Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for simeprevir (as sodium)

Proprietary Product Name: Olysio/Janssen Simeprevir

Sponsor: Janssen-Cilag Pty Ltd

October 2014

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 <http://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

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{24\,h}$	area under the curve over a 24 hour dose interval
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time of intake until infinity
CHC	chronic hepatitis C
CI	confidence interval
C_{max}	maximum plasma concentration.
C_{min}	minimum plasma concentration between 0 hour and τ (τ = dosing interval. For RBV, between 0 and 10 h instead of full dosing interval).
CMI	Consumer Medicine Information
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
G007	Phase III capsule formulation of simeprevir
h	hour/s
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
HR	heart rate
ICH	International Conference on Harmonisation of Technical

Abbreviation	Meaning
	Requirements for Registration of Pharmaceuticals for Human Use
IFN	interferon
IFNα	interferon alfa
IgM	immunoglobulin
ITT	intent to treat
IU	International units
IV	intravenous/ly
L	litre
LS	least squares
MedDRA	medical dictionary for regulatory activities
METAVIR	a scoring system for liver biopsies that assigns two standardised numbers: one to represent the degree of inflammation and the other the degree of fibrosis[1].
NOAEL	no observed adverse effect level
PCR	polymerase chain reaction
PD	pharmacodynamics
PegIFN	pegylated interferon
PegIFNα	pegylated interferon alfa
PI	Product Information
PK	pharmacokinetic/s
PO	per os, oral/ly
PP	per protocol
PPK	population pharmacokinetic/s
PR	PegIFN/RBV
q.d.	quaque die; once daily

[1] **Activity grade**: A0: No activity; A1: Mild activity; A2: Moderate activity; A3: Severe activity. **Fibrosis stage**: F0: No fibrosis; F1: Portal fibrosis without septa; F2: Portal fibrosis with few septa; F3: Numerous septa without cirrhosis; F4: Cirrhosis. Those without advanced hepatic fibrosis have METAVIR score F0, F1, or F2; those with advanced hepatic fibrosis have METAVIR score F3 or F4.

Abbreviation	Meaning
RBV	ribavirin
RGT	response guided therapy/treatment
RMP	Risk Management Plan
RNA	ribonucleic acid
RTV	ritonavir
RVR	rapid virologic response (at Week 4)
SAE	serious adverse event
SD	standard deviation
SE	standard error
SJS	Stevens-Johnson syndrome
SoC	standard of care
SVR	sustained virologic response
SVR12	SVR at 12 weeks after planned end of treatment
SVR24	SVR at 24 weeks after planned end of treatment
SVR4	SVR at 4 weeks after planned end of treatment
SVRW72	SVR at Week 72
$t_{½}$	half life
T_{max}	time to reach the maximum plasma concentration
TMC	simeprevir
TMC435	simeprevir

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	10 July 2014
Active ingredient:	Simeprevir (as sodium)
Product names:	Olysio/Janssen Simeprevir
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park, NSW, 2113
Dose form:	Capsule
Strength:	150 mg
Container:	Blister pack
Pack sizes:	7, 28
Approved therapeutic use:	*the treatment of chronic hepatitis c (CHC) genotype 1 or genotype 4 infection, in combination with other medicinal products for the treatment of CHC infection (see Dosage and Administration, Precautions, Clinical Trials).*
Route of administration:	Oral
Dosage (abbreviated):	150 mg once daily for 12 weeks. Olysio/Simeprevir Janssen must be taken with peginterferon alfa and ribavirin
ARTG numbers:	211696, 211697

Product background

Hepatitis C virus (HCV) is a ribonucleic acid (RNA) virus belonging to the flavivirus family. There are six genotypes of HCV with approximately 40 different subtypes. HCV genotype determines the length, type of treatment and likely response to current medications. According to the sponsor, genotypes 1 to 3 (G1 to G3) have a worldwide distribution, with genotype 1a (G1a) and genotype 1b (G1b) being the most common and accounting for approximately 60% of global HCV infections. Genotypes 1a and 1b (54% prevalence) and 3a (37% prevalence) are also the most common genotypes in Australia.

By the end of 2010, it was estimated that 297,000 people living in Australia had been exposed to HCV, of whom 221 000 were living with chronic HCV infection. The number of new HCV infections is estimated at 10,000 per year (Australasian Society for HIV

Medicine). According to the National Health and Medical Research Council (NHMRC), of 100 people who are infected with hepatitis C, between 25 and 45 will clear the virus up to 12 months (usually within 3-6 months) after infection. Those that do not clear HCV are described as having chronic hepatitis C. Chronic HCV infection can cause long-term liver disease, including cirrhosis and hepatocellular carcinoma.

Simeprevir (also referred to as TMC 435) is a nonstructural protein 3 (NS3)/4A protease inhibitor. Protease inhibitors prevent viral replication by selectively binding to viral proteases such as NS3/4A and blocking proteolytic cleavage of protein precursors that are necessary for the production of infectious viral particles.

This AusPAR describes the application by Janssen-Cilag Pty Ltd (the sponsor) to register capsules containing 15 mg simeprevir for the following indication:

> *the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.*

Combined use of simeprevir with the antiviral agents pegylated interferon alfa (PegIFNα) and ribavirin (RBV) is expected to result in an additive or synergistic antiviral effect.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 18 July 2014.

At the time the TGA considered this application, a similar application had been approved in Canada (18 November 2013) and the USA (22 November 2013) and had received a positive opinion by the CHMP of the European Medicines Agency (20 March 2014).

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 <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

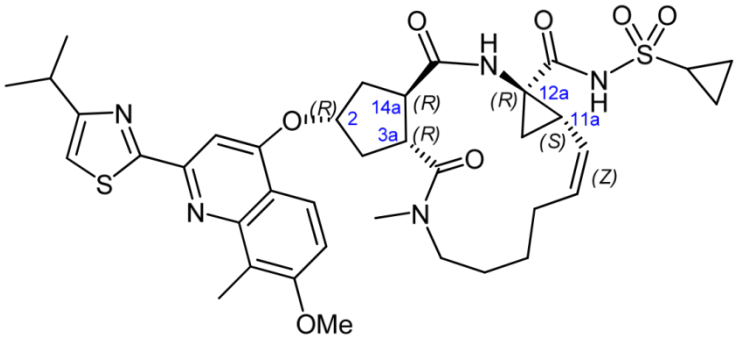
Introduction

Simeprevir has a similar mechanism of action as a number of other new NS3/4A protease inhibitors such as boceprevir and telaprevir. The proposed simeprevir capsules are packaged in PVC/PE/PVdC/Al blister packs containing 7 and 28 capsules.

Drug substance (active ingredient)

The structure of simeprevir is depicted in Figure 1:

Figure 1: Structure of simeprevir



Simeprevir is manufactured by chemical synthesis. Simeprevir is a single enantiomer containing five chiral centres with fixed configurations and has one sterogenic centre at the (Z)-double bond. It is amphiprotic with a basic thiazole moiety and acidic sulfonyl carboxamide group. It is practically insoluble in aqueous media over a wide pH range. Several polymorphs are known but it is manufactured as the most thermodynamically stable form, Polymorph I.

The drug substance specifications include limits for specified impurities. The limits were toxicologically qualified.

Drug product

To improve the aqueous solubility of simeprevir, the drug substance is converted to the amorphous sodium salt, simeprevir sodium. Each capsule contains 154.4 mg of simeprevir sodium, equivalent to 150 mg of simeprevir.

The capsules are white with 'TMC435 150' printed on the body in black ink and are filled with a powder blend of simeprevir sodium and the excipients.

The finished product specifications were acceptable. The capsules show good stability and a shelf-life of 2 years below 30°C has been assigned.

Biopharmaceutics

The following bioavailability and bioequivalence data were evaluated:

Study No. TMC435HPC1002

This was an open label, randomised, 3 panel, 3 way crossover study in healthy subjects that investigated the relative oral (PO) bioavailability of simeprevir administered as two potential paediatric liquid formulations (an oral suspension and an oral solution) and two variants of the formulation used in the stability studies (G019) compared with the reference Phase III capsule under fed conditions.

The effect of a high fat breakfast on the bioavailability of simeprevir administered as the two liquid formulations was also investigated (fed and fasted).

The Phase III capsules and the two variants of G019, representing extremes of manufacturing variables, were found to be bioequivalent under the tested (fed) conditions.

For the oral suspension containing insoluble simeprevir, C_{max} and $AUC_{0\text{-last}}$ were < 1% than for the capsule, under fed conditions.

For the oral solution containing simeprevir sodium, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} were 12%, 11% and 4% higher than for the capsule, under fed conditions.

These results indicate that the capsule formulation is optimised with regard to bioavailability when taken under fed conditions.

Study No. TMC435-TiDP16-C116

This study investigated the effect of different meal type on the bioavailability of simeprevir administered as the gelatin capsule used in the Phase III clinical trials (G007). The PO bioavailability of simeprevir administered as the gelatin capsule formulation (G007) relative to a hypromellose capsule formulation under fasting conditions was also investigated.

With regard to the Phase III capsule (G007), food increased the bioavailability of simeprevir, with $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} 1.60, 1.70 and 1.69 fold higher, respectively, after the consumption of a standard breakfast and, respectively, 1.49, 1.66 and 1.61 fold higher after consumption of high-fat breakfast, compared to fasting conditions. In this context it is noted that the draft PI contains the statement, *'Simeprevir should be taken orally once a day with food. The type of food does not affect exposure to simeprevir'*.

The terminal elimination half-life ($t_{½}$) values determined in the study are similar to that stated in the PI document. However, the range of half-life values in this study for health participants was approximately 9 to 10.5 h compared with the PI statement *'The terminal elimination half-life of simeprevir was 10 to 13 hours in healthy participants.'*

Study No. TMC435-TiDP16-C118

This was conducted to assess the absolute bioavailability and pharmacokinetics (PK) of oral 50 mg and 150 mg (G019) capsule doses and an intravenous (IV) microdose of 100 µg radiolabeled ([^{3}H])-simeprevir. The 150 mg capsule (G019) is identical to that proposed for registration apart from the colour and printing on the capsule shell.

$AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} were more than dose proportionally higher for the 150 mg dose compared to the 50 mg dose. The mean absolute bioavailability was higher after a 150 mg dose (62%) compared to a 50 mg dose (46%). Approximately 85% of the total radioactive dose was excreted in faeces.

Advisory committee considerations

This application was not submitted for advice from the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM)

Quality summary and conclusions

A number of relatively minor issues were raised with the sponsor following the initial evaluation of this application. The company satisfactorily addressed all matters raised. There are no objections to registration from a pharmaceutical chemistry perspective.

III. Nonclinical findings

Introduction

The overall quality of the submitted dossier was high, with all pivotal toxicity studies conducted under good laboratory practice (GLP) conditions using the proposed clinical route (PO). The submitted toxicity studies were of sufficient duration to support the proposed clinical regime. The majority of safety pharmacology studies however, were not GLP-compliant (that is, in vitro and in vivo cardiovascular, respiratory and gastroinintestinal studies). Although this is considered a deficiency in the application, these studies were well designed, comprehensive and well documented. Additionally, there were no PK or toxicology studies submitted to support the use of simeprevir in combination with PegIFNα and ribavirin. The lack of combination studies is consistent with a draft FDA guidance for direct acting antiviral drugs for HCV treatment[2]. Due to the short term frequency of clinical use (12 weeks), no carcinogenicity studies were submitted. Toxicology studies were provided to qualify proposed impurity specifications.

Pharmacology

Simeprevir in vitro virology study reports were provided. Simeprevir nonclinical virology was investigated by structural, biochemical (protease assay), and cell culture (HCV replicon[3]) studies in vitro (below). Simeprevir anti-HCV activity was not investigated in animal studies. Clinical virology studies were provided.

Simeprevir is a macrocyclic, noncovalent, peptidomimetic inhibitor of the HCV NS3/4A serine protease essential to the HCV replication cycle. The two registered HCV NS3/4A protease inhibitors, boceprevir and telaprevir, are linear peptidomimetics with a ketoamide functionality.

Biochemical assays

A biochemical protease assay showed simeprevir median inhibition constant (Ki) values of 0.5 and 1.4 nM against HCV genotype 1a (H77) and genotype 1b (Con1) HCV NS3/4A proteases. Simeprevir also showed inhibitory activity at nanomolar (nM) concentrations against recombinant NS3/4A proteases derived from a panel of HCV genotype 1a, 1b, 2b, 4a and 6a clinical isolates, whereas proteases from genotype 3 and 5 isolates had reduced susceptibility, attributed to the presence of a D168Q (genotype 3), or Q80K+D168E (genotype 5) amino acid substitutions. Simeprevir had reduced protease activity against all NS3 mutants known to reduce simeprevir activity in a replicon-containing cell assay. In a primer dependent transcription assay, simeprevir did not have significant inhibitory activity against HCV genotype 1a, 1b, 2a or 3a recombinant NS5B polymerases.

The inhibitory activity of simeprevir was assessed against a panel of 20 cellular proteases, with inhibition observed for six proteases (human capthepsin S, leucocyte-elastase, cathepsin G, thrombin, trypsin and plasmin, respective 50% inhibitory concentration (IC_{50}) values 0.8, 1.5, 3.8, 5.6, 5.7 and 5.8 μM), however secondary assays with thrombin, and cathepsin S, a lysosomal cysteine protease involved in immune responses, showed no inhibitory activity at respective concentrations of 10 and 300 μM.

[2] FDA (CDER) Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013 (draft).
[3] Lohmann V *et al.* Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999;285(5424):110-113.

Replicon-containing cell studies

The anti-HCV activity of simeprevir was investigated in a number of HCV genotype 1a and 1b (sub)genomic replicon-containing human hepatoma cell lines, using either luciferase reporter gene or reverse transcription polymerase chain reaction (RT-PCR) assays to quantify replication. The simeprevir median 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) values (luciferase assay) against a HCV genotype 1b replicon were 9.4 nM (7.05 ng/mL) and 19 nM (14.25 ng/mL), respectively, and similar inhibition was measured by RT-PCR. The 50% cytotoxic concentration (CC_{50}) of 33,700 nM in the same cell line indicated a selectivity index of 3,600. Median EC_{50} values of 23 and 28 nM were measured in two genotype 1a replicon-containing cell lines. The simeprevir mean plasma minimum concentration (C_{min}) was 1579 ng/mL in clinical study TMC435-C205; hence the respective C_{min}/EC_{50} and C_{min}/EC_{90} ratios are 224 and 111.

The effects of human plasma proteins (α-1 acid glycoprotein, human serum albumin, 10-50% human serum) were determined in replicon-containing Huh7-Luc cells. The largest change in simeprevir EC_{50}, a 2.4 fold increase, was observed with 50% human serum.

Activity against other viruses

In cell-based assays, simeprevir showed no relevant antiviral activity against a panel of 11 viruses, including related flaviviruses, nor was any relevant inhibition of the human immunodeficiency virus type 1(HIV-1) protease seen in an enzymatic assay.

Resistance

Simeprevir resistance selection studies were conducted with genotype 1a and 1b replicon-containing human hepatoma cell lines. Replicons with reduced simeprevir susceptibility were selected by growth at either constant or increasing drug concentrations. In 105 out of 109 cultures, one or more mutations at NS3 protease amino acids F43, Q80, R155, A156 and/or D168 were observed, with those at position D168 (D168V, D168A) being the most common, followed by substitution to E, H, I, T, G, N or Y. Other, less frequent substitutions were F43S, Q80R, Q80K, Q80H, R155K, A156V, A156T, and A156G. These observations were consistent with crystallography data which showed that residues at these positions were located at the drug-binding site.

Simeprevir activity against clinical isolates derived from subjects in clinical trials was assessed in chimeric replicons constructed by insertion of NS3 protease sequences into a luciferase-containing HCV genotype 1b or 2a backbone.

Baseline clinical isolates from HCV genotype 1 infected subjects displayed median (range) simeprevir fold change (FC) values compared with genotype 1b reference replicon of 1.4 (0.4-100) for HCV genotype 1a (N=78) and 0.4 (0.1-26) for genotype 1b (N=59), while reductions in activity were observed with genotype 1a baseline isolates carrying baseline substitution Q80K (median FC = 11), and R155K (median FC = 95), genotype 1b isolates carrying baseline substitution Q80K (median FC=8.4), genotype 2 isolates carrying baseline substitutions Q80G + S122R (median FC = 25), and genotype 3 substitution D168Q (median FC = 1014), but not with any genotype 4 isolate (median FC = 0.4). Fold change values were generally higher for isolates with multiple cf. single substitutions. Simeprevir showed similar (correlation coefficient (r^2) = 0.84) anti-HCV activity against genotype 1 clinical isolates and site-directed mutants carrying corresponding substitutions at NS3 positions 43, 80, 122, 155, 156, and 168 in a wild-type 1a or 1b backbone in the replicon assay, confirming the role of these substitutions in reduced susceptibility.

The anti-HCV activity of simeprevir against site-directed NS3 mutants associated with resistance to other HCV NS3/4A protease inhibitors such as boceprevir and telaprevir, was assessed in replicon assays. Mutations at NS3 positions 36, 54, 55, 107, 158, 162, 170 or 175 associated with resistance to boceprevir and/or telaprevir, other than those known to increase resistance to simeprevir (R155, A156, D168), were fully susceptible (FC < 2 fold increase) to simeprevir, small decreases in susceptibility were observed with V36A (2.8 fold), V36G (3.6 fold), V170A (4.7 fold), and V170T (5.4 fold). Large decreases in simeprevir susceptibility were observed with position 168, with respective reductions of 2830, 1800 and 948 fold for D168V, D168I, and D168A. Certain other mutants at NS3 positions 43, 122, 155 and 156 also reduced simeprevir activity by >10 fold. A mutant frequently observed in genotype 1a-infected subjects at the time of treatment failure, R155K, reduced simeprevir activity 33 and 88 fold in the respective genotype 1b and 1a backbones. These results indicated some cross-resistance between the NS3 inhibitors simeprevir, boceprevir and telaprevir. No cross-resistance was observed between simeprevir and representative HCV NS5A and NS5B nucleoside and non-nucleoside analogue inhibitors.

Simeprevir did not antagonise the anti-HCV activities of IFNα, ribavirin, or representative HCV NS5A nucleoside or NS5B non-nucleoside inhibitors in vitro. Conversely, registered HIV-1 protease inhibitors had no effect on the anti-HCV activity of simeprevir.

Overall, the simeprevir nonclinical virology studies were consistent with the draft FDA guidance for direct-acting anti-HCV drugs[4].

Clinical virology synopsis

In brief, pooled data from clinical trials identified the Q80K substitution at baseline as a variant that had an impact on virological response to simeprevir/PegIFNα/RBV treatment. Prevalence of this substitution varied geographically, in Australian and New Zealand subjects it was 7.1% overall, and 7.1% in genotype 1a. The most prevalent treatment emergent, resistance associated substitutions identified in clinical trials were NS3 R155K, D168E, and D168V (genotype 1a viruses) and Q80R, D168E, and D168V for genotype type 1b viruses. NS3 R155K, and multiple substitutions at NS3 D168 are associated with resistance to NS3/4A protease inhibitors in general.

Secondary pharmacodynamics

Simeprevir at 30 μM (22.5μg/mL) was screened for activity against a panel of 50 receptors, ion channels and transporters. Its most potent secondary actions were antagonism (≥ 50% inhibition of control specific binding) of adenosine A_1, A_3, angiotensin II (AT_1,), cholecystokinin (CCK), endothelin (ET_A), melatonin (MT_1), muscarinic (M_1), neurokinin (NK_2), opioid (δ_2, κ, μ) and serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{5A}) receptors, and chloride channels. These interactions were not further characterised.

An in vivo finding possibly related to CCK antagonism includes delayed gastric emptying in mice and rats as a result of inhibition motility. Cholecystokinin also has a role in the digestion of fats and protein by stimulating the release of digestive enzymes from the pancreas as well as the release of bile. A number of findings in mice, rats and dogs is also likely related to inhibition of CCK in the pancreas and includes decreased pancreatic acinar cell zymogen/basophilia, acinar cell vacuolation, increased lipase and amylase levels, inflammation and apoptosis.

[4] FDA (CDER) Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013 (draft).

The clinical significance of the low order of selectivity is somewhat mitigated, though, by the observation of very limited entry of radiolabelled (^{14}C)-simeprevir derived radioactivity into the central nervous system (CNS) of mice (tissue:blood area under the concentration-time curve over 0 to 7 h ($AUC_{0-7\,h}$) ratio of 0.02 in the brain; C_{max} [0.549 µg eq./g] was 62 times lower than the plasma C_{max}) and limited entry of unlabelled simeprevir into the CNS of rats (tissue:blood $AUC_{0-31\,h}$ ratio of 0.03; C_{max} [36 ng/g] was 40 times lower than the plasma C_{max}).

Safety pharmacology

Specialised safety pharmacology studies examined potential effects of simeprevir on the CNS, cardiovascular, respiratory and gastrointestinal systems. Based on distribution studies, brain penetration of simeprevir was not expected and neurological signs not anticipated. However, effects on CNS function of diminished alertness was observed in rats with simeprevir treatment at 50-500 mg/kg PO (doses producing peak plasma concentrations of simeprevir of 2.3-3.5 µg/mL, about0.5 to 0.8 times the clinical C_{max} of 4.39 µg/mL). In the same study, slight narrowing of palpebral fissure at ≥ 150 mg/kg (0.6-times the clinical C_{max}) and at 500 mg/kg, myoclonic movements of the jaw was reported in 1 out of 5 rats (not seen in other studies; 0.8 times the clinical C_{max}).

There were no notable findings up to 0.3 µM (220 ng/mL) in human ether à go-go (hERG) channel transfected human embryonic kidney (HEK) 293 cells (at 50 times the C_{max} at the clinical dose). However, simeprevir demonstrated blocking activity at the cardiac sodium channel at ≥ 0.3 µM (6.8% at 220 ng/mL; exposure ratio (ER) at the clinical dose is 50 fold, based on C_{max} of 4.39 µg/mL, an estimated plasma protein binding of >99.9% and a free plasma concentration of 4.39 ng/mL) in hH1a cDNA (SCN5A)-transfected CHO cells. The no observed adverse effect level (NOAEL) was 0.1 µM (0.075 µg/mL; ER, 17). This channel blocking effect produced shortening of the cardiac action potential duration and a reduction of the intraventricular conduction time in the isolated Langendorff-perfused rabbit heart at ≥ 1 µM; the NOAEL was 0.3 µM (0.22 µg/mL; ER, 50). At the highest concentration (10 µM), proarrhythmic effects were observed, however precipitation in the heart (80 times the target concentration) was observed and the effects are probably due to high local simeprevir concentrations (range 370-702 µg/g). Simeprevir levels in the heart were similar or slightly higher (about 2 fold) than in plasma following single or repeated dosing in tissue distribution studies, indicating no particular distribution to the heart in vivo.

Simeprevir was administered PO to dogs, and IV to anaesthetised dogs in adequate cardiovascular studies demonstrating sufficient exposure (≤ 160 mg/kg PO, about 20 times the clinical C_{max}; ≤ 5 mg/kg IV, 15 times the clinical C_{max}). Only the in vivo PO study was GLP-compliant and all the submitted in vitro cardiovascular studies were non-GLP. However, the submitted in vitro and in vivo cardiovascular studies were well conducted and documented. In the IV escalating dose study in dogs, there were moderate cardio-haemodynamic alterations of increased vascular resistance, decreased heart rate and cardiac output at ≥ 2.5 mg/kg (ER, 6) as well as effects on the electrocardiogram (EGC) RR interval (29% increase) at 1.25 mg/kg (ER, 2.7). The NOAEL was 0.63 mg/kg (ER, 1.2).

No significant electrocardiogram (ECG) abnormalities were noted in dogs in the PO and IV cardiovascular safety studies, nor in any of the repeat dose toxicity studies conducted in the species at clinically relevant doses (0.1 to 30-times the anticipated clinical exposure).

Respiration (PO studies) and various pulmonary parameters (IV studies) were unaffected in dogs (≤ 160 mg/kg PO; ER, 20; ≤ 5 mg/kg IV; ER, 15). However, simeprevir at a dose of 160 mg/kg significantly delayed gastric emptying (2.7 fold; at an equivalent exposure to the clinical C_{max} [based on data from study TMC435-NC177]) after the stomach contents of rats were evaluated 1 h after a chocolate meal. In the initial screening studies, there were

generally no remarkable drug related effects on the CNS, cardiovascular and gastrointestinal systems or on components of allergy and inflammation using an extensive range of animal, tissue and cell based assays. However, in the arachidonic acid induced platelet aggregation assay, there were treatment related findings of 100% inhibition of rabbit platelet aggregation at 30 µM (22.5 µg/mL; IC_{50}: 12.2 µM [9.1 µg/mL] which is about 2 fold the clinical C_{max} of 5.85 µM [4.39 µg/mL]). In further studies using human platelets, simeprevir at 30 µM did not alter platelet aggregation induced by arachidonic acid, collagen or adenosine diphosphate (ADP) nor did it have a direct effect (that is, shape change effects) on platelets. Similarly there were no adverse findings with simeprevir (up to 300 µM) in haemolysis studies using human red blood cells.

Overall, diminished alertness may be a clinically relevant finding since this effect occurred in rats at levels similar to the exposure at the clinical dose. Potential adverse effects on cardiovascular function may also be a potential risk in high risk patients.

Pharmacokinetics

Absorption

The PK and toxicokinetics of simeprevir were determined in mice, rats, dogs and monkeys using suitably validated non-chiral liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods. The absorption of simeprevir was moderate after a PO dose via gavage in mice, rats, hamsters, rabbits, dogs and monkeys. Peak plasma levels were generally reached within 1-5 h (time to reach maximum concentration (T_{max}); 4-6 h in humans). Following IV dosing, the plasma elimination half-life was fairly similar for rats, rabbits, dogs and monkeys (2.8–6.4 h). In general, following PO (gavage) dosing, the plasma half-life was shorter in laboratory animal species (rat: 2.5 h; dog and rhesus monkey: 4 h) than in humans (10-13 h in healthy participants across the dose range tested [50-600 mg] and 41 h in HCV-infected patients receiving 200 mg simeprevir; from draft PI). Half-lives of about 3-5 h were noted for radioactivity after administration of ^{14}C-simeprevir to laboratory animals. The simeprevir clearance rate was highest in rabbits (7.2 L/h/kg) and lowest in dogs and monkeys (0.07–0.4 L/h/kg). Following dosing to fed animals, PO bioavailability was moderate in rats and hamsters (40–44%), low in rabbits and Cynomolgus monkeys (2.5–19%) and much higher in dogs (72%); PO bioavailability was marginally lower in fasted dogs (by 19%), while a slightly higher bioavailability was seen in fasted Cynomolgus monkeys (1.3 fold). Administration of simeprevir with food to healthy participants increased the relative bioavailability (AUC) by 61–69% and delayed absorption by 1–1.5 h.

Following repeat dosing in repeat dose toxicity studies via gavage in dogs and monkeys and by both gavage and dietary administration in rodents (mice and rats), exposures (AUC) were less than dose proportional in rodents and more than dose proportional in dogs. At higher doses to rodents, absorption from the gastrointestinal tract was prolonged, with peak plasma levels occurring later and the plasma concentration-time profiles flattened. This resulted in a plateau of C_{max} values in mice and rats indicating saturation of the absorption process. There was no accumulation noted in either sex upon repeated dosing in any animal species. However, in mice, exposures (AUC) were lower on later days compared to that at the initiation of dosing. The lower exposures were not associated with an increase in metabolite formation. Overall, there were no consistent sex differences in mice, rats or dogs.

Apparent permeability studies in colon adenocarcinoma cell line (Caco-2) cells indicate that simeprevir (20 µM; 15 µg/mL) is a low permeability agent and is a substrate for the P-glycoprotein (P-gp; IC_{50} of 85.9 µM [64.4 µg/mL]) efflux mechanism in this cell line.

Distribution

Simeprevir was highly bound to plasma proteins (not less than 99.3%) in all laboratory animal species and humans with limited transfer into blood. The extent of binding was independent of concentration and predominantly involved human serum albumin. Protein binding was unaltered in patients with renal or hepatic impairment. The steady state volume of distribution was high in rabbits (41 L/kg), moderate in hamsters and rats (5.3-5.9 L/kg) and low in dogs and monkeys (0.5-1.1 L/kg). In humans the volume of distribution of the central compartment was estimated to be 38.4 L and for the peripheral compartment was 250 L (that is, 0.5 and 3.6 L/kg, respectively, for a 70 kg person).

Single PO doses of ^{14}C-simeprevir or unlabelled simeprevir showed tissue accumulation (highest ratio of tissue:blood concentrations) in the gastrointestinal tract and liver. Except for excretory tissues (mainly the small and large intestine and liver), elimination of simeprevir and/or simeprevir associated radioactivity from tissues followed a similar time course for plasma with substantial elimination at 24 h. There was minimal penetration of the blood-brain barrier. Results in either pigmented C57BL mice or Long Evans rats indicated no special affinity of simeprevir for melanin in eyes, pigmented skin, uveal tract and meninges. In reproductive tissues, the highest tissue:blood AUC ratio was seen in the uterine epithelium. Steady-state tissue (mainly pancreas, liver and heart) levels of simeprevir were determined in the repeat dose toxicity studies in mice, rats and dogs. These investigations confirmed the findings in the single dose distribution studies.

Metabolism

The major pathway for simeprevir metabolism in vivo in all species (including man) was O-demethylation and oxidation. There were more than 20 metabolites. However, the unchanged drug is the main component in rat, dog and human plasma. Like telaprevir, and to a lesser extent boceprevir, cytochrome P450 (CYP) 3A plays a major role in the metabolism of simeprevir (although metabolism in humans and laboratory animal species was low to moderate (6-28%). The CYP3A isoenzymes included CYP3A4, CYP3A5 and CYP3A7. There were also findings of minor roles for CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2E1 (although the findings were inconsistent). The metabolism of simeprevir was limited in animal species and seemed to be higher in humans; unchanged simeprevir was also the main drug-related material in the faeces of rats (84-95%), dogs (52%) and humans (31%), though a spectrum of metabolites was also detectable. Due to the low excretion of drug related material in urine, no metabolites were identified in any species indicating that metabolism is the major route of elimination.

All human metabolites were found in animals in vivo or in vitro. Thus, there were no unique human metabolites detected in vivo that were not observed in either of the key nonclinical species (rats or dogs) involved in toxicity testing. Moreover, all nonclinical species (rats and dogs) were exposed to the predominant circulating human plasma metabolite (M21). In plasma, the M18 (O-desmethyl-simeprevir), M8 (O-desmethyl of M16 [oxidation of simeprevir at the aromatic moiety] or oxidation of M18) and M21 (addition of one oxygen on the macrocycle) metabolites were detected only in rat, dog and human plasma, respectively. Although the latter circulating human metabolite (M21) was not found in the plasma of rats or dogs, it was found in the excreta of these animal species and also detected in in vitro assays with hepatocytes and/or microsomes from rats and dogs.

The M5 metabolite (a minor tertiary metabolite derived from double oxidation and O-demethylation) was only detected in human excreta (comprising only 0.47% of the dose, 200 mg, PO; study TMC435-NC219) and not detected in human plasma (but detected in the plasma of rats and dogs in pilot in vivo studies with unlabelled simeprevir [studies sighted, but not reported]). As the M5 metabolite is not a circulating metabolite, it is not likely to be of toxicological relevance. Similarly, the M23, M24 and M25 metabolites

(oxidation(s) of simeprevir, either at the macrocyclic moiety or at the aromatic moiety, or both) were detected only in human excreta (comprising only 1.27% of the dose). Similarly, in the above mentioned in vivo pilot studies, these 3 metabolites were detected as follows: M23: in faeces of rats and dogs; M24: in faeces of rats and dog plasma; M25: in plasma and faeces of dogs; M23, M24, M25: in rat bile (study TMC435-NC194).

Following repeat dosing to mice, exposures (AUC) were lower on later days than on day 1. However, following repeat PO dosing studies in mice treated for 3 months, rats for 1 month or dogs for 6 months, there were only findings in female rats of a weak, dose related induction of CYP3A activity and a non-dose-related induction of CYP2B activity in male rats (≥ 50 mg/kg/day for both findings; no observed effect levels (NOELs) not established; it is not clear if these are treatment-related findings). CYP450 content (that is, protein content) and CYP1A and CYP2E activities were also significantly lower in dogs (46-78%) that received 45 mg/kg simeprevir (NOEL 15 mg/kg/day, about 1.3 fold the anticipated clinical exposure level). No significant or dose related effects were seen in mice.

Excretion

Mass balance studies in rats and dogs indicated that the major route of excretion of simeprevir associated radioactivity was via the faeces (99% in rodents and 96% in dogs), which is slightly greater than the faecal excretion reported in humans of 91%. Biliary excretion of unchanged drug was demonstrated in rats with M16 the major metabolite in bile, along with other significant metabolites including M17 (oxidized unchanged drug), M18 and M25.

In conclusion, the nonclinical PK data submitted confirm the suitability of the animal species used in the toxicity studies.

Pharmacokinetic drug interactions

Simeprevir is not a clinically relevant inhibitor of cathepsin A enzyme activity (a ubiquitously expressed serine protease shown to play a central role in the activation of a number of HCV and HIV nucleoside analogue prodrugs) (IC_{50} > 37 µg/mL; > 8 times the clinical C_{max}). Similarly, simeprevir was not an inhibitor of uridine diphosphate glucuronosyl transferase (UGT) 1A1 and glucuronidation of bilirubin at physiologically relevant bilirubin concentrations (nor were ribavirin or oestradiol).

Other studies were conducted in order to ascertain potential PK drug interactions.

CYP inhibition/induction

In vitro studies showed simeprevir is a moderate inhibitor of CYP2A6, CYP2C8 and CYP2D6 (IC_{50}: 43 to 60 µM (32-45 µg/mL); 7 to 10 fold the clinical C_{max} (4.39 µg/mL)) and a slight inhibitor of CYP2C19 and CYP3A4/5 (IC_{50} of 86 µM (65µg/mL) and 131 µM (mean value; 98 µg/mL), respectively; 20 to 30 fold the clinical C_{max}). However, simeprevir does not induce CYP1A2 or CYP3A4 in cultured human hepatocytes at 10 µM (7.5 µg/mL; 1.7 fold the clinical C_{max}). As simeprevir is metabolised predominantly by CYP3A4, inhibitors or inducers of CYP3A4, and potentially some other CYP enzymes (shown above), may affect the PK profile of simeprevir.

Membrane transporters

The potential for PK drug interactions with simeprevir as a membrane transporter substrate or inhibitor was investigated. Studies included the transport of simeprevir by membrane transporters in vitro in single transfected cell lines and in rat and human

hepatocytes. Several membrane transporters are involved in the absorption and disposition of simeprevir, including various uptake transporters and efflux pumps. Simeprevir itself was also an inhibitor of several uptake and efflux transporters (IC_{50}: 0.3-86 µM or 0.2-64 µg/mL; 0.04 to 14 fold the clinical C_{max}). Inhibitors/substrates of P-gp and these other transporters are expected to affect the PK profile of simeprevir.

Simeprevir is a substrate of the uptake transporters: organic anion transporting polypeptide (OATP) 1B1, OATP1B3 and OATP2B1 as well as the efflux transporter pumps: P-gp, multidrug resistance protein 2 (MRP2) and mouse breast cancer resistance protein 1 (Bcrp1).

Simeprevir is also an inhibitor of the uptake transporters: OATP1B1 and sodium taurocholate co-transporting peptide (NTCP) and of the efflux transporters: P-gp, MRP2 and bile salt export pump (BSEP2).

The role of uptake transporters in simeprevir disposition in vivo was investigated in a study with Oatp1a/1b transporter deficient (*Oatp1a/1b-/-*) mice. Significantly lower liver:plasma ratios and higher plasma exposures were seen in *Oatp1a/1b* knockout mice.

Uptake into human hepatocytes was also shown to be both passive and active based on significant uptake at 4°C and inhibition of transport by NTCP/OATP inhibitors (ritonavir, rifampicin and cyclosporine; by 19%, 16% and 36%, respectively).

Ritonavir (50 µM) did not significantly inhibit simeprevir transport by the efflux transporters P-gp, MRP2 and mouse Bcrp1. Similarly, ribavirin had no significant inhibitory effect on OATP1B1, NTCP (at 300 µM) or BSEP transport (at ≤ 47.6 µM). However, significant inhibition with ritonavir, rifampicin and cyclosporine was detected on the NTCP uptake transporter and the BSEP canalicular efflux transporters.

A study in human liver microsomes of the direct inhibition of metabolism of budesonide, [^{3}H]-diazepam, digoxin, metoprolol glibenclamide, [^{3}H]-paroxetine and simvastatin showed findings of relatively high IC_{50} values ranging from 21.3 µM (16.0 µg/mL; 3.6 fold the clinical C_{max}) (inhibition of simvastatin metabolism) to 300 µM (225 µg/mL; 50 fold the clinical C_{max}) (inhibition of metoprolol metabolism), suggesting simeprevir is a weak inhibitor of CYP450 metabolism and the metabolism of potential co-medications in vitro. However, based on relatively high plasma concentration in the clinical setting (C_{max} 4.39 µg/mL) together with even higher levels predicted in the liver (10 to 40 fold liver:plasma ratios in mice and rats), drug-drug interaction during clinical use with simeprevir with some of these drugs is likely, possible, and may be clinically relevant. In dogs, ritonavir co-administration at 10 mg/kg (3 times daily) increased simeprevir exposure by 2 to 3 fold after a single dose of 2 or 5 mg/kg (with only limited effects on C_{max}). The finding is attributed to ritonavir mediated inhibition of CYP3A.

Simeprevir in combination with ribavirin and PegIFNα

Simeprevir is proposed to be used in combination with RBV and PegIFNα. However, no PK interaction studies have been conducted with simeprevir in laboratory animals. Since i) the metabolism of PegIFNα is not fully characterised and the cytochrome P450 enzyme system is not involved in the metabolism of ribavirin (PEGASYS RBV Combination Therapy PI); and ii) PegIFNα and RBV do not affect either hepatic CYP3A4 (based on a clinical PK interaction study [Peg-Intron Clearclick PI]) and human P450 enzymes, respectively, a kinetic interaction is not anticipated following concomitant administration of simeprevir with PegIFNα and RBV. The draft PI notes the plasma Cmax and AUC of simeprevir were similar during co-administration of PegIFNα and ribavirin compared with administration of simeprevir alone. On a theoretical basis, no other PK interactions can be identified on the basis of a potential interaction with membrane transporters involved in the disposition of these three co-administered drugs.

Clinical studies

Due to the potential for PK interactions, numerous clinical PK drug interaction studies were undertaken with simeprevir co-administered with other drugs including CYP3A4 substrates and/or inhibitors and inducers, as well as substrates and inhibitors of several drug transporters. The draft PI indicates that co-administration of simeprevir with strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir, while co-administration with strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir, leading to loss of efficacy. It also notes that the inhibition of CYP2C19 and CYP2D6 observed in vitro was not observed in clinical studies. However, simeprevir mildly inhibits the CYP1A2 activity and intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. Thus co-administration of simeprevir with drugs that are predominantly metabolised by CYP3A4 could result in increased plasma levels of such drugs. Moreover, a clinical interaction study in healthy volunteers, indicates that co-administration of digoxin or rosuvastatin with simeprevir resulted in increased plasma exposure of digoxin and rosuvastatin (likely due to inhibition of P-gp and OATP1B1, respectively). Thus, co-administration of simeprevir with drugs that are substrates for OATP1B1 and P-gp transport may result in increased plasma levels of such drugs.

Overall, there is a strong indication that exposure to simeprevir 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.

Toxicology

Acute toxicity

Studies specifically designed as single dose toxicity studies were not submitted. However, some preliminary toxicity studies were conducted using the clinical (PO) route prior to the repeat dose studies (that is, 3 non-GLP single dose escalation studies which included a repeat dose phase in rats, dogs and monkeys. These studies included only limited observations and reporting, no necropsies were done and target organs were not identified. These studies were sighted but were not evaluated. In mice, single doses of simeprevir were also investigated in two (PO) micronucleus studies, where the toxicity findings confirmed adequate exposures in the animals. In these studies, simeprevir was generally well tolerated up to 500 mg/kg in mice, 1000 mg/kg in rats, 160 mg/kg in dogs and in monkeys at 150 (PO) and 5 (IV) mg/kg.

Although no traditional single dose toxicity studies were submitted, the acute toxicity of simeprevir by the proposed clinical route was addressed in the repeat dose studies. This is acceptable based on the current applicable guidelines and the present recognition that data derived from traditional single dose toxicity studies are of limited value and the fact that information on acute toxicity can be obtained in other types of toxicity studies.

Notable acute toxic effects in a 14 day PO (gavage) repeat dose study in mice showed organ weight and histological changes at ≥ 500 mg/kg/day, indicative of centrilobular hepatocellular hypertrophy. At ≥ 1000 mg/kg/day, there were additional findings in the pancreas and small intestine of swelling/vacuolisation of apical enterocytes in the duodenum and jejunum and vacuolisation in the pancreas. In a 14 day PO (gavage) study in rats, at ≥ 120 mg/kg/day there were findings of minor alterations of serum chemistry parameters (increases in potassium and alanine transaminase (ALT) and decreases in total protein, total bilirubin, cholesterol and albumin). However, in a 2 week PO (gavage) study in dogs, acute endocardial and myocardial necrosis was also observed at high doses (which corresponded to systemic exposure levels (AUC), 28 times higher than the clinical exposure at the proposed simeprevir dose of 150 mg/day [animal:human exposure ratio based on AUC (ER_{AUC}) = 28); there were no similar findings in other species or in 6 and 9

month PO (gavage) toxicity studies using dogs at doses of up to 11 and 4 fold the anticipated clinical exposure level, respectively]. In the 2 week dog study, there were also findings at high doses [ER_{AUC}, 28] of moderate to high levels of bilirubin in urine, marked decreases in cholesterol and increases in total and direct bilirubin, cholestasis (minimal canalicular cholestasis) as well as liver necrosis [several minimal hepatocellular necrotic foci at ≥ 40 mg/kg/day (ER_{AUC},12)]. In a 14 day PO (gavage) study in monkeys, there were limited findings of hypersalivation, emesis and increased aspartame transaminase (AST) (4.5 fold) at 20 mg/kg/day [ER_{AUC}, 19]).

There were a number of unscheduled deaths in the 2 week repeat dose PO (gavage) toxicity studies in mice (≥ 500 mg/kg/day), rats (120 mg/kg), dogs (≥ 40 mg/kg/day) and monkeys (200 mg/kg/day). The cause of death was not determined in mice and rats, but the sponsor attributed deaths mostly to aspiration of the vehicle/formulation in dogs or to a gavage accident in a single monkey (200 mg/kg/day). Deaths were observed mainly at high doses.

Repeat dose toxicity

Pivotal studies of up to 3 months were conducted in mice, 6 months in rats, 9 months in dogs and a non-pivotal 2-4 week study was carried out in male monkeys. In a 1 month study in rats and a 1 and 9 month study in dogs, there were 4, 4 and 13 week recovery periods, respectively. The route of administration (gavage) was the same as that proposed clinically (PO), and animals were dosed once a day. The proposed therapeutic dose is taken once daily. The toxicity findings in the rat and dog studies are particular relevant based on the comparable PK and metabolic profile to that of humans. In other respects, the design of the repeat dose studies was consistent with ICH guidelines (duration of pivotal studies, species used (rats and dogs) group sizes and the use of both sexes were consistent with ICH guidelines).

In some studies, there was also investigation of some biomarkers to investigate possible treatment related effects of simeprevir on the heart (troponin, creatine kinase and isoenzymes), pancreas (amylase, lipase) and gastrointestinal system (CCK). In addition, steady-state tissue (primarily the liver and the heart) concentrations of simeprevir were determined in the repeat dose toxicity studies in mice, rats and dogs.

Dietary (feed) dosing studies of up to 13 weeks were also carried out in mice and rats to determine dose levels for potential carcinogenicity studies. In addition, studies using dietary administration were performed in an attempt to increase exposure and/or to avoid mortality or gavage problems related to the entry of the irritant and viscous formulation into the respiratory tract.

Relative exposure

In the table below, exposure ratios have been calculated based on animal:human plasma $AUC_{0\text{-}24\,h}$. Human reference values are from Phase IIb/III trials data in HCV-infected patients administered the proposed human dose of 150 mg. Based on the anticipated clinical exposure (AUC) at the clinical dose, simeprevir animal/human $AUC_{0\text{-}24\,h}$ ratios in the pivotal studies were low in mice and rats (1.2-3.3 in mouse/human [3 month study], 0.5-1.7 in rat/human [3, 6 months]) but was generally adequate in dogs (2.6-14.5 in dog/human [6 and 9 month studies]). Exposures were only slightly higher in the rodent dietary feed studies compared with PO gavage studies. No substantial plasma accumulation of the drug with repeat daily dosing was evident.

Exposure at no effect levels

The NOELs could not be determined in chronic mouse (gavage or dietary) studies due to the range of effects observed. The highest NOAEL in rats was 150 mg/kg/day by PO (gavage) for 6 months (the NOAEL was not established in dietary [feed] administration

studies); in dogs, the highest NOAELs were 15 mg/kg/day for up to 6 months and 5 mg/kg/day for 9 months. At these doses, total daily exposure (AUC) was less than or did not substantially differ from that anticipated in humans. The NOAEL was not established in chronic (male) monkey PO (gavage) studies at doses where the total daily exposure, did not substantially differ from that expected in humans, as shown in the table below (monkey-to-human exposure [AUC]).

Table 1: Relative exposure in pivotal repeat-dose toxicity and non-pivotal monkey studies

Species Study Duration	Dose (mg/kg/day)	Day	C_{max} (µg/mL)		AUC (µg.h/mL)		Exposure Ratio#			
							C_{max}		AUC	
			M	F	M	F	M	F	M	F
Mouse (CD-1) 3 month PO (gavage)	150	90	10.1	15.0	50.9	61.2	2.3	3.4	0.9	1.1
	500	90	17.6	15.0	117	78.8	4.0	3.4	2.0	1.4
	2000/1000[a]	90	14.9	14.3	122	141	3.4	3.3	2.1	2.5
Mouse (CD-1) 13 week ***Dietary***	500	88	-	-	33.3	68.3	-	-	0.6	1.2
	2000	88	-	-	66.7	180	-	-	1.2	3.1
Mouse (CD-1) 13 week ***Dietary***	3000	87	-	-	189	143	-	-	3.3	2.5
Rat (SD) 1 month PO (gavage)	50	28	1.76	2.57	8.80	12.6	0.4	0.6	0.2	0.2
	150 (NOAEL)	**28**	**3.82**	**3.84**	**22.6**	**26.9**	**0.9**	**0.9**	**0.4**	**0.5**
	500	28	4.04	4.74	33.7	42.0	0.9	1.1	0.6	0.7
Rat (SD) 6 month PO (gavage)	50	181	2.11	2.39	8.32	12.7	0.5	0.5	0.1	0.2
	150 (NOAEL)	**181**	**3.65**	**4.76**	**20.9**	**32.8**	**0.8**	**1.1**	**0.4**	**0.6**
	500	181	4.08	7.22	30.2	52.7	0.9	1.6	0.5	0.9
Rat (SD) 13 week ***Dietary***	500	88	-	-	23.8	57.8	-	-	0.4	1.0
	1000	88	-	-	28.3	55.4	-	-	0.5	1.0
	2000	88	-	-	26.8	99.3	-	-	0.5	1.7
Dog (Beagle) 2 week PO (gavage)	**10 (NOAEL)**	**14**	**13.8**	**14.3**	**73.3**	**72.4**	**3.1**	**3.3**	**1.3**	**1.3**
	40	14	71.9	36.5	876	520	16.4	8.3	15.2	9.0
	160 (M) 120 (F)	14	81.2	93.3	1510	1660	18.5	21.2	26.3	28.9
Dog (Beagle) 1 month PO (gavage)	**10 (NOAEL)**	**27**	**4.02**	**4.57**	**15.5**	**18.6**	**0.9**	**1.0**	**0.3**	**0.3**
	30	27	29.5	40.5	201	374	6.7	9.2	3.5	6.5
	90	27	93.5	94.8	1478	1710	21.2	21.6	25.7	29.7
Dog (Beagle) 6 month PO (gavage)	5	177	2.42	2.92	8.98	10.4	0.6	0.7	0.2	0.2
	15 (NOAEL)	**177**	**14.3**	**17.2**	**69.9**	**79.7**	**3.3**	**3.9**	**1.2**	**1.4**
	45	177	41.0	72.7	475	833	9.3	16.6	8.3	14.5
Dog (Beagle) 39 week PO (gavage)	**5 (NOAEL)**	**273**	**1.26**	**2.25**	**4.34**	**9.31**	**0.3**	**0.5**	**0.1**	**0.2**
	15	273	10.5	17.2	47.4	70.1	2.4	3.9	0.8	1.2
	45	273	36.1	24.9	297	152	8.2	5.7	5.2	2.6
Monkey (Rhesus) 14-28 Day PO (gavage) *20 mg/kg - 14 days* *60 mg/kg - 28 days*	20	14	8.8	-	85.2	-	2.0	-	1.5	-
	60	15	40.4	-	663	-	9.2	-	11.5	-
Human[b] *steady state*	150	overall	4.39[c]		57.5		-		-	

NOAEL values are Bolded; (#): Animal:human plasma AUC0–24 h; (a): 2000 mg/kg/day until Day 7; then from Day 8, 1000 mg/kg/day; (b): Exposure data (AUC) in HCV-infected patients after treatment with simeprevir at 150 mg once daily (q.d.) for 12 weeks as triple therapy with PegIFN (180 µg weekly) and ribavirin (RBV; 200 mg twice daily (b.i.d.)) derived from pooled Phase III trials C208, C216 and HPC3007; (c) Cmax from Phase IIb trial C205 in HCV-infected patients (measured 1 day after 4-6 weeks treatment with simeprevir 150 mg q.d as triple therapy with PegIFN (180 µg once weekly) and ribavirin (RBV; b.i.d. (200 mg tablets) totalling 1000 mg q.d. (2 tablets morning/3 tablets evening; 1200 mg q.d. if body weight ≥ 75 kg))

Major toxicities

The main toxicology finding for simeprevir of liver toxicity was consistent with a similar finding with other protease inhibitors that inhibit HCV as a class. The major target organs for simeprevir were the liver (hepatocellular necrosis, centrilobular hypertrophy, increases in bilirubin and liver enzymes) and gastrointestinal tract (vacuolation of apical enterocytes). There were also some effects of simeprevir observed on the pancreas, adrenals and the heart (in dogs). Effects in these organs were generally dose dependent and generally reversible by the end of 4-13 week treatment free recovery periods. However, at the reported NOAELs, exposure to simeprevir in rats and dogs is similar to the anticipated clinical exposure. This is acceptable, based on limited nonclinical findings in the liver and GI tract (see below).

Liver Increases in bilirubin, bile acids and liver enzymes (ALT, AST and alkaline phosphatase (ALP)) accompanied adverse liver histopathology findings in rodents and dogs. Moreover, frequently observed reductions in cholesterol, triglycerides and total protein (associated with lower albumin concentrations) in all species and routes (gavage and dietary) is likely related to simeprevir-induced hepatotoxicity.

Liver toxicity in dogs (PO, gavage) consisted of hepatocellular necrosis (focal and multifocal) associated and (peri) portal mixed inflammatory infiltrate with the (multi) focal presence of brown pigmented Kupffer cells and macrophages in a 6 month dog study at 45 mg/kg (11 times the anticipated clinical exposure at the proposed simeprevir dose of 150 mg/day [ER_{AUC}]) but not after 9 months at the same dose (although much lower exposure levels were achieved [ER_{AUC}, 4 (NOAEL)]). In the 1 month dog study, liver necrosis observed at ≥ 30 mg/kg/day (ER_{AUC}, 5) recovered following a 1 month treatment free recovery period. In the 9 month dog study, hepatic alterations (increases in ALT, ALP and bile acids; decreases in cholesterol) at 45 mg/kg [ERAUC, 11]) were reversible following a 13 week recovery period. Minimal canalicular cholestasis seen in the 2 week dog study at high doses [ER_{AUC}, 28] was not observed in studies of longer duration.

An in vitro cytotoxicity study confirmed the potential hepatic toxicity (liver necrosis [several minimal hepatocellular necrotic foci at ≥ 40 mg/kg/day; ER_{AUC}, 12]) observed in dogs in as early as 2 weeks of dosing. The 50% effective doses ED_{50}s reported for various markers of cytotoxicity (lactate dehydrogenase (LDH) release, neutral red uptake and adenosine triphosphate (ATP) content) were similar across all the nonclinical animal species (rat, dog, monkey: 3-19 µg/mL) and humans (4-26 µg/mL).

In study TMC435-NC108, the maximum concentration of simeprevir found in the rat liver following a single PO dose of 40 mg/kg was 103 µM (77,600 ng/g), which is about 18 fold the clinical C_{max} of 5.85 µM [4.39 µg/mL]). Whilst it is noted that the study was performed with the absence of serum proteins (simeprevir is up to 99.9% protein bound, resulting in a free fraction in plasma of <0.1%), in this rat distribution study the liver:plasma ratio is 39. Therefore, although the hepatocytes in this in vitro study were exposed to very high free drug levels that may not be readily achievable under in vivo conditions, the study highlights that hepatocytes are a potential target of cytotoxicity in vivo as reported in the dog studies.

Adverse toxicological findings in the liver of rodents differed to the findings in dogs. Centrilobular hepatocellular hypertrophy (occasionally with dense staining cytoplasm and prominent mitoses and increased liver weights) was observed in mice following dosing by gavage in 2 week (≥ 500 mg/kg, [ER_{AUC}, 2.8]) and 3 month studies (≥ 500 mg/kg, [ER_{AUC}, 1.7]) or following dietary administration in mice in a 2 week (≥ 500-550 mg/kg, [ER_{AUC}, 3.2]) and a 3 month study (in males at ≥ 500 mg/kg, [ER_{AUC}, 0.6]). The NOAEL for the finding in mice with PO dosing by gavage was 150 mg/kg/day [ER_{AUC}, 1] in the 3 month study, but a NOAEL was not established in the dietary administration study for 3 months. This liver finding was also seen in rats following dietary administration in a 3 month study

(≥ 500 mg/kg, [ER_{AUC}, males: 0.4, females: 1.0]) but not following PO dosing by gavage in rats for periods of up to 6 months at doses up to 500 mg/kg/day [ER_{AUC}, males: 0.5, females: 0.9 (NOAEL)]. Reversibility of the finding was not assessed in any of the rodent dietary administration studies conducted. Although hepatic hypertrophy was not detected in any of the rat PO gavage dosing studies, hepatic alterations of increases in ALT, ALP and bile acids and decreases in cholesterol observed at 500 mg/kg [ER_{AUC}, 0.7]) recovered fully following a 1 month treatment-free recovery period in a 1 month PO gavage study.

The finding in the liver of rodents was considered by the sponsor as an adaptive or compensatory response to slight CYP inhibition/induction noted in ex vivo studies following repeat dosing. However, the evaluator notes this effect of simeprevir on CYP enzymes was very small (slight) in mice and rats and/or lacked a dose response in rats (see *Assessment, metabolism* above). An overall significant effect of simeprevir on hepatic CYP inhibition/induction however, is questionable. Another and/or or a different mechanism resulting in hepatic cellular hypertrophy or trophic effects may be involved and is possibly associated with the (low to moderate) CYP3A metabolism of simeprevir.

Limited findings of increases in bilirubin [60 mg/kg, ER_{AUC}, 12; NOAEL, 20 mg/kg, ER_{AUC}, 2] and AST [20 mg/kg/day; ER_{AUC}, 2; NOAEL not established] were seen in the 2-4 week non-pivotal study in monkeys.

The clinical evaluation report notes that during the first 12 week phase, hyperbilirubinaemia (without concomitant rises in ALT or AST) was seen in both treatment groups (7.9% simeprevir versus 2.8% placebo). Information provided by the sponsor on the possible mechanism/s underlying the effects on increased bilirubin in both the nonclinical studies and clinical studies suggests the finding is related to decreased bilirubin elimination related to inhibition of the hepatic transporters OATP1B1 (bilirubin uptake) and MRP2 (bilirubin efflux) resulting in saturation of the hepatic uptake and biliary excretion of bilirubin. In the clinical studies, hyperbilirubinaemia is possibly also due to RBV-induced haemolysis as well.

The sponsor also suggested that the possible mechanism underlying the effect of increased serum bile salts was via an effect on the hepatocyte BSEP and NTCP transporters.

Gastrointestinal and pancreas toxicity: Occasionally a higher incidence of soft, mucoid or pale faeces was noted in rodents (gavage and dietary dosing) and dogs (gavage). In rodents (3 month gavage and dietary dosing studies in mice or 2 week PO gavage and 3 month dietary dosing studies in rats) simeprevir delayed gastric emptying, resulting in abnormal stomach contents and/or abdominal and gastrointestinal distension. This generally was seen at high doses (≥ 1000 mg/kg in mice and ≥ 500 mg/kg in rats). Additionally, there were often associated findings of swelling/vacuolisation of apical enterocytes in the duodenum and jejunum in rodents in both the gavage and dietary dosing 2 week and/or 13 week studies (≥ 500 mg/kg [ER_{AUC}, 2.8, in mice,]; in the 3 month dietary study the NOAEL was not established in mice, but the NOAEL was 1000 mg/kg in a 3 month dietary study in rats [ER_{AUC}, 0.75]). In dogs, swelling/vacuolisation of apical enterocytes in the small intestine was observed at ≥15 mg/kg [ER_{AUC}, 1.3] in the 6 and 9 month studies, with the NOAEL for the finding 0.2 times the anticipated clinical exposure. Reversibility of the finding was demonstrated in dogs after a treatment free period of 13 weeks in the 39 week study.

There were also findings in the pancreas in mice (diffuse vacuolisation of the exocrine pancreas with more prominent apoptotic acinar cells and decreased zymogen/basophilia) following gavage and dietary dosing in 2 week and 3 month studies at ≥500 mg/kg [ER_{AUC}, 2.8]; the NOAEL in the 3 month (gavage) study was 150 mg/kg [ER_{AUC}, 1]). There were also findings in the pancreas in rats consisting of prominent apoptotic acinar cells following dietary dosing in a 2 week dietary study at ≥ 3375 mg/kg [ER_{AUC}, 2.8]; the NOAEL in the same study was 1350 mg/kg [ER_{AUC}, 0.8]). In both mice and rats, the findings were with

associated increases in plasma amylase and lipase levels and increases in pancreas weight without changes in CCK. The reversibility of this finding was not evaluated. In dogs, the pancreatic findings (at ≥5 mg/kg [ER_{AUC}, 0.1]) included inflammation and mononuclear infiltrates in the 6 and 9 month studies (NOAEL for the finding was not determined), but the findings in dogs were reversed after a 3 month recovery period.

In safety pharmacology studies it was shown that simeprevir was a moderate inhibitor of the CCK receptor in vitro and inhibited gastric emptying in rats in vivo. However, in a subsequent primary screening study employing a large panel of assays (details not specified), simeprevir had no relevant effect in the gastrointestinal tissue assay panel. This suggests there is no direct (functional) effect of simeprevir on CCK. The sponsor therefore considers that the gastrointestinal toxicity may be a local effect of simeprevir as a result of prolonged exposure and contact, related to delayed gastric emptying following the dosing of a viscous formulation. This claim is supported by observations that gastrointestinal toxicity increased with dose despite the absence of any notable increase in systemic exposure. However, gastrointestinal toxicity (swelling/vacuolisation of apical enterocytes) was also frequently reported in dietary dosing studies in mice and rats.

Pancreatic toxicity was suggested by the sponsor to be likely be related to protease inhibition in the pancreas. The sponsor notes that: *"trypsin inhibitors, such as raw soy and Camostat, have been demonstrated to suppress pancreatic proteases in the small intestines, thereby blocking their inhibiting effect (= negative feedback) on CCK, resulting in an increase in CCK release from the intestinal mucosa. Such an inhibitory action on pancreatic proteases by simeprevir may explain the findings. The major physiological function of the hormone CCK is stimulation of pancreatic enzyme secretion; CCK is also a physiologic regulator of gastric emptying. Elevated CCK levels will delay gastric emptying and stimulate the secretory activity of the exocrine pancreas. The increased pancreas weight, morphological findings (vacuolisation, basophilia/decreased zymogen and prominent apoptotic acinar cells) and elevated amylase/lipase levels are confirmative for an increased secretory activity of the exocrine pancreas."*

The evaluator notes that in mice and rats, plasma CCK levels (measured in dietary dosing studies) were unaltered. Therefore, the finding of pancreatic toxicity in rodents was probably a result of (and exacerbated by) the prolonged exposure and contact with simeprevir in the gastrointestinal tract as a result of delayed gastric emptying following the dosing of a viscous formulation. The possible mechanism underlying the pancreatic findings in dogs (inflammation and mononuclear infiltrates) in the 6 and 9 month studies was not specifically addressed by the sponsor, but could also involve local effects of simeprevir as a result of prolonged exposure and contact also following the dosing of a similar viscous formulation. However, pancreatic toxicity was also frequently reported in dietary dosing studies in mice and rats.

Overall, the gastrointestinal and/or pancreatic toxicities may be considered secondary to the local effects of high concentrations and prolonged periods of exposure of simeprevir in the intestinal lumen and therefore are not likely to be clinically relevant adverse toxicological findings.

Cardiovascular: In a 2 week repeat PO (gavage) dose acute toxicity in dogs, acute endocardial and myocardial necrosis was also seen at high doses which corresponded to systemic exposure levels (AUC), 28 times higher than the clinical exposure at the proposed simeprevir dose of 150 mg/day. One male dog dosed at 160 mg/kg/day showed acute myocardial necrosis, restricted to the endocardial and subendocardial area of the left ventricle and a single female receiving a high dose of 120 mg/kg/day showed a small focus, consistent with acute myocardial necrosis, in the papillary muscle of the left ventricle. The findings were not associated with alterations in the cardiac biomarkers: cardiac troponin I, creatinine (CK) and CK isoenzymes. However, limited evidence of

cardiac toxicity in this 2 week study was not confirmed in the pivotal studies at relative exposures of 11 and 4 fold in 6- and 9-month studies, respectively.

There were also minor findings in monkeys of inflammatory cell foci in heart in 2 out of 2 monkeys dosed at 20 mg/kg [ER_{AUC}, 1.5] for 14 days and 3/3 monkeys dosed at 60 mg/kg [ER_{AUC}, 12]) for 28 days; the NOAEL for the finding was not determined. However, there were no associated changes in ECGs, cardiac (transthoracic) echocardiography or the cardiac clinical chemistry panel. Similarly, there were no significant ECG abnormalities noted in dogs in either the PO and IV cardiovascular safety studies, or in any of the repeat-dose toxicity studies in dogs conducted at clinically relevant doses (0.1 to 30-times the anticipated clinical exposure [based on AUC]).

However, in the safety IV dog study, there were moderate cardio-haemodynamic alterations of increased vascular resistance, decreased heart rate and cardiac output at ≥ 2.5 mg/kg (ER, 6) as well as effects on the RR interval (29% increase) at 1.25 mg/kg (ER, 2.7). The NOAEL was 0.63 mg/kg (ER, 1.2, based on plasma levels at the end of the infusion period). There also some findings in the dog 39 week PO (gavage) study of significant increases in the P wave and PR intervals (on ECG, time in seconds from the beginning of the P wave to the beginning of the QRS complex). Moreover, in the safety studies, there were in vitro findings of blocking activity at the cardiac sodium (Na+) channel (the NOAEL was 0.1 µM [0.075 µg/mL; ER, 17], resulting in shortening of the cardiac action potential duration and a reduction of the intraventricular conduction time in the isolated Langendorff-perfused rabbit heart at ≥ 1 µM; the NOAEL was 0.3 µM (0.22 µg/mL; ER, 50).

On balance and taking into consideration all the findings, cardiac toxicity maybe a clinically relevant finding in some high risk patients or those who may achieve high plasma levels of simeprevir.

Adrenal glands" Adrenal toxicity was also identified in rodents and dogs. In mice, a prominent X zone (minimal) and cortical atrophy was noted at the high dose of 3000 mg/kg ([ER_{AUC}, 2.5]; NOAEL was 2000 mg/kg [ER_{AUC}, 3]) in the 3 month dietary dosing study in female mice. At the high dose in both the rat 2 week gavage study in females (360 mg/kg [ER_{AUC}, 0.7]; NOAEL was 120 mg/kg [ER_{AUC}, 0.5]) and the 1 month gavage study in males (500 mg/kg [ER_{AUC}, 0.6]; NOAEL was 150 mg/kg [ER_{AUC}, 0.4]), organ weight increases were identified with no histopathological correlates. Similarly, at the high dose in males (500 mg/kg [ER_{AUC}, 0.5]; NOAEL was 150 mg/kg [ER_{AUC}, 0.4]) in the rat 6 month gavage study, there were findings of organ weight increases at the 3 month interim kill as well as histopathological findings of minimal focal unilateral cortical hyperplasia in 1 of 10 and 1 of 20 males, at the 3 month interim kill and 6 month terminal kill, respectively. The finding of an increase in the adrenal gland organ weight was reversible in the 1 month gavage study in rats after a 1 month recovery period. The potential clinical relevance of adverse toxicological findings in the adrenal gland is uncertain.

Drug combination repeat-dose toxicity studies

The effects of concomitant drug administration, as clinically intended (simeprevir, PegIFNα and RBV), were not evaluated in either nonclinical PK or toxicity studies. The sponsor was requested by TGA to comment on this and to comment on whether any interactions are anticipated. In response, the sponsor advised (in part) that: *"In conclusion, only liver and gastrointestinal tract are common target organs with simeprevir and PegIFN/RBV. A synergistic effect cannot be excluded in nonclinical drug combination repeat dose toxicity studies. However, the risk is low for both target organs and parameters such as liver function can be monitored and managed in the clinic."*

Although the sponsor's response is noted, it is emphasised that the discussion points provided by the sponsor (not shown above) are predictions only. Potential (toxicological)

adverse effects following administration of the combination could be additive/synergistic at the organ level and/or at the level of the individual toxicities.

Genotoxicity

Adequate in vitro (Ames, mouse lymphoma) and in vivo (mouse micronucleus) genotoxicity studies were negative.

Carcinogenicity

Carcinogenicity studies were not conducted for simeprevir and they were not required, as the treatment duration is 12 weeks, and genotoxicity studies were negative[5].

Reproductive toxicity

Reproductive toxicity studies included a study of fertility and early embryonic development in male and female rats, teratology studies in mice and rats, and a pre- and postnatal development study in rats. All studies complied with GLP guidelines, and were adequate with respect to species, numbers of animals and study design. The timing and duration of treatment were appropriate during appropriate gestational periods.

Single dose PK for simeprevir were determined in rabbits using a number of formulations (0.5% methocel suspension, capsules and aqueous nano-suspension) and routes of administration (PO, IV and subcutaneous (SC)). However, in rabbits, clearance of simeprevir was very high resulting in a very low exposure to simeprevir and poor bioavailability (2.5%). Therefore, the rabbit was deemed as not suitable for embryo-foetal development studies and the mouse was used instead.

The rat is considered an appropriate nonclinical model to evaluate developmental and reproductive endpoints given its demonstrated exposure to simeprevir and its major human metabolites in vivo. Whilst extensive metabolic profiling was not performed in mice, exposure to simeprevir in vivo has been demonstrated, but not for the predominant human plasma metabolites.

[5] ICH S1A Guideline on the need for carcinogenicity studies of pharmaceuticals, 1995.

Table 2: Relative exposure in reproductive toxicity studies

Species Study Details (Study No.)	Dose (mg/kg/day)	Day	Cmax (µg/mL)		AUC (µg.h/mL)		Exposure Ratio#			
							Cmax		AUC	
			M	F	M	F	M	F	M	F
Fertility Study **Rat** Study TMC435-NC190 (TOX8714) Expected systemic exposures in M & F from **Rat** 6 month PO (gavage) study (TMC435-NC179) ***3 month TK sampling point***	50	90	1.64	3.08	9.45	11.7	0.4	0.7	0.2	0.2
	150	90	3.73	4.34	22.5	25.6	0.8	1.0	0.4	0.4
	500	90	3.21	5.75	30.2	46.4	0.7	1.30	0.5	0.8
***Mouse**, EFD* PO (gavage) (TMC435-NC189)	150	GD15	-	13.1	-	90.7	-	3.0	-	1.6
	500 (NOAEL)	**GD15**	**-**	**17.5**	**-**	**221**	**-**	**4.0**	**-**	**3.8**
	1000	GD15	-	25.0	-	352	-	5.7	-	6.1
Rat, *EFD* PO (gavage) (TMC435-NC188)	50	GD17	-	2.24	-	16.4	-	0.5	-	0.3
	150	GD17	-	3.45	-	28.3	-	0.8	-	0.5
	500 (NOAEL)	**GD17**	**-**	**3.59**	**-**	**29.3**	**-**	**0.8**	**-**	**0.5**
Rat, *^Pilot PND Study* PO (gavage) (TMC435-NC227)	150	LD6	-	4.99	-	38.2	-	1.1	-	0.7
	500	LD6	-	6.39	-	42.5	-	1.5	-	0.7
	1000	LD6	-	7.50	-	56.1	-	1.7	-	1.0
Human[a]	150	overall	4.39[b]		57.5		-		-	

NOAEL Bolded: no observed adverse effect level; (#): Animal:human plasma $AUC_{0-24\,h}$, (^): Toxicokinetics: not performed in main PND study - evaluated in pilot study only at same doses, (a): Exposure data in HCV-infected patients after treatment with TMC435 at 150 mg q.d. for 12 weeks were derived from C205 Phase IIb trial (C_{max}) and from pooled C208, C216 and HPC3007 Phase III trials (AUC) (b): C_{max} from C205 Phase IIb trial

Plasma exposure in pregnant rats was comparable to that observed in non-pregnant rats, although exposure in in pregnant mice was about 40-50% lower than that observed in non-pregnant mice. The fertility study in rats was not supported by toxicokinetic data, but relative exposure levels were estimated using toxicokinetic data from the 6 month repeat dose toxicity study using the 3 month interim sampling point. Additionally, toxicokinetic data to support the main pre/postnatal study was derived from a pilot study at the same doses. Based on the anticipated clinical exposures at the proposed clinical dose, simeprevir animal/human $AUC_{0-24\,h}$ ratios at the high doses employed in the pivotal studies in rodents were low in the fertility/early embryonic development, teratology and pre/postnatal development studies in rats (0.5-1.0) and moderate (6.1) in the teratology study in mice.

Simeprevir associated radioactivity was not able to cross the placenta of pregnant rats when administered as a single PO dose of 120 mg/kg of [^{14}C]-simeprevir by gavage on gestation day (GD) 18. Distribution of radioactivity throughout fetal tissues was low, with total radioactivity levels in the whole fetus and fetal liver and below the lower limit of quantitation (LLOQ) of 0.79 µg eq/g, indicating placental transfer of simeprevir or its metabolites to the fetus was negligible. Total radioactivity (AUC) values in maternal reproductive tissues (ovary, vagina, uterus) including the mammary gland and placenta were comparable to or lower than the AUC in blood, except for uterine epithelium (tissue:blood $AUC_{0-32\,h}$ of 4.6).

Transfer of simeprevir associated radioactivity into the milk of lactating rats not measured directly. However, in a pilot pre/post-natal toxicity study in rats, simeprevir was detected in the plasma of suckling pups, indicating excretion of simeprevir in milk. Additionally, pup liver samples were collected on day 6 of lactation with findings of simeprevir in liver

with exposure ($AUC_{0\text{-}24\,h}$) values 3 to 4 times higher than corresponding plasma levels. As placental transfer is likely negligible, it is probable that exposure to simeprevir in suckling pups is due to excretion via milk.

In a fertility and early embryonic development study with daily dosing of up to 500 mg/kg in male and female rats, simeprevir showed adverse findings in male rats of no motile sperm (100% static), small testes and epididymides in 3 males (2 out of 24 at 50 mg/kg/day and 1 out of 24 at 500 mg/kg/day). This resulted in infertility in 2 of 3 affected males (1 male at 50 mg/kg and 1 male at 500 mg/kg). The simeprevir exposure multiple at the dose level of 50 mg/kg/day was 0.2 fold the anticipated clinical exposure based on AUC. A similar finding to small testes in the rat fertility study was seen in the 6 month repeat dose toxicity study in dogs at ≥ 5 mg/kg ([ER_{AUC}, 0.2]; the NOAEL was not established). The finding in dogs comprised minimal to slight testicular atrophy and tubular hypoplasia. Although this potentially clinical relevant and significant effect occurred at very low incidences across studies/species in rats (in the fertility study) and dogs (in the repeat dose study), this may have been due to the relatively low exposures achieved based on AUC [as was the case for rats in most of the repeat dose toxicity studies; although in dogs, exposure were generally higher[6]]. Reversibility was not assessed in the 6 month dog study.

In the fertility study, female rats showed an 11% decrease in bodyweight gain at the high dose of 500 mg/kg/day ([ER_{AUC}, 0.8]; NOAEL, 150 mg/kg [ER_{AUC}, 0.4]) over gestation days 8-13 (that is, after cessation of dosing), with findings of increases in post-implantation losses of 1.7 and 2.1 times the control value at the low and high doses of 50 mg/kg [ER_{AUC}, 0.2] and 500 mg/kg, respectively. A NOAEL was not determined.

In the main embryo-fetal development study in pregnant mice dosed with simeprevir during organogenesis, there were notable findings at the high dose level of 1000 mg/kg ([ER_{AUC}, 6.1]) comprising 2 out of 24 maternal deaths, increased post-implantation losses and decreased fetal weights [1.0 g compared with controls, 1.11 g; $p < 0.01$]. The NOAEL for these findings was 500 mg/kg [ER_{AUC}, 3.8]).

Skeletal variations involving rib development (consisting primarily of short 13/14, 14/14 supernumerary and full supernumerary 14th ribs) were also observed in the mouse study at all doses (that is, at ≥ 150 mg/kg ([ER_{AUC}, 3.8]; the NOAEL was not established). In this study, an additional skeletal variation (costal cartilage [8th connected to sternum]) was observed at the high dose level only of 1000 mg/kg [ER_{AUC}, 6.1] with a NOAEL of 500 mg/kg [ER_{AUC}, 3.8]) for the finding. Although all the above fetal incidences (11-52%) clearly exceeded those of the respective control incidences (0.7-22%), the incidences seen in all the simeprevir treated groups fell into (or were similar to) the historical control data (HCD) range (52%) provided for the 2 variations involving rib development. However, the historical control data (compiled since 2007) appeared somewhat limited, with only a small number of fetuses (48) and litters (8) examined by the study facility.

There was no evidence of fetal malformations or adverse variations in the offspring of pregnant rats exposed to simeprevir during the period of organogenesis at 0.5 times the clinical systemic exposure level based on AUC. However, in rats, the exposures achieved were markedly lower than in mice.

Pregnant rats given simeprevir at 150, 500, 1000 mg/kg/day from organogenesis through to weaning showed maternal toxicity consisting of mortality at 1000 mg/kg/day [ER_{AUC}, 1.0], suppression of body weight (10-12%; during lactation: 25-40%) at ≥ 150 mg/kg/day

[6] Based on the anticipated clinical exposure (AUC) at the clinical dose, simeprevir animal/human $AUC_{0\text{-}24h}$ ratios in the pivotal studies were low in rats (0.5-1.7 in rat/human [3, 6 months]), but was generally higher in dogs (2.6-14.5 in dog/human [6 and 9 month studies]).

([ER_{AUC}, 0.7]; mostly transient, except at high dose during gestation) and decreased food intake at ≥ 150 mg/kg/day [ER_{AUC}, 0.7]).

In the F1 generation, there was a marked decrease in bodyweights at all doses up to the end of lactation (10-37%). Consequently, there were findings of small build in 39 pups from 7 litters at 1000 mg/kg/day. In addition to delays in growth, there were also significant findings in development, specifically related to motor activity (including ambulatory activity) at 1000 mg/kg/day. However, there was no effect of treatment on subsequent survival, behaviour and reproductive performance of the F1 generation or on survival of the F2 generation.

NOAELs were not established for general toxicity and reproduction in dams (that is, < 150 mg/kg due to effects on bodyweight) or for the F1 generation (that is, < 150 mg/kg also due to effects on bodyweight). As mentioned, in the pilot pre/post-natal toxicity study in rats, simeprevir was detected in the plasma of suckling pups, indicating excretion of simeprevir in milk. It is very likely that in this study, there was also exposure to simeprevir in suckling pups via milk. Therefore, findings in pups on bodyweight and development may have been secondary effects due to exposure of simeprevir via the dam's milk.

Pregnancy classification

The sponsor proposes Category X[7] for the use of Olysio with RBV/PegIFNα. This is acceptable.

For simeprevir itself, the sponsor proposed an Australian pregnancy category of B1[8], however an Australian category of B3[9] is considered appropriate, due to findings in an embryo-fetal study.

The revised classification is a result of observations in a mouse embryofetal study of significantly increased post-implantation losses and significantly decreased fetal weights following simeprevir dosing at the high-dose of 1000 mg/kg/day, which is 6 times the mean exposure in humans at the recommended dose (based on AUC). Additionally, there were findings at estimated exposures similar to the clinical exposure in rat offspring of significantly decreased bodyweight gains and delayed physical growth and development (motor activity) at a maternal dose of 1000 mg/kg/day in a pre/post-natal toxicity study. This classification is in accord with the FDA Category C[10] classification in the USA for simeprevir.

Local tolerance

Simeprevir showed no evidence of skin irritation following topical application to the skin of rabbits (left flank) and no evidence of skin irritation following topical application to the ears of mice in the skin sensitisation test (see below).

[7] The definition of Category X for use of medicines in pregnancy is: *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.*

[8] The definition of Category B1 for use of medicines in pregnancy is: *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.

[9] The definition of Category B3 for use of medicines in pregnancy is: *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.

[10] FDA Category C: *Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women,* or *No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women*.

However, in the in vitro bovine corneal opacity and permeability (BCOP) assay there was evidence of very mild ocular irritation following the application of a 20% suspension in saline for 4 h. Findings included a small increase in opacity and permeability measurements in the cornea (opacity was assessed using an opacitometer and corneal permeability by the passage of sodium fluorescein from the anterior to posterior cornea).

There was no evidence of skin sensitisation by simeprevir in the local lymph node assay in mice.

In the Balb/c 3T3 mouse fibroblast assay, a validated test[11], simeprevir was phototoxic to cells following exposure to ultraviolet A (UVA) light. Phototoxicity was observed in both the absence and/or presence of serum binding proteins (2 g/100 mL BSA), and microscopic evaluation of cells 24 h after treatment showed clear cytotoxicity at ≥ 7.42 µg/mL (+UVA; ≥ 14.84 µg/mL -UVA); following UVA irradiation, the IC_{50} was 0.5 µg/mL and with no UVA irradiation of cells, the IC_{50} was 7 µg/mL.

In in vivo biodistribution studies, concentrations of total radioactivity in pigmented tissues in rats were mostly below the LLOQ (0.79 µg eq/g; except in the eyeball at 4 and 8 h post-dose) and less than the blood level in mice (based on tissue:blood radioactivity $AUC_{0\text{-}24\,h}$ ratios) following [^{14}C]-simeprevir dosing. This indicates there was no specific affinity or retention of drug-related material in pigmented tissues and that there is probably limited distribution to tissues such as eyes and skin. However, no in vivo nonclinical phototoxicity studies were carried out to further investigate the potential clinical relevance of this phototoxicity finding.

This in vitro nonclinical phototoxicity finding is consistent with reports noted in the clinical evaluation report of photosensitivity reactions[12] in the primary pooling (although the clinical evaluation report notes that there have been no serious skin reactions in the Phase IIb/III study program to date). The majority of photosensitivity reactions occurred during the first 12 weeks of treatment. Although no in vivo nonclinical phototoxicity studies were carried out, a clinical study (C125, from clinical evaluation report) demonstrated that a dose of 150 mg of simeprevir administered once daily days 1 to 9) to healthy subjects in a dedicated photosensitivity study was not associated with delayed photosensitising effects in a photosensitivity test (subjects underwent a series of photosensitivity tests on days 8 to 10 and the photosensitizing potential was assessed by evaluating the subject's cutaneous responses to controlled light exposures). Results of this study indicate that simeprevir does not act as a cutaneous photosensitising agent.

Impurities

Several simeprevir impurities were adequately qualified in general toxicity and genotoxicity studies.

Paediatric use

Simeprevir is not indicated for use in children, and no specific nonclinical studies were submitted for paediatric use.

Nonclinical summary and conclusions

- The sponsor has conducted adequate studies on the pharmacology, PK and toxicity of simeprevir according to the relevant guidelines. All definitive toxicity studies were

[11] EMEA. CPMP. Note for guidance on photosafety testing. CPMP/SWP/398/01.
[12] There was a higher incidence of photosensitivity reactions in simeprevir patients (3.3%) compared with placebo patients (0.5%). Two (0.3%) simeprevir patients had SAEs, both photosensitivity reactions requiring hospitalisation (one Grade 2 and one Grade 3).

conducted under good laboratory practice (GLP) conditions. The majority of safety pharmacology studies however, were not GLP-compliant, but these studies were well conducted, comprehensive and well documented.

- In primary pharmacology studies in vitro, simeprevir had median Ki values of 0.5 and 1.4 nM against HCV genotype 1a (H77) and genotype 1b (Con1) HCV NS3/4A proteases. Simeprevir median EC_{50} and EC_{90} values for were 9.4 and 19 nM in genotype 1b replicon-containing Huh7-Luc cells, respectively; activity was reduced by ≤ 2.4 fold by human serum proteins. Simeprevir was also active against HCV genotype 4 clinical isolates in vitro.
- Simeprevir did not exhibit specific activity against the HCV NS5B polymerase, cellular proteases, or human kinases, nor did it display antiviral activity against a panel of 11 viruses including related flaviviruses. Some cross-resistance is expected between the NS3 inhibitors simeprevir, boceprevir and telaprevir, primarily by R155K. Simeprevir-resistant mutants were susceptible to HCV NS5A, and NS5B nucleoside and non-nucleoside analogue polymerase inhibitors. Combination of simeprevir with HIV protease inhibitors did not affect the anti-HCV activity of simeprevir, nor the anti-HIV activity of the HIV PIs.
- In human hepatoma cell line assays with replicons carrying NS3 mutations, single or combined mutations at NS3 positions 43, 80, 122, 155, 156 and 168 resulted in the largest reductions in simeprevir anti-HCV activity, with D168V having the largest reduction (2380 fold). However these pre-existing polymorphisms were uncommon (≤ 1.3%) at baseline in pooled clinical Phase IIb/III studies, with the exception of Q80K (13.7% overall), which reduced simeprevir activity 7.7 fold (genotype 1b) and 9.3 fold (genotype 1a) in vitro.
- Secondary pharmacodynamic (PD) studies revealed antagonist activity for the drug at a number of receptors (most notably CCK) and chloride channels. Safety pharmacology studies covered the CNS, cardiovascular, respiratory and gastrointestinal systems. Diminished alertness was seen in rats at simeprevir levels similar to the anticipated clinical exposure. Alterations in cardio-haemodynamic parameters were observed in dogs in IV dosing studies (3 to 6 times the clinical C_{max}). ECG abnormalities were not observed in simeprevir-treated animals.
- Overall, the PK profile in animals was qualitatively similar to that of humans. Pharmacokinetic studies indicated a moderate rate of absorption of simeprevir in all species (1-5 h in mice, rats, rabbits, dogs and monkeys; 4-6 h in humans). The plasma half-life of simeprevir was generally shorter in the laboratory animal species (typically ≤ 6 h) compared with humans (10–13 h in healthy subjects and 41 h in HCV-infected patients). Oral absorption in fed animals (marginally improved by food) was moderate in rats, hamsters (40–44%), low in rabbits and Cynomolgus monkeys (2.5–19%) and higher in dogs (72%). Increases in exposure based on AUC were less than dose proportional in rodents and more than dose proportional in dogs. At high doses in rodents, there was a plateau of C_{max} values indicating saturation of absorption.
- Plasma protein binding was high (≥ 99.3%) in humans and the laboratory animal species. PO administration of radiolabelled and/or unlabelled simeprevir to rodents resulted in extensive tissue distribution, with the gastrointestinal tract and liver exhibiting tissue accumulation (but not pigmented tissues). After repeated dosing, simeprevir was mainly distributed in the liver in mice, rats and dogs. Penetration of the blood-brain barrier was very poor.
- The main metabolic pathways of simeprevir include O-demethylation and oxidation. The low to moderate metabolic clearance of simeprevir involves CYP3A4 (and to a much lesser extent, CYP2A6, CYP2B6, CYP2C8, CYP2C19 and CYP2E1), but unchanged simeprevir was the dominant circulating species. Faecal excretion dominated after PO

dosing in rats and dogs, as it does in humans (91% of the dose). Excretion of drug-related material in urine was < 0.1%.

- Simeprevir does not induce CYP1A2 or CYP3A4 in human hepatocytes at concentrations up to 2 fold the clinical C_{max}. There was slight (CYP2C19, CYP3A4/5) to moderate (CYP2A6, CYP2C8 and CYP2D6) inhibition of the human CYP450 isozymes at concentrations 20 to 30 fold and 7 to 10 fold the clinical C_{max}, respectively. As simeprevir is metabolised predominantly by the CYP3A enzymes, inhibitors or inducers of these enzymes are likely to affect the PK profile of simeprevir (no PK interaction studies have been conducted with simeprevir in laboratory animals with concomitantly administered PegIFNα and RBV).
- The drug is also a substrate of the uptake transporters: OATP 1B1/3, OATP2B1 and efflux transporter pumps: P-gp, MRP2, Bcrp1] and an inhibitor of the uptake transporters: OATP1B1, NTCP and efflux transporters: P-gp, MRP2 and BSEP. Similarly, inhibitors/substrates of P-gp and these other transporters are also expected to affect the PK profile of simeprevir.
- Acute toxicity was addressed in the repeat dose studies. Notable acute toxicities in 14 day studies in mice or rats included liver hepatocellular hypertrophy and alterations in liver enzymes, as well as swelling/vacuolisation of apical enterocytes in the small intestine and pancreas. In dogs, the heart (acute endocardial/myocardial necrosis) and liver (minimal necrotic foci, cholestasis and bilirubin) were also identified as target organs.
- Pivotal studies of up to 3 months were conducted in mice, 6 months in rats, 9 months in dogs and 4 weeks (non-pivotal) in monkeys using single daily PO doses of simeprevir. Dietary (feed) dosing studies of up to 13 weeks were also carried out in rodents to determine dose levels for potential carcinogenicity studies. These studies were GLP compliant, used relevant nonclinical species, the intended clinical (PO) route, animal numbers and were of sufficient duration.
- Levels of systemic exposure in rodents were low (at or below the anticipated clinical exposure level), but were generally adequate in dogs and monkeys. NOAELs (established in rats or dogs) corresponded to total daily exposure (AUC) that was less than or did not substantially differ from that anticipated in humans, but is acceptable based on the limited nonclinical findings observed in the liver and GI tract (see below). No studies were conducted with simeprevir in combination with PegIFNα/RBV.
- The main target organs were the liver in rodents (centrilobular hepatocellular hypertrophy) and in dogs (hepatocellular necrosis), as well as the gastrointestinal tract in rodents and dogs. There were also some effects of simeprevir on the pancreas, adrenals and the heart (in dogs).
- Liver findings were possibly associated with slight CYP inhibition/induction in rodents and with a cytotoxic effect of simeprevir in dogs. Increases in bilirubin and liver enzymes accompanied adverse liver histopathology findings. The liver findings are a well-known class effect of protease inhibitors that inhibit HCV and generally occurred at a lower relative exposure (AUC) margins or not substantially different from that expected in humans. The NOAEL for hepatic toxicity in rats was similar to the anticipated clinical exposure in humans and in dogs, 4 fold.
- Gastrointestinal and pancreatic toxicity in rodents and dogs, likely resulted from a direct effect of simeprevir, secondary to local toxicity as a result of high concentrations in the intestinal lumen.
- Increased bilirubin in both the nonclinical and clinical studies is likely related to inhibition of the hepatic transporters OATP1B1 (bilirubin uptake) and MRP2 (bilirubin efflux).

- Based on several cardiotoxicity signals, cardiac toxicity maybe a potential clinical risk in some high risk patients or those who achieve high plasma levels of simeprevir.
- The clinical relevance of adverse toxicological findings in the adrenal gland is uncertain.
- The sponsor discussed theoretical potential risks of simeprevir, ribavirin and PegIFNα co-administration. There may be an increased risk for liver toxicity.
- The potential genotoxicity of simeprevir was investigated in a standard battery of tests. The results were negative in all tests and simeprevir is unlikely to pose a mutagenic or clastogenic risk to humans.
- Carcinogenicity studies were not conducted for simeprevir, and they were not required as treatment duration is 12 weeks.
- Simeprevir associated radioactivity did not appear to cross the placenta of pregnant rats as distribution to the fetus and fetal liver was negligible. Simeprevir was detected in the plasma of suckling pups indicating excretion of simeprevir in milk.
- Reduced fertility was seen in male rats given PO doses of 50 mg/kg/day (less than the anticipated clinical simeprevir exposure based on AUC) as a result of no motile (100% static) sperm with related findings of small testes/epididymides. Degenerative testicular changes were also seen in dogs (6 month study) at PO doses of 5 mg/kg/day at subclinical exposures. In the rat fertility study, increases in post-implantation losses were observed (about 2 times the control values) at 50 mg/kg and 500 mg/kg (0.2 and 0.8 times the anticipated clinical exposure, based on AUC, respectively; a NOAEL was not determined).
- There was no indication that simeprevir was teratogenic in pivotal studies. However, there were adverse fetal development findings in mice whose dams were treated with simeprevir during the period of organogenesis at 1000 mg/kg (6 times the mean exposure in humans at the recommended dose) and consisted of decreased fetal weights, as well as maternal deaths and increased post-implantation losses. The NOAEL for these findings was 500 mg/kg (3.8 times the anticipated clinical exposure). In mice, a number of skeletal variations (mainly involving rib development) were also seen at all doses (4–6 times the expected clinical exposure). No remarkable effects on embryofetal development were observed in pregnant rats given PO simeprevir doses up to 500 mg/kg/day during organogenesis (0.8 times the anticipated clinical exposure).
- Pre/post-natal development studies in rats showed maternal mortality at 1000 mg/kg/day (0.5 times the mean clinical AUC) and reductions in body weight at ≥ 500 mg/kg/day (0.7 times the anticipated clinical exposure). At 1000 mg/kg/day, the offspring showed marked reductions in body weight and delays in growth and development (motor activity). In the offspring, these are possibly secondary effects due to exposure of simeprevir via the dam's milk.
- Simeprevir did not produce skin irritation and did not cause skin sensitisation. However, it produced mild ocular irritation in vitro in bovine cornea.
- Simeprevir was clearly phototoxic in the in vitro Balb/c 3T3 mouse fibroblast assay following exposure to ultraviolet A (UVA) light. This is a potentially clinically relevant finding (see *Assessment*).
- Levels of specific individual and total impurities proposed for Olysio® are qualified on nonclinical grounds.

Recommendation

There are no nonclinical objections to registration of simeprevir.

Revisions were recommended to nonclinical statements in the draft PI; details of these are beyond the scope of the 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

Simeprevir is a novel NS3/4A protease inhibitor for the treatment of chronic hepatitis C.

The proposed indication is

> *for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.*

Clinical rationale

It is estimated that 130 to 210 million people worldwide are infected with HCV with 2 to 4 million new infections annually. Approximately 300,000 Australians were infected with HCV in 2011. Acute infections become chronic in 70% to 90% of cases and this leads commonly to cirrhosis, chronic liver failure, hepatocellular carcinoma, liver transplantation and death.

Approximately 30% of patients with HIV-1 worldwide have HCV co-infection although only 13% of HIV-1 patients in Australia are co-infected. Highly active antiretroviral therapy (HAART) has revolutionised the treatment of HIV. However, co-infection increases the progression of HCV liver disease which remains a largely unmet medical need.

Hepatitis C virus has six genotypes (G) and multiple subtypes, with genotypes 1 to 3 distributed worldwide. Genotypes 1a and 1b account for 60% of global HCV infections. In Australia, the most common genotypes are 1a and 1b (54% prevalence) and 3a (37% prevalence). G4 is most prevalent in North Africa and the Middle East but it is spreading to Europe and the rest of the world through immigration and IV drug use. Until recently, the standard of care treatment for chronic HCV infection for all genotypes was the combination of PegIFN and ribavirin (RBV; PegIFN/RBV) for 48 weeks. The response to treatment varies according to HCV genotype and host IL28B genotypic subtypes (CC, CT, TT). However, in patients with G1 infection, sustained viral response (SVR) rates are only 45% in treatment-naïve patients and significantly lower in prior relapsers and non-responders. Moreover, the side effect profile of PegIFN/RBV is unfavourable with a high incidence of lethargy, fatigue, depression and anaemia. The NS3/4A protease inhibitors telaprevir and boceprevir in combination with PegIFN/RBV have improved SVR rates in treatment-naïve and treatment-experienced patients, and shortened treatment duration to 24 weeks in many patients. However, these combinations are associated with increased rates and severity of adverse events, including rash in addition to the common side effects of PegIFN/RBV. Moreover, telaprevir and boceprevir both require three times daily therapy.

It is hoped that simeprevir will increase SVR rates, shorten treatment duration, provide once daily dosing and improve safety and tolerability.

Guidance

The sponsors had a pre-submission meeting with the TGA on 13 April 2013. Issues discussed included the validity of SVR rates at 12 weeks after planned end of treatment (SVR12) rather than at 24 weeks (SVR24); the use of interim data in certain studies; the interchangeable use of PegIFNα-2a or PegIFNα-2b in certain studies; the data required to support the use of simeprevir in HIV-1/HCV co-infected patients; and the low numbers of patients with HCV G4 studied. The sponsor stated that they have addressed all outcomes from the TGA meeting in the current application.

Contents of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 33 clinical pharmacology studies, including 23 that exclusively provided PK data and a further 10 that provided both PK and PD data.
- 10 population PK (PPK) analyses.
- Three pivotal efficacy/safety studies, C208, C216 and HPC3007.
- Two dose-finding studies, C205 and C206.
- Five other efficacy/safety studies, C201, C202, C213, C212 and HPC3011.

Module 2:

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were conducted to the principles of Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 below shows the studies relating to each PK topic.

Table 3: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	C102	Bioavailability of 3 different capsule formulations.
		C106	Bioavailability of 4 solid formulations compared with powder blend sodium

PK topic	Subtopic	Study ID	*
			salt capsule.
		HPC1002	2 different liquid formulations compared with Phase III 150 mg capsule in fed and fasted state.
		C119	Potential Phase III formulations (G006, G007) compared with Phase IIb capsule (F021).
		C116	Capsule (G011) compared with gelatin capsule (G007) in fed and fasted state.
		C121	Potential Phase III formulations (G002, G004) compared with Phase IIb capsule (F021) in fed and fasted state.
		C101	PK after single PO doses from 50 mg up to 1200 mg in fed and fasted state.
		C109	PK after PO doses of 100 mg, 200 mg, and 400 mg in healthy Japanese males
		HPC1004	PK after PO doses of 100 and 200 mg in healthy Chinese subjects
		C103	Mass balance study
PK in special populations	Target population	C201	4 different regimens, given alone or with PegIFNα-2a and RBV in treatment-naïve and experienced genotype 1 HCV-infected subjects.
		C202	PK after 200 mg once daily (q.d.) for 7 days in treatment-naïve, genotype 2 to 6 HCV-infected subjects.
		C205	PK of 4 different regimens with PegIFNα-2a and RBV.
		C215	PKs with PegIFNα-2a and RBV in treatment-naïve Japanese with genotype 1 HCV.
		C206	PKs of 6 different regimens with PegIFNα-2a and RBV.
	Hepatic	C113	Steady-state PKs in subjects with moderate and severe hepatic

PK topic	Subtopic	Study ID	*
	impairment		impairment.
	Renal impairment	C126	Steady-state PKs in subjects with severe renal impairment compared with matched subjects with normal renal function.
Extrinsic factors	Drug-drug interaction	C107	CYP Substrates (CYP1A2, CYP2C9, CYP2D6, CYP3A and CYP2C19)
		C104	RTV
		C115	Erythromycin and darunavir/RTV
		HPC1005	BMS-790052 (daclatasvir)
		C114	Rilpivirine and tenofovir disoproxil fumarate
		C124	Ethinylestradiol and norethindrone
		HPC1006	Atorvastatin and simvastatin
		C112	Escitalopram
		C110	Methadone
		C120	Cyclosporine and tacrolimus
		HPC1001	TMC647055
		C123	Efavirenz and raltegravir
		C105	Rifampin
		C108	Digoxin and rosuvastatin
		GS-US-256-0129	GS-5885
Population PK analyses		Simeprevir Global PPK Study	Population PK meta-analysis
		C205-C206 PPK	Bayesian estimation
		C208 PPK	Bayesian estimation
		C216 PPK	Bayesian estimation

PK topic	Subtopic	Study ID	*
		HPC3007 PPK	Bayesian estimation
		C212 PPK	Bayesian estimation
		HPC3011 PPK	Bayesian estimation
		C201-C205 PPK	Effect of bilirubin
		C215 PPK	Effect of bilirubin

* 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.

Evaluator's summary and conclusions on pharmacokinetics

Pharmacokinetics in healthy subjects

- Following single, PO, 200 mg doses of either the Phase IIa (F007) or IIb (F020) capsule formulations in healthy subjects the median T_{max} of simeprevir was 6.0 h and the mean $t_{½}$ values were 10.5 h to 10.94 h, respectively.
- The absolute bioavailability of simeprevir is not known at this time.
- Relative to an oral solution formulation of simeprevir the C_{max} and $AUC_{0-\infty}$ values for the Phase III trial formulation (G007) were 15% and 20% lower, respectively whereas, the shape of the simeprevir plasma concentration-time profiles were similar.
- No studies directly examined the bioequivalence of the various clinical trial formulations and the to-be-marketed formulation.
- The G007 capsule and the Phase IIb capsule (F021) were bioequivalent in regards to AUC and C_{max} values and the median T_{max} and mean $t_{½}$ were similar (approximately 5.0 h and 9.4 h, respectively).
- The F007 and F020 capsules were bioequivalent following a 200 mg PO dose in healthy fed subjects.
- Although the F007 capsule formulation and F002 liquid formulation, which had been used in the early clinical studies, were bioequivalent in regards to C_{max}, the least squares (LS) ratio for AUC was just outside the lower bound of the level of bioequivalence.
- Following a 150 mg dose of the G007 capsule in healthy subjects the C_{max}, AUC_{last} and $AUC_{0-\infty}$ values for simeprevir were 1.60, 1.70, and 1.69 fold higher, respectively, following a standard breakfast and 1.49, 1.66, and 1.61 fold higher, respectively, following a high-fat breakfast compared to the PK under fasted conditions. Under fed conditions, T_{max} was also shorter, with a treatment difference of 1.0 h observed after a high-fat breakfast and 1.5 h following a standard breakfast.
- In healthy, predominantly Caucasian subjects under fed conditions, the mean C_{max} and AUC values for simeprevir increased with increasing dose; however, at higher doses the C_{max} and AUC values increased more than dose-proportionally (for example, from 100 to 200 mg there was approximately a 5 fold increase for both C_{max} and AUC_{inf}). By

contrast, the median T_{max} was 5 or 6 h across the dose range tested and the mean terminal $t_{½}$ was approximately 10 to 13 h.

- The C_{min}, C_{max}, and $AUC_{24\,h}$ values for simeprevir following administration for 5 days increased more than dose proportionally (for example, from 100 to 200 mg q.d. the mean $AUC_{24\,h}$ increased approximately 4 fold on Day 1 and 10 fold on Day 5). On Day 5, the median T_{max} was 4 h for all dose groups. Mean terminal $t_{½}$ increased with dose for the q.d. dosing groups.
- No studies specifically examined the effect of administration timing on the PK of simeprevir.
- The volume of distribution of the central compartment was estimated to be 38.4 L and for the peripheral compartment it was 250 L.
- The in vitro binding of simeprevir to human plasma proteins was >99.9%, primarily human serum albumin.
- In humans, irrespective of hepatic or renal function, the plasma protein binding of simeprevir was very high (> 99.9%).
- Blood to plasma ratios for total radioactivity were time-independent, with mean values ranging from 61% to 69% indicating that simeprevir did not bind to nor was it distributed to blood cells to any significant extent.
- The distribution of simeprevir into compartments other than the plasma has not been evaluated in humans, whereas in animals, the highest concentrations of simeprevir were observed in the gastrointestinal tract and liver.
- In vitro studies indicated that the metabolism of simeprevir was low to moderate in human liver microsomes and hepatocytes. In vitro CYP reaction phenotyping of simeprevir metabolism demonstrated that simeprevir metabolism to the M18, M23, and M25 metabolites was mainly catalysed by CYP3A enzymes, although involvement of CYP2C8 and CYP2C19 could not be excluded.
- Almost all ^{14}C-simeprevir-related radioactivity from a single 200 mg dose administered as an oral solution was excreted in faeces (approximately 91%). Unchanged simeprevir in faeces accounted for a mean of 31.0% of the administered dose.
- The major simeprevir-related circulating substance in plasma was unchanged drug and only one minor metabolite peak was observed, which represented metabolite M21.
- In faeces the most abundantly detected metabolites were M21 and M22 (mean of 25.9% of the dose; M21/M22 ratio of 60/40). Four other metabolites (M11, M16, M18, and M27) each accounted for >1% of the dose.
- The PK of the simeprevir metabolites in plasma were not assessed.
- No meaningful differences in allele frequency were observed for 10 genes, including genes encoding for CYP enzymes and transporters involved in hepatic uptake and solute carrier family and elimination, and no marker was identified to explain the high inter-subject variability in simeprevir exposure.
- Simeprevir excreted in urine was very low, ranging from 0.009 to 0.138% of the dose.
- The inter-subject variability of simeprevir PK is generally moderate to high, which the sponsor indicates reflects the non-linear drug disposition of simeprevir.

Target population

- Following 1 week of simeprevir monotherapy in treatment-naïve genotype 1 HCV-infected subjects a more than dose proportional increase in simeprevir plasma concentrations was observed for the dose increase from 75 mg to 200 mg q.d
- Steady-state conditions were reached by Day 7 for simeprevir in treatment-naïve subjects.
- Following the initial simeprevir dose the mean C_{max} and $AUC_{24\,h}$ values for simeprevir were approximately 1.8 and 2.3 fold higher in treatment-experienced HCV-infected subjects than in healthy subjects. On Day 5, the mean C_{max} and $AUC_{24\,h}$ were approximately 1.9 and 2.6 fold higher in HCV-infected subjects relative to healthy subjects, respectively. The median T_{max} was 4 h in both groups. The mean accumulation ratios for $AUC_{24\,h}$ were 3.16 and 3.45 for healthy subjects and HCV-infected subjects, respectively.
- In treatment-naïve, genotype 2 to 6 HCV-infected subjects, the PK of simeprevir were consistent for genotypes 4, 5 and 6 with values previously reported for genotype 1 infected subjects, whereas a trend for lower exposure was observed in subjects infected with genotypes 2 and 3. The reason for these lower exposures is currently unknown.
- On day 1 following administration of simeprevir as either a monotherapy or in combination with PegIFNα-2a and RBV, T_{max} occurred at 6 h post-dose and the mean plasma concentration-time profiles obtained for simeprevir monotherapy were comparable to the profiles obtained for the combination therapy, especially when considering the inter-subject variability in plasma concentrations.
- When given in combination with PegIFN and RBV, simeprevir exposure was similar following both 12 and 24 weeks treatment.

Intrinsic factors

- Following administration of simeprevir at 150 mg q.d. in subjects with moderate hepatic impairment, the mean C_{max} and $AUC_{24\,h}$ values for simeprevir were 1.71 and 2.44 fold higher, respectively, relative to matched subjects with normal hepatic function.
- In subjects with severe hepatic impairment, the mean C_{max} and $AUC_{24\,h}$ values for simeprevir were 3.13 and 5.22 fold higher, respectively, relative to subjects with normal hepatic function.
- Following administration of simeprevir at 150 mg q.d. in subjects with severe renal impairment, the mean C_{min}, C_{max}, and $AUC_{24\,h}$ values for simeprevir were increased 1.71, 1.34, and 1.62 fold, respectively, relative to matched subjects with normal renal function, whereas, the median T_{max} was 6 h for both treatment groups.
- Population PK studies identified that age, sex, body weight, total bilirubin at baseline and METAVIR score[13] were significant covariates for simeprevir exposure. However, when the covariates were examined in combination the simulated high and low extremes fell within the 90% prediction intervals of the whole study population. Moreover, the level of random variability in exposure of simeprevir was larger than the variation induced by the significant covariates.
- It must be noted that no studies have examined the PKs of simeprevir in paediatric subjects.

[13] a scoring system for liver biopsies that assigns two standardised numbers: one to represent the degree of inflammation and the other the degree of fibrosis.

- Following multiple dosing of 100 mg q.d. simeprevir for 5 days in healthy subjects, the mean $AUC_{24\,h}$ of simeprevir was 2.3 and 1.9 fold higher in Japanese and Chinese subjects, respectively than in a predominantly Caucasian population.
- Following multiple dosing in HCV-infected subjects with 100 mg q.d. simeprevir, the mean $AUC_{24\,h}$ was 1.5 fold higher in Japanese than in Caucasian subjects.
- In a pooled analysis of the Phase III individual post-hoc PPK estimates, the median exposure of simeprevir in Asian subjects, following administration of 150 mg q.d., was 5.7 to 6.4 fold higher than other races (White, Black, or Other).
- Simeprevir is a mild inhibitor of intestinal CYP3A activity and a mild CYP1A2 inhibitor in healthy subjects, whereas, it did not affect hepatic CYP3A activity and had no relevant effect on the activity of CYP2C9, 2C19, or 2D6.

Extrinsic factors

- In vivo, simeprevir is both a substrate for and mild inhibitor of CYP3A as well as being a substrate for P-gp, MRP2, BCRP, OATP1B1, OATP2B1, and OATP1B3.
- Drug-drug interaction studies in healthy subjects clearly indicate that steady state simeprevir exposure increases dramatically when simeprevir is co-administered with drugs that are moderate or strong inhibitors of CYP3A, which are also inhibitors of P-gp, such as erythromycin (C_{min} increased by 12.74 fold) and ritonavir (C_{min} increased by 14.35 fold). Simeprevir generally increased the exposure of other CYP3A inhibitors when the CYP3A inhibitors were co-administered with simeprevir.
- When simeprevir was co-administered with other CYP3A substrates, such as rilpivirine and ethinylestradiol, there was little to no effect on the PK of simeprevir, nor were the PK of the other CYP3A substrates unduly affected.
- When co-administered with daclatasvir, a CYP3A substrate and a P-gp inhibitor, there was a 1.5 to 2.68 fold increase in exposure to both drugs possibly suggesting that although co-administration with CYP3A substrates has little effect on the PK of simeprevir, P-gp inhibitors may induce moderate increases in simeprevir exposure.
- When co-administered with 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, such as atorvastatin and simvastatin, which are substrates for CYP3A and OATP1B1 there was little to no effect on the PKs of simeprevir, whereas simeprevir increased exposure to both atorvastatin and simvastatin and their active metabolites by 1.5 to 3.0 fold.
- CYP3A inducers, such as TMC647055, rifampin and efavirenz, significantly decrease simeprevir exposure by up to 90%, whereas simeprevir has little effect on the PK of efavirenz and rifampin. By contrast, exposure to TMC647055, which is a moderate inducer of CYP3A at high concentrations, a CYP3A substrate and a weak inhibitor of CYP3A, increased by up to 1.87 fold when co-administered with simeprevir.
- Simeprevir co-administration increased exposure to P-gp substrates, inducing moderate increases in digoxin exposure (1.4 fold) and greatly increasing rosuvastatin exposure (approximately 3 fold). The effects of these drugs on the PK of simeprevir are not reported.
- Ledipasvir (GS-5885), which does not inhibit or induce CYP enzymes, MRP2 or OATP1B1, increased simeprevir exposure by approximately 2.6 fold. Similarly, ledipasvir exposure was increased by approximately 1.8 fold when co-administered with simeprevir. This finding suggests that pathways other than those previously identified are in part responsible for the metabolism of simeprevir and that the PK of other drugs that are not metabolised by these previously identified pathways may be affected by co-administration with simeprevir.

- Overall these drug-drug interactions are well documented in the proposed PI. However, if daclatasvir or ledipasvir are approved for marketing in the future a suitable caution should be included in the PI regarding interactions with these drugs. In addition, as ledipasvir does not appear to be metabolised by the same pathways as simeprevir a more general warning regarding the possible PK effects of simeprevir on non-CYP3A or P-gp metabolised drugs may need to be included in the PI.
- Population PK studies indicated that the PK of simeprevir could be characterised by a two-compartment model with first order absorption (with lag time), saturable clearance, described using Michaelis-Menten kinetics and a dose-dependent relative bioavailability (F1).
- Empirical Bayesian estimation methods indicated that simeprevir exposure (based on pre-dose plasma concentration or minimum concentration ($C_{0\,h}$) and $AUC_{24\,h}$) increased more than dose-proportionally.
- In subjects co-infected with HCV genotype 1 and HIV-1, the estimates for simeprevir exposure were slightly lower than the estimates in subjects infected with HCV genotype 1 without HIV-1 co-infection.
- Simeprevir exposure in subjects infected with HCV genotype 4 appeared to be higher than estimates of simeprevir exposure in subjects infected with HCV genotype 1.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 below shows the studies relating to each PD topic.

Table 4: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on anti-viral activity	C101	Antiviral activity of simeprevir
		C201	Dose-dependency of antiviral effect using 4 dosing regimens
	Effect on sustained virological response	C205	Sustained virologic response at Week 72 in treatment-naïve HCV infected subjects
		C206	Proportion of treatment-experienced, HCV-infected subjects achieving SVR24
Secondary Pharmacology	Effect on QTc[14]	C117	Thorough QT study
	Effect on photosensitivity	C125	Cutaneous photosensitising potential of multiple doses
PD Interactions	Norethindrone and ethinylestradiol	C124	Effect of simeprevir on hormone levels after co-administration of norethindrone and ethinylestradiol

[14] ECG QT interval corrected for heart rate

PD Topic	Subtopic	Study ID	*
	Atorvastatin and simvastatin	HPC1006	HMG-CoA reductase inhibitory activity in the presence and absence of simeprevir
	Methadone	C110	PD effects of concurrent use of simeprevir and methadone
	TMC647055	HPC1001	Antiviral activity following the co-administration of TMC647055 and simeprevir
Population PD and PK-PD analyses	Target population	C208-C216 PPD	Multivariate analysis of prognostic factors

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

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

Evaluator's summary and conclusions on pharmacodynamics

Primary PD

Antiviral-activity

- Following a single dose of simeprevir 200 mg q.d. under fed conditions in HCV genotype 1 infected subjects, viral load values decreased to 4.43 $\log_{10}$ IU/mL. Following 6 days of dosing, viral load values were further decreased to 2.89 $\log_{10}$ IU/mL and remained low at Days 7 and 8 (2.98 and 3.04 $\log_{10}$ IU/mL, respectively). During follow-up, viral load values returned to levels observed before treatment.
- After 7 days monotherapy with simeprevir, a clear dose dependent antiviral activity was observed with greater mean changes in plasma HCV RNA levels ($\log_{10}$ IU/mL) with 200 mg simeprevir q.d. (-4.18) compared to 25 mg simeprevir q.d. (-2.63) and 75 mg simeprevir q.d. (-3.48). By contrast, following 7 days monotherapy with placebo, no change in mean plasma HCV RNA levels ($\log_{10}$ IU/mL) was observed: -0.08 in Cohort 1 and 0.30 in Cohort 2.
- When PegIFN/RBV were administered in combination with simeprevir, a greater mean change in plasma HCV RNA levels ($\log_{10}$ IU/mL) was observed on Day 7 compared to the 1 week simeprevir monotherapy for all simeprevir dose groups (25 mg q.d.; -3.47, 75 mg q.d.; -4.55, and 200 mg q.d.; -4.68) and the placebo group (-1.73 in Cohort 1 and -1.64 in Cohort 2). On Day 28, changes from baseline in HCV RNA ($\log_{10}$ IU/mL) were -4.74, -5.52, and -5.44 in the 25 mg, 75 mg, and 200 mg simeprevir q.d. dose groups, respectively. Mean changes from baseline in plasma HCV RNA ($\log_{10}$ IU/mL) on Day 28 in the control group (placebo plus standard of care) were smaller compared to the simeprevir dose groups: -3.74 in Cohort 1 and -3.26 in Cohort 2.
- The proportion of subjects achieving plasma HCV RNA levels < 25 IU/mL on Day 28 was 66.7%, 100%, and 100% in the 25 mg, 75 mg, and 200 mg simeprevir q.d. in combination with PegIFN/RBV dose groups, respectively, and 42.9% and 33.3% in the placebo in combination with PegIFN/RBV groups in Cohort 1 and 2, respectively.
- The presence of a Q80K mutation at baseline had no clear effect on the response to simeprevir treatment at doses of 75 mg and 200 mg q.d. at Week 4.

- Viral breakthrough was observed in 10 (13.5%) subjects, whereas, viral breakthrough did not occur in the placebo groups (that is, the PegIFN/RBV only group). Nine out of 10 subjects with viral breakthrough had emerging mutations in the NS3 protease domain known to confer reduced susceptibility to simeprevir in vitro (mainly R155K and/or D168V or D168E).
- Viral relapse was observed in 4 out of 47 simeprevir-treated subjects who had undetectable plasma HCV RNA at end of treatment (that is, 2, 1, and 1 subjects in the 25 mg, 75 mg, and 200 mg simeprevir q.d. dose groups, respectively). Three out of 4 simeprevir-treated subjects with viral relapse had emerging mutations in the NS3 protease domain. In the placebo groups, 2 out of 17 subjects with undetectable plasma HCV RNA at end of treatment had a viral relapse.
- Following 28 days of administration of simeprevir in combination with PegIFN/RBV a dose dependent reduction in plasma HCV RNA from baseline was observed with greater changes in plasma HCV RNA levels with 150 mg simeprevir q.d. (-5.46) and 200 mg simeprevir q.d. (-5.26) compared to with 75 mg simeprevir q.d. (-4.28). By contrast, on Day 28, the mean change in plasma HCV RNA levels were smaller in the placebo group (-1.53).
- On Day 28, the majority of subjects in the simeprevir dose groups achieved plasma HCV RNA levels < 25 IU/mL with a greater proportion of subjects in the 150 mg (77.8%) and 200 mg (70.0%) simeprevir q.d. dose groups than in the 75 mg simeprevir q.d. dose group (44.4%).
- Plasma HCV RNA levels < 25 IU/mL on Day 28 were not observed in any of the subjects in the placebo group (standard of care only).
- In subjects treated with 200 mg simeprevir q.d. in combination with standard of care, the mean change from baseline in plasma HCV RNA on Day 28 was -5.86 $\log_{10}$ IU/mL and 3 out of 4 (75.0%) subjects who were treated for 4 weeks achieved rapid virologic response (at Week 4; RVR) with the remaining subject achieving plasma HCV RNA levels < 25 IU/mL detectable.

Sustained virological response

- In subjects treated with the triple therapy (simeprevir/PegIFN/RBV) or placebo (placebo/PegIFN/RBV), a larger proportion of subjects in the simeprevir treatment groups (70.7% to 84.8%) achieved SVR at week 72 (SVRW72) compared with the placebo group (64.9%).
- In subjects treated with the triple therapy (simeprevir/PegIFN/RBV) or placebo (placebo/PegIFN/RBV), a larger proportion of subjects with SVR24 were observed in the simeprevir treatment groups (60.6% to 80.0%) compared with the placebo group (22.7%).
- A trend for higher SVR rates was observed in the 150 mg q.d. simeprevir dose group compared with the 100 mg q.d dose group in partial and null responders, as well as across multiple subgroups (including subjects with Q80K polymorphism, higher body mass index, and advanced fibrosis).
- There was a trend for lower SVR in subjects infected with HCV genotype 1a compared to subjects with HCV genotype 1b.

Secondary pharmacodynamic effects

- Supratherapeutic doses of simeprevir have no effect on QT interval.
- Simeprevir (150 mg q.d.) does not act as a cutaneous photosensitising agent.

Time course of PD effects

- In treatment-naïve and experienced genotype 1 HCV-infected subjects, antiviral response could be detected following 7-days of treatment and antiviral activity peaked following 28 days of dosing. By Week 12, antiviral response was similar or slightly lower than at the 28 day time point.

Relationship between drug concentration and PD effects

- There was no clear relationship between simeprevir exposure and change in plasma HCV RNA from baseline following triple therapy with simeprevir at 75 mg q.d. or higher doses in treatment-naïve and treatment-experienced subjects (that is, 150 mg and 200 mg q.d. doses).
- In contrast, an exposure-response relationship was observed following simeprevir monotherapy for 1 week where higher exposures to simeprevir were associated with a greater decrease in plasma HCV RNA.
- In treatment-naïve and treatment-experienced subjects, a trend for mild increases from baseline in direct, indirect, and total bilirubin was observed with higher exposure to simeprevir. No consistent relationship was observed between simeprevir exposures and changes from baseline in ALP, AST, or ALT.
- There was no relationship between simeprevir exposure and QT and simeprevir exposure and photosensitivity.

Prognostic factors for determining PD effectiveness

- In subjects treated with simeprevir and PegIFN/RBV, IL28B genotype and combination of HCV genotype/subtype with baseline Q80K polymorphism were the most important baseline characteristics for predicting the probability of achieving SVR12.
- Combination of HCV genotype/subtype with baseline Q80K polymorphism was not predictive of outcome.
- Rapid virologic response and meeting the response guided treatment (RGT) criteria were the most important on-treatment factors in predicting the probability of achieving SVR12.
- Baseline characteristics combination of HCV genotype/subtype with baseline Q80K polymorphism and IL28B genotype were important factors for predicting the probability of achieving RVR, achieving HCV RNA < 25 IU/mL at Week 4 and meeting the RGT criteria.

Pharmacodynamic interactions

Norethindrone and ethinylestradiol

Co-administration of steady-state concentrations of simeprevir (150 mg q.d.) had no effect on norethindrone and ethinylestradiol induced changes in follicle stimulating hormone, leutinising hormone, and progesterone serum levels.

Atorvastatin and simvastatin

The mean C_{max} and $AUC_{12\,h}$ values for HMG-CoA reductase inhibitory activity were increased 2.23 and 2.55 fold, respectively, when atorvastatin was co-administered with steady state simeprevir relative to the PD effects of atorvastatin when given alone.

The mean C_{max} and $AUC_{12\,h}$ values for HMG-CoA reductase inhibitory activity were increased 1.54 and 1.83 fold, respectively, when steady-state simvastatin was co-administered with simeprevir relative to the PD effects of simvastatin when given alone.

Methadone

Co-administration of simeprevir with methadone had little to no effect on craving for opiates, desires for drugs questionnaire item scores, and median resting pupil diameter.

TMC647055

Co-administration of TMC647055 (1000 mg every 12 h) and simeprevir (150 mg every 24 h) for 10 days to a population with a majority of genotype 1a infected patients (7 genotype 1a, 1 genotype 1b), substantially increased the antiviral activity compared to monotherapy with TMC647055, provided a continuous suppression of HCV RNA levels during dosing, and reduced HCV RNA levels below 25 IU/mL in 3 subjects. No viral breakthroughs were observed.

Dosage selection for the pivotal studies

Study C205

This was a Phase IIb, randomised, 5-arm, double-blind, placebo-controlled study of different regimens of simeprevir/PegIFN/RBV versus PegIFN/RBV alone in treatment-naïve patients with HCV genotype 1 infection. Patients were randomised to one of five treatment arms:

- TMC12/PR24/48 75 mg arm: 12 weeks simeprevir 75 mg q.d. plus PegIFN/RBV followed by placebo/PegIFN/RBV for 12 weeks followed by either no or 24 weeks additional PegIFN/RBV based on response guided therapy criteria and 24 weeks post-therapy follow-up.
- TMC24/PR24/48 75 mg arm: 24 weeks simeprevir 75 mg q.d. plus PegIFN/RBV followed by either no or 24 weeks additional PegIFN/RBV based on response guided therapy criteria and 24 weeks post-treatment follow-up.
- TMC12/PR24/48 150 mg arm: 12 weeks simeprevir 150 mg q.d. plus PegIFN/RBV followed by placebo/PegIFN/RBV for 12 weeks followed by either no or 24 weeks additional PegIFN/RBV based on response guided therapy criteria and 24 weeks post-therapy follow-up.
- TMC24/PR24/48 150 mg arm: 24 weeks simeprevir 150 mg q.d. plus PegIFN/RBV followed by either no or 24 weeks additional PegIFN/RBV based on response guided therapy criteria and 24 weeks post-treatment follow-up.
- Control arm: 48 weeks of PegIFN/RBV with placebo for the first 24 weeks and 24 weeks of post-therapy follow-up.

The primary endpoint was the proportion of patients in each group achieving sustained virologic response at Week 72 (SVRW72).

> **Evaluator comment:** This was a well-designed study with adequate treatment-naïve patient numbers to detect meaningful differences between a range of simeprevir dose and time treatment regimens. The majority of patients in each treatment group achieved SVR, and the SVR12, SVR24 and SVR72 rates were similar in the simeprevir groups. There were no major differences in efficacy between simeprevir 75 mg and 150 mg doses or duration in treatment although there were some trends in favour of the 150 mg dose. Simeprevir was generally well tolerated and the data support use of the simeprevir 150 mg dose for 12 weeks in the Phase III studies.

Study C206

This was a Phase IIb, randomised, 7-arm, double-blind, placebo-controlled study comparing the efficacy and safety of different regimens of simeprevir/PegIFN/RBV in patients with HCV genotype 1 infection who had failed at least one previous course of PegIFN/RBV therapy.

Patients were randomised 1:1:1:1:1:1:1 to one of 7 treatment arms. Randomisation was stratified by HCV genotype 1 subtype (1a, 1b, and other) and previous response to PegIFN/RBV (null responders, partial responders, and relapsers).

- TMC12PR48 100 mg arm : 12 weeks simeprevir 100 mg q.d. plus PegIFN/RBV followed by 36 weeks of placebo/PegIFN/RBV (N=66)
- TMC12PR48 150 mg arm: 12 weeks simeprevir 150 mg q.d. plus PegIFN/RBV followed by 36 weeks of placebo/PegIFN/RBV (N=65)
- TMC24PR48 100 mg arm: 24 weeks simeprevir 100 mg q.d. plus PegIFN/RBV followed by 24 weeks of placebo/PegIFN/RBV (N=66)
- TMC24PR48 150 mg arm: 24 weeks simeprevir 150 mg q.d. plus PegIFN/RBV followed by 24 weeks of placebo/PegIFN/RBV (N=66)
- TMC48PR48 100 mg arm: 48 weeks simeprevir 100 mg q.d. plus PegIFN/RBV (N=68)
- TMC48PR48 150 mg arm: 48 weeks simeprevir 150 mg q.d. plus PegIFN/RBV (N=65)
- Control arm: 48 weeks of placebo/PegIFN/RBV therapy (N=66)

Evaluator comment: This was a well-designed study with adequate patient numbers to allow meaningful comparison of different simeprevir dose and treatment durations in patients who failed on previous PegIFN/RBV treatment. A response guided optional TMC12PR24/48 arm was not included, presumably because low SVR rates were predicted after 24 weeks PegIFN/RBV therapy. SVR24 rates were seen in all simeprevir treatment groups compared to placebo irrespective of whether the patients were previous null or partial responders, or relapsers. A trend for higher SVR24 rates was seen in the simeprevir 150 mg group compared with the simeprevir 100 mg group. Simeprevir was generally well tolerated and the data support use of simeprevir 150 mg in Phase III trials in treatment-experienced patients.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

Study C208 (QUEST-1)

This was a multi-centre, Phase III, randomised, double-blind, parallel-group, controlled trial of simeprevir 150 mg or placebo combined with PegIFN/RBV in treatment-naïve, HCV G1 infected patients with compensated liver disease including cirrhosis. The primary objective was to demonstrate the superiority of simeprevir versus placebo measured as the proportion of patients with SVR after 12 weeks treatment.

Study C216 (QUEST-2)

This is a randomised, double-blind, placebo controlled study to investigate the efficacy, safety and tolerability of simeprevir versus placebo as part of a treatment regimen including PegIFNα-2a (Pegasys) and ribavirin (Copegus) or PegIFNα-2b (PegIntron) and ribavirin (Rebetol) in treatment-naïve, genotype 1, HCV infected patients. The primary

efficacy endpoint was to demonstrate superior SVR12 rates for simeprevir versus placebo combined with PegIFNα-2a/RBV or PegIFNα-2b/RBV.

Study HPC3007 (PROMISE)

This is an ongoing Phase III comparison of simeprevir and placebo in HCV genotype 1 patients who relapsed after previous PegIFN therapy with documented undetectable HCV RNA at the end of treatment. It was a randomised, double-blind, placebo-controlled, 2-arm study to compare the efficacy and safety of simeprevir versus placebo combined with PegIFNα-2a and RBV in patients with HCV genotype 1 who received at least 24 weeks of PegIFN based therapy and relapsed within one year after the end of treatment. The primary efficacy endpoint was the proportion of patients in each treatment group achieving SVR12.

Other efficacy studies

Study 212

This is an ongoing, open label, single arm study of simeprevir/PegIFN/RBV in patients infected with HCV and HIV-1 co-infection. No control group was included in the study. Instead, the data are compared to historical SVR data obtained from Phase III studies in patients infected with HCV alone.

This study does not meet the criteria for a pivotal study as it is open-label with historical controls and the data analysis is preliminary. However, it was summarised in the CER (attachment 2) in some detail because the data are used to support the proposed HIV-1 co-infection indication.

Study C202

This was a Phase IIb, open-label, proof of concept study to assess the antiviral activity of simeprevir in patients infected with HCV genotype 2, 3, 4, 5, or 6.

Study C213

This is an ongoing, exploratory Phase III, open label trial of simeprevir/PegIFN/RBV for HCV genotype 1 infected patients who participated in the placebo groups of a Phase IIb/III study (C201, C205, C206, C208, C216 or HPC3007), or who received up to 14 days of direct acting antiviral treatment in Phase I studies.

Study HPC3011

This is an interim analysis of an on-going multicentre, open-label, single arm, Phase III study of simeprevir/PegIFN/RBV in treatment-naïve or treatment-experienced HCV genotype 4 infected patients.

Analyses performed across trials (pooled analyses and meta-analyses)

A pooled efficacy analysis of studies C208 and C216 treatment-naïve patients was performed.

Evaluator's conclusions on efficacy

Conclusions are provided on clinical efficacy of simeprevir for the treatment of chronic hepatitis C genotype 1 or genotype 4 infection, in combination with pegIFNα and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without HIV-1 co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

The combination of simeprevir/PegIFN/RBV in response guided treatment regimens is statistically significantly superior to PegIFN/RBV alone in treatment-naïve patients and prior relapsers ($p < 0.001$). The SVR12 benefit in favour of simeprevir was approximately

30% in treatment-naïve patients and 42% in prior relapsers, both clinically meaningful and important. The treatment benefit in favour of simeprevir was similar in all subgroups defined by demographics, HCV genotype/subtype, IL28B genotype, baseline HCV RNA or METAVIR scores, and the type of PegIFNα used. Prior null and partial responders were included in the controlled dose ranging study C206 with SVR12 rates of 91% and 65%, respectively. No prior null or partial responder patients in the open-label roll-over study C213 had SVR12 data available at the interim analysis. The data are limited in these patient groups and it is unclear why they were excluded from the pivotal study HPC3007.

Current EMA guidelines[15] state that randomised, controlled trials in HCV/HIV co-infected patients may not be mandated if a clear treatment benefit has been established in patients with HCV mono-infection. Single-arm studies in patients with co-infection may be sufficient for marketing approval if enhanced efficacy compared to historical controls can be convincingly demonstrated. The sponsors adopted this recommendation in C212 and the early data are in line with those observed in patients with HCV mono-infection. However, the results are preliminary and patient numbers with evaluable efficacy data are low. The Phase I study C202 confirmed the antiviral activity of simeprevir 200 mg q.d. in 8 patients with HCV genotype 4 for 7 days. Efficacy was studied in HPC3011 and the early data were similar to those observed in patients with genotype 1 infection. However, SVR12 rates were evaluable in only 9 patients at the time of the interim analysis.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Two double-blind, placebo-controlled, pivotal Phase III studies (C208, C216) in treatment-naïve patients and one double-blind, placebo-controlled, pivotal Phase III study (HPC3007) in patients who relapsed after prior PegIFN therapy.
- Three open-label, uncontrolled studies in patients co-infected with HIV-1 (C212), patients previously enrolled in the placebo group of Phase II and III studies (C213), and in patients with HCV genotype 4 (HPC3011).
- Two double-blind, placebo-controlled, dose ranging studies in treatment-naïve (C205) and treatment-experienced patients (C206).

All studies were on-going at the cut-off date for the safety analysis (18 January 2013).

Pooled safety data are presented as follows:

Primary pooling: An analysis of the 3 double-blind, placebo-controlled, pivotal Phase III studies (C208, C216 and HPC3007) at Week 60. A total of 781 patients received 12 weeks of treatment with simeprevir 150 mg q.d. followed by 12 or 36 response guided treatment with PegIFN/RBV.

Secondary pooling: An analysis of the primary pooling dataset with the addition of the dose ranging Phase IIb studies (C205 and C206). In this pooling, 924 patients were included in the simeprevir 150 mg q.d. 12 weeks group, and 1486 patients were included in the all simeprevir group (simeprevir at all doses and treatment durations).

A total of 806 healthy subjects received any dose of simeprevir and 634 of these received simeprevir 150 mg q.d. in Phase I studies. These are not included in the main poolings.

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

[15] EMEA/CHMP/EWP/30039/2008. Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C (23 April 2009)

- Study C205 and C206 provided data on simeprevir at different doses in treatment naïve and experienced patients, respectively.
- Study C213 provided data in treatment-experienced patients.
- Study C202 was a proof of principle study in patients with genotypes 2-6 inclusive.
- Study C212 provided data on the use of simeprevir in patients with HCV/HIV-1 co-infection.
- Study HPC3011 provided data on patients with HCV genotype 4 infection.

Patient exposure

The treatment exposure for simeprevir and placebo in the primary pooling analysis is shown in Table 5.

Table 5: Extent of exposure; ITT (Primary pooling)

	PBO	TMC435 150 mg
Analysis Set: ITT	397	781
Treatment duration of TMC435/PBO (weeks)		
N	397	781
Median	5.90	12.00
Range	(0.1; 12.9)	(0.9; 19.0)
Total TMC435/PBO Exposure (person years)	59.28	174.23
Treatment duration of PR (weeks)[a]		
N	397	781
Median	48.00	24.10
Range	(1.0; 50.1)	(1.7; 50.0)
Total PR Exposure (person years)	291.27	361.50

The total simeprevir exposure was 174.23 patient years and the total median treatment duration was 12.0 weeks for simeprevir patients and 5.9 weeks for placebo patients (placebo patients were more subject to virologic stopping rules).

Safety issues with the potential for major regulatory impact

Liver toxicity

There is no evidence of liver toxicity to simeprevir in the Phase IIb/III study program to date. In simeprevir/PegIFN/RBV and placebo/PegIFN/RBVgroups, mean ALT and AST levels fell from baseline during the first 4 weeks of treatment. The fall was more pronounced in the simeprevir patient group, presumably reflecting a favourable biochemical response to treatment. During the first 12 week phase, hyperbilirubinaemia (without concomitant rises in ALT/AST) was observed in both treatment groups (7.9% simeprevir versus 2.8% placebo). Grade 4 events were reported in only 2 (0.3%) simeprevir patients and there were no serious AEs (SAEs). In the first 2 weeks of treatment, mean total bilirubin increased from baseline in both group and decreased to baseline after completion of simeprevir treatment. The higher incidence of bilirubin elevations in simeprevir patients is attributed to decreased bilirubin elimination related to inhibition of the hepatic transporters OATP1B1 and MRP2, and possibly due to RBV-induced haemolysis.

Haematological toxicity

There is no evidence of haematological toxicity to simeprevir in the Phase IIb/III study program to date. There is no evidence that simeprevir increases the incidence of anaemia or worsens its severity. During the first 12 weeks of treatment, the incidence of anaemia was similar in both treatment groups (13.4% simeprevir, 10.8% placebo). Grade 3 events

were reported in 1% and 1.8% of simeprevir and placebo patients, respectively; and there were no Grade 4 events or SAEs in simeprevir patients. The incidence of anaemia declined to baseline in simeprevir patients but remained elevated in placebo/PegIFN/RBV patients until Week 52. There is no evidence that simeprevir increases the incidence of neutropaenia or worsens its severity. During the first 12 weeks of treatment, in the incidence of neutropaenia was 16.5% and 15.1% in the simeprevir and placebo groups, respectively. Grade 4 events were reported in 2.4% and 1.5% of simeprevir and placebo patients, respectively. In both treatment groups, there was an immediate reduction in neutrophil count which returned to baseline when simeprevir/PegIFN/RBV treatment was stopped but continued in placebo/PegIFN/RBV patients. There were no meaningful changes in other haematological parameters in either treatment group.

Serious skin reactions

There have been no serious skin reactions in the Phase IIb/III study program to date. During the first 12 weeks of treatment in the primary pooling, the incidence of rash (any type) was 23.2% and 16.9% in the simeprevir and placebo patients, respectively. Grade 3 events were reported in 5 (0.6%) simeprevir patients but there were no Grade 4 events. Two (0.3%) simeprevir patients had SAEs, both photosensitivity reactions requiring hospitalisation (one Grade 2 and one Grade 3). There was a higher incidence of photosensitivity reactions in simeprevir patients (3.3%) compared with placebo patients (0.5%) but there were no Grade 4 events. The majority of photosensitivity reactions occurred during the first 12 weeks of treatment. The incidence of pruritus was higher in simeprevir patients (22.0%) than placebo patients (14.9%) but there were no Grade 4 events and no SAEs.

Cardiovascular safety

No cardiovascular safety issues were identified. QTcF[16] values between 450 and 480 msec were observed in 1.5% and 0.5% of simeprevir and placebo patients, respectively. No QTcF increases > 60 msec from baseline were observed. Electrocardiogram abnormalities other than QT increases were recorded in < 2% of either treatment group.

Unwanted immunological events

Not applicable.

Postmarketing data

Not applicable.

Evaluator's conclusions on safety

In the primary and secondary poolings, simeprevir 150 mg q.d. was generally well tolerated and the incidence of AEs by type and preferred term were similar in the simeprevir and placebo patient groups. As expected, there was a high frequency of adverse drug reactions (ADRs) related to PegIFN/RBV therapy (fatigue, headache, influenza-like illness) but the incidence of each was similar in the simeprevir and control groups. Most AEs were Grade 1 or 2. The incidence of Grade 3 AEs (20% simeprevir, 21.9% placebo) and Grade 4 AEs (2.9% simeprevir, 2.8% placebo) were similar in both treatment groups. The frequency of SAEs was low in both treatment groups (2.0% simeprevir, 2.5% placebo) and there were no deaths in the simeprevir groups during the first 12 weeks of treatment. There was a higher frequency of hyperbilirubinaemia in simeprevir patients, probably related to inhibition of OATP1B1 and MRP2 hepatic transporters. It was not associated with other liver function test (LFT) abnormalities and it can be considered benign. There

[16] QT interval corrected for heart rate according to Fridericia

was a high incidence of anaemia and neutropenia but the rates were similar in the simeprevir and placebo groups. There was a higher incidence of rash of any type in simeprevir patients but most events were mild to moderate and there were no serious skin reactions. Photosensitivity reactions occurred in 3.3% of simeprevir patients compared with 0.5% in the placebo group. The incidence of pruritus was significantly higher (22.0% simeprevir, 14.9% placebo) but most events were mild. There were no noteworthy differences in AE profiles related to age, gender, race, region, body mass index or METAVIR fibrosis score. The frequency and type of AEs in patients with HCV/HIV co-infection and genotype 4 were generally in line with the overall population although patient numbers and exposure were low. Simeprevir appears to be well tolerated in patients with moderate to severe hepatic impairment and in patients with severe renal impairment. However, most of the data were recorded in short-term Phase I studies.

Overall, simeprevir appears to be safe and well tolerated and no major safety signals have been identified. There is the potential for significant, multiple drug-drug interactions which are of particular concern in patients with HCV/HIV co-infection.

First round benefit-risk assessment

First round assessment of benefits

The benefits of simeprevir 150 mg q.d. in the proposed usage are:

- SVR12 achieved in approximately 80% of treatment-naïve patients and patients with prior relapse.
- Higher SVR12 rates compared with placebo in prior partial and null responders (preliminary data).
- A high rate of patients eligible for a 24 week response guided overall treatment period.
- Similar SVR12 rates compared with telaprevir and boceprevir.
- SVR12 rates strongly predict SVR24 rates allowing prompt treatment decisions.
- Treatment benefits maintained across all demographic subgroups and baseline disease characteristics.
- Benefits observed in patients with cirrhosis, HCV/HIV co-infection and HCV genotype 4 infection (preliminary data).
- Once daily dosing with assumed compliance benefits.
- Generally safe and well tolerated.
- A more favourable safety profile compared with telaprevir with fewer skin rash ADRs.

First round assessment of risks

The risks of simeprevir 150 mg q.d. in the proposed usage are:

- Reversible hyperbilirubinaemia.
- Emerging drug resistance.
- Limited efficacy and safety data in treatment-experienced prior partial and null responders.
- Limited efficacy and safety data in patients with HCV/HIV co-infection and patients with genotype 4 infection.

- Limited or no data in elderly patients aged >65 years, paediatric patients, breast-feeding women, patients with decompensated liver disease and patients with severe renal failure.

First round assessment of benefit-risk balance

The benefit-risk balance of simeprevir 150 mg is unfavourable given the proposed usage. However it may become favourable following incorporation of changes recommended in *First Round recommendation regarding authorisation*, below, and after review of responses to questions raised under *Clinical questions*, below.

First round recommendation regarding authorisation

Authorisation is not recommended for the proposed indication of '*the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin*'. However, approval is recommended for the modified indication of

> *the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) who are treatment-naïve or who have relapsed following previous peginterferon therapy with or without ribavirin.*

The fact that only prior relapsers were studied in HPC3007 is highlighted in the proposed PI. However, the claim for efficacy in treatment-experienced patients (which would include null and partial responders) is not supported by the pivotal data. Supportive data in null and partial responders are provided in a Phase IIb study but the patient numbers are small and additional clinical trial data should be provided when available. The data in patients with HCV/HIV co-infection or HCV genotype 4 infection are encouraging but too preliminary to support authorisation. It is recommended that the full clinical study reports for both indications should be evaluated before authorisation is approved. The sponsor should provide efficacy data in patients who have failed previous therapy with non-pegylated interferon therapy before the claim can be approved.

Clinical questions

Pharmacokinetics

1. The evaluator requests that, if Study C118 has now been completed, the sponsor provides details from this study regarding the absolute bioavailability of simeprevir.
2. Does co- administration of cyclosporine or tacrolimus affect the PK of simeprevir?
3. Does co-administration of digoxin or rosuvastatin affect the PK of simeprevir?

Pharmacodynamics

1. In Study C202, the antiviral activity of simeprevir was compared directly in patients with HCV genotypes 2-6 inclusive. Has the sponsor made direct comparisons in a single study of the antiviral activity of simeprevir mono-therapy in genotypes 1 and 4?

Efficacy

1. It is recommended that the clinical study reports for the completed Studies C212 and HPC3011 be submitted for evaluation to support proposed use for patients with HCV/HIV co-infection and HCV genotype 4 infection.
2. It is not clear why prior partial or null responders were excluded from the pivotal Study HPC3007. Only 40 such patients (23 prior partial and 17 prior null) were treated with simeprevir 150 mg for 12 weeks in Study C206, and TMC 100 mg data were used in a pooled analysis. Please justify the proposed indication given the paucity of data in prior partial and null responders
3. Please state what studies have been performed in patients who have failed previous non-pegylated IFN therapy (as stated in the indication).

Safety

No questions.

Second round evaluation of clinical data submitted in response to questions

A summary of the sponsor's responses and the evaluator's evaluation of these responses are shown. See Attachment 2 (extract from the CER) for full details.

Pharmacokinetics

Response to Question 1: The full clinical study report of study C118 was provided in the sponsor's original submission dossier. The conclusion of study C118 is that the mean average absolute bioavailability of simeprevir after intake of a single PO 150 mg dose was 62% and after intake of a single PO 50 mg dose was 46%.

Evaluator comment: The sponsor's response is acceptable.

Response to Question 2: Study C120 was designed to evaluate the effect of simeprevir at steady-state on the single-dose PK of cyclosporine or tacrolimus. Pharmacokinetic profiles of simeprevir were measured only in the presence of cyclosporine or tacrolimus. The C_{max} and AUC for simeprevir in the presence of a single dose of cyclosporine was 4799 ng/mL and 55360 ng.h/mL respectively, and in the presence of tacrolimus was 3151 ng/mL and 38240 ng.h/mL respectively.

A pooled analysis of Phase I studies in which PK data were obtained after 7 days of simeprevir administration as the Phase IIb or Phase III capsule at 150 mg q.d. is described in the original submission dossier. The inter-subject variability was high for all PK parameters (coefficient of variation [CV] ranges from 73% to 139%).

Following 7 days of simeprevir administration at 150 mg q.d., the geometric mean steady-state C_{max} was 1992 ng/mL, and the geometric mean $AUC_{24\,h}$ was 22850 ng.h/mL. Although the exposure of simeprevir in the presence of cyclosporine and tacrolimus is somewhat higher than the pooled parameters from Phase I studies, there were individual studies in which simeprevir dosed alone also gave high AUC values, for example in studies C126 and C115 measured AUCs were 44380 and 43400 ng.h/mL with C_{max} values of 3378 and 3788 ng.h/mL respectively (original submission dossier).

In conclusion, although the observed simeprevir exposures in the presence of cyclosporine and tacrolimus are at the high end of those observed in other Phase 1 studies, clear conclusions cannot be drawn from cross-study comparisons of simeprevir PK, due to the large inter-study and inter-subject variability.

Evaluator comment: The evaluator believes that a caution should be included in the *"Interactions with other medicines"* section of the PI that co-administration of tacrolimus or cyclosporine with simeprevir may result in significant increases in simeprevir exposure and that the monitoring of blood concentrations of simeprevir is recommended.

Response to Question 3: Study C108 was designed to investigate the effect of simeprevir at steady-state on the single dose PK of digoxin and rosuvastatin. PK profiles of simeprevir were measured only in the presence of digoxin or rosuvastatin. The C_{max} and AUC for simeprevir in the presence of a single dose of digoxin were 1376 ng/mL and 15890 ng.h/mL respectively and in the presence of a single dose of rosuvastatin 1972 ng/mL and 21000 ng.h/mL respectively.

A pooled analysis of Phase I studies in which PK data were obtained after 7 days of simeprevir administration as the Phase IIb or Phase III capsule at 150 mg q.d. is described in the original submission dossier. The inter-subject variability was high for all PK parameters (CV was 73% to 139%). Following 7 days of simeprevir administration at 150 mg q.d., the geometric mean steady-state C_{max} was 1992 ng/mL, and the geometric mean $AUC_{24\,h}$ was 22850 ng.h/mL.

Considering the high inter-study variability in the exposure of simeprevir, the exposure in the presence of digoxin or rosuvastatin can be considered similar to that observed in other Phase 1 studies in which simeprevir was administered alone.

Evaluators comment: The sponsor's response is satisfactory.

Pharmacodynamics

Response to Question 1: The sponsor did not perform a direct comparison in a single study of the antiviral activity of simeprevir mono-therapy in genotypes 1 and 4. Patient baseline factors are not expected to affect the response to monotherapy and thus a comparison of antiviral activity across studies was performed.

Antiviral activity of simeprevir monotherapy in genotype 1 and 4 was assessed in 3 different studies (see Attachment 2 of this AusPAR for details).

In summary, the sponsor considers the monotherapy data from Study C101, C201 and C202 adequate to conclude that simeprevir displays similar antiviral activity in GT1 and GT4 infected patients. The similar activity seen with simeprevir monotherapy in GT1 and GT4 infected patients is consistent with in vitro data showing similar EC_{50} values of simeprevir against replicons carrying NS3 sequences from GT4 and GT1 clinical isolates. In addition, the high SVR12 rates in genotype 4 infected patients treated with simeprevir in combination with PegIFN/ribavirin in the Phase III Study HPC3011 confirmed the genotype 4 activity of simeprevir

Evaluator comment: The sponsor's response to the pharmacodynamics question is satisfactory. The antiviral activity of simeprevir has not been compared directly in patients with GT1 and GT4 HCV infection. However, changes from baseline in HCV RNA in patients receiving monotherapy with simeprevir 200 mg q.d. were similar in Studies C101 and C201 (in treatment-naïve patients with GT1 infection) and Study C202 (in treatment-naïve patients with GT4 infection). The results of these studies are in line with in vitro data which demonstrated similar EC_{50} values of simeprevir against replicons from GT1 and GT4 clinical isolates. Overall, the data support the premise that the antiviral activity of simeprevir is similar in patients with GT1 and GT4 HCV infection.

Efficacy

Response to Question 1: The completed C212 clinical study report and the Week 60 interim analysis for HPC3011 have been provided.

> **Evaluator comment:** The sponsor's response to efficacy question 1 is satisfactory. The sponsor has submitted the C212 clinical study report for the now completed study, and a further interim analysis of HPC3011 with a Week 60 cut-off. The additional data confirm the results of earlier interim analyses and support the use of simeprevir in patients with HCV/HIV co-infection and in patients with HCV GT4 infection.

Response to Question 2: Prior partial and null responders were excluded from the pivotal Study HPC3007 on regulatory advice. These patient populations had previously relapsed after PegIFN/RBV treatment alone and data from the Phase II program was still preliminary. This issue is addressed in the Phase III study HPC3001, an on-going, non-inferiority study comparing simeprevir/PegIFN/RBV with telaprevir/PegIFN/RBV without a placebo/PegIFN/RBV control group. To date SVR12 data are available to the study data monitoring committee (DMC) from 145 prior partial responders and 234 prior null responders and the sponsor states that the non-inferiority of simeprevir has been observed in the trial to date.

> **Evaluator comment:** The sponsor's response to efficacy question 2 is satisfactory although the limited data from C206 remains the only data to support for this indication. The Study HPC3001 is still on-going and blinded to the sponsor and investigators. However, the study DMC is unblinded and it has voted to continue the study. From this, the sponsor infers that the data to date are likely to confirm non-inferiority. Overall, it is reasonable to approve the proposed indication in view of the still unmet medical need in this group of patients. However, it would also be reasonable if the TGA Delegate prefers to wait for an interim analysis of Study HPC3001.

Response to Question 3: In the pivotal Study HPC3007, only 9 (2.3%) patients had previously received non-pegylated IFN/RBV therapy. The sponsor acknowledges that the patient numbers are not sufficient to draw conclusions on efficacy but there may now be an insufficient pool of patients who have previously received non-pegylated IFN. However, the sponsor notes that historically SVR rates are significantly higher with pegylated IFN than with non-pegylated IFN combination therapy. Therefore, they predict that the response to simeprevir/PegIFN/RBV therapy will be better or at least no worse in patients who have previously failed or relapsed on non-pegylated IFN.

> **Evaluator comment:** The sponsor's response to efficacy question 3 is satisfactory. The sponsor's argument that the response to simeprevir/PegIFN/RBV therapy will be better or at least no worse in patients who have previously failed or relapsed on non-pegylated IFN is not unreasonable although it is based on supposition without supporting clinical data.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Olysio (simeprevir) in the proposed usage are unchanged from those identified in the *First round assessment of benefits*, above.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Olysio (simeprevir) in the proposed usage are unchanged from those identified in the *First round assessment of risks,* above.

Second round assessment of benefit-risk balance

The benefit-risk balance of Olysio (simeprevir), given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Authorisation is recommended for the proposed indication of

> *the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.*

In the *First round evaluation*, the clinical aspects of the PI were considered satisfactory but the data did not fully support the indication for use in patients with HCV genotype 4 infection, patients with HCV/HIV co-infection, and prior partial and null responders. The main deficiency was the paucity of clinical data in each of these patient groups. The sponsor has addressed these issues with the addition of more clinical trial data which confirm the sparse previous interim data and are in line with efficacy rates in treatment-naïve patients with HCV genotype 1 infection. The sponsor has not provided additional clinical data relating to efficacy in prior partial and null responders over those previously provided in C206. This deficiency is being addressed in the on-going, non-inferiority Study HPC3001 comparing simeprevir/PegIFN/RBV and telaprevir/PegIFN/RBV which is still blinded. On balance, authorisation for use in prior partial and null responders is recommended based on Study C206 but subject to the results of Study HPC3001 being provided in a timely manner.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), EU-RMP Version 1.0 Dated 18th January 2013 with an Australian Specific Annex (ASA) Version 1.0 Dated 15th April 2013, which was reviewed by the TGA's Office of Product Review (OPR).

The RMP evaluator noted that simeprevir will be used always in combination therapy with pegIFNα and RBV. No specific consideration was given in the RMP to the safety specifications of the latter combination.

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the TGA Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the TGA Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor are as listed in Table 6.

Table 6: Summary of Safety Concerns

Ongoing safety concerns	
Important potential risks	Development of drug resistance
Important missing information	Use in children and adolescents (≥ 3 to < 18 years) Use in older patients (> 65 years) Use in pregnant or breast-feeding women Use in patients with moderate or severe hepatic impairment or decompensated liver disease Use in patients with GFR < 30 mL/min/1.73 m^2 Use in organ transplant patients Use in HCV/HBV co-infection Use in patients previously treated with a HCV protease inhibitor or other direct-acting antivirals Drug-drug interactions

HCV=hepatitis C virus; HBV=hepatitis B virus; GFR=glomerular filtration rate

RMP reviewer comment: Pending the evaluation of the nonclinical and clinical aspects of the SS, this is not acceptable as a complete list of ongoing safety concerns.

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities to monitor and further elucidate the 1 important potential risk and 9 areas of missing information. The additional activities include 12 ongoing studies and 2 planned studies.

Risk minimisation activities

The sponsor's conclusion in regard to the need for risk minimisation activities is: "*No specific Australian risk minimisation activities are planned for Olysio other than routine risk minimisation activities.*"

Routine risk minimisation activities are proposed for all important potential risks and important areas of missing information. No additional risk minimisation activities are proposed.

RMP reviewer comment: The list of ongoing safety concerns is incomplete, therefore the sponsor's conclusion regarding the need for additional risk minimisation activities is not acceptable.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the OPR's first round evaluation and recommendations[17] in relation to the RMP, the sponsor's responses to issues raised by the OPR, and the OPR's evaluation of the sponsor's responses.

[17] Recommendations in relation to revisions to the text in the draft PI are beyond the scope of the AusPAR and are not included here.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
It is recommended that the ASA be revised to include the following: All studies referenced in the pharmacovigilance plan should be listed in the ASA. This includes all planned studies and the anticipated dates for their submission in Australia. The sponsor should detail within the ASA the wording by which risk minimisation is exercised in the Australian PI.	It is the sponsor's understanding that the ASA should only include studies in which there were Australian sites involved. For other studies, the relevance to the safety profile is described in the EU-RMP and is cross referenced in the ASA. For ongoing studies, the anticipated study completion dates are provided. Clinical study reports for these studies will be submitted once completed. Janssen will update the ASA to reflect these amended dates. The sponsor does not consider that there are any risk management activities additional to the EU-RMP that are required to be included in the Australian ASA.	The recommendation remains for the sponsor to amend the ASA. It is important that the ASA contains all studies referenced in the pharmacovigilance plan, and the anticipated dates for their submission in Australia. Furthermore, the exact wording by which routine risk minimisation is exercised in the Australian PI should be documented in the ASA.
The sponsor should add the following important identified risks for simeprevir: · Rash and severe cutaneous adverse reactions · Photosensitivity · Development of drug resistance	The sponsor does not consider it warranted to include rash and severe cutaneous adverse reactions as ongoing safety concern. Development of drug resistance, which is currently included as an important potential risk, is not considered an important identified risk. Photosensitivity is added as an important identified risk to the simeprevir RMP version 1.1. Justification is provided.	The sponsor has agreed to include photosensitivity as an important identified risk. The recommendation to include rash and severe cutaneous adverse reactions as an ongoing safety concern remains. This issue is deferred to the Delegate for consideration, along with advice from the clinical evaluator.
The following are important identified risks for pegIFN and RBV (as agreed by the sponsor in the RMP). Furthermore, these are	At time of the Marketing Authorisation Application (MAA) submission for a medicinal product in the EU, the sponsor must submit an	The safety of simeprevir cannot be separated from that of pegIFN and RBV as these products are dosed together as part of triple

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
included as important identified risks for other protease inhibitors used in combination with pegIFN and RBV · Anaemia · Lymphopenia/neutropenia · Thrombocytopenia	RMP for the medicinal product for which the marketing authorisation is requested. As marketing authorisation is requested for simeprevir, the RMP solely discusses simeprevir as the compound of interest. As such, assessment of the risks associated with PegIFN and/or RBV, or any other compound that is administered in combination with simeprevir in the future, is beyond the scope of the simeprevir RMP and should be discussed in their own respective RMPs, which are the responsibility of their respective Marketing Authorisation Holders. For this reason, identified risks of PegIFN and/or RBV, but which are not attributable to simeprevir, are not listed as important identified risk or important potential risk in the simeprevir RMP. Nevertheless, as it is important to be aware of the risks associated with PegIFN and/or RBV, references were made throughout the simeprevir RMP to the respective PI.	therapy. This issue of including important risks related to PegIFNα and RBV treatment is deferred to the Delegate for consideration.
The sponsor should add the following important potential risks: · Acute hypersensitivity reactions	No acute hypersensitivity reactions to simeprevir as active substance were observed during the clinical development program. In addition, each Olysio 150 mg capsule contains 78.4 mg of lactose (as monohydrate) and as per the proposed Australian PI section Contraindications, Olysio is contraindicated for those with hypersensitivity to the active substance or to	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	any of the excipients listed. The sponsor considers this contraindication to be sufficient to prevent an impact of acute hypersensitivity reactions on public health or on the individual. Therefore, the sponsor does not consider it warranted to add acute hypersensitivity reactions as an Important Potential Risk in the simeprevir RMP.	
The Sponsor should add the following important missing information: · Off-label use, including use in the absence of pegIFN and/or RBV, or with interferon drugs other than PegIFNα. · Use in other HCV genotypes · Patient's with previous triple therapy simeprevir/PegIFN/ RBV treatment failure · Long term therapy · Exposure in patients with psychiatric disorders · Use in patients of Aboriginal and Torres Strait Islander descent · Use in patients with HIV co-infection	Details of sponsor's full response and justification are not included here.	The OPR evaluator acknowledges the sponsor's response regarding the inclusion of these areas of missing information. However, the recommendation remains to include the following two areas of important missing information: Use in other HCV genotypes Use in patients of Aboriginal and Torres Strait Islander descent
The following important identified risks are known to be associated with pegIFN and RBV treatment (as agreed by the sponsor in the RMP): · Psychiatric disorders	As mentioned above, identified risks of PegIFN and/or RBV which are not attributable to simeprevir, are not listed as important identified risk or important potential risk in the simeprevir RMP.	The safety of simeprevir cannot be separated from that of pegIFN and RBV as these products are dosed together as part of triple therapy. This issue of including important risks related to

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
· Diabetes mellitus · Thyroid disorders · Specific skin disorders (cutaneous leukocytoclastic vasculitis, lichen planus, polyarteritis nodosa, porphyria cutanea tarda)		pegIFN and RBV treatment is deferred to the Delegate for consideration.
The following are known class effects of protease inhibitors: · Hyperuricaemia · QT prolongation	Based on the mechanism of action, simeprevir belongs to the pharmacological class of the HCV NS3/4A protease inhibitors, which also includes telaprevir and boceprevir. However, the chemical structure of the molecules is different: both telaprevir and boceprevir are α-ketoamid derivatives whereas simeprevir is a macro-cyclic derivative with potent and selective inhibitory activity against the HCV NS3/4A protease. Due to the different structure of the molecule, different safety profiles can be expected. Nevertheless this diversification of the pharmacological class, potential side effects can only be considered pharmacological class effects if they are common to all compounds of that particular pharmacological class. Although hyperuricemia and QT prolongation are potential adverse reactions of telaprevir and boceprevir, this is not the case for simeprevir.	This is acceptable.
It is recommended that the sponsor clarify if Australian patients will be included in trial HPC2001.	Trial HPC2001 has been cancelled. Consequently, no further details will be entered in the ASA for this	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Furthermore, the planned start date and planned submission dates should be clarified. Finally, this study (with milestones) should also be listed within the ASA.	study.	
The list of ongoing safety concerns is incomplete, therefore the sponsor's conclusions regarding the need for additional risk minimisation activities is not acceptable. The evaluator is concerned that the following risks in particular will require additional risk minimisation activities and should be added to the list of ongoing safety concerns. Furthermore, other protease inhibitor drugs within the same class and indication as simeprevir have been required to implement additional risk minimisation for the following risks: · Anaemia, thrombocytopenia and neutropenia These risks are known to be serious risks associated with pegIFN and RBV treatment (as agreed by the sponsor in the RMP). Educational materials regarding the management of these risks should be applied. This has been implemented for other products that are prescribed in combination with pegIFN and RBV · Rash/severe cutaneous adverse reactions.	As already mentioned (above), the sponsor does not consider it required to add anaemia, thrombocytopenia, neutropenia and rash/severe cutaneous adverse reactions as important identified risk or important potential risk to the simeprevir RMP. Therefore, no additional risk minimisation activities will be included in the simeprevir RMP for these non-simeprevir related risks.	The safety of simeprevir cannot be separated from that of pegIFN and RBV as these products are dosed together as part of triple therapy. This issue of including important risks related to pegIFN and RBV treatment is deferred to the Delegate for consideration.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
This is a serious adverse reaction, for which other protease inhibitor drugs have implemented additional risk minimisation		

Summary and recommendations

It is considered that the sponsor's response to the TGA request for information has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The recommendation remains for the sponsor to amend the ASA in regards to pharmacovigilance and risk minimisation. It is important that the ASA contains all studies referenced in the pharmacovigilance plan, and the anticipated dates for their submission in Australia. Furthermore, the exact wording by which routine risk minimisation is exercised in the Australian PI should be documented in the ASA.

The OPR evaluator acknowledges the sponsor's response regarding the expansion of the list of ongoing safety concerns to include the risks listed in the RMP Round 1 report. This is acceptable, except in regards to "Use in other HCV genotypes" and "Use in patients of Aboriginal and Torres Strait Islander descent". The sponsor is requested to include these risks in the table of ongoing safety concerns. If appropriate, the OPR will accept the inclusion of these risks in the ASA only.

Issues that require consideration from the Delegate

The safety of simeprevir cannot be separated from that of pegIFN and RBV, as these products are dosed together as part of triple therapy. Simeprevir has been studied as part of a triple therapy regimen. The issue of including important risks and information in the RMP and Australian PI document related to pegIFN and RBV treatment is deferred to the Delegate for consideration.

The recommendation to include rash and severe cutaneous adverse reactions as an ongoing safety concern remains. This issue is deferred to the Delegate for consideration, along with advice from the clinical evaluator.

Final decisions regarding the PI are deferred to the Delegate.

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

Advice on the pharmacovigilance aspects of this application were sought from the ACSOM at its meeting on 7th March 2014. This advice was provided to the Delegate.

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator made the following comment on the safety specification of the RMP in the first round clinical evaluation report:

"Routine pharmacovigilance activities will be conducted locally by Janssen-Cilag Pty Ltd Australia. All global risk minimisation activities will be applied in Australia and no specific local activities are proposed.

In the randomised, blinded clinical trial population, 1,486 patients have been exposed to simeprevir for a total of 472.7 patient-years. The population were mostly male (61.2%) and White (91.7%). Only 2.5% of patients were aged >65 years. Most patients (59.0%) had mild or moderate renal impairment and 27.3% had METAVIR fibrosis score F3 or F4. The most significant risk is the development of drug resistance and this is being evaluated in the on-going clinical trial program. Other specific safety concerns and risk minimisation measures will be identified in the current clinical trial program scheduled to complete in 2021. Data are lacking in children < 18 years old, pregnant or breast-feeding women, patients aged > 65 years, patients with moderate or severe hepatic impairment or decompensated liver disease, patients with severe renal impairment, organ transplant patients, patients with HCV/HBV co-infection, patients previously treated with other protease inhibitors or direct-acting antiviral agents and patients exposed to drug-drug interactions. A paediatric study has commenced but routine pharmacovigilance activities will monitor exposure in the other patient groups and be reported in the Periodic Safety Update Reports (PSURs).

Overall, simeprevir appears to be safe and well tolerated. Safety concerns and missing information in special populations have been identified appropriately in the proposed PI. The draft RMP is satisfactory with an appropriate balance between additional clinical trial data and routine pharmacovigilance."

Nonclinical evaluation report

Advice from the nonclinical evaluator was unavailable at this time.

Key changes to the updated RMP

In their response to the TGA requests for further information, the sponsor provided an updated EU-RMP Version 1.1 dated 14th November 2013, with data lock point 16th September 2013, with an ASA Version 1.1 dated 28th January 2014. The OPR evaluator has identified the following major changes from the version evaluated at Round 1:

Table 8: Key changes from RMP version 1.0 to version 1.1

RMP updates	
Safety specification	Addition of important identified Risk: Photosensitivity conditions Alteration of missing information "Use in older patients (> 65 year)" to "Use in elderly patients (> 65 years)". Addition of missing information "Olysio + medicinal products other than PegIFNα and ribavirin".
Pharmacovigilance activities	Addition of routine pharmacovigilance for the risk of Photosensitivity conditions. Additional pharmacovigilance activities assigned to the risk of "drug-drug interactions" and "Olysio + medicinal products other than PegIFNα and ribavirin". Updates to the status of studies in the pharmacovigilance plan, including completed studies. Addition of Trial IDX-06A-005c:A randomised study to evaluate the safety and efficacy of IDX719 in combination with simeprevir and ribavirin for 12 weeks in subjects with chronic hepatitis C infection Addition of Trial HPC1009

RMP updates	
Risk minimisation activities	Addition of routine risk minimisation activities for the important identified Risk "Photosensitivity conditions" and missing information of "Olysio + medicinal products other than PegIFNα and ribavirin".

The OPR evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

Recommendation

The OPR evaluators recommend to the Delegate that the updated version of the RMP is implemented as follows:

- The European Risk Management Plan Version 1.1 dated 14th November 2013, with data lock point 16th September 2013, with an Australian Specific Annex Version 1.1 dated 28th January 2014 to be revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Background

Simeprevir is an inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease. HCV protease inhibitors block the NS3/4A protease-dependent cleavage of the HCV polyprotein, inhibiting viral replication in infected host cells. Currently approved protease inhibitors for HCV are boceprevir and telaprevir.

This application is to register a new chemical entity, simeprevir, 150 mg capsules, for:

> *the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin (see Clinical Trials).*

Quality

There are no objections to registration from a pharmaceutical chemistry perspective.

The submission was not presented to the Pharmaceutical Subcommittee (PSC) as there was no issue requiring PSC advice.

Study TMC435-TiDP16-C118 was conducted to assess the absolute bioavailability and PK of 50 mg and 150 mg (G019) capsule doses and an IV microdose of 100 µg [^{3}H]-simeprevir. The 150 mg capsule (G019) is identical to that proposed for registration apart from the colour and printing on the capsule shell. $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} were more than dose-proportionally higher for a 150 mg dose compared to a 50 mg dose. The mean absolute bioavailability was higher after a 150 mg dose (62%) compared to a 50 mg dose (46%).

Nonclinical

There were no nonclinical objections to registration of simeprevir.

In vitro virology studies showed that simeprevir is a specific inhibitor of the HCV NS3/4A protease at nanomolar concentrations, and anti-HCV activity was shown against genotype 1a, 1b and genotype 4 clinical isolates. In vitro selection studies identified amino acid substitutions which conferred reduced susceptibility to simeprevir. Some cross resistance between NS3/4A protease inhibitors is anticipated. Virology studies were not conducted in animals in vivo.

On a theoretical basis, there may be an increased risk for liver toxicity following co-administration of simeprevir, ribavirin and PegIFNα. Therefore, the potential for liver effects should also be considered in any laboratory monitoring program.

Cardiac toxicity may be a potential clinical risk in some high risk patients who may achieve very high plasma levels of simeprevir.

Simeprevir was phototoxic in an in vitro study in BALB/c 3T3 fibroblasts. No phototoxicity studies were conducted in animals in vivo. This nonclinical finding is of potential clinical relevance.

Although there were no teratogenic findings, there were a number of findings across all the reproductive toxicity studies of reduced fertility in male rats, maternal deaths/increases in post implantation losses in pregnant mice and rats, reduced body weight in pregnant rats, reduced fetal weights and fetal skeletal variations. In offspring of rats there were growth/development delays.

Concerns over the reproductive toxicity findings are mitigated by the fact that simeprevir will be contraindicated in pregnancy because it will be co-administered with ribavirin, a known teratogen. For simeprevir itself, A B3 category is recommended (mainly owing to fetal findings of reduced bodyweight).

Clinical

The following key points from the clinical evaluation report were noted:

Pharmacokinetics

Following single, PO, 200 mg doses of either the Phase IIa (F007) or IIb (F020) capsule formulations in healthy subjects the median T_{max} of simeprevir was 6.0 h and the mean t½ values were 10.5 h to 10.94 h, respectively.

The evaluator concluded that in healthy, predominantly Caucasian subjects under fed conditions, the mean C_{max} and AUC values for simeprevir increased with increasing dose; however, at higher doses the C_{max} and AUC values increased more than dose proportionally, for example, from 100 to 200 mg there was approximately a 5 fold increase for both C_{max} and AUC_{inf}. By contrast, the median T_{max} was 5 or 6 h across the dose range tested and the mean $t_{½,term}$ was approximately 10 to 13 h.

In humans, irrespective of hepatic or renal function, the plasma protein binding of simeprevir was very high (> 99.9%).

Almost all ^{14}C-simeprevir-related radioactivity from a single 200 mg dose administered as an oral solution was excreted in faeces (approximately 91%). Unchanged simeprevir in faeces accounted for a mean of 31.0% of the administered dose. Simeprevir excreted in urine was very low, ranging from 0.009 to 0.138% of the dose.

The inter-subject variability of simeprevir PK was generally moderate to high, which the sponsor indicates reflects the non-linear drug disposition of simeprevir.

In treatment-naïve, genotype 2 to 6 HCV-infected subjects, the PK of simeprevir were consistent for genotypes 4, 5 and 6 with values previously reported for genotype 1 infected subjects, whereas a trend for lower exposure was observed in subjects infected with genotypes 2 and 3. The reason for these lower exposures is currently unknown.

Hepatic impairment

Following administration of simeprevir at 150 mg q.d. in subjects with moderate hepatic impairment, the mean C_{max} and $AUC_{24\,h}$ values for simeprevir were 1.71 and 2.44 fold higher, respectively, relative to matched subjects with normal hepatic function. In subjects with severe hepatic impairment, the mean C_{max} and $AUC_{24\,h}$ values for simeprevir were 3.13 and 5.22 fold higher, respectively, relative to subjects with normal hepatic function.

Renal impairment

Following administration of simeprevir at 150 mg q.d. in subjects with severe renal impairment, the mean C_{min}, C_{max}, and $AUC_{24\,h}$ values for simeprevir were increased 1.71, 1.34, and 1.62 fold, respectively, relative to matched subjects with normal renal function, whereas, the median T_{max} was 6 hours for both treatment groups.

There were no data examining use of simeprevir in the paediatric population.

Drug interactions

The range of submitted studies examined the potential for interaction between simeprevir and other drugs either likely to be used in combination or metabolised through similar pathways.

Simeprevir is both a substrate for and mild inhibitor of CYP3A in vivo as well as being a substrate for P-gp, MRP2, BCRP, OATP1B1, OATP2B1, and OATP1B3.

Drug-drug interaction studies in healthy subjects indicated that steady-state simeprevir exposure increases considerably when simeprevir is co-administered with drugs that are moderate or strong inhibitors of CYP3A and which are also inhibitors of P-gp, such as erythromycin. Therefore, administration with drugs such as these would be expected to increase both the efficacy of simeprevir and the incidence of AEs and SAEs. Similarly, simeprevir generally increased the exposure of other CYP3A inhibitors when the CYP3A inhibitors were co-administered.

Ledipasvir is an NS5A replication complex inhibitor in development for the treatment of HCV genotype 1 infection. Although ledipasvir does not inhibit or induce CYP enzymes and does not inhibit MRP2 or OATP1B1, potential drug-drug interactions between simeprevir and ledipasvir were investigated in Study GS-US-256-0129 as combinations of the two antiviral agents are expected to be used in the future.

Study HPC1005 examined the effects of steady-state simeprevir on the steady-state PK of daclatasvir (BMS-790052) in healthy subjects and the steady-state BMS-790052 on the steady-state PK of simeprevir in healthy subjects. Daclatasvir is also an NS5A replication complex inhibitor in development)

The Delegate concurs with the evaluator that drug-drug interactions were well documented in the proposed PI and that if daclatasvir or ledipasvir are approved for marketing in the future, an appropriate caution should be included in the PI regarding potential interactions.

Population PK

The submission contained nine PPK studies. The largest of these was the Simeprevir Global PPK Study which was a meta-analysis that included covariate analysis of simeprevir in two Phase II (C205 and C206) and three Phase III global trials (C208, C216 and HPC3007).

Population PK studies identified that age, sex, body weight, total bilirubin at baseline and METAVIR score were significant covariates for simeprevir exposure. However, when the covariates were examined in combination, the simulated high and low extremes fell within the 90% prediction intervals of the whole study population. Moreover, the level of random variability in exposure of simeprevir was larger than the variation induced by the significant covariates.

Population PK studies demonstrated that the PK of simeprevir could be characterised by a two-compartment model with first order absorption (with lag time), saturable clearance, described using Michaelis-Menten kinetics and a dose-dependent relative bioavailability.

In a pooled analysis of the Phase III individual post-hoc PPK estimates, the median exposure of simeprevir in Asian subjects, following administration of 150 mg q.d., was 5.7 to 6.4 fold higher than other races.

In subjects co-infected with HCV genotype 1 and HIV-1 (Study C212 PPK), the estimates for simeprevir exposure were slightly lower than the estimates in subjects infected with HCV genotype 1 without HIV-1 co-infection (Studies C208, C216 and HPC3007); however, due to the high inter-subject variability they were considered to be comparable.

Pharmacodynamics

The proportion of subjects achieving plasma HCV RNA levels < 25 IU/mL on Day 28 was 66.7%, 100%, and 100% in the 25 mg, 75 mg, and 200 mg simeprevir once daily in combination with PegIFN/RBV dose groups, respectively, and 42.9% and 33.3% in the placebo in combination with PegIFN/RBV groups in Cohort 1 and 2, respectively.

The presence of a Q80K mutation at baseline had no clear effect on the response to simeprevir treatment at doses of 75 mg and 200 mg q.d. at Week 4.

Viral breakthrough was observed in 10 (13.5%) subjects, whereas, viral breakthrough did not occur in the placebo groups (that is, the PegIFN/RBV only group). Nine out of 10 subjects with viral breakthrough had emerging mutations in the NS3 protease domain known to confer reduced susceptibility to simeprevir in vitro (mainly R155K and/or D168V or D168E).

Following 28 days of administration of simeprevir in combination with PegIFN/RBV, a dose-dependent reduction in plasma HCV RNA from baseline was observed with greater changes in plasma HCV RNA levels with 150 mg simeprevir q.d. (-5.46) and 200 mg simeprevir q.d. (-5.26) compared to with 75 mg simeprevir q.d. (-4.28). By contrast, on Day 28, the mean change in plasma HCV RNA levels were smaller in the placebo group (-1.53).

In treatment naïve subjects treated with the triple therapy (simeprevir/PegIFN/RBV) or placebo (placebo/PegIFN/RBV), a larger proportion of subjects in the simeprevir treatment groups (70.7% to 84.8%) achieved a SVR at week 72 compared with the placebo group (64.9%). In treatment experienced subjects treated with the triple therapy or placebo, a larger proportion of subjects with a sustained virologic response at week 24 of follow-up were observed in the simeprevir treatment groups (60.6% to 80.0%) compared with the placebo group (22.7%).

A trend for higher SVR rates was observed in the 150 mg q.d. simeprevir dose group compared with the 100 mg q.d dose group in partial and non-responders, as well as across multiple subgroups (including subjects with Q80K polymorphism, higher body mass index, and advanced fibrosis).

There was a trend for lower SVR in subjects infected with HCV genotype 1a compared to subjects with HCV genotype 1b.

Supratherapeutic doses of simeprevir had no effect on QT interval.

Simeprevir (150 mg q.d.) did not act as a cutaneous photosensitising agent in the phototoxicity study C125 where 12 patients were treated with simeprevir 150 mg PO daily and compared to placebo or ciprofloxacin. According to publically available documents from the FDA website[18], the FDA independent review from the Division of Dermatology and Dental products reached different conclusions, reporting that the results from Study C125 added to the body of evidence that simeprevir is a photosensitiser. Immediate photosensitivity was noted in 33% of subjects in the simeprevir group and in no subjects in the ciprofloxacin or placebo groups. Subjects with the highest simeprevir plasma levels exhibited immediate photosensitivity reactions. Correlation between plasma exposure and incidence of adverse events including rash and pruritus were also noted in the FDA Pharmacometrics Review.

In treatment-naïve and experienced genotype 1 HCV-infected subjects, antiviral response could be detected following 7 days of treatment and antiviral activity peaked following 28 days of simeprevir dosing. After 12 weeks of PegIFN/RBV dosing, antiviral response was similar or slightly lower than at the 28 day time point.

In subjects treated with simeprevir and PegIFN/RBV, IL28B genotype and combination of HCV genotype/subtype with baseline Q80K polymorphism were the most important baseline characteristics for predicting the probability of achieving SVR12.

Efficacy

Three Phase III trials and two Phase IIb trials were submitted in support of the proposed indication in HCV genotype 1, including relapsers, null-responders, and partial responders. One open label study was submitted in support of the indication in HCV/HIV co-infection and in HCV genotype 4 respectively.

All Phase III studies were ongoing at the time of this submission.

The primary endpoint for each of the pivotal Phase III trials was SVR12, which has been accepted as a valid clinical endpoint by regulatory authorities, given most relapses occur within the first 12 weeks after cessation of therapy.

There were no studies comparing simeprevir in combination with PegIFN/ribavirin with currently registered protease inhibitors. At the time the Phase III trials were initiated, other protease inhibitors had not been approved and PegIFN/ribavirin was standard therapy.

Table 9: Dose finding studies

Trial	Study design	Study population	Simeprevir dose and duration	N*	Primary efficacy endpoint	Status
Study C205	Phase IIb, Randomised, double-blinded, active-control (PegIFN/RBV)	Genotype 1 Treatment-naïve	75 or 150 mg q.d., as TMC12/PR24/48 or TMC24/PR24/48	388	SVR72	Completed

[18] Centre for Drug Evaluation and Research. Application number: 205123Orig1s000. Medical Review(s) Available from <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000MedR.pdf> (accessed 1st April 2014)

Trial	Study design	Study population	Simeprevir dose and duration	N*	Primary efficacy endpoint	Status
Study C206	Phase 2b, Randomised, double-blinded, active-control (PegIFN/RBV)	Genotype 1 Relapsers, Null-responders, and Partial responders	100 or 150 mg q.d., as TMC12/PR48, TMC24/PR48 or TMC48/PR48	463	SVR24	Completed

*number of patients randomised; TMC: simeprevir, PR: PegIFN/RBV; the number 12, 24 or 48 indicates weeks of treatment, for example, TMC12/PR24 = simeprevir for 12 weeks PegIFN/RBV for 24 weeks.

Table 10: Pivotal studies

Trial	Study design	Study population	Simeprevir dose and duration	N*	Primary efficacy endpoint	Status
Study C208	Phase III, Randomised, double-blinded, active-control (PegIFN/RBV)	Genotype 1 Treatment-naïve	150 mg q.d., as TMC12/PR24 or TMC12/PR48#	395	SVR12	Ongoing
Study C216†	Phase III, Randomised, double-blinded, active-control (PegIFN/RBV)	Genotype 1 Treatment-naïve	150 mg q.d., as TMC12/PR24 or TMC12/PR48#	393	SVR12	Ongoing
Study HPC 3007	Phase III, Randomised, double-blinded, active-control (PegIFN/RBV)	Genotype 1 Relapsers	150 mg q.d., as TMC12/PR24 or TMC12/PR48#	394	SVR12	Ongoing

†Study 216 included patients taking either PegIFNα-2a or PegIFNα-2b with ribavirin; # Based on response-guided therapy; *number of patients randomised; TMC: simeprevir, PR: PegIFN/RBV; the number 12, 24 or 48 indicates weeks of treatment, for example, TMC12/PR24 = simeprevir for 12 weeks PegIFN/RBV for 24 weeks.

Table 11: Other efficacy studies

	Study design	Study population	Simeprevir dose and duration	N*	Primary efficacy endpoint	Status
Study 212	Open label, single arm	HCV-HIV co-infected subjects	150 mg q.d. as TMC12/PR24 or TMC12/PR48#	106	SVR12	Completed
Study HPC 3011	Open-label single arm, Phase III	Genotype 4 Treatment-naïve or Treatment experienced	150 mg q.d., as TMC12/PR24 or TMC12/PR48#	136	SVR12	Ongoing

	Study design	Study population	Simeprevir dose and duration	N*	Primary efficacy endpoint	Status
Study 213	Phase III open-label	Genotype 1 who were in the placebo groups of a Phase IIb/III study or who received 14 days of a DAA in Phase I studies.	150 mg q.d. as TMC12/PR24 or TMC12/PR48#	60**	SVR12†	Ongoing

*Number of patients enrolled; †At the time of interim analysis, no data were available for SVR12; #Based on response-guided therapy; **270 planned; TMC: simeprevir, PR: PegIFN/RBV; the number 12, 24 or 48 indicates weeks of treatment, for example, TMC12/PR24 = simeprevir for 12 weeks PegIFN/RBV for 24 weeks; DAA = direct acting antiviral agent.

Study C205. Dose finding study. Genotype 1 Treatment-Naïve

This was a Phase IIb, randomised, 5 arm, double-blind, placebo controlled study of different regimens of simeprevir/PegIFN/RBV versus PegIFN/RBV alone in treatment-naïve patients with HCV genotype 1 infection, to assess optimal dose and duration of therapy. It has been published as the PILLAR study[19]. The majority of patients achieved SVR72 with higher proportions in the simeprevir groups compared with the control groups. Similar SVR24 rates were observed with the different simeprevir doses (75 mg and 150 mg) and in the different simeprevir treatment duration groups (12 or 24 weeks). Differences in SVR72 rates in the pooled simeprevir 150 mg q.d. and placebo groups were statistically significant ($p < 0.025$) but the difference between the pooled simeprevir 75 mg and placebo groups did not achieve statistical significance ($p = 0.051$). There were trends towards higher SVR24 rates in the simeprevir 150 mg dose groups compared to the 75 mg dose groups among patients infected with HCV genotype 1a (66.7% versus 55.0%), among patients with METAVIR score F3 (75% versus 63.0%), among patients aged > 45 years (82.1% versus 70.4%), among patients with body mass index ≥ 30 kg/m^2 (90.0% versus 66.7%), among male patients (86.2% versus 75.9%) and among Black patients (100% versus 60.0%).

Overall, simeprevir was generally well tolerated and the data support use of the 150 mg dose for 12 weeks in the Phase III studies, however the study was not powered to provide definitive data across subgroups.

Study C206. Dose finding study. Genotype 1 Relapsers, Null-responders and Partial responders

This was a Phase IIb, randomised, 7 arm, double-blind, placebo controlled study comparing the efficacy and safety of different regimens of simeprevir/PegIFN/RBV in patients with HCV genotype 1 infection who had failed at least one previous course of PegIFN/RBV therapy. The majority of patients achieved SVR24, the primary endpoint with higher proportions in the simeprevir groups compared with the control group. In the simeprevir treatment arms, SVR24 was achieved in 69.7%, 66.2%, 60.6%, 66.7%, 72.1% and 80% in the TMC12/PR48 100 mg, TMC24/PR48 100 mg, TMC48/PR48 100 mg,

[19] Fried MW, Buti M, Dore GJ et al. Once-Daily Simeprevir (TMC435) With Pegylated Interferon and Ribavirin in Treatment-Naive Genotype 1 Hepatitis C: The Randomized PILLAR Study. *Hepatology* 2013;58:1918-1929.

TMC12/PR48 150 mg, TMC24/PR48 150 mg and TMC48/PR48 150 mg treatment arms, respectively. SVR24 was achieved in 22.7% of the control arm with a treatment difference in favour of simeprevir observed in prior null responders, partial responders and relapsers. The differences in SVR rates between the pooled simeprevir 100 mg and 150 mg groups and the placebo group were each statistically significant ($p < 0.025$). The differences in SVR rates in each individual simeprevir treatment group were also statistically significant ($p < 0.017$).

It was suggested by the clinical evaluator that a response guided optional TMC12/PR24/48 arm was not included, presumably because low SVR rates were predicted after 24 weeks PegIFN/RBV therapy.

It is noted that these data (along with data from Study HPC3007) have been submitted to support the indication in patients who have failed previous interferon therapy, however numbers of patients in subgroups are small and prior null and partial PegIFN/RBV responders were excluded from Study HPC3007(see below).

Study C208. Pivotal study. Genotype 1 Treatment-naïve

Study C208 was a multi-centre, Phase III, randomised, double-blind, parallel-group, controlled trial of simeprevir 150 mg or placebo combined with PegIFN/RBV in treatment-naïve, HCV G1 infected patients with compensated liver disease including cirrhosis. The primary efficacy endpoint was SVR12, defined as undetectable HCV RNA levels at the end of treatment and HCV RNA < 25 IU/mL 12 weeks after the planned end of treatment.

In the primary intent-to-treat (ITT) analysis, the proportion of patients with SVR12 was 79.5% (95% confidence interval (CI): 74.7, 84.0) in the simeprevir/PegIFN/RBV group compared with 50.0% (95% CI: 42.1%, 58.1) in the placebo/PegIFN/RBV group. The treatment difference in favour of the simeprevir/PegIFN/RBV group was 29.3% (95% CI: 20.1, 38.6, $p<0.001$). Similar response rates were observed in a sensitivity logistic regression analysis. The proportions adjusted for stratification factors including HCV genotype subtype and IL28B status did not affect the treatment difference p-values. Treatment failure occurred less frequently in the simeprevir group compared with placebo. Failure was associated with emerging mutations in 92.1% of patients.

Study C216. Pivotal study. Genotype 1 Treatment-naïve

This was a randomised, double-blind, placebo controlled study to investigate the efficacy, safety and tolerability of simeprevir versus placebo as part of a treatment regimen including PegIFNα-2a (Pegasys) and ribavirin (Copegus) or PegIFNα-2b (PegIntron) and ribavirin (Rebetol) in treatment-naïve, genotype 1, HCV infected patients.

The study design was virtually the same as study C208 except that PegIFNα-2b was studied in a limited number of selected European countries. In these countries, subjects were randomised in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/RBV with the intent to randomise no greater than 30% of the overall study population to a PegIFNα-2b containing regimen. 77 patients were randomised to receive PegIFNα-2a/RBV plus simeprevir and 80 patients were randomised to receive PegIFNα-2b/RBV plus simeprevir.

In the primary analysis, the proportion of patients with SVR12 was 81.3% in the simeprevir/PegIFN/RBV group compared with 50.0% in the placebo/PegIFN/RBV group. The stratum adjusted benefit in favour of the simeprevir/PegIFN/RBV group was 32.2% (95% CI: 23.3, 41.2) which was statistically significant ($p < 0.001$) after controlling for the type of PegIFN/RBV and the stratification factors. The results of the logistic regression sensitivity analysis confirmed the primary analysis with a 41.2% difference in favour of the simeprevir/PegIFN/RBV group ($p < 0.001$). Irrespective of the type of PegIFN/RBV, HCV genotypic subtype and IL28B genotype, the SVR12 rate was statistically significantly higher in the simeprevir/PegIFN/RBV group compared with the placebo/PegIFN/RBV group ($p \leq 0.003$).

Pooled efficacy results for treatment-naïve populations (C208 and C216)

Based on the similarity in design and patient population, results of these studies were pooled for analysis. The baseline demographics and disease characteristics were generally balanced between treatment groups. The evaluator commented that the results of the pooled efficacy analysis confirmed the superiority of simeprevir compared with placebo in treatment-naïve patients. Overall, the results were similar to the individual study findings. It was noted that in HCV genotype 1a subjects with the Q80K polymorphism at baseline, no statistically significant difference in SVR12 rates were present when comparing simeprevir to the control group (49/84 (58.3%) and 23/44, (52.3%), respectively). This was also highlighted in the FDA review, with the possibility of screening for Q80K polymorphism prior to initiating treatment with simeprevir.

Study HPC3007. Genotype 1 relapsers

This was a randomised, double-blind, placebo controlled, two arm study to compare the efficacy and safety of simeprevir versus placebo combined with PegIFNα-2a and RBV in patients with HCV genotype 1 who received at least 24 weeks of PegIFN based therapy and relapsed within one year after the end of treatment. The primary efficacy endpoint was the proportion of patients in each treatment group achieving SVR12.

In the primary ITT analysis, the stratum adjusted proportion of patients with SVR12 was 79.6% (95% CI: 74.8, 84.4) in the simeprevir/PegIFN/RBV group compared with 36.6% (95% CI: 28.7, 44.5) in the placebo/PegIFN/RBV group. The treatment difference in favour of the simeprevir/PegIFN/RBV group was 43.0% (95% CI: 33.8, 52.3, $p < 0.001$). Similar response rates were observed in a sensitivity logistic regression analysis.

The evaluator commented that while the primary endpoint of the study was met, it is unclear why prior null and partial PR responders were excluded from this study given the claimed indication includes patients *'who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin'*. In the response to the TGA request for further information, the sponsor outlined that this exclusion occurred due to the timing of the availability of supportive data in treatment experienced patients in Study C206. Consistent with regulatory guidance, studies of non-responders in Phase III could only begin after initial supportive data from Phase II.

It is noted that no additional clinical data relating to efficacy in prior partial and null responders has been provided over those previously provided in C206. This deficiency is being addressed in the on-going, non-inferiority Study HPC3001 comparing simeprevir/PegIFN/RBV and telaprevir/PegIFN/RBV. On balance, the evaluator recommends authorisation for use in prior partial and null responders based on C206 but subject to the results of HPC3001 being provided in a timely manner.

Study 212 HCV-HIV co-infected subjects

This is an ongoing, open label, single arm study of simeprevir/PegIFN/RBV in patients infected with HCV and HIV-1 co-infection. The primary efficacy endpoint was SVR12 assessed by prior HCV treatment response and by HIV treatment experience at baseline. There was no control group. Data were compared to historical SVR data obtained from Phase III studies in patients infected with HCV alone.

The sponsor provided the full study report with the response to the TGA request for further information. A total of 106 patients were treated, of which 97(91.5%) completed the study. Overall, SVR12 was achieved in 73.6% (78/106) of patients. SVR12 was achieved in 79.2% (42/53) of HCV treatment-naïve patients, 86.7% (13/15) prior HCV relapsers, 70.0% (7/10) prior HCV partial responders, and 57.1% (16/28) prior HCV null responders. In the final analysis, SVR12 was achieved in 75.35 (70/93) of patients on HAART and in 61.5% (8/13) patients not on HAART.

For HCV treatment-naïve subjects and prior HCV null responders, the SVR12 response rate was compared with the SVR24 rate in historical control data (PegIFNα-2a/RBV only treatment). This analysis was not planned for prior HCV partial responders and prior HCV relapsers given the small number of subjects in these categories.

SVR12 rates for simeprevir in combination with PegIFN/RBV were higher than in historical controls treated with PegIFN/RBV only (79.2% versus 29.0%, $p < 0.001$ for HCV treatment-naïve patients and 57.1% versus 5.4%, $p < 0.001$ for HCV prior non-responders).

Based on these data, the evaluator's recommendations changed from the Round 1 evaluation to support the proposed indication in patients with HCV/HIV co-infection. It is noted that numbers are small and that historical controls were used for comparison. The EMA guideline states that the efficacy of PegIFN/RBV in co-infected patients is considerably lower than in mono-infected patients and that there is an urgent medical need for better therapies for this patient group[20]. Co-infected patients are a heterogeneous group, however if a considerable effect relative to PegIFN/RBV has been demonstrated in mono-infected patients, randomised controlled trials in co-infected patients may not be mandated (EMEA/CHMP/EWP/30039/2008).

HPC 3011 Genotype 4 Treatment-naïve or Treatment experienced

This is an interim analysis of an on-going multicentre, open-label, single arm, Phase III study of simeprevir/PegIFN/RBV in treatment-naïve or treatment-experienced HCV genotype 4 infected patients. The primary endpoint was SVR12 in the different sub-populations (treatment-naïve, previous relapsers and previous non-responders).

Further data, to Week 60, were provided with the response to the TGA request for further information. At the Week 60 cut-off, 70.1% of patients had completed the study, 2.8% had discontinued and 27.1% were on-going. In the ITT population, SVR12 was achieved in 70/107 (65.4%) patients. In the ITT population, SVR24 was achieved in 55/63 (87.3%) patients and treatment failure was observed in 37/107 (34.6%) patients. Overall, viral breakthrough occurred in 20/107 (18.7%) patients (11.4% in treatment-naïve patients, 4.5% in prior relapsers, 20.0% in prior partial responders and 32.5% in prior null responders).

Based on these data, the evaluator's recommendations changed from the Round 1 evaluation to support the proposed indication in patients with HCV genotype 4 infection. It is noted that HPC 3011 is a single-arm open-label study. Draft EMA guidance[21] states that activity of PegIFN/RBV is similar for Genotypes 1 and 4 and that for an investigational compound used in combination with PegIFN/RBV, specific demonstration of efficacy against Genotype 4 may not be necessary for labelling. Currently adopted TGA-adopted EMA guidelines (EMEA/CHMP/EWP/30039/2008) recommend that patients with genotype 4 infection should be studied in separate trials, as efficacy against genotype 4 for a direct-acting antiviral effective against genotype 1 cannot be assumed.

Study 213

This is an ongoing exploratory Phase III , open label trial of simeprevir/PegIFN/RBV for HCV genotype 1 infected patients who participated in the placebo groups of a Phase IIb/III study (C201, C205, C206, C208, C216 or HPC3007), or who received up to 14 days of direct

[20] EMEA/CHMP/EWP/30039/2008. Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C.
[21] European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C. Draft. EMEA/CHMP/51240/2011. <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102109.pdf>

acting antiviral treatment in Phase I studies. The primary efficacy endpoint was SVR12, with an interim analysis dated October 2013 provided in response to a request from TGA.

At the time of this interim analysis, SVR12 was available for 34 subjects in the Phase II/III group and 16 subjects in the Phase I group. For subjects in the Phase II/III group, the SVR12 rate was 70.6% (24/34) overall. The SVR12 rate in prior viral relapsers, prior viral breakthroughs, prior partial responders and prior null responders was 92.9% (13/14), 75% (3/4), 60% (3/5) and 50% (5/10), respectively. For subjects in the Phase I group the SVR rate was 37.5% (6/16).

Safety

The safety of simeprevir in combination with PegIFN/RBV was evaluated in patients with chronic hepatitis C receiving simeprevir (n = 781) or placebo (n = 397) at the proposed 150 mg daily dose and 12 week duration. The primary safety analysis at week 60 (n = 781) included the three Phase III trials (C208, C216 and HPC3007).

The secondary pooling included an analysis of the primary pooling dataset with the addition of the dose ranging Phase IIb studies (C205 and C206). In this pooling, 924 patients were included in the simeprevir 150 mg once daily 12 weeks group, and 1486 patients were included in the all simeprevir group (simeprevir at all doses and treatment durations).

Data from healthy subjects in the Phase I studies (n = 806) were not included in these safety analyses.

For the primary pooling, discontinuations due to AEs were encountered in 14/781 (1.8%) of patients on simeprevir compared with 5/397(1.3%) on placebo. In the secondary pooling, there were two additional withdrawals due to AEs.

Specific safety issues are discussed below and include dermatological reactions, haematological abnormalities, gastrointestinal side effects, liver function tests, dyspnoea and psychiatric events.

Table 12: Number (%) of subjects with Events of Special Interest: ITT (Primary pooling)

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	TMC435 150 mg	PBO	TMC435 150 mg
Analysis Set: ITT	397	781	397	781
Events of special interest				
Increased bilirubin	11 (2.8%)	62 (7.9%)	12 (3.0%)	64 (8.2%)
Events of clinical interest				
Rash (Any Type)	67 (16.9%)	181 (23.2%)	99 (24.9%)	218 (27.9%)
Photosensitivity conditions	2 (0.5%)	26 (3.3%)	2 (0.5%)	26 (3.3%)
Pruritus	59 (14.9%)	172 (22.0%)	99 (24.9%)	217 (27.8%)
Neutropenia	60 (15.1%)	129 (16.5%)	88 (22.2%)	164 (21.0%)
Anemia	43 (10.8%)	105 (13.4%)	91 (22.9%)	150 (19.2%)

Dermatological events

Dermatological events including photosensitivity, rash and pruritus were the primary safety issues identified. The incidence of treatment-related rash of any type was 19.1% in the simeprevir group compared with 9.3% in the placebo group.

An additional review by the FDA Division of Dermatology and Dental Procedures (August 27, 2013[22]) described the two subjects treated with simeprevir who were subsequently admitted to hospital with photosensitivity reactions. For one patient, treatment required systemic corticosteroids and treatment with simeprevir was interrupted but ultimately completed. Another patient had three apparent photosensitivity events and the possibility of porphyria cutanea tarda was considered. This patient completed treatment with simeprevir.

There were no documented cases of Stevens Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis (TEN) in the drug development program to date, although rashes consistent with erythema multiforme and 'severe rashes with concomitant apthous stomatitis' were reported[23]. It was suggested that photosensitivity may have been underestimated as there was considerable overlap between AEs categorised broadly as rash and those categorised as photosensitivity.

With respect to pruritus, there was one (0.1%) Grade 3 event in the simeprevir group but no Grade 4 events and no SAEs. One (0.1%) patient discontinued because of a Grade 2 event.

Haematological abnormalities

The clinical evaluator concluded that there was no evidence of haematological toxicity with simeprevir in the Phase IIb/III study program to date and that there was no evidence that simeprevir increased the incidence or severity of anaemia. During the first 12 weeks of treatment, the incidence of anaemia was similar in both treatment groups (13.4% simeprevir, 10.8% placebo). Grade 3 events were reported in 1.0% and 1.8% of simeprevir and placebo patients, respectively. There were no Grade 4 events in simeprevir patients and no treatment discontinuations.

In both treatment groups, mean neutrophil counts decreased from baseline during the first 4 weeks of treatment and remained stable thereafter. Mean values increased towards baseline after completion of PegIFN/RBV therapy (at Week 24 in the majority of simeprevir patients). There were no differences in mean values over time between the treatment groups for platelets, leucocytes and lymphocytes.

Gastrointestinal side effects

There was a higher incidence of gastrointestinal side effects in the simeprevir group (45%) compared to the control group (40%) during the first 12 weeks of treatment, largely due to increased reporting of AEs due to nausea and vomiting in the simeprevir group.

Liver function tests

A greater frequency of AEs associated with increased bilirubin occurred in the simeprevir group, compared with the control group. No association between hyperbilirubinaemia and clinically relevant hepatotoxicity was noted. The clinical evaluator and FDA Medical review concur with the sponsor that the higher incidence of bilirubin elevations in simeprevir patients is attributed to decreased bilirubin elimination due to inhibition of the hepatic transporters OATP1B1 and MRP2, (and possibly due to RBV-induced haemolysis).

[22] Centre for Drug Evaluation and Research. Application number: 205123Orig1s000. Medical Review(s) Available from <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000MedR.pdf> (accessed 1st April 2014)
[23] Centre for Drug Evaluation and Research. Application number: 205123Orig1s000. Summary Review. Available from <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000SumR.pdf> (accessed 1st April 2014)

Other AEs

Dyspnoea

The FDA review noted a difference in frequency due to dyspnoea in the treatment group, compared with the control group. A separate analysis to determine whether this was related to anaemia was performed which confirmed that irrespective of controlling for anaemia, dyspnoea rates were 50% higher in the simeprevir group (FDA Medical Review). The clinical evaluator stated that dyspnoea was initially examined as an event of clinical interest but was not retained when the data did not suggest a link with simeprevir therapy.

Psychiatric events

The FDA analysis of psychiatric disorders reported an equal incidence in the simeprevir group (38%) and the control group (38%) during the first 12 weeks of treatment. A small increase in incidence was noted in the category of 'anxiety disorders and symptoms' for the simeprevir group.

Serious adverse events

Serious AEs were reported in 2.0% of patients treated with simeprevir and in 2.5% of patients on placebo.

Deaths

No deaths were reported during the first 12 weeks in the primary pooling (pivotal studies). Three patients in the simeprevir group died after simeprevir treatment was completed and none were considered related to the study treatment (colon carcinoma, sudden death, pneumonia with septic shock). No deaths were recorded during simeprevir treatment in the secondary pooling. There was one additional death compared with the primary pooling which occurred after simeprevir treatment (brain injury and meningitis).

Clinical evaluator's recommendation

The clinical evaluator recommended authorisation for use in prior partial and null responders based on Study C206 but subject to the results of HPC3001 being provided in a timely manner. The indication recommended for approval was:

> *the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.*

Risk management plan

Following the Round 2 evaluation, the following outstanding issues were identified by the RMP evaluator:

- The recommendation remains for the sponsor to amend the ASA in regards to pharmacovigilance and risk minimisation. The ASA should contain all studies referenced in the pharmacovigilance plan, and the anticipated dates for their submission in Australia.

The Delegate noted the sponsor's response was that *"….only studies that have Australian sites should be referenced. The ASA is an annex to the EU RMP and should be read in conjunction with the EU RMP. To copy all the information from the EU RMP again into the ASA, is a redundant activity that serves no purpose."* This was accepted by the Delegate.

- The RMP evaluator acknowledged the sponsor's response regarding the expansion of the list of ongoing safety concerns to include the risks listed in the Round 1 report. This was acceptable, except in regards to 'Use in other HCV genotypes' and 'Use in patients of Aboriginal and Torres Strait Islander descent'. The sponsor was requested to include these risks in the table of ongoing safety concerns. If appropriate, the OPR will accept the inclusion of these risks in the ASA only.

The Delegate requested the sponsor implement this recommendation.

- The safety of simeprevir cannot be separated from that of pegIFN and RBV, as these products are dosed together as part of triple therapy. Simeprevir has been studied as part of a triple therapy regimen. The issue of including important risks and information in the RMP and Australian PI is deferred to the Delegate for consideration.

The Delegate agreed with the sponsor that assessment of the risks associated with PegIFN and/or RBV, or any other compound that is administered in combination with simeprevir in the future, was beyond the scope of the simeprevir RMP.

- The recommendation to include rash and severe cutaneous adverse reactions as an ongoing safety concern remained.

It was noted that the sponsor had implemented this recommendation.

Advice from the Advisory Committee on the Safety of Medicines

Advice on the pharmacovigilance aspects of this application from the ASCOM was provided to the Delegate and presented to the ACPM meeting.

Risk-benefit analysis

Delegate's considerations

Efficacy for simeprevir compared with PegIFN/RBV alone has been demonstrated in two pivotal clinical trials of genotype 1 treatment-naïve HCV patients. At the time the Phase III trials were initiated, other protease inhibitors had not been approved and PegIFN/RBV was standard therapy.

Efficacy in genotype 1 relapsers has been demonstrated in one pivotal clinical trial. There is a paucity of data to support the proposed indication in prior null and partial PegIFN/RBV responders. It was noted that the final study report for Study HPC3001[24] was awaited by the FDA as confirmatory evidence of efficacy in this patient group. The Delegate proposed that results from Study HPC3001 be submitted prior to recommending approval for this patient group.

Data has demonstrated efficacy in a study of 106 patients co-infected with HIV compared historical controls. While this is not ideal, it was acknowledged that the EMA guidance states that if a considerable effect relative to PegIFN/RBV has been demonstrated in mono-infected patients, randomised controlled trials in co-infected patients may not be mandated (EMEA/CHMP/EWP/30039/2008. *Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C* (23 April 2009)). The quality of the data needs to be balanced with the need for better therapies in this patient group.

[24] A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435 versus Telaprevir, both in Combination with PegIFNα-2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior pegylated interferon alfa and Ribavirin Therapy

An open label, single arm study of 136 treatment-naïve or treatment experienced patients with HCV genotype 4 was provided to support the indication for this patient group. It is known that the activity for PegIFN/RBV is similar for patients with genotypes 1 and 4. ACPM advice would be sought to confirm whether the submitted data are sufficient to support approval, noting the EMA guidance for the study of patients with HCV genotype 4.

There is a paucity of data in people of East Asian descent, with the results of an ongoing Phase III trial in Chinese and Korean people evaluating simeprevir 100 mg and 150 mg daily with PegIFN/RBV awaited to guide appropriate dosing. The Delegate suggested the results from this study be made available to the TGA when completed. Variability in response was noted in these patients in clinical trials and lower doses may be needed. The mechanism for these differences is not clear and, in accordance with ACSOM advice, the sponsor was requested to provide an explanation for these differences in its response to this overview.

The potential benefits of simeprevir are once daily dosing, less risk of anaemia (compared to boceprevir and telaprevir) and the potential for a shorter duration of PegIFN/RBV therapy. However, patients are still required to have a minimum of 24 weeks PegIFN/RBV as part of treatment.

Advice from ACPM would be sought regarding the reduced response to simeprevir in patients with Q80K polymorphism and whether recommendations for screening at baseline (as recommended in the US) are appropriate in the Australian population with HCV. Submitted data demonstrates a higher prevalence of this polymorphism in the US (34.4% overall, 48.1% in genotype 1a) compared with Australia and New Zealand (7.1% overall, 7.1% in genotype 1a). The ACSOM had suggested that screening is not necessary but that inclusion of a statement in the PI stating that Q80K polymorphism may cause reduced efficacy would be appropriate.

There is a considerable risk of rashes and photosensitivity, which has been highlighted by the FDA review as a pre-marketing signal. While there were no documented cases of Steven's Johnson's syndrome, DRESS or toxic epidermal necrolysis, considering the small numbers of patients in the pre-marketing data and the serious skin reactions noted with telaprevir, clear, specific warnings are needed in the PI and CMI, should registration be approved. The Delegate proposed to seek ACPM advice regarding inclusion of a table in the *Precautions* section of the PI similar to telaprevir, with recommendations to prescribers regarding skin reactions.

While simeprevir may be administered once daily with the possibility of a shorter duration of treatment with PegIFN/RBV and less haematological toxicity (compared with currently approved protease inhibitors), there is currently little post-marketing data to confirm the safety issues identified in the clinical trials. Furthermore, the possibility of interferon-free regimens for hepatitis C currently in development means the ultimate role for simeprevir is not yet known.

Proposed action

The Delegate had no reason to say, at this time, that the application for simeprevir should not be approved for registration. However, the following points are noted:

- Given the paucity of data in patients who were prior partial or null responders, approval should be considered for the slightly modified indication of

  the treatment of chronic hepatitis C genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have relapsed following previous peginterferon therapy with or without ribavirin

- A final decision to recommend approval for patients co-infected with HIV and for patients with genotype 4 infection would be made following advice from ACPM.
- Approval would be subject to implementation of the EU-RMP Version 1.0 Dated 18th January 2013 with an Australian Specific Annex Version 1.0 Dated 15th April 2013.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. Whether the data to support use in patients with HIV co-infection and in patients with genotype 4 HCV are sufficient to approve the indications.
2. Whether the data are sufficient to support use in patients who were prior partial or null responders.
3. The clinical virology and resistance issues and whether screening for Q80K polymorphism, prior to treatment (as recommended by the FDA) is appropriate in Australia.
4. The potential for photosensitivity and serious skin reactions, given the signal identified in the pre-marketing data. Related to this, whether inclusion of a table in the PI similar to that in the telaprevir PI, with recommendations to prescribers regarding skin reactions, is indicated.
5. Whether adverse effects due to pruritus and rashes pose a significant risk of non-adherence to therapy.

Response from Sponsor

Introduction

Janssen concurs with the TGA clinical evaluator's and Delegate's recommendation to approve Olysio simeprevir, and notes the clinical evaluator's support for the originally proposed indication:

> *Olysio/Janssen Simeprevir is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus- 1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin (see Clinical Trials).*

The sponsor addressed each of the issues raised by the Delegate in order to demonstrate that the data fully supports all aspects of our proposed indication.

Delegate's Issue 1: Whether the data to support use in patients with HIV co-infection and in patients with genotype 4 HCV are sufficient to approve these indications.

The EMA guideline EMEA/CHMP/51240/2011 states *"that the efficacy of PegIFN/RBV in co-infected patients is considerably lower than in mono-infected patients and that there is an urgent medical need for better therapies for this patient group. Co-infected patients are a heterogeneous group, however if a considerable effect relative to PegIFN/RBV has been demonstrated in mono-infected patients, randomised controlled trials in co-infected patients may not be mandated." Similarly the EMEA guideline EMEA/CHMP/EWP/30039/2008 states "If a considerably increased effect relative to standard of care has been demonstrated in mono-infected patients, randomised controlled trials in the co-infected population may not be mandated. In such a scenario, single-arm studies in co-infected patients may be sufficient*

for licensure, if these demonstrate convincingly enhanced efficacy compared to historical controls."

Simeprevir has demonstrated a convincingly enhanced efficacy against historical controls (SVR12 79% for simeprevir against 29% for PegIFN/RBV alone, $p < 0.001$) and similar efficacy to that seen with simeprevir in HCV mono-infected patients, which the clinical evaluator acknowledged in their report. Janssen has met all the guideline requirements for indication approval for HIV/HCV co-infected patients. Especially as this is a patient population for which there is a medical need for better therapies.

For patients with genotype 4, the TGA clinical evaluator stated that the updated Study HPC3011 results showed that in the ITT population, SVR12 was achieved in 70/107 (65.4%) patients and SVR24 was achieved in 55/63 (87.3%) patients and treatment failure was observed in 37/107 (34.6%) patients. These results showed a similar level of efficacy to the results observed in genotype 1 HCV patients. The in vitro virology studies further demonstrated simeprevir was efficacious against genotype 4 clinical isolates (TGA nonclinical evaluation report). The latest EU guideline EMEA/CHMP/51240/2011 states *"The activity of pegIFN + ribavirin against GT4 is considered of similar magnitude as against GT1. GT4 may be studied in trials together with GT1, provided that the in vitro activity of the investigational compound against these genotypes is roughly similar. For an investigational compound used in combination with pegIFN and ribavirin, a specific demonstration of efficacy against GT4 would not be necessary for labelling, given that in vitro activity and available viral response data, including early viral kinetics and SVR rates, show adequate consistency between GT1 and GT4."* Janssen has met the EU guideline requirements for labelling of demonstrating in vitro efficacy against genotype 4 isolates and also demonstrated comparable clinical efficacy responses in genotype 4 patients to those seen in genotype 1 HCV patients in a separate clinical Study HPC3011; a fact acknowledged by the clinical evaluator. Thus the sponsor considered the proposed indication in genotype 4 HCV patients should be approved, especially as this patient population also has an unmet medical need for better therapies.

Delegate's Issue 2: Whether the data are sufficient to support use in patients who were prior partial or null responders.

At the time the response to the TGA request for further information was sent to TGA the sponsor did not have the results of the HPC3001, to supplement the existing data from Study C206 demonstrating simeprevir efficacy in 23 prior partial and 17 prior null responders. A top-line study report, dated 6 March 2014, from the week 60 analysis of Study HPC3001 was provided as an attachment to this response as requested by the TGA Delegate and clinical evaluator. Study HPC3001 is a Phase III, double-blind study to establish the non-inferiority of simeprevir to telaprevir in 763 genotype 1 HCV patients who were previous non responders (472 prior null responders and 291 prior partial responders) to PegIFNα and RBV. In the ITT population, SVR12 rates were 53.6% and 54.7% in the simeprevir and telaprevir arms, respectively. The stratum adjusted (95% CI) difference in proportions was -1.1% (-7.8%; 5.5%), so non-inferiority of simeprevir towards telaprevir was concluded ($p < 0.001$) with respect to SVR12.

In the prior null responder subpopulation of HPC3001, the SVR12 rates were 102/234 (43.6%) and 110/238 (46.2%) for simeprevir and telaprevir treated subjects respectively. In the prior partial responder subpopulation of HPC3001, the SVR12 rates were 101/145 (69.7%) and 100/146 (68.5%) for simeprevir and telaprevir treated subjects, respectively. When results from Studies HPC3001 and C206 are combined, Janssen has demonstrated the favourable efficacy of simeprevir in a substantial number of prior partial and prior null responders.

In the HPC3001, simeprevir was shown to be non-inferior to telaprevir with a better safety profile than telaprevir. TGA have approved telaprevir for use in relapsers and prior partial

or null responders. As simeprevir has been demonstrated to be non-inferior to telaprevir in prior partial or null responders, simeprevir should also be approved for an indication for the treatment of prior partial or null responders.

Delegate's Issue 3: The clinical virology and resistance issues and whether screening for Q80K polymorphism, prior to treatment (as recommended by the FDA) is appropriate in Australia.

Janssen agrees with both the TGA clinical evaluator and ACSOM that screening for Q80K in Australia is not necessary for the following reasons. Firstly, the prevalence of the Q80K polymorphism in Australia and New Zealand during the simeprevir clinical trial program was 7.1% overall and 7.1% in genotype 1a, compared to the US 34.4% overall and 48.1% in genotype 1a. The sponsor also provided a letter from an expert discussing a research project involving resistance profiling and sequencing in hepatitis C patients in New South Wales. Of the 380 genotype 1a chronic hepatitis C patients assessed, only 21 (5.6%) had the Q80K polymorphism. Secondly, as the TGA clinical evaluator stated in their evaluation report *"Combination of HCV geno/subtype with baseline Q80K polymorphism was not predictive of outcome"*.

Thirdly, as stated in the draft PI, even in patients who had the Q80K polymorphism at baseline, 77-79% still achieved an SVR12. *"In the pooled analysis of Studies C208 and C216, 63% of OLYSIO treated HCV genotype 1a infected patients (n=53/84) with Q80K polymorphism at baseline had undetectable HCV RNA at Week 4 (Rapid Virologic Response; RVR), and 79% of these patients (n=42/53) achieved SVR12. Among the OLYSIO treated genotype 1a patients with Q80K and HCV RNA < 25 IU/mL detectable at Week 4 (13%; n=11/84), 45% (n=5/11) achieved SVR12. In Study HPC3007, 43% of OLYSIO treated HCV genotype 1a infected patients (n=13/30) with Q80K polymorphism at baseline had undetectable HCV RNA at Week 4 (RVR), and 77% of these patients (n=10/13) achieved SVR12. Among the OLYSIO treated genotype 1a patients with Q80K and HCV RNA < 25 IU/mL detectable at Week 4 (40%; n=12/30), 33% (n=4/12) achieved SVR12."*

Fourthly, under the *Dosage and Administration* section of the Olysio PI, as part of response guided therapy, Janssen have proposed treatment stopping rules. As it is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR), the sponsor proposes that a patient at week 4 of treatment who has HCV RNA ≥ 25 IU/mL should discontinue treatment with simeprevir, pegIFN and RBV. Additionally if patients have detectable HCV RNA in treatment week 12 they should discontinue further treatment with pegIFN and RBV. This will ensure that any patients, including those patients who do have the Q80K polymorphism, who do not achieve an adequate virologic response by week 4 will not be subjected to unnecessary additional treatment with simeprevir or pegIFN and RBV if they are unlikely to achieve a sustained virological response.

Finally, there is no uniform reimbursed access to Q80K testing in Australia and thus any recommendation mandating Q80K testing would deny patients the ability to access a more efficacious and better tolerated treatment than existing therapies.

The TGA Delegate requested the sponsor add a statement that Q80K polymorphism may cause reduced efficacy in the appropriate section of the PI. Janssen already has a statement in the PI stating *"In the pooled analysis of the Phase 3 Studies C208 and C216, and in Study HPC3007, the presence of Q80K at baseline was associated with lower SVR rates in HCV genotype 1a Olysio treated patients compared to HCV genotype 1a Olysio treated patients without Q80K."*

To address the Delegate's request, Janssen is also proposing to add the following text to the Precautions section: *"Use in patients with HCV genotype 1a Sustained virologic response (SVR) rates of Olysio in combination with pegIFN and RBV were reduced in patients with*

hepatitis C genotype 1a with NS3 Q80K polymorphism compared to patients without Q80K polymorphism (see Pharmacodynamics)."

Delegate's Issue 4: The potential for photosensitivity and serious skin reactions, given the signal identified in the pre-marketing data. Related to this, whether inclusion of a table in the PI similar to telaprevir, with recommendations to prescribers regarding skin reactions is indicated.

Janssen does not believe that the addition of a table in the PI similar to telaprevir, with recommendations to prescribers regarding skin reactions, is required. Study HPC3001 clearly showed in a head-to-head study with telaprevir, that the incidence of pruritus and rash of any type was ≥ 10% lower with simeprevir. Fewer Grade 3/4 rashes were observed in Study HPC3001 (2 in simeprevir arm versus 6 for telaprevir arm, and no rash SAEs for simeprevir versus 3 in telaprevir arm) during simeprevir/telaprevir phase. Also the incidence of anaemia with simeprevir was one-third the rate seen with telaprevir. Simeprevir has a more favourable safety profile than telaprevir. The inclusion of "class-effect" labelling on rash, would imply rash occurs at a similar frequency with simeprevir as observed with telaprevir. Janssen proposing to add an alternative statement on rash[25].

Delegate's Issue 5: Whether adverse effects due to pruritis and rashes pose a significant risk of non-adherence to therapy.

As stated in the sponsor's Summary of clinical safety: *"in TMC435-treated subjects, 97.6% of subjects who completed 12 weeks of TMC435 treatment were ≥ 97% adherent to the planned dosing of TMC435"*.

In Study HPC3001, simeprevir was directly compared to telaprevir and shown to be non-inferior to telaprevir with a better safety profile than telaprevir. Serious AEs in HPC3001 were reported in 2.1% of subjects in the simeprevir arm and in 8.6% of subjects in the telaprevir arm during simeprevir/telaprevir + pegIFNα/RBV phase. AEs leading to permanent cessation of the investigational drug occurred less frequently in the simeprevir arm (1.8%) than in the telaprevir arm (8.3%) during the simeprevir/telaprevir + pegIFNα/RBV phase. More specifically, the incidence of pruritus and rash was ≥ 10% lower in simeprevir arm versus telaprevir arm (32% versus 44% respectively for pruritus) and (21% versus 31% respectively for rash of any type). The PI of Olysio has the following text. *"Discontinuation of Olysio due to rash or pruritus occurred in 0.8% and 0.1% of Olysio treated patients, compared to 0.3% and no patients treated with placebo, pegIFNα and RBV, respectively."* As such there is a low risk of non-adherence to therapy as a consequence of pruritus and rashes.

Other issues raised by Delegate

Delegate's request to include information on "Use in other HCV genotypes" and "Use in patients of Aboriginal and Torres Strait Islander descent" in the RMP.

Janssen does not consider it is necessary to include information in the ASA of the simeprevir RMP on "use in other HCV genotypes". The proposed Olysio PI clearly states in the *Precautions* subsection *"Use in patients with other HCV genotypes Clinical data are insufficient to support the use of Olysio in patients with HCV genotypes 2, 3, 5 or 6."* Given the clear PI warning against use outside HCV genotypes 1 and 4, there is unlikely to be usage in other genotypes. Use in other genotypes, if it did occur, would be captured under "off-label" use or "lack of efficacy" and fall under routine pharmacovigilance.

As there was no requirement to include information on patients of Aboriginal and Torres Strait Islander descent in the ASA of the telaprevir RMP, a compound in the same class as simeprevir, Janssen considers it is unnecessary to request the inclusion of such information in the ASA of the simeprevir RMP. Especially when there has been no evidence

[25] Details of proposed text in the PI are beyond the scope of the AusPAR.

hinting at a possible signal in patients of Aboriginal and Torres Strait Islander descent. Janssen also believes the suggestion by ACSOM *"that it may be appropriate for a pharmacokinetic study or registry to be conducted for Australians of Aboriginal or Torres Strait Islander descent*" is inappropriate and unwarranted especially in the absence of any potential signal. The sponsor included a copy of a letter from an Australian hospital liver clinic which serves as an outpatient clinic of the Aboriginal Medical Service. Due to a number of factors listed in the letter, including poor adherence to complex treatment regimens, the letter states *"it is our opinion that conducting a clinical trial in Australia to obtain clinical data specific to this patient population is impractical, due to low treatment uptake rates and hence difficulty in recruitment in this patient group"*.

Delegate's request to please include important identified risks for the combination therapy, specifically anaemia, lymphopenia/neutropenia, thrombocytopenia, psychiatric disorders, diabetes mellitus, thyroid disorders and specific skin disorders (cutaneous leukocytoclastic vasculitis, lichen planus, polyarteritis nodosa, porphyria cutanea tarda), as per ASCOM and RMP advice.

Janssen does not believe all the risks named above that are associated with the use pegIFNα and RBV should be included in the simeprevir PI. Zytiga (abiraterone) is TGA approved for use in combination with prednisone and yet the Zytiga PI does not list out all the risks associated with the use of prednisone. It is more appropriate for the Olysio PI to refer prescribers to the PI documents for pegIFNα and RBV, as Janssen, who is not the ARTG sponsor of either product, will not have access to the most current adverse event data for both products. By compelling prescribers to consult the most current PI documents of both pegIFNα and RBV, Janssen is preventing the possibility of a serious AE occurring as a result of prescribers not being cognisant of the most current safety information for both pegIFNα and RBV. The sponsor acknowledged that the TGA Delegate agreed with Janssen's position *"that assessment of the risks associated with PegIFN and/or RBV, or any other compound that is administered in combination with simeprevir in the future, is beyond the scope of the simeprevir RMP".* As such all educational activities, including the updating the Olysio PI on the risks associated with pegIFNα and RBV, are in Janssen's opinion the responsibility of the sponsors of the individual medicines.

PI changes requested by Delegate

Details of these are beyond the scope of the AusPAR.

Conclusion

Given the positive benefit/risk profile, Janssen agrees with the TGA clinical evaluator's and Delegate's recommendation to approve Olysio simeprevir. It is also considered that with the efficacy and safety data from Studies HPC3001, HPC3011 and C212, the sponsor has convincingly demonstrated that Olysio should be approved for the originally proposed indication shown below:

> *Olysio/Janssen Simeprevir is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin (see Clinical Trials).*

This is especially pertinent for genotype 1 HCV patients who were prior partial or null responders, as well as patients with HCV genotype 4 and HCV/HIV co-infection, who have an unmet medical need for new therapies that are efficacious and with a more favourable safety profile. Olysio delivers this with the added convenience to patients of one capsule once daily PO dosing.

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 submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Olysio/Janssen Simeprevir capsule containing 150 mg of simeprevir sodium to have an overall positive benefit–risk profile for the amended indication;

> *Olysio is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy with or without ribavirin (see Clinical Trials and Dosage and Administration sections for detailed information on the studied combinations, dose regimens, and treatment durations for different subgroups of CHC patients).*

ACPM recommended a more simplified indication, similar to the European Summary of Product Characteristics for Olysio.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/ CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI which are detailed in the section *Specific advice* below.

Specific advice

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

1. Whether the data to support use in patients with HIV co-infection and in patients with genotype 4 HCV are sufficient to approve these indications.

EMA guidelines have endorsed single arm studies in HIV/HCV co-infection; however, in the current rapidly evolving therapeutic environment appropriate comparator information is critical. There are limited data to support comparable efficacy for directly acting antiviral agents (DAAs) but not all available agents used in combination with PegIFN/RBV for patients with genotype 4 and genotype 1 infection. Whilst the trial in patients with HIV/HCV co-infection met the EMA guideline, it provided no data on the current comparators and demonstrated a 79% response in HCV treatment naïve patients. In subjects with genotype 4 infection, the number of patients was very small, the study was open label and there were concerns regarding the adequacy of these data. These findings should be included in the PI along with all DAA studies.

2. Whether the data are sufficient to support use in patients who were prior partial or null responders.

The ACPM expressed considerable concern that the data from Study HPC3001 had not been evaluated, despite opportunities provided with two prior rounds of evaluation. While there was prima facie support that SVR12 in non-responders and partial responders were similar for simeprevir and telaprevir, this unevaluated data should not be included in the indication, but may be included in the appropriate section of the PI. Evaluated confirmation is required.

ACPM also expressed concern that data regarding dual combination with sofosbuvir, included in the European Summary of Product Characteristics, was not made available to the TGA with this submission or included with the pre-ACPM response on foreign PI.

3. The clinical virology and resistance issues and whether screening for Q80K polymorphism, prior to treatment (as recommended by the FDA) is appropriate in Australia.

Some difference in outcomes was demonstrated when data were stratified by Q80K status but there is still a response in these patients. The ACPM advised that screening was under development but not yet available in Australia but information on testing should remain in the PI and lack of the test should be included in Precautions. In practice the presence of the Q80K mutation might be an indication for alternative treatment in patients infected with genotype 1aHCV.

4. The potential for photosensitivity and serious skin reactions, given the signal identified in the pre-marketing data. Related to this, whether inclusion of a table in the PI similar to telaprevir, with recommendations to prescribers regarding skin reactions is indicated.

The ACPM advised that a table similar to that found in the telaprevir PI is appropriate in this case. Simeprevir appears to be more like telaprevir than boceprevir in toxicity profile. The occurrence of skin rashes and photosensitivity appears to be about half as frequent for simeprevir versus telaprevir but remains a real concern. The ACPM noted that Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been described with telaprevir pre-registration data but not with simeprevir pre-registration trials to date.

5. Whether adverse effects due to pruritus and rashes pose a significant risk of non-adherence to therapy.

It is possible that this will be a significant risk, but in the view of the ACPM it is acceptable and manageable. IFN is usually the limiting component of HCV treatment regimens.

The ACPM further agreed with delegate on inclusion of a statement that there are no data for genotypes 2, 3, 5 and 6.

The ACPM agreed with the sponsor that no statement regarding Indigenous Australians is required.

The ACPM agreed with the delegate that a statement regarding the potential for interaction with illicit drugs should be included in the PI, as it is important information and has been recommended by ACSOM and the RMP evaluator.

The ACPM agreed with the delegate that the sponsor should include important identified risks for combination therapy in the PI, as per ACSOM, RMP advice.

The ACPM advised that the 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 Olysio/Janssen Simeprevir capsules containing 150 mg simeprevir (as sodium), indicated for:

> *Olysio/Janssen Simeprevir are indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with other medicinal products for the treatment of CHC infection (see Dosage and Administration, Precautions, Clinical trials).*

Specific conditions of registration applying to these goods

- For simeprevir (as sodium), the European Risk Management Plan Version 1.1 dated 14th November 2013, with data lock point 16th September 2013, with an Australian Specific Annex Version 1.1 dated 28th January 2014 to be revised to the satisfaction of the TGA, must be implemented.

Attachment 1. Product Information

The Product Information approved for Olysio at the time this AusPAR was published is at Attachment 1. The PI for Janssen Simeprevir is identical except for the product name. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au