed potential effects on cardiovascular function. The only cardiovascular (CV) related effects were increased blood pressure in anesthetised rabbits (relative exposure ≥ 36 based on C_{max}) and mild potassium (hERG) channel inhibition (relative exposure 1500 based on C_{max}). There were no effects on Purkinje fiber action potential duration (relative exposure >4000 based on C_{max}), no elecltrocardiogram (ECG) changes in the *ex vivo* rabbit heart assay (relative exposure ≤ 22000 based on C_{max}) and no effects on CV parameters in dogs given a single oral dose (cardiovascular telemetry study; relative exposure 120 based on C_{max}) or repeat doses for ≤ 9 months (relative exposure ≤ 82 based on AUC) or in dogs or monkeys given asunaprevir in combination with daclatasvir, BMS-791325 or pegIFNα/RBV for ≤ 3 months at asunaprevir (relative exposure ≤ 21 based on AUC). It is unlikely that asunaprevir will cause electrocardiogram (ECG) effects in humans since at high multiples of the recommended highest dose (RHD) C_{max}, no action potential duration effects were seen and only mild ion channel inhibition (hERG) occurred.

No independent safety pharmacology studies were conducted to assess the potential central nervous system (CNS) or respiratory effects of asunaprevir. In distribution studies conducted with pigmented and albino rats, there were no quantifiable concentrations of asunaprevir-related radioactivity in the CNS. No asunaprevir metabolites were independently evaluated in safety pharmacology studies as there are no major or unique human metabolites. Only mild gastrointestinal effects were observed at high relative exposures in the repeat dose toxicity studies.

In the repeat-dose toxicity studies in which high doses were used, there were no clinical signs of adverse CNS, cardiovascular or respiratory effects in mice (at relative exposures 266 to 434 based on AUC), rats (at relative exposures of 87 to 25 based on AUC) or dogs (at relative exposures of 60 to 103 based on AUC).

Overall, asunaprevir is not expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use.

Pharmacokinetics

The oral bioavailability of asunaprevir free base (the proposed commercial form and used in all but 2 studies) was high in dogs (42 to 100%) and much lower in mice, rats and monkeys (28%, 1 to 14% and 10%, respectively). Absorption was not formulation-

dependent in rats but was dose dependent in rats and dogs and C_{max} tended to occur between 1.3 to 6 h post dose in rats, dogs, monkeys and mice. Exposure was increased when the clinical tablet (but not a capsule or solution) was administered to dogs.

Following PO dosing, the elimination half-life was short in dogs and monkeys ($t_{½}$ 2.4 and 1.1 h, respectively) and longer in wild-type mice and rats ($t_{½}$ 4.6 h and 4.5-8 h, respectively). Following multiple dose administration of asunaprevir in healthy subjects, the terminal elimination half-life ranged from 17 to 23 h. Due to the fact that the half-life is shorter in animals, it would have been advisable to dose animals twice daily like the proposed dosing in humans, instead of once daily.

Hepatic extraction of asunaprevir was considered moderate, with the clearance values being 64, 70, 50 to 61 and 42% of the reported blood flow in mice, rats, dogs and monkeys, respectively. First-pass metabolism was negligible since AUC was similar after intravenous (IV) and intra-portal vein administration in rats. There were no gender differences in pharmacokinetic parameters and no evidence of accumulation in animal species or human subjects.

Plasma protein binding was high in all nonclinical species; asunaprevir being greater than 97% plasma protein bound in all species irrespective of drug concentration up to 10 μM (7.48 μg/mL). Ex vivo protein binding of asunaprevir in plasma from HCV infected patients and in vitro testing, demonstrated ≥ 98.8% protein binding, concentration independently. The free fraction was not taken into account when calculating animal/human relative exposure.

Asunaprevir preferentially distributed into the plasma compartment in the animal species tested (blood-to-plasma ratio 0.34 to 0.82) and in humans (blood-to-plasma ratio 0.55). The volume of distribution was similar to or greater than total body water in mice, rats, dogs and monkeys, suggesting extensive extravascular distribution. Tissue distribution in rats after oral administration of radiolabelled asunaprevir was limited to 13 out of 42 tissues sampled and was highest in the liver. There was no penetration of the blood-brain barrier. Liver concentrations of asunaprevir were higher than plasma levels in mice (liver: serum ratio ≥83), rats, dogs and monkeys (liver: plasma ratios ≥257, 40 and ≥78, respectively).

In rats, asunaprevir-derived radioactivity was secreted in milk and while it also crossed the placenta, it was only detected in fetal liver (4 to 12 h post dose) and gastrointestinal tract (24 to 48 h post-dose).

Metabolites of asunaprevir were formed by mono- and bis-oxidation, N-dealkylation, loss of isoquinoline ring, and O-demethylation. In vivo metabolite profiles were qualitatively similar in all species and there were no unique human metabolites. Fifteen metabolites were detected in excreta of humans. Asunaprevir was the predominant radioactive component in mouse, rat, rabbit, dog, and monkey plasma, and no metabolite accounted for more than 15% of the dose in any species. The fraction of the dose recovered as metabolites was lower in animals (18-54%) than in humans (76%). All circulating human metabolites were seen in the plasma of at least one animal species.

The clinical significance of the possible production of a reactive metabolite (there was glutathione (GSH) attenuated irreversible binding of radioactive material to microsomal proteins) is unknown, however there was no hepatic toxicity at high exposure multiples in repeat dose toxicity studies.

In vitro studies indicated asunaprevir's metabolism is primarily mediated by CYP3A4 and CYP3A5, with minor activity from CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP2D6.

The elimination of asunaprevir in animals involves multiple pathways, including biliary clearance, metabolic clearance, and (possibly) direct intestinal secretion (faecal radioactivity observed in bile duct cannulated (BDC) animals after IV administration of

radiolabelled asunaprevir), predominantly leading to excretion of asunaprevir and its metabolites in the faeces.

Overall, the pharmacokinetic profile of asunaprevir in rats and dogs is considered adequately comparable for these animal species to serve as models for toxicity.

Pharmacokinetic drug interactions

As asunaprevir is metabolised by CYP3A4 and CYP3A5 and is a substrate for P-gp, organic anion transporter polypeptide (OATP) 1B1 and 2B1, inhibitors/inducers of these CYP450 enzymes and transporters may alter the exposure of asunaprevir.

Asunaprevir is a reversible inducer of CYP3A4 (IC_{50} = 7-33 µM), and a time-dependent inhibitor of CYP3A (IC_{50} = 2.4-5.4 µM) and CYP2D6 (IC_{50} = 5.7 µM). Asunaprevir inhibited P-gp , BCRP , OATP1B1 , OATP2B1 , OATP1B3 , organic cation transporter polypeptide (OCT1), OCT2 , OAT1 , OAT3 , NTCP , BSEP , and MRP2 , in vitro. Asunaprevir is predicted to have drug interactions with substrates of P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1, and NTCP but not with substrates of OAT1, OAT3, OCT1 and OCT2 (see Table 3 below).

Table 3: Translation of in vitro transporter inhibition data for asunaprevir into in vivo predictions

Transporter	IC_{50} (µM)	Calculated Ki IC_{50}/2	Criterion used for comparison	Adjusted criterion	Ki < adjusted criterion? Interpretation
Hepatic uptake transporters					
OATP1B1	0.3	0.15 µM	0.18 µM: predicted unbound hepatic inlet concentration	4.5 µM (0.18 µM x 25)*	Yes. Predicted drug interactions with substrates of these transporters
OATP1B3	3.0	1.5 µM			
OATP2B1	0.27	0.13 µM			
NTCP	3.56	1.78 µM			
Renal transporters					
OAT1	11.8	5.9 µM	5.6 nM : unbound C_{max} (560 nM x 0.01)	280 nM (5.6 nM x 50)*	No. Drug interactions not expected with substrates of these transporters
OAT3	71.9	35.9 µM			
OCT1	76.8	38.4 µM			
OCT2	>80	>40 µM			
Other transporters					
P-gp	50.6	25.3 µM	1070 µM: estimated intestinal concentration	107 µM (107 µM x 0.1)*	Yes. Potential to affect oral absorption of co-administered drugs that are substrates for these
BCRP	>50	>25 µM			

Transporter	IC_{50} (µM)	Calculated Ki $IC_{50}/2$	Criterion used for comparison	Adjusted criterion	Ki < adjusted criterion? Interpretation
					transporters
MRP2	94.8	47.4 µM	4 µM: predicted unbound liver concentration	4 µM	No. Risk of inhibition of these transporters low.
BSEP	8.81	4.4 µM			

* = EMA guideline: CPMP/EWP/560/95/Rev. 1 Corr.* Guideline on the Investigation of Drug Interactions

Asunaprevir inhibited uridine-diphosphoglucuronosyl transferase (UGT) 1A1 in vitro (IC_{50} = 14.9 µM), however no consistent effects on total bilirubin have been observed in humans (bilirubin is a UGT1A1 substrate), therefore UGT1A1-mediated glucuronidation may not be affected clinically.

Overall, there is a strong indication that exposure to asunaprevir will affect and be affected by a wide range of drugs and this will warrant post-market monitoring of individual drug levels, particularly for drugs with a low therapeutic index.

Other HCV drug interactions

Co-administration with daclastavir or BMS-791325 in rats (1 month), daclastavir in monkeys (1 and 3 months), and daclastavir + BMS-791325 in dogs (1 month) increased exposure to asunaprevir. Co-administration with pegIFNα + ribavirin in monkeys (DS09019/DCN 930039091) did not lower exposure to asunaprevir (1 month), nor was there any evidence that asunaprevir reduced exposure to pegIFNα or ribavirin. Co-administration with daclatasvir in rats (1 month) and monkeys (1 and 3 months) increased exposure to daclatasvir.

Furthermore, since (like asunaprevir) a significant fraction of daclatasvir elimination is mediated by CYP3A4, daclatasvir is a substrate of P-gp, an inducer and inhibitor of CYP3A, and an inhibitor of P-gp and OATP, the potential exists for pharmacokinetic drug interactions to occur between asunaprevir and daclatasvir.

Toxicology

A comprehensive package of toxicology studies was submitted in support of asunaprevir registration. These studies documented acute toxicity in mice, rats, and dogs, chronic toxicity in rats and dogs (up to 6 to 9 months), genotoxicity in vitro and in vivo, reproductive toxicity in rodents, juvenile toxicity in rats, local tolerance, phototoxicity and carcinogenicity (transgenic mice and SD rats). Combination (asunaprevir + daclatasvir, BMS-791325, or pegIFNα/ribavirin) toxicity studies were performed in rats, dogs and monkey for up to 3 months. Pivotal nonclinical species examined were exposed to asunaprevir and its main human metabolites, and are therefore considered appropriate models for toxicity testing.

Acute toxicity

Deaths were observed after a single dose of 2000 mg/kg asunaprevir in mice. The maximum non-lethal acute doses of asunaprevir were 300 mg/kg in dog, 600 mg/kg in

mice and 2000 mg/kg in rat. Asunaprevir displayed a low order of acute toxicity by the clinical route.

Repeat-dose toxicity

Pivotal repeat-dose toxicity studies of up to 1 month duration in mice, 6 months duration in rats and 9 months duration in dogs, as well as combination studies (+ daclatasvir, BMS-791325 or pegIFNα/ribavirin) in rats, dogs, and monkeys were conducted. All pivotal toxicology studies complied with GLP, with asunaprevir administered orally (by gavage), consistent with the proposed clinical route of administration. Unless otherwise stated animals were dosed using an asunaprevir solution in a vehicle consisting of 60% polyethylene glycol-400 (PEG-400) and 40% vitamin E d-α tocopheryl polyethylene glycol 1000 succinate (TPGS). The duration of the pivotal studies, the species used, group sizes and the use of both sexes were consistent with ICH guidelines14. While the clinical route (PO) was used in all studies, the clinical dosing regimen (twice daily) was not used. This is not expected to affect the validity of the toxicity studies, given the high exposures achieved, however it is a deficiency since the plasma half-life of asunaprevir in animals is significantly shorter than in human subjects. The duration of the pivotal toxicity studies (6 or 9 months) was adequate to support the proposed duration of use (24 weeks) use in humans. Doses used are considered generally acceptable, achieving high relative exposures to asunaprevir (see Table 4 below).

Relative exposure

The level of the relative exposure in repeat dose toxicity studies was very high.

Table 4: Relative exposure in repeat-dose toxicity and carcinogenicity studies†

Species; study duration	Dose mg/kg /day	$AUC_{0-24\,h}$ µg·h/mL		Exposure ratio#	
		male	female	male	female
Rat **1 week, oral TK and tolerability study (TPGS-Free Formulation) (DM10042/93004 8998)**	60	9.97	15.4	2.7	**4.2**
	200	75.3	59.2	20	**16**
	600	228	170	62	**46**
	800	485	540	131	**146**
	1000	572	627	155	**170**
	1500	NR	NR	-	**-**
Rat **2 weeks, oral TK (DM10016/DCN 930045886)**	60	34.7	27.8	9.4	**7.5**
	200	104	318	28	**102**
	600	198	206	54	**56**
Rat	30	4.09	4.2	1.1	**1.1**

[14] ICH M3(R2): Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

Species; study duration	Dose mg/kg	$AUC_{0-24\,h}$ µg·h/mL		Exposure ratio#	
2 weeks, oral gavage (DN07002)	100	135	155	37	**42**
	300	147	294	40	**80**
Rat **1 month, oral gavage** **(DM07024/ 930024094)**	30	1.88	1.34 (AUC0–12 h)	0.5	**0.4**
	100	83.2	98.2	23	**27**
	600	227	371	62	**101**
Rat **6 months, oral gavage (DM08025)**	40	3.99	11.6	1.1	**3.1**
	80	39.3	144	11	**39**
	200	321	684	87	**185**
Dog **1 month, Oral gavage (DM07020)**	20	4.58	16.3	1.2	**4.4**
	60	102	98.5	28	**27**
	300	1410	1360	382	**369**
Dog **9 months, Oral gavage (DM08026/93003 8894)**	15	5.46	15.6	1.5	**4.2**
	50	47.2	80.9	13	**22**
	100	223	380	60	**103**
Monkey **1 week, oral gavage (DM08018)**	30	0.483	0.24	0.1	**0.07**
	150	5.44	6.16	1.5	**1.7**
	300	982	411	266	**111**
Mouse, CByB6F1-Tg(HRAS)2Jic **Hemizygous (transgenic).** **6 month (oral gavage), carcinogenicity (DM11012)**	25	13.5	13.8	3.7	**3.7**
	100	256	417	69	**113**
	200	983	1,600	266	**434**
Rat, **2 year (oral gavage), carcinogenicity**	50 (M)	20.7	-	5.6	**-**
	75 (M)	58.1	-	16	**-**
	125	193	-	52	**-**

Species; study duration	Dose mg/kg	$AUC_{0-24\,h}$ µg·h/mL		Exposure ratio#	
(DM11023)	**(M)**				
	40 (F)	-	51.5	-	**14**
	60 (F)	-	162	-	**44**
	80 (F)	-	202	-	**55**
CByB6F1 Hybrid Mice **2 weeks, oral Toxicokinetic, TPGS-Free Formulation (DM10017/DCN 930047624)**	50	16.4 (AUC_{0-8h})	18.6 (AUC_{0-8h})	4.4	**5.0**
	150	90.6 (AUC_{0-8h})	94.9	24.6	**25.7**
	500	382	1220	103.5	**330.6**
CByB6F1 Hybrid Mice (non-transgenic) 28-day oral exploratory tox study (DM09022/DCN 930050534)	50	16.1	29	4.4	**7.9**
	150	171	426	46.3	**115.4**
	500	922	2310	249.9	**626.0**
Rat Juvenile Development **PND 21-90, oral (DN11187)**	40	28	21.6	7.6	**5.9**
	125	456	268	124	**73**
	400	287	196	78	**53**
Human (HCV infected)	**100 mg BD**	**3.69**	3.69	–	**–**

† = values obtained after dosing on the last day; # = animal:human plasma AUC0–24 h; bold doses are NOAEL; NR = not reported; DRF = dose range finding; EFD = embryofetal development; in HCV-infected subjects given 200 mg tablet twice per day (Study AI447016), the week 12 human Cmax value was 0.419 µg/mL (560 nM) and the AUC (3.69 µg.h/mL).

Table 5. Relative exposure to asunaprevir in oral dual combination repeat-dose toxicity studies

Species; study duration	Dose mg/kg /day	Sex	C_{max} µg/mL	AUC 0-24h ng.h/mL	C_{max} µg/mL	AUC 0-24h ng.h/mL	Asunaprevir Relative Exposure	
							C_{max} based	AUC based

Species; study duration	Dose mg/kg /day	Sex	C_{max} µg/	AUC 0-24h ng.h/mL	C_{max} µg/	AUC 0-24h ng.h/mL	Asunaprevir Relative Exposure	
Rat **1 month** **Asunaprevir and Daclatasvir** **(DS08126/DCN 930035562)**			**Asunaprevir**		**Daclatasvir**		-	
	30/10	M	0.182	2.19	0.334	3.57	0.4	**0.6**
		F	0.433	2.11	0.584	3.55	1.0	**0.6**
	60/60	M	6.65	27.9	4.06	34.5	15.9	**7.6**
		F	10.8	54.9	5.16	35.6	25.8	**14.9**
Rat **1 month** **Asunaprevir and BMS-791325 (DM09003/DCN 930037771)**			**Asunaprevir**		**BMS-791325**		-	
	30/15	M	0.704	4	5.76	59.6	1.7	**1.1**
		F	1.13	7.28	6.15	56.6	2.7	**2.0**
	60/30	M	7.68	61.6	15.5	191	18.3	**16.7**
		F	11	92.2	15.3	192	26.3	**25.0**
Monkey **1 month** **Asunaprevir and Daclatasvir** **(DS08143/DCN 930035546)**			**Asunaprevir**		**Daclatasvir**		-	
	72/15	M	1.13	4.57	0.571	4.78	2.7	**1.2**
		F	2.37	7.77	0.57	5.43	5.7	**2.1**
	129.5/50	M	9.64	73.9	2.65	36.8	23.0	**20.0**
		F	10	60.2	3.18	35.2	23.9	**16.3**
Monkey			**Asunaprevir**		**Daclatasvir**		-	

Species; study duration	Dose mg/kg /day	Sex	C_{max} µg/	AUC 0-24h ng.h/mL	C_{max} µg/	AUC 0-24h ng.h/mL	Asunaprevir Relative Exposure	
3 months Asunaprevir and Daclatasvir (DM09008/DCN 930039780)	45/15	M	0.919	2.8	0.556	4.19	2.2	**0.8**
		F	1.11	2.87	0.476	3.69	2.6	**0.8**
	80/50	M	6.42	31.7	2.67	29.4	15.3	**8.6**
		F	2.94	13.9	2.59	27.9	7.0	**3.8**

In HCV-infected subjects given 200 mg tablet twice per day (Study AI447016), the week 12 human Cmax value was 0.419 µg/mL (560 nM) and the AUC (3.69 µg.h/mL).

Table 6: Relative exposure to asunaprevir in oral triple-combination repeat-dose toxicity studies

Species; study duration	Dose mg/kg/ day	sex	Cmax µg/ mL	AUC_{0-t}* ng.h/ mL	Cmax µg/ mL	AUC_{0-t}* ng.h/ mL	Cmax µg/ mL	AUC_{0-t}* ng.h /mL	Asunaprevir Relative Exposure	
									Cmax based	AUC based
Dogs			**Asunaprevir**		**Daclatasvir**		**BMS-791325**		**-**	
1 month Asunaprevir, Daclatasvir, and BMS-791325 (DM09009/DCN 930040309)	7.5/3/1.5	M	0.48	1.26	0.09	1.04	2.35	39.2	1.1	**0.3**
		F	0.725	1.75	0.104	0.894	2.09	30	1.7	**0.5**
	15/15/3	M	2.82	8.42	0.643	7.08	4.72	85	6.7	**2.3**
		F	5.7	18	0.803	9.17	6.96	120	13.6	**4.9**
Monkey			**Asunaprevir**		**pegIFNα**		**Ribavirin**		**-**	
1 month Asunaprevir, pegIFNα and RBV (DS09019/DCN 930039091)	0/4.5/40	M	NA	NA	0.0104	0.3120	1.61	28.6	-	-
		F	NA	NA	0.0051	0.0600	1.55	24.7	-	-
	45/4.5/40	M	0.602	2.81	0.0095	0.1950	1.48	31	1.4	**0.8**
		F	0.721	2.22	0.0051	0.0867	1.34	24.4	1.7	**0.6**

Species; study duration	Dose mg/kg/ day	sex	Cmax µg/	AUC_{0-t}* ng.h/	Cmax µg/	AUC_{0-t}* ng.h/	Cmax µg	AUC_{0-t}* ng.h	Asunaprevir Relative Exposure	
	80/4.5/ 40	M	1.19	6.95	0.0092	0.2470	1.36	26.8	2.8	**1.9**
		F	0.816	3.51	0.0034	0.0287	1.25	25.1	1.9	**1.0**
	80/0/0	M	1.91	5.53	NA	NA	NA	NA	4.6	**1.5**
		F	**0.863**	**4.56**	**NA**	**NA**	**NA**	**NA**	**2.1**	**1.2**

* = In the dog study Asunaprevir's $AUC_{(0-T)}$ values, T = 4, 6, 8, or 24 hours in the 7.5/3/1.5-mg/kg/day dose group, T = 8 or 24 hours in the 15/15/3-mg/kg/day dose group. For pegIFNα's $AUC_{(0-T)}$ values, T = 24 hours for individual dogs at all doses, except in 1 male and 1 female dog on Days 1 and 29, respectively, in the 3/7.5/1.5-mg/kg/day dose group, where T = 8 hours. For BMS-791325, $AUC_{(0-24h)}$. In the monkey study's $AUC_{(0-T)}$, T = 8 to 24 hours post dose for asunaprevir; 8 to 48 hours post dose for pegIFNα, and 24 hours post dose for RBV. *In HCV-infected subjects* given 200 mg tablet twice per day (Study AI447016), the week 12 human C_{max} value was 0.419 µg/mL (560 nM) and the AUC (3.69 µg.h/mL).

Major toxicities

Repeat-dose toxicity studies were conducted in mice (1 month), rats (up to 6 months) and dogs (up to 9 months) using the oral route. No consistent target organs for toxicity were identified at low relative exposures. At very high multiples of exposure, the gastrointestinal tract and the liver were target organs for asunaprevir in rats and dogs.

Liver

Increased liver weight was observed in rats receiving asunaprevir for 1 month (≥100 mg/kg; relative exposure of ≥23) and 6 months (≥40 mg/kg; relative exposure ≥1), and this was only accompanied by increase in alanine aminotransferase (ALT) and total bilirubin in rats receiving asunaprevir for 1 month at higher doses (600 mg/kg; relative exposure approximately 60 to 100). Liver weight was not affected in dogs receiving asunaprevir for 1 month (≤300 mg/kg; relative exposure ≤370) or 9 months (100 mg/kg; relative exposure approximately 60 to 100). Hepatocellular necrosis, increased ALT, total bilirubin and gamma-glutamyl transferase (GGT) were observed in dogs receiving asunaprevir for 1 month (300 mg/kg; relative exposure approximately 370). No clinically relevant findings were seen in rats or dogs.

Gastro-intestinal tract (GIT)

GIT effects observed in rats and dogs were likely due to local irritation. Administration of asunaprevir to rats for 1 month caused reversible small intestine enterocyte hypertrophy at a relative exposure of 81 based on AUC (62 for males and 101 for females).

Repeat-dose administration of asunaprevir to rats for 6 months resulted only in soft faeces and increased food consumption, at relative exposure of 136 based on AUC (87 for males and 185 for females). Repeat-dose administration of asunaprevir to dogs for 1 month resulted only in emesis, at relative exposure of up to 375 based on AUC (382 for males and 369 for females), whereas administration for 9 months resulted only in hypersalivation, at relative exposure of up to 81 based on AUC (60 for males and 103 for females).

Combination studies

Repeat dose toxicity studies were conducted for asunaprevir in combination with other direct acting antivirals (daclatasvir for 1 month in rats and up to 3 months in monkeys; BMS-791325 for 1 month in rats daclatasvir plus BMS-791325 for 1 month in dogs) or pegylated interferon alpha (pegIFNα) plus ribavirin (1 month in monkeys). In all of these

combination studies, there was no evidence that the toxicity profile of asunaprevir was altered by co-administration with other HCV drugs. The available combination studies in animals were adequate to assess the potential effect of other HCV drugs on the toxicity profile of asunaprevir.

Genotoxicity

The potential genotoxicity of asunaprevir was investigated in the standard battery of tests, conducted in accordance with ICH guidelines.[15] All assays were appropriately validated and conducted under GLP conditions. Asunaprevir was not mutagenic in bacterial mutation assays or clastogenic in vitro (in CHO cells) or in vivo (in the rat micronucleus test). Given the absence of mutagenic and clastogenic activity in in vitro assays and the absence of drug related tumours in the mouse and rat carcinogenicity studies at relatively high exposures, the weight of evidence indicates asunaprevir is not genotoxic.

Carcinogenicity

The sponsor stated that carcinogenicity studies were initiated when the clinical treatment was believed to be as long as 48 weeks. The clinical duration for asunaprevir containing combination therapies is now ≤ 24 weeks, a duration for which carcinogenicity assessment are not required.[16]

The carcinogenic potential of asunaprevir by the oral route was assessed in rats following daily dosing for 83 weeks and in transgenic Tg.rasH2 mice treated for 26 weeks at adequate exposure multiples of the human dosage. The doses selected for carcinogenicity studies were in accordance with recommendations from the Executive Carcinogenicity Assessment Committee (CAC) of US Food and Drug Administration (FDA) and were based upon a 28-day study in Tg-rasH2 non transgenic mice and the 6 month study for rats. The group sizes used and duration of dosing were appropriate for the species. In the transgenic mouse study, a concurrent positive control group (N-nitroso-N-methylurea-treated) was included and tumours expected from administration of a mutagen were observed, confirming the validity of the study. There were no asunaprevir related neoplastic findings in any of the treated groups (≤200 mg/kg/day PO in mice and ≤80/125 mg/kg/day in rats; relative exposures >260 and >50, respectively). Therefore, based on these studies, asunaprevir is not expected to pose a carcinogenic risk during clinical use.

Reproductive toxicity

A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (mice and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used during appropriate gestational periods. Maximum doses in rats were acceptable, achieving several multiples of the clinical asunaprevir exposure (see table below), whereas exposure ratios in pregnant rabbits were generally low (maximum exposure ratio 1.2 at 200 mg/kg/day in the pivotal EFD study). It is nevertheless possible that significantly higher exposures were not achievable (possibly due to saturation of absorption) since a dose of 400 mg/kg (in the DRF study) produced a relative exposure 2.9, and a dose of 1000 mg/kg (in an exploratory study in non-pregnant female rabbits) produced a relative exposure of 3.3.

Fertility was unaffected in rats when treated males were paired with treated females (≤600 mg/kg; relative exposure approximately100 in both sexes). No adverse effects on fertility are predicted in patients. Placental transfer of asunaprevir and/or its metabolites

[15] ICH S2(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.
[16] ICH S1A: Guideline on the need for carcinogenicity studies of pharmaceuticals.

was observed in rats. No adverse embryofetal effects were observed in either mice or rabbits at the highest tested doses: 500 mg/kg PO (relative exposure 472) in mice and 200 mg/kg/day PO (relative exposure 1.2) in rabbits.

Transfer of asunaprevir related material into milk was shown. In a pre and postnatal development study in rats, decreased viability, body weight, and food consumption were evident in F1[17] litters at 400 mg/kg/day (relative exposure 193) but not at the relatively high dose of 125 mg/kg (relative exposure 76).

Table 7: Relative exposure in reproductive studies

Species; study duration	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg·h/mL)	Exposure ratio#
Rat Oral Fertility and early EFD. M: ≤ 64 days F: 22-35 days (DN08069)	50	53/29.9 (M/F)	14/8.1
	200	454/545 (M/F)	123/148
	600	386/373 (M/F)	105/101
Pregnant mice 10-day oral DRF (DN08014/DCN 930068598)	60	57.8	15.7
	125	603	163
	250	1810	491
	500	2380	645
Mouse Oral EFD, 10 days GD15 (DN08022)	10	0.851	0.2
	50	19.1	5.2
	250	737	200
	500	1740	472
Nonpregnant Rabbits 5 days oral Exploratory (DN08015/DCN 930068281)	50	0.707	0.2
	150	2.55	0.7
	300	5.52	1.5
Nonpregnant Rabbits 7 days oral Exploratory (DN09022/DCN	250	3.06	0.8
	500	4.11	1.1
	750	5.61	1.5

[17]The F1 generation is the first generation of offspring produced by a set of parents. The 'F' in 'F1' stands for 'filial.

Species; study duration	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg·h/mL)	Exposure ratio#
930068775)	1000	12.3	3.3
Pregnant Rabbits 13-Day oral DRF, GD19 (DN08021/DCN 930068624)	50	0.76	0.2
	100	2.11	0.6
	200	5.02	1.4
	400	10.6	2.9
Rabbit Oral EFD, 13 days (GD7-GD19) (DN08056/DCN 930043164)	50	1.17	0.3
	100	2.79	0.8
	200	4.4	1.2
Rat Oral pre/postnatal development GD 6-LD 20, (DN11186)	40	26.8	7.3
	125	282	76
	400	711	193
Human (HCV infected)	100 mg BID	3.69	–

In HCV-infected subjects given 200 mg tablet twice per day (Study AI447016), the week 12 human C_{max} value was 0.419 µg/mL (560 nM) and the AUC (3.69 µg.h/mL). # = animal: human plasma AUC_{0-24} h

Pregnancy classification

The sponsor has proposed Pregnancy Category 'B' for Sunvepra® (which lacks ribavirin). Pregnancy Category B1[18] is consistent with the absence of any drug related findings in adequately conducted reproductive toxicity studies with asunaprevir. Asunaprevir is proposed for use with daclatasvir (Category B3[19]), or daclatasvir and pegintreferon and ribavirin (Category X[20]), in which cases the most restrictive pregnancy category is applicable.

The sponsor has proposed Pregnancy Category X for Sunvepra® when used with peginterferon alfa and ribavirin. Since Category X is consistent with the pregnancy category for ribavirin, this is considered appropriate.

Pregnancy Category 'B3' applies for Sunvepra® when used with daclatasvir. Developmental toxicity has been observed with daclatasvir alone in rats and rabbits (see

[18] 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.

[19] Category B3: 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 shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

[20] 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.

AusPAR for Daklinza) and the use of daclatasvir is not recommended in pregnant women or women of childbearing potential not using a highly effective method of contraception.

Local tolerance and phototoxicity

Asunaprevir showed no evidence of skin irritation following topical application to the skin of rabbit, or of skin sensitization following topical application to the ears of mice. The nonclinical overview states that asunaprevir absorbs light between 290 and 700 nm. In rats, asunaprevir distributed to pigmented and non-pigmented skin but not to the eye. In Balb/c 3T3 mouse fibroblasts, asunaprevir showed phototoxic potential, although it was not phototoxic after oral administration to pigmented rats at 600 mg/kg. Asunaprevir showed evidence of ocular irritation in the in vitro bovine corneal opacity and permeability assay.

Taken together, asunaprevir is potentially phototoxic and an ocular irritant.

Impurities

The proposed specifications for impurities in the drug substance are below the ICH qualification thresholds. There are no degradants in the drug product requiring toxicological qualification.

Paediatric use

Asunaprevir is not proposed for paediatric use. No particular concerns, including systems in development which are targets for toxicity at clinically relevant exposure levels were identified in a juvenile toxicity study or in general repeat-dose toxicity.

Nonclinical summary and conclusions

- The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to GLP, and with high exposure margins employed.
- Asunaprevir inhibits the RNA replication of HCV genotypes 1 and 4 by inhibiting the activity of the non-structural protein 3 (NS3) protease.
- In vitro, asunaprevir inhibited the activity of purified NS3/4A protease enzyme complexes from HCV strains of genotypes 1b (IC_{50} 0.3 nM), 1a (IC_{50} 0.7 to 1.8 nM), 6a (IC_{50} 0.9 nM), 4a (IC_{50} 1.6 nM), 5a (IC_{50} 1.7 nM) and with a significantly lower potency 2a (IC_{50} 15 nM), 2b (IC_{50} 78 nM) and 3a (IC_{50} 320 nM). Except for genotype 2b, asunaprevir was more potent than telaprevir.
- In cell-based HCV replicon assays, asunaprevir inhibited HCV genotype 1a (EC_{50} 4 nM), 1b (EC_{50} 1.2 nM), and 2a (EC_{50} 230 nM), replication. Hybrid replicons encoding the NS3 protease domain representing HCV genotype 4a were inhibited with EC_{50} values of 1.8 to 7.6 nM, whereas GT-2b and GT-3a NS3 protease replicon hybrids were inhibited with EC_{50} values of 0.48 mM and 1.2 mM, respectively. The potency of asunaprevir in subgenomic GT-1b (Con1) HCV replicon assays was reduced by approximately6.5 fold in the presence of 40% human serum, suggesting asunaprevir's clinical efficacy can be attenuated by serum protein binding..
- Asunaprevir is unlikely to be active against genotype 2a, 2b and 3a at the proposed clinical dose (clinical C_{max} was 0.419 µg/mL = 560 nM).
- Treatment of HCV GT-1b replicon cells with combinations of asunaprevir and IFN alpha or RBV, and/or direct-acting antivirals targeting HCV NS5A (daclatasvir) and/or HCV NS5B (BMS-791325) displayed additive to synergistic effects. Asunaprevir also

showed additive and/or synergistic interactions with valopicitabine, BMS-790453, HCV-796, BMS-762407, and Intron A in two or three drug combination studies. No antagonism of antiviral activity was observed.

- Mutations in the NS3 protease domain at T40A, Q41E, V51A, R62K, D79E, T95A, I114V, R123G, R155K, D168G, I170T, N174Y, L175P, G176E (genotype 1a), Q41R, Q80R, Q86R, P89L, Y105C, D168A/G/H/V/Y, E173G, and E176G (genotype 1b), conferred resistance to asunaprevir.
- Asunaprevir exhibited no to moderate cross-resistance against HCV replicons conferring resistance to NS3 inhibitors such as boceprevir and telaprevir:
  - GT-1a replicons carrying NS3 protease substitutions at amino acid positions V36 (V36A/M), T54 (T54A/S), R155 (R155K), and V36-R155 (V36M- R155K): EC_{50} values ranging from 0.33 to 42 nM (parent GT-1a replicon EC_{50} = 0.76 nM).
  - GT-1b replicons carrying NS3 protease substitutions at amino acid positions A156 (A156 to serine, threonine or valine), demonstrated low to moderate resistance with EC_{50} values of 5.4 to 17 nM (parent GT-1b replicon EC_{50} = 0.86 nM).
- The susceptibility of GT-1a to asunaprevir was decreased by 373 and 713 fold due to NS3 substitutions D168V and Q80K+D168V, respectively. The susceptibility of GT-1b to asunaprevir was decreased by 127 to 280 fold due to NS3 substitutions D168A, D168Y, and D168V.
- Treatment of HCV GT-1a replicons and HCV GT-1a replicons carrying the NS3 substitution R155K with a combination of asunaprevir, daclatasvir, and interferon-alfa similarly suppressed HCV RNA replication. Furthermore, combinations of asunaprevir with other classes of HCV inhibitors including interferons alfa and lambda, ribavirin, NS5A, NS5B nucleoside and NS5B allosteric inhibitors showed additive to synergistic antiviral activity in vitro. This suggests that drugs targeting multiple viral targets are of potential value against emerging resistant virus. It is noted that asunaprevir is not indicated as monotherapy due to the propensity for resistance. Cross-resistance with daclatasvir, peginterferon alfa and ribavirin is not expected due to their differing mechanisms of action.
- Asunaprevir exerted minimal to no activity against the closely related viral serine protease, GBV-B NS3 protease (IC_{50} 21 μM) and a panel of 10 human serine and cysteine proteases. No off-target activities are predicted during clinical use.
- Based on findings in cardiovascular, CNS and respiratory endpoints evaluated as part of repeat-dose toxicity studies and dedicated cardiovascular safety studies, asunaprevir is not expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use. No asunaprevir metabolites were independently evaluated in safety pharmacology studies as there were no major metabolites.
- Absorption of asunaprevir was variable within species following PO administration of asunaprevir solution, with peak concentration occurring with the first few (1 to 6) h of administration. The oral bioavailability was moderate in mice (28%) and rats (1 to 14%), high in dogs (42 to 100%) and low in monkeys (10%). Asunaprevir's bioavailability increased with increasing in dose in rats and dogs. Bioavailability was not affected by the formulation of asunaprevir, but in dogs the administration of food with asunaprevir (in a tablet form used in clinical treatment) significantly increased absorption of the drug. Plasma protein binding was high in all nonclinical species and humans; asunaprevir being greater than 97 % plasma protein bound in all species. Asunaprevir is unlikely to cross the blood brain barrier. Highest concentrations of asunaprevir-associated radioactivity appeared in bile and liver and not in eye or CNS tissues.

- Comparison of AUC after IV and intra-portal vein administration in rats suggested that oral bioavailability of asunaprevir is not limited by first-pass metabolism.
- Inducers/inhibitors of P glycoprotein, OATP 1B1 and 2B1 or CYP3A may alter the systemic exposure to asunaprevir. In vitro studies indicate asunaprevir has the potential to affect the disposition of co-administered drugs that are substrates for CYP2D6, CYP3A, and UGT1A1. There is some potential for asunaprevir and daclatasvir to affect exposure to each other.
- Acute oral toxicity was assessed in a single dose studies with asunaprevir in mice, rats and dogs. Single doses up to 300 (dogs), 600 (mice) and 2000 (rats) mg/kg caused no mortality and had no notable effects indicating a low order of acute toxicity.
- Repeat-dose toxicity studies were conducted in mice (1 month), rats (up to 6 months) and dogs (up to 9 months) using the oral route with once daily administration. Following PO dosing, the elimination half-life was shorter in dogs, monkeys, mice and rats ($t_{½}$ 2.4, 1.1 h, 4.6 h and 4.5 to 8 h, respectively) than in human subjects (elimination half-life 17 to 23 h) and therefore it would have been advisable to dose animals twice daily like the proposed dosing in humans, instead of once daily.
- The liver was a target organ for toxicity in rats and dogs but only at very high multiples of exposure. Increased liver weight was observed in rats receiving asunaprevir for 1 month (≥100 mg/kg; relative exposure of ≥23) and 6 months (≥40 mg/kg; relative exposure ≥1), and this was only accompanied by increase in ALT and total bilirubin in rats receiving asunaprevir for 1 month at higher doses (600 mg/kg; relative exposure approximately 60 to 100). Liver weight was not affected in dogs receiving asunaprevir for 1 month (≤300 mg/kg; relative exposure ≤370) or 9 months (100 mg/kg; relative exposure approximately 60 to 100). Hepatocellular necrosis, increased ALT, total bilirubin and GGT were observed in dogs receiving asunaprevir for 1 month (300 mg/kg; relative exposure approximately370). No clinically relevant findings were seen in rats or dogs.
- Repeat dose toxicity studies were also conducted with asunaprevir in combination with other direct acting antivirals (daclatasvir for 1 month in rats and up to 3 months in monkeys; BMS-791325 for 1 month in rats; daclatasvir plus BMS-791325 for 1 month in dogs) or pegylated interferon alpha (pegIFNα) plus ribavirin (1 month in monkeys). There was no evidence that the toxicity profile of asunaprevir was altered by co-administration with other HCV drugs.
- A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (mice and rabbits) and pre/postnatal development (rats). There were no drug related findings. Placental transfer and transfer of drug related material into milk were shown in rats.
- Pregnancy Category B1 is acceptable for asunaprevir. When used in combination with daclatasvir (Category B3), or daclatasvir and peginterferon alfa and ribavirin (Category X), the most restrictive category is applicable.
- Asunaprevir was not genotoxic in the standard battery of tests. No drug related tumours were evident in rats treated with asunaprevir for 83 weeks or in transgenic Tg.rasH2 mice treated for 6 months at adequate exposure multiples of the human dosage. Asunaprevir is unlikely to pose a mutagenic, clastogenic or carcinogenic risk to humans.
- No particular targets for toxicity at clinically relevant exposure levels were identified in a juvenile toxicity study or in general repeat-dose toxicity studies.
- Asunaprevir did not produce skin irritation and did not cause skin sensitisation. Asunaprevir is potentially phototoxic and an ocular irritant.

There are nonclinical objections to the registration of asunaprevir. The draft Product Information should be amended as directed [the details of these recommendations are beyond the scope of this AusPAR].

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

Approximately 150 to 160 million people worldwide are chronically infected with HCV. The majority of infected individuals progress to chronic hepatitis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

Chronic hepatitis C (CHC) infection is associated with variable degrees of hepatic inflammation and progression of fibrosis. Liver disease progression takes place over several decades, and is accelerated in the presence of co-factors such as alcohol consumption, diabetes mellitus, old age, HIV co-infection, or hepatotropic virus co-infection. Between 10-40% of patients with CHC will develop cirrhosis depending on the presence of these co-factors. Deaths, related to the complications of cirrhosis, occur at an incidence of approximately 4% per year, and HCC occurs in this population at an estimated incidence of 1-5% per year. Given that HCC often goes undiagnosed until late into the disease, once diagnosed with HCC, patients have an approximate 33% probability of death during the first year.

Various HCV genotypes (GT) have been described that respond differently to current treatment regimens. HCV GT-1 (subtypes 1a and 1b) is the most prevalent worldwide with a higher prevalence of GT-1a in the United States and GT-1b in Europe. GT-3 is the second most prevalent GT in some European countries and India, and is associated with an increased likelihood of developing hepatic complications, from steatosis to HCC. Due to the migration from North-East and Sub-Saharan Africa, HCV GT-4 accounts for up to 19% of cases in Mediterranean countries and in 5-8% in Central and Western European countries. GT-2 is found in clusters in the Mediterranean region, while GT-5 and GT-6 are more rarely found in Europe.

Comment: There is no discussion of the prevalence of genotypes in Australia in the application but in a reference quoted in the Risk Management Plan (RMP) and supported by a publication not provided in the submission it is estimated that in Australia, approximately 32 to 35% of people with hepatitis C have subtype GT-3 (mostly being GT-3a), 15 to 35% have GT-1a, 15 to 23% have GT-1b and 7 to 9.3%, have GT-2, 5.5% have GT-4 and 1.7% have GT-6.[21,22]

Peginterferon alfa in combination with ribavirin (pegIFNα/RBV) was the traditional well accepted standard of care for the treatment of CHC until 2011. This treatment regimen is administered for either 48 weeks (GT-1, -4, -5, -6) or for 24 weeks (GT-2 and _3), inducing sustained virologic response at 24 weeks (SVR24) rates of 42% to 46% in patients with HCV GT-1 and GT-4, and 76% and 82% in patients with GT-2 and GT-3 infections.

[21] Dore G.J., Law M., MacDonald M. et al. Epidemiology of Hepatitis C virus infection in Australia. *Journal of Clinical Virology* 2003; 26(2):171-84.
[22] Kaba S., Dutta U, Byth K., Crewe E. B., Khan M, H., Coverdale S. A., Lin R., Liddle C., and Farrell C. Molecular Epidemiology of Hepatitis C in Australia. Journal of Gastroepidemiology and Hepatology 1998; 13: 914-920

In recent years the introduction of DAAs, which target specific viral enzymes, have improved patient outcomes.[23,24] In 2011, 2 DAA agents, the HCV NS3/4A protease inhibitors telaprevir (TVR) and boceprevir (BOC), added on to pegIFNα/RBV were approved in the United States (US) and European Union (EU). These DAA/ pegIFNα/RBV regimens were then considered the standard of care for treating CHC patients in the EU, US, Japan and other regions.

Comment: Boceprevir (BOC) and telaprevir (TVR) have been approved for marketing in Australia and were entered into the Australia Register of Therapeutic Goods (ARTG) in January 2012 and March 2013 respectively.

Recently, other agents including sofosbuvir (Sovaldi) (SOF), a nucleoside NS5B polymerase inhibitor, and simeprevir (Olysio) (SMV), an NS3/4A protease inhibitor, have been approved in the US offering new treatment options to patients with CHC.

Comment: SOF and SMV were approved in Australia in June and July 2014 respectively.

The introduction of these newer options has provided an improvement over the use of IFN-based therapies alone for patients with GT-1. However, there is still a need for improved efficacy in HCV GT-1 patients, particularly in patients with limited response to pegIFNα/RBV or in patients who are intolerant or ineligible for IFN based therapy, and for patients who have failed current protease inhibitor therapies.

Treatment duration with pegIFNα/RBV can be long (24 to 48 weeks) depending on the GT, and because pegIFNα requires parenteral administration, treatment adherence, compliance, and complications arising from injections can be a challenge.

Side effects associated with pegIFNα/RBV include flu-like symptoms (chills, pyrexia, myalgia, fatigue), psychiatric disorders (depression, irritability, anxiety), and haematologic abnormalities (anaemia and neutropenia). TVR and BOC are associated with serious dermatologic side effects (rash and/or pruritus) and additional decreases in haemoglobin and absolute neutrophils when combined with pegIFNα/RBV, compared to IFN-based therapy alone. SMV treatment is associated with increased rates of hyperbilirubinaemia and photosensitivity.

Despite the treatment advancement with the first generation DAAs and recently approved DAAs, there is still an unmet medical need for new therapeutic agents that are more effective, pangenotypic, less toxic than INF- and RBV-based therapies and less complex with simpler administration, monitoring and management of adverse events to ensure the most optimal combination of DAAs are available to patients. Currently, there is a need for improved therapies in subjects who have failed TVR- and BOC-regimens as well as INF ineligible/intolerant patients and non-responders to pegIFNα/RBV.

Asunaprevir (ASV) has shown additive to synergistic interactions in combination with DCV with no cross resistance between the two agents. This data supports the combination therapy of DCV and ASV in HCV infected patients.

Contents of the clinical dossier

Scope of the clinical dossier

Of particular note, the efficacy studies for the requested regimens of combination therapy were all common to the DCV submission and have been assessed in the DCV clinical evaluation report.[25] Only brief summaries are provided in this report.

[23] Chan J. Hepatitis C. *Disease-a-Month*; 2014; 60: 201-212.
[24] Kohli A, Shaffer A, Sherman A et al. Treatment of Hepatitis C - A Systematic Review. *JAMA*. 2014. 312: (6): 631-640.
[25] Attachment 2 AusPAR for Daklinza

The clinical studies contained in the application are as follows:

- 3 bioavailability studies that examined bioequivalence between various formulations and the effect of food;
- 1 absolute bioavailability study;
- 6 ascending dose studies examining pharmacokinetics (PK) and initial tolerability. Four were conducted in healthy subjects and two in subjects with chronic HCV infection.
- 1 mass balance study;
- 2 studies in special populations (1 in hepatic impairment and 1 in renal impairment);
- 12 interaction studies;
- 4 studies examining population PK and population PK/exposure-response;
- 1 pharmacodynamic (PD) study examining effects on QT interval.
- 1 efficacy/safety study not provided in the DCV dossier

Also, Integrated Summaries of Efficacy and Safety have been submitted in place of Summary of Clinical Efficacy, and Summary of Clinical Safety but the documents are titled Summary of Clinical Efficacy and Summary of Clinical Safety.

The following additional clinical information was also provided:

- Clinical Overview, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Summary of Clinical Pharmacology (SCP) and literature references.

Paediatric data

The submission did not include paediatric data.

The sponsor states that there is an agreed Paediatric Plan in the USA. No date for submission of a Paediatric Assessment is provided. There is a waiver for submission of a Paediatric Assessment for children under the age of 3 as they will not benefit significantly from the therapy due to the higher spontaneous resolution of HCV infection in children than in adults and that HCV infection is milder within this age group; milder liver inflammation, less frequent cirrhosis, lower viral load and shorter duration of infection.

Good clinical practice

The study reports all state that the studies were conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

All protocols were reviewed by appropriate ethics committees and patients signed appropriate informed consent prior to any study procedures.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 8 shows the studies relating to each PK topic.

Table 8: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	AI447-001	*
	- Multi-dose	AI447-003	*
		AI447-005	*
	Bioequivalence† - Single dose	AI447-008	*
		AI447-024	*
	Absolute bioavailability	AI447-027	*
	Food effect	AI447-024	
		AI447-043	*
	Mass balance	AI447-010	*
PK in special populations	Target population - Single dose	AI447-002	*
	- Multi-dose	AI447-004	*
	Hepatic impairment	AI447-012	*
	Renal impairment	AI447-033	*
Genetic/gender-related PK	Caucasian versus Chinese subjects	AI447-030	*
PK interactions (with ASV)	Midazolam	AI447-007	*
	Ketoconazole	AI447-014	*
	Rosuvastatin	AI447-	*

PK topic	Subtopic	Study ID	*
		015	
	Rifampicin	AI447-018	*
	Norgestimate and Ethinyl oestradiol	AI447-019	*
	Metabolic probe cocktail	AI447-020	*
	Digoxin	AI447-021	*
	Escitalopram and Sertraline	AI447-032	*
	Methadone	AI447-038	*
Population PK analyses	Population PK (ASV)	-	*
	Exposure-response for efficacy and safety (DCV+ASV)	-	*

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of these PK studies had deficiencies that excluded their results from consideration. The submission included some other early phase studies which have not been reviewed in this report. These studies have been reviewed and summarised as part of the clinical evaluation of early phase studies for DCV.[26] These studies are listed in Table 9.

Table 9: Pharmacokinetic studies submitted but not reviewed in this report.

Study ID	Subtopic(s)
AI444-003	Multiple dosing of DCV in healthy subjects
AI444-012	Interaction study between DCV and rifampicin
AI447-009	Interaction study between ASV and DCV
AI447-039	Interaction study between AS+DCV combination and oral contraceptive
AI447-040	Interaction study between AS+DCV combination and digoxin
930077408	Exposure-response analysis for efficacy for AS+DCV combination

[26] Attachment 2 AusPAR for Daklinza

Study ID	Subtopic(s)
930077407	Exposure-response analysis for safety for AS+DCV combination

Evaluator's conclusions on pharmacokinetics

The early phase clinical studies have provided sufficient data to adequately describe the PK of ASV. The requirements outlined in the relevant EU guidelines adopted by the TGA have generally been met. In particular, an extensive program of interaction studies has been conducted, as required by the guideline on DAAs for HCV infection.[27]

Pharmacodynamics

Studies providing pharmacodynamic data

Table 10 shows the studies relating to each pharmacodynamic (PD) topic.

Table 10: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on HCV viral load	AI447-002	*
		AI447-004	*
Secondary Pharmacology	Effect on QT interval	AI447-025	*

* Indicates the primary aim of the study.

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

Evaluator's conclusions on pharmacodynamics

The PD data provided were acceptable.

Dosage selection for the pivotal studies

ASV was shown to be active as monotherapy. In the Phase I single-ascending dose study (A1447002: table 25). GT-1 subjects with HCV receiving a single dose of ASV 200 mg experienced a mean maximum decline in HCV RNA (log_{10} IU/mL) from baseline of 2.26 in 21.6 h (mean). In the sponsor's Summary of Clinical Pharmacology it is indicated that a dose of 200 mg twice daily (BD) (with the tablet formulation) was chosen for Phase II studies. This was based on an exposure-response analysis of data from the Phase II Study AI447-016. This study also informed the dose to be used in the Phase III studies with DCV and DCV + pegIFNα + RBV. It investigated the safety and efficacy of ASV + PegIFNα + RBV and is summarised and evaluated below.

[27] European Medicines Agency. Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.) 2012. Available from: http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinical

Discussion

In the DCV/ASV Phase II studies (AI447011 and AI447017[28]), the following ASV doses were tested: 200 mg once daily (QD) (AI447011 only), 200 mg BD and 600 mg BD. In Study AI447016 in non-Japanese subjects, ASV 200 mg BD, ASV 600 mg QD and ASV 600 mg BD doses were evaluated. All 3 studies (AI447011, AI447016, and AI447017) were conducted using the tablet formulation of ASV.

Although all Phase II ASV doses (200 mg QD to 600 mg BD of the tablet formulation) were generally well tolerated, a trend in the frequency and magnitude of ALT and aspartate aminotransferase (AST) elevations was observed at ASV doses > 200 mg BD of the tablet formulation and this trend was associated with greater plasma exposure of ASV in an initial exposure-safety assessment conducted using data from the Stage 1 portion of Study AI447016**.** The analysis demonstrated a higher probability of Grade 2 or higher ALT (and AST) elevations with higher plasma exposures of ASV, as measured by AUC.

The dose of 200 mg BD of the tablet formulation was selected as the ASV dose in all on-going and future Phase II studies. The prediction that ASV 200 mg tablet BD offered the best balance of safety and antiviral activity was confirmed by the observed liver function test (LFT) data and high response rates in Phase II studies. The safety and efficacy for DCV/ASV in Japanese subjects in Phase II was comparable, with a similar benefit-risk profile, despite the differences in ASV plasma exposures between Japanese and non-Japanese subjects. No dose adjustment was needed in Japanese subjects.

A 100 mg BD soft gel capsule formulation of ASV was selected as the Phase III formulation based on the results from a relative bioavailability study that indicated the bioavailability for the soft gel capsule formulation was approximately 2 fold higher compared with the ASV Phase II tablet administered with food (Study AI447043). Moreover, the soft gel capsule formulation mitigated the significant food effect observed with the Phase II tablet. Based on these data, the soft gel capsule at a dose of ASV 100 mg BD administered either with or without meals was expected to approximate the AUC of the ASV 200 mg Phase II tablet administered with food in Phase II studies; and using the prior exposure-response assessments it was concluded that there would be no meaningful alterations in the antiviral activity or safety profile of ASV at the 100 mg BD dose of soft gel capsule without regard to food.

Efficacy

Studies providing efficacy data

Treatment of HCV – ASV combined with DCV

Two pivotal and two supportive studies were included for this indication. These have been evaluated in the DCV clinical evaluation report.[29]

Evaluator's conclusions on clinical efficacy for combination therapy with DCV

As ASV is requested to be used only in combination with DCV, the approval of ASV is dependent on the approval of DCV.

For the ASV/DCV regimen and the QUAD regimen the duration of treatment requested is 24 weeks which matches the treatment period in the studies.

[28] *Pharmacokinetics* in Attachment 2 AusPAR for Daklinza
[29] Attachment 2 AusPAR for Daklinza

ASV/DCV regimen

The SVR12 rates[30] achieved with the DCV/ASV therapy in treatment naïve HCV GT-1b-infected subjects were 90.6% (95% CI: 86.6, 94.6). This is similar to the SVR rates in patients who were IFN/RBV-based therapy intolerant/ineligible GT-1b in AI447028: 82.6% (95% CI: 77.7, 87.4), AI447026: 88.1% (95% CI: 82.7, 93.6) and AI447017: 63.6% (95% CI: 43.5, 83.7.

The SVR12 rates achieved with the DCV/ASV therapy in HCV GT-1b-infected prior non-responders were 82.4% (95% CI: 77.2, 87.6) in Study AI447028, 80.5% (95% CI: 72.1, 88.8) in AI447026 and 83.3% (95% CI: 66.1, 100.0) in AI447011.

Further:

- In GT-1b prior null responders, the SVR12 rates were 82.4% in AI447028, 81.3% in AI447026, and 83.3% in AI447011.
- In GT-1b prior partial responders, the SVR12 rates were 82.1% in AI447028 and 77.8% in AI447026.

Overall, in DCV/ASV-treated subjects, SVR12 rates were comparable across all subgroups of baseline host factors including age (<65 and ≥65 years), gender, cirrhosis status, IL-28B polymorphism, prior treatment history (null or partial response to HCV therapy, or IFN/RBV-based therapy intolerant/ineligible) and viral factors (such as viral load). The rates of VBT were low (4 to 13%).

QUAD regimen

The SVR12 rates achieved with DCV Quad therapy in:

- GT-1 prior non-responders were 330/354, 93.2% (95% CI: 90.6, 95.8) in AI447029 (DCV CER[31]) and 19/20, 95.0% (95% CI: 81.9, 99.5) in AI447011 (DCV CER[31]):
- GT-1 prior null responders, the SVR12 rates were 93.6% in AI447029 (DCV CER section 7.3.1) to 95.0% in AI447011 (DCV CER[31])
- GT-1 prior partial responders, the SVR12 rate was 91.7% in AI447029 (DCV CER)
- GT-4 prior non-responders, the SVR12 rate was 44/44, 100.0% (95% CI: 100.0, 100.0) in AI447029 (DCV CER[31]).

SVR12 rates with DCV QUAD therapy were consistently high across all host factor subgroups (including age, gender, cirrhosis status, IL-28B polymorphism, prior null or partial response to HCV therapy) and viral factors (such as viral load). SVR12 rates with DCV QUAD therapy were minimally affected by baseline NS5A-L31, NS5A-Y93H and NS3-R155 polymorphisms and not affected by NS3-D168 polymorphisms.

Safety

Studies providing safety data

Except for Study AI447016 (the ASV/PegIFNα/RBV combination) the major studies for safety always included ASV used in combination with DCV and are covered in the DCV evaluation report.[32] The following provides a brief summary of information in the DCV evaluation report. There is also summary information from Study AI447016 which is presented in more detail in Attachment 2.

[30] Sustained viral response (SVR): undetectable viral load 12 weeks (SVR-12) after treatment ended.
[31] Pharmacokinetics in Attachment 2 AusPAR for Daklinza
[32] Attachment 2 AusPAR for Daklinza

Patient exposure

The following tables summarise the number of subjects treated with ASV combination regiments at the recommended dose and according to dose and duration.

Table 11: Summary of subjects treated with ASV combination regimens at the recommended dose (100 mg capsule BD or 200 mg tablet BD)

Number of Subjects				
Study Number	DCV/ASV	DCV Quad	ASV/pegIFNα/RBV	Total ASV
Pivotal Studies				
AI447028	645	---	---	645
AI447026	222	---	---	222
AI447029	---	398	---	398
Supportive Studies				
AI447011	18	20	---	38
AI447017	33	---	---	33
Other Studies				
AI447016	---	---	189	189
Total	**918**	**418**	**189**	**1,525**

Safety data from DCV 60 mg QD in combination with a dose of ASV other than ASV 100 mg BD softgel capsule or ASV 200 mg BD (that is, ASV at 600 mg BD and ASV at 200 mg QD) are not integrated in the overall by-regimen safety analyses; however, these data are summarised by cohort in this Summary of Clinical Safety (SCS).

Table 12: Exposure to asunaprevir in clinical studies according to dose and duration

Study	DCV median dose (range)	ASV median dose (range)	Median duration (weeks)
AI447028 and AI447026	60 mg (51.1 - 80.5 mg)	200 mg* (157.0 - 210.7 mg)	24 (0.3 - 28.7)
AI447017 and AI447011	60 mg (57.0 - 60.0 mg)	400 mg* (346.4 - 400.0 mg)	24 (0.3 - 28.7)

* In Studies AI447028 and AI447026 ASV soft gel capsules were used. In Studies AI447017 and AI447011 ASV tablets were used – doses are stated to be comparable.

Table 13: DCV Quad Regimen

Study	DCV median dose (range)	ASV median dose (range)	PegIFNα median dose (range)	RBV median dose* (range)	Median duration (Weeks)
AI447029	60 mg (48.6 - 64.9 mg)	200 mg* (100.0 - 203.0 mg)	180 µg (73.8 - 187.5)	1056.7 mg (422.2 - 1200.0)	24.0 (4.0 - 25.0)
AI447011 (Group B1)	60.0 mg (55.5 - 65.9)	400.0 mg† (359.3 - 400.0)	180.0 µg (144.4 - 180.0)	1098.2 mg (717.9 - 1207.1)	23.9 (23.7 - 24.1)

*Capsule formulation. †Tablet formulation

Table 14: ASV/IFN/RBV regimen

Study	ASV median dose (range)	PegIFNα median dose (range)	RBV median dose* (range)	Median duration (Weeks)
AI447016	400.0 mg* (272.9 - 536.5)	180 µg (105.0 - 187.5)	1084.0 mg (533.7 - 1285.7)	24.0 (0.1 - 68.0)

*Tablet formulation. Studies AI447028, AI447026, AI447029, AI447011 and AI447017: DCV CER Attachment 2. Study AI447016: see Attachment 2

Safety issues with the potential for major regulatory impact

Liver toxicity

Safety in subjects with cirrhosis

A total of 229 subjects were enrolled with baseline cirrhosis it the DCV/ASV studies, 93 subjects in DCV/ASV Quad regimen studies and 16 in the ASV/peg INF/RBV studies.

- The frequency of SAEs regardless of study drugs was low and similar among subjects with cirrhosis and those without
  - DCV/ASV regimen: 15 (6.6%) with cirrhosis and 41 (6.0%) without cirrhosis
  - DCV/ASV QUAD regimen: 4 (4.3%) with cirrhosis and 18 (5.9%) without cirrhosis
  - ASV/pegIFN/RBV regimen: 3 (18.8%) with cirrhosis and 13 (7.5%) without cirrhosis

Resistance

Genotypic and phenotypic assays were performed in all ASV studies to identify the individual and combinations of substitutions known to confer resistance to specific antiviral agents. The impact to certain baseline NS5A and NS3 polymorphisms and IL-28B (RS12979860) GT on virologic response appeared to be treatment specific. Baseline NS5A polymorphism at L31 and Y93H appeared to be associated with virologic failure in the DCV/ASV therapy in subjects infected with GT-1b, while baseline NS3-D168E appeared to

be associated with virologic failure to a lesser extent. The non-CC IL-28B (RS12979860) GT appeared to correlate more with virologic failures in subjects receiving a DAA add on to pegIFNα/RBV therapy. Baseline polymorphisms had no or minimal impact on SVR in the DCV QUAD regimen (confounded by small numbers of subjects failing treatment).

With the DCV/ASV and the QUAD regimen the majority of subjects with virologic failure who met the criteria for resistance testing had resistance associated substitutions to both DCV and ASV.

Once a subject failed a DCV/ASV regimen. Emergent NS5A RAVs generally persisted in the majority of subjects throughout the duration of the study (follow up Week 48), whereas NS3 RAVs were more likely to be replaced or partially replaced by baseline sequence during this time frame.

Post-marketing data

There is no post-marketing experience as the product has not been marketed in any country.

Evaluator's conclusions on safety

The all oral therapy of DCV (60 mg QD) in combination with ASV (100 mg BD) has a favourable safety and tolerability profile compared to the currently approved standard therapy regimens in HCV GT-1b subjects who are treatment naïve, treatment experienced, or ineligible/intolerant to IFN/RBV-based therapy including subjects with compensated cirrhosis and the elderly.

The adverse events (AEs) reported for PegIFNα/RBV or TVR or BOC plus pegIFNα/RBV such as haematologic disorders (anaemia, neutropenia and thrombocytopaenia), psychiatric disorders (depression), flu like symptoms, rash and anorectal disorders) were reported infrequently with the DCV/ASV regimen.

The major AE for the combination is ALT/AST elevations, which appears to be due to both ASV and DCV components. Concurrent (within ±4 weeks of each other) Grade 3/4 ALT and Grade 3/4 AST laboratory abnormalities were reported in 2.9% of DCV/ASV-treated subjects. The events appeared to be easily monitored and readily corrected after cessation of study therapy.

The safety profile of the DCV Quad regimen (DCV/ASV in combination with pegIFNα/RBV) in HCV GT 1 or 4 subjects who failed previous IFN/RBV-based therapy, was similar to that reported historically with pegIFNα/RBV alone (that is, Grade 3 to 4 haematologic abnormalities and other AEs characteristic of pegIFNα/RBV therapy), with the exception of similar elevated transaminase levels as observed in the other ASV studies.

First round benefit-risk assessment

First round assessment of benefits

The benefits of asunaprevir in the proposed usage are:

- High rates of SVR12 (and SVR24) in patients infected with HCV GT-1b treated with ASV in combination with DCV treated for 24 weeks:
  - Treatment naïve: 90.6% (184/205)
  - Prior non-responders to pegIFNα or IFNβ/RBV: 80.5% to 90.9%
  - PegIFNα/RBV intolerant/ineligible subjects: 63.6% to 82.6%

- High rates of SVR12 in prior non-responders (partial and null responders) with:
  - GT-1: 93% (330/354) and 95% (19/20)
  - GT-4: 100% (44/44)
- Similar rates were seen across various baseline factors including males and females, patients ≥65 and <65 years, with and without cirrhosis and HCV RNA ≥ 800,000 IU/mL and < 800,000 IU/mL and subjects with IL28B and non-CC genotypes
- There were no deaths attributable to ASV and low rates of serious AEs (SAEs) and AEs of increased hepatic transaminases were generally reversible on discontinuation and most patients with increases achieved SVR12

First round assessment of risks

The risks of asunaprevir in the proposed usage are:

- Increases in hepatic transaminases were reported across all treatment groups
- Increased risk of Grade 3/4 transaminase elevations in combination with DCV

First round assessment of benefit-risk balance

The benefit-risk balance of asunaprevir, given the proposed usage, is favourable.

First round recommendation regarding authorisation

Based on the clinical efficacy and safety data provided by the sponsor it is recommended that asunaprevir be approved.

Clinical questions

No clinical questions were raised.

Second round evaluation of clinical data submitted in response to questions

Despite no questions being raised by the clinical evaluator, the sponsor has provided 25 pages of comments on the first round evaluation. Some of the comments are duplicated from those provided for the daclatasvir evaluation. As these issues were dealt with in that evaluation they have not been repeated in detail here. The sponsor has provided some important new data on the safety of ASV which is relevant to the recommendations in the Product Information for Sunvepra.

Safety

The sponsor has provided new information on the safety of ASV in relation to the following:

- A new review of the hepatic safety based on the data in the submission as well as data from studies that were ongoing at the time of the submission
- A new recommendation for ASV dose reduction to once daily dosing for patients with severe renal impairment not receiving haemodialysis based on a new study of a fixed dose combination of DCV/ASV and beclabuvir (Study AI443110)

Hepatic safety

Preliminary hepatic safety data are briefly presented for 2 hepatic cases of clinical interest from ongoing studies in the DCV/ASV/BCV (DCV 3DAA) clinical program. The combination regimen includes DCV, a HCV NS5A replication complex inhibitor, ASV, a HCV NS3/4A protease inhibitor, and BCV (BMS-791325), a HCV NS5B thumb 1 non-nucleoside polymerase inhibitor.

Ongoing DCV 3DAA studies include:

- Three global studies conducted in the United States (US), France, Canada, and Australia:
  - **AI443102**: A Phase III, two-cohort (treatment naïve and treatment experienced), open label two-arm study comparing DCV, ASV, and BCV (DCV/ASV/BCV) administered as a fixed dose combination (FDC) tablet BD versus historical control in 416 randomised subjects with GT-1 HCV infection without cirrhosis. All subjects received DCV/ASV/BCV FDC BD for 12 weeks and were followed for 24 weeks post treatment. GT-1b enrolment was capped at 40%.
  - **AI443113**: A Phase III, two-cohort (treatment naïve and treatment experienced), open label, four-arm, blinded placebo-controlled RBV study comparing DCV/ASV/BCV FDC BD administered with or without RBV in 202 randomised subjects with GT-1 HCV infection and compensated cirrhosis. All subjects received DCV/ASV/BCV BD with or without RBV for 12 weeks and were followed for 24 weeks post treatment. Enrolment was capped at approximately40% for GT-1b subjects and at 100 for treatment experienced subjects.
  - **AI443014**: A Phase II open label proof of concept study assessing single agent daclatasvir (DCV 60 mg QD or 30 mg BD) in combination with asunaprevir (ASV 200 mg BD) and BMS-791325 75 mg or 150 mg, administered for 12 or 24 weeks in 320 subjects. Subjects had GT-1 (n=299/320) or GT-4 (n=21/320) HCV infection were treatment naïve (n=274/320) or null responders to previous pegIFNα/RBV treatment (n=46/320) and were not cirrhotic (n=300/320) or had compensated cirrhosis (n=20/320). All subjects were followed for 48 weeks post treatment.
- One ongoing DCV 3DAA study was conducted in Japan:
  - **AI443117**: A Phase III two-cohort study. Cohort 1 is a double blind, two-arm comparison of DCV 3DAA for 12 weeks versus DCV/ASV for 24 weeks in treatment naïve subjects with GT-1b HCV infection (n = 216 planned to be randomised 1:1); GT-1a subjects in Cohort 1 were not randomised but received open label DCV 3DAA. Cohort 2 is an open label, single-arm study of DCV 3DAA for 12 weeks in IFN experienced subjects with GT-1a/1b (n = 60) planned). All subjects are to be followed for 24 weeks post treatment. Approximately 20% of compensated cirrhotics were enrolled.

From these ongoing studies, 2 cases of potential drug-induced liver injury (pDILI) were reported. One patient developed Grade 4 abnormal AST/ALT elevation on Day 43 of treatment but returned to normal with cessation of study drugs. The other patient had study drug ceased on Day 42 when he presented with jaundice and was hospitalised due to hyperbilirubinaemia (Grade 4), AST increased (Grade 4), ALT increased (Grade 4), alkaline phosphatase (ALP) increased (Grade 1). The patient experienced clinical signs of hepatic encephalopathy (asterixis) which was resolving but not normal at time of follow up.

The conclusions of the sponsor were:

- *When ASV was combined with DCV ± pegIFNα/RBV), ALT elevations were observed, which are associated with ASV use.*

- *In general, these ALT elevations to date have been reversible after study drug has been discontinued.*
- *Infrequently, these ALT elevations are associated with increased bilirubin (subjects meeting biochemical criteria for Hy's law or pDILI criteria) without clinical evidence of hepatic decompensation. However, one case of a subject with severe liver injury, who exhibited evidence of hepatic encephalopathy, has been reported among subjects receiving HCV 3DAA (DCV/ASV/BCV); further evaluation of this case is ongoing.*

Given the above, patients receiving DCV/ASV or DCV/ASV/pegIFNα/RBV, should have close monitoring of liver enzymes: at least once every 2 weeks for the initial 12 weeks of treatment and every 4 weeks thereafter until completion of therapy. Any upward trend in ALT/AST levels warrants more frequent monitoring. If on-treatment elevations in ALT levels 10 times the upper limit of normal (ULN) or greater occur, treatment should be discontinued immediately and not be resumed.

It is noted that this recommendation for monitoring is now included in the revised PI.

Renal safety

In the submission and the clinical evaluation report there was no recommendation for dose adjustment in subjects with any degree of renal impairment based on the results of the PK study (AI447033) in normal subjects and those with end stage renal disease on dialysis. The sponsor has now provided the synopsis and brief summary of a new study (AI443110) of the DCV/ASV/BCV (DCV 3DAA) combination. In this study the effect of renal impairment on the PK of all 3 components was evaluated.

Study AI443110 was an open label, multi-dose study that assessed the PK of the DCV 3DAA FDC tablet (that is, DCV 30 mg/ASV 200 mg/ BCV 75 mg) administered BD to HCV uninfected subjects with normal renal function and various degrees of renal impairment (normal, mild moderate, severe and end-stage renal disease (ESRD)) for 10 to 12 days. The sponsor reports the results as showing:

The PK properties of ASV were studied across a total of 41 subjects with normal renal function (N = 8), mild renal impairment (N = 9), moderate renal impairment (N = 8), severe renal impairment not on haemodialysis (N = 8), and ESRD on haemodialysis (N = 8) groups. Compared with subjects with normal renal function, the C_{max} of ASV was estimated to be 29%, 65% and 88% higher, and the AUC of ASV was estimated to be 33%, 76% and 109% higher in subjects with mild, moderate and severe renal impairment, respectively. Asunaprevir unbound C_{max} was estimated to be 37%, 87% and 119% higher, and ASV unbound AUC was estimated to be 41%, 99% and 137% higher for subjects with mild, moderate and severe renal impairment, respectively, compared with subjects with normal renal function. Subjects with ESRD requiring haemodialysis had an 11% decrease in ASV C_{max} and a 16% decrease in AUC soon after haemodialysis compared with subjects with normal renal function. Asunaprevir unbound C_{max} and AUC decreased 2% and 6%, respectively, soon after haemodialysis in subjects with ESRD requiring haemodialysis compared with subjects with normal renal function.

As a result of this study the sponsor is now recommending that for patients with severe renal impairment (creatinine clearance (CrCl) less than 30 mL/min) who are not receiving haemodialysis, the recommended dose of ASV should be reduced to 100 mg once daily. No dose adjustment of ASV is recommended for those patients with mild or moderate renal impairment (CrCl 30 mL/min or greater) or those receiving haemodialysis.

In light of this new study the sponsor's recommendation for the dose reduction is supported.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly the benefits of asunaprevir are unchanged from those identified in the First round evaluation.

Second round assessment of benefit-risk balance

No new clinical information was submitted in response to questions. New information was provided on the safety of asunaprevir. After consideration of this new data the risks of asunaprevir are unchanged from those identified in the First round evaluation.

Second round recommendation regarding authorisation

Based on the review of the new information provided by the sponsor in response to the First round evaluation the recommendation is unchanged from that stated above, that is, asunaprevir is recommended for approval as requested by the sponsor (Table 15):

Table 15: Recommended Regimens for SUNVEPRA 100 mg Twice Daily Combination Therapy

HCV Genotype [a]	Treatment	Duration
Genotype 1b	Sunvepra and Daklinza	24 weeks
Genotype 1 & 4	Sunvepra, Daklinza, peginterferon alfa and ribavirin	24 weeks

a Treatment-naïve or failed prior treatment with peginterferon alfa/ribavirin

This approval matches the recommended approval for daclatasvir.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Asunaprevir Company Core RMP (version 1, dated 7 March 2014, data lock point 16 December 2013) and Australian-specific Annex (version 1, dated 31 March 2014).

Safety specification

The sponsor provided a summary of Ongoing safety concerns which are shown at Table 16.

Table 16: Summary of Ongoing safety concerns

Important identified risk	Hepatic toxicity
Important potential risks	Drug-induced pyrexia Development of drug resistance

Drug interactions	Inducers of CYP3A Inhibitors of CYP3A Inhibitors of OATPs Substrates of CYP2D6 Substrates of P-gp Substrates of OATP1B1, OATP2B1 and OATP1B3 Combined hormonal oral contraceptives (estrogens and progesterones)
Missing information	Moderate/severe hepatic impairment Decompensated liver disease Use during pregnancy and lactation Use in children and adolescents (<18 years of age) Post-liver transplant HIV/HCV co-infection HBV/HCV co-infection

Pharmacovigilance plan

Routine pharmacovigilance is proposed to monitor the one important identified risk, two important potential risks and seven items of missing information. No additional pharmacovigilance activities are proposed.

Risk minimisation activities

Routine risk minimisation is proposed for the Ongoing safety concerns. No additional risk minimisation activities are proposed.

Reconciliation of issues outlined in the RMP report

Table 17 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 17: Reconciliation of issues outlined in the RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for further information and/or the nonclinical and clinical evaluation reports respectively. It is	*The sponsor confirms that safety considerations raised by the nonclinical and clinical evaluators through the nonclinical and clinical evaluation reports respectively have been assessed, and no additions/amendments to the Risk Management Plan have been made as result of these TGA evaluations.*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.		
2. 'Patients who have failed prior NS3 protease inhibitor treatment' should be added as an additional item of missing information.	*BMS will add 'Patients who have failed prior NS3 protease inhibitor treatment' to the ASV CCRMP, as an additional item of missing information.* *The updated ASV CCRMP will be submitted to TGA as soon as available.*	The TGA has received the updated CCRMP/ASA. This is acceptable.
3. The sponsor is requested to add the following risks to the summary of Ongoing safety concerns or alternatively provide a justification as to why they should not be included: Anaemia (class effect), Neutropaenia (class effect), Thrombocytopaenia (class effect), Severe skin reactions including Stevens-Johnson Syndrome (class effect), Increased risk of psychiatric disorders including depression and anxiety when used in combination therapy.	The sponsor has disagreed with this recommendation and provided the requested justification.	The sponsor's justification for not including these risks is acceptable at this time.
4. Missing information 'Post-liver transplant'	*The sponsor agrees to amend the ASV CCRMP for the safety concern,*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
should be amended to 'Pre, peri- and post-liver transplant'.	*Limited or Missing Information 'Use in Post-liver transplant' to 'Use in pre-, peri- and post-liver transplant patients'.*	
5. The post-authorisation efficacy studies are not strictly considered part of the pharmacovigilance plan as they are not designed to investigate nor are attributed to a particular safety concern. Despite their lack of utility as targeted pharmacovigilance these studies may contribute extra information regarding the safety profile of asunaprevir and such safety information should be included in PSURs and submitted to the TGA in an appropriate manner.	*BMS agrees that any safety information obtained through post-authorisation efficacy studies will be included in the PSUR and submitted to the TGA in an appropriate manner.*	This is acceptable.
6. The sponsor is requested to provide a plan for anti-viral resistance monitoring due to the identified low barrier to resistance with NS3 protease inhibitors. This plan should be documented in the pharmacovigilance section of the RMP and/or ASA.	*The resistance barrier to NS3 protease inhibitors when combined with other direct-acting antiviral agents of different mechanisms of action is increased, compared to when dosing NS3 protease inhibitors in monotherapy. In an integrated analysis of Phase II and Phase III clinical data from the daclatasvir+asunaprevir DUAL regimen studies AI447011, AI447017, AI447026, and AI447028, assessing the association of baseline NS3 polymorphisms on response rates in patients infected with HCV genotype 1b and treated with daclatasvir plus asunaprevir, there did not appear to be any significant impact. The most pertinent NS3 polymorphism is at D168 since substitutions at this amino acid emerge in the majority of patients not achieving SVR (94.1% [111/118 virologic failures*	The sponsor's plan, including the follow-up study, is acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	meeting the criteria for resistance testing (HCV RNA ≥1000 IU/mL)]). The low prevalence of NS3 D168 polymorphisms limited their impact on response rates. In the integrated resistance analysis of patients with the baseline NS3-D168E, *50% achieved SVR; however, its prevalence was <1%, therefore its impact on the overall SVR rate was not observed; 85.0% in patients without baseline NS3-D168E versus 84.8% for the study.* *For patients not achieving SVR to ASV, emergent NS3 D168 variants have been shown to be replaced by wild-type sequence when monitored for ≥36 weeks post-treatment. In the two Phase II studies AI447011 and AI447017, emergent NS3-D168 variants were replaced by baseline sequence in 88.9% (8/9) of patient-derived NS3 sequences from virologic failures by population based sequencing. There is an ongoing 3 year long term follow-up study (AI444046) where the persistence of emergent D168 variants will be described in more detail. Results of this study will be discussed in the PSUR, and any significant safety findings will be reflected in the CCRMP and CCDS as warranted. Any significant safety findings will be submitted to the TGA in an appropriate manner.*	
7. A pharmacovigilance plan should be formulated for all risks added and should be detailed in an update to the RMP and/or ASA.	*The RMP evaluator's recommendations have been noted by the sponsor.* *See responses to RMP questions 2, 3 and 4.* *Routine pharmacovigilance will be utilised to assess missing information 'prior NS3 protease inhibitor failures'. The PI states that 'The safety and efficacy of*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	Sunvepra combination therapy in the treatment of patients who are pre-, peri-, or post-liver transplant have not been established.' Routine pharmacovigilance will be utilized to monitor the use of ASV in transplant patients.	
8. A risk minimisation plan should be formulated for all risks added and should be detailed in an update to the RMP and/or ASA.	*The RMP evaluator's recommendations have been noted by the Sponsor.* *See responses to RMP questions 2, 3 and 4.* *Risk minimization for missing information 'prior NS3 protease inhibitors' currently consists of monitoring to determine the effects of ASV treatment of patients who have failed prior NS3 PI therapy; further actions may be taken if it is determined that this represents a safety risk. Risk minimisation for transplant patients is represented by the information presented in the Product Information, indicating that there is no data on use of ASV in pre-, peri- or post-liver transplant patients.*	This is acceptable.
9. The PI should contraindicate use of asunaprevir in patients who are hypersensitive to the active substance or its excipients.	*The statement 'SUNVEPRA is contraindicated in patients with previously demonstrated hypersensitivity to asunaprevir or any component of the product' has been added to the CONTRAINDICATIONS section of the proposed PI.*	This is acceptable from a RMP perspective and is subject to final consideration by the Delegate.
10. The proposed PI contains advice that when co-administered with asunaprevir, a combination hormonal oral contraceptive should contain at least 30 µg of ethinyl estradiol to offset the reduction in exposure caused by the drug-drug	*The RMP evaluator's recommendation has been noted. In accordance with this request, in the PRECAUTIONS section of the Sunvepra PI, a new subsection Oral Contraceptives, detailing the recommendation for dosing of oral contraceptives when administered with ASV and DCV, has been added.*	This is acceptable from a RMP perspective and is subject to final consideration by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
interaction. This advice is found in the 'Use in Pregnancy' and 'Drug Interactions' sections. Given its clinical importance, the prevalence of oral contraceptive use and the requirement to use effective contraception during asunaprevir combination treatment it is recommended to the Delegate that such information is included as a separate precaution in the PI.		
11. The precaution 'Liver Enzymes' contains advice to monitor enzymes 'periodically during Sunvepra therapy. If clinically significant elevations in ALT levels ≥ 10 x upper limit of normal (ULN) are observed, treatment should be discontinued immediately and not be resumed'. The sponsor should confirm which guidelines this recommendation is based on, if any. Furthermore it is recommended to the Delegate that this precaution be expanded to advise that if any increase is seen in liver enzymes they should be monitored closely to document resolution. The frequency of liver enzyme testing should be guided by clinical judgement.	*The sponsor has completed hepatic safety analyses of data from regimens that include ASV in Studies in the BMS HCV DAA clinical development program evaluating the regimens that include ASV. The overview of these analyses is provided in Module 5.3.5.3 - Overview of Hepatic Safety (DCN 930085333).* *Based on these analyses, labelling recommendations are proposed for monitoring of liver enzymes. The Sunvepra PI provided along with this response has been revised to include the updated monitoring recommendations.* *The updated Sunvepra PI is provided (clean copy and changes highlighted).*	The evaluator notes the changes, which are subject to final consideration by the Delegate.
12. Given the prevalence of HBV and/or HIV co-infection with HCV the PI should contain a specific	*The sponsor agrees to add the following subsection to the PRECAUTIONS section of the proposed PI for Sunvepra:*	This is acceptable from a RMP perspective

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
precaution providing information that the safety and efficacy of asunaprevir have not been established in HCV patients co-infected with HBV and/or HIV.	*Co-infection with Human Immunodeficiency Virus (HIV) or Hepatitis B Virus (HBV)* *The safety and efficacy of SUNVEPRA in the treatment of chronic HCV infection in patients who are co-infected with HIV or HBV have not been established.*	and is subject to final consideration by the Delegate.
13. For clarity the precaution 'Liver Transplant Patients' should align with the information in table 5.1-1 of the CCRMP that 'the safety and efficacy of asunaprevir in the treatment of chronic HCV in patients who are pre-, peri-, or post-liver transplant have not been established'.	*The sponsor agrees to revise the subsection of PRECAUTIONS titled 'Liver Transplant Patients' in the proposed PI to align with Table 5.1-1 of the ASV CCRMP.*	This is acceptable from a RMP perspective and is subject to final consideration by the Delegate.
14. Any changes to PI statements as a result of the evaluation process should be updated accordingly in ASA Table 4-1.	*The sponsor will update Table 4-1 in the ASA v2.0 to reflect changes in the proposed PI.*	This is acceptable.
15. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information (CMI) document be revised as necessary to reflect changes made to the PI during the evaluation process.	*The sponsor notes the evaluator's comments that the Consumer Medicine Information (CMI) be updated to reflect changes made to the PI.* *Based on the Sunvepra PI updates proposed in this response, the Sunvepra CMI has been updated accordingly.* *The updated Sunvepra CMI is provided (clean copy and changes highlighted).*	This is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has adequately addressed all of the issues identified in the RMP evaluation report. However there is an additional recommendation based on the sponsor's response (see below).

Outstanding issues

Issues in relation to the RMP evaluation report

There are no outstanding issues in relation to the RMP evaluation report for this submission.

Additional recommendation based on the sponsor's response

According to Table 4-1 in the revised Australia Specific Annex (version 2), the following PI precaution is proposed for the new item of missing information 'Patients who failed prior treatment with NS3 protease inhibitors': '*SUNVEPRA has not been studied in patients who have previously failed therapy with a treatment regimen that includes SUNVEPRA or other HCV NS3/4A protease inhibitors*'. This precaution does not appear in the draft PI and should be included.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

Asunaprevir Company Core RMP (version 1, dated 7 March 2014, data lock point 16 December 2013) and Australia Specific Annex (version 1, dated 31 March 2014) has been superseded by: Asunaprevir Company Core RMP (version 2, dated 22 December 2014, data lock point 15 November 2014) + Australia Specific Annex (version 2, dated 29 December 2014). A summary of the changes made are shown in Table 18.

Table 18: Summary of key changes made to CCRMP and ASA

Summary of key changes between CCRMP (v 1)/ASA (v 1) and CCRMP (v 2)/ASA(v 2)	
Safety specification	• New important identified risk: 'Drug-drug interactions' • New important potential risk: 'Increased risk of hepatic adverse events in patients with severe renal impairment not receiving hemodialysis' • New missing information: 'Patients who failed prior treatment with NS3 protease inhibitors' • Amended missing information: 'Use in liver transplant patients' has been changed to 'Use in pre-, peri-, and post-liver transplant patients'.
Pharmacovigilance activities	Routine pharmacovigilance is proposed for the newly added risks.
Risk minimisation activities	Routine risk minimisation (ie product labelling statements) is proposed for the newly added risks.
ASA	Changes have been made to the PI text proposed for Australia in response to TGA evaluation reports.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document or not included inadvertently or otherwise. The suggesting wording is:

Implement Asunaprevir Company Core RMP (version 2, dated 22 December 2014, data lock point 15 November 2014) with Australia Specific Annex (version 2, dated 29 December 2014) 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

Registration of the proposed 'Sunvepra' asunaprevir 100mg soft gelatin capsules is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved.

Nonclinical

There are nonclinical objections to the registration of asunaprevir.

The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to GLP, and with high exposure margins employed.

In vitro, asunaprevir inhibited the activity of purified NS3/4A protease enzyme complexes from HCV strains of genotypes 1b, 1a, 6a, 4a, 5a, and with a lower potency 2a, 2b, and 3a. Except for genotype 2b, asunaprevir was more potent than telaprevir.

Asunaprevir is unlikely to be active against genotype 2a, 2b and 3a at the proposed clinical dose.

Based on findings the relevant nonclinical studies, asunaprevir is not expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use.

Absorption of asunaprevir was variable within species following oral administration of asunaprevir solution, with peak concentration occurring with the first few (1 to 6) h. Plasma protein binding was high in all nonclinical species and humans.

Inducers/inhibitors of P glycoprotein, OATP 1B1 and 2B1 or CYP3A may alter the systemic exposure to asunaprevir. In vitro studies indicate asunaprevir has the potential to affect the disposition of co-administered drugs that are substrates for CYP2D6, CYP3A and UGT1A1. There is some potential for asunaprevir and daclatasvir to affect exposure to each other.

The liver was a target organ for toxicity in rats and dogs but only at very high multiples of exposure.

A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (mice and rabbits) and pre/postnatal development (rats). There were no drug related findings. Placental transfer and transfer of drug related material into milk were shown in rats.

Pregnancy Category B1 is acceptable for asunaprevir. When used in combination with daclatasvir (B3) or daclatasvir and peginterferon alfa and ribavirin (Category X), the most restrictive category is applicable.

Asunaprevir was not genotoxic in the standard battery of tests. Asunaprevir is unlikely to pose a mutagenic, clastogenic or carcinogenic risk to humans.

No particular targets for toxicity at clinically relevant exposure levels were identified in a juvenile toxicity study or in general repeat-dose toxicity studies.

Asunaprevir did not produce skin irritation and did not cause skin sensitisation. Asunaprevir is potentially phototoxic and an ocular irritant.

Clinical

Pharmacology

The submitted pharmacokinetic studies are summarised in Attachment 2.

Absolute bioavailability was estimated to be 9.3%, with the proposed softgel capsule formulation**.** With the soft gel capsule formulation proposed for marketing, co-administration with a high fat meal resulted in increased bioavailability (AUC) by approximately 20%, with a 34% increase in C_{max}. T_{max} was reduced by about 1.0 h. In ascending dose studies, increases in ASV AUC and C_{max} were more than proportional to the increases in dose. Following IV use of [^{14}C] ASV, volume of distribution at steady state was estimated to be 194 litres suggesting extensive tissue distribution. In blood samples collected at trough and at T_{max}, protein binding was >99%.

Only trace amounts of an orally administered dose of ASV are recovered in the urine, with most being recovered in the faeces. Most of the drug related material in faeces is the form of metabolites, with only 7.5% of the dose being unchanged ASV. These data indicate that metabolism is the major route of clearance for ASV.

In clinical interaction studies, co-administration of ASV with agents that inhibited CYP3A4 resulted in increased ASV systemic exposure; for example ketoconazole and ritonavir. Co-administration of ASV with rifampicin, an agent that induces CYP3A4, resulted in some decrease in ASV systemic exposure.

Following IV [^{14}C] ASV, total clearance was estimated to be 49.5 L/hr (825 mL/min). The $t_{1/2}$ was estimated to be 13.7 h. Following multiple doses of the soft gel capsule formulation at the 100 mg BD, the mean t1/2 across studies was 17.7 h.

Subjects with moderate or severe hepatic impairment had markedly increased systemic exposure to ASV compared to healthy volunteers (32 fold increase in AUC for Child-Pugh class C and 9.8 fold increase for class B).[33] Subjects with mild (Class A) hepatic impairment did not have increased exposure. In the draft PI, ASV is contraindicated in subjects with moderate to severe hepatic impairment. No dosage reduction is recommended for subjects with mild hepatic impairment.

[33] The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. It is used to determine the prognosis as well as the required strength of treatment and the necessity of liver transplantation. Chronic liver disease is classified into Child-Pugh class A to C as follows:

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Patients with end stage renal disease on haemodialysis did not have an increased exposure to ASV based on AUC and C_{min} values. Mean C_{max} values were increased by approximately 25%. No dosage adjustment was initially recommended in the draft PI for subjects with impaired renal function. The second round clinical evaluation evaluated a new study (A144311) which supported a recommendation for dose reduction to 100 mg QD in patients with severe renal impairment not receiving dialysis.

No dedicated studies were conducted examining the effect of age and gender on ASV PK. In a population PK analysis, age and female gender was identified as a significant covariate. However, the magnitude of any effect on ASV exposure was small and unlikely to be clinically significant.
PK drug interactions are discussed in Attachment 2. Of note, a number of contraindications are listed in the draft ASV PI as results of drug interactions. ASV is contraindicated

- in patients receiving moderate or strong CYP3A4 inhibitors
- in patients receiving moderate or strong CYP3A4 inducer
- in patients receiving strong inhibitors of OAT-1B1/2B1
- in patients receiving CYP2D6 substrates with a narrow therapeutic range

ASV had no effect on the PK of substrates for CYP2C9 (losartan), CYP2C19 (omeprazole), and CYP1A2 (caffeine).Nonclinical data suggested that ASV inhibited P-gp. This was confirmed in a clinical study where ASV increased digoxin AUC by 30%. The draft PI recommends monitoring of serum digoxin concentrations when co-prescribed with ASV. In vitro, ASV was an inhibitor of OATP-1B1, 1B3, 2B1 and breast cancer resistance protein (BCRP). In a clinical study, ASV caused increased systemic exposure to rosuvastatin (an OATP1B1, OATP1B3 and BCRP substrate).

Dose selection

In the Phase II studies, the following ASV doses were tested: 200 mg QD, 200 mg BD and 600 mg BD. In Study AI447016 in non-Japanese subjects, ASV 200 mg BD, ASV 600 mg QD, and ASV 600 mg BD doses were evaluated. All 3 studies (AI447011, AI447016, and AI447017) were conducted using the tablet formulation of ASV. Although all these ASV doses were generally well tolerated, a trend in the frequency and magnitude of ALT and AST elevations was observed at ASV doses > 200 mg BD of the tablet formulation and this trend was associated with greater ASV exposure. The observed LFT data and high response rates in Phase II studies supported the prediction that ASV 200 mg tablet BD offered the best balance of safety and efficacy.

A 100 mg BD soft gel ASV capsule formulation was selected as Phase III formulation based on the results from a relative bioavailability study that indicated the bioavailability of the soft gel capsule was approximately 2 fold higher compared with the tablet administered with food (Study AI447043). Moreover, the soft gel capsule formulation mitigated the significant food effect observed with the tablet formulation. Based on these data, the soft gel ASV capsule at a dose of 100 mg BD administered either with or without meals was expected to approximate the AUC of the ASV 200 mg tablet administered with food in Phase II studies

Efficacy

The efficacy studies for the requested regimens of combination therapy were all common to the DCV submission and have been assessed in the DCV clinical evaluation report. They are cross referenced to that report and only brief summaries are provided in this report.

Dual regimen (ASV/DCV)

Two pivotal and two supportive studies were included to support for ASV/DCV combination. These have been evaluated in the DCV clinical evaluation report.[34] Brief summaries are provided here.

Pivotal efficacy studies

Study AI447028 was a randomised, multicentre, parallel group study with 3 cohorts of subjects with HCV GT-1b infection. The study included treatment naïve subjects (N=203), prior pegIFNα/RBV non-responders (null and partial responders, N=205) and IFN intolerant/ineligible subjects (N=235). Overall 206/643 (32.0%) had compensated cirrhosis at baseline. Subjects in the treatment naïve cohort were randomised 2:1 to receive DCV 60 mg QD and ASV soft gel capsule 100 mg BD for 24 weeks and then followed for 24 weeks post treatment or placebo for 12 weeks (and then enrolled into another study of DCV/ASV open label for 24 weeks). There was no randomisation of the other 2 cohorts (all subjects received DCV 60 mg QD and ASV 100 mg BD).

Study AI447026 was an open label study in 2 groups of Japanese subjects with HCV GT-1b infection. The study included prior pegIFNα/RBV or IFNβ/RBV non-responders (null and partial responders N=87) or IFN intolerant/ineligible subjects (N=135). Overall, 22/222 (9.9%) subjects had compensated cirrhosis at baseline. All subjects were treated with DCV/ASV therapy (DCV 60 mg QD and ASV 100 mg soft gel capsule BD) for 24 weeks and followed for 24 weeks post treatment.

Supportive efficacy studies

Study AI447017 was an open label study in Japanese subjects with HCV GT-1 infection. The study included pegIFNα/RBV prior null responders (N=21) and IFN intolerant/ineligible subjects (N=22). Subjects with baseline cirrhosis were excluded. All subjects received DCV 60 mg QD and ASV 600 mg or 200 mg tablets BD for 24 weeks. Subjects with virologic failure were followed for 48 weeks post treatment and all other subjects were followed for 24 weeks post treatment.

Study AI447011 included groups who received DUAL (DCV/ASV) or QUAD (DCV+ASV+ pegIFNα/RBV) regimens. It was an open label study in pegIFNα/RBV prior null responders (N=122) with HCV GT-1a or 1b. Subjects with cirrhosis were excluded. In the DCV/ASV group, 49 subjects received DCV 60 mg and ASV 600 mg tablet BD (N=11) or 200 mg tablet BD (N=18) or 200 mg tablet QD (N=20). The treatment period was 24 weeks and subjects were then followed for 48 weeks post treatment

Table 19: Efficacy of DUAL regimen in the pivotal and supportive studies

Endpoint [b]	Virologic Response: Number of Subjects (%) [95% CI [a]]			
	Pivotal AI447028[c]	Pivotal AI447026[c]	Supportive AI447017 [d, e]	Supportive AI447011 [d, f]
Treatment naïve				
SVR12	184/205 (90.6) [86.6, 94.6]	NA	NA	NA

[34] Attachment 2 AusPAR for Daklinza.

Endpoint [b]	Virologic Response: Number of Subjects (%) [95% CI [a]]			
SVR24	155/203 (76.4) [f]	NA	NA	NA
Ineligible/intolerants				
SVR12	194/235 (82.6) [77.7 , 87.4]	119/135 (88.1) [82.7 , 93.6]	14/22 (63.6) [43.5, 83.7]	
SVR24	168/235 (71.5) [g]	118/135 (87.4)	14/22 (63.6)	NA
Prior non-responders				
SVR12	169/205 (82.4) [77.2 , 87.6]	70/87 (80.5) [72.1, 88.8]	10/11 (90.9) (73.9, 100.0]	15/18 (83.3) [66.1, 100]
SVR24	152/205 (74.1) [f]	70/87 (80.5)	10/11 (90.9)	16/18 (88.9)

a Confidence intervals presented for planned analyses; b On-treatment virologic rates; c Included null and partial responders (all subjects infected with GT-1b); d Includes null responders only; e Subjects in Cohort 2 (prior null responders; N = 11) and Cohort 3/4 (ineligible-naïve/intolerants; N = 22) treated in Expansion Phase of study for 24 weeks at recommended dose; f Subjects in Cohort 1A (prior null responders, N = 18) treated in Expansion Phase of study for 24 weeks at recommended dose; g AI447028 CSR completed for primary endpoint (SVR12). SVR24 rates are based on database as of 22-Nov-2013 in which 83 subjects remained in follow-up.

In treatment naïve HCV GT-1b-infected subjects, the SVR12 rates were 90.6% (95% CI: 86.6, 94.6) in AI447028.

In HCV GT-1b-infected patients who were IFN/RBV-based therapy intolerant/ineligible, the SVR12 rates was 82.6% (95% CI: 77.7, 87.4) in AI447028, 88.1% (95% CI: 82.7, 93.6) in AI447026 and 63.6% (95% CI: 43.5, 83.7) in AI447017.

In HCV GT-1b-infected patients who were prior non-responders, the SVR12 rates achieved were 82.4% (95% CI: 77.2, 87.6) in Study AI447028, 80.5% (95% CI: 72.1, 88.8) in AI447026, and 83.3% (95% CI: 66.1, 100.0) in AI447011.

Further:

- In GT-1b prior null responders, the SVR12 rates were 82.4% in AI447028, 81.3% in AI447026 and 83.3% in AI447011.
- In GT-1b prior partial responders, the SVR12 rates were 82.1% in AI447028 and 77.8% in AI447026.

Overall, in DCV/ASV-treated subjects, SVR12 rates were comparable across all subgroups of baseline host factors including age (<65 and ≥65 years), gender, cirrhosis status, IL-28B polymorphism, prior treatment history (null or partial response to HCV therapy, or IFN/RBV-based therapy intolerant/ineligible) and viral factors (such as viral load). The rates of Viral Breakthrough were low (4 to 13%).

QUAD regimen (ASV+DCV+pegIFNα+RBV)

Pivotal studies

Study A1447029 was a Phase III, open label, single arm study with ASV and DCV plus pegIFNα/RBV (QUAD) in adults with chronic HCV GT1 or 4 infection who were partial or null responders to treatment with peginterferon alfa 2a or 2b and ribavirin. The primary efficacy endpoint was the SVR12.
There were 354 subjects with HCV GT-1 (89%) and 44 subjects with GT-4(11%). The 398 treated subjects had a median age of 53 years; 69% were male; 76% were White, 12% were Asian, 9% were Black; 9% were Hispanic/Latino. The mean baseline HCV RNA level was 6.46 log10 IU/mL; 23% of subjects had compensated cirrhosis (Child-Pugh A); 91% of subjects had non-CC IL28B genotype.
Subjects received DCV 60 mg QD, ASV100 mg BD, peginterferon alfa 2a or 2b weekly injection, and ribavirin 1000 mg per day (body weight less than 75 kg) or 1200 mg per day (at least 75 kg) in two divided doses for 24 weeks followed by 24 weeks of follow-up after completion of treatment or early discontinuation.
Results for the primary efficacy outcome are presented in Table 20 below.

Table 20: Key efficacy results for Study A1447029

Study Information	Treatment Regimen	Number of Total Treated Subjects GT	Study Population Prior Non Responders (n)
Pivotal: AI447029	24 weeks	398	398
Phase 3	ASV: 100 mg[a] BID	GT-1a/1b (n=354)	
Global	DCV: 60 mg QD	GT-4 (n=44)	
Non-randomized[a], open-label	peg IFNα-2a/RBV		
Key Efficacy Results		SVR12	374/398 (94.0%)
		Virologic Breakthrough	11/398 (2.8%)
		Relapse	8/380 (2.1%)
		Missing Post Treatment Data	4/380 (1.1%)

The efficacy of QUAD regimen (DCV/ASV/peginterferon alfa/RBV) in HCV genotype 1 and 4 null responders indicates that this regimen is expected to be effective in HCV genotype 1 and 4 subjects who are treatment-naive.

Supportive study

Study AI447011 was an open label study. The aim of this Phase II proof-of-concept study (AI447011) was to combine DCV+ASV+/pegIFNα/RBV or RBV for up to 24 weeks in prior null responders to pegIFNα/RBV therapy. This study used an open label design to permit frequent examination of antiviral and safety data from a sentinel cohort of prior null responders (Group A receiving Dual therapy and Group B receiving Quad therapy) intended to inform the design of subsequent expansion cohorts receiving Dual (Groups A1

and A2) and Quad (20 subjects in Group B1 and 20 in Group B2) therapy. An additional group (Group B3) received DCV/ASV/RBV.

The QUAD therapy group comprised 51 subjects:

- B1: DCV 60 mg QD / ASV 200 mg tablet BD (N=20)
- B2: DCV 60mg QD/ ASV 200 mg tablet QD (N=21)
- B3: DCV 60 mg QD/ASV 600 mg tablet BD (N=10)

The treatment period was 24 weeks and subjects were then followed for 48 weeks post treatment.

Results for efficacy outcomes showed that the QUAD therapy produced high rates of virologic response in prior null responders with GT-1b and -1a.

SVR12 (Primary efficacy endpoint) were 95.0% in Group B1 and 95.2% in Group B2.

Virologic response rates during treatment (RVR[35], cEVR[36], EOTR[37]) and SVR12/SVR24 rates during follow-up were consistently high in both Group B1 and B2. Among subjects with HCV RNA results at follow-up Weeks 12 and 24, the concordance of SVR24 with SVR12 (based on the criteria HCV RNA < LLOQ, TND) was 100% in both Group B1 and B2.

Overall, for the QUAD regimen, the SVR12 rates achieved in:

- GT-1 prior non-responders were 330/354, 93.2% (95% CI: 90.6, 95.8) in AI447029 and 19/20, 95.0% (95% CI: 81.9, 99.5) in AI447011:
- GT-1 prior null responders, the SVR12 rates were 93.6% in AI447029 to 95.0% in AI447011
- GT-1 prior partial responders, the SVR12 rate was 91.7% in AI447029
- GT-4 prior non-responders, the SVR12 rate was 44/44, 100.0% (95% CI: 100.0, 100.0) in AI447029

SVR12 rates with the QUAD therapy were consistently high across all host factor subgroups (including age, gender, cirrhosis status, IL-28B polymorphism, prior null or partial response to HCV therapy) and viral factors (such as viral load). SVR12 rates with DCV QUAD therapy were minimally affected by baseline NS5A-L31, NS5A-Y93H and NS3-R155 polymorphisms and not affected by NS3-D168 polymorphisms.

Safety

The all oral therapy of DCV (60 mg QD) in combination with ASV (100 mg BD) has a favourable safety and tolerability profile compared to the currently approved standard therapy regimens in HCV GT-1b subjects who are treatment naïve, treatment experienced, or ineligible/intolerant to IFN/RBV-based therapy, including subjects with compensated cirrhosis and the elderly.

The AEs reported for PegIFNα/RBV or TVR or BOC plus pegIFNα/RBV such as haematologic disorders (anaemia, neutropenia and thrombocytopaenia), psychiatric disorders (depression), flu like symptoms, rash and anorectal disorders) were reported infrequently with the DCV/ASV regimen.

The major AE for the combination is ALT/AST elevations. The second round clinical evalaution accepts this appears to be due to the ASV component. Concurrent (within ±4 weeks of each other) Grade 3/4 ALT and Grade 3/4 AST laboratory abnormalities were

[35] Rapid viral response (RVR): an undetectable viral load after X4 weeks treatment (RVR-X).
[36] Complete early viral response: (EVR) undetectable viral load.
[37] End of treatment response (EOTR): undetectable viral load at the end of treatment.

reported in 2.9% of DCV/ASV-treated subjects. The events appeared to be easily monitored and readily corrected after cessation of study therapy.

The safety profile of the DCV Quad regimen (DCV/ASV in combination with pegIFNα/RBV) in HCV GT 1 or 4 subjects who failed previous IFN/RBV-based therapy, was similar to that reported historically with pegIFNα/RBV alone (that is, Grade 3 to 4 haematologic abnormalities and other AEs characteristic of pegIFNα/RBV therapy), with the exception of similar elevated transaminase levels as observed in the other ASV studies.

New safety information submitted

The sponsor has provided new information on the safety of ASV in relation to the following:

- A new review of the hepatic safety based on the data in the submission as well as data from studies that were ongoing at the time of the submission

Hepatic safety

Preliminary hepatic safety data are briefly presented for 2 hepatic cases of clinical interest from ongoing studies in the DCV/ASV/BCV (DCV 3DAA) clinical program. The combination regimen includes DCV, a HCV NS5A replication complex inhibitor, ASV, a HCV NS3/4A protease inhibitor, and BCV (BMS-791325), a HCV NS5B thumb 1 nonnucleoside polymerase inhibitor.

From these ongoing studies 2 further cases of pDILI were reported. One patient developed Grade 4 abnormal AST/ALT elevation on Day 43 of treatment but returned to normal with cessation of study drugs. The other patient had study drug ceased on Day 42 when the patient presented with jaundice and was hospitalised due to hyperbilirubinaemia (Grade 4), AST increased (Grade 4), ALT increased (Grade 4), ALP increased (Grade 1). The patient experienced clinical signs of hepatic encephalopathy (asterixis) which was resolving but not normal at time of follow up.

The conclusions of the sponsor were:

- *When ASV was combined with DCV ± pegIFNα/RBV), ALT elevations were observed, which are associated with ASV use.*
- *In general, these ALT elevations to date have been reversible after study drug has been discontinued.*
- *Infrequently, these ALT elevations are associated with increased bilirubin (subjects meeting biochemical criteria for Hy's law or pDILI criteria) without clinical evidence of hepatic decompensation. However, one case of a subject with severe liver injury, who exhibited evidence of hepatic encephalopathy, has been reported among subjects receiving HCV 3DAA (DCV/ASV/BCV); further evaluation of this case is ongoing.*

Given the above, patients receiving DCV/ASV or DCV/ASV/pegIFNα/RBV, should have close monitoring of liver enzymes: at least once every 2 weeks for the initial 12 weeks of treatment, and every 4 weeks thereafter until completion of therapy. Any upward trend in ALT/AST levels warrants more frequent monitoring. If on-treatment elevations in ALT levels 10 times ULN or greater occur, treatment should be discontinued immediately and not be resumed.

It is noted that this recommendation for monitoring is now included in the revised PI.

Risk management plan

The RMP evaluation report is included for ACPM information. There are no outstanding issues in relation to the RMP evaluation report for this submission. ACSOM advice was not sought for this submission.

The RMP evaluator has suggested the following wording as the conditions of registration:

- Implement Asunaprevir Company Core RMP (version 2, dated 22 December 2014, data lock point 15 November 2014) with Australia Specific Annex (version 2, dated 29 December 2014) and any future updates as a condition of registration.

Additional recommendation based on the sponsor's response

According to Table 4-1 in the revised Australia Specific Annex (version 2), the following PI precaution is proposed for the new item of missing information 'Patients who failed prior treatment with NS3 protease inhibitors': 'SUNVEPRA has not been studied in patients who have previously failed therapy with a treatment regimen that includes SUNVEPRA or other HCV NS3/4A protease inhibitors'. This precaution does not appear in the draft PI and should be included

Risk-benefit analysis

Delegate's considerations

Based on the review of the new information provided by the sponsor in response to the first round evaluation, the clinical evaluator recommends the registration approval of Sunvepra (asunaprevir) for the proposed indications:

> *Sunvepra (asunaprevir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) in combination with:*
>
> - *Daklinza, an NS5A replication complex inhibitor, for patients with HCV genotype 1b infection (See Clinical Trials and Dosage And Administration)*
> - *Daklinza, peginterferon alfa, and ribavirin for patients with HCV genotype 1 or 4 infection (see Clinical Trials and Dosage and Administration)*

The recommended regimens and treatment durations are as follows (Table 21):

Table 21: Recommended Regimens for Sunvepra 100 mg Twice Daily Combination Therapy

HCV Genotype [a]	Treatment	Duration
Genotype 1b	Sunvepra and Daklinza	24 weeks
Genotype 1 and 4	Sunvepra, Daklinza, peginterferon alfa, and ribavirin	24 weeks

a Treatment-naïve or failed prior treatment with peginterferon alfa/ribavirin

This approval matches the recommended approval for daclatasvir.

In dose selection studies a trend in the frequency and magnitude of ALT and AST elevations was observed at ASV doses > 200 mg BD of the tablet formulation. When ASV was combined with DCV ± pegIFNα/RBV), ALT elevations were observed. For the DCV/ASV regimen Grade 3/4 AE reported were increased ALT (4%) and increased AST (3%). The review of hepatic safety based on Phase II studies of ASV and DCV reports[38] somewhat higher frequency of Grade 3-4 ALT (9.8%) and AST (7.8%) abnormalities with DCV+ASV. The CER considers transaminase elevations appear to be easily monitored and

[38] Presented in second round CER for DCV (Attachment 2 AusPAR for Daklinza)

readily corrected after cessation of study therapy. Close monitoring of liver enzymes now recommended in draft PI.

Infrequently, these ALT elevations are associated with increased bilirubin (subjects meeting biochemical criteria for Hy's law[39] or pDILI criteria) without clinical evidence of hepatic decompensation. However, one case of a subject with severe liver injury, who exhibited evidence of hepatic encephalopathy, has been reported among subjects receiving HCV 3DAA (DCV/ASV/BCV).

ASV is contraindicated for patients with moderate or severe hepatic impairment.

Patient numbers assessed for safety in the ASV combination regimens at the recommended dose total 918 for DCV/ASV, 418 for DCV Quad and 189 for ASV/pegIFN/RBV.

Summary of issues

In dose selection studies a trend in the frequency and magnitude of ALT and AST elevations was observed at ASV doses > 200 mg BD of the tablet formulation. When ASV was combined with DCV ± pegIFNα/RBV), ALT and AST elevations were observed. For the DCV/ASV regimen Grade 3/ 4 AE reported were increased ALT (4%) and increased AST (3%). The review of hepatic safety presented in second round CER for DCV (p104) based on Phase II studies of ASV and DCV reports somewhat higher frequency of Grade 3-4 ALT (9.8%) and AST (7.8%) abnormalities with DCV+ASV . The CER considers transaminase elevations appear to be easily monitored and readily corrected after cessation of study therapy. Close monitoring of liver enzymes now recommended in draft PI. ASV is contraindicated in patients with moderate or severe hepatic impairment.

Infrequently, these ALT elevations are associated with increased bilirubin (subjects meeting biochemical criteria for Hy's law or pDILI criteria) without clinical evidence of hepatic decompensation. However, one case of a subject with severe liver injury, who exhibited evidence of hepatic encephalopathy, has been reported among subjects receiving HCV 3DAA (DCV/ASV/BCV). Numbers assessed for safety in the ASV combination regimens at the recommended dose total 918 for DCV/ASV, 418 for DCV Quad and 189 for ASV/pegIFN/RBV.

Comparative data are not available for DCV+ASV to newer medicines for the treatment of CHC. In USA, the ASV submission has been withdrawn with the reason stated by the sponsor as '*Due to evolving HCV treatment landscape resulting in access to multiple all-oral treatment options with high cure rates and 12-week treatment duration for HCV genotype 1 patients in the U.S., 24 week treatment with daclatasvir (DCV)+ASV and DCV+ASV+peginterferon-alfa/ribavirin is considered not to be competitive in the U.S.*'

Delegate's proposed action

The Delegate agrees with the clinical evaluator and proposes the registration approval for Sunvepra for use in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease.

The proposed regimens and treatment durations are considered acceptable.

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

[39] Based on Hy Zimmerman's inductive reasoning, term coined by Robert Temple in 1980s as a 'biomarker' of drug hepatotoxicity, a signal for potential serious risk. Applied only to hepatocellular toxicity, not to cholestatic reactions or other liver diseases.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Are Sunvepra (asunaprevir) indications proposed, which include two specific combination regimens, considered acceptable compared to the DAKLINZA (daclatasvir) indications which rely on referral [see CLINICAL TRIALS and DOSAGE and ADMINISTRATION]?
2. Has hepatic safety of asunaprevir has been adequately established in chronic hepatitis C patients?
3. 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

The sponsor acknowledges the Delegate's proposal to approve the registration of Sunvepra for use in combination with other medicinal products for the treatment of chronic hepatitis C (HCV) infection in adults with compensated liver disease. The sponsor welcomes the opportunity to comment on the questions asked of the ACPM in the Delegate's Request for ACPM's Advice (DRA).

Advice sought and sponsor's comments

Question 1: Are Sunvepra (asunaprevir) indications proposed, which include two specific combination regimens, considered acceptable compared to the Daklinza (daclatasvir) indications which rely on referral [see Clinical Trials and Dosage and Administration]?

The sponsor acknowledges that the presentation of the Sunvepra indications section is inconsistent with the presentation of the Daklinza indications section, and also with that of other newer direct acting antiviral agents (DAA) approved in Australia (Olysio and Sovaldi).

The sponsor is willing to align the indications section of the Sunvepra PI to maintain consistency with all new DAAs approved in Australia and proposes to reformat as shown below:

> *Sunvepra (asunaprevir) is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) [see Clinical Trials and Dosage and Ddministration].*

Question 2: Has hepatic safety of asunaprevir has been adequately established in chronic hepatitis C patients?

The sponsor provided an Overview of Hepatic Safety for asunaprevir with their response to TGA's request for further information, summarising hepatic safety analyses from all clinical development programs which have studied regimens of asunaprevir (daclatasvir [DCV]/asunaprevir [ASV], pegIFN/RBV, or DCV/ASV/ beclabuvir [DCV/ASV/BCV]).

Based on the sponsor's current understanding of the hepatic safety analyses presented in the report:

- When ASV was combined with DCV (pegIFNα/RBV), ALT elevations were observed, which are associated with ASV use.
- In general, these ALT elevations to date have been reversible after study drug has been discontinued.
- Infrequently, these ALT elevations are associated with increased bilirubin (subjects meeting biochemical criteria for Hy's law or pDILI criteria) without clinical evidence of

hepatic decompensation. However, one case of a subject with severe liver injury, who exhibited evidence of hepatic encephalopathy, has been reported among subjects receiving HCV 3DAA (DCV/ASV/BCV); further evaluation of this case is ongoing.

The sponsor consequently recommends that patients receiving DCV/ASV or DCV/ASV/pegIFNα/RBV should have close monitoring of liver enzymes: at least once every 2 weeks for the initial 12 weeks of treatment, and every 4 weeks thereafter until completion of therapy. Any upward trend in ALT/AST levels warrants more frequent monitoring. If on-treatment elevations in ALT levels 10 times ULN or greater occur, treatment should be discontinued immediately and not be resumed.

Comprehensive text regarding this monitoring and discontinuation guidance (if on-treatment elevations in ALT levels 10 times ULN or greater occur, treatment should be discontinued immediately and not be resumed) has been added to the Australian Sunvepra PI. This text has been accepted by the clinical evaluator in the second round evaluation. As also noted by the Delegate, asunaprevir is contraindicated for patients with moderate or severe hepatic impairment. The sponsor believes that these PI measures are appropriate as one of the risk minimisation strategies to ensure patient safety during treatment with asunaprevir.

The sponsor is committed to ongoing surveillance of the hepatic safety of asunaprevir worldwide. The combination of DCV/ASV was introduced into the market in Japan on 3 September 2014. The third interim report of the Early Post-Marketing Phase Vigilance (EPPV, an enhanced routine pharmacovigilance program requirement for all new drugs during their first 6 months on the market in Japan), covering the period 3 September 2014 through 2 January 2015, provided an estimated exposure of approximately 15,000 patients. There have been 70 serious adverse event reports (including 111 events) received during this period, with the greatest number (21/70, 30%) involving the hepatobiliary system. No cases with fatal outcome were reported.

In conclusion, the sponsor believes that the hepatic safety of ASV is adequately established and the recommendations for hepatic monitoring and guidance on when to discontinue treatment, along with post-marketing monitoring, are sufficient.

Sponsor's comments on other aspects

Population Pharmacokinetic Analysis and Pharmaceutical Subcommittee (PSC) Discussions

The PSC recommended that the numerical value of the impact of co-variates reported in the population pharmacokinetic analysis should be reported in the PI sections concerning elderly patients, gender and race. The magnitude of all these covariate effects on ASV exposure is not considered clinically relevant and the sponsor is updating the PI accordingly.

The sponsor notes that there are no outstanding RMP issues and confirms that the PI has been updated to include a new *Precaution* regarding the missing information for patients who failed prior treatment with protease inhibitors.

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, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy advised that Sunvepra soft gelatin capsules, containing 100 mg asunaprevir has an overall positive benefit–risk profile for the following modified indication:

Sunvepra (asunaprevir) is indicated in combination with other active treatments for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) [see Clinical Trials and Dosage and Administration].

In making this recommendation the ACPM:

- Advised that the combination of DCV and ASV for 24 weeks should be for the treatment of HCV genotype 1b in patients who have received no prior treatment or who have failed peginterferon alfa/RBV combination, which is similar to the Japanese population enrolled in Study AI447017.
- Noted that the QUAD treatment regimen containing DCV/ASV/pegINF/RBV appeared to provide an increased response rate but at the cost of increased toxicity.
- Expressed concern regarding the elevations of bilirubin and liver transaminases with asunaprevir containing regimens.

Proposed conditions of registration

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

- a requirement to monitor and report liver toxicity in patients receiving asunaprevir-containing regimens.

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:

- Inclusion of a black box warning to highlight the risk of elevated bilirubin levels and liver transaminases when using asunaprevir containing regimens and ensure appropriate monitoring.
- Specify a lower level of ALT elevation of five times the upper limit of normal (ULN) for treatment discontinuation for patients receiving asunaprevir containing regimens.
- Replacement of Table 10 in *Dosage and Administration* as follows:

Recommended Regimens with Daklinza 60 mg Once Daily Combination Therapy

Genotype	Prior treatment experience	Combination	Duration
1b	None, or failed peginterferon alfa/ribavirin	Daclatasvir and asunaprevir	24 weeks
1 or 4	None, or failed peginterferon alfa/ribavirin	Daclatasvir, asunaprevir, peginterferon alfa, and ribavirin	24 weeks

Specific advice

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

1. *Are Sunvepra (asunaprevir) indications proposed, which include two specific combination regimens, considered acceptable compared to the Daklinza (daclatasvir) indications which rely on referral [see Clinical Trials and Dosage and Administration]?*

   The ACPM advised that there was sufficient evidence for an indication which reflected the Japanese population in Study AI447017, that is, HCV genotype 1b infection, in combination with DCV, in patients who have received no prior treatment or who have failed peginterferon alfa/RBV combination.

   Regarding the QUAD combination therapy (DCV/ASV/pegINF/RBV) in patients with HCV genotype 1 or 4, the ACPM noted that this combination appeared to provide an increased response rate but at the cost of increased toxicity. The ACPM was concerned about liver toxicity with the combination therapy, particularly as the evidence suggests a strong liver toxicity signal with asunaprevir –containing regimens. The ACPM noted that the Periodic Safety Update Report (PSUR) reported serious (cumulative) increases in ALT in 5 patients, and 18 not classified as serious.

   The ACPM noted the sponsor's proposed monitoring strategy for liver toxicity in the PI, which instructs prescribers to monitor LFTs 2 weekly for 12 weeks, then 4 weekly until 24 weeks. In addition the PI states that ASV is contraindicated for patients with moderate or severe hepatic impairment. The ACPM considered that these warnings should be strengthened by a black box warning about monitoring for liver toxicity with asunaprevir-containing regimens (see response to Question 2 below).

2. *Has hepatic safety of asunaprevir has been adequately established in chronic hepatitis C patients?*

   The ACPM was concerned about the risk of liver toxicity with asunaprevir–containing regimens and considered that there was sufficient evidence of a strong liver toxicity signal. The ACPM noted that the risk was not unmanageable with regular monitoring of LFTs and bilirubin. However, the ACPM advised that the warning about liver toxicity should be strengthened by use of a black box warning to highlight the risk of elevated bilirubin levels and liver functions tests when using asunaprevir containing regimens to ensure appropriate monitoring.

   The ACPM also advised that, rather than the proposed ten times levels, a lower level of ALT elevation of five times the upper limit of normal should be specified for treatment discontinuation for patients receiving asunaprevir-containing regimens.

3. *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.*

The ACPM advised that the place of ASV in the treatment of HCV is uncertain as there are combination therapies available with a treatment duration of 12 weeks, as opposed to 24 weeks for ASV-combination therapy. There is also concern regarding hepatic safety with ASV-containing regimens.

The ACPM considered that interactions of ASV with other medicines that use the CYP3A4 metabolic pathway may limit use in patients with human immunodeficiency virus (HIV)/HCV co-infection.

The ACPM considered that non-inferiority studies would be preferable rather than single arm studies in order to ascertain efficacy of new treatments compared with current standard of care regimens.

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 Sunvepra (asunaprevir) 100 mg capsule blister for oral administration, indicated for:

> *Sunvepra (asunaprevir) is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) [see Clinical Trials and Dosage and Administration.]*

Specific conditions of registration applying to these goods

The Sunvepra (asunaprevir) Company Core Risk Management Plan (RMP), (version 2, dated 22 December 2014, data lock point 15 November 2014) with Australia Specific Annex version 2, dated 29 December 2014) provided with the submission PM-2014-00648-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Sunvepra at the time this AusPAR was published is at Attachment 1. For the most recent Product Information 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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